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Phenolic Oxidation of *o,o'*-Dihalogenated Phenols

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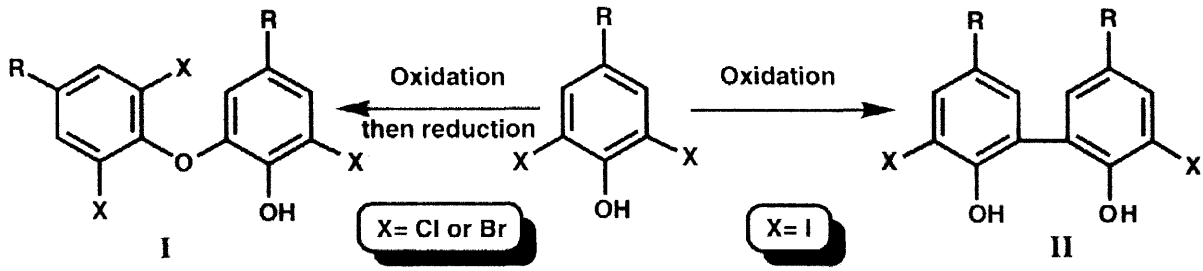
Abstract: A detailed inspection of phenolic oxidation products derived from the *o,o'*-dihalogenated cresol derivatives (**1a - 1e**) indicated that the bromo and chloro substituents promoted the oxidation leading to the corresponding diaryl ethers, whereas the iodo derivatives provided the diaryls. Selective reduction of **6d** and its tyrosine derivative afforded the corresponding diaryl ethers carrying two chlorine atoms (**14**, **15**). Interpretation of the selectivity of the phenolic oxidation was attempted by employing theoretical calculations. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: anodic oxidation; *o,o'*-dihalogenated phenol; diaryl ether; diaryl; *ab initio* calculations

Isodityrosine-class natural products, sharing diaryl ethers, are of interest from the viewpoint of their diverse biological activities as well as the challenging peptide framework. Since the first synthesis of marine sponge-derived bastadins carrying 28-membered-ring lactam structures,[1] we have accomplished a number of related investigations by the phenolic oxidation methodology employing thallium (III) salts and anodic oxidations.[2] Basically, in our methodology, both ortho-positions of phenol groups were substituted by appropriate halogen atoms to control oxidation potentials. Intramolecular oxidation leading to such cyclic isodityrosine derivatives as vancomycin, K-13, OF-4949s, and piperazinomycin, can be performed only under the TTN (thallium trinitrate) conditions, whereas both methods provide dimerization reactions to isodityrosine [type **I**: X= H, R= $CH_2CH(NH_2)COOH$] and dityrosine [type **II**: X= H, R= $CH_2CH(NH_2)COOH$][3] derivatives. Empirically, bromine substituents promote the diaryl ether formation, while iodine substitutions prefer to produce diaryls.[4] However, the specificity of the reaction and the factors that control the oxidation mode are still unclear in our phenolic oxidation chemistry. We describe herein an inspection of the anodic



Scheme 1. Oxidation of *o,o'*-dihalogenated phenols

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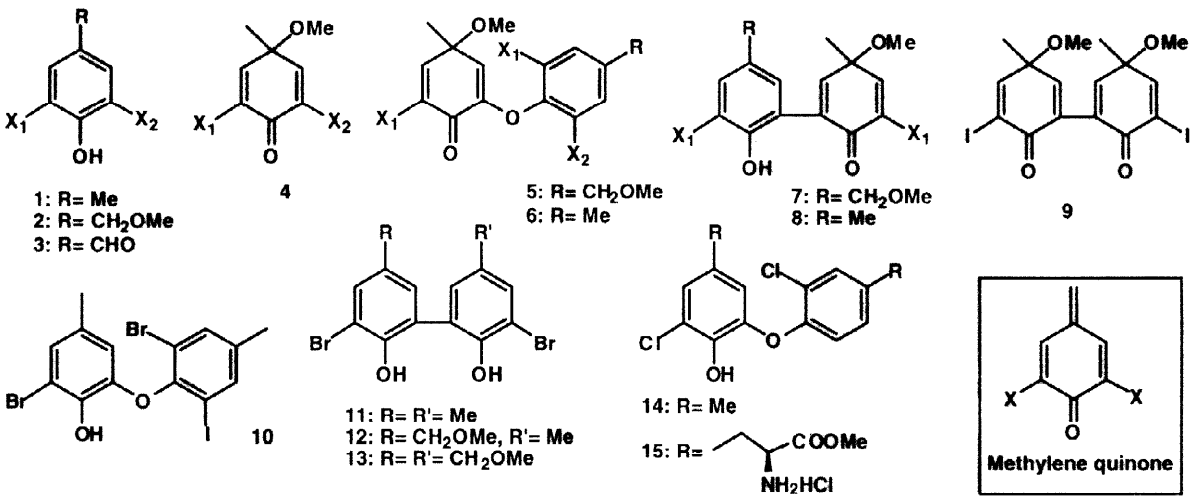
Table 1. Anodic Oxidation Products

