efficiency in charge carrier production (Table III), showing that the structure of the electron relay (not just the electrochemical driving force) is important in determining the rate of colloid-catalyzed water splitting.[44]

Acknowledgment. This research was supported by the Department of Energy, Office of Basic Energy Sciences. We also acknowledge the advice and assistance of Professor Morton Z. Hoffman and Dr. D. R. Prasad.

(44) Whitten has reported that $CMMP^+$ is less effective than MV^{2+} as a relay for photocurrent generation (at a Pt electrode) sensitized by benzophenone in isopropyl alcohol.[45] Launikonis et al. have shown the H_2 yields are a function of pH, $E_{1/2}$ (between −0.5 and −0.7 V), and the structure of diquaternary pyridiniums (hydrogenation susceptibility).[46]

(45) Chandrasekaran, K.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7270.

(46) Launikonis, A.; Loder, J. W.; Mau, A. W.-H.; Sasse, W. H. F.; Summers, L. A.; Wells, D. *Aust. J. Chem.* **1982**, *35*, 1341.

Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Aza Dienes. Studies on the Total Synthesis of Lavendamycin: Investigative Studies on the Preparation of the CDE β-Carboline Ring System and AB Quinoline-5,8-quinone Ring System

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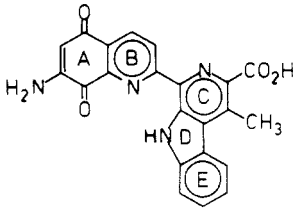
The investigation and utilization of the inverse electron demand [4 + 2] cycloaddition of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine with electron-rich olefins and the subsequent implementation of a palladium(0)-mediated β-carboline synthesis for the preparation of the CDE ring system of lavendamycin are detailed. Studies on the introduction and preparation of the 7-aminoquinoline-5,8-quinone AB ring system of lavendamycin are described.

Lavendamycin (1)[2], an antitumor antibiotic[3] recently isolated from *Streptomyces lavendulae* and structurally related to streptonigrin, has been the focus of synthetic efforts[4] since its initial structural identification.[2] A recent,



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reported total synthesis of lavendamycin methyl ester, which proved identical with material derived from natural lavendamycin, has verified the proposed structure 1.[4a] Herein we describe full details[5] of initial efforts designed to construct the β-carboline CDE ring system and the 7-aminoquinoline-5,8-quinone AB ring system of lavendamycin which have been conducted in the development of a total synthesis of lavendamycin[6] and concurrent with our efforts to define the structural features responsible for or potentiating the antimicrobial and cytotoxic properties of quinoline-5,8-quinone antitumor antibiotics.

Studies on the Preparation of the CDE Ring System of Lavendamycin: Inverse Electron Demand Diels–Alder Reaction of 1,2,4-Triazines and Palladium(0)-Mediated β-Carboline Preparation. In recent reports we have detailed the utility of the inverse electron demand Diels–Alder reaction of electron-deficient, substituted 1,2,4-triazines with electron-rich olefins in the preparation of 4-arylpyridines and further demonstrated the potential of this process in a formal total synthesis of streptonigrin.[7,8] In a continued exploration of the factors governing the reactivity and regioselectivity of the [4 + 2] cycloaddition reactions of 1,2,4-triazines, we describe here full details of a short, effective approach to the preparation of the lavendamycin CDE ring system based on a regioselective inverse electron demand Diels–Alder reaction of 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine and the implementation of a newly developed palladium(0)-mediated β-carboline synthesis (eq 1).[5]

Thermal cycloaddition of the pyrrolidine enamine of *o*-bromopropiophenone (**5a**) with 3,5,6-tris(ethoxy-

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(2) Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.-H.; Meows, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595. For a recent review, see: Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 77.

(3) Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot.* **1982**, *35*, 259.

(4) For the total synthesis of lavendamycin methyl ester and comparison with that derived from natural material, see: (a) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923. Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J. Lorah, D. P.; Lodge, E. *Heterocycles* **1984**, *21*, 91. Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261. For the preparation of desmethyllavendamycin and related studies, see: (b) Hibino, S.; Okazaki, M.; Sato, K.; Morita, I. *Heterocycles* **1983**, *20*, 1957. (c) Rao, A. V. R.; Chavan, S.; Sivadasan, L. *Indian J. Chem.* **1984**, *23B*, 496.

(5) Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1984**, *25*, 3175.

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(7) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621. (b) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745.

(8) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1982**, *47*, 3763; Idem *Ibid.* **1981**, *46*, 2179. Boger, D. L.; Panek, J. S.; Meier, M. M. *Ibid.* **1982**, *47*, 895. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

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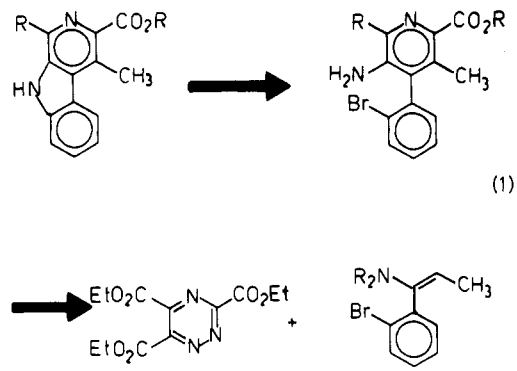
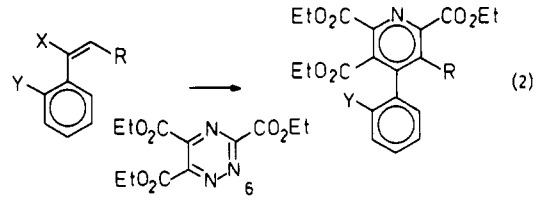


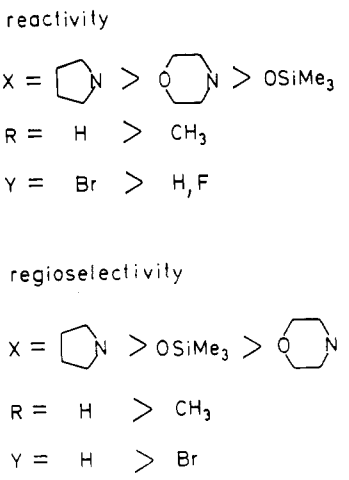
(1)

carbonyl)-1,2,4-triazine (**6**)[9] *proceeds at room temperature* to afford predominantly 4-(2-bromophenyl)-5-methyl-2,3,6-tris(ethoxycarbonyl)pyridine (**7a**) (Scheme I) accompanied by a small amount of the isomeric 3-arylpyridine. The desired adduct **7a** arises from cycloaddition across C-3/C-6 of the 1,2,4-triazine nucleus with the nucleophilic carbon of the electron-rich olefin attaching to C-3. The minor adduct, 5-(2-bromophenyl)-4-methyl-2,3,6-tris(ethoxycarbonyl)pyridine, similarly arises from addition across C-3/C-6 of **6** but with the nucleophilic carbon of the electron-rich olefin attaching to C-6 of the 1,2,4-triazine. This observed regioselectivity of the [4 + 2] cycloaddition is in full agreement with the observations detailed in prior investigations[7] with the exception that the [4 + 2] cycloaddition and subsequent aromatization proceed under milder conditions than anticipated or previously observed. This may be attributed to the enhanced reactivity of the pyrrolidine enamine of *o*-bromopropiophenone due to the presence of a large aryl ortho substituent and partial loss of the stabilizing aryl–olefin conjugation. Table I summarizes representative results of a study of this [4 + 2] cycloaddition reaction and illustrates three additional important observations. Modest increases in the reaction temperature decrease the regioselectivity of the [4 + 2] cycloaddition, and this observation is consistent with those detailed in prior investigations.[7] In addition, the morpholino enamine of 2-bromopropiophenone is less reactive than the corresponding pyrrolidine enamine and participates in a [4 + 2] cycloaddition with **6** with less (no) regioselectivity. While unanticipated, this observation is consistent with those described in a related recent investigation.[7] A third, important feature of the [4 + 2] cycloaddition reactions of substituted 1,2,4-triazines with α-styryl enamines that can be derived from these and related studies[7] is the decrease in rate and regioselectivity of the reaction that generally accompanies alkyl substitution of the β-styryl position of the α-styryl enamines (eq 2).

