of recovered nitro ester **25**.

Acid-Catalyzed Reaction of α-Ethoxycarbonylnitromethane with Substituted Benzenes. (A) *p*-Xylene. A similar reaction of α-ethoxycarbonylnitromethane (**25**) with xylene (10 equiv, 140 °C/760 mmHg) in the presence of TFSA (10 equiv) with methylene chloride as a cosolvent at 5 °C for 2 h gave the oxime **28** in 68% yield: mp 106–106.5 °C (recrystallized from *n*-hexane, colorless needles); anal. C$_{10}$H$_{11}$NO$_3$; ^{1}H NMR 7.16 (2 H, s), 6.97 (1 H, s), 4.33 (2 H, q, 7.3 Hz), 2.34 (3 H, s), 2.19 (3 H, s), 1.33 (3 H, t, 7.3 Hz); ^{13}C NMR 156.7 (s), 155.1 (s), 148.3 (s), 110.7 (s), 63.6 (t, 146.7 Hz), 13.9 (q, 129.1 Hz).

The corresponding sodium salt of α-ethoxycarbonylnitromethane (**27**) also reacted with *p*-xylene in the presence of TFSA (10 equiv) at 5 °C for 4 h to give the oxime **28** (62% yield) and diethoxycarbonylfuroxane (22% yield).

(B) Anisole. A similar reaction of α-ethoxycarbonylnitromethane (**25**) with anisole (10 equiv, 85 °C/70 mmHg) in the presence of TFSA (10 equiv) at 10 °C for 28 h gave a mixture of the oximes **29** in 86% yield (*o*/*p* ratio 1:2. estimated from the ^{1}H NMR spectra). *p*-**29**: mp 124–125.5 °C (recrystallized from *n*-hexane, colorless needles); anal. C$_{11}$H$_{13}$NO$_4$; ^{1}H NMR 7.54 (2 H, d, 8.4 Hz), 6.96 (2 H, d, 8.8 Hz), 4.36 (2 H, q, 7.3 Hz), 3.85 (3 H, s), 1.37 (3 H, t, 7.3 Hz). *o*-**29**: 7.40 (1 H, t, d, 7.9 Hz, 1.8 Hz), 7.36 (1 H, d, d, 7.7 Hz, 1.83 Hz), 7.02 (1 H, t, 7.7 Hz), 6.96 (1 H, d, 8.4 Hz), 4.30 and 4.12 (2 H, q, 7.3 Hz), 3.78 (3 H, s), 1.29 and 1.25 (3 H, t, 7.3 Hz).

The corresponding sodium salt of α-ethoxycarbonylnitromethane (**27**) also reacted with *p*-xylene in the presence of TFSA (10 equiv) at 5 °C for 4.5 h to give a mixture of the oximes **29** (51% yield, *o*/*p* ratio 1:3.3) and diethoxycarbonylfuroxane (15% yield).

Acid-Catalyzed Reaction of α-Benzoylnitromethane with Benzene. The acid-catalyzed reaction of α-benzoylnitromethane (**30**) with benzene was performed as described in the case of α-ethoxycarbonylnitromethane (**25**). α-Benzoylnitromethane (**30**) was allowed to react in a mixture of TFSA (3.5 mL, 10 equiv) and benzene (3.5 mL, 10 equiv) with methylene chloride (4 mL) as a cosolvent at 5 °C for 2 h. The residue, obtained by aqueous workup. was purified by flash column chromatography with (CH$_2$CL$_2$–*n*-hexane 2:1) to give 639 mg (71%) of benzil monooxime (**31**), together with 28.6 mg (6%) of benzaldoxime (**32**) and 26.6 mg (5%) of benzoic acid (**33**). **31**: mp 134–138.5 °C (recrystallized from *n*-hexane); anal. C$_{14}$H$_{11}$NO$_2$; ^{1}H NMR 8.02 (2 H, d, d, 8.6 Hz, 1.5 Hz), 7.62–7.58 (3 H, m), 7.48 (2 H, t, 7.7 Hz), 7.45–7.26 (3 H, m). The two byproducts **32** and **33** were identical with the authentic samples in terms of the IR and ^{1}H NMR spectra.

Acid-Catalyzed Reaction of α-Benzoylnitromethane with Substituted Benzenes. (A) *p*-Xylene. A similar reaction of α-benzoylnitromethane (**30**) with *p*-xylene (10 equiv) in the presence of TFSA (10 equiv) at 0

°C for 1.5 h gave **34** in 72% yield, (2,5-dimethylphenyl)carboaldoxime (**35**) in 21% yield, benzoic acid (**33**) in 11% yield, and 2,5-dimethylbenzophenone (**36**) in 4% yield. **34**: mp 132–133 °C (recrystallized from *n*-hexane, colorless needles); anal. C$_{16}$H$_{15}$NO$_2$; ^{1}H NMR 8.07 (2 H, d, d, 8.3 Hz, 1.5 Hz), 7.96 (1 H, bs, OH), 7.61 (2 H, t, t, 7.3 Hz, 1.5 Hz), 7.49 (2 H, t, 7.33 Hz), 7.19 (1 H, d, 7.69 Hz), 7.15 (1 H, d, d, 8.43 Hz, 1.5 Hz), 7.03 (1 H, s), 2.35 (3 H. s), 2.24 (3 H, s). **35**: mp 64–64.5 °C (recrystallized from *n*-hexane, colorless cubes); anal. C$_9$H$_{11}$NO; ^{1}H NMR 8.64 (1 H, bs, OH), 8.40 (1 H, s), 7.48 (1 H, s), 7.10 (1 H, d, 8.1 Hz), 7.07 (1 H, d, 7.7 Hz), 2.38 (3 H, s), 2.32 (3 H, s); mass spectrum (*m*/*e*) 149. **33** was identical with an authentic sample in terms of IR and ^{1}H NMR spectra. **36** was identical with an authentic sample, prepared from the acid-catalyzed reaction of benzoic acid with *p*-xylene in the presence of TFSA at room temperature for 5 h (68% yield), in terms of the IR and ^{1}H NMR spectra: ^{1}H NMR 7.81 (2 H, d, 8.1 Hz), 7.58 (1 H, t, 7.3 Hz), 7.49 (2 H, t, 7.7 Hz), 7.20 (1 H, d, 7.7 Hz), 7.17 (1 H, d, 7.7 Hz), 7.12 (1 H, s), 2.33 (3 H, s), 2.27 (3 H, s).

