Synthesis of 3-Aryloxy-2-iodoemodines by Oxidation of Emodin with (Diacetoxyiodo)arenes

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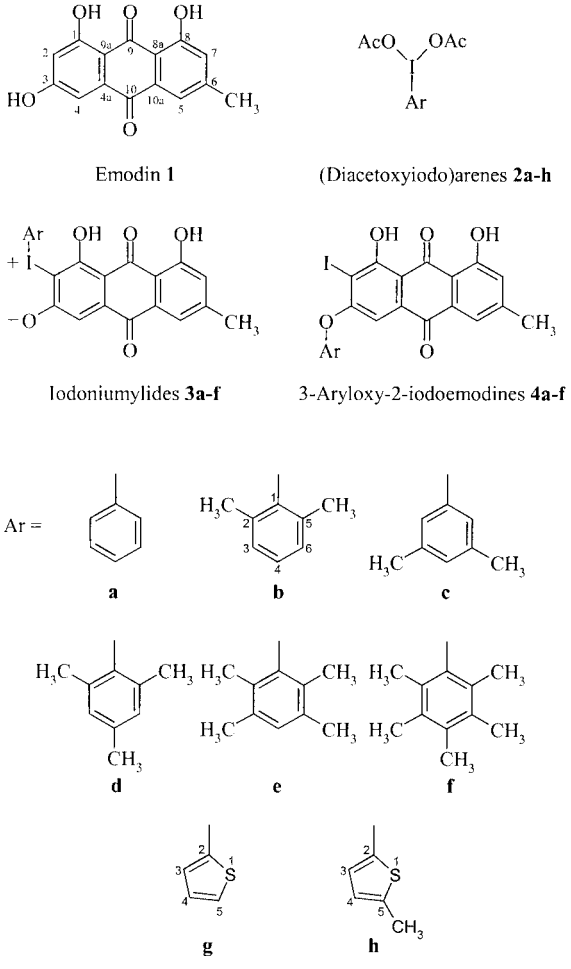
Dedicated to Professor Peter Welzel, Universität Leipzig, on the occasion of his 65th birthday

Keywords: Oxidation / Natural products / Ylides / Iodine / Emodin

Hypervalent iodine oxidation of emodin (**1**) with various (diacetoxyiodo)arenes **2a–f** in potassium hydroxide/methanol leading to 3-aryloxy-1,8-dihydroxy-2-iodo-anthraquinones **4a–f** is reported. Mechanistic studies showed reaction via iodonium ylides.

Introduction

The use of hypervalent iodine reagents in organic synthesis has become popular during the last three decades.[1–5] Depending on the substrate, hypervalent iodine oxidation with (diacetoxyiodo)benzene (DIB) and potassium hydroxide in methanol leads to different classes of substances. Where 2,4-dihydroxyacetophenones are involved, oxidation with DIB yields 2-hydroxy-3-iodo-4-phenoxyacetophenones by rearrangement of iodonium ylides.[6,7] We tried to use this reaction in our survey on derivatization of emodin (1,3,8-trihydroxy-6-methylanthraquinone, **1**), whose "left wing" has a structural similarity to 2,4-dihydroxyacetophenone (Scheme 1). Emodin occurs in different plants (rhubarb, aloe) and is a widespread dye in fungi and lichens. It belongs to the anthraquinones as do daunorubicin and mitoxantrone, which are some of the most powerful cytostatics. Emodin possesses diuretic[8] and vasodilatory[9] effects as well as antineoplastic,[10,11] antibiotic[12,13] and antiviral[14,15] activity. It is a tumor cell growth inhibitor[16] and is also supposed to sensitize cancer cells.[17] Thus, emodin sensitizes HER/neu-overexpressing cancer cells to chemotherapeutic agents such as cisplatin, doxorubicin, etoposide and paclitaxel.[18] This paper reports on the hypervalent iodine oxidation of emodin (**1**) with various (diacetoxyiodo)arenes **2a–f** via iodonium ylides **3a–f** to 3-aryloxy-2-iodo-emodines **4a–f** (Scheme 1). In contrast



Scheme 1

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  DOI: 10.1002/ejoc.200300317