The introduction of the 3-pyridyl amine, which was anticipated to be derived from a modified Curtius rearrangement of a free C-3 carboxylate and necessarily preceded the β-carboline closure, required effective differentiation of the hindered C-3 ethoxycarbonyl group from the accessible C-2/C-6 ethoxycarbonyl groups. A related approach has been effectively employed in studies directed toward the total synthesis of streptonigrin,[7,10] and the results of our studies are detailed in Scheme I. Exhaustive ester hydrolysis of **7a** followed by selective Fischer esterification of the accessible C-2/C-6 carboxylates afforded 4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methyl-

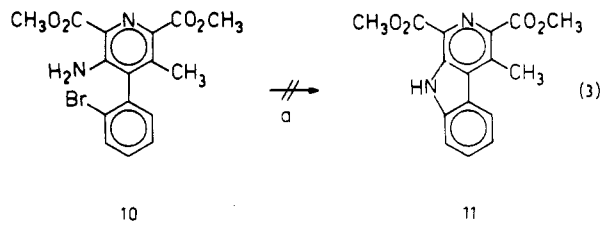


(2)



pyridine-3-carboxylic acid (**9**). Conversion of the free C-3 carboxylate to an amine utilizing a modified Curtius rearrangement and the Yamada–Shioiri reagent, diphenyl phosphoroazidate,[11] afforded **10**.

It was anticipated that conventional methods[12] for the formation of an aryl–nitrogen bond would provide the final stage for the CDE ring construction of the β-carboline. Initial, unsuccessful attempts to promote this closure are summarized in eq 3. The inability of these approaches



(3)

10 11

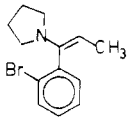
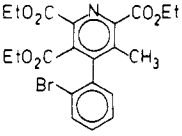
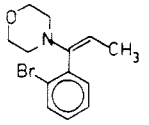
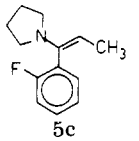
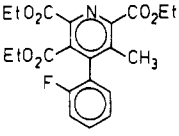
(a) NaH, CuBr;[12a] K_2CO_3, CuI;[12b] K_2CO_3, Cu(Zn);[12c] *t*-BuOK, Me_2SO.[12e]

to provide the desired β-carboline may be due to the noncoplanarity of the biaryl ring system, the result of two ortho substituents forcing the 4-aryl ring into a perpendicular arrangement relative to the pyridyl ring, and the inability of the nitrogen to readily reach the 2′-position necessary for β-carboline formation. In contrast, palladium(0) treatment of **10** under conditions conducive to oxidative insertion[13] into aryl halide bonds provided the β-carboline **11** smoothly. The rationale for the study of this process, which may account for the success, was the accessible formation of the six-membered intermediate **i** which may precede a reductive elimination with formation of the aryl–nitrogen bond and β-carboline generation (eq

(9) Ratz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931.
(10) Martin, J. C. *J. Org. Chem.* **1982**, *47*, 3761. Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271. Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *Ibid.* **1982**, *104*, 536.

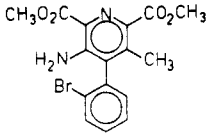
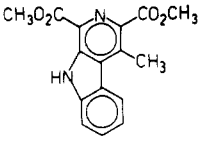
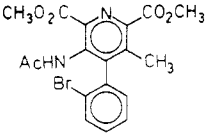
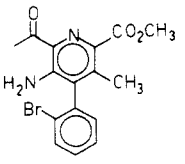
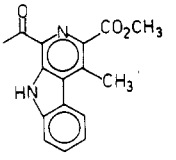
(11) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203; *Tetrahedron* **1974**, *30*, 2151.
(12) (a) Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277. (b) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 460. Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *Ibid.* **1976**, 389. (c) Miller, R. B.; Stowell, J. G. *J. Org. Chem.* **1983**, *48*, 886. (d) Kauffmann, T.; Fischer, H. *Chem. Ber.* **1973**, *106*, 220. (e) Sahyun, M. R. V.; Cram, D. J. *Org. Syn.* **1965**, *45*, 89.
(13) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6. Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287.

Table I. [4 + 2] Cycloaddition of 3,5,6-Tris(ethoxycarbonyl)-1,2,4-triazine (6) with α-Aryl Enamines

entry	enamine	conditions: equiv enamine	solvent	temp, °C	time, h	product[a]	% yield[b,c]
1[d]	 5a	1.0	$CHCl_3$	60	19	 7a	28 (3.1:1)
		1.5	$CHCl_3$	60	20		51 (3.1:1)
		1.5	CH_2Cl_2	40	22		51 (6.5:1)
		2.5					54 (6.5:1)
		1.5		25	24		50 (7.5:1)
					48		45 (7.5:1)
2[d]	 5b	2.0	$CHCl_3$	45	24	7a	trace
		2.0	$CHCl_3$	60	20		58 (1:1)
3[d]	 5c	2.0	$CHCl_3$	50	24	 7c	52 (>95%)

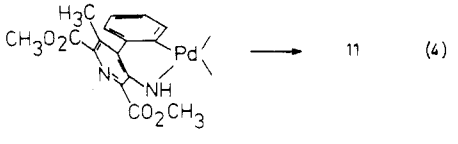
[a] Each product exhibited the expected ^1H NMR, IR, and MS characteristics consistent with the assigned structure, and each gave satisfactory CHN analyses or HRMS information. [b] Yields are based on pure material isolated by chromatography (SiO_2). [c] Ratio of regioisomers isolated from the reaction mixture. The ratio was determined by isolation of the pure isomers or by ^1H NMR integration or the separable $ArCH_3$ signals. [d] The enamine substrates **5a–c** were prepared from the corresponding propiophenones with the aid of $TiCl_4$, see: White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

Table II. Palladium(0)-Mediated β-Carboline Synthesis

entry	substrate	conditions: equiv $(Ph_3P)_4Pd$	solvent	temp, °C	time, h	product[a]	% yield[b]
1	 10a	1.0	THF	80	20[c]	 11	50
		1.2	THF	80	21[c]		81
		1.5	THF	80	21[c]		84
		1.2	dioxane	100	20		50
		1.5	dioxane	100	24		80
		1.2	toluene	100	24		43
		0.01	THF	80	24[c]		0
2[d]		1.2	dioxane	100	22	11[e]	50
3[d]		1.4	dioxane	100	10		60
		1.5	dioxane	100	36		87

[a] Each product exhibited the expected ^1H NMR, IR, and MS characteristics consistent with the assigned structure and each gave satisfactory CHN analyses or HRMS information. [b] Yields are based on pure material isolated by chromatography (SiO_2). [c] The reaction was run in a sealed (Teflon) Kontes vial. [d] A detailed procedure for the preparation of the substrate is described in the accompanying report.[6] [e] Deacylation of the β-carboline presumably occurs upon workup and purification.

4).[14] Table II details representative results of a study of this process.



(4)

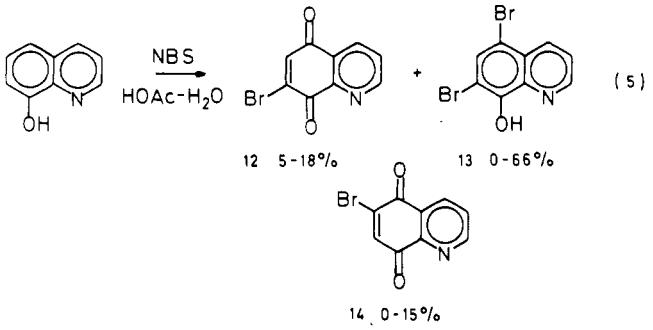
i

(14) (a) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444. Venanzi, A. I.; Pugin, B. *J. Organomet. Chem.* **1981**, *214*, 125. (b) Dillon, K. B.; Waddington, T. C.; Younger, D. *J. Chem. Soc., Dalton Trans.* **1975**, 790.

The cyclization reactions detailed in Table II may involve a nitrogen–palladium(II) reductive elimination with nitrogen–carbon bond formation, and the successful observation of such a process may be attributed to the reduced nucleophilicity of the aryl amine, the result of methoxycarbonyl delocalization, and a weakened N–Pd coordination.[14a] The rate of the cyclization reaction is consistent with the initial oxidative insertion reaction being operative and rate determining. The rate of oxidative addition reactions of palladium(0) with aryl bromides is comparable[13] to the rate of β-carboline formation, and trace amounts of debromo substrate have been detected if the cyclization reactions were quenched prior to the complete

consumption of substrate.[6] The requirement for stoichiometric $(Ph_3P)_4Pd$ for effective promotion of the β-carboline closure potentially arises from a competitive oxidative addition of liberated HBr with catalyst.[14b]

Studies on the Preparation of the AB Quinoline-5,8-quinone Ring System of Lavendamycin. Assured that the CDE ring system of lavendamycin could arise from a 4-arylpyridine generated through the use of an inverse electron demand [4 + 2] cycloaddition reaction of a 1,2,4-triazine, efforts focused on the preparation and utilization of an appropriately substituted amino aldehyde for use in a Friedlander condensation[15] and introduction of the AB 7-aminoquinoline-5,8-quinone ring system found in lavendamycin.[6] Initial studies which were conducted with 7-bromoquinoline-5,8-quinone (**12**), prepared in modest yield in a one-step oxidative bromination of 8-hydroxyquinoline (eq 5)[16] or by modification of a previ-