(B) Anisole. A similar reaction of α-benzoylnitromethane (**30**) with anisole (10 equiv) in the presence of TFSA (10 equiv) at 5 °C for 2.5 h gave the phenylated oximes **37** in 73% yield (*o*/*p* ratio 2:3, estimated from the ^{1}H NMR spectra). *o*-**37**: ^{1}H NMR 8.02 (2 H, d, d, 7.9 Hz, 1.83 Hz), 7.57 (2 H, m), 7.46 (2 H, t, 7.7 Hz), 7.41 (1 H, t, 7.32 Hz), 7.06 (1 H, t, 7.3 Hz), 6.94 (2 H, d, 8.8 Hz), 3.80 (3 H, s). *p*-**37**: 7.99 (2 H, d, d, 8.1 Hz, 1.5 Hz), 7.64 (2 H, d, 8.8 Hz), 7.58 (1 H, t, 7.3 Hz), 7.46 (2 H, t, 7.7 Hz), 6.94 (2 H, d. 8.8 Hz), 3.83 (3 H, s).

Calculation Methods. The calculations were performed at the Computer Center of the University of Tokyo. The ab initio calculations were carried by using a modified version of the Gaussian 80 computer programs (Gaussian 80H).[48] Structures of neutral molecules and cations were optimized by using Martaugh–Sargent gradient optimization techniques and the standard 4-31G basis set.[13] The optimizations were done with the assumed restriction of C_s symmetry for all species, except for H$_2$O (C_{2v}), NH$_3$ (C_{3v}), and **11** (C_{2v}). To estimate the energetics accurately, single-point calculations on 4-31G-optimized geometries were also performed with d-polarized 6-31G*.[16]

Preparation and NMR Studies of Ions in Acids. All samples of ions in TFSA and TFSA–SbF$_5$ (2.5:1, mole ratio) were prepared below −45 °C in a dry ice-ethanol bath. The digital resolutions in the observed NMR spectra are as follows: ±0.49 Hz in ^{1}H NMR and ±2.9 Hz in ^{13}C NMR spectra. Other experimental details have been described previously.[5a]

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An Entry to the Ring B:Ring C Bishydroquinone Leucodaunomycin Series Containing an Intact Carbohydrate

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Abstract: It has been found that diacetylation of the phenolic hydroxyl groups at C-6 and C-11 of daunomycin provides a product (see compound **12**) that undergoes reduction of the ring C quinone to a hydroquinone without loss of the glycosyloxy function at C-7. Access to a stable heptaacetate (see compound **14**) incorporating the nuclear bishydroquinone ensemble is thus provided. Basic hydrolysis of **14** accompanied by oxidation restores *N*-acetyldaunomycin. The success of this reaction reveals a surprising resistance to quinone methide formation via such leuco intermediates.

Introduction and Scope of the Investigation

It has been claimed[1] that the spectrum of applications of the anthracycline antibiotics[2] (see daunomycin (**1a**) and adriamycin (**1b**)) in cancer chemotherapy is second only to that of the classical alkylating agents. Of the naturally occurring antitumor compounds, the anthracyclines are the most widely used. The considerable efforts that have been expended in understanding the

chemistry of the anthracyclines and their interactions with other biomolecules have identified a variety of possibilities for their mechanism(s) of action.[3,4] Among the pathways that have been
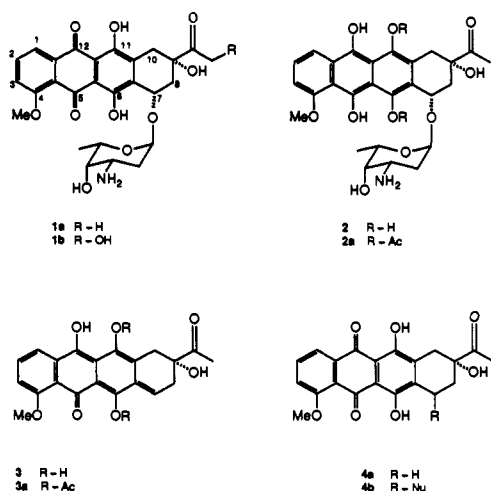
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(1) Myers, C. E., Jr.; Chabner, B. A. In *Cancer Chemotherapy*; Chabner, B. A., Collins, J. M., Eds; J. B. Lippincott: Philadelphia, 1990; Chapter 14, p 356.
(2) (a) Lown, J. W., Ed. *Anthracycline and Anthracenedione-Based Anticancer Agents*; Elsevier: Amsterdam, 1988. (b) Suarato, A.; Angelucci, F.; Bargiotti, A. *Chim. Oggi* **1990**, *8*, 9. (c) Arcamone, F. *Med. Res. Rev.* **1984**, *4*, 153.

Chart I

Scheme I

advanced to account for DNA damage and cytoxicity are (i) intercalation, (ii) inhibition of topoisomerase II activity, (iii) formation of hydroxyl and superoxide radical species via one-electron reduction of the quinone chromophore, and (iv) formation of quinone methide type alkylating species via reduction. Indeed, several of these pathways may be operative in vivo both in accomplishing antineoplastic activity and in causing side effects such as cardiotoxicity or myelosuppression.

The chemistry that is triggered upon overall two-electron reduction of the of the anthracyclines has been investigated in some detail. A picture has evolved wherein the presumed bishydroquinone 2, arising from reduction of 1, suffers rapid loss of the glycosyloxy group at C-7 resulting in an electrophilic quinone methide entity of the type 3 (see Chart I). This species might react with various bionucleophiles.[5] Trapping of the quinone methide has been demonstrated in vitro with several nucleophiles (vide infra).

The precise kinetic details of the expulsion of the glycosyloxy group at C-7 from intermediate 2 are difficult to ascertain because this compound, with the intact sugar, has not been obtained or spectroscopically characterized in detail. The usual fate of reductions of systems such as 1, in the absence of competing nucleophiles, is the formation of the 7-deoxydaunomycinone (4a), presumably via protonation of quinone methide 3.

Pivotal contributions in facilitating the understanding of the reduction chemistry of anthracyclines have been provided by Fisher[6,7] and by Koch.[8,9] Fisher, using sodium dithionite as the reducing agent, described the trapping of the presumed quinone methide 3 by various nucleophiles (NuH) to give, upon oxidation, 4b.[6] Furthermore, the 7-deoxydaunomycinone (4a), produced by tautomerization of 3, can suffer further reduction to the leucodesoxy system 5.[7] The latter can undergo further tautomerization to afford the epimeric mixture of diketones 6. Alternatively, 5 is converted to 7 and 8, presumably by related prototropic routes that lead to alternate possibilities for dehydration (see Scheme I, proposed intermediates 7a and 8a).