	Educts			Products (%)												
Entry	X_1	X_2	Condition	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
a	Br	Br	A	28	37	-	-	-	28	-	-	-	-	-	-	-
			N	27	33	-	-	3	13	-	-	-	-	-	-	-
b	Cl	Cl	A	-	6	5	-	9	69	-	-	-	-	-	-	-
			N	-	8	5	-	13	61	-	-	-	-	-	-	-
c	I	I	A	23	23	-	4	-	-	16	24	9	-	-	-	-
d	Cl	Br	A	13	26	3	-	5	48	-	-	-	-	-	-	-
e	Br	I	A	21	19	2	-	-	-	-	20	-	3	2	-	-
			A*	16	18	1	-	-	-	8	37	-	9	-	4	3
			N	20	20	1	-	-	-	-	9	-	2	10	7	5

A = acidic conditions. N = neutral conditions. * 1.32 mmol of **1e** was used.



oxidation of *o,o'*-dihalogenated cresols as well as theoretical investigations of the reaction mode.

RESULTS AND DISCUSSION

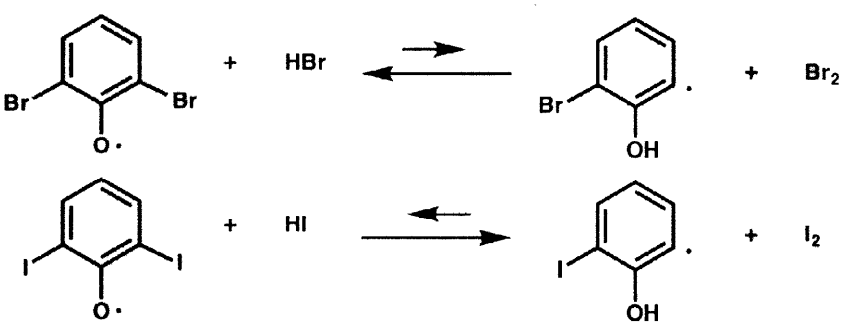
To investigate the nature of the oxidation reactions, a variety of dihalogenated cresols (**1a** - **1e**),[5] involving the derivatives carrying different halogen atoms (**1d, 1e**), were submitted to anodic oxidation. As can be seen in Table 1, all entries provided the two-electron oxidation products (**2**, **3**), produced via the methylene quinone intermediates. However, clear distinction was observed between the Cl / Br series, and the I derivatives; **1a** and **1b** provided the dimers bearing diaryl ethers (**5a**, **5b**, **6a** and **6b**), while the diaryls (**7c**, **8c** and **9**) were obtained from **1c**. The chlorinated compound **1b** yielded more diaryl ethers (**5**, **6**) than **1a**.

Additionally, the cresol with both bromine and chlorine atoms (**1d**) exhibited an interesting chemoselectivity, where the ether linkage was exclusively formed at the bromine side, leading to **5d** and **6d**. No products with an opposite selectivity could be detected by mass spectroscopy of the crude mixture. Successive reduction (Zn / AcOH, then H_2, Pd-C) of **6d** underwent selective removal of the bromine atom to give the dichloro-diaryl ether **14**. A similar selectivity was also observed in the synthesis of the

Table 2. Reaction Model for the Comparison of Relative Stability of O-radicals vs. C-radicals

Method	X	Ar-O• (Hartree)	HX (Hartree)	Ar• (Hartree)	X_2 (Hartree)	Reaction Energy (Kcal/mol)	Difference of Relative Stability Br vs. I
ROHF/STO-3G	Br	-5389.32478	-2545.22819	-2845.16850	-5089.32787	35.5	125.7
	I	-14001.19984	-6851.25478	-7151.19290	-13701.40565	-90.2	
ROHF/LANL2DZ	Br	-329.52645	-13.49788	-317.15803	-25.82995	22.8	14.3
	I	-325.98846	-11.72609	-315.38912	-22.31185	8.5	
UMP2/LANL2DZ	Br	-330.14572	-13.53047	-317.74136	-25.88719	29.8	10.3
	I	-326.60150	-11.75328	-315.96909	-22.35463	19.5	
B3LYP/LANL2DZ	Br	-331.89553	-13.75765	-319.28941	-26.30905	34.3	17.3
SCRF	I	-328.33049	-11.97698	-317.51088	-22.76939	17.0	

Energies of each species are denoted in Hartree, while reaction and relative energies are shown in Kcal/mol.