12 5-18% 13 0-66% (5)

14 0-15%

ously detailed three-step procedure,[17,18] secured the suitability of such a precursor for introduction of a 7-aminoquinoline-5,8-quinone (Scheme II).[17,18] Treatment of 7-bromoquinoline-5,8-quinone (**12**) with sodium azide,[19] a reaction that was found to be sensitive to the presence of excess reagent,[19b] followed by reduction of 7-azidoquinoline-5,8-quinone (**17**) with triphenylphosphine provided 7-aminoquinoline-5,8-quinone (**18**). The use of excess sodium azide (1.5 equiv) in the displacement reaction did lead to the predominant formation of 7-amino-6-azidoquinoline-5,8-quinone,[19] and initial attempts at reduction of 6-azidoquinoline-5,8-quinone (**17**) with sodium hydrosulfite[4a,19] failed to provide the 7-aminoquinoline-5,8-quinone (**18**) in acceptable yields (10–20%). In contrast, the use of stoichiometric sodium azide in the conversion of **12** to **17** and azide reduction with triphenylphosphine followed by mild, aqueous hydrolysis of the resulting phosphine imine[20] provided **18** in excellent yields without competitive quinone to hydroquinone reduction. The direct azide displacement of 7-bromoquinoline-5,8-quinone was confirmed by comparison of **18** with authentic 7-aminoquinoline-5,8-quinone of unambiguous structure.[17]

Assured that a 7-bromoquinoline-5,8-quinone could serve as an immediate precursor for the introduction of the lavendamycin AB 7-aminoquinoline-5,8-quinone ring system, the preparation of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**23**) for use in a Friedlander condensation and 7-bromoquinoline-5,8-quinone introduction was investigated and is detailed in Scheme III.[21] The selection of **23** as the amino aldehyde component for use in a Friedlander condensation and subsequent lavendamycin AB quinoline introduction was based on the recognized observations that 6-substituted 2-aminobenzaldehydes, agents that possess two substituents ortho to the aryl aldehyde, participate in a Friedlander condensation in only low to modest yields.[15] Thus, the choice of **23** represents one in which the amino aldehyde possesses suitable functionality for introduction of the 7-aminoquinoline-5,8-quinone and one in which the Friedlander condensation would be expected to proceed in satisfactory yield.

Consistent with these expectations, condensation[15] of **23** with 2-acetylpyridine (**24**) provided 8-(benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline (**25**) in excellent yield (Scheme IV). Deprotection of the phenol in **25**, which was most effectively accomplished with anhydrous hydrogen bromide in benzene,[22] provided **26**. Direct conversion of **26** to the 7-bromoquinoline-5,8-quinone **27** was effected with the use of potassium nitrosodisulfonate, Fremy's salt,[23] in an oxidation that was not especially sensitive to

(15) Cheng, C. C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.

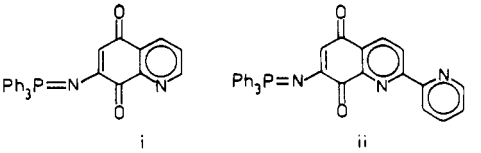
(16) (a) Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305.

(17) (a) Petrow, V.; Sturgeon, B. *J. Chem. Soc.* **1954**, 571. (b) Authentic 7-aminoquinoline-5,8-quinone was also prepared by the sequence 70% HNO_3–H_2SO_4, 0–25 °C, 1 h, 75% [8-hydroxyquinoline to 5,7-dinitro-8-hydroxyquinoline]; H_2, 5% Pd/C, THF–EtOH, 25 °C, 48 h [5,7-dinitro-8-hydroxyquinoline to 5,7-diamino-8-hydroxyquinoline: ^1H NMR ($CDCl_3$, ppm) 8.85 (1 H, dd, J = 5, 1 Hz, C-2 H), 8.65 (1 H, dd, J = 9, 1 Hz, C-4 H), 7.54 (1 H, dd, J = 9, 6 Hz, C-3 H), 6.12 (1 H, s, C- H)]; 10 equiv of Fremy's salt, CH_3OH–0.05 M K_2HPO_4, 25 °C, 14–48 h and proved to be identical with the material prepared by the sequence detailed in Scheme II.

(18) Details of the preparation of **12** are provided in supplementary material.

(19) (a) Kuo, H. S.; Yoshina, S. *Yakugaku Zasshi* **1977**, *97*, 827. (b) In a related study, treatment of 2-bromo-1,4-naphthoquinone with 1.5 equiv of sodium azide (THF or DMF, 25 °C, 0.5–2 h) led to the predominant formation of 2-amino-3-azido-1,4-naphthoquinone: ^1H NMR ($CDCl_3$, ppm) 8.06–7.50 (4 H, m, aromatic), 5.07 (2 H, br s, NH_2); IR (KBr) ν_{max} 3470, 3264 (NH), 2120 (N_3), 1680 cm^{-1}; MS m/e 214 (M^+). The dissolution of sodium azide in water or methanol prior to addition to a solution of **12** resulted in a substantial increase in the isolated yield of **17**. The displacement reaction proceeds more rapidly (6 min, EtOH–H_2O, 25 °C, 87%; 12 min, THF–H_2O, 25 °C, 91%) than the studies of others imply [4a,19a] (1.5 equiv of NaN_3, 3 h, 25 °C), and a small amount of 7-aminoquinoline-5,8-quinone (**18**, 3–13%) is formed directly in the reaction of **12** with sodium azide. For related observations, see: Fieser, L. F.; Hartwell, J. L. *J. Am. Chem. Soc.* **1935**, *57*, 1482. (c) Treatment of *suspensions* of 7-bromoquinoline-5,8-quinone (**27**) in THF, CH_3OH, DMF, and HMPA with 1 equiv of NaN_3 (predissolved in H_2O or CH_3OH) afforded predominantly 7-amino-6-azido-2-(2-pyridyl)quinoline-5,8-quinone: ^1H NMR ($CDCl_3$, ppm) 8.89 (1 H, d, J = 8 Hz, C-4 H), 8.61 (2 H, rough d, J = 7.5 Hz, pyridyl C-3/C-6 H), 8.41 (1 H, d, J = 8 Hz, C-3 H), 7.82 (1 H, ddd, J = 8, 7.5, 1.5 Hz, pyridyl C-4 H), 7.47–7.22 (1 H, m, pyridyl C-5 H); IR (KBr) ν_{max} 3459, 3389 (NH), 2116 (N_3), 1688, 1619, 1586, 1451, 1402, 1375, 1312, 1291, 1264, 1244, 1181, 1148, 1107, 1076, 1055, 997 cm^{-1}; MS m/e 292 (M^+), 266 (M^+–N_2 + H_2), 264 (M^+ – N_2), 250 (M^+ – N_3). This results from an effective concentration of NaN_3 in excess of 1.0 equiv. The two-phase reaction conditions utilized in the conversion of **27** to **28** minimizes the effective concentration of sodium azide present in the organic phase and allows the reaction to be conducted under conditions in which the 7-bromoquinoline-5,8-quinone is soluble.

(20) (a) Mungall, W. S.; Greene, G. L.; Heavner, G. A.; Letsinger, R. L. *J. Org. Chem.* **1975**, *40*, 1659. (b) Corey, E. J.; Samuelsson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682. The phosphine imine **i** was isolated by chromatography (SiO_2, 68%) upon treatment of **17** with Ph_3P (1.1 equiv, 25 °C, CH_2Cl_2, 1 h) and characterized. Hydrolysis of purified **i** (HOAc–H_2O–THF, 3:2:1, 25 °C) provided **18** (93%, 10 min; 48%, 2.7 h). Similarly, **ii** was isolated and characterized in the conversion of **28** and **29**.