Koch and colleagues have made extensive use of 2-oxomorpholin-3-yl radicals of the type 9 as reducing agents to foster quinone methide formation.[8] This kind of reducing agent has been proposed as part of a chemotherapeutic strategy to detoxify adriamycin recipients after administration of large and therapeutically useful doses of the drug.[8d] The detoxification arises from loss of the sugar moiety with formation of the 7-deoxy system, which is apparently biologically inactive.[1,10]

Koch's work with dithionite as the reducing agent identified another pathway wherein the presumed hydroquinone 2, at pH ~3, undergoes bisketonization of the B ring to deliver a mixture of ketone epimers 10 with the glycoside bond intact.[9] Treatment of one isomer of 10 at pH 7.4 generates transiently the presumed 2 (λ_{max} 420 nm) and shortly thereafter the quinone methide 3 (λ_{max} 620 nm). The latter undergoes trapping at C-7 with indigenous nucleophile (cf., formation of the N-acetyl-L-cysteine adduct 11).

We began this investigation by posing a simple question: Can the stability of a bishydroquinone-type system (cf., 2) be enhanced by acylation of its two phenolic hydroxyl groups? The hope was that such acylation would erode the "internal nucleophilicity" of the system with respect to quinone methide formation. Therefore, the activation energy required to go from 2a to 3a would be higher than is involved in going from 2 → 3. Accordingly, we hoped to gain access to stable compounds containing the ring B:ring C bishydroquinone network of the anthracyclines with the carbohydrate *intact*. From that point, one could probe the chemistry of such systems. These expectations have been realized. *In the following text we report on the first stable anthracyclines containing the carbohydrate system in the context of the ring B:ring C bishydroquinone.*

Discussion of Results

Our initial experiment, conducted for purposes of reference and orientation, involved reduction of daunomycin hydrochloride (1a·HCl) in pyridine with hydrogen over palladium. Workup after 3 min afforded a near-quantitative yield of 7-deoxydaunomycinone (4a).

We then prepared the pentaacetate 12[11a] (mp 259 °C) by treatment of a solution of 1a in pyridine with acetic anhydride in the presence of 4-(dimethylamino)pyridine. While there would

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(4) Lown, J. W. *Mol. Cell. Biochem.* 1983, *55*, 17.

(5) (a) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* 1981, *1*, 249. (b) Moore, H. W.; Czerniak, R.; Hamdan, A. *Drugs Exp. Clin. Ref.* 1986, *12*, 475. (c) Moore, H. W. *Science* 1977, *197*, 527.
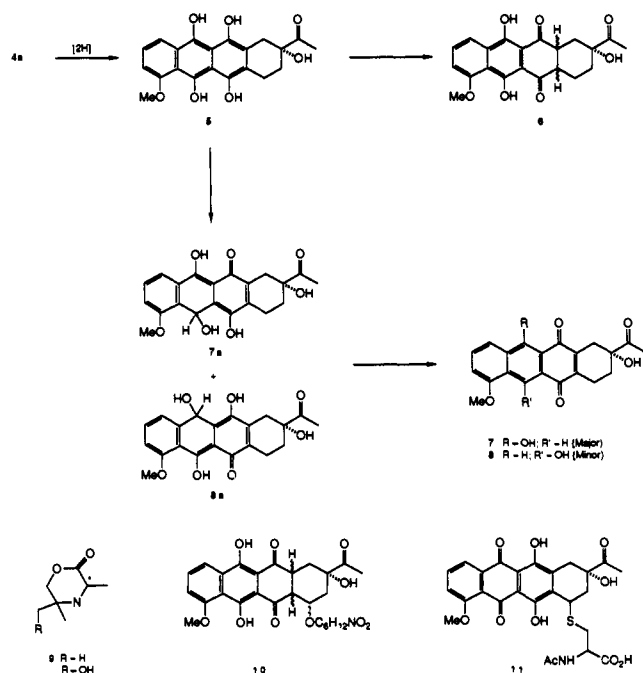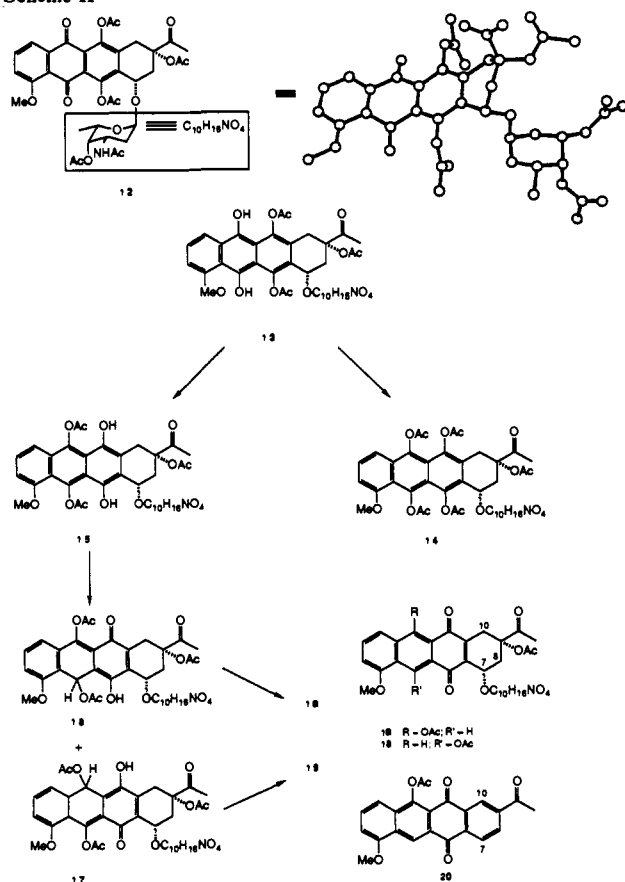
(6) (a) Ramakrishnan, K.; Fisher, J. *J. Med. Chem.* 1986, *29*, 1215. (b) Ramakrishnan, K.; Fisher, J. *J. Am. Chem. Soc.* 1983, *105*, 7187.

(7) Systems 6 and 10 have been referred to as leucodaunomycins. In this paper, the term leucodaunomycin is reversed for the B:C bishydroquinone chromophore. (a) Brand, D. J.; Fisher, J. *J. Am. Chem. Soc.* 1986, *55*, 2518. (b) Brand, D. J.; Fisher, J. *J. Am. Chem. Soc.* 1986, *108*, 3088.

