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Bostrycin: Structure Correction and Synthesis

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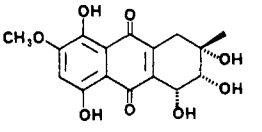
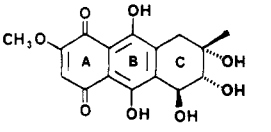
The first synthesis of (±)-bostrycin (Scheme I), which is achieved with regio- and stereochemical control, is described. This synthesis, coupled with X-ray crystallographic and other studies, establishes that the structure of bostrycin is **2**, which differs from the previously accepted structure (**1**) both stereochemically and tautomerically.

The classical dictum[2] "synthesis is the final proof of structure" has endured the test of time. Despite the proof's circumstantial nature, the rare instances of its failure (e.g., patchouli alcohol[3] and albene[4]) are no more frequent than the errors[5] attending application of the absolute method of X-ray diffraction. We now report that the structure of bostrycin (**1**) which was assigned[6,7] in 1968 and "confirmed"[8] in 1978 by synthesis of its desmethoxy derivative is incorrect and that the correct structure is **2**, which differs from **1** both stereochemically and tautomerically.



1



2

As part of a program directed toward the development of a general rationale for the control of regiochemistry in the Diels–Alder reactions of substituted naphthoquinones,[9] we initially undertook the synthesis of bostrycin in 1977. Superficial synthetic analysis suggests that (±)-**1** might be readily accessible by implementation of the route outlined in eq 1.

Critical appraisal of the putative sequence in eq 1 reveals a number of potential pitfalls, however. One possible difficulty is that **3** has a fleeting lifetime, existing instead largely as its tautomer **6**.[10] But this concern proved un-

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(2) See, inter alia: Woodward, R. B. In "Perspectives in Organic Chemistry", Todd, A. R., Ed.; Interscience: New York, 1956; pp 165–167. Eschenmoser, A.; Wintner, C. E. *Science (Washington, D.C.)* **1977**, *196*, 1410–1420.

(3) Original structure assignment: Büchi, G.; Erickson, R. E.; Wakabayashi, N. *J. Am. Chem. Soc.* **1961**, *83*, 927–938. "Confirmation" by synthesis: Büchi, G.; MacLeod, Jr., W. D. *Ibid.* **1962**, *84*, 3205–3206. Revision of structure: Dobler, M.; Dunitz, J. D.; Gubler, B.; Weber, H. P.; Büchi, G.; Padilla, O. J. *Proc. Chem. Soc., London* **1963**, 383. Büchi, G.; MacLeod, Jr., W. D.; Padilla, O. J. *J. Am. Chem. Soc.* **1964**, *86*, 4438–4444.

(4) Original structure assignment: Vokáč, K.; Samek, Z.; Herout, V.; Šorm, F. *Tetrahedron Lett.* **1972**, 1665–1668. "Confirmation" by synthesis: Lansbury, P. T.; Boden, R. M. *Ibid.* **1973**, 5017–5020. Revision of original structure: Kreiser, W.; Janitschke, L.; Scheldrick, W. S. *J. Chem. Soc., Chem. Commun.* **1977**, 269–270. Kreiser, W.; Janitschke, L. *Tetrahedron Lett.* **1978**, 601–604 and later papers. See also: Baldwin, J. E.; Barden, T. C. *J. Org. Chem.* **1981**, *46*, 2442–2445.

(5) For corrections of structures previously determined by X-ray, see, inter alia: Fehr, T.; Keller-Juslén, C.; King, H. D.; Loosli, H.-R.; Kuhn, M.; von Wartburg, A. *J. Antibiot.* **1979**, *32*, 535–536. Seto, H.; Mizoue, K.; Otake, N.; Gachon, P.; Kergomard, A.; Westley, J. W. *Ibid.* **1979**, *32*, 970–971. For revisions of absolute configurations assigned by X-ray, see, inter alia: Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 4197–4198. Biskupiak, J. E.; Ireland, C. M. *Ibid.* **1984**, *25*, 2935–2936. For general caveats, see: Jones, P. G. *Chem. Soc. Rev.* **1984**, *13*, 157–172.

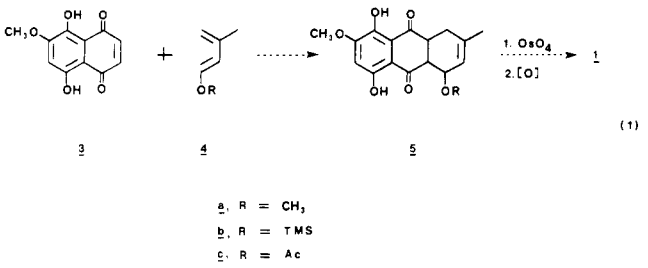
(6) (a) Noda, T.; Take, T.; Otani, M.; Miyauchi, K.; Watanabe, T.; Abe, J. *Tetrahedron Lett.* **1968**, 6087–6090. (b) Takenaka, A.; Furusaki, A.; Watanabe, T. *Ibid.* **1968**, 6091–6094. (c) Noda, T.; Take, T.; Watanabe, T.; Abe, J. *Tetrahedron* **1970**, *26*, 1339–1346.

(7) For other reports of the isolation of bostrycin, see: (a) Charudattan, R.; Rao, K. V. *Appl. Environ. Microbiol.* **1982**, *43*, 846–849. (b) Stevens, K. L.; Badar-ud-Din; Ahmad, A.; Ahmad, M. *Phytochemistry* **1979**, *18*, 1579–1580. (c) Van Eijk, G. W. *Experientia* **1975**, *31*, 783–4. (d) Furuya, K.; Shirasaka, M.; *Sankyo Kenkyusho Nempo* **1969**, *21*, 165–168.

(8) Rösner, A.; Tolkiehn, K.; Krohn, K. *J. Chem. Res., Synop.* **1978**, 306–307; *J. Chem. Res., Miniprint* **1978**, 3831–3848.

(9) For a leading reference, see: Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, Jr., R. N.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569–4577.