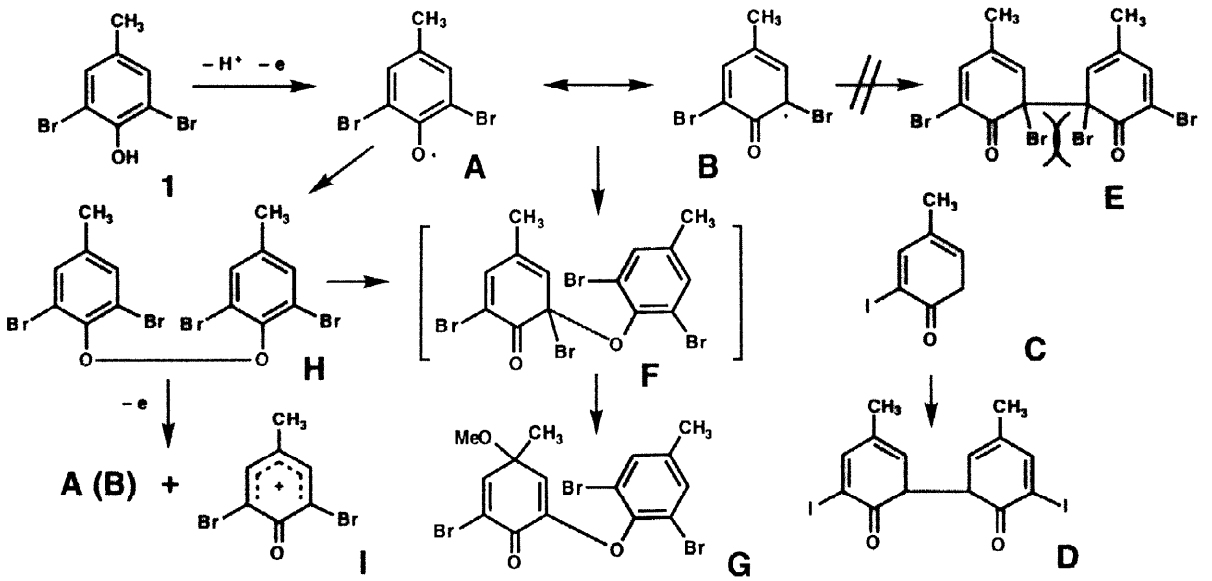


dichloroisodityrosine derivative **15**, where anodic oxidation of Z-3-bromo-5-chloro-L-tyrosine methyl ester, followed by Zn reduction afforded the corresponding diaryl ether in comparable yield (41%) to the case of **6d**. This mixed-halogen method is considered to be a useful one to produce such diaryl ethers as **14** and **15**, since oxidation of monohalogenated phenols afforded the corresponding products generally in low yields.[6] High substrate concentration (0.25→1.32 mmol) afforded the coupling products (for example **8e**, 37%) in higher yield than in the usual case (**8e**, 20%).

Interestingly, diaryls (**11** - **13**) obtained from **1e** underwent the coupling exclusively at the iodine position. In addition, production of **10** possesses a lower oxidation state than **5** and **6**, strongly indicating the generation of the phenyl radical by abstraction of an iodine.

To explain the experimental results, we suspected the C-radical is more stable with diiodo cresol, while the O-radical is more stable with dibromo and dichloro cresols. Accordingly, we investigated the following model system to compare the relative stability of the C-radical and O-radical. Computational results by *ab initio* MO and DFT calculations at several levels of theory are listed in Table 2. Clearly, STO-3G largely overestimates the stability of the C-radical of iodo phenol, but the calculations with LANL2DZ basis at different levels of theory gave rather consistent results. With the model we used, the O-radicals is always preferred over the C-radical. For the dibromo system, the preference is about 20 ~ 30 Kcal/mol, and for the diiodo system, the preference decreased to about 8 ~ 20 Kcal/mol. Overall, the preference of the O-radical over the C-radical is larger for the dibromo phenol than the diiodo phenol by 10 ~ 15 Kcal/mol.

The calculated solvent effect at B3LYP/LANL2DZ lowered the reaction energy by about 2.5 ~ 4.5 Kcal/mol, indicating the larger solvation energy (higher dipole moment) of the O-radical over the C-radical. The calculated solvent effect for the relative stability of the O- and C-radicals between the diiodo and dibromo systems was



Scheme 2. Plausible reaction process to the diaryl ether and diaryl

within the order of 1Kcal/mol. Although our computational model oversimplifies the situation by not explicitly considering the formation of halogen radicals, it is safe to say that it shows the C-radical is easier to form from diiodo phenol than from dibromo phenol.

Considering these results, the oxidation pathway of the bromo derivatives to the diaryl ether products takes the following into account: the O-radical **A** may be resonated with radical **B**, as shown in Scheme 2. Contrary to the iodine case (**C** → **D**),[7] a homogeneous coupling of **B** to **E** is impeded by repulsion of the bromine substituents. Two radical centers of **A** and **B** can approach each other to produce the diaryl ether linkage (**F** → **G**). Upon the generation of peroxide **H**, its high reactivity will cause further reaction to **F** through an intramolecular rearrangement, or a radical species (**A** or **B**) along with cation **I** through a further one-electron oxidation. Attack of nucleophiles (ex. alcoholic solvent) effects transformation of **I** into such two-electron oxidation products as **2** and **4**.