(8) (a) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* 1984, *106*, 2380. (b) Gaudiano, G.; Koch, T. H. *J. Org. Chem.* 1987, *52*, 3073. (c) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* 1983, *105*, 2504. (d) Averbuch, S. D.; Gaudiano, G.; Koch, T. H.; Bachur, N. R. *J. Clin. Oncol.* 1986, *4*, 88.

(9) Bird, D. M.; Boldt, M.; Koch, T. H. *J. Am. Chem. Soc.* 1989, *111*, 1148.

(10) Averbuch, S. D.; Gaudiano, G.; Koch, T. H.; Bachur, N. R. *Cancer Res.* 1985, *45*, 6200.

(11) (a) Arcamone, F.; Cassinelli, G.; Franceschi, G.; Mondelli, R.; Orezzi, P.; Penco, S. *Gazz. Chim. Ital.* 1970, *100*, 949. (b) Mondelli, R.; Ragg, E.; Fronza, G. *J. Chem. Soc., Perkin Trans. 2* 1987, 27.

B;C Bishydroquinone Leucodaunomycin Series

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Scheme II

Scheme III

ordinarily be no need to question the assignment of this compound, some of its subsequent chemistry (see formation of compounds **18** and **19**) was sufficiently anomalous that we deemed it prudent to rigorously confirm its structure. A single-crystal X-ray determination indeed established the pentaacetate to be **12**.[12]

Catalytic hydrogenation of **12** was carried out as described previously. In one set of conditions, reduction was conducted in the presence of acetic anhydride (Scheme II). There was isolated the target heptaacetate **14** (mp 190 °C), whose structure was established by spectroscopic and analytic means. It was presumed that **14** arose from acetylation of the bishydroquinone derivative **13**. The intermediacy of structure **13** was suggested by executing the reduction and diacetylation phases as discrete steps. Thus, reduction of **12** was carried out for 15 min under the same conditions as were used for **1a·HCl**. To the resulting fluorescent solution of presumed intermediate **13** was added acetic anhydride. This two-step procedure again provided the heptaacetate **14**. While the corresponding acylated bishydroquinone had been reported by Koch in the 7-deoxy series,[13] *compound **14** is the first instance of a characterized anthracycline that contains the ring B:ring C bishydroquinone ensemble with the glycosyloxy function at C-7 in place.*
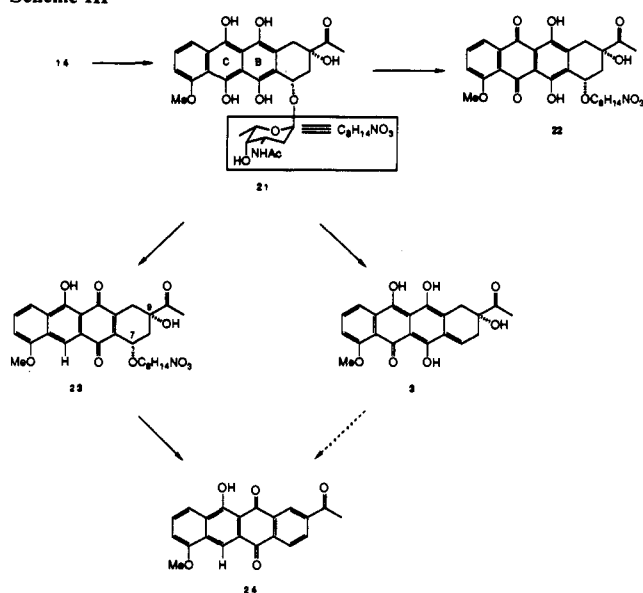
When the pyridine solution, presumed to contain dihydropentaacetate **13**, was maintained under anaerobic conditions for 2 h and worked up, three characterized products in the ratio of 1.8:9.2:1.0 were separated by HPLC.[14] The isomeric tetraacetates **18** and **19** were the first to be eluted, with the former predominating. The structural assignments of **18** and **19** were fully supported by spectroscopic and analytic measurements. Decisive in distinguishing the two compounds were the NMR proton shifts of the aryl hydrogens of ring C (for **18** δ 9.04; for **19** δ 8.52) in

conjunction with data previously reported by Fisher[7] in the 7-deoxy series.

The formation of **18** or **19** from **13** does not entail any change of overall oxidation level. Two acyl migrations would give rise to **15**. The latter could tautomerize to produce either **16** or **17**. Aromatization via β-elimination of acetic acid from **16** leads to **18**, while the corresponding elimination on intermediate **17** leads to **19**. A related route to a 5-deoxyanthracycline via hydrogenation over platinum(IV) oxide was reported by Cameron[15] (in contrast to other catalysts that led to deoxygenation at C-7).

The product with the longest retention time was assigned structure **20**. This structure is in accord with spectral and analytical measurements. The position of the ring C acetoxyl function was demonstrated by the fact that the same compound could be obtained by treatment of **18** with pyridine. Presumably, **20** arises from deprotonation at C-10 followed by loss of the acetate group. With the C-10–C-9 double bond in place, aromatization of the A ring via deprotonation at C-8 and loss of the glycosyloxy group at C-7 would be expected to rapidly follow.

The stage was now set to probe the stability of **21**, the N-acetyl version of the generic bishydroquinone **2**. Compound **14** was treated with 7 equiv of lithium hydroxide in THF under argon. The six oxygen-bound acetyl groups were cleaved. After adjustment of the pH to 7, molecular oxygen was admitted. There was obtained a 43% yield of **22**, the N-acetyl derivative of **1a** (Scheme III).[11,16] *Remarkably, deacetylation and air oxidation had been accomplished in a moderately efficient way without interdiction by quinone methide formation.* Apparently, the bishydroquinone system **21** enjoys reasonable stability when approached via a hydrolytic pathway as opposed to a reductive route (vide supra).[17] A possible interpretation is that the entity undergoing expulsion of the C-7 hetero group in the previous works may not be the bishydroquinone **2**, but an intermediate along the reduction/tautomerization pathway.

The hydrolysis of heptaacetate under more basic conditions (14 equiv) of lithium hydroxide was also probed. When cleavage of all esters was assumed to be complete, oxygen was admitted to the system. Under these conditions there was isolated a 40% yield of **24**. This compound was also obtained by hydrolysis of the previously described **18** with lithium hydroxide. This latter

(12) The protocol for the crystallography on compound **12** is found in the supplementary material, together with the data.