0022-3263/85/1950-3679$01.50/0

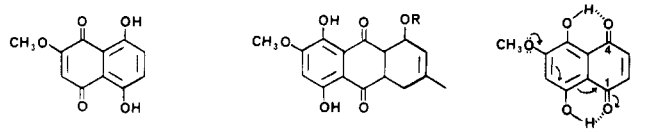


(1)

3 4 5

a, R = CH_3
b, R = TMS
c, R = Ac

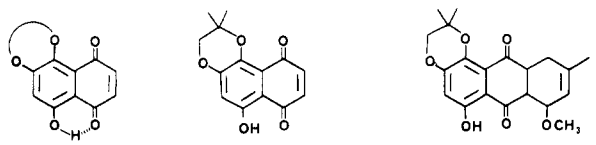
founded since tautomer **6** exhibits no tendency to undergo a Diels–Alder reaction and adducts of **3** are accessible via the facile—albeit unfavorable—equilibrium between **6** and **3**. Nontheless, two other questions remained to be addressed: stereochemistry (see below) and regiochemistry. The latter loomed as a serious complication since it was predicted[10] that reacion of **3** and **4** would lead to the for-



6 7 8

a, R = CH_3

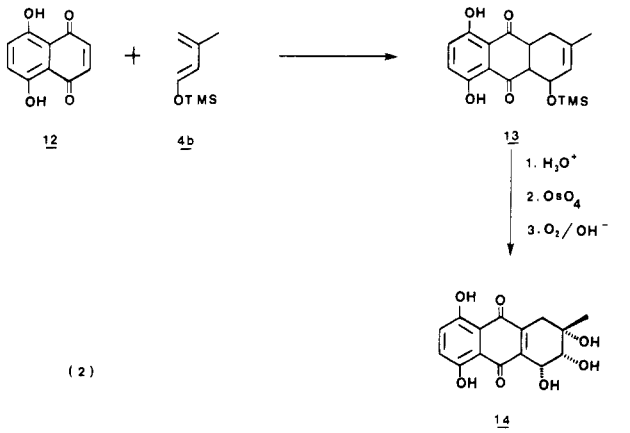
mation of the unwanted regioisomer (**7**) as the principal adduct. This prediction was based on the expectation that the effects of the two hydrogen bonding interactions in **3** (see **8**) would approximately cancel and that the C-4 carbonyl should therefore control the regiochemical outcome of the cycloaddition because of "deactivation" of the C-1 carbonyl by resonance donation from the methoxy group. This predicted—but undesired—outcome indeed obtains: reaction of **3** with **4a** affords a 3:1 mixture of **7a** and **5a**.[10] However, further application[10] of the same considerations allowed one to anticipate that replacement of **3** with a molecule endowed with the general constitution indicated in **9** should provide a way to overcome the regiochemical obstacle since the electronic effects of the two ether groups should cancel, leaving the hydrogen bond as the only uncompensated interaction. Translating the general concept



9 10 11

of **9** into a specific molecule proved more difficult than expected; but **10** was ultimately prepared,[10] although in poor yield, and shown to give exclusively **11** upon reaction with **4a**. The regiochemical element of a bostrycin synthesis was thus solved,[10] at least in principle, although fabrication of bostrycin would necessitate development of a directing group operationally equivalent to that in **10** but removable under conditions compatible with the functionality in the C ring of bostrycin.

Shortly after the above work appeared in print (1978)[10] Krohn et al. reported[8] the synthesis of (±)-demethoxybostrycin (**14**) summarized in eq 2. The ^1H NMR spectrum of the chiral portion of **14** was stated to be nearly

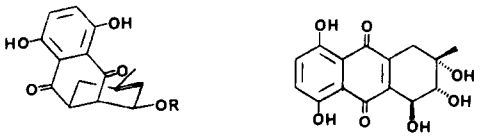


(2)

12 4b 13 14

identical with the spectrum of bostrycin, thereby[8] "confirming the structure (**1**) for bostrycin." The results of eq 2 when taken with the solution to the regiochemical problem appeared to render a synthesis of bostrycin itself an exercise bordering on the trivial and consideration of other priorities led us to suspend further work in this area.

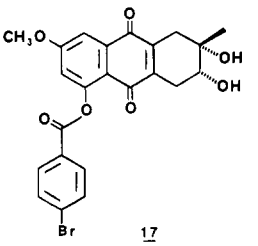
But over the intervening years a nagging question persisted: stereochemistry. For if **12** and **4b** react through an endo transition state (as is well-documented[11] in closely related systems), the adduct (**13**) will have stereostructure **15a**. Attack of OsO_4 on the more accessible face of the derived **15b** should ultimately lead to **16**, not **14**.[12] Thus, to our mind, the structure (**14**) attributed to the product of eq 2 (and, therefore, bostrycin also) was not entirely secure.



15a, R = TMS
15b, R = H

16

The structure and absolute stereochemistry of bostrycin were originally assigned[6] largely on the basis of an X-ray determination of the structure of the degradation product **17**. Placement of the remaining hydroxyls was made primarily on the basis of ^1H NMR data.



17

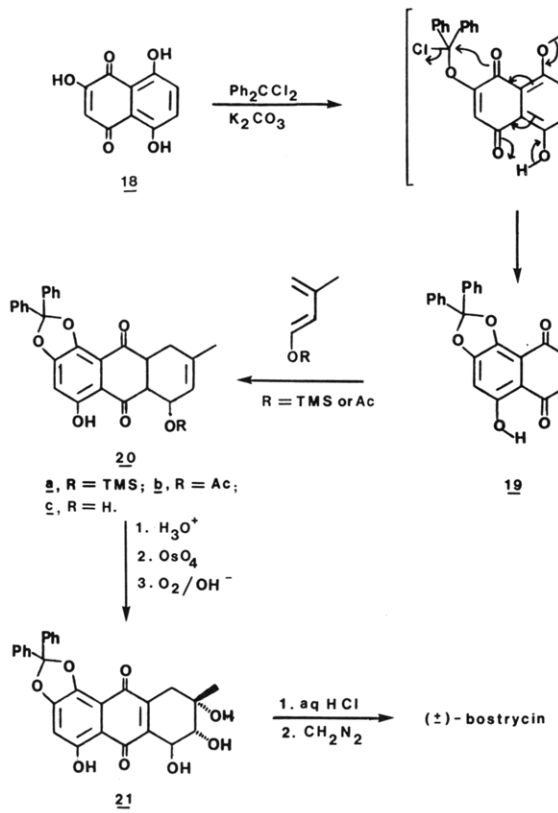
But in view of the stereochemical misgivings noted above, we undertook to develop a synthesis of bostrycin. Once **19**, a selectively labile embodiment of **9** (which had eluded us in earlier forays) was in hand, the synthesis

(10) Kelly, T. R. *Tetrahedron Lett.* **1978**, 1387–1390. The chemical shifts for the peri-OH proton resonances (which appear as sharp singlets) reported in this reference for **22** and **23** were recorded on a 60-MHz instrument and the absolute values are slightly different from those now obtained at 300 MHz (**22**: δ 13.40, 13.52; **23**: δ 13.46, 13.50). The relative positions of the peaks have not changed, of course.

