Total Synthesis of Phomazarin

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Abstract: A concise total synthesis of phomazarin (**1**) is detailed enlisting a heterocyclic azadiene inverse electron demand Diels−Alder reaction (1,2,4-triazine → pyridine) for preparation of the fully substituted and appropriately functionalized pyridine C-ring. Thus, [4 + 2] cycloaddition (85%) of triethyl 1,2,4-triazine-3,5,6-tricarboxylate (**2**) with trimethoxyethylene (**3**) followed by conversion of the cycloadduct **11** to the cyclic anhydride **13** provided the phomazarin C-ring with the three carboxylates suitably differentiated. Linkage of the A- and C-rings through selective nucleophilic addition of the aryllithium reagent **9** to the least hindered anhydride carbonyl of **13** followed by Friedel−Crafts closure of the B-ring provided the fully functionalized phomazarin skeleton. The successful structural correlation of synthetic **1** with natural material and its derivatives confirmed the latest structural assignment for the natural product.

Isolated from cultures of *Phoma terrestris* Hansen (*Pyrenochaeta terrestris* Hansen) in 1940,[1] phomazarin (**1**) is the most widely known and extensively studied aza anthraquinone (Figure 1). The original structural assignment[1] has been revised twice,[2,3] based largely on biosynthetic considerations advanced by Birch[4] in conjunction with chemical degradation studies and reevaluations with increasingly modern NMR spectroscopic techniques. To date, confirmation of the structure by total synthesis has not been realized and phomazarin has been the subject of only limited synthetic effort.[5]

Herein, we report its total synthesis which serves to unambiguously establish the structure **1** for phomazarin on the basis of the implementation of a heteroaromatic azadiene Diels−Alder reaction.[6] Thus, inverse electron demand Diels−Alder reaction of the electron-deficient 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine (**2**)[7,8] with 1,1,2-trimethoxyethylene (**3**)[9] was anticipated to provide **11** ideally functionalized for elaboration to the pentasubstituted pyridine C-ring (Scheme 1). The dienophile methoxy substituents serve to enhance its nucleophilic character and introduce the phomazarin C3 and C4 hydroxy groups. In a complementary manner, the three electron-withdrawing ester groups substituting the 1,2,4-triazine nucleus increase its [4 + 2] cycloaddition reactivity toward such electron-rich dienophiles and provide the necessary functionality for introduction of the natural product C2 carboxylic acid and C9/C10 quinone carbonyls. Formation of cyclic anhydride **13** followed by a projected selective nucleophilic addition to the sterically more accessible anhydride carboxylate enlisting the aryllithium reagent **9** would serve to introduce the phomazarin A-ring and differentiate the three ester groups. Final intramolecular Friedel−Crafts acylation and selective *O*-demethylation would then serve to complete the total synthesis. Because the *O*-methyl derivatives of phomazarin methyl ester have been extensively characterized

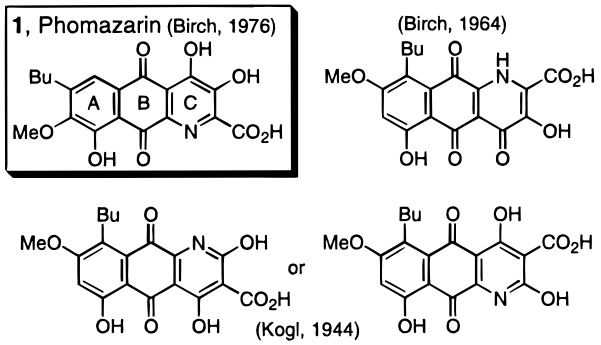

Figure 1.

(1) Kögl, F.; Sparenburg, J. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 1180. Kögl, F.; Quackenbush, F. W. *Recl. Trav. Chim. Pays-Bas* **1944**, *63*, 251. Kögl, F.; van Wessem, G. C.; Elsbach, O. I. *Recl. Trav. Chim. Pays-Bas* **1945**, *64*, 23.

(2) Birch, A. J.; Butler, D. N.; Rickards, R. W. *Tetrahedron Lett.* **1964**, 1853.

(3) Birch, A. J.; Effenberger, R.; Rickards, R. W.; Simpson, T. J. *Tetrahedron Lett.* **1976**, *27*, 2371. Birch, A. J.; Butler, D. N.; Effenberger, R.; Rickards, R. W.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 807.

(4) Birch, A. J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 816.

(5) Guay, V.; Brassard, P. *J. Heterocycl. Chem.* **1987**, *24*, 1649. Guay, V.; Brassard, P. *Synthesis* **1987**, 294.

(6) Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149. Boger, D. L. *Bull. Chim. Soc., Belg.* **1990**, *99*, 599. Boger, D. L.; Patel, M. In *Progress in Heterocyclic Chemistry 1989*; Suschitzky, H., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1989; Vol. 1; p 30. Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic: San Diego, CA, 1987. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

(7) Boger, D. L.; Panek, J. S.; Yasuda, M. *Org. Synth.* **1987**, *66*, 142.

(8) (a) Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, 5171. Burg, B.; Dittmar, W.; Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2897. Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2901. (b) Neunhoeffer, H.; Fruhauf, H.-W. *Liebigs Ann. Chem.* **1972**, *758*, 120. Neunhoeffer, H.; Werner, G. *Liebigs Ann. Chem.* **1973**, 1955. Neunhoeffer, H.; Frey, G. *Liebigs Ann. Chem.* **1973**, 1963. Oeser, E. *Liebigs Ann. Chem.* **1973**, 1970. Neunhoeffer, H.; Werner, G. *Liebigs Ann. Chem.* **1973**, 1955. (c) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782. Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1984**, *25*, 3175. Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1982**, *47*, 3763.

(9) Bakker, C. G.; Scheeren, J. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 13. Spinning band distillation required to separate **3** from methyl methoxyacetate and 1,1,1,2-tetramethoxyethane was unnecessary, and material that was as low as 40% **3** worked satisfactorily in the thermal cycloaddition reaction. See also: Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033. and Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.

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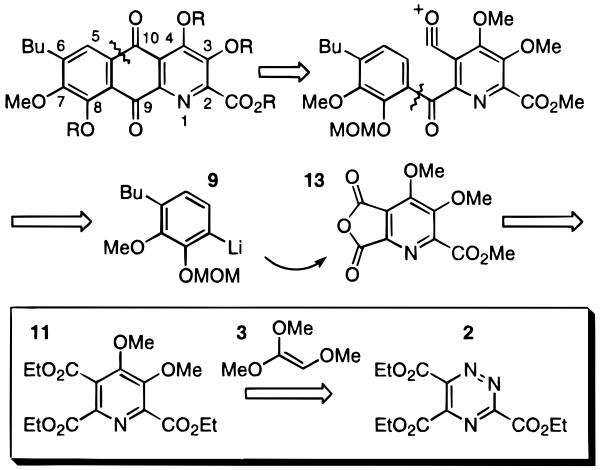
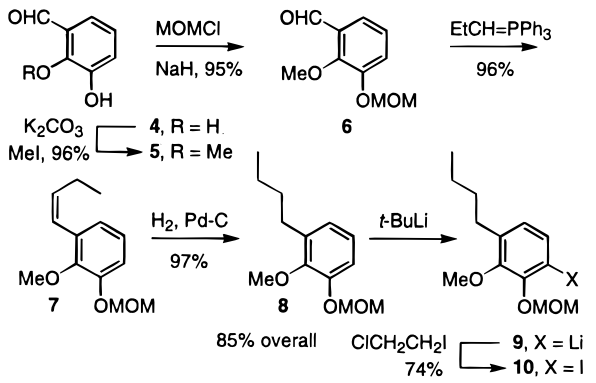
Scheme 1



