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An Intramolecular Cyclization of Phenol Derivatives Bearing Aminoquinones Using a Hypervalent Iodine Reagent

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The hypervalent iodine oxidation of phenol derivatives bearing aminoquinones at the *ortho* (**9**) or *meta* positions (**19**) in 2,2,2-trifluoroethanol was investigated with the aim of preparing novel antitumor compounds. Azacarbocyclic spirodienone derivatives (**13**) or phenol derivatives containing the 2,3-dihydro-1*H*-azepine systems (**17**, **20**) were selectively obtained by the reaction of these phenol derivatives and the hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate). The application of this reaction to phenol derivatives bearing aminoquinones (**10**−**12**) is also described.

Introduction

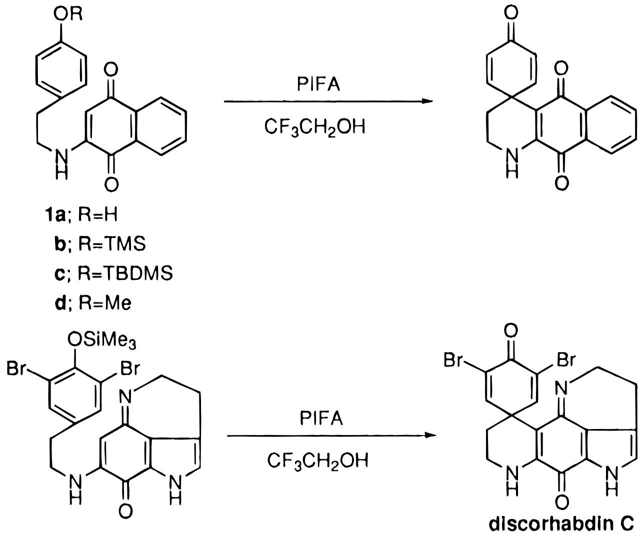
Hypervalent iodine compounds have attracted much attention as useful synthetic reagents,[1] first because of their reactivity which closely resembles that of heavy metal salts such as Hg(II), Tl(III), or Pb(IV) and second because of their lower toxicity and ready availability. As part of our continuing studies on hypervalent iodine chemistry,[2,3] we have reported the intramolecular cyclization of *para*-substituted phenolic aminoquinones (**1**) using phenyliodine(III) bis(trifluoroacetate) (PIFA)[4] (Scheme 1) and applied this method to the total synthesis of discorhabdin C,[5] which was isolated from the sponge of *Latrunculia* du Bocage in New Zealand, as exemplified in Scheme 1.

We now report that the intramolecular cyclization of phenol derivatives bearing aminoquinones at the *ortho* or *meta* positions provides a versatile route to the otherwise difficult to obtain heterocyclic compounds.

Results and Discussion

1. Reaction of Phenol Derivatives Bearing Aminoquinones at the *Ortho* Position. We first examined the reactivity of phenol derivatives bearing aminoquinones at the *ortho* position. The starting *ortho*-substituted phenol derivatives (**9**−**12**) were prepared from 2-hydroxybenzaldehyde (**2**) via 2-hydroxy-β-phenethylamine (**5**). Thus, the aldehyde **2** was alkylated to give the benzyl ether (**3**). Condensation of **3** with nitromethane under standard conditions gave the α,β-unsaturated nitro compound (**4**), which was reduced with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) followed by catalytic hydrogenation to give **5**. To a solution of **5** in ethanol was added the naphthoquinone derivatives (**6**−**8**)[6] to give the corresponding *ortho*-substituted phenol derivatives (**9a**, **10**−**12**). The silyl ethers (**9b**,**c**) were readily prepared from **9a** by standard methods[7] (Scheme 2).

Scheme 1. Spirocyclization of *Para*-Substituted Phenol Derivatives with PIFA



Treatment of the *ortho*-substituted phenol derivative **9a** with PIFA in CF$_3$CH$_2$OH at room temperature gave the azacarbocyclic spirodienone derivative (**13**) in 74% yield. Similarly, the (trimethylsilyl)oxy and (*tert*-butyldimethylsilyl)oxy phenol derivatives **9b** and **9c** were converted to **13** in good yields (75−76%). Treatment of other phenol derivatives (**10**−**12**) with PIFA in CF$_3$CH$_2$OH gave the corresponding spirodienone derivatives (**14**−**16**) under similar conditions. These results are summarized in Table 1. A reasonable mechanism for these

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(1) Reviews, see: (a) Banks, D. F. *Chem. Rev.* **1966**, *66*, 243. (b) Varvoglis, A. *Chem. Soc. Rev.* **1981**, *10*, 377. (c) Koser, G. F. *Hypervalent Halogen Compounds in The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Chapter 18, p 721. (d) Varvoglis, A. *Synthesis* **1984**, 709. (e) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244. (f) Ochiai, M.; Nagao, Y. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 660. (g) Moriarty, R. M.; Valid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (h) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers, Inc.: New York, 1992. (i) Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, *3*, 113. (j) Kita, Y.; Tohma, H. *Farumasia* **1992**, *28*, 984.

(2) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837. (b) Kita, Y.; Yakura, T.; Terashi, H.; Haruta, J.; Tamura, Y. *Chem. Pharm. Bull.* **1989**, *37*, 891 and references cited therein.

(3) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *Ibid.* **1991**, *56*, 435. (c) Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126.

(4) (a) Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119. (b) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Kikuchi, K.; Yakura, T. *Ibid.* **1991**, *32*, 2035.

(5) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *J. Am. Chem. Soc.* **1992**, *114*, 2175.

(6) (a) Otsuji, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2596. (b) Prett, Y. T.; Drake, N. L. *J. Am. Chem. Soc.* **1960**, *82*, 1155. (c) Warren, J. D.; Lee, V. J.; Angier, R. B. *J. Hetrocycl. Chem.* **1979**, *16*, 1617.

