Diels–Alder Approaches to Model Compounds Related to Fredericamycin A

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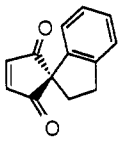
A series of model compounds related to the antitumor and antibiotic compound fredericamycin A has been prepared. Spiro[3-cyclopentene-1,1′-indan]-2,5-dione (**2**) has been prepared and established as a novel spiro dienophile in the Diels–Alder reaction with 1,3-butadiene, Danishefsky's diene, a triacetoxy-substituted *o*-quinodimethane, and two isobenzofuran intermediates. Thus, the cycloaddition of 3-cyano-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (**35**) and **2** afforded 4,9-dihydroxy-5,6,8-trimethoxyspiro[2*H*-benz[*f*]indene-2,1′-indan]-1,3-dione (**38**) in 62% yield. This methodology provides a viable synthetic route to the quinone portion of fredericamycin A that contains the seven requisite oxygens.

Fredericamycin A[1] is unique among recently isolated antitumor and antibiotic compounds in that it contains a spiro ring system (Figure 1). This hexacycle is the most active of several compounds produced by a soil bacterium of the *streptomyces griseus* family, a class of bacteria that produces many other antibiotics, including the tetracyclines and streptomycin. Since its isolation and characterization in 1981, a variety of synthetic approaches have been reported,[2] including one successful total synthesis.[3]

Our synthetic strategy for the construction of the one (spiro) quaternary center of asymmetry in this quinone–isoquinolone containing molecule embodies a spiroexpansion–spiroannulation reaction involving an acyl migration (Scheme I).[2f,i] The principal purpose of the present paper is to demonstrate the utility of spiro[3-cyclopentene-1,1′-indan]-2,5-dione (**2**) as a novel dienophile in the



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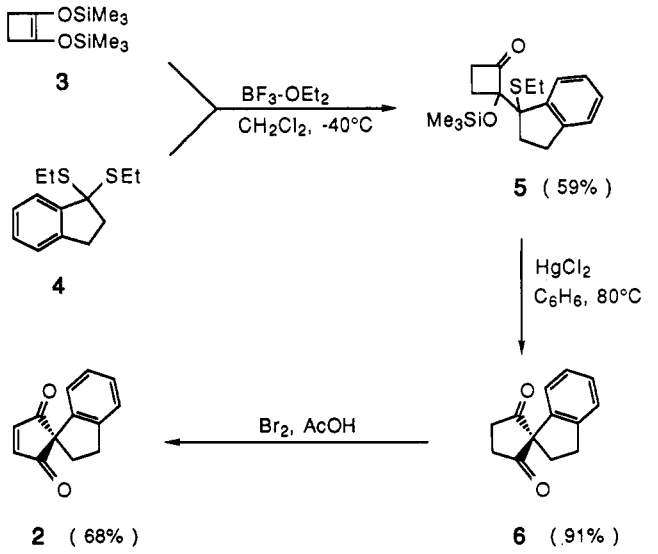
preparation of fredericamycin A analogues. It is well known that the 2-cycloalkenones are poor dienophiles in the thermal Diels–Alder reaction,[4a] although Lewis acids do improve their reactivity.[4b] In principle, the increased conjugation due to a second carbonyl group on the double bond should lower the LUMO in an enedione such as **2** relative to a simple cyclopent-2-en-1-one and markedly

Scheme I



improve its capacity to function as a dieneophile. An earlier report suggested that the 2,2-dimethyl derivative of the parent enedione was a relatively sluggish dieneophile as a result of steric interactions.[4c]

Results and Discussion

Dienophile **2** was prepared by an adaption of the Kuwajima[5] annelation procedure. We chose to utilize a thioketal and a mercuric salt as the thiophile since we have found these reaction conditions to be more compatible with other functionality in the molecule. This procedure also greatly simplified both the workup and the isolation of the 1,3-dione resulting from acyl migration. The benzo-substituted spiro[4.4]nonane-1,4-dione **6** needed to prepare dienophile **2** was synthesized under unusually mild reaction conditions by utilizing a mercury-mediated 1,2-carbonyl migration. The overall reaction sequence proved to be a generally effective procedure for the introduction of spiro centers.

As outlined in Scheme I, the acyloin condensation of diethyl succinate in the presence of chlorotrimethylsilane afforded 1,2-bis(trimethylsilyloxy)cyclobutene (**3**).[6]

(1) (a) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389. (b) Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *34*, 1402.

(2) (a) Ramo Rao, A. V.; Reddy, D. R.; Deshpande, V. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1119. (b) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181. (c) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1985**, *26*, 3063. (d) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4723. (e) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Ibid.* **1985**, *26*, 4725. (f) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1986**, *51*, 749; **1985**, *50*, 5438. (g) Braun, M.; Veith, R. *Tetrahedron Lett.* **1986**, *27*, 179. (h) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878. (i) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1986**, *27*, 1983. (j) Mehta, G.; Subrahmanyam, D. *Tetrahedron Lett.* **1987**, *28*, 479. (k) Clive, D. J.; Gaëton, Angoh, A.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339. (l) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835. (m) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183. (n) Ramo Rao, A. V.; Reddeppa Reddy, R.; Annapurna, G. S.; Deshpande, V. H. *Tetrahedron Lett.* **1987**, *28*, 451. (o) Ramo Rao, A. V.; Shreenivassan, N.; Reddeppa Reddy, R.; Deshpande, V. H. *Ibid.* **1987**, *28*, 455. (p) Clive, D. L. J.; Sedgeworth, J. *J. Heterocycl. Chem.* **1987**, *24*, 509. (q) Domagala, J. M.; Bach, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 3118.