Scheme 2



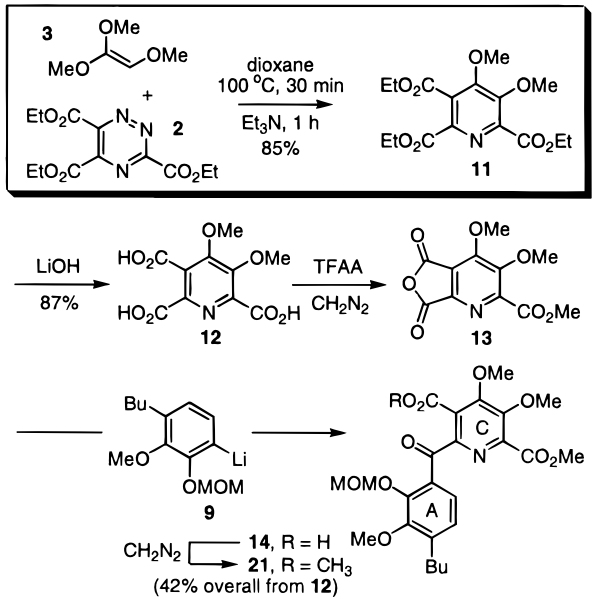
and are considerably easier to work with than the insoluble, oxidatively labile, and polar (zwitterionic) phomazarin itself, the approach was designed to pass through 3,4-*O*-dimethyl phomazarin methyl ester as a more manageable comparison derivative despite the challenge this poses for the final deprotection to provide the natural product.

Preparation of the A-Ring. Selective methylation of the more acidic C2-hydroxy group of 2,3-dihydroxybenzaldehyde (**4**, 1 equiv of K_2CO_3, 1.3 equiv CH_3I, DMF, 25 °C, 96%) and subsequent MOM protection of the remaining C3-hydroxy group of **5**[10] provided **6** (95%), Scheme 2. The MOM protecting group was enlisted to promote directed metalation at C4 for linkage of the A-ring with the pyridyl C-ring. The *n*-butyl side chain was introduced by Wittig reaction of **6** with propylidenetriphenylphosphorane (96%, 11:1 cis:trans) followed by catalytic hydrogenation of **7** to provide **8** (97%) in 85% overall yield from **4**. Directed ortho metalation of **8** occurred cleanly at temperatures >−20 °C with *n*-BuLi or more effectively with *t*-BuLi (1.1 equiv, Et_2O, 0 °C 1 h, 23 °C, 1 h) to provide **9** in situ. Preliminary studies on this metalation were conducted using 1-chloro-2-iodoethane as an electrophile providing **10**[11] (74%), an alternative metalation precursor to **9**.

Heterocyclic Azadiene Diels−Alder Preparation of the C-Ring and Coupling with the A-Ring. The key inverse electron demand Diels−Alder reaction of the 1,2,4-triazine **2**[7] with 1,1,2-trimethoxyethylene (**3**)[9] proceeded effectively providing the fully substituted C-ring precursor **11** (85%). The [4 + 2] cycloaddition reaction was observed even at 25 °C, albeit proceeding more slowly (5 h, $CHCl_3$, 22%; 12 h, 60−70%),

(10) Kessar, S. V.; Gupta, Y. P.; Mohammad, T.; Goyal, M.; Sawal, K. K. *J. Chem. Soc., Chem. Commun.* **1983**, 400.

Scheme 3



and typically provided a mixture of the unaromatized cycloadduct and **11** (Scheme 3). Thus, the complementary match of the electron-rich character of the dienophile and the electron-deficient nature of the 1,2,4-triazine imparted by the substituents provides an uncatalyzed Diels−Alder cycloaddition reaction that proceeds effectively even at room temperature. In the optimization of the reaction, we established that the slow and final elimination step involving the loss of CH_3OH was promoted at higher reaction temperatures (100 °C, dioxane, 30 min) and could be driven to completion by a brief Et_3N treatment (25 °C, 1 h) prior to purification isolation. Exhaustive ester hydrolysis of **11** (4 equiv of LiOH, THF/CH_3OH/H_2O 3:2:1, reflux, 36 h, 87%) cleanly provided the tricarboxylic acid **12** and set the stage for differentiation of the three carboxylates.[12] Treatment of **12** with TFAA followed by CH_2N_2 esterification provided the key cyclic anhydride **13** in which the C2 carboxylate had been converted to a methyl ester.[13] The two-step conversion of **12** to **13** proved uniquely successful with TFAA and was not achieved with Ac_2O. Presumably, this may be attributed to the enhanced reactivity of the trifluoroacetyl mixed anhydrides, the entropic assistance for closure of an intermediate half acid anhydride to the cyclic anhydride, and the subsequent ease of hydrolysis of the remaining C2 trifluoroacetyl mixed anhydride[14] by adventitious water upon exposure to the diazomethane esterification conditions.[15] The remaining addition of the A-ring aryllithium reagent **9** provided **14** with selective

(11) Data for **10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, 1H, J = 8.2 Hz), 6.68 (d, 1H, J = 8.2 Hz), 5.15 (s, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 2.56 (t, 2H, J = 7.3 Hz), 1.50−1.48 (m, 2H), 1.35 (sextet, 2H, J = 7.3 Hz), 0.91 (t, 3H, J = 7.3 Hz); IR (neat) ν_{max} 2929, 2856, 1569, 1463, 1440, 1416, 1390, 1263, 1204, 1161, 1080, 1010, 839 cm^{-1}; FABHRMS (NBA−CsI) m/z 483.9439 (M^+ + Cs, $C_{13}H_{19}O_3I$ requires 482.9433).