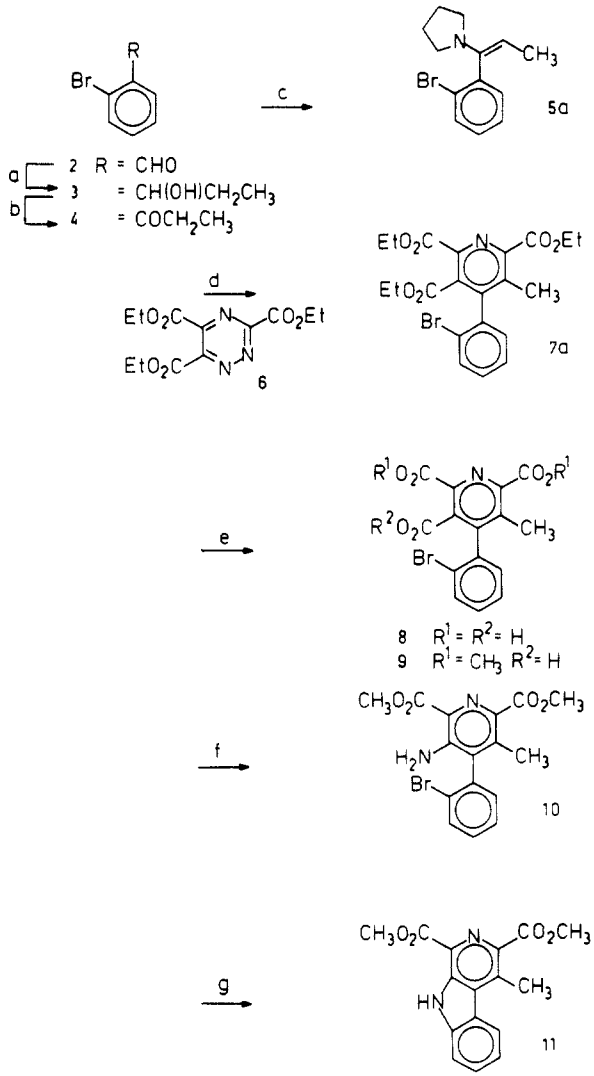


i ii

(21) Seela, F. *J. Med. Chem.* **1972**, *15*, 684. The yield of isolated product in the sodium hydrosulfite conversion of **22** to **23** decreases with increasing reaction time (93%, 0.5 h; 80%, 12 h) due to a slow, competing reduction of the aldehyde group.

(22) Initial efforts to remove the benzyl ether with CF_3CO_2H (neat, 60 °C, 7–17 h) were as effective (90–98%) but on occasion provided substantial or predominant amounts of the pyridinium *N*-benzyl derivative of **26**: ^1H NMR ($CDCl_3$, ppm) 4.33 (2 H, s, NCH_2Ph). For related observations, see: Marsh, J. P., Jr.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2491. Kiso, Y.; Isawa, H.; Kitagawa, K.; Akita, T. *Chem. Pharm. Bull.* **1978**, *26*, 2562. Deprotection of the phenol in CH_2Cl_2 [HBr(g), 25 °C, 1 h] was equally effective (95–100%).

Scheme I[a]



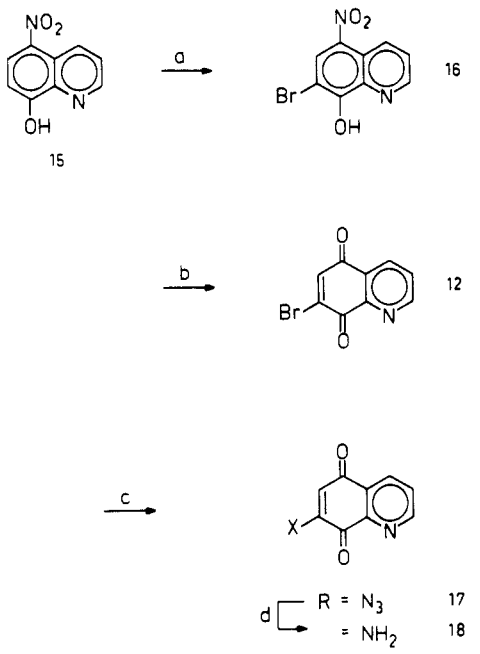
[a] (a) 1.0 equiv of EtMgBr, THF, −78 to +25 °C, 3.5 h; (b) 1.2 equiv of H_2CrO_4, Et_2O, 25 °C, 3.0 h, 94% from **2**; (c) 4 equiv of pyrrolidine, 0.5 equiv of $TiCl_4$, Et_2O, 0–25 °C, 12–16 h, 80–88%; (d) Table I; (e) 15 equiv of LiOH, THF-CH_3OH-H_2O (3:2:1), reflux, 28–30 h; 10% HCl-CH_3OH, 25 °C, 18–20 h, 67% from **7a**; (f) 2.2 equiv of $(PhO)_2P(O)N_3$, 2.2 equiv of Et_3N, benzene, reflux, 2.5 h; H_2O-benzene, reflux, 2 h, 72%; (g) Table II.

the substrate concentration.[22b,24]

Conversion of the reactive 7-bromoquinoline-5,8-quinone **27**[24] to 7-amino-2-(2-pyridyl)quinoline-5,8-quinone (**29**) followed the protocol described beforehand and is detailed in Scheme IV.

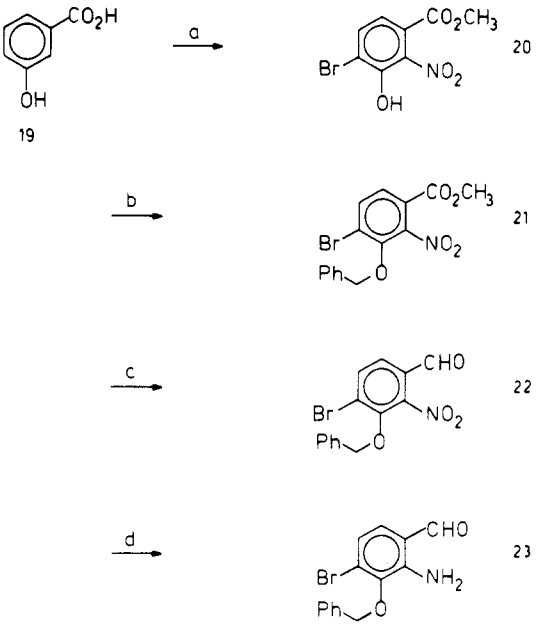
Application of these studies in the total synthesis of lavendamycin (**1**) is detailed in the accompanying report.[6] Current studies on the antimicrobial, cytotoxic, and antitumor properties of quinoline-5,8-quinones including the lavendamycin partial structures detailed herein will be reported separately.

Scheme II[a]



[a] (a) 1.05 equiv of NBS, THF, catalytic H_2SO_4, 25 °C, 2.5 h, 88%; (b) 5.0 equiv of $Na_2S_2O_4$, THF-H_2O, 60 °C, 10 min, 74%; 2.0 equiv of $K_2Cr_2O_7$, CH_2Cl_2-5% aqueous H_2SO_4, 25 °C, 30 min, 64%; (c) 1.1 equiv of NaN_3, THF-H_2O, 25 °C, 0.2 h, 91% **17** and 3% **18**; (d) 1.1 equiv of Ph_3P, CH_2Cl_2, 25 °C, 1 h, 68–79%; HOAc-H_2O-THF (3:2:1), 25 °C, 10 min, 93%.

Scheme III[a]



[a] (a) Br_2, HOAc; HNO_3; HCl, CH_3OH;[21] (b) 1.2 equiv of NaH, DMF, 0 °C, 10 min; 1.1 equiv of $PhCH_2Br$, 0–25 °C, 20 h, 85%; (c) 3.0 equiv of $LiBH_4$, THF, 25 °C, 21 h, 93–97%; 1.5 equiv of PDC, CH_2Cl_2, 25 °C, 11 h, 83%; (d) 5 equiv of $Na_2S_2O_4$, H_2O-THF, 60 °C, 0.5 h, 93%.

Experimental Section[25]

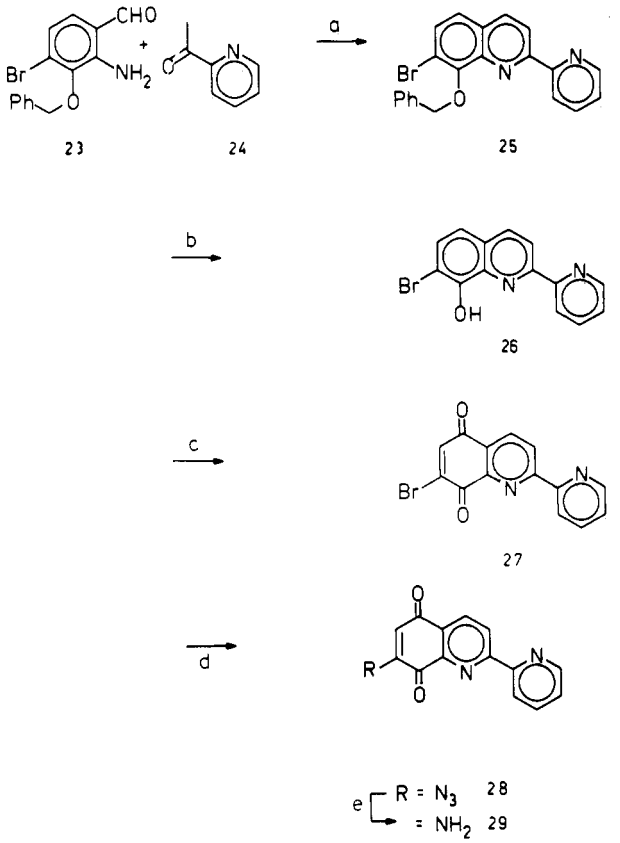
Triethyl 4-(2-Bromophenyl)-5-methylpyridine-2,3,6-tricarboxylate (7a). A solution of triethyl 1,2,4-triazine-3,5,6-

(23) (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229. (b) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745. Attempts to convert **26** to **27** with ceric ammonium nitrate[4b] or potassium dichromate[4a,17] led to the consumption of **26** without product formation. No reaction was observed upon treatment of **26** with Fremy's salt (5–15 equiv, THF, 25 °C), HIO_4 (1.5 equiv, CH_3OH–$CHCl_3$, 2:1, 25 °C, 20 h) (see: Rao, K. V.; Kuo, H.-S. *J. Heterocycl. Chem.* **1979**, *42*, 232).