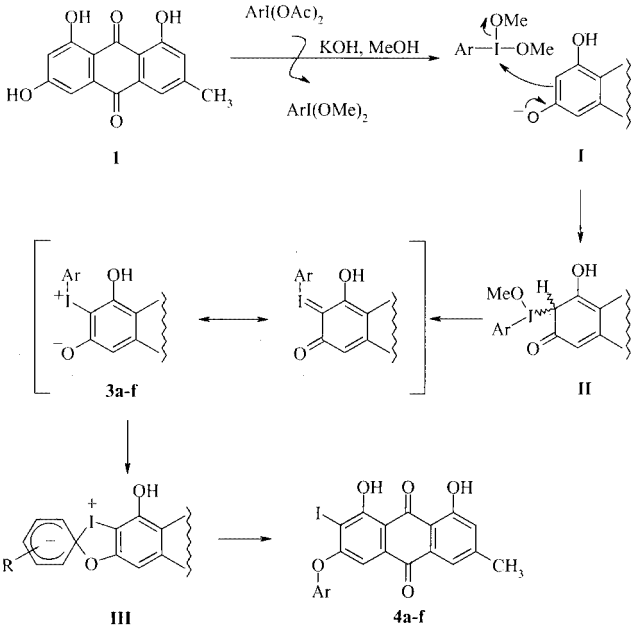
sensitivity to oxidation and lowered solubility in many solvents. Their biological activity is under investigation.

Results and Discussion

Emodin (**1**) oxidation was carried out with DIB and various methylated (diacetoxyiodo)arenes **2a**−**f** to produce 3-aryloxy-1,8-dihydroxy-2-iodoemodines **4a**−**f** (Table 1). **2a**−**f** could be obtained by oxidation of the respective iodobenzene derivatives with sodium perborate in acetic acid according to McKillop.[19] A mechanistic pathway similar to the oxidation of 2,4-dihydroxyacetophenones with DIB for the reaction of emodin (**1**) to **4a**−**f** with various (diacetoxyiodo)arenes **2a**−**f** is outlined in Scheme 2. We assume that (diacetoxyiodo)arenes [ArI(OAc)$_2$] are converted into (dimethoxyiodo)arenes [ArI(OMe)$_2$] under highly alkaline conditions (KOH in MeOH),[20] while emodin changes into the corresponding emodinate **I** in situ. (Dimethoxyiodo)-arenes attack emodin at position 2 to form intermediates **II** followed by formation of the iodonium ylides **3a**−**f**. The orange-red-colored iodonium ylides finally rearrange to 3-aryloxy-2-iodoemodines **4a**−**f**, which is probably due to an intermediary *spiro*-Meisenheimer complex **III** as suggested by Spyroudis et al. where 2,4-dihydroxyacetophenones are involved.[21] Using the absorption maximum of the yellow-colored aryloxyiodoemodins **4a**−**f** ($\lambda_{max.}$ [acetone] = 437 nm), the migration of the aryl group could be followed by UV/Vis spectroscopy (Figure 1). Owing to the fast rearrangement of the iodonium ylides **3a**−**f** into the corresponding iodoethers **4a**−**f**, even at low temperature (1−10 °C), clean isolation of the zwitterionic iodonium ylides **3a**−**f** was not possible. However, emodin (**1**) is a much more complex molecule than 2,4-dihydroxyacetophenone; it contains a 1,4-benzoquinone moiety and presents many more mesomeric opportunities, so other mechanistic pathways may also be available. The position of the aryl substituent in **4a**−**f** could not be elucidated by NMR experiments since no coupling between 4-H and C-1′ was observed. However, the structure could be unambiguously verified by X-ray diffraction analysis (Figure 2). Thiophene derivatives **2g** and **2h** yielded multicomponent mixtures; no products could be isolated.