(13) Barone, A. D.; Atkinson, R. F.; Wharry, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 1606.

(14) A fourth product, the structure of which has yet to be fully delineated, comprised ~9% of the product mixture.

(15) Cameron, D. W.; Feutrill, G. I.; Griffiths, P. G. *Tetrahedron Lett.* **1988**, 4629.

(16) As in the case of daunomycin hydrochloride, catalytic reduction (H_2 and 10% Pd/C in pyridine) of N-acetyldaunomycin provides 7-deoxydaunomycinone.

(17) We emphasize that the bishydroquinone system (i.e., **21**) has not been characterized. However, the conversion of **14** to **22** has passed, minimally, through a diacetyl bishydroquinone.

transformation is a counterpart of the process wherein treatment of **18** with the milder base, pyridine, affords **20** (vide supra).

A likely formulation is that the route from heptaacetate **14** to the ring A aromatic compound **24** passes through the phenolic version of **18**, i.e., **23**. This intermediate presumably arose from the bishydroquinone system **21** via a progression analogous to that proposed for the formation of **18** from **13**, using proton shifts[7b] rather than acetyl migrations. The transformation of **23** to **24** presumably involves two β-eliminations (first the C-9 oxygen and the C-7 oxygen with concurrent aromatization) and does not necessitate changes in the overall oxidation level of the molecule.

Thus, two lines of chemistry during hydrolysis of heptaacetate **14** have been identified. Under the mild conditions, the acetates are cleaved and the product bishydroquinone undergoes subsequent air oxidation to give rise to **22**. Under somewhat more forcing conditions, the bishydroquinone system undergoes what is effectively internal redox chemistry, wherein the B ring is oxidized and the C ring is deoxygenated (see formation of **24**). While the C-7 glycosyloxy group has indeed been eliminated, this would seem to have occurred via **23** rather than through quinone methide **3**. Though a pathway from such a hypothetical quinone methide involving deoxygenation at C-5 could be proposed, it would invoke the occurrence of a more complex sequence of events.

Summary

Routes to ring B:ring C bishydroquinone versions of dihydro-daunomycin have been achieved. The heptaacetate **14** has been fully characterized. The intermediacy of the pentaacetates of **13** and **15** is strongly inferred from the formation of **14** from the former and **18** (as well as **19**) from the latter. There is no demonstrated tendency for **13** (or **15**) to unravel to acylated versions of quinone methides. More surprising is the resistance of the postulated bishydroquinone intermediate **21** to undergo quinone methide formation by expulsion of N-acetyldaunosamine from C-7. When generated under relatively neutral conditions, **21** survives until it is oxidized to **22**, wherein the C-7 glycosyloxy group is intact. Under more strongly basic conditions, the sugar function is eventually eliminated (see formation of **24**). However, even in this transformation, the most straightforward mechanism would not pass through quinone methide **3**. Rather, the ejection of daunosamine is most likely to occur at a late stage (cf., **23** → **24**).

While a full integration of our findings with earlier results from other laboratories awaits further experimentation, it is already appropriate to reevaluate the simple construct embodied in the progression of **1** → **2** → **3**. Since the presumption of the near spontaneity of the conversion of **2** → **3** is now open to considerable question, it is not beyond belief that a better understanding of the way in which anthracyclines operate in vivo could be gained from such continued inquiries.

Experimental Section

General Data. Anhydrous pyridine and 10% palladium over carbon was purchased from the Aldrich Chemical Co. Buffer (pH 7.00, standard buffer solution) was obtained from Mallinckrodt Chemical Co. Tetrahydrofuran was distilled from deep blue solutions of benzophenone ketyl and further deoxygenated by passing argon through the solvent for 0.5 h. The solutions of lithium hydroxide were freeze–pump–thawed four times. Unless otherwise stated, all reactions were run at room temperature. Liquid chromatographic HPLC was performed on a Waters Model 510 dual-pump system, a Rainin Microsorb C18 column (10 mm × 25 cm, 5-μm particle size), and a Waters Model 440 absorbance detector. The detection of products was done at 254 nm, and the values are not corrected for variation in extinction coefficient. Column chromatography was carried out on silica gel buffered with KH_2PO_4 prepared by stirring a mixture of silica gel 60 (E. Merck 9285, 230–400 mesh, 125 g) in an aqueous solution of 2% KH_2PO_4 for 1 h, and then the silica gel was collected, air-dried, and dried in an oven overnight. Thin-layer chromatographic analysis was conducted on 0.25-mm silica gel plates with a 254-nm ultraviolet indicator (E. Merck silica gel 60 F-254). Spectroscopic analysis was carried out on the following instruments: IR, Perkin-Elmer 1420; UV–vis, Cary 219; NMR, 250-MHz, Brucker WM 250. High-resolution (EI, CI, and FAB) mass spectrometric analyses were conducted on a Kratos MS 80 RFA. Positive ion fast atom bombardment mass spectral data were acquired by use of a 3-nitrobenzyl

alcohol matrix containing sodium iodide. Low-resolution mass spectrometric analyses were conducted on a Hewlett-Packard 5985 mass spectrometer. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Optical rotations were taken on a Perkin-Elmer 241 polarimeter.

7-Deoxydaunomycinone (4a). A stream of argon was passed through a solution of daunomycin hydrochloride (**1a·HCl**; 9.4 mg, 0.017 mmol) in pyridine (1 mL) for 15 min. To the orange solution was then added 10% palladium over carbon (2–3 mg) and hydrogen passed through the mixture for 3 min. The reaction mixture was diluted with dichloromethane (25 mL) and washed with 10% $CuSO_4$ (3 × 10 mL), water (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford 5 mg of **4a** as a red solid: mp 232.0–233.0 °C (lit.[18] mp 229–231 °C); ^1H NMR (CDCl$_3$, 250 MHz) δ 13.85 (s, 1 H, phenolic OH), 13.47 (s, 1 H, phenolic OH), 8.02 (d, 1 H, J = 7.7 Hz, H-1), 7.76 (app t, 1 H, J = 7.4 Hz, H-2), 7.40 (d, 1 H, J = 8.4 Hz, H-3), 4.08 (s, 3 H, 4-OCH$_3$), 3.80 (s, 1 H, 9-OH), 3.22–2.89 (m, 4 H, H$_2$-7, H$_2$-10), 2.39 (s, 3 H, 9-COCH$_3$), 2.03–1.88 (m, 2 H, H$_2$-8); IR (CHCl$_3$) 3500, 3020, 1705, 1615, 1585, 1445, 1410, 1285, 1255 cm^{-1}.