(24) Oxidations of **26** to **27** with Fremy's salt proceed well under a range of conditions (4–20 equiv of Fremy's salt, 0.07–0.002 M **26**, MeOH or acetone–0.05 M KH_2PO_4, 1.5–2.5 h, 53–100%). A two-phase Fremy's salt oxidation[4a] of **26** (20–40 equiv Fremy's salt, H_2O–CH_2Cl_2, 25 °C, 2–5 h) in the presence of $(n\text{-}Bu)_4NHSO_4$ (1.0 equiv) as a phase-transfer catalyst provided **27** (50–70%). The 7-bromoquinoline-5,8-quinone **27** is not completely stable to chromatography on silica gel.

(25) General experimental details are provided in the accompanying report.[6]

Scheme IV[a]



[a] (a) 4 equiv of Triton B, THF, 25 °C, 18 h, 81–90%; (b) HBr(g), C_6H_6, 60 °C, 7 h, 98%; (c) 20 equiv of $\cdot ON(SO_3K)_2$, acetone, 0.05 M KH_2PO_4, 25 °C, 2.0 h, 77% (100%);[24] (d) 1.1 equiv of NaN_3, CH_2Cl_2–H_2O, 23 h, 25 °C, 85% **28** and 8% **29**; (e) 1.0 equiv of Ph_3P, CH_2Cl_2, 1 h, 25 °C; HOAc–H_2O–THF (3:2:2), 25 °C, 0.3 h.

tricarboxylate[9,26] (**6**; 5.0 g, 16.8 mmol) in methylene chloride (60 mL) was treated with the pyrrolidine enamine **5a**[26] (6.77 g, 25.2 mmol, 1.5 equiv) in methylene chloride (5.0 mL) at 25 °C under N_2. The reaction mixture was stirred at 25 °C for 24 h and the solvent was removed in vacuo. MPLC (SiO_2, 25 × 500 cm, 30% ether–hexane eluant) afforded 3.90 g (7.79 g theor, 50%) of **7a** (7.5:1 regioisomer). For **7a**: ^1H NMR ($CDCl_3$) δ 7.74–7.09 (4 H, m, aromatic), 4.45 (2 H, q, J = 8 Hz, CH_2), 4.40 (2 H, q, J = 8 Hz, CH_2), 4.00 (2 H, q, J = 8 Hz, CH_2), 2.24 (3 H, s, $ArCH_3$), 1.44 (3 H, t, J = 8 Hz, CH_3), 1.40 (3 H, t, J = 8 Hz, CH_3), 0.97 (3 H, t, J = 8 Hz, CH_3); IR (film) ν_{max} 3025, 2985, 1725, (C=O), 1552, 1456, 1358, 1323, 1265, 1236, 1200, 1080, 1000, 892, 840, 735, 708 cm^{-1}; EIMS m/e (relative intensity) 464/466 (M^+, 1/1, 4), 420/418 (10), 392/390 (15), 385 (40), 384 (97), 356 (24), 331 (20), 319 (35), 318 (30), 316 (20), 311 (22), 310 (base), 282 (48), 238 (27), 210 (35), 209 (24), 194 (26), 167 (35), 166 (43), 165 (44), 164 (49), 140 (40), 139 (51), 138 (20), 116 (21); HRMS m/e for $C_{21}H_{22}BrNO_6$, calcd 463.0629, found 463.0590.

4-(2-Bromophenyl)-3-carboxy-2,6-bis(methoxycarbonyl)-5-methylpyridine (9). A solution of triethyl 4-(2-bromophenyl)-5-methylpyridine-2,3,6-tricarboxylate (**7a**; 560 mg, 1.2 mmol) in THF–MeOH (50 mL, 3:2) was treated with a solution of LiOH (762 mg, 18.1 mmol, 15.0 equiv) in H_2O (10 mL) at 25 °C under N_2. The resulting reaction mixture was warmed at reflux for 36 h. The reaction mixture was cooled, diluted with H_2O (30 mL), acidified to pH 2–3 using 1 N HCl, and extracted with EtOAc (2 × 40 mL). The organic extracts were washed with saturated NaCl, dried (Na_2SO_4), and filtered and the solvent was removed in vacuo. A solution of the crude triacid **8** in absolute MeOH (10 mL) was added to a stirred solution of 10% HCl–MeOH (40 mL) at 25 °C. The reaction was stirred at 25 °C (18 h). The solvent was removed in vacuo. Chromatography (SiO_2, 3% MeOH–$CHCl_3$ eluant) afforded 331 mg (489 mg theor, 67%) of pure **9** as a white foam:[29b] mp 250 °C dec; ^1H NMR ($CDCl_3$) δ 7.72–7.40 (1 H, m, aromatic), 7.38–7.05 (3 H, m, aromatic), 4.00 (3 H, s, CO_2CH_3), 3.93 (3 H, s, CO_2CH_3), 2.26 (3 H, s, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3600–2400 (br, CO_2H), 3000, 2927, 1728, 1588, 1435, 1345, 1300, 1250, 1218, 1110, 1038, 1012 cm^{-1}; EIMS m/e (relative intensity) 392/390 (3), 364/362 (3), 343 (16), 342 (75), 297 (19), 296 (base), 268 (12), 264 (6), 252 (8), 237 (5), 236 (10), 225 (9), 224 (27), 209 (10), 208 (11), 207 (5), 194/192 (8), 193 (8), 181 (7), 180 (8), 167 (15), 166 (16), 165 (26), 164 (48), 153 (17), 152 (15), 140 (16), 139 (25), 138 (21), 137 (11), 127 (11), 126 (17), 115 (10), 114 (8), 100 (9), 99 (9), 89 (10), 88 (12).

Anal. Calcd for $C_{17}H_{14}BrNO_6$: C, 50.01; H, 3.45; N, 3.45. Found: C, 50.38; H, 3.09; N, 3.10.

3-Amino-4-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-5-methylpyridine (10). A solution of 4-(2-bromophenyl)-3-carboxy-2,6-bis(methoxycarbonyl)-5-methylpyridine (**9**; 347 mg, 0.85 mmol) in dry benzene (15 mL) was treated with diphenyl phosphorazidate[11] (514 mg, 1.87 mmol, 2.2 equiv) and triethylamine (223 mg, 0.3 mL, 2.2 equiv) at 25 °C under N_2. The reaction mixture was warmed at reflux for 2.5 h and cooled, and H_2O (0.25 mL) was added. The reaction mixture was warmed at reflux for an additional 2.0 h. The solvent was removed in vacuo, and chromatography (SiO_2, 50% EtOAc–hexane eluant) afforded 232 mg (322 mg theor, 72%) of pure **10** as a white solid: mp 146–148 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.76 (1 H, dd, J = 10 Hz, J = 2 Hz, aromatic), 7.45–7.05 (3 H, m, aromatic), 5.82 (2 H, br s, $ArNH_2$), 3.98 (3 H, s, CO_2CH_3), 3.96 (3 H, s, CO_2CH_3), 2.24 (3 H, s, $ArCH_3$; ^{13}C NMR ($CDCl_3$) δ 166.0/164.5 (two s, CO_2CH_3), 145.9 (s, C3), 138.9 (s, C2), 136.1 (s, C6), 135.2 (s, C5), 133.9 (d, C10), 130.8/130.6 (two d, C9/C11), 130.5 (s, C4), 128.8 (d, C12), 125.3 (s, C7), 123.7 (s, C8, CBr), 53.6/52.5 (two q, CO_2CH_3), 17.3 (q, CH_3); IR ($CHCl_3$) ν_{max} 3510 and 3380 (NH_2), 3010, 2960, 1722, 1695, 1588, 1435, 1348, 1305, 1268, 1250, 1230, 1113, 895 cm^{-1}; EIMS m/e (relative intensity) 378/380 (M^+, 1/1, 30), 347 (11), 322/320 (55), 299 (39), 290/288 (32), 269 (11), 267 (33), 240 (19), 239 (96), 224 (12), 210/208 (20), 209 (base), 196 (4), 195 (9), 183 (7), 182 (20), 181 (30), 152 (24), 141 (11), 140 (18), 128/126 (21), 127 (36), 77 (40), 76 (15), 75 (13), 63 (20), 59 (16), 51 (16).