Table 1. Oxidation of emodin with various (diacetoxyiodo)arenes ArI(OAc)$_2$ **2a**−**f**

Ar	Ar−I(OAc)$_2$ **2**	Product **4**	Yield **4** (%)
Benzene	**a**	**a**	21
2,6-Dimethylbenzene	**b**	**b**	32
3,5-Dimethylbenzene	**c**	**c**	5
2,4,6-Trimethylbenzene	**d**	**d**	16
2,3,5,6-Tetramethylbenzene	**e**	**e**	23
2,3,4,5,6-Pentamethylbenzene	**f**	**f**	22



Scheme 2. Mechanistic pathway of formation of 3-aryloxy-2-iodoemodines **4a**−**f**

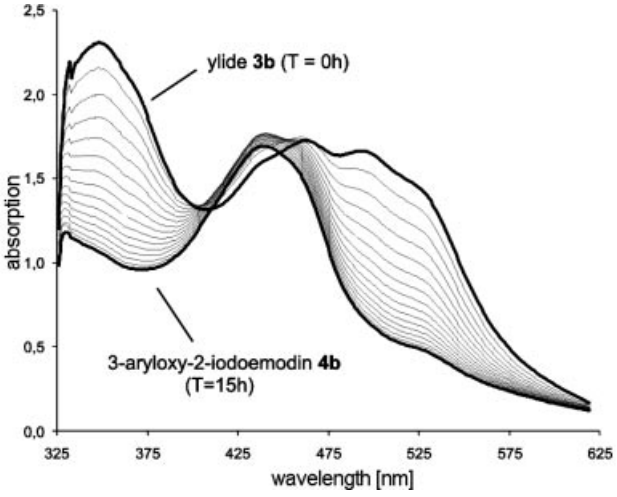


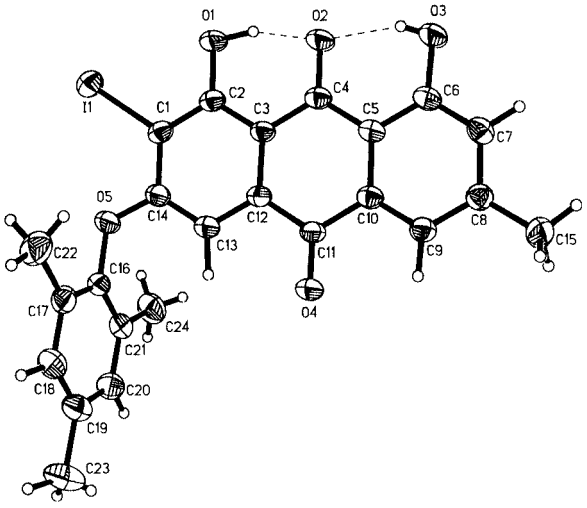
Figure 1. Monitoring the rearrangement from **3b** to **4b** in acetone by UV/Vis spectroscopy

Conclusion

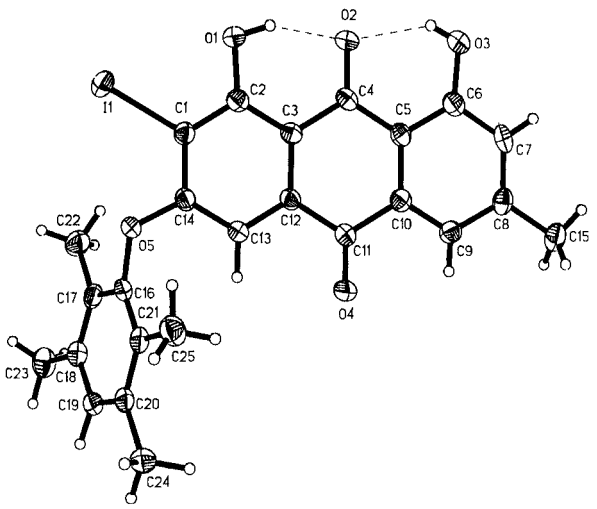
In summary, 3-aryloxy-2-iodoemodines **4a**−**f** were synthesized for the first time. Their structures were conclusively determined by X-ray diffraction analysis. The potential of these highly functionalized compounds as biologically active substances is under investigation.

Experimental Section

General: Melting points were measured in open capillaries in an oil bath and are corrected. IR spectra were obtained in KBr disks



4d



4e

Figure 2. X-ray crystallographic structures of **4d** and **4e**

using a Perkin−Elmer FT-IR PC 16 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX (400 MHz) instrument. ^{13}C-HMBC and ^{13}C-HMQC were observed with a Bruker DRX (600 MHz) instrument. EI MS was performed with a Bruker Daltonics mass spectrometer operating at 70 eV. MALDI-TOF-MS was performed with a Perspective Biosystems Voyager-DE™ RP. Colorimetric measurements were carried out with a Perkin−Elmer Lambda 16 UV/Vis spectrophotometer. TLC was performed using Merck silica-gel 60 F_{254} plates and column chromatography using Merck Kieselgel 60 (0.063−0.200 mm).