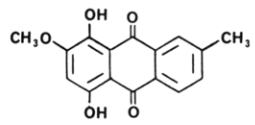
(11) See, inter alia, footnote 12 in: Fariña, F.; Prados, P. *Tetrahedron Lett.* **1979**, 477–480. Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596. Gupta, R. C.; Harland, P. A.; Stoodley, R. J. *Tetrahedron* **1984**, *40*, 4657–4667.

(12) The directing effect of the allylic hydroxyl group should reinforce steric influences: osmylation of cyclohex-2-en-1-ol occurs almost exclusively trans to the OH [Cha, J. K.; Christ, J. W.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946].

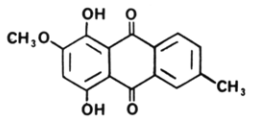
Scheme I



proved relatively straightforward (Scheme I), giving (±)-bostrycin in 57% overall yield from naphthopurpurin (**18**). Diels–Alder reaction of **19** with **4b** or **4c** gave approximately 3:1 and 3:2 mixtures, respectively, of regioisomers (**20** predominating in both cases), but use of tetraacetyl diborate[13,14] as a catalyst with **4b** or **4c** overcame this deficiency, yielding **20** regiospecifically. (Regiochemistry was determined by degradation to **22**/**23** which are readily distinguished by high field NMR.[10,16] Synthetic



22



23

22 has been known for several years;[6,10] very recently it has also been isolated[17] from a red Australian toadstool of the genus *Cortinarius*.) Routine elaboration of **20a** gave, virtually (>95%) stereospecifically, a compound identical with bostrycin by direct comparison in 60% yield from **19** (proceeding via acetate **20b** gave a lower overall yield). This stereochemical outcome is consistent with the observations of Krohn et al.[8] but leaves unaddressed the assignment of C-4 relative stereochemistry.

X-ray crystallography was enlisted to resolve the stereochemical question unequivocally. (±)-Bostrycin failed

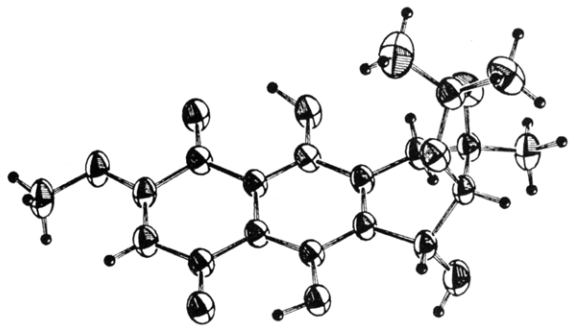
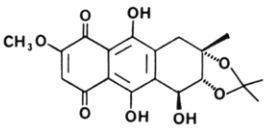
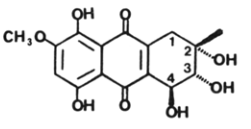


Figure 1. ORTEP drawing of crystal structure of one antipode of (±)-bostrycin acetonide (**24**).

to yield suitable crystals, but its acetonide (acetone, Dowex 50X4), a known[7a] but structurally uncharacterized derivative of bostrycin, yielded crystals suitable for X-ray diffraction. The X-ray structure determination (Figure 1, see Experimental Section for details) establishes **24** as the structure of the acetonide with the C-4 hydroxyl having a β-, rather than the accepted, α-configuration.



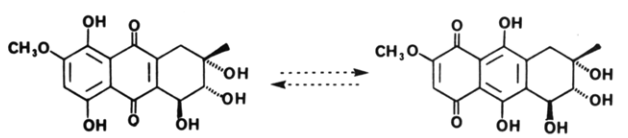
24



25

Acetonide **24** can be hydrolyzed in high yield to bostrycin.[7a] To exclude the remote but still conceivable possibility that conversion of bostrycin to its acetonide is accompanied by inversion of configuration at C-4 and that the hydrolysis of the acetonide back to bostrycin is also attended by (a second) inversion at C-4, the hydrolysis of **24** to bostrycin was conducted separately with D_2O/DCl and 99% ^{18}O-labeled H_2O/HCl. These experiments establish that the hydrolysis of **24** to bostrycin is not accompanied by fission of either the C–H or the C–OH bond at C-4 and that the *stereochemistry* of bostrycin (and **21**) is thus that shown in **25** not **1**.[18]

The final question that remained was whether bostrycin exists as **2** or **25**. A facile tautomeric equilibrium between the two isomers should obtain, so in one sense this aspect



25 **2**

of the structure of bostrycin is of lesser moment than the stereochemical one. Nonetheless, the finding that the acetonide of bostrycin (**24**) exists—in the crystal—with the A ring rather than the B ring quinoidal is in contrast to the way bostrycin has always been represented. Although

(13) (a) Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978**, 4309–4310. (b) Kelly, T. R.; Montury, M. *Ibid.* 4311–4314.

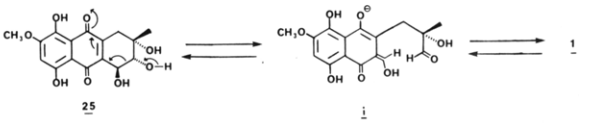
(14) Also known (incorrectly)[15] as boron triacetate.

(15) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. "Natural Products Synthesis Through Pericyclic Reactions" (ACS Monograph 180); American Chemical Society: Washington, D.C., 1983; p 195.

(16) For a more malevolent application of high field NMR, see: Wambaugh, J. "The Delta Star"; Bantam Books, Inc.: New York, 1984.

(17) Gill, M.; Strauch, R. J. *Tetrahedron Lett.* **1985**, *26*, 2593–2596. We thank Dr. Gill for communication of this information prior to publication.