Anal. Calcd for $C_{16}H_{15}BrN_2O_4$: C, 50.67; H, 3.98; N, 7.38. Found: C, 50.59; H, 4.00; N, 7.20.

The conversion of **7a** (7.5:1 **7a**/regioisomer, 3.34 g, 7.2 mmol) to **10** without the prior separation of the **7a**/regioisomer mixture afforded **10** (1.50 g, 4.0 mmol, 56% overall). Separation of **10** from the isomeric product, dimethyl 3-amino-5-(2-bromophenyl)-4-methylpyridine-2,6-dicarboxylate[29a] (0.20 g, 7%), proved convenient at this stage.

1,3-Bis(methoxycarbonyl)-4-methyl-β-carboline (11). A solution of **10** (159 mg, 0.42 mmol) in 4.0 mL of dioxane was treated with tetrakis(triphenylphosphine)palladium(0) (728 mg, 0.628 mmol, 1.5 equiv) under an argon atmosphere and was warmed at 100 °C for 24 h. The reaction mixture was cooled and the solvent was removed in vacuo. Chromatography (SiO_2, 30% EtOAc–hexane eluant) afforded 100 mg (125 mg theor, 80%) of pure **11** as a yellow solid: mp 217–219 °C (EtOH); ^1H NMR ($CDCl_3$) δ 10.17 (1 H, br s, NH), 8.35 (1 H, d, J = 8 Hz, aromatic), 7.68–7.40 (3 H, m, aromatic), 4.11 (3 H, s, CO_2CH_3), 4.04 (3 H, s, CO_2CH_3), 3.22 (3 H, s, $ArCH_3$); ^{13}C NMR[27] ($CDCl_3$) δ 166.8 and 165.2 (CO_2CH_3), 141.5 (C-8), 137.3 (C-6), 135.8 (C-5), 132.8 (C-2), 129.8 (C-4), 128.6 (C-10), 128.4 (C-3), 123.6 (C-12), 123.4 (C-7), 120.7 (C-11), 113.1 (C-9), 52.10 and 52.08 (CO_2CH_3), 16.3 (CH_3); IR ($CHCl_3$) ν_{max} 3422 (NH), 3005, 2928, 1723, 1700, 1590,1490,

(26) Full details for the preparation are provided in the supplementary material.

(27) Assignments are based in part on a comparison with the ^{13}C NMR assignments of lavendamycin; see ref 3.

(28) Available from Aldrich Chemical Co.

(29) (a) For 3-amino-5-(2-bromophenyl)-2,6-bis(methoxycarbonyl)-4-methylpyridine: ^1H NMR ($CDCl_3$, ppm) 6.98–7.72 (4 H, m aromatic), 6.28 (2 H, br s, NH_2), 3.99 (3 H, s, CO_2CH_3), 3.71 (3 H, s, CO_2CH_3), 1.88 (3 H, s, CH_3); IR (KBr) ν_{max} 3457, 3353, 1728, 1694, 1611, 1476, 1435, 1358, 1300, 1233, 1206, 1163, 1113, 1021, 903, 793, 762 cm^{-1}, EIMS (relative intensity) m/e 378/380 (M^+, 1/1, 1), 299 (M^+ – Br, base), 240 (3), 223 (2). (b) Fischer esterification (10% HCl–CH_3OH), 25 °C, 18 h) of purified 4-(2-bromophenyl)-5-methylpyridine-2,3,6-tricarboxylic acid (**8**) afforded **9** in 78% yield.

(30) Salesin, E. D.; Gordon, L. *Talanta* **1960**, *4*, 75.

1458, 1438, 1342, 1297, 1272, 1241, 1098, 1062 cm^{-1}; mass spectrum m/e (relative intensity) 298 (M^+, 65), 267 (11), 266 (20), 241 (9), 240 (63), 239 (16), 238 (37), 209 (18), 208 (base), 207 (7), 206 (28), 181 (8), 180 (18), 179 (32), 178 (9); HRMS m/e for $C_{16}H_{14}N_2O_4$, calcd 298.0953, found 298.0940.

In the same manner, **10** (20 mg, 0.053 mmol) in 1.0 mL of THF was treated with $(Ph_3P)_4Pd$ (92 mg, 0.08 mmol, 1.5 equiv) and the reaction mixture was warmed at 80 °C in a sealed Kontes vial for 21 h. Chromatography (SiO_2, 30% EtOAc–hexane) afforded 13 mg (82%) of pure **11**.

7-Azidoquinoline-5,8-quinone (17). A stirred solution of 7-bromoquinoline-5,8-quinone (**12**; 26 mg, 0.11 mmol)[18] in 0.35 mL of THF was treated with a solution of sodium azide (8 mg, 0.12 mmol, 1.1 equiv) in 0.05 mL of H_2O at 25 °C under a N_2 atmosphere, and the mixture was stirred at 25 °C for 0.2 h. The solution was poured onto 5 mL of cold water and extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1 × 13 cm, 50–100% ethyl acetate–hexane eluant; gradient elution) afforded 20 mg (22 mg theor, 91%) of **17** as an orange solid: mp 135–137 °C (lit.[19a] mp 136–138 °C); ^1H NMR ($CDCl_3$) δ 8.96 (1 H, rough d, J = 5 Hz, C-2 H), 8.38 (1 H, dd, J = 8, 1.5 Hz, C-4 H), 7.62 (1 H, dd, J = 5, 8 Hz, C-3 H), 6.48 (1 H, s, C-6 H); IR (KBr) ν_{max} 2132, 1698, 1653, 1578, 1323, 1260, 1136, 947 cm^{-1}. It also gave 1 mg (37 mg theor, 3%) of **18** as a red, crystalline solid identical with the material described below.

7-Aminoquinoline-5,8-quinone (18). A stirred solution of **17** (27 mg, 0.14 mmol) in dry CH_2Cl_2 (0.15 mL) under a N_2 atmosphere was treated with a solution of triphenylphosphine (39 mg, 0.15 mmol, 1.1 equiv) in 0.15 mL of CH_2Cl_2 with stirring. Evolution of nitrogen was visible within 1 min after addition of Ph_3P. Stirring was continued at 25 °C for 1 h. Concentration of the reaction mixture in vacuo gave 70 mg of dark brown residue. Chromatography (SiO_2, 1.5 × 17 cm, 60% ethyl acetate–hexane eluant) afforded 40.5 mg (60 mg theor, 68%) of the phosphine imine as a brown solid: mp 214–215 °C; ^1H NMR ($CDCl_3$) δ 8.68 (1 H, dd, J = 5, 1.5 Hz, C-2 H), 8.25 (1 H, dd, J = 8, 1.5 Hz, C-4 H), 7.12–7.91 (16 H, m, phenyl H and C-3 H), 6.47 (1 H, s, C-6 H); IR (KBr) ν_{max} 3434, 1686, 1620, 1584, 1437, 1331, 1285, 1267, 1065, 889 cm^{-1}; MS m/e (relative intensity) 434 (M^+, 42), 262 (base), 183 (79), 108 (25).

Similarly, a solution of **17** (12 mg, 0.06 mmol) in CH_2Cl_2 (0.1 mL) under a N_2 atmosphere was treated with a solution of Ph_3P (17.3 mg, 0.066 mmol, 1.1 equiv) in 0.1 mL of CH_2Cl_2 and stirred at 25 °C for 1 h. Rapid chromatography (SiO_2, 1 × 17 cm, 60–70% ethyl acetate–hexane gradient elution) afforded 20.6 mg (26.1 mg theor, 79%) of the phosphine imine.

A solution of the phosphine imine (36 mg, 0.083 mmol) in 0.3 mL of THF was treated with 0.9 mL of acetic acid and 0.6 mL of H_2O, and the solution was allowed to stir at 25 °C for 10 min. The reaction solution was diluted with 5 mL of H_2O, extracted with ethyl acetate (3 × 10 mL, 3 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 20 cm, 60% ethyl acetate–hexane eluant) and washing with ether to remove triphenylphosphine oxide afforded 13.5 mg (14.5 mg theor, 93%) of **18** as a red, crystalline solid: mp 263 °C (ethyl acetate, lit.[19a] mp 263 °C); ^1H NMR ($CDCl_3$) δ 8.88 (1 H, dd, J = 5, 1.5 Hz, C-2 H), 8.37 (1 H, dd, J = 8, 1.5 Hz, C-4 H), 7.59 (1 H, dd, J = 5, 8 Hz, C-3 H), 6.03 (1 H, s, C-6 H), 5.25 (2 H, br s, NH_2); IR (KBr) ν_{max} 3440, 3295, 1701, 1615, 1555, 1420, 1356, 1267, 1146, 1003, 818 cm^{-1}.