In conclusion, the one-electron oxidation of phenol derivatives produced diaryl ethers (**I**) or diaryls (**II**). The product distribution specifically depended on the halogen substituents. The *ab initio* calculations strongly indicated that the O-radicals are stable in bromo derivatives, contrary to the C-radical in iodo derivatives. Accordingly, the former species are transformed into diaryl ether **I**, and the latter to diaryl **II**, which are compatible with experimental results.

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EXPERIMENTAL

All of the melting points were obtained on a Yanaco MP-S3 melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a JEOL JNM EX-270, a JEOL JNM GX-400 or a JNM ALPHA-400 NMR spectrometer in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard, unless otherwise stated. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. High-resolution mass spectra were

obtained on a Hitachi M-80 B GC-MS spectrometer operating at the ionization energy of 70 eV. Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F_{254}, E. Merck A. G., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Katayama silica gel (K 070) was used for column chromatography.

General procedure of anodic oxidation. A solution of a phenol derivative (0.25 mmol) in a solvent [MeOH (22.5 ml) - 60% $HClO_4$ (2.5 ml) for acidic conditions: MeOH (25 ml) for neutral conditions: 0.05 M NaOMe / MeOH for basic conditions] containing an electrolyte (ca. 540 mg, $LiClO_4$) was electrolyzed (C.C.E. at 0.13 mA / cm^2: 1.4 F / mol), using a glassy carbon beaker as an anode and a platinum wire as a cathode. The reaction mixture was partitioned between an organic solvent and H_2O. The organic layer was dried over anhydrous $MgSO_4$, and evaporated to give a crude product, which was purified by preparative TLC.

Anodic oxidation of 2,6-dibromo-4-methylphenol (1a).
a) *Acidic condition*: electrolysis of **1a** (66 mg, 0.25 mmol) [C.C.E.: +902 → 1056 mV vs SCE] provided **2a** (27 mg, 37%), **6a** (17 mg, 28%), and recovered **1a** (18 mg, 28%).
b) *Neutral condition*: electrolysis of **1a** (67 mg 0.25 mmol) [C.C.E.: +902 → 1056 mV vs SCE] provided **2a**[2a] (25 mg, 33%), **5a** (2 mg, 3%), **6a**[2a] (7.8 mg, 13%), and recovered **1a** (18 mg, 27%).
5a: IR (film) 1695, 1650, and 1605 cm^{-1}; δ_H 1.43 (3H, s), 3.21 (3H, s), 3.45 (3H, s), 4.42 (2H, s), 5.36 (1H, d, J= 2.65 Hz), 7.22 (1H, d, J= 2.65 Hz), and 7.58 (2H, s). **6a**: IR (film) 1725, 1695, 1650, and 1605 cm^{-1}; δ_H 1.43 (3H, s), 2.35 (3H, s), 3.21 (3H, s), 5.36 (1H, d, J= 2.6 Hz), 7.22 (1H, d, J= 2.6 Hz), and 7.41 (2H, s).

Anodic oxidation of 2,6-dichloro-4-methylphenol (1b).
a) *Acidic condition*: electrolysis of **1b** (42 mg 0.24 mmol) [C.C.E.: +958 → 1190 mV vs SCE] provided **2b** (3 mg, 6%), **3b** (2.3 mg, 5%), **5b** (4 mg, 9%), and **6b** (28 mg, 69%).
b) *Neutral condition*: electrolysis of **1b** (44 mg, 0.25 mmol) [C.C.E.: +906 → 1111 mV vs SCE] provided **2b** (4 mg, 8%), **3b** (2.3 mg, 5%), **5b** (6.1 mg, 13%), and **6b** (26.5 mg, 61%).
2b: IR (film) 3560, 3200, 1605, and 1570 cm^{-1}; δ_H 3.37 (3H, s), 4.34 (2H, s), 5.83 (1H, s), and 7.25 (2H, s). **3b** IR (film) 3370, 1690, and 1565 cm^{-1}; δ_H 7.83 (2H, s) and 9.81 (1H, s). **5b** IR (film) 1690, 1650, 1615 cm^{-1}; δ_H 1.43 (3H, s), 3.18 (3H, s), 3.46 (3H, s), 4.42 (2H, s), 5.39 (1H, d, J= 3 Hz), 6.96 (1H, d, J= 3 Hz), and 7.38 (2H, s); δ_C 27.2, 29.8, 53.4, 58.9, 73.0, 122.8, 128.1, 129.0, 132.8, 138.4, 141.6, 143.6, 148.0, 148.3, and 169.8. Found: m/z 377.0097. Calcd for $C_{16}H_{16}Cl_3O_4$: M+1, 377.0112. **6b** IR (film) 1695, 1650, and 1615 cm^{-1}; δ_H 1.44 (3H, s), 2.35 (3H, s), 3.18 (3H, s), 5.38 (1H, d, J= 2.6 Hz), 6.96 (1H, d, J= 2.6 Hz), and 7.20 (2H, s); δ_C 20.7, 27.1, 53.2, 76.5, 122.5, 128.2, 129.8, 132.6, 137.7, 143.3, 147.9, 148.1, and 172.9. Found: m/z 345.9912. Calcd for $C_{15}H_{13}Cl_3O_3$: M, 345.9929.