(7) The trimethylsilyl ether (**9b**) was prepared by the reaction of **9a** with the *O*-silylated ketene acetal in CH$_2$Cl$_2$ under nitrogen and used without further purification; see ref 4a.

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Scheme 2. Synthetic Method for *Ortho*-Substituted Phenol Derivatives

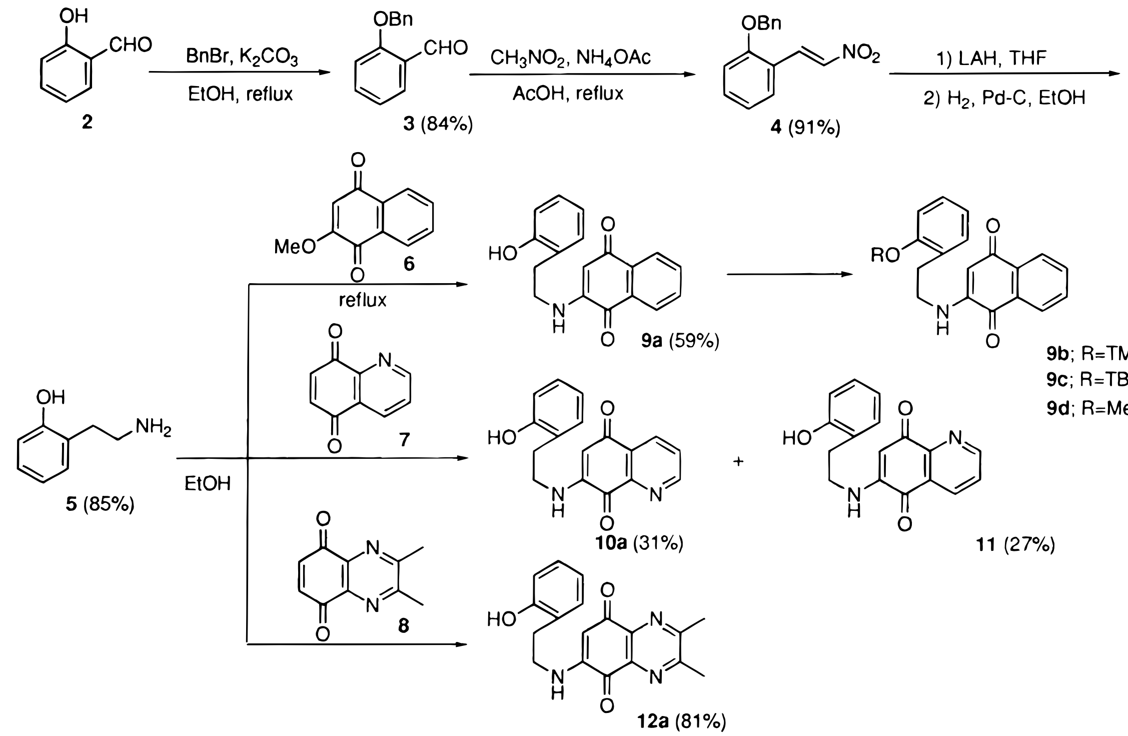
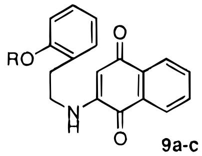
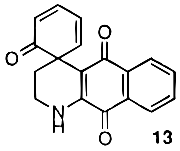
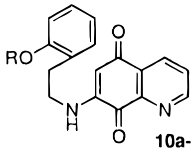
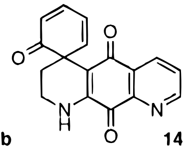
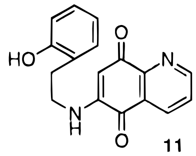
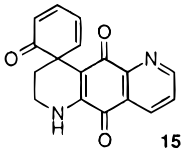
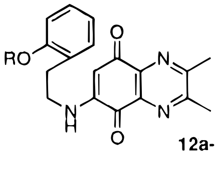
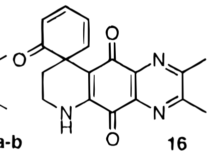


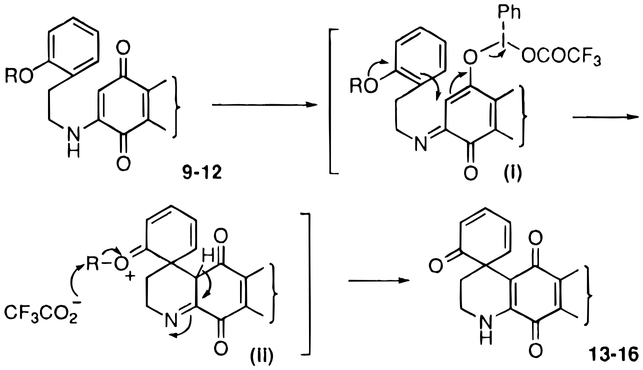
Table 1. Spirocyclization of *Ortho*-Substituted Phenol Derivatives with PIFA

Run	Substrate	Product	Yield (%)
1	 9a-c	 13 a; R=H	74
2		b; R=TMS	75
3		c; R=TBDMS	76
4	 10a-b	 14 a; R=H	40
5		b; R=TMS	37
6	 11	 15	51
7	 12a-b	 16 a; R=H	35
8		b; R=TMS	30

transformation is explained in Scheme 3. PIFA reacts selectively with the aminoquinone moiety of the *ortho*-substituted phenol derivatives **9a**–**c**, **10a**,**b**, **11**, and **12** to give the intermediates (**i**), which cyclize to the spirodienones **13**–**16**. This is probably due to the ready cleavage of the R–O bond (R = H or SiR_3) of the spirodienone intermediates (**ii**) by a nucleophilic attack of the generated trifluoroacetoxy anion.