Pentaacetate 12. To a solution of daunomycin hydrochloride (40 mg, 0.071 mmol) and 4-(dimethylamino)pyridine (2–3 mg) in pyridine (1.5 mL) was added acetic anhydride (0.50 mL, 4.52 mmol). The reaction mixture was stirred for 5 days, diluted with dichloromethane (50 mL), and washed with 10% $CuSO_4$ (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was chromatographed on 2% KH_2PO_4–silica gel (20:1 chloroform–methanol) to afford 48 mg (92%) of **12** as a yellow solid. Recrystallized from methanol: mp 259–260 °C (lit.[11] mp 268–270 °C); [α]$^{22}_D$ = +19.9° (c 0.2, CHCl$_3$); ^1H NMR (CDCl$_3$, 250 MHz) δ 7.71 (d, 1 H, J = 7.7 Hz, H-1), 7.63 (app t, 1 H, J = 8.2 Hz, H-2), 7.25 (d, 1 H, J = 9.7 Hz, H-3), 5.26 (d, 1 H, J = 7.5 Hz, H-7), 5.11 (m, 2 H, H-1′, H-4′), 4.45 (m, 1 H, H-3′), 4.24 (q, 1 H, J = 6.3 Hz, H-5′), 3.96 (s, 3 H, 4-OCH$_3$), 3.40–3.08 (m, 2 H, H$_2$-10), 2.61 (m, 2 H, H$_2$-8), 2.49 (s, 3 H, aromatic OAc), 2.48 (s, 3 H, aromatic OAc), 2.18 (s, 3 H), 2.17 (s, 3 H), 2.13 (s, 3 H), 1.87 (s, 3 H, NHAc), 1.87–1.75 (m, 2 H, H$_2$-2′), 1.13 (d, 3 H, J = 6.5 Hz, 5′-CH$_3$); ^{13}C NMR (CDCl$_3$, 62.9 MHz)[19] δ 204.4 (C-13), 182.0 (C-12), 181.1 (C-5), 171.3, 170.6, 169.2 (2 C), 168.9 (4 OAc, NHAc), 159.5 (C-4), 145.7, 145.2 (C-11, C-6), 136.7, 135.9, 135.4 (C-12a, C-10a, C-6a), 134.8 (C-2), 126.0, 125.2 (C-5a, C-11a), 122.4 (C-4a), 119.3 (C-1), 117.9 (C-3), 98.0 (C-1′), 81.8 (C-9), 71.2, 67.2 (C-3′, C-4′), 66.1 (C-7), 56.7 (4-OCH$_3$), 43.8 (C-5′), 34.9 (C-2′), 30.6 (C-10), 29.5 (C-8), 23.3, 23.1, 21.4, 21.2, 21.0, 20.7 (4 OAc, NHAc, COCH$_3$), 17.0 (C-6′); IR (CHCl$_3$) 3430, 3020, 1770, 1735, 1680, 1585, 1370, 1190, 1025 cm^{-1}; UV–vis λ$_{max}$ (MeOH) 384 (ε 4500) 254 (26000), 220 (26500); HRMS (FAB) m/e 760.2198 (M + Na)$^+$, calcd for C$_{37}$H$_{39}$O$_{15}$NNa 760.2218. Anal. Calcd for C$_{37}$H$_{39}$O$_{15}$N: C, 60.24; H, 5.33; N, 1.90. Found: C, 59.68; H, 5.31; N, 1.84.

Heptaacetate 14. To a solution of daunomycin hydrochloride (25 mg, 0.044 mmol) and 4-(dimethylamino)pyridine (2–3 mg) in pyridine (0.75 mL) was added acetic anhydride (0.25 mL, 2.26 mmol). After 5 days, 10% palladium over carbon (1–2 mg) was added and hydrogen passed through the solution for 15 min. Stirring was continued for 20 h. The reaction mixture was diluted with dichloromethane (25 mL) and washed with 10% $CuSO_4$ (3 × 10 mL), water (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was chromatographed on 2% KH_2PO_4–silica gel (20:1 chloroform–methanol) to afford 24 mg (66%) of **14** as a yellow solid: mp 190 °C dec; [α]$^{22}_D$ = +32.3° (c 0.2, CHCl$_3$); ^1H NMR (CDCl$_3$, 250 MHz) δ 7.48 (m, 1 H), 7.42 (t, J = 7.9 Hz, 1 H), 6.81 (d, J = 7.0 Hz, 1 H), 5.42 (m, 1 H), 5.28 (d, J = 8.2 Hz, 1 H), 5.15 (d, J = 8.0 Hz, 1 H), 5.03 (m, 1 H), 4.60 (m, 1 H), 4.20 (m, 1 H), 3.95 (s, 3 H), 3.10 (m, 2 H), 2.48 (br s, 14 H), 2.24 (br s, 3 H), 2.18 (br s, 3 H), 2.04 (s, 3 H), 1.91 (br s, 3 H), 1.80–1.75 (m, 2 H), 1.17 (d, J = 6.5 Hz, 3 H); ^1H NMR (pyr-d_5, 332 K, 250 MHz) δ 7.70 (d, 1 H, J = 8.7 Hz, H-1), 7.36 (t, 1 H, J = 8.3 Hz, H-2), 6.78 (d, 1 H, J = 7.7 Hz, H-3), 5.57 (br s, 1 H, H-1′), 5.31 (m, 1 H, H-7), 5.01 (m, 1 H, H-4′), 4.38 (m, 2 H, H-3′, H-5′), 3.82 (s, 3 H, 4-OCH$_3$), 3.53 (br d, J = 15.5 Hz, 1 H, H-10), 2.97 (m, 1 H, H-10), 2.61 (s, 3 H), 2.53 (s, 3 H), 2.50 (m, 2 H, H$_2$-8), 2.50 (s, 6 H), 2.34 (s, 3 H), 2.19 (s, 3 H), 2.05 (m, 1 H, H-2′$_{eq}$), 1.98 (s, 3 H), 1.97 (s, 3 H), 1.72 (dd, 1 H, J = 10.8, 2.1 Hz, H-2′$_{ax}$), 1.29 (d, 3 H, J = 6.4 Hz, 5′-CH$_3$); IR (CHCl$_3$) 3440, 3000–2900, 1770, 1735, 1680, 1510, 1370, 1200 cm^{-1}; UV–vis λ$_{max}$ (MeOH) 418 (ε 3100)

(18) Gleim, R. D.; Trenbeath, S.; Mittlal, R. S. D.; Sih, C. J. *Tetrahedron Lett.* **1976**, 3385.