Anodic oxidation of 2,6-diiodo-4-methylphenol (1c).
Acidic condition: electrolysis of **1c** (91 mg, 0.25 mmol) [C.C.E.: +892 → 1026 mV vs SCE] provided **2c** (23 mg, 23%), **4c** (4 mg, 4%), **7c** (10.5 mg, 16%), **8c** (15 mg, 24%), **9c** (6 mg, 9%), and recovered **1c** (21 mg, 23%).
2c: IR (film) 3110 and 1540 cm^{-1}; δ_H 3.36 (3H, s), 4.30 (2H, s), 5.76 (1H, s), and 7.65 (2H, s). **4c**: IR (film) 1665 and 1585 cm^{-1}; δ_H 1.46 (3H, s), 3.28 (3H, s), and 7.60 (2H, s). Found: m/z 390.8714. Calcd for $C_8H_9{}^{127}I_2O_2$: M+1, 390.8694. **7c**: IR (film) 3460, 1670, and 1595 cm^{-1}; δ_H 1.52 (3H, s), 3.34 (3H, s), 3.37 (3H, s), 4.35 (2H, s), 5.99 (1H, s), 6.89 (1H, d, J= 2.97 Hz), 7.07 (1H, d, J= 2 Hz), 7.63 (1H, d, J= 2.97 Hz), and 7.69 (1H, d, J= 2 Hz). Found: m/z 526.9199. Calcd for $C_{16}H_{17}{}^{127}I_2O_4$: M+1, 526.9217. **8c**: IR (film) 3490, 1670, and 1595 cm^{-1}; δ_H 1.52 (3H, s), 2.26 (3H, s), 3.33 (3H, s), 5.80 (1H, s), 6.86 (1H, d, J=

2.97 Hz), 6.88 (1H, d, J= 1.97 Hz), 7.53 (1H, d, J= 1.97 Hz), and 7.62 (1H, d, J= 2.97 Hz); δ_C 19.9, 25.9, 53.9, 76.0, 131.85, 131.89, 136.1, 139.3, 150.1, 151.9, 160.7, and 178.5. Found: m/z 495.9031. Calcd for $C_{15}H_{14}{}^{127}I_2O_3$: M, 495.9033. **9c**: IR (film) 1665 and 1595 cm^{-1}; δ_H 1.49 (3H, s), 1.51 (3H, s), 3.32 (3H, s), 3.35 (3H, s), 6.83 (1H, d, J= 3 Hz), and 7.58 (1H, d, J= 3 Hz). Found: m/z 525.9116. Calcd for $C_{16}H_{16}{}^{127}I_2O_4$: M, 525.9139.

Anodic oxidation of 2-bromo-6-chloro-4-methylphenol (1d).

Acidic condition: Electrolysis of **1d** (56 mg, 0.25 mmol) [C.C.E.: +919 → 1101 mV vs SCE] provided **2d** (16.5 mg, 26%), **3d** (2 mg, 3%), **5d** (5.3 mg, 5%), **6d** (48 mg, 48%), and recovered **1d** (7 mg, 13%).

2d: IR (film) 3250 and 1565 cm^{-1}; δ_H 3.37 (3H, s), 4.33 (2H, s), 5.93 (1H, s), 7.28 (1H, d, J= 2 Hz), and 7.39 (1H, d, J= 2 Hz). **3d** IR (film) 3370, 1675, 1585, and 1555 cm^{-1}; δ_H 7.86 (1H, d, J= 2 Hz), 7.97 (1H, d, J= 2 Hz), and 9.80 (1H, s). **5d**: IR (film) 1690, 1610, and 1560 cm^{-1}; δ_H 1.43 (3H, s), 3.19 (3H, s), 3.45 (3H, s), 4.42 (2H, s), 5.38 (1H, d, J= 2.65 Hz), 6.96 (1H, d, J= 2.65 Hz), 7.42 (1H, d, J= 1.65 Hz), and 7.54 (1H, d, J= 1.65 Hz); δ_C 27.1, 53.3, 58.8, 72.7, 74.3, 117.7, 122.7, 122.8, 128.6, 128.8, 131.1, 132.6, 145.9, 148.2, and 172.8. Found: m/z 419.9539. Calcd for $C_{16}H_{15}{}^{79}Br^{35}Cl_2O_4$: M, 419.9530. **6d**: IR (film) 1690 and 1610 cm^{-1}; δ_H 1.44 (3H, s), 2.35 (3H, s), 3.19 (3H, s), 5.37 (1H, d, J= 3 Hz), 6.96 (1H, d, J= 3Hz), 7.24 (1H, d, J= 1.3 Hz), and 7.37 (1H, d, J= 1.3 Hz): δ_C 20.5, 27.1, 53.3, 74.3, 117.2, 122.6, 128.1, 130.5, 132.7, 132.8, 138.2, 144.4, 147.8, 148.1, and 172.9. Found: m/z 389.9393. Calcd for $C_{15}H_{13}{}^{79}Br^{35}Cl_2O_3$: M, 389.9424.