The methyl ether **9d**, on the other hand, when treated with PIFA gave the rearrangement product, the 2,3-dihydro-1*H*-azepine derivative (**17**) in 61% yield, with none of the spirodienone derivative **13** being obtained. The reaction presumably proceeds first with spirocyclization to give the intermediate (**iii**), which undergoes a dienone/phenol rearrangement from one side by electron donation of the nitrogen atom, to give the azepine derivatives **17**. A similar rearrangement took place with the reaction of the spirodienone product **13** with $BF_3 \cdot Et_2O$ to give a single product (**18**) in an almost quantitative yield based on the reacted spirodienone product (Scheme 4).

Scheme 3. A Reasonable Mechanism for the Spirocyclization of *Ortho*-Substituted Phenol Derivatives



2. Reaction of Phenols Bearing Aminoquinones at the *Meta* Position. *Meta*-substituted phenol derivatives (**19a**–**d**) are obtained using a method[8] similar to that for the preparation of *ortho*-substituted phenol derivatives **9**. Using these phenol derivatives **19a**–**d**, we examined the reactivity of *meta*-substituted compounds with PIFA. It was found that treatment of the *tert*-butyldimethylsilyl ether **19a** or the methyl ether **19b** with PIFA in CF_3CH_2OH at room temperature gave the corresponding substitution products 2,3-dihydro-1*H*-azepine derivatives (**20a** and **20b**), respectively, in moderate yields (Scheme 5).

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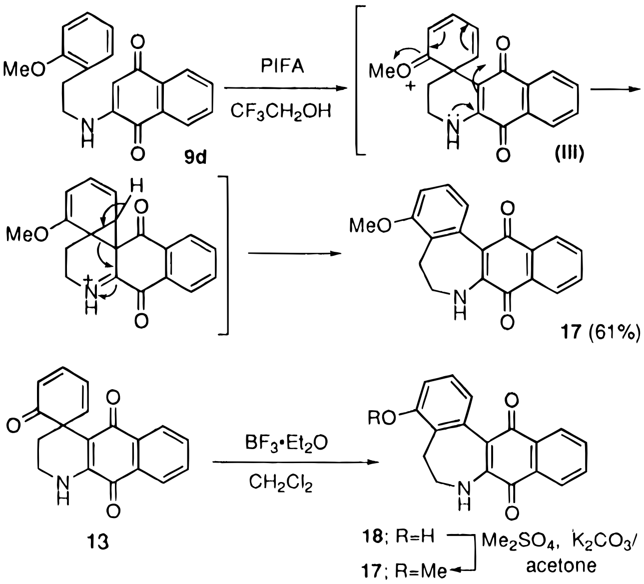
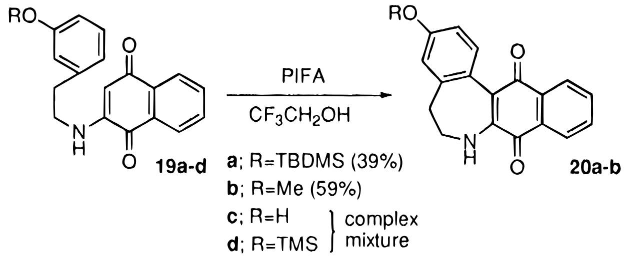
[8] 3-Hydroxy-β-phenethylamine and 3-methoxy-β-phenethylamine were prepared by the reported method: Dally, L.; Horner, L.; Witkop, B. *J. Am. Chem. Soc.* **1961**, *83*, 4787.

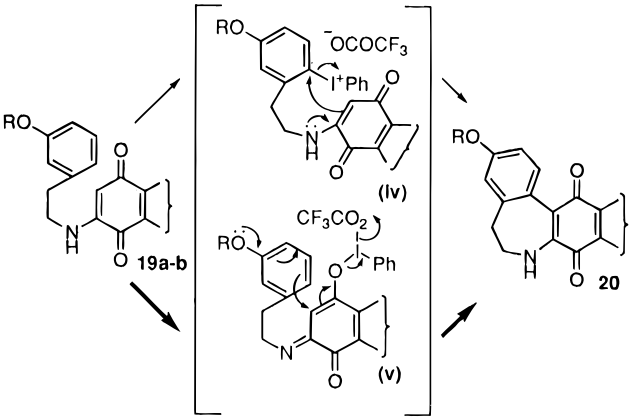
Scheme 4. Cyclization of the *Ortho*-Substituted Anisole with PIFA



Scheme 5. Cyclization of *Meta*-Substituted Phenol Derivatives with PIFA



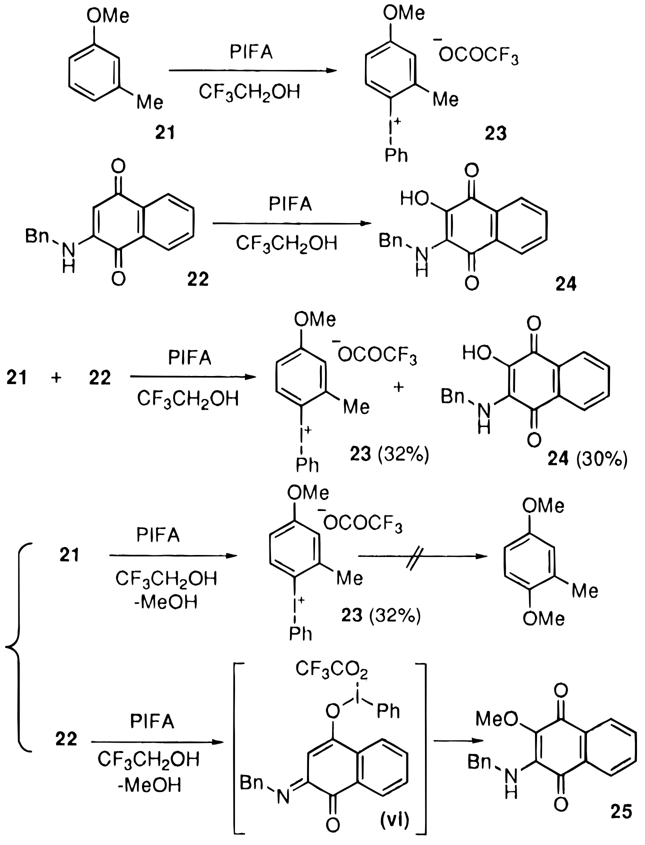
Scheme 6. Reaction Mechanism of the Cyclization of *Meta*-Substituted Phenol Derivatives with PIFA