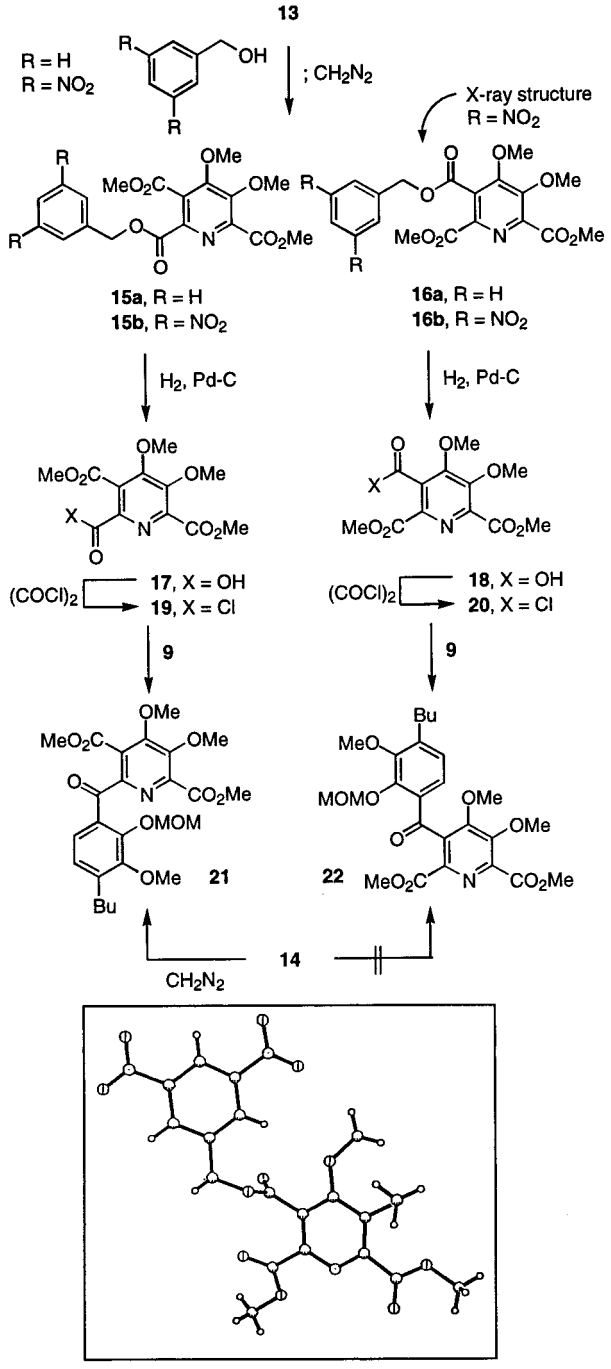
(12) When this reaction was conducted at room temperature (10 equiv of LiOH, 25 °C, 16 h, quantitative), the C3 ethyl ester was not hydrolyzed. Data for 4,5-dimethoxy-3-(ethoxycarbonyl)pyridine-2,6-dicarboxylic acid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.31 (q, 2H, J = 7.2 Hz), 3.97 (s, 3H), 3.90 (s, 3H), 1.28 (t, 3H, J = 7.2 Hz).

(13) Deliberate hydrolysis of **13** provided 4,5-dimethoxy-6-(methoxycarbonyl)pyridine-2,3-dicarboxylic acid: ^{1}H NMR (D_2O, 400 MHz) δ 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H).

(14) The crude product representing the corresponding cyclic anhydride/C2 mixed trifluoroacetyl mixed anhydride exhibits the following data: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.57 (s, 3H), 4.07 (s, 3H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.39 (s, 3H), 3.90 (s, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −7.03 (s).

(15) Boger, D. L.; Baldino, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 11418.

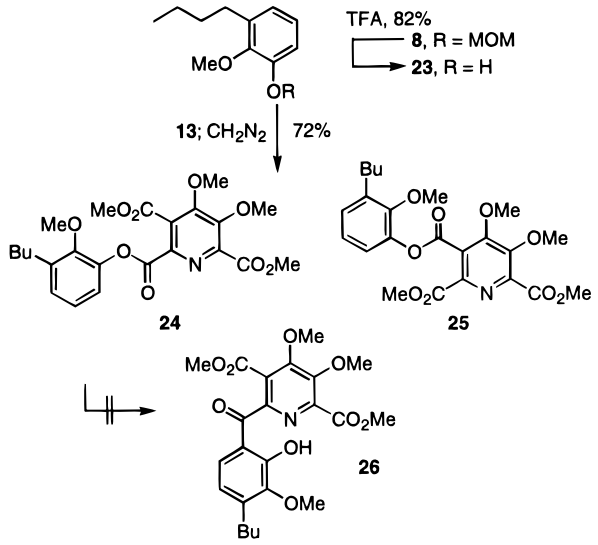
Scheme 4



nucleophilic addition to the least hindered of the cyclic anhydride carbonyls. The four-step sequence for the conversion of triacid **12** to **21** was typically carried out without intermediate purifications providing **21** in 30−42% yield overall.

Establishment of the Regioselectivity of the A and C Ring Coupling. In preliminary efforts to differentiate the three carboxylates on the pyridine **11**, simple regioselective esterification of the cyclic anhydride **13** was also examined. Although this did not prove especially successful, an X-ray structure determination of an intermediate and its subsequent correlation with the coupling product **14** confirmed the structural assignments. Thus, reaction of **13** with benzyl alcohol or 3,5-dinitrobenzyl alcohol followed by CH_2N_2 esterification of the liberated carboxylic acid provided a separable 63:37 mixture of **15** and **16** (50−81%) derived from alcohol nucleophilic attack at the less hindered and more hindered anhydride carbonyl,[16] respectively (Scheme 4). The single-crystal X-ray structure determination[17] of **16b** unambiguously provided the structure of the minor product and established the regioselectivity preference of nucleophilic attack. Hydrogenolysis deprotection of both **15a**,**b** provided the same carboxylic acid **17**, and deprotection of both **16a**,**b** provided the isomeric acid **18**. Although equilibration isomerism between pyridine-2,3-dicarboxylic acid monoesters and monoacid chlorides has been observed,[18] no isomerism between **17** and **18** was observed at 25 °C (48 h, CH_3OH). However at reflux, a 62:38 mixture of **18**:**17** was observed after 48 h (CH_3OH) starting with **18**. Activation of **17** and **18** for nucleophilic attack by conversion to the acid chlorides followed by addition of the C-ring aryllithium reagent **9** or its corresponding higher order cuprate provided **21** and **22**, respectively. Diazomethane esterification of **14**, derived from the route detailed in Scheme 3, also provided **21** correlating it with the sample that was established to contain the A-ring linked to the C6 versus C5 carboxylate.

Scheme 5



Concurrent with these efforts, we briefly examined the potential of regioselective esterification of **13** with the A-ring phenol **23** followed by Fries rearrangement of **24** to provide **26** as an alternative approach to linking the A and C rings (Scheme 5). Esterification of anhydride **13** with **23** followed by CH_2N_2 esterification of the liberated carboxylic acid proceeded surprisingly effectively (72%) albeit to provide a 57:43 mixture of **24** and **25**. Initial attempts to promote the Fries rearrangement of **24** ($BF_3{\cdot}OEt_2$, CH_2Cl_2) were not successful. Given the rather nonselective esterification of **23**, these studies were not pursued further.