(19) Chemical shift assignments for the carbons of daunomycinone tetra-acetate, see: Casey, M. L.; Paulick, R. C.; Whitlock, H. W. *J. Org. Chem.* **1978**, 43, 1627.

395 (4000), 380 (4400), 362 (2600), 271 (44 000), 252 (25 000); HRMS (FAB) m/e 846.2581 (M + Na)$^+$, calcd for $C_{41}H_{45}O_{17}NNa$ 846.2584. Anal. Calcd for $C_{41}H_{45}O_{17}N$ + H_2O: C, 58.49; H, 5.63; N, 1.66. Found: C, 58.84; H, 5.61, 1.84.

Reduction of Pentaacetate 12. A stream of argon was passed through a solution of pentaacetate **12** (190 mg, 0.258 mmol) for 15 min. To the yellow solution was then added 10% palladium over carbon (2–3 mg) and hydrogen passed through the mixture for 15 min. After the solution was stirred under an atmosphere of argon for 2 h, a stream of oxygen was passed through the mixture for 2 min, followed by dilution with dichloromethane (20 mL). The orange solution was washed with 10% $CuSO_4$ (4 × 20 mL), water (20 mL), and finally brine (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The composition of this product mixture (as determined by reversed-phase liquid chromatography) is as follows: **18**, 64%; **19**, 15%; **20**, 12%; and an unknown compound, 9%. The mixture was chromatographed on 2% KH_2PO_4–silica gel (gradient elution, chloroform to 20:1 chloroform–methanol) to afford **20** as an orange solid and a mixture of **18** and **19**. The major product, **18**, was selectively crystallized from methanol overnight. A sample of **19** was obtained by semipreparative reversed-phase chromatography with a mobil phase of 85% methanol and 15% water at a flow rate of 3.0 mL/min.

Naphthacene derivative 20: R_t = 11.73 min; mp 258.0 °C dec; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 9.30 (d, 1 H, J = 0.5 Hz, H-5), 8.83 (d, 1 H, J = 1.7 Hz, H-10), 8.47 (d, 1 H, J = 8.1 Hz, H-7), 8.36 (dd, 1 H, J = 8.2, 1.7 Hz, H-8), 7.75 (d, 1 H, J = 8.2 Hz, H-1), 7.67 (app t, 1 H, J = 7.4 Hz, H-2), 7.07 (d, 1 H, J = 7.4 Hz, H-3), 4.10 (s 3 H, 4-OCH$_3$), 2.76 (s, 3 H, 9-COCH$_3$), 2.69 (s, 3 H, 12-OAc); IR (CHCl$_3$) 3010, 1770, 1680, 1615, 1425, 1295, 1270, 1245 cm^{-1}; UV–vis λ_{max} (CHCl$_3$) 437 (ε 3000), 320 sh (1500), 305 (4500), 293 (5400), 265 (27 800); HRMS (CI) m/e 389.1025 (M + H)$^+$, calcd for $C_{23}H_{17}O_6N$ 389.1022.

Tetraacetate 18: R_t = 6.50 min; mp 248.0–249.0 °C; $[\alpha]^{22}_D$ = +22.2° (c 0.02, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 250 MHz) δ 9.04 (s, 1 H, H-5), 7.68 (d, 1 H, J = 8.2 Hz, H-1), 7.63 (app t, 1 H, J = 7.2 Hz, H-2), 7.04 (dd, 1 H, J = 7.1, 1.3 Hz, H-3), 5.69 (br s, 1 H, H-1′), 5.31 (d, 1 H, J = 8.2 Hz, NHAc), 5.09 (br s, 1 H, H-4′), 5.05 (br d, 1 H, J = 5.4 Hz, H-7), 4.36 (m, 1 H, H-3′), 4.19 (q, 1 H, J = 6.6 Hz, H-5′), 4.05 (s, 3 H, 4-OCH$_3$), 3.26 (app d, J = 19.3 Hz, 1 H, H-10), 2.78 (app d, J = 15.8 Hz, 1 H, H-8), 2.60 (s, 3 H, aromatic OAc), 2.49 (app d, J = 19.4 Hz, 1 H, H-10), 2.23 (s, 3 H), 2.22 (s, 4 H), 2.20 (s, 3 H), 1.88 (s, 3 H, NHAc), 1.84 (m, 2 H, H$_2$-2′), 1.15 (d, 3 H, J = 6.6 Hz, 5′-CH$_3$); ^{13}C NMR (CDCl$_3$, 62.9 MHz) δ 205.6 (C-13), 188.0 (C-11), 182.9 (C-6), 171.6, 170.9, 169.2, 168.9 (3OAc, NHAc), 157.3 (C-4), 147.5 (C-12), 143.0, 141.0 (C-6a, C-10a), 131.4, 130.7 (C-5a, C-2), 127.9 (C-4a), 122.0 (C-12a), 118.5 (C-5), 115.5 (C-1), 110.0 (C-11a), 108.2 (C-3), 100.0 (C-1′), 81.3 (C-9), 71.6, 68.0 (C-3′, C-4′), 66.1 (C-7), 55.9 (4-O-CH$_3$), 44.0 (C-5′), 32.0, 31.3, 30.7 (C-10, C-8, C-2′), 23.4, 23.1, 21.5, 21.1, 20.8, 16.9 (C-6′); IR (CHCl$_3$) 3420, 3010, 1775, 1740, 1670, 1615, 1435, 1375, 1275, 1030 cm^{-1}; UV–vis λ_{max} (MeOH) 448 (ε 4500) 298 (7000), 265 (8000), 248 (49 700); HRMS (FAB) m/e 702.2134 (M + Na)$^+$, calcd for $C_{35}H_{37}O_{13}NNa$ 702.2163. Anal. Calcd for $C_{35}H_{37}O_{13}N$: C, 61.85; H. 5.49; N, 2.06. Found: C, 61.36; H, 5.46, 2.02.