Anodic oxidation of 2-bromo-6-iodo-4-methylphenol (1e).

a) *Acidic condition*: electrolysis of **1e** (86 mg, 0.28 mmol) (C.C.E. at 0.1 mA/cm^2, 1.4 F/mol: +910 → 1014 mV vs SCE) provided **2e** (18 mg, 19%), **3e** (1.8 mg, 2%), **8e** (2.7 mg, 20%), **10** (4 mg, 3%), **11** (2 mg, 2%), and recovered **1e** (18 mg, 21%).

b) *Acidic condition*: electrolysis of **1e** (414 mg, 1.32 mmol) (C.C.E. at 0.28 A/cm^2, 1.4 F/mol: +1023 → 1168 mV vs SCE) provided **2e** (83 mg, 18%), **3e** (4.3 mg, 1%), **7e** (56 mg, 8%), **8e** (243 mg, 37%), **10** (59 mg, 9%), **12** (21 mg, 4%), **13** (17 mg, 3%), and recovered **1e** (66 mg, 16%).

c) *Neutral condition*: electrolysis of **1e** (56 mg, 0.28 mmol) (C.C.E. at 0.1 mA/cm^2, 1.4 F/mol: +940 → 1050 mV vs SCE) provided **2e** (12 mg, 20%), **3e** (0.6 mg, 1%), **8e** (8 mg, 9%), **10** (1.8 mg, 2%), **11** (6.6 mg, 10%), **12** (5 mg, 7%), **13** (4 mg, 5%), and recovered **1e** (11 mg, 20%).

2e: IR (film) 3580 cm^{-1}; δ_H 3.36 (3H, s), 4.32 (2H, s), 5.89 (1H, s), 7.46 (1H, d, J= 1.98 Hz), 7.64 (1H, d, J= 1.98 Hz). **3e**: IR (film) 3590 and 1730 cm^{-1}; δ_H 6.42 (1H, s), 8.02 (1H, d, J= 1.65 Hz), 8.18 (1H, d, J= 1.65 Hz), and 9.77 (1H, s). Found: m/z 326.8519. Calcd for $C_7H_5{}^{79}Br^{127}IO_2$: M+1, 326.8512. **7e**: IR (film) 3550, 1750, 1690, and 1630 cm^{-1}; δ_H 1.54 (3H, s), 3.34 (3H, s), 3.38 (3H, s), 4.37 (2H, s), 5.88 (1H, s), 6.87 (1H, d, J= 2.97 Hz), 7.07 (1H, d, J= 1.98 Hz), 7.29 (1H, d, J= 2.97 Hz), and 7.50 (1H, d, J= 1.98 Hz); δ_C 26.2, 53.8, 58.2, 73.4, 75.1, 111.2, 123.3, 125.4, 129.8, 131.6, 131.9, 136.6, 149.4, 151.6, 151.9, and 177.0. Found: m/z 429.9414. Calcd for $C_{16}H_{16}{}^{79}Br_2O_4$: M, 429.9406. **8e**: IR (film) 3480, 1722, 1675, and 1650 cm^{-1}; δ_H 1.54 (3H, s), 2.28 (3H, s), 3.33 (3H, s), 5.70 (1H, s), 6.85 (1H, d, J= 2.97 Hz), 6.89 (1H, d, J= 1.98 Hz), 7.28 (1H, d, J= 2.97 Hz), and 7.32 (1H, d, J= 1.98 Hz); δ_C 20.2, 26.2, 53.7, 75.1, 111.0, 123.1, 125.5, 130.9, 131.1, 132.8, 136.9, 147.7, 151.3, 151.9, and 177.1. Found: m/z 401.9290. Calcd for $C_{15}H_{14}{}^{79}Br^{81}BrO_3$: M, 401.9292. **10**: IR (film) 3525 and 1500 cm^{-1}; δ_H 2.15 (3H, s), 2.35 (3H, s), 5.91 (1H, s), 6.11 (1H, d, J= 1.98 Hz), 7.01 (1H, d, J= 1.98 Hz), 7.45 (1H, d, J=1.98 Hz), and 7.66 (1H, d, J= 1.98 Hz). Found: m/z 499.8133. Calcd for $C_{14}H_{11}{}^{79}Br_2{}^{127}IO_2$: M, 499.8133. **11**: IR (film) 3550 cm^{-1}; δ_H 2.31 (6H, s), 5.79 (2H, s), 7.01 (2H, d, J= 1.98 Hz), and 7.36 (2H, d, J= 1.98 Hz); δ_H 20.3, 30.1, 110.9, 125.3, 131.4, 131.6, 132.6, and 147.1. Found: m/z 371.9184. Calcd for $C_{14}H_{12}{}^{79}Br^{81}BrO_2$: M, 371.9178. **12**: IR (film) 3500 and 3350 cm^{-1}; δ_H 2.31 (3H, s), 3.40 (3H, s), 4.40