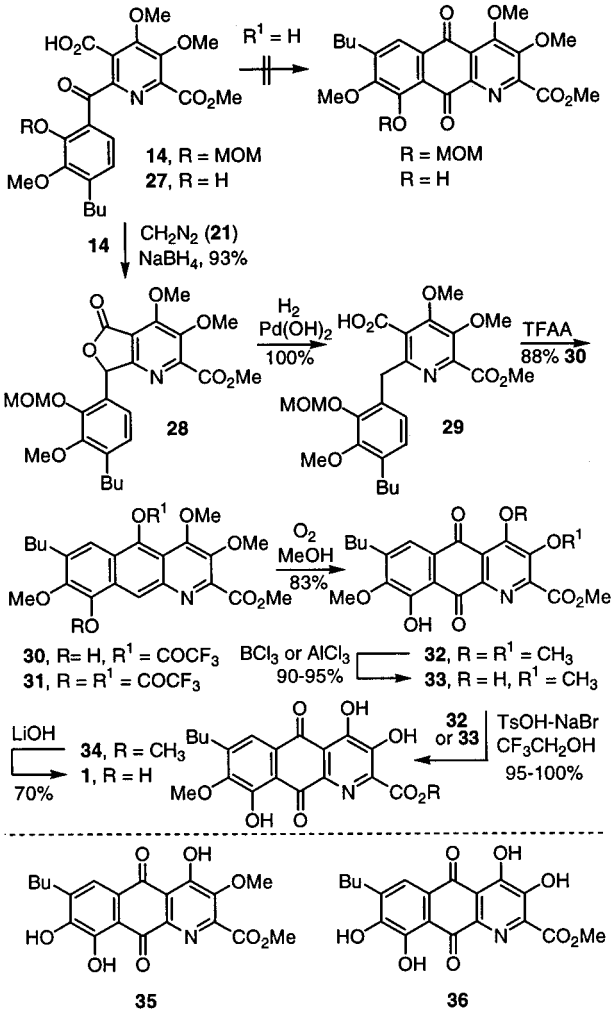
Intramolecular Friedel−Crafts Acylation and Completion of the Phomazarin Total Synthesis. In contrast to initial expectations, efforts to promote the Friedel−Crafts closure of the B-ring with **14** directly were not successful (Scheme 6). Under a range of mild reaction conditions only MOM deprotection[19] was observed without evidence of ring closure. More forcing conditions led to the consumption of **14** and **27** but

(16) In an analogous manner, treatment of **13** with *t*-BuOH (30%) and $(Ph)_2CHOH$ (70%) provided 70:30 and 58:42 mixtures of the corresponding C6:C5 esters (**15c,d**:**16c,d**). Details are provided in the Supporting Information.

(17) Details of the X-ray structure of **16b** are supplied in the Supporting Information and have been deposited with the Cambridge Crystallographic Data Centre.

(18) Kenyon, J.; Thaker, K. *J. Chem. Soc.* **1957**, 2531. Chase, B. H.; Hey, D. H. *J. Chem. Soc.* **1952**, 553.

Scheme 6



without evidence of B-ring closure. The electron-withdrawing properties of the A-ring C1 carbonyl, the competitive MOM deprotection, coupled with reaction of the A-ring C2 hydroxy group and, more significantly, the C1 keto carbonyl with the intermediate acylium ion appeared to be contributing to this failure to close the B-ring with **14**. This was successfully addressed by removal of the ketone by $NaBH_4$ reduction of **21** to provide the lactone **28** (93%) followed by hydrogenolysis to provide **29** (100%). Exposure of **29** to TFAA cleanly resulted in Friedel−Crafts closure of the B-ring and concurrent MOM deprotection providing a variable and inconsequential mixture of **30** and **31** with no detection of the intermediate bisphenol. Conditions were devised that provided cleanly the single mono-(trifluoroacetate) **30** (88%; TFAA, 50 °C, 72 h) which has been tentatively assigned as the C5 trifluoroacetate on the basis of its air oxidation stability and the downfield C10−H chemical shift of δ 9.05. Subsequent methanolysis of **30** or the mixture of trifluoroacetates (30 °C, CH_3OH) in the presence of air led directly to **32** (83%) resulting from deprotection followed by an unusually facile oxidation to the B-ring quinone without detection of the intermediate phenol. The resulting 3,4-*O*-dimethyl phomazarin methyl ester (**32**) proved identical in all respects (^1H and ^{13}C NMR, IR) to authentic material[3] derived from the natural product confirming the Birch 1976 structural assignment.[3]

Completion of the total synthesis required selective cleavage of the C3 and C4 versus C7 methyl ethers and methyl ester hydrolysis to provide **1**. A variety of conditions were explored, and no single-step deprotection was found capable of converting **32** directly to **1**. However, clean C4 methyl ether deprotection to provide **33** was accomplished with BCl_3 (10 equiv, CH_2Cl_2, −78 to −50 °C, 3 h, ≥95%), $AlCl_3$ (14−15 equiv, CH_2Cl_2, 25 °C, 24 h or reflux, 7 h, 90%), or NaBr−TsOH (20 equiv each, CH_3OH, reflux, 12 h, 74%), and the latter reaction also provided phomazarin methyl ester (**34**) in 10%. With enlistment of CF_3CH_2OH as solvent,[21] the latter treatment with NaBr−TsOH (20 equiv each) cleanly provided only **33** at 25 °C (24 h, 100%) and, more importantly, effectively provided phomazarin methyl ester (**34**) at 100 °C (36 h, 95−100%) derived from the desired selective C3 and C4 methyl ether deprotections. In contrast, treatment of either **32** or **33** with BBr_3 (10 equiv, −78 to −40 °C, 6 h) provided a 1:1 mixutre of **34** and **35** derived from C4 and nonselective C3 or C7 methyl ether deprotections along with a trace of **36**. Both **33** and **34** correlated with the corresponding materials derived from phomazarin described by Birch further confirming the structure of the natural product. Diagnostic of the site of methyl ether deprotection,[3] the adjacent carbonyls exhibited perturbed IR carbonyl stretches derived from H-bonding to the proximal free phenol: C4−OH/C10 quinone (1670 → 1640 cm^{-1}), C3−OH/ester carbonyl (1740 → 1680 cm^{-1}). Final hydrolysis of phomazarin methyl ester (**34**) with LiOH (20 equiv, THF−H_2O, 30 °C, 24 h, 70%) provided phomazarin identical in all respects with authentic material.[1−3]

Table 1. Cytotoxic Activity

compd	IC_{50}, μg/mL (L-1210)	compd	IC_{50}, μg/mL (L-1210)
32	0.3	**1**	>100
33	0.03	**35**	1.6
34	2.5	**36**	25

In Vitro Cytotoxic Activity. A preliminary cytotoxicity screen of **1** and the closely related synthetic intermediates revealed that phomazarin was inactive but that two of its immediate precursors, **32** and **33**, exhibit useful levels of activity (Table 1). Although the free carboxylic acids were less potent (e.g. **1** versus **34**),[22] the methyl esters exhibited interesting levels of cytotoxic activity, and capping both the C7 and C3 phenols as methyl ethers (**34** versus **36** and **33** versus **34** or **35** versus **36**) increased the cytotoxic activity 10−100× while conversion of the C4 phenol to a methyl ether (**32** versus **33**) lowered the potency 10×.