Tetraacetate 19: R_t = 5.42 min; $[\alpha]^{22}_D$ = +19.6° (c 0.02, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 250 MHz) δ 8.52 (s, 1 H, H-12), 7.64–7.61 (m, 2 H, H-1, H-2), 7.04 (dd, 1 H, J = 8.39, 2.52 Hz, H-3), 5.64 (br s, 1 H, H-1′), 5.07 (m, 3 H, H-7, H-4′, NHAc), 4.34 (m, 1 H, H-3′), 4.20 (q, 1 H, J = 6.5 Hz, H-5′), 3.98 (s, 3 H, 4-OCH$_3$), 3.27 (app d, 1 H, J = 19.2 Hz, H-10), 2.81 (app d, 1 H. J = 15.7 Hz, H-8), 2.57 (app d, 1 H, J = 19.3 Hz, H-10), 2.47 (s, 3 H, aromatic OAc), 2.23 (s, 3 H), 2.22 (m, 4 H), 2.20 (s, 3 H), 1.88 (s, 3 H, NHAc), 1.90–1.82 (m, 2 H, H$_2$-2′), 1.17 (d, 3 H, J = 6.5 Hz, 5′-CH$_3$); IR (CHCl$_3$) 3575, 3120, 3020, 2950, 1785, 1715, 1660, 1510, 1430. 1420, 1270 cm^{-1}; UV–vis λ_{max} (MeOH) 438 (ε 4500), 290 (7000), 263 (8000), 244 (49 700); HRMS (FAB) m/e 702.2123 (M + Na)$^+$. calcd for $C_{35}H_{37}O_{13}NNa$ 702.2163.

N-Acetyldaunomycine (22).^{11} To a degassed solution of heptaacetate **14** (10 mg, 0.012 mmol) in THF (2 mL) was added a degassed aqueous solution of 0.1 N LiOH (0.850 mL, 0.085 mmol). The reaction mixture was stirred for 14 h under an atmosphere of argon to provide a purple-blue solution. The mixture was quenched with a pH 7 buffer (5 mL); after 5 min the orange-yellow solution was oxygenated for 3 min and extracted with dichloromethane (3 × 20 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The crude product was chromatographed on 2% KH_2PO_4–silica gel (gradient elution, chloroform to 20:1 chloroform–methanol) to afford 3 mg (43%) of **22** as a red-orange residue: $[\alpha]^{22}_D$ = +19.4° (c 0.04, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 250 MHz) δ 13.99 (s, 1 H, phenolic OH), 13.29 (s, 1 H, phenolic OH), 8.04 (d, 1 H, J = 8.2 Hz, H-1), 7.78 (app t, 1 H, J = 8.0 Hz, H-2), 7.38 (d, 1 H, J = 8.5 Hz, H-3), 5.77 (d, 1 H, J = 8.3 Hz, NHAc), 5.49 (d, 1 H, J = 3.8 Hz, H-1′), 5.25 (br s, 1 H, H-7), 4.42 (s, 1 H, 9-OH), 4.23 (q, 1 H, J = 6.7 Hz, H-5′), 4.12 (m, 1 H, H-3′), 4.08 (s, 3 H, 4-OCH$_3$), 3.64 (d, 1 H, J = 6.11 Hz, H-4′), 3.25 (d, 1 H, J = 19.0, Hz, H-10), 2.94 (d, 1 H, J = 18.9 Hz, H-10), 2.41 (s, 3 H, 9-COCH$_3$), 2.32 (d, 1 H, J = 14.8 Hz, H-8$_{eq}$), 2.11 (dd, 1 H, J = 14.8, 4.2 Hz, H-8$_{ax}$), 1.94 (s, 3 H, NHAc), 1.90 (m, 1 H, H-2′$_{eq}$), 1.74 (td, 1 H, J = 12.8, 4.2 Hz, H-2′$_{ax}$), 1.28 (d, 3 H, J = 6.5 Hz, 5′-CH$_3$); IR (CHCl$_3$) 3410, 3600–3200, 3000, 1715, 1665, 1620, 1585, 1510, 1450, 1415, 1355, 1290 cm^{-1}; UV–vis λ_{max} (CH$_3$OH) 520 (ε 4000), 490 (8000), 480 (8000), 280 (7000), 258 (17 000), 225 (25 000); HRMS (FAB) m/e 592.1831 (M + Na)$^+$, calcd for $C_{29}H_{31}O_{11}NNa$ 592.1795.

Naphthacene Derivative 24. To a degassed solution of heptaacetate **14** (10 mg, 0.012 mmol) in THF (2 mL) was added a degassed aqueous solution of 0.1 N LiOH (1.70 mL, 0.170 mmol). The reaction mixture was stirred for 14 h under an atmosphere of argon to provide a purple-blue solution. The mixture was quenched with a pH 7 buffer (5 mL); after 5 min, the orange-yellow solution was oxygenated for 3 min and extracted with dichloromethane (3 × 20 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The crude product was chromatographed on 2% KH_2PO_4–silica gel (gradient elution, chloroform to 20:1 chloroform–methanol) to afford 2 mg (50%) of **24** as a brown-orange solid: mp >275 °C; ^{1}H NMR (CDCl$_3$, 250 MHz) δ 14.40 (s, 1 H, phenolic OH), 8.92 (d, 1 H, J = 1.8 Hz, H-10), 8.81 (s, 1 H. H-5), 8.48 (d, 1 H, J = 8.0 Hz, H-7), 8.37 (dd, 1 H, J = 8.3, 1.7 Hz, H-8), 8.11 (d, 1 H, J = 8.2 Hz, H-1), 7.65 (app t, 1 H, J = 8.0 Hz, H-2), 7.11 (d, 1 H, J = 8.1 Hz, H-3), 4.07 (s, 3 H, 4-OCH$_3$), 2.77 (s, 3 H, 9-COCH$_3$); IR (CHCl$_3$) 1675 cm^{-1}; UV–vis λ_{max} (CH$_3$OH) 472 (ε 6000), 278 (20 000), 225 (46 000); HRMS (CI) m/e 347.0919 (M + H)$^+$, calcd for $C_{21}H_{15}O_5$ 347.0900.

Registry No. 1a·HCl, 23541-50-6; **4a**, 32384-98-8; **12**, 32469-19-5; **14**, 130830-83-0; **18**, 130830-85-2; **19**, 130858-20-7; **20**, 130830-84-1; **22**, 32385-10-7; **24**, 130858-21-8.

Supplementary Material Available: Tables of fractional coordinates, bond distances, torsional angles, and anisotropic temperature factors, and summary of the protocols for the X-ray crystallographic determination of compound **12** (17 pages). Ordering information is given on any current masthead page.