(Diacetoxyiodo)arenes 2b−h: (Diacetoxyiodo)arenes were prepared by oxidation of iodoarenes with sodium perborate in glacial acetic acid using the procedure described by McKillop et al.[22] These authors have previously described the synthesis of **2b** and **2e**. The synthesis of **2c** and **2d** by iodoarene oxidation with peracetic acid was reported by Shah et al.[23] The pentamethylbenzene derivative **2f** is a new compound. Since no NMR spectroscopic data have been generated from any of these compounds until now, these data are listed below. Thiophene derivative **2g** and the new compound **2h** were prepared using the procedure described by Togo et al.[24] These heterocyclic derivatives are less stable than the (diacetoxyiodo)benzene derivatives **2a−f**, so that 5-methylthiophene derivative **2h** decomposes even at room temperature.

General Procedure: Sodium perborate tetrahydrate (16.9 g, 110 mmol) was added to a solution of iodoarene (10 mmol) in glacial acetic acid (90 mL) in portions over a time of 20 min. The mixture was heated to 50 °C and stirred at this temperature for 6 h. The product was extracted with dichloromethane (3 × 50 mL). The organic phase was washed with water (2 × 100 mL), dried with anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by crystallization from hexane.

(Diacetoxyiodo)arene 2b: Yield 2.0 g (57%), m.p. 151−153 °C. ^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 6 H, $COCH_3$), 2.70 (s, 6 H, CH_3), 7.22−7.31 (m, 3 H, H_{ar}) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.43 ($CO\mathit{C}H_3$), 26.99 (CH_3), 128.14 (C-3, C-5), 132.54 (C-4), 133.04 (C-1), 141.49 (C-2, C-6), 176.40 ($\mathit{C}OCH_3$) ppm.

(Diacetoxyiodo)arene 2c: Yield 2.2 g (63%), m.p. 142−148 °C. ^{1}H NMR ($CDCl_3$): δ = 2.00 (s, 6 H, $COCH_3$), 2.38 (s, 6 H, CH_3), 7.20 (s, 1 H, 4-H), 7.72 (s, 2 H, 2-H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.43 ($CO\mathit{C}H_3$), 21.36 (CH_3), 121.39 (C-4), 132.57 (C-2, C-6), 133.76 (C-1), 141.10 (C-3, C-5), 176.40 ($\mathit{C}OCH_3$) ppm.

(Diacetoxyiodo)arene 2d: Yield 2.5 g (67%), m.p. 160−163 °C. ^{1}H NMR ($CDCl_3$): δ = 1.98 (s, 6 H, $COCH_3$), 2.37 (s, 3 H, 4-CH_3), 2.72 (s, 6 H, 2-CH_3, C6-CH_3), 7.12 (s, 2 H, 3-H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.43 ($CO\mathit{C}H_3$), 21.22 (4-CH_3), 26.76 (2-CH_3, 6-CH_3), 129.00 (C-1), 129.72 (C-3, C-5), 141.37 (C-2, C-6), 176.40 ($\mathit{C}OCH_3$) ppm.

(Diacetoxyiodo)arene 2e: Yield 2.2 g (58%), m.p. 150−157 °C. ^{1}H NMR ($CDCl_3$): δ = 1.97 (s, 6 H, $COCH_3$), 2.36 (s, 6 H, 3-CH_3, 5-CH_3), 2.65 (s, 6 H, 2-CH_3, 6-CH_3), 7.15 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.37 ($CO\mathit{C}H_3$), 21.72 (3-CH_3, 5-CH_3), 24.58 (2-CH_3, 6-CH_3), 135.55 (C-4), 135.93 (C-3, C-5), 136.10 (C-1), 176.44 ($\mathit{C}OCH_3$) ppm.