In general, *meta*-substituted phenol ethers usually react with PIFA to give diaryliodonium salts.[9] Therefore, *meta*-substituted phenol derivatives **19** react with PIFA to give the diaryliodonium salt (**iv**) or the intermediate (**v**) by the nucleophilic attack of the aminoquinone site of **19** on the iodo center of PIFA (Scheme 6).

To confirm the reaction mechanism of this reaction, we performed the following experiment using the *meta*-substituted phenol ether (**21**) and the aminoquinone (**22**) as model compounds, each having the reactive moieties of **19**. Treatment of **21** or **22** with PIFA in CF_3CH_2OH produced the diaryliodonium salt (**23**) or the naphthoquinone derivative (**24**), respectively. To a solution containing equimolar amounts of **21** and **22** was added PIFA, which gave similar amounts of **23** and **24**. There is, therefore, little difference in the reactivity toward PIFA between **21** and **22**. Compound **21** was treated with PIFA in CF_3CH_2OH containing a small quantity of methanol to give the diaryliodonium salt **23**, while **22**, when treated with PIFA under similar conditions, gave compound **25** having the methoxy group on the quinone ring due to nucleophilic attack of methanol on the intermediate **vi**. The reactivity of the intermediate **vi** derived from **22** is, therefore, higher than that of the diaryliodonium salt **23** derived from **21** (Scheme 7).

Scheme 7. Reaction of Model Compounds Each Having the Reactive Moieties of 19 with PIFA



In addition, diaryliodonium salts having electron-donating groups such as **23** are usually very stable and may react with only very strong nucleophiles to give substituted products;[10] therefore, nucleophilic substitution of **19** may not proceed because of the weak nucleophilicity of the aminoquinone site of **19**.

The cyclization reaction presumably proceeds with the initial attack of the PIFA iodo center on the aminoquinone site of **19** and subsequent nucleophilic attack of the aromatic ring to give **20**.

Conclusions

Azacarbocyclic spirodienones or phenol derivatives containing the 2,3-dihydro-1*H*-azepine systems were selectively obtained by the reaction of *ortho*-substituted

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(9) An intramolecular nucleophilic substitution on an aryliodonium salt has been reported by us, see: Kita, Y.; Okunaka, R.; Kondo, M.; Tohma, H.; Inagaki, M.; Hatanaka, K. *J. Chem. Soc., Chem. Commun.* **1992**, 429.

(10) Iodonium salts of phenols having electron-withdrawing groups react with strong nucleophiles such as ^-OH, ^-OR, or H_2NR, while they are nonreactive in the presence of weak nucleophiles; Spiroudis, A.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 135.

phenol derivatives and PIFA. This intramolecular cyclization was applied to the preparation of spirodienone compounds bearing aminoquinones. Furthermore, treatment of *meta*-substituted phenol derivatives with PIFA only gave phenol derivatives containing the 2,3-dihydro-1*H*-azepine systems. In conclusion, we confirmed the difference in reactivities between the *ortho*- and *meta*-substituted phenol derivatives protected by methyl or silyl groups and could selectively obtain the pharmacologically important azacarbocyclic spirodienones or 1*H*-azepine derivatives in good yields.

Experimental Section

All melting points are uncorrected. Infrared (IR) absorption spectra were recorded with $CHCl_3$ as a solvent. E. Merck silica gel 60 for column chromatography and E. Merck precoated TLC plates, silica gel F_{254} for preparative thin layer chromatography (preparative TLC) were used. Organic layers were dried with anhydrous Na_2SO_4. PIFA is commercially available. Starting materials (**2**, **21**) were purchased, and compounds **6**,[6a] **7**,[6b] **8**,[6c] and **22**[11] were prepared by the reported methods.

2-Hydroxy-β-phenethylamine (5). To a solution of 2-(benzyloxy)benzaldehyde (**3**) (10.5 g, 49.6 mmol) in acetic acid (40 mL) containing ammonium acetate (1.5 g, 19.8 mmol) was added nitromethane (9.1 g, 148.9 mmol). The reaction mixture was refluxed for 1.5 h and then concentrated in vacuo. The residue was dissolved in methylene chloride (CH_2Cl_2) and washed with water. The solution was dried and evaporated to give 2-(benzyloxy)-β-nitrostyrene (**4**) (11.5 g, 91%). To a suspension of LAH (0.38 g, 10.0 mmol) in THF (10 mL) was added a solution of **4** (1.03 g, 4.01 mmol) in THF (10 mL) at 0 °C under nitrogen, and then the solution was stirred at room temperature for 3 h. Water (0.40 mL) and 15% aqueous NaOH (0.40 mL) were added to a reaction mixture. The organic layer was dried and evaporated. The residue was hydrogenated in ethanol (90 mL) over 10% Pd−C (90 mg) at room temperature for 24 h under a hydrogen atmosphere (3.8 atm). After filtration, the filtrate was evaporated to give **5** (793.7 mg, 85%). The spectra (^1H NMR and IR) data of **5** were in good accord with the literature.[12]