Methyl 3-(Benzyloxy)-4-bromo-2-nitrobenzoate (21). A solution of methyl 4-bromo-3-hydroxy-2-nitrobenzoate[21] (**20**; 1.80 g, 6.52 mmol) in dry DMF (40 mL) was cooled to 0 °C under N_2 and treated with sodium hydride (313 mg, 7.80 mmol, 1.2 equiv). The reaction mixture was stirred for 10 min (0 °C) before benzyl bromide (1.22 g, 7.20 mmol, 1.1 equiv) was added. The reaction mixture was allowed to warm to 25 °C (0.5 h), and stirring was continued for an additional 20 h. A solution of saturated NaCl (10 mL) was added, and the reaction mixture was further diluted with H_2O (60 mL). The aqueous layer was extracted with Et_2O (4 × 40 mL). The combined ether extracts were washed with H_2O (1 × 20 mL), washed with saturated NaCl (1 × 10 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo. MPLC (SiO_2, 25 × 500 cm, 15% EtOAc–hexane eluant) afforded 2.02 g (2.38 g theor, 85%) of pure **21** as light yellow crystals: mp 85–87 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 7.80 (1 H, d, J = 8 Hz, aromatic), 7.68 (1 H, d, J = 8 Hz, aromatic), 7.46–7.25 (5 H, m, Ph), 5.13 (2 H, s, OCH_2Ph), 3.90 (3 H, s, CO_2CH_3); IR (KBr) ν_{max} 2959, 1723, 1587, 1561, 1547, 1458, 1433, 1366, 1304, 1132, 1003, 903, 847, 752 cm^{-1}; EIMS m/e (relative intensity) 365/367 (M^+, 1/1, 1), 259/261 (19), 92 (base), 65 (72).

Anal. Calcd for $C_{15}H_{12}BrNO_5$: C, 49.19; H, 3.30, N, 3.82. Found: C, 48.89; H, 3.20; N, 3.78.

3-(Benzyloxy)-4-bromo-2-nitrobenzaldehyde (22). A solution of methyl 3-(benzyloxy)-4-bromo-2-nitrobenzoate (**21**; 1.20 g, 33.0 mmol) in THF (30 mL) was treated with $LiBH_4$ (216 mg, 9.90 mmol, 3.0 equiv) at 25 °C under N_2. The reaction mixture was stirred at 25 °C (21 h). Saturated ammonium chloride (10 mL) was added and the reaction mixture diluted with H_2O (50 mL) and extracted with EtOAc (2 × 25 mL). The organic extract was washed with saturated NaCl, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. MPLC (SiO_2, 15 × 250 cm, 10–15% EtOAc–hexane gradient elution) afforded 1.04 g (1.11 g theor, 93%, 93–97%) of pure 3-(benzyloxy)-4-bromo-2-nitrobenzyl alcohol as a beige solid: mp 65–67 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.69 (1 H, d, J = 8 Hz, aromatic), 7.44–7.34 (5 H, m, Ph), 7.20 (1 H, d, J = 8 Hz, aromatic), 5.13 (2 H, s, CH_2Ph), 4.64–4.57 (2 H, m, $ArCH_2OH$); IR (KBr) ν_{max} 3408, 2962, 1536, 1466, 1456, 1366, 1275, 1221, 1047, 1003, 762 cm^{-1}; EIMS m/e (relative intensity) 337/339 (M^+, 1/1, 1), 303/305 (1), 231/233 (1), 213/215 (1), 107 (9), 91 (base); HRMS m/e for $C_{14}H_{12}BrNO_4$, calcd 336.9948, found 336.9942.

A solution of 3-(benzyloxy)-4-bromo-2-nitrobenzyl alcohol (500 mg, 1.48 mmol) in CH_2Cl_2 (35 mL) was treated with pyridinium dichromate (835 mg, 2.22 mmol, 1.5 equiv) at 25 °C under N_2. The reaction mixture was stirred at 25 °C (11.0 h), filtered through Celite, washed with 5% aqueous HCl (1 × 15 mL) and saturated NaCl (1 × 15 mL), and dried (Na_2SO_4) and the solvent was removed in vacuo. MPLC (SiO_2, 15 × 250 cm, 10% EtOAc–hexane eluant) afforded 410 mg (497 mg theor, 82%) of pure **22** as a yellow solid: mp 92–94 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 9.89 (1 H, s, ArCHO), 7.90 (1 H, d, J = 8 Hz, aromatic), 7.59 (1 H, d, J = 8 Hz, aromatic), 7.39 (5 H, br s, Ph), 5.15 (2 H, s, CH_2Ph); IR (KBr) ν_{max} 3093, 2957, 2895, 1696, 1582, 1555, 1535, 1360, 1262, 895, 791, 695 cm^{-1}; CIMS (NH_3) m/e (relative intensity) 355/353 (M^+ + 18, 1/1, 1), 304 (3), 150 (5), 108 (10), 91 (base).

Anal. Calcd for $C_{14}H_{10}BrNO_4$: C, 50.02; H, 2.99; N, 4.16. Found: C, 50.18; H, 3.00; N, 4.13.

2-Amino-3-(benzyloxy)-4-bromobenzaldehyde (23). A solution of 3-(benzyloxy)-4-bromo-2-nitrobenzaldehyde (**22**; 1.0 g, 2.96 mmol) in THF (70 mL) was treated with a solution of sodium hydrosulfite (2.57 g, 14.8 mmol, 5.0 equiv) in H_2O (35 mL). The reaction mixture was warmed at 60 °C (0.5 h), cooled, poured onto H_2O (50 mL), and extracted with EtOAc (3 × 50 mL). The EtOAc layer was washed with saturated NaCl (1 × 30 mL) and dried (Na_2SO_4) and the solvent removed in vacuo. Chromatography (SiO_2, 10% EtOAc–hexane eluant) afforded 0.842 g (0.906 g theor, 93%) of **23** as a light yellow solid: mp 81.5–82.5 °C (Et_2O–hexane); ^1H NMR ($CDCl_3$) δ 9.83 (1 H, s, ArCHO), 7.48–7.30 (5 H, m, Ph), 7.14 (1 H, d, J = 6 Hz, aromatic), 6.81 (1 H, d, J = 6 Hz, aromatic), 6.34 (2 H, br s, $ArNH_2$), 4.99 (2 H, s, CH_2Ph); IR (KBr) ν_{max} 3466, 3346, 2962, 2841, 2804, 1663, 1601, 1538, 1462, 1445, 1380, 1221, 765, 737 cm^{-1}; EIMS m/e 304/306 (M^+, 1/1, 3), 226 (3), 214 (2), 186 (1), 107 (1), 106 (1), 91 (base), 78 (7), 65 (15); HRMS for $C_{14}H_{12}NO_2Br$, calcd 305.0050, found 305.0028.

Anal. Calcd for $C_{14}H_{12}NO_2Br$: C, 54.92; H, 3.96; N, 4.57. Found: C, 55.30; H, 3.99; N, 4.30.

8-(Benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline (25). A solution of 2-acetylpyridine (**24**; 198 mg, 1.63 mmol, 1.0 equiv) in THF (17 mL) was treated with a 40% solution of *N*-benzyltrimethylammonium hydroxide (Triton-B,[28] 2.73 g, 6.52 mmol, 4 equiv) at 25 °C under N_2. A solution of **23** (0.50 g, 1.63 mmol) in THF (3.0 mL) was added to the reaction mixture. The reaction mixture was stirred at 25 °C (18 h), diluted with saturated ammonium chloride (1.5 mL), and further diluted with H_2O (20 mL) before being extracted into EtOAc (4 × 20 mL). The organic extract was dried (Na_2SO_4) and the solvent was removed in vacuo. Chromatography (SiO_2, 20% EtOAc–hexane eluant) afforded 0.516 g (0.638 g theor, 81%, 81–90%) of pure **25** as a beige solid: mp 91–92 °C (CH_2Cl_2–hexane); ^1H NMR ($CDCl_3$) δ 8.71–8.41 (1 H, m, aromatic), 8.57 (1 H, d, J = 9 Hz, aromatic), 8.17 (1 H, d, J

= 9 Hz, aromatic), 7.38–7.17 (10 H, m, aromatic), 5.55 (2 H, s, CH_2Ph); IR (KBr) ν_{max} 2952, 1605, 1586, 1472, 1441, 1377, 1096, 1082, 1019, 739 cm^{-1}; EIMS m/e (relative intensity) 390/392 (M^+, 1/1, 5), 313/315 (13), 299/301 (12), 284/286 (7), 205 (17), 192 (14), 164 (4), 141 (5), 114 (4), 91 (base), 78 (10); HRMS m/e for $C_{21}H_{15}N_2OBr$ calcd 390.0366, found 390.0374.