(Diacetoxyiodo)arene 2f: Yield 3.3 g (85%), m.p. 137−140 °C. ^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 6 H, $COCH_3$), 2.32 (s, 3 H, 4-CH_3), 2.36 (s, 6 H, 3-CH_3, 5-CH_3), 2.75 (s, 6 H, 2-CH_3, 6-CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.52 (4-CH_3), 18.75 (3-CH_3, 5-CH_3), 20.45 ($CO\mathit{C}H_3$), 26.29 (2-CH_3, 6-CH_3), 134.35 (C-1), 134.55, 136.59 (C-3, C-5, C-2, C-6), 176.44 ($\mathit{C}OCH_3$) ppm.

(Diacetoxyiodo)arene 2g: Yield 1.1 g (34%), m.p. 112−119 °C (decomposition). ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 6 H, $COCH_3$), 2.75 (d, J = 3.6 Hz, 1 H, 3-H), 7.12−7.15 (m, 1 H, 4-H), 7.64 (d, J = 5.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.37 ($CO\mathit{C}H_3$), 106.33 (C-2), 128.64, 134.87, 139.07 (C-3, C-4, C-5), 177.01 ($\mathit{C}OCH_3$) ppm.

(Diacetoxyiodo)arene 2h: Yield 1.2 g (35%). ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 6 H, $COCH_3$), 2.68 (s, 3 H, CH_3), 6.82 (d, J = 3.8 Hz, 1 H, 4-H) 7.63 (d, J = 3.8 Hz, 1 H, 3-H) ppm. ^{1}H NMR ([D_6]acetone): δ = 1.95 (s, 6 H, $COCH_3$), 2.72 (s, 3 H, CH_3), 6.97 (d, J = 3.9 Hz, 1 H, 4-H), 7.80 (d, J = 3.9 Hz, 1 H, 3-H) ppm.

3-Aryloxy-1,8-dihydroxy-2-iodo-6-methylanthraquinones 4a−f. General Procedure: A solution of KOH (280 mg, 5 mmol) and emodin

(270 mg, 1 mmol) in methanol (25 mL) was added to a solution of (diacetoxyiodo)arene **2a**−**f** (1 mmol) and stirred at 0 °C for 4 h. Acetone (250 mL) was added, and the solution was stirred at 30 °C for 24 h. The reaction's progress was monitored by TLC. After completion of the reaction, the organic solvent was removed by rotary evaporation at reduced pressure. The residue was suspended in a solvent mixture of petroleum ether/ethyl acetate/acetic acid (20/20/1) and filtered. The filtrate was evaporated under reduced pressure and purified by column chromatography and/or recrystallization.

1,8-Dihydroxy-2-iodo-6-methyl-3-phenoxyanthraquinone (4a): Yield 100 mg (21%), m.p. 263−264 °C, yellow plates. UV (acetone): $\lambda_{max.}$ = 433 nm. IR (KBr): $\tilde{\nu}$ = 3423, 1672, 1625, 1560 cm^{-1}. MS calculated for $C_{21}H_{13}IO_5$ [M]: 472.24, MALDI-MS $[M]^-$ found: 472.2. ^1H NMR ($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 6.84 (s, 1 H, 4-H), 7.47 (s, 1 H, 5-H), 7.21−7.23 (m, 3 H, 2′-H, 6′-H, 7-H), 7.37 (d, *J* = 7.6 Hz, 1 H, 4′-H), 11.93 (s, 1 H, 8-OH), 13.32 (s, 1 H, 1-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.27 (CH_3), 84.21 (C-2), 103.95 (C-9a), 107.47 (C-4), 111.03 (C-8a), 120.60 (C-2′, C-6′), 121.57 (C-5), 124.83 (C-7), 125. 89 (C-4′), 125.89 (C-4′), 130.45 (C-3′, C-5′), 132.10, 132.97 (C-4a, C-10a), 149.29 (C-6), 153.97 (C-1′), 164.67, 163.91, 167.69 (C−OH), 181.15 (C-10), 190.51 (C-9) ppm.