2-[[2-(2-Hydroxyphenyl)ethyl]amino]-1,4-naphthoquinone (9a). To a solution of **5** (55.0 mg, 0.365 mmol) in ethanol (5 mL) was added **6** (68.6 mg, 0.365 mmol) at room temperature under nitrogen. The reaction mixture was refluxed for 5 h and then concentrated in vacuo. The residue was purified by column chromatography with CH_2Cl_2 to give **9a** (59.4 mg, 59%) which was recrystallized from *n*-hexane−ethyl acetate to give a pure sample as a dark brown powder: mp 184−185 °C; IR 3300, 3250, 3010, 1680, 1610, 1570, 1510, 1360, 1260; ^1H NMR (270 MHz, $CDCl_3$) δ 3.03 (t, 2H, J = 6.9 Hz), 3.45 (q, 2H, J = 6.9 Hz), 5.81 (s, 1H), 6.48 (brs, 1H), 6.80 (d, 1H, J = 7.9 Hz), 6.89 (t, 1H, J = 7.6 Hz), 7.10−7.16 (m, 2H), 7.60 (td, 1H, J = 7.6, 1.3 Hz), 7.72 (td, 1H, J = 7.6, 1.3 Hz), 8.01 (dd, 1H, J = 7.6, 1.3 Hz), 8.10 (dd, 1H, J = 7.6, 1.3 Hz). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.43; H, 5.24; N, 4.70.

2-{[2-[2-((*tert*-Butyldimethylsilyl)oxy)phenyl]ethyl]amino}-1,4-naphthoquinone (9c). To a solution of **9a** (50.6 mg, 0.173 mmol) in DMF (0.5 mL) were added imidazole (35.3 mg, 0.519 mmol) and *tert*-butyldimethylsilyl chloride (39.0 mg, 0.259 mmol) at room temperature under nitrogen. The mixture was stirred for 3.5 h and then concentrated in vacuo. The residue was purified by column chromatography with *n*-hexane−ethyl acetate to give **9c** (67.0 mg, 95%) which was recrystallized from *n*-hexane−CH_2Cl_2 to give a pure sample as red crystals: mp 105−106 °C; IR 3390, 2930, 2860, 1680, 1610, 1570, 1510, 1470, 1360; ^1H NMR (270 MHz, $CDCl_3$) δ 0.28 (s, 6H), 1.01 (s, 9H), 2.97 (t, 2H, J = 6.8 Hz), 3.42 (q, 2H, J = 6.8 Hz), 5.72 (s, 1H), 6.11 (brs, 1H), 6.87 (m, 2H), 7.12 (td, 2H, J = 7.3, 2.0 Hz), 7.57 (td, 1H, J = 7.6, 1.3 Hz), 7.69 (td, 1H, J = 7.6, 1.3 Hz), 8.00 (dd, 1H, J = 7.4, 1.2 Hz), 8.10 (dd, 1H, J = 7.4, 1.2 Hz). Anal. Calcd for $C_{24}H_{29}NO_3Si$: C, 70.71; H, 7.19; N, 3.44. Found: C, 70.70; H, 7.21; N, 3.41.

2-[[2-(2-Methoxyphenyl)ethyl]amino]-1,4-naphthoquinone (9d). To a solution of 2-methoxy-β-phenethylamine (149.5 mg, 0.990 mmol) in ethanol (12 mL) was added **6** (186.1 mg, 0.990 mmol) at room temperature under nitrogen. The reaction mixture was refluxed for 3 h and then concentrated in vacuo. The residue was purified by column chromatography with *n*-hexane−ethyl acetate to give **9d** (236.1 mg, 78%) which was recrystallized from *n*-hexane−CH_2Cl_2 to give a pure sample as brown crystals: mp 140−141 °C; IR 3390, 3020, 1680, 1610, 1570, 1510, 1490, 1350; ^1H NMR (270 MHz, $CDCl_3$) δ 3.02 (t, 2H, J = 6.6 Hz), 3.38 (q, 2H, J = 6.3 Hz), 3.96 (s, 3H), 5.75 (s, 1H), 6.50 (brs, 1H), 6.80−6.95 (m, 2H), 7.15−7.28 (m, 2H), 7.59 (td, 1H, J = 7.3, 1.3 Hz), 7.70 (td, 1H, J = 7.3, 1.3 Hz), 8.01 (d, 1H, J = 7.7 Hz), 8.09 (d, 1H, J = 7.9 Hz). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 73.97; H, 5.69; N, 4.49.

7-[[2-(2-Hydroxyphenyl)ethyl]amino]quinoline-5,8-dione (10a). To a solution of **5** (414.4 mg, 3.02 mmol) in ethanol (39 mL) was added **7** (480.9 mg, 3.02 mmol) at room temperature under nitrogen. The mixture was stirred for 15 min and then concentrated in vacuo. The residue was purified by column chromatography with MeOH−CH_2Cl_2 to give **10** (277.8 mg, 31%) which was recrystallized from CH_2Cl_2−ethyl acetate to give a pure sample as red crystals: mp 239−242 °C; IR 3030, 1690, 1605, 1570, 1460, 1330; ^1H NMR (270 MHz, CD_3OD) δ 2.98 (t, 2H, J = 7.2 Hz), 3.49 (q, 2H, J = 6.9 Hz), 5.97 (s, 1H), 6.72−6.80 (m, 2H), 7.01−7.12 (2H, m), 7.69 (q, 1H, J = 7.9 Hz), 8.41 (dd, 1H, J = 7.7, 1.7 Hz), 8.89 (d, 1H, J = 4.0 Hz); HRMS calcd for $C_{17}H_{14}N_2O_3$ (M^+) 294.1002, found 294.0987.