(18) It is theoretically conceivable that C-4 epimerization could occur by C–C bond fission via an intermediate such as i, but i would be expected to close to a mixture of C-3 and/or C-4 epimers (not observed) and

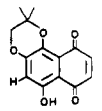
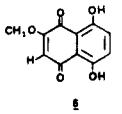
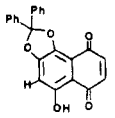
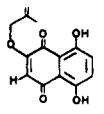
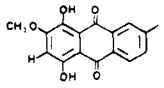
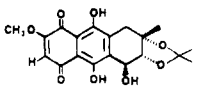
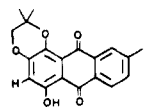
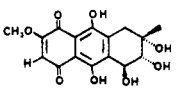
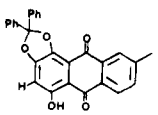
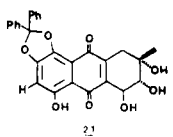


25 i **1**

undergo C-3 oxygen exchange and/or C-4 oxygen or hydrogen exchange (none of which are observed). We view such a mechanism for C-4 epimerization as vanishingly remote.

Table I. ^{1}H NMR Data (for Circled Proton) for Assignment of Position of A/B Tautomeric Equilibria

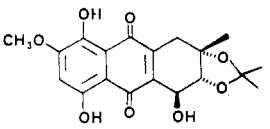
A B

Compound	^{a}CDCl$_3$	^{b}DMSO-d_6	^{a}CDCl$_3$, ^{b}DMSO-d_6		Compound
 10	6.72	6.85	6.17[26]	6.41	 6
 19	6.71	7.05±.05	6.10	6.42	 25[10]
 22	6.73	insol	6.15	6.44	 24
 27[10]	6.72	6.88	insol	6.45	 2 (bostrycin)
 28	6.60	7.09			
 21	6.60	7.06			

it is certainly possible that the tautomer observed in the crystal and the one predominating in solution could be different, we submit that **24** exists as the tautomer shown (**24**) in solution as well and that the predominant tautomer of bostrycin is **2**.

These conclusions were reached by comparison of the ^{1}H NMR data for bostrycin (**2**) and its acetonide (**24**) with the chemical shifts of relevant protons of related compounds tabulated in Table I. Moore and Scheuer[19] carried out an extensive study correlating the tautomerism of naphthazarin and related substances with ^{1}H NMR chemical shifts. That correlation shows that the circled proton in B-type molecules would appear at δ 6.1–6.2 (in $CDCl_3$). The data of Moore and Scheuer,[19] augmented by the chemical shifts of the analogous proton in several compounds locked into the alternative tautomer generalized as A, indicate that the circled hydrogen in A should give rise to a peak at δ 6.6–6.7 (in $CDCl_3$), which is substantially downfield of that in B (see Table I). In $CDCl_3$ **24** exhibits a one-proton singlet at δ 6.15 which is in excellent agreement with the position predicted for tautomer **24** (but not for **26**). Bostrycin is insufficiently soluble in $CDCl_3$ to record its ^{1}H NMR spectrum in that solvent, but it is soluble in Me_2SO-d_6. Me_2SO shifts the resonance of the proton of interest downfield[19] (compare the shifts in

(19) Moore, R. E.; Scheuer, P. J. *J. Org. Chem.* **1966**, *31*, 3272–3283.



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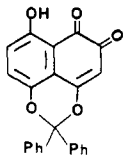
6 and **24**), but the chemical shift for the aromatic proton of bostrycin is essentially identical with that for **24**. Due to the internal consistency of the data cited in Table I and elsewhere,[19] we suggest that bostrycin is more accurately represented as **2** rather than the tautomer **25**.

Experimental Section

^{1}H NMR spectra were recorded on an Hitachi Perkin-Elmer Model R-24 or a Varian FT-80A instrument; chemical shifts are reported in parts per million downfield from internal Me_4Si. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 599B spectrophotometer. Ultraviolet (UV) spectra were recorded on a Perkin-Elmer spectrophotometer (Coleman 575), and the peak maxima are reported in nanometers. Analytical thin-layer chromatography was performed on EM silica gel 60 F_{254} plastic plates (0.2 mm), and column (gravity) chromatography was performed on silica gel 60 (particle size 0.040–0.063 mm, EM reagents). Melting points (Pyrex capillary) are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc. Routine mass spectra were recorded on an Hitachi Perkin-Elmer RMS-4 spectrometer.

All reactions were carried out in flame-dried glassware under an atmosphere of argon or nitrogen unless otherwise stated. Petroleum ether refers to the fraction boiling at 40–60 °C. The phrase "concentrated in vacuo" or equivalent expressions means that volatiles were removed on a rotary evaporator at aspirator pressure and the residue was placed under high vacuum.

5-Hydroxy-2,2-diphenylnaphtho[1,2-*d*]-1,3-dioxole-6,9-dione (19) and 7-Hydroxy-2,2-diphenylnaphtho[1,8-de]-1,3-dioxin-5,6-dione (30). To a stirred mixture of 213 mg (1.0 mmol) of naphthopurpurin (**18**)[10] and 370 mg (2.2 mmol) of crystalline K_2CO_3·1.5H_2O in 15 mL of dry CH_3CN at room temperature was added dropwise 0.22 mL (1.1 mmol) of dichlorodiphenylmethane over 3 min. After being stirred for 20 h, the mixture was slowly acidified to pH 2 with 5 mL of 1 N HCl and was diluted with 25 mL of water. The mixture was extracted with six 75-mL portions of ether; the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residual red solid was chromatographed on 15 g of silica gel (deactivated by mixing with 1.5 mL of water), eluting first with 500 mL of 1:1 dichloromethane–petroleum ether, to give 207 mg (54%) of the protected naphthopurpurin **19** as a red solid. Further elution with 200 mL of dichloromethane and, finally, 50 mL of ether gave 170 mg (44%) of dione **30** as a red solid which could be converted back to **18** in 90% yield (vide infra). The yield of **19** based on unrecoverable **18** is thus 95%.



30

Recrystallization of compound **19** from ether gave orange-red crystals: mp 188–189 °C; IR (KBr) 1670, 1645, 1610, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.23 (1 H, s), 7.41 (10 H, m), 6.84 (2 H, s), 6.71 (1 H, s); UV/vis λ_{max} (ϵ) (95% EtOH), 224 nm (38 300), 270 (7900), 490 (6300); MS, *m/e* 370 (M^+).