Experimental Section

3-Hydroxy-2-methoxybenzaldehyde (5). A solution of **4** (6.0 g, 43.4 mmol) in anhydrous DMF (100 mL) was treated with K_2CO_3 (6.0 g, 43.4 mmol) at 25 °C, and the mixture was stirred for 30 min. Methyl iodide (3.50 mL, 56.2 mmol) was added, and the reaction mixture was further stirred for 20 h before being quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum. Recrystallization (EtOAc−hexane) afforded **5**[10] (6.31 g, 96%) as a pale yellow solid: mp 109 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ

(19) Data for **27**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, 1H, J = 8.4 Hz), 6.68 (d, 1H, J = 8.4 Hz), 4.16 (s, 3H), 4.02 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H), 2.65 (t, 2H, J = 7.8 Hz), 1.56 (m, 2H), 1.37 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz); ^1H NMR (CD_3OD, 400 MHz) δ 7.19 (d, 1H, J = 8.3 Hz), 6.68 (d, 1H, J = 8.3 Hz), 4.11 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 2.65 (t, 2H, J = 7.7 Hz), 1.56 (m, 2H), 1.37 (m, 2H), 0.93 (t, 3H, J = 7.3 Hz); ^1H NMR (acetone-d_6, 400 MHz) δ 7.48 (s, 1H), 7.22 (d, 1H, J = 7.8 Hz), 6.82 (d, 1H, J = 7.8 Hz), 5.01 (s, 1H), 4.18 (s, 3H), 4.00 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 2.73 (t, 2H, J = 7.4 Hz), 1.66 (m, 2H), 1.48 (m, 2H), 1.04 (t, 3H, J = 7.3 Hz).

(20) Details are provided in the Supporting Information.

(21) Boger, D. L.; Cassidy, K. C.; Nakahara, S. *J. Am. Chem. Soc.* **1993**, *115*, 10733.

10.27 (s, 1H), 7.38 (dd, 1H, J = 1.7, 7.7 Hz), 7.24 (dd, 1H, J = 1.7, 8.0 Hz), 7.15 (t, 1H, J = 7.9 Hz), 5.86 (br s, 1H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.5, 149.4, 149.1, 129.0, 125.1, 121.83, 121.76, 63.9; IR (neat) ν_{max} 3193, 1666, 1605, 1582, 1475, 1444, 1372, 1295, 1220, 997 cm^{-1}; FABHRMS (NBA−NaI) m/z 153.0557 (M^+ + H, $C_8H_8O_3$ requires 153.0552).

2-Methoxy-3-(methoxymethoxy)benzaldehyde (6). A suspension of NaH (60% in oil, 600 mg, 15.0 mmol) in anhydrous THF (20 mL) was treated with **5** (1.98 g, 13.0 mmol) in anhydrous THF (5 mL) dropwise at 0 °C over 5 min. The mixture was stirred for 10 min before (MOM)Cl (1.20 mL, 15.7 mmol) was added. The resulting mixture was stirred at 25 °C for 2 h before it was poured into H_2O (20 mL). The aqueous phase was extracted by Et_2O (3 × 20 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated under vacuum. Chromatography (SiO_2, 15% EtOAc−hexane) afforded **6** (2.44 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.43 (s, 1H), 7.49 (dd, 1H, J = 1.6, 7.8 Hz), 7.41 (dd, 1H, J = 1.6, 8.0 Hz), 7.12 (t, 1H, J = 8.0 Hz), 5.26 (s, 2H), 4.01 (s, 3H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.9, 153.2, 150.5, 130.0, 124.2, 122.5, 120.9, 95.2, 62.5, 56.4; IR (neat) ν_{max} 2938, 2900, 2832, 1690, 1584, 1480, 1386, 1250, 1154, 1087, 1023, 1000, 923, 905 cm^{-1}; FABHRMS (NBA−NaI) m/z 197.0820 (M^+ + H, $C_{10}H_{12}O_4$ requires 197.0814). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.89; H, 6.39.

1-(1-Butenyl)-2-methoxy-3-(methoxymethoxy)benzene (7). A solution of *n*-$PrPPh_3Br$ (500 mg, 1.30 mmol) in anhydrous THF was treated with *t*-BuOK (157 mg, 1.40 mmol) at 25 °C, and the resulting orange solution was stirred for 30 min before a solution of **6** (197 mg, 1.00 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was stirred for 1 h during which time the orange color disappeared. The reaction mixture was poured into saturated aqueous NH_4Cl (10 mL), and the aqueous phase was extracted by Et_2O (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum. Chromatography (SiO_2, 5% EtOAc−hexane) afforded **7** (213 mg, 96%) as a mixture of cis and trans isomers (11:1) as a colorless oil. Data for major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (dd, 1H, J = 1.6, 8.0 Hz), 6.99 (t, 1H, J = 8.0 Hz), 6.93 (dd, 1H, J = 1.4, 7.6 Hz), 6.50 (d, 1H, J = 11.6 Hz), 5.73 (dt, 1H, J = 7.4, 11.6 Hz), 5.21 (s, 2H), 3.80 (s, 3H), 3.53 (s, 3H), 2.27 (m, 2H), 1.03 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 147.7, 135.3, 132.2, 123.6, 123.4, 123.3, 115.4, 95.2, 60.6, 56.1, 22.0, 14.3; IR (neat) ν_{max} 2952, 1575, 1471, 1427, 1401, 1261, 1222, 1154, 1087, 1034, 1010, 926 cm^{-1}; FABHRMS (NBA−NaI) m/z 222.1247 (M^+, $C_{13}H_{18}O_3$ requires 222.1256). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 69.91; H, 8.47.

1-Butyl-2-methoxy-3-(methoxymethoxy)benzene (8). A suspension of **7** (144 mg, 0.649 mmol) and 10% Pd−C (7 mg) in EtOH (5 mL) was stirred for 17 h under 1 atm of H_2. The reaction mixture was filtered through a pad of Celite (EtOH, 3 × 5 mL), and the solvent was removed under vacuum. Chromatography (SiO_2, 5% EtOAc−hexane) afforded **8** (141 mg, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (dd, 1H, J = 1.9, 8.2 Hz), 6.93 (t, 1H, J = 8.1 Hz), 6.82 (dd, 1H, J = 1.9, 8.2 Hz), 5.20 (s, 2H), 3.82 (s, 3H), 3.50 (s, 3H), 2.60 (t, 2H, J = 7.8 Hz), 1.53−1.61 (m, 2H), 1.36 (sextet, 2H, J = 7.3 Hz), 0.91 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 147.9, 136.9, 123.7, 123.2, 114.1, 95.1, 60.7, 56.1, 32.9, 29.6, 22.6, 13.9; IR (neat) ν_{max} 2959, 2930, 1579, 1477, 1266, 1221, 1154, 1087, 1032, 924 cm^{-1}; FABHRMS (NBA−NaI) m/z 224.1416 (M^+, $C_{13}H_{20}O_3$ requires 224.1412). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.37; H, 9.31.