6-[[2-(2-Hydroxyphenyl)ethyl]amino]quinoline-5,8-dione (11) was obtained by the same method as described (242.0 mg, 27%) as red crystals: mp 225−227 °C; IR 3300, 3030, 1690, 1630, 1570, 1510, 1460, 1340; ^1H NMR (270 MHz, $CDCl_3$) δ 3.07 (t, 2H, J = 7.2 Hz), 3.48 (q, 2H, J = 6.9 Hz), 5.85 (s, 1H), 6.79−6.96 (m, 2H), 7.09−7.12 (m, 2H), 7.64 (dd, 1H, J = 7.8, 4.8 Hz), 8.41 (dd, 1H, J = 7.9, 1.7 Hz), 8.87 (dd, 1H, J = 4.8, 1.8 Hz); HRMS calcd for $C_{17}H_{14}N_2O_3$ (M^+) 294.1002, found 294.0993. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.02; H, 4.90; N, 9.47.

2,3-Dimethyl-6-[[2-(2-hydroxyphenyl)ethyl]amino]quinoxaline-5,8-dione (12a). To a solution of **5** (161.7 mg, 1.18 mmol) in ethanol (16 mL) was added **8** (222.4 mg, 1.18 mmol) at room temperature under nitrogen. The mixture was stirred for 20 min and then concentrated in vacuo. The residue was purified by column chromatography with MeOH−CH_2Cl_2 to give **12a** (307.4 mg, 81%) which was recrystallized from *n*-hexane−CH_2Cl_2 to give a pure sample as red crystals: mp 226−227 °C; IR 3030, 1690, 1610, 1460, 1340; ^1H NMR (270 MHz, $CDCl_3$) δ 2.62 (s, 3H), 2.67 (s, 3H), 2.97 (t, 2H, J = 6.4 Hz), 3.39−3.43 (m, 2H), 5.88 (s, 1H), 6.73−6.79 (m, 2H), 7.02 (t, 2H, J = 7.6 Hz); HRMS calcd for $C_{18}H_{17}N_3O_3$ (M^+) 323.1270, found 323.1271.

General Procedure for the Oxidation of *Ortho*-Substituted Phenol Derivatives to Spirodienons. To a stirred suspension of the phenol derivative (0.1 mmol) in CF_3CH_2OH (2 mL) was added PIFA (0.12 mmol) at room temperature under nitrogen, and the solution was stirred for 0.5 h. Water was added to the reaction mixture, and then the solution was extracted with CH_2Cl_2. The organic layer was washed with saturated sodium chloride, dried, and evaporated. The residue was purified by column chromatography to give the spirodienone derivative in reasonable yield.

1,2,3,4,5,10-Hexahydrobenzo[*g*]quinoline-5,10-dione-4-spiro-1′-cyclohexa-3′,5′-dien-2′-one (13). Reactants: **9a** (107.0 mg, 0.365 mmol); PIFA (188.4 mg, 0.438 mmol); CF_3CH_2OH (8 mL). **13** (78.1 mg, 74%): red crystals; mp 240−243 °C (from CH_2Cl_2−ethyl acetate); IR 3410, 3010, 1680, 1660, 1630, 1610, 1570, 1520, 1360, 1350; ^1H NMR (270 MHz, $CDCl_3$) δ 1.88−2.10 (m, 2H), 3.40−3.68 (m, 2H), 6.18 (brs, 1H), 6.28 (d, 1H, J = 9.9 Hz), 6.35−6.37 (m, 2H), 7.13 (ddd, 1H, J = 7.4, 4.8, 2.5 Hz), 7.65 (td, 1H, J = 7.5, 1.4 Hz), 7.66 (td, 1H, J = 7.5, 1.4 Hz), 7.98 (dd, 1H, J = 2.8, 1.3 Hz), 8.00 (dd, 1H, J = 2.6, 1.7 Hz); HRMS calcd for $C_{18}H_{13}NO_3$ (M^+) 291.0893, found

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291.0893. Anal. Calcd for $C_{18}H_{13}NO_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.02; H, 4.90; N, 9.47.

5,6,7,8,9,10-Hexahydropyrido[3,2-*g*]quinoline-5,10-dione-6-spiro-1′-cyclohexa-3′,5′-dien-2′-one (14). Reactants: **10a** (20.1 mg, 0.0634 mmol); PIFA (44.1 mg, 0.103 mmol); CF_3CH_2OH (3 mL). **14** (7.4 mg, 40%): orange crystals; mp >300 °C (from $CH_3OH-CH_2Cl_2$); IR 3400, 3250, 1680, 1660, 1620, 1610, 1570, 1520, 1330, 1320; ^1H NMR (270 MHz, $CDCl_3$) δ 1.90−2.12 (m, 2H), 3.44−3.66 (m, 2H), 6.18 (brs, 1H), 6.25 (d, 1H, J = 9.9 Hz), 6.34 (d, 1H, J = 3.6 Hz), 7.12 (td, 1H, J = 9.9, 3.7 Hz), 7.51(dd, 1H, J = 7.8, 4.8 Hz), 8.30 (dd, 2H, J = 7.8, 2.0 Hz), 8.92 (d, 1H, J = 3.6 Hz); HRMS calcd for $C_{17}H_{12}N_2O_3$ (M^+) 292.0847, found 292.0847.