Anal. Calcd for $C_{23}H_{14}O_5$: C, 74.59; H, 3.78. Found: C, 74.62; H, 3.77.

Further purification of dione **30** was achieved by recrystallization from ether to provide orange-red crystals, mp 194–197 °C: IR (KBr) 1670, 1650, 1628, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.37 (1 H, s), 7.40 (12 H, m), 6.13 (1 H, s); UV/vis λ_{max} (ϵ) (95% EtOH) 208 nm (50 240), 258 (24 900), 490 (6400), MS, *m/e* 370 (M^+).

Anal. Calcd for $C_{23}H_{14}O_5$: C, 74.59; H, 3.78. Found: C, 74.34; H, 3.94.

Hydrolysis of 30 Back to Naphthopurpurin (18). To a solution of 44 mg (0.12 mmol) of **30** in 10 mL of 95% ethanol was added 5 mL of 1 N HCl. The mixture was heated under reflux for 4 h, cooled, and extracted with three 25-mL portions of ether. The combined ether extracts were washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was washed with petroleum ether (4 × 50 mL, to remove benzophenone) which provided 22 mg (90%) of pure **18**.

7,8,9,10-Tetrahydro-5,7,8,9-tetrahydroxy-9-methyl-2,2-diphenylanthra[1,2-*d*]-1,3-dioxole-6,11-dione (21). To a stirred mixture of 880 mg (2.3 mmol) of protected naphthopurpurin **19** and 1.04 g (5.5 mmol) of tetraacetyldiborate[14,20] in 35 mL of absolute ether was added 720 mg (4.6 mmol) of diene **4b**,[8] and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 90 mL of ether, washed with water (3 × 50 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo gave 1.33 g of Diels–Alder adduct **20a** which was ordinarily used immediately without further purification: IR (film) 1700, 1675 (sh), 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.0 (1 H, s), 7.25 (10 H, m), 6.5 (1 H, s), 5.4 (1 H, m), 4.3 (1 H, m), 3.1 (2 H, m), 2.1 (2 H, m), 1.65 (3 H, s), −0.4 (9 H, s).

To a solution of 1.33 g of the crude Diels–Alder adduct **20a** in 16 mL of carbon tetrachloride was added 1.0 g (3.9 mmol) of osmium tetraoxide. After being stirred for 3.5 h at room temperature, the mixture was combined with 100 mL of THF and 1 g of sodium hydrogen sulfite in 15 mL of water, and the mixture was stirred for an additional 2 h. The mixture was then basified to pH 9 by the addition of 20 mL of 5% NaOH solution and stirred for another 0.5 h open to the air. The reaction mixture was poured into 300 mL of pH 7 buffer and extracted with six 200-mL portions of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give a mixture of **21** and its silylated derivative. The mixture was dissolved in 20 mL of absolute ethanol, treated with 0.23 mL of 1 N HCl, and stirred at room temperature for 15 min. The solution was diluted with 50 mL of ether, and the ether solution was washed with 50 mL of pH 7 buffer. The organic layer was separated and the aqueous layer was extracted with two 25-mL portions of ether. The combined ether extracts were concentrated in vacuo, and the residual orange solid was chromatographed on 50 g of silica gel (previously deactivated by mixing with 7.5 mL of water), eluting with 1.5 L of dichloromethane to give 768 mg (66.4% from **19**) of the tetrahydroxy compound **21** as an orange solid. Recrystallization of **21** from ether gave tiny orange-red crystals, mp 209–212 °C: IR (film) 3600–3100, 1730, 1715, 1660, 1640, 1610, 1600, 1590 cm^{-1}; ^1H NMR (Me_2SO, D_2O) δ 7.51 (10 H, s), 7.06 (1 H, s), 4.66 (1 H, d, J = 4.7 Hz), 3.47 (1 H, d, J = 4.7 Hz), 2.56 (2 H, s), 1.21 (3 H, s).

Anal. Calcd for $C_{28}H_{22}O_8$: C, 69.13; H, 4.52. Found: C, 68.98; H, 4.60.

6a,7,10,10a-Tetrahydro-5,7-dihydroxy-9-methyl-2,2-diphenylanthra[1,2-*d*]-1,3-dioxole-6,11-dione (20c). To a solution of 32 mg of Diels–Alder adduct **20a** in 10 mL of 95% ethanol was added 0.12 mL of 1 N HCl. The solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 15 mL of ether, and the ethereal solution was washed with 10 mL of pH 7 buffer, dried ($MgSO_4$), and concentrated in vacuo. The residual yellow solid was chromatographed on 2 g of silica gel (20 mm diameter column), eluting with 150 mL of dichloromethane to provide 36 mg (95%) of allylic alcohol **20c** as light yellow crystals, mp 174–175 °C. An analytical sample, mp 174–175 °C, was obtained by recrystallization from ether: IR (KBr) 3660–3140 (br, alcoholic OH), 1690, 1635, 1625, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.97 (1 H, s), 7.51 (5 H, m), 7.37 (5 H, m), 6.67 (1 H, s), 5.65 (1 H, m), 4.42 (1 H, m), 3.19 (2 H, m), 2.79 (1 H, m), 2.17 (1 H, m), 1.78 (3 H, s); MS m/e 454 (M^+).

Anal. Calcd for $C_{28}H_{22}O_6$: C, 74.00; H, 4.84. Found: C, 74.00; H, 5.01.

7-Acetoxy-6a,7,10,10a-tetrahydro-5-hydroxy-9-methyl-2,2-diphenylanthra[1,2-*d*]-1,3-dioxole-6,11-dione (20b). To a stirred mixture of 183 mg (0.50 mmol) of protected naphthopurpurin **19** and 300 mg (1.6 mmol) of tetraacetyldiborate[14,20] in 7 mL of absolute ether was added 222 mg (1.76 mmol) of 1-acetoxy-3-methyl-1,3-butadiene (**4c**).[21] The reaction mixture was stirred for 21 h at room temperature. The mixture was then diluted with 30 mL of ether, and the ethereal solution was washed with water (3 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residual solid (332 mg) was purified by flash chromatography, eluting with dichloromethane, to provide 153 mg (63%) of Diels–Alder adduct **20b** as a yellow solid, mp 170–173 °C: ^1H NMR ($CDCl_3$) δ 12.9 (1 H, s), 7.3 (10 H, m), 6.62 (1 H, s), 5.5 (2 H, m), 3.25 (2 H, s), 2.2 (2 H, m), 1.8 (3 H, s), 1.25 (3 H, s); MS, m/e 496 (M^+). Adduct **20b** was too unstable to obtain an analytically pure sample; it was, however, converted to **28** (vide infra) which analyzed correctly.