4,5-Dimethoxy-2,3,6-tris(ethoxycarbonyl)pyridine (11). A solution of triethyl 1,2,4-triazine-3,5,6-tricarboxylate[7] (**2**, 70 mg, 0.24 mmol) in anhydrous 1,4-dioxane (1 mL) was treated with trimethoxyethylene (**3**, purity 40%,[9] 400 mg, 1.34 mmol) at 25 °C, and the mixture was warmed at 100 °C with stirring for 30 min. The reaction mixture was cooled to 25 °C, and Et_3N (0.5 mL) was added to complete elimination of CH_3OH from the Diels−Alder product. The mixture was stirred for 1 h at 25 °C, and the volatiles were removed under vacuum. Chromatography (SiO_2, 15% EtOAc−hexane) afforded **11** (71 mg, 85%) as a pale yellow oil which upon recrystallization from Et_2O−hexane (−78 °C) provided a colorless solid: mp 49−50 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.46 (q, 2H, J = 7.2 Hz), 4.43 (q, 2H, J = 7.2 Hz), 4.41 (q, 2H, J = 7.2 Hz), 4.03 (s, 3H), 3.96 (s, 3H), 1.41 (t, 3H, J = 7.2 Hz), 1.382 (t, 3H, J = 7.2 Hz), 1.380 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2, 163.9, 163.2, 157.6, 150.0, 146.4, 141.0, 129.2, 62.4, 62.2, 62.1, 62.0, 61.5, 14.0 (2C), 13.9; IR (neat) ν_{max} 2982, 1743, 1569, 1550, 1466, 1371, 1343, 1268, 1155, 1047, 963, 864 cm^{-1}; FABHRMS (NBA−NaI) m/z 356.1352 (M^+ + H, $C_{16}H_{21}NO_8$ requires 356.1345). Anal. Calcd for $C_{16}H_{21}NO_8$: C, 54.08; H, 5.96; N, 3.94. Found: C, 53.78; H, 5.91; N, 3.67.

This reaction was conducted on 100 mg−2.5 g scales in yields ranging from 73 to 86%.

4,5-Dimethoxypyridine-2,3,6-tricarboxylic Acid (12). A solution of **11** (60 mg, 0.619 mmol) in $THF/CH_3OH/H_2O$ (3/2/1, 3 mL) was treated with $LiOH\cdot H_2O$ (106 mg, 2.54 mmol) at 25 °C, and the mixture was warmed at 90 °C and was stirred for 36 h. The reaction mixture was cooled to 25 °C, and H_2O (3 mL) was added. The aqueous phase was washed with Et_2O (3 mL) before it was acidified to pH 2−3 by the addition of 1 N aqueous HCl. The aqueous phase was saturated with NaCl and extracted with EtOAc (5 × 5 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under vacuum. After the trituration with Et_2O−hexane, **12** (40 mg, 87%) was obtained as a white solid: mp 157−159 °C (decomp); ^{1}H NMR (CD_3OD, 400 MHz) δ 4.06 (s, 3H), 4.01 (s, 3H); ^{1}H NMR (D_2O, 400 MHz) δ 4.13 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.7, 167.0, 165.9, 159.3, 152.1, 146.8, 141.3, 131.5, 62.8, 62.3; IR (neat) ν_{max} 3700−2700 (br), 1722, 1462, 1380, 1283, 1216, 1038 cm^{-1}; FABHRMS (NBA−NaI) m/z 272.6415 (M^+ + H, $C_{10}H_9NO_8$ requires 272.0406). Anal. Calcd for $C_{10}H_9NO_8$: C, 44.29; H, 3.35; N, 5.17. Found: C, 44.11; H, 3.42; N, 4.96.

4,5-Dimethoxy-6-(methoxycarbonyl)-2,3-dicarboxylic Anhydride (13). A sample of **12** (16 mg, 0.059 mmol) was stirred in trifluoroacetic anhydride (1 mL) at 25 °C for 2 h. The volatile material was removed under vacuum, the crude product[14] was dissolved in THF (1 mL), and ethereal CH_2N_2 was added at 0 °C until the color of the solution remained yellow. The resulting solution was stirred for 5 min before the solvent was removed under vacuum. The crude product **13**[13] (12 mg) was used for the next reaction without purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.51 (s, 3H), 4.00 (s, 3H), 3.98 (s, 3H); FABHRMS (NBA) m/z 267.0376 (M^+, $C_{11}H_9NO_7$ requires 267.0379).

2-[(4'-Butyl-3'-methoxy-2'-(methoxymethoxy)phenyl)carbonyl]-4,5-dimethoxy-6-(methoxycarbonyl)pyridine-3-carboxylic Acid (14) and Methyl 2-[(4'-Butyl-3'-methoxy-2'-(methoxymethoxy)phenyl)-carbonyl]-4,5-dimethoxy-6-(methoxycarbonyl)pyridine-3-carboxylate (21). The lithium reagent **9**, generated by the treatment of **8** (28 mg, 125 μmol) with *t*-BuLi (1.5 M in hexane, 75 μL, 113 μmol) in Et_2O (200 μL) at 0 °C for 45 min, was added at −78 °C through a cannula to a solution of **13** (crude product generated from the triacid **12**, 28.4 mg, 105 μmol) in anhydrous THF (500 μL). After further stirring at −78 °C for 5 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (200 μL). The aqueous phase was extracted with EtOAc (4 × 2 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under vacuum to give 46.4 mg of crude material. A 3.3 mg of the sample of crude **14** in THF (0.3 mL) was treated with ethereal CH_2N_2 at 25 °C. Concentration and chromatography (SiO_2, 30% EtOAc−hexane) gave the single isomer **21** (1.2 mg) identical in all respects with authentic **21** prepared as shown in Scheme 4.[20]

The residual 43.1 mg of the crude sample was purified by chromatography (SiO_2, 30% EtOAc, 5% CH_3OH + 1% HOAc−CH_2Cl_2) afforded **14** (21.9 mg, 42%) as a pale yellow oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.18 (d, 1H, J = 8.2 Hz), 6.98 (d, 1H, J = 8.2 Hz), 4.99 (s, 2H), 4.07 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.35 (s, 3H), 2.66 (t, 2H, J = 7.8 Hz), 1.55−1.63 (m, 2H), 1.39 (sextet, 2H, J = 7.3 Hz), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 151.1, 149.7, 141.9, 130.2, 128.9, 128.5, 126.0, 124.6, 99.5, 61.8, 61.5, 60.6, 57.4, 52.5, 32.6, 29.8, 22.7, 14.0; IR (neat) ν_{max} 3435, 2946, 1739, 1667, 1596, 1448, 1397, 1346, 1265, 1214, 1163, 1041, 995 cm^{-1}; FABHRMS (NBA−NaI) m/z 514.1661 (M^+ + Na, $C_{24}H_{29}NO_{10}$ requires 514.1689).

Typically, crude **14** (0.1−0.2 mmol) in THF (0.1 M) was treated with a slight excess of CH_2N_2 at 25 °C. Concentration and chroma-

tography (SiO_2, 30% EtOAc−hexane) gave **21** quantitatively and in 30−42% overall yield from **12**: ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.21 (d, 1H, J = 7.9 Hz), 7.07 (d, 1H, J = 7.9 Hz), 4.92 (s, 2H), 4.06 (s, 3H), 3.98 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.22 (s, 3H), 2.68 (t, 2H, J = 7.8 Hz), 1.60 (br p, 2H, J = 7.7 Hz), 1.40 (sextet, 2H, J = 7.6 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.3, 165.0, 164.6, 157.9, 151.0, 149.8, 149.7, 149.2, 145.3, 142.4, 130.2, 126.6, 125.8, 124.8, 99.2, 62.1, 61.7, 60.6, 57.2, 53.0, 52.8, 32.6, 29.3, 22.7, 13.9; IR (neat) ν_{max} 2946, 1739, 1673, 1596, 1448, 1402, 1346, 1265, 1153, 1041, 995 cm^{-1}; FABHRMS (NBA−CsI) m/z 638.1024 (M^+ + Cs, $C_{25}H_{31}NO_{10}$ requires 638.1002).