3-(2,6-Dimethylphenoxy)-1,8-dihydroxy-2-iodo-6-methylanthraquinone (4b): Yield 160 mg (32%), m.p. 302−304 °C, yellow plates. UV (acetone): $\lambda_{max.}$ = 436 nm. IR (KBr)[1]: $\tilde{\nu}$ = 3425, 1663, 1633, 1522 cm^{-1}. MS calculated for $C_{23}H_{17}IO_5$ [M]: 500.29, MALDI-MS $[M + Na]^+$ found: 523.3. ^1H NMR ($CDCl_3$): δ = 2.13 (s, 6 H, 2′-CH_3, 6′-CH_3), 2.44 (s, 3 H, 6-CH_3), 6.78 (s, 1 H, 4-H), 7.10 (s, 1 H, 7-H), 7.16 (s, 3 H, 3′-H, 4′-H, 5′-H), 11.94 (s, 1 H, 8-OH), 13.32 (s, 1 H, 1-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.28, 22.27 (CH_3), 84.13 (C-2), 104.62 (C-4), 110.89 (C-9a), 113.23 (C-8a), 121.46 (C-5), 124.81 (C-7), 126.46 (C-4′), 129.48 (C-3′, C-5′), 130.64 (C-2′, C-6′), 132.99, 135.23 (C-4a, C-10a), 149.13 (C-6), 150.48 (C-1′), 162.69, 163.64, 163.94 (C-OH), 181.53 (C-10), 190.67 (C-9) ppm.

3-(3,5-Dimethylphenoxy)-1,8-dihydroxy-2-iodo-6-methylanthraquinone (4c): Yield 25 mg (5%), m.p. 252−254 °C, yellow plates. UV (acetone): $\lambda_{max.}$ = 437 nm. IR (KBr): $\tilde{\nu}$ = 3440, 1675, 1625, 1560 cm^{-1}. MS calculated for $C_{23}H_{17}IO_5$ [M]: 500.29, MALDI-MS $[M + Na]^+$ found: 523.3. ^1H NMR ($CDCl_3$): δ = 2.34 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.44 (s, 3 H, 6-CH_3), 6.73 (s, 2 H, 2′-H, 6′-H), 6.91 (s, 1 H, 7-H), 7.10 (s, 1 H, 4-H), 7.13 (s, 1 H, 4′-H), 7.57 (s, 1 H, 4′-H), 11.94 (s, 1 H, 8-OH), 13.32 (s, 1 H, 1-OH) ppm.

1,8-Dihydroxy-2-iodo-6-methyl-3-(2,4,6-trimethylphenoxy)-anthraquinone (4d): Yield 82 mg (16%), m.p. 257−258 °C, yellow plates. UV (acetone): $\lambda_{max.}$ = 437 nm. IR (KBr): $\tilde{\nu}$ = 3425, 2918, 1670, 1622, 1554 cm^{-1}. MS calculated for $C_{24}H_{19}IO_5$ [M]: 514.32, MALDI-MS $[M + H]^+$ found: 515.3. ^1H NMR ($CDCl_3$): δ = 2.07 (s, 6 H, 2′-CH_3, 6′-CH_3), 2.33 (s, 3 H, 3′-CH_3), 2.44 (s, 3 H, 6-CH_3), 6.79 (s, 1 H, 4-H), 7.10 (s, 1 H, 7-H), 7.26 (s, 2 H, 3′-H, 5′-H), 11.94 (s, 1 H, 8-OH), 13.32 (s, 1 H, 1-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.33, 21.02, 22.39 (CH_3), 84.21 (C-2), 104.85 (C-4), 110.87 (C-9a), 113.38 (C-8a), 121.56 (C-5), 124.81 (C-7), 130.22 (C-3′, C-5′), 130.30 (C-4′), 133.15, 135.32 (C-4a, C-10a), 136.08 (C-2′, C-6′), 148.43 (C-6), 149.23 (C-1′), 162.80 (C-3), 164.04 (C-1, C-8), 181.72 (C-10), 190.78 (C-9) ppm.