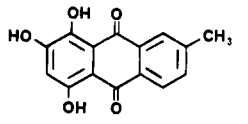
When the reaction of compound **19** and diene **4c** was carried out in the absence of tetraacetyldiborate, a 3:2 mixture of adduct **20b** and its regioisomer was obtained in 55% yield. The regiochemical composition was determined by conversion (using the procedure outlined below for conversion of pure **20b** to **22**) of the mixture to compounds **22** and **23** and assay[10] by 300-MHz ^1H NMR.

Treatment of the crude adduct **20b** (101 mg) by a method similar to that used in the conversion of adduct **20a** to **21** gave, after purification, 15 mg (20% from **19**) of tetrahydroxy compound **21**.

5-Hydroxy-9-methyl-2,2-diphenylanthra[1,2-*d*]-1,3-dioxole-6,11-dione (28). To a solution of 74 mg of the adduct **20b** in 20 mL of ethanol was added 5 mL of 40% aqueous KOH in one portion. The solution was stirred for 10 min at room temperature in air. The reaction mixture was acidified with 40 mL of 10% tartaric acid (aqueous) and was extracted with three 30-mL portions of ether. The combined ether extracts were washed sequentially with three 25-mL portions of water and two 25-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo to provide 50 mg (77% from **20b**) of pure anthraquinone derivative **28** as a yellow solid, mp 239.5–240 °C after recrystallization from ethyl acetate: IR (KBr) 1670, 1630, 1600, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.89 (1 H, s), 8.14 (3 H, m), 7.43 (10 H, m), 6.76 (1 H, s), 2.52 (3 H, s).

Anal. Calcd for $C_{28}H_{18}O_5$: C, 77.42; H, 4.15. Found: C, 77.27; H, 4.18.

1,4-Dihydroxy-2-methoxy-7-methylanthracene-9,10-dione (22). To a stirred solution of 20 mg (0.046 mmol) of **28** in 15 mL of dry dichloromethane was added 0.3 mL of BCl_3 (1 M solution in hexane) dropwise over 2 min at room temperature during which time the yellow solution turned purple. After the reaction was stirred for 6 h, 15 mL of water was added. The mixture was stirred for an additional 15 min, poured into a separatory funnel, and shaken vigorously to ensure complete hydrolysis of the borate complex. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to provide 18 mg of a red solid, which was the deprotected compound **31**.[10]



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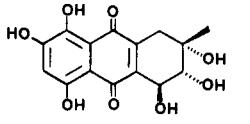

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Resolution of the compound **31** in 5 mL of ether was followed by the dropwise addition of a distilled ethereal solution of diazomethane. The reaction was monitored by TLC using 10:1 dichloromethane/methanol as eluent. During the addition of diazomethane a small amount of compound **22** precipitated. The solvent was removed in vacuo and the residue was purified by chromatography on 2 g of silica gel (20 mm diameter column) using 150 mL of dichloromethane as eluent to provide 12 mg (92%) of **22** as an orange yellow solid, mp 233–235 °C, identical with material prepared previously.[10]

(±)-Bostrycin. To a solution of 40 mg (0.095 mmol) of **21** in 15 mL of 95% EtOH was added 15 mL of 0.2 N HCl, and the

(20) For a preparation[14] see footnote 5 in ref 13b.

(21) Snider, B. B.; Amin, S. G. *Synth. Commun.* **1978**, *8*, 117–125. The ^1H NMR spectrum for diene **4c** is reported incorrectly in this paper. The correct spectrum in $CDCl_3$ is δ 7.35 (1 H, d, J = 13 Hz), 6.1 (1 H, d, J = 13 Hz), 4.95 (2 H, s), 2.15 (3 H, s), 1.85 (3 H, s) [lit. ^1H NMR ($CDCl_3$) δ 7.35 (1 H, d, J = 13 Hz), 5.12 (1 H, d, J = 13 Hz), 4.95 (2 H, s, br), 2.5 (3 H, s), 1.85 (3 H, d, J = 2 Hz)].

mixture was heated under reflux for 5 h. The reaction mixture was cooled and extracted with four 50-mL portions of ethyl acetate, and the combined extracts were concentrated in vacuo. The residual red solid (**32**) was not purified but was immediately used in the next reaction. The solid was suspended in a mixture of 20 mL of distilled THF and 20 mL of absolute ether. A distilled ethereal solution of diazomethane was added in small portions, and the progress of the reaction was monitored by TLC in a 1:1 THF/CH_2Cl_2 solvent system. Complete dissolution of the insoluble material occurred during the addition of diazomethane. After the reaction was judged to be complete by TLC analysis, the solvent was removed, and the residue was washed with petroleum ether (3 × 150 mL). Dissolution in THF and trituration with petroleum ether gave 25 mg (90%) of essentially pure (±)-bostrycin which melted at 218–220 °C dec after recrystallization from THF [lit.[6,7] mp for the (−) enantiomer, 222–224 °C dec]. The TLC behavior of synthetic and natural bostrycin is identical in four different solvent systems [(1) 4:1:1 *n*-BuOH/HOAc/H_2O; (2) 1:1 THF/CH_2Cl_2; (3) 9:1 CH_2Cl_2/MeOH; and (4) 4:1 CH_2Cl_2/Et_2O]; UV, IR, and ^1H NMR spectra are in agreement with the literature.[6]