(2H, s), 5.77 (1H, s), 5.96 (1H, s), 7.03 (1H, d, J= 2.31 Hz), 7.18 (1H, d, J= 1.98 Hz), 7.37 (1H, d, J= 2.31 Hz), and 7.53 (1H, d, J= 1.98 Hz); δ_C 20.3, 58.2, 73.5, 110.9, 111.2, 125.1, 125.6, 130.4, 131.6, 131.7, 131.7, 132.1, 132.7, 147.1, and 149.0. Found: m/z 400.9387. Calcd for $C_{15}H_{15}{}^{79}Br_2O_3$: M, 371.9178. **13**: IR (film) 3400 cm^{-1}; δ_H 3.39 (3H, s), 4.39 (2H, s), 5.92 (1H, s), 7.20 (1H, d, J= 1.98 Hz), 7.54 (1H, d, J= 1.98 Hz); δ_C 58.2, 73.4, 125.2, 130.5, 131.7, 132.1, and 148.9. Found: m/z 399.9133. Calcd for $C_{15}H_{12}{}^{79}Br^{81}BrO_3$: M-MeOH, 399.9162.

Conversion of 6d to 2-Chloro-6-(2-chloro-4-methylphenoxy)-4-methylphenol (14). A mixture of **6d** (24 mg, 0.06 mmol) and excess amounts of zinc powder (200 mg) in THF (10 ml) - AcOH (1 ml) was stirred at room temperature for 10h. The resulting mixture was filtered, and the filtrate was evaporated to give a residue, which on purification by preparative TLC (hexane - EtOAc = 4:1) yielded a phenol derivative (22 mg, quantitative yield) as an oil: IR (film) 3535 and 1600 cm^{-1}; δ_H 2.14 (3H, s), 2.36 (3H, s), 5.85 (1H, s), 6.12 (1H, d, J= 1 Hz), 6.86 (1H, d, J= 1 Hz), 7.26 (1H, d, J= 1 Hz), and 7.38 (1H, d, J= 1 Hz); δ_C 20.6, 20.7, 112.7, 118.0, 120.2, 124.2, 128.8, 129.8, 130.5, 132.7, 138.0, 139.6, 144.3, and 145.5.
A solution of the phenol (22 mg, 0.06 mmol) in MeOH (15 ml) in the presence of catalytic amounts of 10% Pd-C was stirred at room temperature for 3 h under a hydrogen atmosphere. The mixture was filtered, and the filtrate was evaporated to give a residue. Purification by preparative TLC (hexane - EtOAc = 8:1) afforded **14** (16 mg, 93%) as an oil: IR (film) 3520 and 1590 cm^{-1}; δ_H 2.18 (3H, s), 2.34 (3H, s), 6.42 (1H, d, J= 1.7 Hz), 6.89 - 6.92 (2H, complex), 7.04 (1H, dd, J= 2, 8 Hz), and 7.28 (1H, d, J= 2 Hz); δ_C 20.6, 116.2, 120.3, 120.5, 124.7, 125.2, 128.6, 130.2, 131.2, 135.5, 140.8, 144.6, and 149.2. Found: m/z 282.0232. Calcd for $C_{14}H_{12}{}^{35}Cl_2O_2$: M, 282.0214.