1,8-Dihydroxy-2-iodo-6-methyl-3-(2,3,5,6-tetramethylphenoxy)-anthraquinone (4e): Yield 121 mg (23%), m.p. 281−283 °C, yellow plates. UV ($CHCl_3$): $\lambda_{max.}$ = 440 nm. IR (KBr): $\tilde{\nu}$ = 3440, 2920, 1670, 1625 cm^{-1}. MS calculated for $C_{25}H_{21}IO_5$ [M]: 528.35, MALDI-MS $[M + H]^+$ found: 529.4. ^1H NMR ($CDCl_3$): δ = 1.97 (s, 6 H, 3′-CH_3), 2.26 (s, 6 H, 2′-CH_3, 6′-CH_3), 2.43 (s, 3 H, 6-CH_3), 6.74 (s, 1 H, 4-H), 6.95 (s, 1 H, 4′-H), 7.08 (s, 1 H, 7-H), 7.52 (s, 1 H, 5-H), 11.93 (s, 1 H, 8-OH), 13.30 (s, 1 H, 8-OH), 13.30 (s, 1 H, 1-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.58, 19.76, 22.26 (CH_3), 84.01 (C-2), 104.98 (C-4), 110.72 (C-9a), 113.23 (C-8a), 121.38 (C-5), 124.78 (C-7), 126.15 (C-2′, C-6′), 129.47 (C-4′), 133.01, 135.15 (C-4a, C-10a), 149.03 (C-6), 150.24 (C-1′), 162.65, 163.91, 164.10 (C-OH), 181.66 (C-10), 190.61 (C-9) ppm.

1,8-Dihydroxy-2-iodo-6-methyl-3-(2,3,4,5,6-pentamethylphenoxy)-anthraquinone (4f): Yield 120 mg (22%), m.p. 300−305 °C, yellow plates. UV ($CHCl_3$): $\lambda_{max.}$ = 440 nm. IR (KBr): $\tilde{\nu}$ = 3429, 2923, 1675, 1625 cm^{-1}. MS calculated for $C_{26}H_{23}IO_5$ [M]: 542.37, MALDI-MS $[M]^-$ found: 542.3. ^1H NMR ($CDCl_3$): δ = 2.02 (s, 6 H, 3′-CH_3, 5′-CH_3), 2.24 (s, 6 H, 2′-CH_3, 6′-CH_3), 2.27 (s, 3 H, 4′-CH_3), 6.74 (s, 1 H, 4-H), 7.09 (s, 1 H, 7-H), 7.52 (s, 1 H, 5-H), 11.95 (s, 1 H, 8-OH), 13.32 (s, 1 H, 1-OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.42, 18.53, 28.23, 22.30 (CH_3), 84.13, 105.15, 110.66 (C-9a), 113.23 (C-8a), 121.36 (C-5), 124.78 (C-7), 125.66 (C-2′, C-6′), 134.31 (C-4′), 134.94 (C-3′, C-5′), 133.01, 135.11 (C-4a, C-10a), 148.15 (C-6), 148.15 (C-6), 148.97 (C-1′), 162.61, 163.88, 164.38 (C-0 H), 181.74 (C-10), 190.57 (C-9) ppm.

Crystallographic Data. 4d: Crystal system: triclinic; space group $P\bar{1}$; *a* = 8.088(1) Å, *b* = 9.759(1) Å, *c* = 14.451(1) Å, α = 76.13(1)°, β= 75.24(1)°, γ = 70.40(1)°, *V* = 1024.1(2) $Å^3$, *Z* = 2, $\rho_{calcd.}$ = 1.668 $g \cdot cm^{-3}$, collected reflections 6504; unique reflections 4697; number of parameters 347; R_1 = 0.0340; wR_2 0.0800 for $[I > 2\sigma(I)]$. **4e:** Crystal system: triclinic; space group $P\bar{1}$; *a* = 6.898(1) Å, *b* = 8.513(1) Å, *c* = 18.367(2) Å, α = 88.94(1)°, β = 84.53(1)°, γ = 73.25(1)°, *V* = 1028.0(2) $Å^3$, *Z* = 2, $\rho_{calcd.}$ = 1.707 $g \cdot cm^{-3}$, collected reflections 5950; unique reflections 4323; number of parameters 364; R_1 = 0.0340; wR_2 0.0800 for $[I > 2\sigma(I)]$. The structures of **4d** and **4e** were solved by the direct method using the SHELXL-97 program.[25] All hydrogen atoms were located and refined isotropically, all non-hydrogen atoms were refined anisotropically. CCDC-189425 and -189426 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (international) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

The authors are grateful to Fonds der Chemischen Industrie and Deutsche Forschungsgemeinschaft (DFG) Graduiertenkolleg "Mechanistische und Anwendungsaspekte nichtkonventioneller Oxidationsreaktionen" for financial support. We thank Prof. Joachim Sieler for generating X-ray crystallographic data from **4e** and for technical support.

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Received May 23, 2003