Isopropylidene Derivative of (±)-Bostrycin (24). To a solution of 137 mg (0.40 mmol) of (±)-bostrycin in 20 mL of acetone (dried over 4A molecular sieves) was added 275 mg of Dowex 50X4 ion exchange resin (200 to 400 mesh). The mixture was heated under reflux in a dry atmosphere for 20 h, cooled, and filtered through a Celite pad. The filtrate was concentrated in vacuo to give 80 mg of a red solid. The crude isopropylidene derivative was chromatographed on 4 g of deactivated silica gel (previously treated with a 0.025 M solution of KH_2PO_4 in 1:1 H_2O/MeOH, filtered, and oven-dried at 120 °C for 12 h). Elution with 100 mL of CH_2Cl_2, followed by 100 mL of CH_2Cl_2 containing 1% (v/v) EtOH, and finally 100 mL of CH_2Cl_2 containing 3% (v/v) EtOH, afforded 35 mg (23%, not optimized) of pure isopropylidene derivative (±)-**24**, as a red solid: mp 208–209 °C [lit.[7a] mp for **24** derived from natural, presumably optically active bostrycin, 200–201 °C]; IR 3600–3220 (br OH), 1730, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.12 (1 H, s), 12.56 (1 H, s), 6.15 (1 H, s), 5.45 (1 H, d, J = 3 Hz), 4.35 (1 H, d, J = 3 Hz), 3.93 (3 H, s), 3.50–2.55, (2 H, AB q, J = 18 Hz), 1.61 (3 H, s), 1.35 (3 H, s), 1.01 (3 H, s).

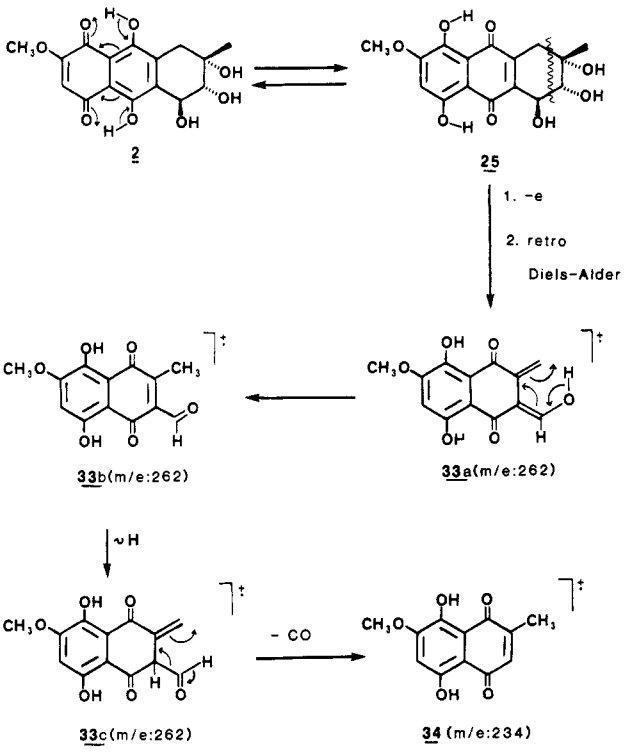
Anal. Calcd for $C_{19}H_{20}O_8$: C, 60.63; H, 5.32. Found: C, 60.56; H, 5.38.

Hydrolyses of (±)-24 to (±)-Bostrycin with $^{16}OH_2$, D_2O, and $^{18}OH_2$. To a solution of 13 mg (0.034 mmol) of (±)-**24** in 2 mL of CH_3OD were added 100 μL of D_2O and 14 μL of distilled CH_3COCl. After 1 h of heating under reflux in a nitrogen atmosphere the solvent was removed on a high vacuum pump without any external heating. The ^1H NMR spectrum of the bostrycin in Me_2SO-d_6 showed no exchange of the C-4 hydrogen with deuterium.

Similar treatment of (±)-**24** (18 mg) with 2 mL of dry methanol, 100 μL of $^{18}OH_2$ (99% ^{18}O), and 14 μL of CH_3COCl provided bostrycin (a parallel hydrolysis experiment was performed with $^{16}OH_2$ at the same time under identical conditions for the calibration of experimental and MS conditions) which was shown by mass spectroscopy (EI, using a MAT 731 instrument) to be approximately 70% unlabeled (M^+ = 336). Thus at least 70% of the hydrolysis of **24** to bostrycin had occurred without scission of the C-4 carbon–oxygen bond. For that portion of the sample (ca. 30% M^+ = 338) which contains ^{18}O, we believe that label was incorporated by exchange of a carbonyl oxygen and not the C-4 OH. This conclusion is supported by the constancy of the isotopic ratio (70:30) in the molecular ion and two fragments with m/e (for unlabeled molecules) of 262 and 234 assigned (Scheme II) structures **33** and **34** (or effectively equivalent tautomers emanating from **2** or **25**). That **2**, **33**, and **34** possess an elemental composition in agreement with the structures assigned was confirmed by high resolution mass spectrometry (EI) on a CEC 110 instrument.

Crystallographic Data Collection and Reduction for (±)-24. Crystals of (±)-**24** were grown by slow evaporation of a solution of (±)-**24** in CH_2Cl_2 over the course of 19 days at 0 °C. A red crystal of approximate dimensions of 0.18 × 0.21 × 0.37 mm was mounted on a glass fiber by using epoxy cement with the longest dimension coincident with the glass fiber axis. The

Scheme II



crystal was centered optically on an Enraf-Nonius four-circle CAD4 automated diffractometer controlled by a PDP8 computer. A full rotation orientation photograph was taken by using the Polaroid cassette accessory. Twenty intense reflections were chosen and centered by using manufacturer-supplied software.[22] The INDEX program was used to obtain an orientation matrix and unit cell parameters. Successive centerings and least-squares refinements of 20 values found for the 20 precisely centered reflections gave the refined triclinic lattice constants: a = 8.047 (2) Å, b = 11.126 (3) Å, c = 11.442 (2) Å, α = 113.60 (2)°, β = 106.52 (2)°, γ = 99.67 (2)°, and V = 852 (1) Å^3. A small test data set (axial and zero layer reflections) was collected to determine the space group. The choice $P\bar{1}$ over $P1$ was confirmed by the successful refinement of the structure. The number of formula units per unit cell Z was determined to be 2 based on a calculated density of 1.466 g cm^{-3}.