7-Bromo-8-hydroxy-2-(2′-pyridyl)quinoline (26). A solution of 8-(benzyloxy)-7-bromo-2-(2-pyridyl)quinoline (**25**; 100 mg, 0.26 mmol) in benzene (4 mL) saturated with HBr gas was warmed at 60 °C for 7 h. The reaction mixture was cooled and diluted with CH_2Cl_2 (10 mL), and saturated $NaHCO_3$ (5 mL) was added, with stirring, until the yellow suspension had gone into solution. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography (SiO_2, 75% EtOAc–hexane eluant) afforded 75.7 mg (77 mg theor, 98%) of **26** as an off-white solid: mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 8.74 (1 H, dd, J = 4.9, 1.3 Hz, C-6′ H), 8.64 (1 H, d, J = 8.6 Hz, C-4 H), 8.54 (1 H, d, J = 7.7 Hz, C-3′ H), 8.25 (1 H, d, J = 8.7 Hz, C-3 H), 7.89 (1 H, dt, J = 7.6, 1.8 Hz, C-4′ H), 7.62 (1 H, d, J = 8.8 Hz, C-6 H), 7.36 (1 H, ddd, J = 7.6, 4.8, 1.3 Hz, C-5′ H), 7.26 (1 H, d, J = 8.7 Hz, C-5 H); IR (KBr) ν_{max} 3379, 3055, 1589, 1558, 1475, 1398, 1331, 1257, 1113, 1068, 865, 785 cm^{-1}; EIMS m/e (relative intensity) 300/302 (M^+, 100/85), 272/274 (12/13), 221 (20), 193 (32), 192 (37), 166 (10), 141 (11), 137 (20), 136 (20), 89 (10), 87 (12), 83 (23), 78 (38), 63 (31), 62 (14); HRMS m/e for $C_{14}H_9BrN_2O$, calcd 299.9897, found 299.9900.

7-Bromo-2-(2′-pyridyl)quinoline-5,8-quinone (27). Fremy's Oxidation of 26. A solution of 7-bromo-8-hydroxy-2-(2-pyridyl)quinoline (**26**; 5.0 mg, 0.016 mmol) in acetone (2.0 mL) was added to a solution of potassium nitrosodisulfonate (Fremy's salt;[23] 89 mg, 0.33 mmol, 20 equiv) in 0.05 M KH_2PO_4 buffer (8.0 mL) at 25 °C. The reaction was stirred at 25 °C for 1.5 h. The reaction was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. Rapid chromatography[24] (SiO_2, 50% ethyl acetate–hexane eluant) afforded 5.2 mg (5.2 mg theor, 100%) of **27** as a yellow solid: mp 223 °C dec (yellow needles from CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.88 (1 H, d, J = 9 Hz, C-4 H), 8.76–8.56 (2 H, m, C-3′ H and C-6′ H), 8.50 (1 H, d, J = 9 Hz, C-3 H), 7.90 (1 H, dt, J = 9 Hz, 1 Hz, C-4′ H), 7.60 (1 H, s, C-6 H), 7.42–7.38 (1 H, m, C-5′H); IR (KBr) ν_{max} 3055, 1696, 1659, 1578, 1321, 1123 cm^{-1}; EIMS m/e (relative intensity) 314/316 (M^+, 1/1, base), 235 (15), 207 (57), 179 (78); HRMS m/e for $C_{14}H_7BrN_2O_2$, calcd 313.9690, found 313.9692.

In larger scale reactions, a solution of **26** (100 mg, 0.33 mmol) in acetone (30 mL) was added to a solution of Fremy's salt (1.78 g, 6.6 mmol, 20 equiv) in 0.05 M KH_2PO_4 buffer (100 mL) at 25 °C and stirred for 2.0 h. Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 80.5 mg (105 mg theor, 77%) of **27**. Repetitive reactions (10–20 equiv of Fremy's salt, 2–5 h) provided **27** (75–85%).

Similarly, **26** (11.0 mg, 0.035 mmol) in MeOH (2.0 mL) was added to a solution of Fremy's salt (36.0 mg, 0.134 mmol, 4.0 equiv) in 0.05 M KH_2PO_4 buffer (3.0 mL) at 25 °C and stirred for 2.5 h. Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 5.8 mg (11.0 mg theor, 53%) of **27**.

7-Azido-2-(2′-pyridyl)quinoline-5,8-quinone (28). A stirred solution of 7-bromo-2-(2′-pyridyl)quinoline-5,8-quinone (**27**; 6 mg, 0.019 mmol) in 0.15 mL of CH_2Cl_2 was treated with a solution of sodium azide (1.4 mg, 0.021 mmol, 1.1 equiv) in 0.02 mL of H_2O at 25 °C under a N_2 atmosphere, and the mixture was stirred at 25 °C for 23 h. Removal of the solvent in vacuo and chromatography (SiO_2, 1 × 16 cm, 50–60% ethyl acetate–hexane eluant; gradient solution) afforded 4.5 mg (5.3 mg theor, 85%) of **28** as an orange-yellow solid: ^1H NMR ($CDCl_3$) δ 8.82 (1 H, d, J = 8 Hz, C-4 H), 8.55–8.78 (2 H, m, C-3′ H and C-6′ H), 8.46 (1 H, d, J = 8 Hz, C-3 H), 7.96 (1 H, dt, J = 8 Hz, C-4′ H), 7.25–7.48 (1 H, m, C-5′ H), 6.50 (1 H, s, C-6 H); IR (KBr) ν_{max} 2124, 1696, 1651, 1597, 1580, 1451, 1356, 1325, 1266, 1196, 1129, 1096, 976 cm^{-1}; EIMS m/e (relative intensity) 251 (5), 249 ($M^+ - N_2$, 29), 221 (7), 195 (4), 182 (13), 154 (14), 78 (28).

A number of similar experiments (5–37 mg scale) provided **28** (70–85%).

7-Amino-2-(2′-pyridyl)quinoline-5,8-quinone (29). A stirred solution of **28** (49 mg, 0.177 mmol) in dry CH_2Cl_2 (1.0 mL) under a N_2 atmosphere was treated with a solution of triphenylphosphine (46.4 mg, 0.177 mmol, 1.0 equiv) in 0.5 mL of CH_2Cl_2 with stirring. Evolution of nitrogen was visible within 1 min after addition of Ph_3P. Stirring was continued at 25 °C for 1.0 h. Removal of the solvent in vacuo and chromatography (SiO_2, 1 × 10 cm, 60% ethyl acetate–hexane eluant) afforded 46.5 mg (90.5 mg theor, 51%) of the phosphine imine as a purple solid: ^1H NMR ($CDCl_3$) δ 8.62 (1 H, d, J = 7.5 Hz, C-4 H), 8.39 (1 H, d, J = 7.5 Hz, C-3 H), 8.42–8.65 (2 H, m, C-3′ H and C-6′ H), 7.12–7.97 (17 H, m, C-4′ H, C-5′ H, 3 Ph), 6.40 (1 H, s, C-6 H); IR (KBr) ν_{max} 3061, 1688, 1619, 1588, 1555, 1538, 1437, 1408, 1323, 1262, 1184, 1136, 1109, 1051, 1036, 9611, 849 cm^{-1}; EIMS m/e (relative intensity) 511 (M^+, 21), 262 (base), 183 (91), 108 (42).

A suspension of the phosphine imine (46.5 mg, 0.091 mmol) in 0.40 mL of THF was treated with 0.60 mL of acetic acid and 0.40 mL of H_2O, and the solution was allowed to stir at 25 °C for 0.3 h. Chromatography (SiO_2, 1 × 10 cm, 80–100% ethyl acetate–hexane gradient elution) and washing with ether to remove triphenylphosphine oxide afforded 22.5 mg (22.9 mg theor, 98%) of **29** as a red-orange solid: mp >300 °C (EtOAc); ^1H NMR (Me_2SO-d_6) δ 8.66 (1 H, d, J = 8 Hz, C-4 H), 8.25–8.68 (2 H, m, C-3′ H, C-6′ H), 8.35 (1 H, d, J = 8 Hz, C-3 H), 7.98 (1 H, dd, J = 8 Hz, C-4′ H), 7.38–7.60 (1 H, m, C-5′ H), 7.32 (2 H, br s, NH_2), 5.85 (1 H, s, C-6 H); IR (KBr) ν_{max} 3426, 3299, 1703, 1646, 1588, 1453, 1385, 1356, 1266, 1190, 1148, 1105, 1075, 1055, 752 cm^{-1}; EIMS m/e (relative intensity) 251 (M^+, 49), 224 (17), 195 (14), 182 (11), 156 (19), 78 (23); HRMS m/e for $C_{14}H_9N_3O_2$, calcd 251.0694, found 251.0704.

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Supplementary Material Available: Detailed procedures for the preparation of **3–5a**, 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine (**6**), **7c**, 7-bromoquinoline-5,8-quinone (**12**), **15**, and **16** (7 pages). Ordering information is given on any current masthead page.