5,6,7,8,9,10-Hexahydropyrido[2,3-*g*]quinoline-5,10-dione-9-spiro-1′-cyclohexa-3′,5′-dien-2′-one (15). Reactants: **11** (34.5 mg, 0.117 mmol); PIFA (60.5 mg, 0.141 mmol), CF_3CH_2OH (3 mL). **15** (16.6 mg, 51%): red powder; mp 270−273 °C (from $CH_3OH-CH_2Cl_2$); IR 3400, 3020, 1730, 1690, 1660, 1600, 1560, 1520, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 1.92−2.13 (m, 2H), 3.42−3.74 (m, 2H), 6.29 (d, 1H, J = 9.6 Hz), 6.38 (d, 2H, J = 8.9 Hz), 6.45 (brs, 1H) 7.13−7.20 (m, 1H), 7.57−7.62 (m, 1H), 8.32 (dd, 2H, J = 7.9, 1.7 Hz), 8.88 (dd, 2H, J = 4.6, 1.3 Hz); HRMS calcd for $C_{17}H_{12}N_2O_3$ (M^+) 292.0846, found 292.0839.

5,6,7,8,9,10-Hexahydro-2,3-dimethylpyrido[2,3-*g*]quinoxaline-5,10-dione-9-spiro-1′-cyclohexa-3′,5′-dien-2′-one (16). Reactants: **12a** (134.2 mg, 0.415 mmol); PIFA (268.0 mg, 0.623 mmol); CF_3CH_2OH (8 mL). **16** (46.6 mg, 35%): red crystals; mp >300 °C (from $CH_3OH-CH_2Cl_2$); IR 3400, 3010, 1690, 1660, 1630, 1610, 1560, 1540, 1520, 1340; ^1H NMR (270 MHz, CD_3OD) δ 1.91−1.95 (m, 2H), 2.66 (s, 6H), 3.43−3.64 (m, 2H), 6.18 (d, 1H, J = 9.6 Hz), 6.34 (dd, 1H, J = 9.2, 5.9 Hz), 6.53 (d, 1H, J = 9.6 Hz), 7.21 (dd, 1H, J = 8.7, 4.7 Hz); HRMS calcd for $C_{18}H_{13}NO_3$ (M^+) 321.1114, found 321.1117.

5,6,8,13-Tetrahydro-4-methoxynaphtho[*a*][3]benzazepine-8,13-dione (17a). Reactants: **9d** (20.0 mg, 0.065 mmol); PIFA (33.6 mg, 0.078 mmol); CF_3CH_2OH (3 mL). **17a** (12.1 mg, 61%): red crystals; mp 195−196 °C (from *n*-hexane−CH_2Cl_2); IR 3350, 3000, 1670, 1630, 1600, 1530, 1460, 1440, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 3.19 (t, 2H, J = 4.6 Hz), 3.78−3.83 (m, 2H), 3.74 (s, 3H), 6.53 (d, 1H, J = 9.6 Hz), 7.21 (dd, 1H, J = 8.7, 4.7 Hz); HRMS calcd for $C_{19}H_{15}NO_3$ (M^+) 305.1051, found 305.1051. Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.73; H, 4.96; N, 4.59. Found: C, 74.45; H, 4.98; N, 4.56.

The Dienone Phenol-Type Rearrangement of the Spirodienone Compound 13. To a solution of **13** (23.2 mg, 0.080 mmol) in CH_2Cl_2 (4 mL) was added $BF_3{\cdot}Et_2O$ (22.6 mg, 0.159 mmol) at room temperature under nitrogen and stirred for 48 h. The solution was evaporated, and the residue was purified by preparative TLC to give **18** (15.2 mg, 66%) and unreacted starting material **13** (7.9 mg, 34%).

To a solution of **18** (6.4 mg, 0.022 mmol) in anhydrous acetone containing potassium carbonate (15.2 mg, 0.110 mmol) was added dimethyl sulfate (0.008 mL, 0.084 mmol) at room temperature, and the solution was refluxed for 3 h. The solution was evaporated, and a saturated aqueous solution of sodium bicarbonate was then added which was then extracted with CH_2Cl_2. The organic layer was dried and evaporated. The residue was purified by preparative TLC to give **17a** (3.0 mg, 47%).

2-{[2-[3-[(*tert*-Butyldimethylsilyl)oxy]phenyl]ethyl]amino}-1,4-naphthoquinone (19a). To a solution of **19c** (22.6 mg, 0.0771 mmol) in DMF (1 mL) were added imidazole (15.8 mg, 0.231 mmol) and *tert*-butyldimethylsilyl chloride (17.4 mg, 0.116 mmol) at room temperature under nitrogen. The mixture was stirred for 4.5 h and then concentrated in vacuo. The residue was purified by preparative TLC with *n*-hexane−ethyl acetate to give **19a** (21.9 mg, 70%) which was recrystallized from *n*-hexane−CH_2Cl_2 to give a pure sample as red crystals: mp 135−136 °C; IR 3390, 3010, 1680, 1610, 1570, 1510, 1490, 1350, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (s, 6H), 1.57 (s, 9H), 2.92 (t, 2H, J = 7.1 Hz), 3.44 (q, 2H, J = 6.6 Hz), 5.78 (s, 1H), 5.98 (brs, 1H), 6.70−6.76 (m, 2H), 6.82 (d, 1H, J = 7.9 Hz), 7.19 (t, 1H, J = 7.7 Hz), 7.61 (td, 1H, J = 7.4, 1.3 Hz), 7.73 (td, 1H, J = 7.6, 1.3 Hz), 8.03 (dd, 1H, J = 7.6, 1.3 Hz), 8.10 (dd, 1H, J = 7.6, 1.3 Hz). Anal. Calcd for $C_{24}H_{29}NO_3Si$: C, 70.71; H, 7.19; N, 3.44. Found: C, 70.49; H, 7.27; N, 3.31.