Methyl 3-(4'-Butyl-3'-methoxy-2'-(methoxymethyl)phenyl)-6,7-dimethoxy-1-oxo-1,3-dihydrofuro[3,4-*b*]pyridine-5-carboxylate (28). A solution of **21** (19.7 mg, 0.04 mmol) in CH_3OH (3 mL) was treated with $NaBH_4$ (4.43 mg, 0.12 mmol) and stirred at −10 °C for 40 min. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (0.2 mL) and extracted with EtOAc (2 × 2 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 20% EtOAc−hexane) afforded **28** (17.2 mg, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, 1H, J = 8.0 Hz), 6.62 (d, 1H, J = 8.0 Hz), 6.62 (s, 1H), 5.17 (d, 1H, J = 5.0 Hz), 4.99 (d, 1H, J = 5.0 Hz), 4.50 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.77 (s, 3H), 3.51 (s, 3H), 2.57 (t, 2H, J = 7.8 Hz), 1.51 (br p, 2H, J = 7.7 Hz), 1.34 (sextet, 2H, J = 7.6 Hz), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 165.2, 165.0, 159.9, 151.0, 150.2, 149.1, 146.1, 139.6, 126.4, 125.4, 123.8, 111.9, 99.3, 78.9, 63.6, 62.4, 60.6, 57.9, 53.0, 32.7, 29.5, 22.7, 13.9; IR (neat) ν_{max} 2955, 1765, 1740, 1582, 1480, 1448, 1415, 1300, 1277, 1247, 1163, 1089, 1027, 996, 930, 778 cm^{-1}; FABHRMS (NBS−CsI) m/z 608.0875 (M^+ + Cs, $C_{24}H_{29}NO_9$ requires 608.0897).

2-(4'-Butyl-3'-methoxy-2'-(methoxymethyl)phenyl)methyl-4,5-dimethoxy-6-(methoxycarbonyl)pyridine-3-carboxylic Acid (29). A solution of **28** (17.5 mg, 0.04 mmol) in EtOH (4 mL) under H_2 was treated with 20% $Pd(OH)_2$ on carbon (17.5 mg) and stirred at 25 °C for 2 h. The reaction mixture was filtered through Celite and concentrated to afford **29** (17.5 mg, 100%) as a colorless oil. Following this procedure, **28** (5−20 mg, 0.01−0.04 mmol) typically provided analytically pure **29** in over 95% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78 (d, 1H, J = 8.0 Hz), 6.74 (d, 1H, J = 8.0 Hz), 5.06 (s, 2H), 4.24 (s, 2H), 4.01 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 2.51 (t, 2H, J = 7.8 Hz), 1.50 (br p, 2H, J = 7.7 Hz), 1.33 (sextet, 2H, J = 7.6 Hz), 0.89 (t, 3H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7, 165.1, 157.7, 153.6, 150.4, 149.1, 147.7, 146.7, 135.6, 130.1, 126.7, 125.2, 125.1, 99.0, 62.0, 61.2, 60.4, 57.7, 52.9, 35.5, 32.9, 29.3, 22.7, 13.9; IR (neat) ν_{max} 2955, 1734, 1560, 1457, 1406, 1348, 1269, 1161, 1069, 1041, 997, 758 cm^{-1}; FABHRMS (NBS−CsI) m/z 610.1072 (M^+ + Cs, $C_{24}H_{31}NO_9$ requires 610.1053).

Methyl 7-Butyl-9-hydroxy-5-(trifluoroacetoxy)-3,4,8-trimethoxybenzo[*g*]quinoline-2-carboxylate (30). A solution of **29** (15.8 mg, 0.03 mmol) in trifluoroacetic anhydride (3 mL) in a sealed vessel was warmed in a 50 °C oil bath for 72 h. Concentration in vacuo and chromatography (SiO_2, 20% EtOAc−hexane) afforded **30** (14.8 mg, 88%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (s, 1H), 7.29 (s, 1H), 6.20 (s, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 3.98 (s, 3H), 3.89 (s, 3H), 2.83 (t, 2H, J = 7.8 Hz), 1.71 (br p, 2H, J = 7.7 Hz), 1.43 (sextet, 2H, 7.6 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 156.1, 156.0 (q, J = 39.0 Hz), 153.2, 149.9, 143.6, 142.2, 141.3, 141.1, 140.0, 137.0, 125.2, 123.0, 115.4, 115.0 (q, J = 284.5 Hz), 110.8, 62.2, 61.5 (2C's), 53.2, 31.9, 30.7, 22.6, 13.9; IR (neat) ν_{max} 3821, 2956, 1804, 1740, 1522, 1458, 1225, 1133, 760 cm^{-1}; FABHRMS (NBA−NaI) m/z 512.1547 (M^+ + H, $C_{24}H_{24}F_3NO_8$ requires 512.1532).[23]

Methyl 7-Butyl-5,10-dihydro-9-hydroxy-3,4,8-trimethoxy-5,10-dioxobenzo[*g*]quinoline-2-carboxylate (32; 3,4-*O*-Dimethyl Phomazarin Methyl Ester). A solution of **30** (21.9 mg, 0.04 mmol) in CH_3OH (15 mL) was stirred at 30 °C open to the air for 72 h. Concentration in vacuo and chromatography (SiO_2, 20% EtOAc−hexane) afforded **32** (15.2 mg, 83%) identical in all compared respects with material derived from the natural product:[3] mp 127 °C (lit. mp 131−133 °C);[3] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.66 (s, 1H), 7.63 (s, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 4.04 (s, 3H), 4.01 (s, 3H), 2.73 (t, 2H, J = 7.8 Hz), 1.60 (br p, 2H, J = 7.7 Hz), 1.39 (sextet, 2H, 7.3 Hz), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.1, 180.5, 164.2, 161.2, 155.7, 152.4, 151.8, 149.3, 145.43, 145.38, 128.0, 126.2, 121.6, 115.0, 62.55, 62.48, 60.8, 53.2, 32.1, 30.5, 22.6, 13.9; IR (neat) ν_{max} 2954, 2863, 1741, 1672, 1641, 1446, 1409, 1271 cm^{-1}; FABHRMS (NBA−CsI) m/z 562.0494 (M^+ + Cs, $C_{22}H_{23}NO_8$ requires 562.0478).