Intensity data were collected at room temperature [21 (±1) °C] using Mo K_α radiation (λ = 0.71073 Å) with a graphite single-crystal monochromator (takeoff angle = 2.8°). A θ–2θ scan mode was used, with 2θ ranging from (0.90 + 0.347 tan θ)° below and above the calculated position of the $K_{\alpha 1}$ and $K_{\alpha 2}$ reflections. The scan rate at which a reflection was measured was varied automatically from 1.0° to 5.0° min^{-1}, depending on the intensity of reflection as determined by a preliminary brief scan. Background counts were measured with the detector stationary and positioned at the beginning and end of the scan for each $^1/_4$ of the total scan time. Three standard reflections were measured every hour of X-ray irradiation time, and the same reflections were checked for centering automatically after every 350 reflections to check on the crystal orientation and stability (anisotropic decay correction, 0.933–1.023). A total of 2670 reflections were collected in the range $3.2 \leq 2\theta \leq 48.06°$. Of these there were 2372 unique non-zero reflections. ψ scans indicated that absorption was not severe (μ = 1.077 cm^{-1}), and no absorption corrections were applied.

Structure Solution and Refinement for (±)-24. The structure was solved by direct methods using MULTAN. The remaining non-hydrogen atoms were located with several Fourier syntheses. Hydrogen atoms were located from a difference Fourier map and refined by using fixed isotropic temperature parameters

(22) Structure determination package was provided by Molecular Structure Corp.

(B = 5.0 Å^2). In the final cycles of least-squares refinements the structure converged (max shift 0.030) using 2080 reflections ($I \geq 2\sigma(I)$) on 304 variables. Variables included the overall scale factor, positional parameters for all atoms, and anisotropic thermal parameters for all non-hydrogen atoms. Convergence was achieved with final R values of R_1 = 0.036, R_2 = 0.046, and an ESD of 1.563 using a non Poisson type distribution[23] with a weighting factor of 0.04. A final difference Fourier map showed no peaks greater than 0.27 e Å^{-3}.

Acknowledgment. We thank the National Institutes of Health for support of this project (Grant CA 17631). We are grateful to Drs. T. Noda[6] and R. Charudattan[7a] for gifts of natural bostrycin, Mr. Kevin Tracey for preliminary studies, Dr. Jack DeMember (Polaroid) for recording the high field ^{1}H NMR spectra, Dr. C. E. Costello and the Staff at the NIH-supported (RR00317) Regional Mass Spectrometry facility at MIT for recording mass spectra and assisting in their interpretation, and BASF for a generous gift of 3-methylbut-2-en-1-al.

Registry No. **2**, 21879-81-2; (±)-**2**, 97467-36-2; **4b**, 73912-36-4; **4c**, 52062-24-5; **6**, 14918-66-2; **10**, 67402-67-9; **18**, 13379-22-1; **19**, 97467-30-6; **20a**, 97485-97-7; **20b**, 97485-99-9; **20b** (regioisomer), 97486-00-5; **20c**, 97467-33-9; (±)-**21**, 97467-32-8; (±)-**21** (7-TMS ether), 97485-98-8; **22**, 67402-63-5; **23**, 67402-64-6; (±)-**24**, 97467-37-3; **28**, 97467-34-0; **28** (regioisomer), 97467-38-4; **30**, 97467-31-7; **31**, 67402-70-4; **31** (regioisomer), 97467-39-5; (±)-**32**, 97467-35-1; Ph_2CCl_2, 2051-90-3.

Supplementary Material Available: Tables of positional parameters, bond lengths, bond angles, and U values for the structure determination of (±)-**24** (5 pages). Ordering information is given on any current masthead page. Tables of calculated and observed structure factors (F_o and F_c) are available from the authors.

(23) $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $R_2 = [\sum\omega(|F_o| - |F_c|)^2/\sum\omega F_o^2]^{1/2}$, $\omega = 1/(\sigma(F_o))^2$, $\sigma(F_o) = \sigma(F_o^2)/2F_o$, $\sigma(F_o^2) = [(\sigma(I_{raw}))^2 + (0.04F_o^2)^2]^{1/2}$; ESD is the estimated standard deviation of an observation of unit weight.

Photoinduced Electron-Transfer Reactions of 2(3*H*)-Furanones and Bis(benzofuranones). Spectral and Kinetic Behavior of Radicals and Radical Cations[1]

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The spectral and kinetic behaviors of radical cations produced under efficient electron-transfer quenching of 1,4-dicyanonaphthalene or 9,10-dicyanoanthracene singlet by a number of 2(3*H*)-furanones and bis(benzofuranones) have been examined by nanosecond laser flash photolysis (337.1 and 425 nm). The efficiencies of net electron transfer in the course of quenching processes are moderately high (0.2–0.6) in acetonitrile. The radical cations from bis(benzofuranones) and several 2(3*H*)-furanones containing a benzyl group at the 3-position undergo fragmentation to benzofuranoxy and furanoxy radicals (+ benzyl or benzofuranoyl carbocations) with rate constants of 0.3–6 × 10^6 s^{-1}. The long-lived furanoxy radicals, independently generated via hydrogen abstraction by *tert*-butoxy radicals from 2(5*H*)-furanones and 3-phenyl-2(3*H*)-benzofuranone, as well as via direct photolysis of 3-benzoyl-3,5-diphenyl-2(3*H*)-furanone, are characterized by sharply structured absorption spectra and relatively slow second-order decay kinetics (6–8 × 10^8 M^{-1} s^{-1} in 1:2 benzene–di-*tert*-butyl peroxide, v/v).

Oftentimes, organic photoreactions leading to isomerization,[3] rearrangement/fragmentation,[4] small-molecule extrusion,[5] etc, occur as effectively under electron-transfer (e.t.) photosensitization as under direct irradiation. Characterization of the intermediates, namely, exciplexes, ion pairs, and radical ions, involved in phototransformations under e.t. sensitization, is critically important for understanding the related photochemical reaction mechanisms. In some cases, the radical ions undergo[6] clevage along a weak bond (intramolecular e.t.) giving ions and radicals; the latter then become the active species that undergo addition/disproportionation reactions, form peroxy radicals with oxygen, or initiate polymerization.

In a recent paper,[7] we have reported on the photochemistry of a number of 2(3*H*)-furanones and bis(benzofuranones) based on steady-state irradiation, product analysis, and laser flash photolysis. The two major pathways[7] for photoreactions of 2(3*H*)-furanones are singlet-mediated decarbonylation to α,β-unsaturated carbonyl compounds and cyclization leading to 4a,4b-dihydro-

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