2-[[2-(3-Methoxyphenyl)ethyl]amino]-1,4-naphthoquinone (19b). To a solution of 3-methoxy-β-phenethylamine (576.3 mg, 3.82 mmol) in ethanol (45 mL) was added **6** (717.5 mg, 3.82 mmol) at room temperature under nitrogen. The mixture was stirred for 48 h and then concentrated in vacuo. The residue was purified by column chromatography with CH_2Cl_2 to give **19b** (640.4 mg, 55%) which was recrystallized from *n*-hexane−CH_2Cl_2 to give a pure sample as dark brown crystals: mp 126−127 °C; IR 3390, 3020, 1680, 1610, 1570, 1510, 1490, 1350, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 2.92 (t, 2H, J = 7.1 Hz), 3.45 (q, 2H, J = 6.7 Hz), 3.81 (s, 3H), 5.79 (s, 1H), 5.96 (brs, 1H), 6.76−6.86 (m, 3H), 7.26 (t, 1H, J = 7.8 Hz), 7.61 (td, 1H, J = 7.4, 1.0 Hz), 7.72 (td, 1H, J = 7.4, 1.3 Hz), 8.03 (d, 1H, J = 7.6 Hz), 8.10 (d, 1H, J = 7.9 Hz). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.00; H, 5.64; N, 4.51.

2-[[2-(3-Hydroxyphenyl)ethyl]amino]-1,4-naphthoquinone (19c). To a solution of 3-hydroxy-β-phenethylamine (42.0 mg, 0.223 mmol) in ethanol (3 mL) was added **6** (30.6 mg, 0.223 mmol) at room temperature under nitrogen. The mixture was refluxed for 3 h and then cooled. The mixture was concentrated in vacuo, and the residue was purified by column chromatography with CH_2Cl_2 to give **19c** (50.2 mg, 77%) which was recrystallized from *n*-hexane−CH_2Cl_2 to give a pure sample as a reddish brown powder: mp 171−173 °C; IR 3390, 3030, 1680, 1610, 1570, 1510, 1460, 1360, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 2.91 (t, 2H, J = 7.1 Hz), 3.44 (q, 2H, J = 6.4 Hz), 5.79 (s, 1H), 6.07 (brs, 1H), 6.73−6.75 (m, 3H), 7.18 (td, 1H, J = 7.6, 1.5 Hz), 7.61 (td, 1H, J = 7.6, 1.3 Hz), 7.73 (td, 1H, J = 7.6, 1.3 Hz), 8.02 (dd, 1H, J = 7.6, 1.3 Hz), 8.09 (dd, 1H, J = 7.6, 1.3 Hz). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.29; H, 5.29; N, 4.66.

General Procedure for the Oxidation of *Meta*-Substituted Phenol Derivatives. To a stirred suspension of the phenol derivative (0.1 mmol) in CF_3CH_2OH (2 mL) was added PIFA (0.12 mmol) at room temperature under nitrogen, and the solution was stirred for 20 min. Water was added to the reaction mixture, which was then extracted with CH_2Cl_2. The organic layer was washed with saturated sodium chloride, dried, and evaporated. The residue was purified by preparative TLC to give the dihydroazepine derivative in moderate yield.

3-[(*tert*-Butyldimethylsilyl)oxy]-5,6,8,13-tetrahydronaphtho[*a*][3]benzazepine-8,13-dione (20a). Reactants: **19a** (22.2 mg, 0.056 mmol); PIFA (29.0 mg, 0.067 mmol); CF_3CH_2OH (3 mL). **20a** (8.6 mg, 39%): red crystals; mp 116−117 °C (from *n*-hexane−CH_2Cl_2); IR 3360, 3010, 2960, 2930, 2860, 1670, 1600, 1570, 1530, 1470, 1350, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.25 (s, 9H), 2.96 (t, 2H, J = 4.6 Hz), 3.82 (q, 2H, J = 4.6 Hz), 6.27 (brs, 1H), 6.38 (d, 1H, J = 2.3 Hz), 6.78 (dd, 1H, J = 8.6, 2.6 Hz), 7.24 (d, 1H, J = 8.6 Hz), 7.62 (td, 1H, J = 7.6, 1.3 Hz), 7.74 (td, 1H, J = 7.6, 1.1 Hz), 8.06 (dd, 1H, J = 7.6, 1.3 Hz), 8.19 (dd, 1H, J = 7.6, 1.3 Hz); HRMS calcd for $C_{24}H_{27}NO_3Si$ (M^+) 405.1758, found 405.1758. Anal. Calcd for $C_{24}H_{27}NO_3Si$: C, 71.08; H, 6.71; N, 3.45. Found: C, 70.94; H, 6.86; N, 3.45.

5,6,8,13-Tetrahydro-3-methoxynaphtho[*a*][3]benzazepine-8,13-dione (20b). Reactants: **19b** (31.0 mg, 0.101 mmol); PIFA (52.1 mg, 0.121 mmol); CF_3CH_2OH (3 mL). **20b** (18.3 mg, 59%): red crystals; mp 228−230 °C (from *n*-hexane−CH_2Cl_2); IR 3360, 3010, 1670, 1600, 1570, 1520, 1500, 1470, 1350, 1330; ^1H NMR (270 MHz, $CDCl_3$) δ 3.00 (t, 2H, J = 4.6 Hz), 3.76−3.91 (m, 2H), 3.84 (s, 3H), 6.51 (brs, 1H), 6.65 (d, 1H, J = 2.6 Hz), 6.86 (dd, 1H, J = 8.9, 3.0 Hz), 7.50 (d, 1H, J = 8.9 Hz), 7.62 (td, 1H, J = 7.6, 1.3 Hz), 7.73 (td, 1H, J = 7.6, 1.1 Hz), 8.05 (dd, 1H, J = 7.6, 1.3 Hz), 8.18 (dd, 1H, J = 7.6, 1.3 Hz); HRMS calcd for $C_{19}H_{15}NO_3$ (M^+) 305.1052, found 305.1063.

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