Methyl 7-Butyl-5,10-dihydro-4,9-dihydroxy-3,8-dimethoxy-5,10-dioxobenzo[*g*]quinoline-2-carboxylate (33). A solution of **32** (1.3 mg, 3.0 μmol) in CF_3CH_2OH (0.5 mL) was treated with TsOH (20 equiv, 11.5 mg) and NaBr (20 equiv, 6.2 mg), and the mixture was stirred at 25 °C for 24 h. Concentration in vacuo and chromatography (SiO_2, $CHCl_3$/EtOAc/CH_3OH/TFA = 40/2/2/3) afforded **33** (1.3 mg, 100%) as an orange-yellow solid: mp 178 °C (lit. mp 180−182 °C);[3] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 13.27 (s, 1H), 12.81 (s, 1H), 7.71 (s, 1H), 4.14 (s, 3H), 4.08 (s, 3H), 3.99 (s, 3H), 2.73 (t, 2H, J = 7.5 Hz), 1.60 (br p, 2H, J = 7.6 Hz), 1.39 (sextet, 2H, 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.9, 184.8, 164.2, 161.8, 156.6, 153.6, 147.60, 147.53, 145.1, 143.6, 125.8, 122.5, 117.3, 115.3, 62.0, 61.1, 53.2, 32.0, 30.5, 22.6, 13.9; IR (neat) ν_{max} 2951, 2867, 1744, 1637, 1447, 1413, 1267 cm^{-1}; FABHRMS (NBA−NaI) m/z 438.1179 (M^+ + Na, $C_{21}H_{21}NO_8$ requires 438.1165).

Methyl 7-Butyl-5,10-dihydro-3,4,9-trihydroxy-8-methoxy-5,10-dioxobenzo[*g*]quinoline-2-carboxylate (34, Phomazarin Methyl Ester). Method A. A solution of **32** (1.5 mg, 3.5 μmol) in CF_3CH_2OH (1.0 mL) in a sealed vessel was treated with TsOH (20 equiv, 13.3 mg) and NaBr (20 equiv, 7.2 mg), and the mixture was stirred in a 100 °C oil bath for 36 h. Concentration in vacuo and chromatography (SiO_2, $CHCl_3$/EtOAc/CH_3OH/TFA = 40/2/2/3) afforded **34** (1.4 mg, 100%).

Method B. A solution of **32** (3.8 mg, 8.9 μmol) in CH_2Cl_2 was treated with BBr_3 (10 equiv, 1 M in CH_2Cl_2, 90 μL) at −78 °C and stirred at −78 °C for 2 h. The mixture was slowly warmed to −40 °C over 2 h and stirred at −40 °C for an additional 2 h before the reaction was quenched with the addition of CH_3OH (0.1 mL). Concentration in vacuo and chromatography (SiO_2, $CHCl_3$/EtOAc/CH_3OH/TFA = 40/2/2/3) afforded **34** (1.2 mg, 34%) along with **33** (1.0 mg, 27%) and **35** (1.2 mg, 34%).

Data for **34**: mp 208 °C (lit. mp 213 °C);[3] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 13.20 (s, 1H), 12.94 (s, 1H), 11.41 (s, 1H), 7.72 (s, 1H), 4.11 (s, 3H), 4.09 (s, 3H), 2.73 (t, 2H, J = 7.8 Hz), 1.60 (br p, 2H, J = 7.6 Hz), 1.39 (sextet, 2H, 7.5 Hz), 0.94 (t, 3H, J = 7.5 Hz); IR (neat) ν_{max} 2925, 1682, 1631, 1452, 1327, 1282, 1231 cm^{-1}; FABHRMS (NBA−CsI) m/z 534.0187 (M^+ + Cs, $C_{20}H_{19}NO_8$ requires 534.1065).

Data for methyl 7-butyl-5,10-dihydro-4,8,9-trihydroxy-3-methoxy-5,10-dioxobenzo[*g*]quinoline-2-carboxylate (**35**): mp 203−208 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.41 (s, 1H), 12.94 (s, 1H), 7.73 (s, 1H), 6.49 (s, 1H), 4.14 (s, 3H), 3.99 (s, 3H), 2.76 (t, 2H, J = 7.6 Hz), 1.63 (br p, 2H, J = 7.6 Hz), 1.40 (sextet, 2H, 7.6 Hz), 0.95 (t, 3H, J = 7.3 Hz); IR (neat) ν_{max} 2915, 2850, 1741, 1721, 1626, 1452, 1268 cm^{-1}; FABHRMS (NBA−NaI) m/z 424.0092 (M^+ + Na, $C_{20}H_{19}NO_8$ requires 424.1008).

Data for methyl 7-butyl-5,10-dihydro-3,4,8,9-tetrahydroxy-5,10-dioxo-benzo[*g*]quinoline-2-carboxylate (**36**): mp 198−200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.35 (s, 1H), 12.77 (s, 1H), 11.41 (s, 1H), 7.75 (s, 1H), 6.50 (s, 1H), 4.11 (s, 3H), 2.76 (t, 2H, J = 7.8 Hz), 1.62 (br p, 2H, J = 7.6 Hz), 1.40 (sextet, 2H, 7.6 Hz), 0.95 (t, 3H, J = 7.2 Hz); IR (film) ν_{max} 2917, 2858, 1681, 1631, 1442, 1282, 1208 cm^{-1}; MALDIHRMS (CHCA) m/z 388.1043 (M^+ + H, $C_{19}H_{17}NO_8$ requires 388.1032).

7-Butyl-5,10-dihydro-3,4,9-trihydroxy-8-methoxy-5,10-dioxobenzo[*g*]quinoline-2-carboxylic Acid (1, Phomazarin). A solution of **34**

(22) The corresponding carboxylic acid of **32** was 25× less potent (IC_{50} = 8 μg/mL).

(23) In preliminary studies of the reaction before optimization, small amounts of **31** were detected in the crude reaction products: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (s, 1H), 7.74 (s, 1H), 4.12 (s, 3H), 4.07 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H), 2.85 (t, 2H, J = 7.8 Hz), 1.70 (br p, 2H, J = 7.6 Hz), 1.48 (sextet, 2H, J = 7.4 Hz), 0.98 (t, 3H, J = 7.3 Hz); FABMS (NBA) m/z 608 (M^+ + H, $C_{26}H_{23}F_{16}NO_8$ requires 608). Under the optimized reaction conditions, **31** was not detected.

(0.7 mg, 1.8 μmol) in THF/H_2O (3/1, 0.1 mL) was treated with aqueous 1 N LiOH (35 μL, 20 equiv), and the mixture was stirred in a 30 °C oil bath for 24 h. After removal of solvent, the residue was dissolved in CH_3OH and acidified with cation-exchange resin (Dowex 50WX8-100) until the color of the solution turned yellow. Filtration through a cotton plug and concentration in vacuo afforded **1** (0.5 mg, 70%): mp 191 °C (lit. mp 196 °C);[3] ^{1}H NMR (TFA-*d*, 400 MHz) δ 8.00 (s, 1H), 4.17 (s, 3H), 2.86 (t, 2H, J = 7.7 Hz), 1.68 (br p, 2H, J = 7.6 Hz), 1.44 (sextet, 2H, J = 7.2 Hz), 1.00 (t, 3H, J = 7.2 Hz); IR (film) ν_{max} 1693, 1633, 1445, 1301, 1203, 1138 cm^{-1}; FABHRMS (NBA−NaI) m/z 410.0841 (M^+ + Na, $C_{19}H_{17}NO_8$ requires 410.0852) identical in all compared respects with the natural product.

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Supporting Information Available: Text of experimental details for the preparation and characterization of **15a**−**d**, **16a**−**d**, **17**, **18**, and **21**−**25** and text, tables, and figures providing details of the X-ray structure determination of **16b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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