Dichloroisodityrosine Methyl Ester (15). Methyl (2*S*)-3-(3-bromo-5-chloro-4-hydroxyphenyl)-2-[(phenylmethoxy)carbonylamino]propanoate (111 mg, 0.25 mmol) was electrolyzed (C.C.E. at 0.13 mA / cm^2; 1.2 F / mol, +952 - 1289 mV vs SCE) in MeOH (25 ml) in the presence of $LiClO_4$ (0.54 g). After the mixture was evaporated, the residue was dissolved in THF (20 ml), then zinc powder (200 mg) and AcOH (1 ml) were added; the suspension was stirred at room temperature for 1h. The resulting slurry was filtered through a Celite pad, and the filtrate was diluted with H_2O, then extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was separated by preparative TLC (hexane - EtOAc = 1:1) to give the starting material (25 mg, 23%) and the corresponding diaryl ether (41 mg, 41%): as an oil: $[\alpha]_D{}^{20}$ +47.4° (*c* 1.00, $CHCl_3$); IR (film) 3350, 3030, and 1710 cm^{-1}; δ_H 2.89 - 3.21 (4H, complex), 3.59 (3H, s), 3.74 (3H, s), 4.51 (1H, d, J= 6.93 Hz), 4.62 (1H, d, J= 6.27 Hz), 5.06 (2H, s), 5.11 (2H, s), 5.21 (1H, d, J= 6.93 Hz), 5.47 (1H, d, J= 6.93 Hz), 6.01 (1H, s), 6.03 (1H, s), 6.82 (1H, s), 7.16 (1H, s), and 7.34 (11H, complex). Found: m/z 694.0113. Calcd for $C_{29}H_{25}N_2{}^{79}Br^{35}Cl_2O_9$: M-$C_7H_8O$, 694.0119.
A solution of the diaryl ether (35 mg, 0.044 mmol) in MeOH (5 ml) containing catalytic amounts of 10% Pd-C and 12M HCl (0.1 ml) was stirred at room temperature for 3 h under a hydrogen atmosphere. The resulting mixture was filtered, and the filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography ($CHCl_3$ - MeOH = 7:1) to give **16** as an amorphous solid: $[\alpha]_D{}^{22}$ +14.1° (*c* 1.00, MeOH); IR (nujol) 3390, 1745, and 1585 cm^{-1}; δ_H (CD_3OD) 3.08 (2H, complex), 3.22 (2H, complex), 3.73 (3H, s), 3.81 (3H, s), 4.25 (1H, t, J= 7 Hz), 4.34 (1H, t, J= 7 Hz), 6.65 (1H, d, J= 2 Hz), 6.93 (1H, d, J= 8 Hz), 7.09 (1H, d, J= 2 Hz), 7.21 (1H, dd, J= 2, 8 Hz), and 7.46 (1H, d, J= 2 Hz); δ_C (CD_3OD) 36.2, 36.4, 54.1, 55.1, 55.2, 119.5, 121.3, 123.5, 126.2, 127.0, 127.3, 130.7, 132.3, 132.8, 145.7, 146.6, 153.3, 170.0, and 170.04. Found: m/z 456.0847. Calcd for $C_{20}H_{22}N_2{}^{35}Cl_2O_6$: M, 456.0853.

Computational procedure *Ab initio* calculations were carried out using GAUSSIAN94 program package (ref. 8). Due to the presence of an iodine atom, available basis sets are limited. We used STO-3G for

preliminary calculations and LANL2DZ for the following calculations. Molecular orbital calculations at ROHF and UMP2 levels and density functional calculations with B3LYP methods were performed. Geometries of the presented structures were fully optimized at each level of theory. SCRF calculations were carried out with methanol as solvent (ε= 32.6). Born radii of each structure were calculated using volume option implemented in the GAUSSIAN94 program at gas phase optimized geometry.

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3. Di-N-formylation (HCO_2H, Ac_2O) of dityrosine synthesized by this method provided aldostatin [type **II** X=H, R= $CH_2CH(NHCHO)CO_2H$]: $[\alpha]_D^{27}$ +42.7° (*c* 0.50, H_2O); IR (film) 3389, 1720 and 1666 cm^{-1}; δ_H (CD_3OD) 3.01 (2H, dd, J= 7.10, 13.86 Hz), 3.16 (2H, dd, J= 5.28, 13.86 Hz), 4.87 (2H, dd, J= 7.10, 5.28 Hz), 6.83 (2H, d, J= 8.17 Hz), 7.07 (2H, dd, J= 2.09, 8.17 Hz), 7.12 (2H, d, J= 2.09 Hz), and 8.04 (2H, s); δ_C (DMSO) 36.2, 52.9, 115.9, 125.9, 128.0, 129.2, 132.7, 153.0, 161.2, and 173.1. Found: m/ z 417.1354 Calcd for $C_{20}H_{21}O_8N_2$: 417.38942 (isolation and structural determination: Yaginuma, A.; Asahi, A.; Takada, M. *Chem. Abstr.* **1988**, *108*, 185265). Part of this synthesis was presented: Nishiyama, S.; Kim, M. H.; Yamamura, S. *Novel Trends in Electroorganic Synthesis*, (S. Torii Ed.), Kodansha, **1995**, 285 - 286 .
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5. These compounds were synthesized by the following reactions. **1a**: Br_2 / AcOH: δ_H 2.25 (3H, s), 5.71 (1H, s), and 7.25 (2H, s). **1b**: Cl_2 / AcOH: δ_H 2.23 (3H, s), 5.73 (1H, s), and 7.03 (2H, s). **1c**: I_2, KI / $(CH_2NH_2)_2$; δ_H 2.22 (3H, s), 5.58 (1H, s), and 7.49 (2H, s). **1d**: i) Cl_2 / AcOH; ii) Br_2 / AcOH: δ_H 2.25 (3H, s), 5.68 (1H, s), 7.10 (1H, d, J= 1.3 Hz), and 7.22 (1H, d, J= 1.3 Hz). **1e**: i) I_2, KI / $(CH_2NH_2)_2$; ii) Br_2 / $CHCl_3$: δ_H 2.20 (3H, s), 5.70 (1H, s), 7.24 (1H, d, J= 1 Hz), and 7.45 (1H, d, J= 1 Hz).
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