(3) Kelly, T. R.; Ohashi, N.; Armstrong-Chong, R. J.; Bell, S. H. *J. Am. Chem. Soc.* **1986**, *108*, 7100.

(4) (a) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056. (b) Fringuelli, F.; Pizzo, F.; Taticci, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802. (c) Agosta, W. C.; Smith, A, B. III *J. Org. Chem.* **1970**, *35*, 3856.

(5) (a) Nakamura, E.; Kuwajima, I. *Organic Synthesis*; Vedejs, E., Ed.; Wiley: New York, 1987; Vol. 65, p 17. (b) Kuwajima, I.; Shimad, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E. *J. Am. Chem. Soc.* **1984**, *106*, 1759. (c) Kuwajiua, I.; Azegami, I. *Tetrahedron Lett.* **1979**, 2369. (d) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961. (e) Kuwajima, I.; Hashimoto, K.; Nakamura, E. *J. Org. Chem.* **1977**, *42*, 4166.

(6) (a) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React. (N.Y.)* **1976**, *23*, 259. (b) Bloomfield, J. J.; Nelke, J. M. *Organic Synthesis*; Johnson, C. R., Ed.; Wiley: New York, 1977; Vol. 57, p 1. (c) Bloomfield, J. J. *Tetrahedron Lett.* **1968**, 587.

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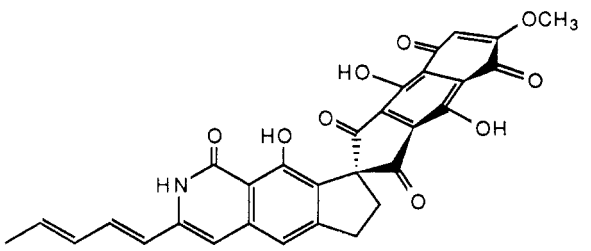

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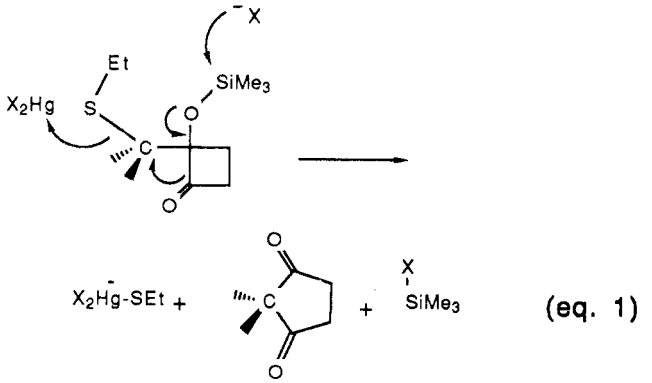
Figure 1. Fredericamycin A (1).

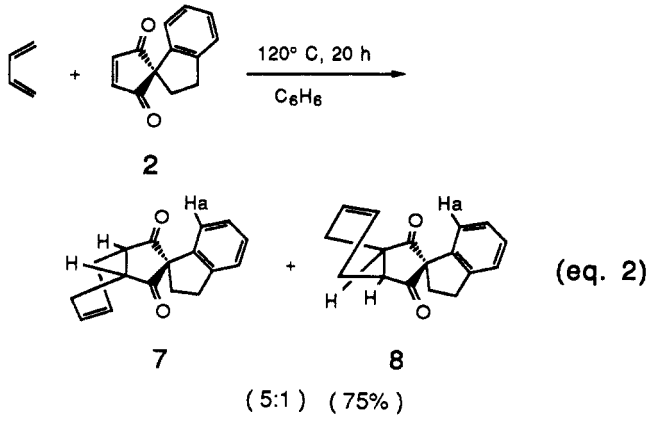
Treatment of 1-indanone and ethanethiol in methylene chloride at −40 °C with stannic chloride afforded 1,1-bis(ethylthio)indan (4) in 74% yield. α-Thioalkylation of 4 was readily achieved under the influence of the relatively mild Lewis acid, boron trifluoride etherate.[7] Reaction of thioketal 4 with boron trifluoride etherate and bis(silyl ether) 3 in methylene chloride at −40 °C afforded thioindanyl cyclobutanone 5 in 59% yield after purification by column chromatography. The pinacol-type rearrangement of 5 to 6 was readily achieved by the action of the mild thiophile mercuric chloride in refluxing benzene. Stereospecific acyl migration may also be smoothly effected by the more electrophilic Lewis acid mercuric trifluoroacetate in benzene at 0 °C.[2f] Mechanistic rational for this rearrangement is depicted by eq 1. Thus, treatment of



(eq. 1)

cyclobutanone 5 with mercuric chloride in refluxing benzene afforded a 91% yield of spiro 2,5-dione 6. The preparation of dienophile 2 was completed by a room-temperature bromination–dehydrobromination procedure in 68% yield.

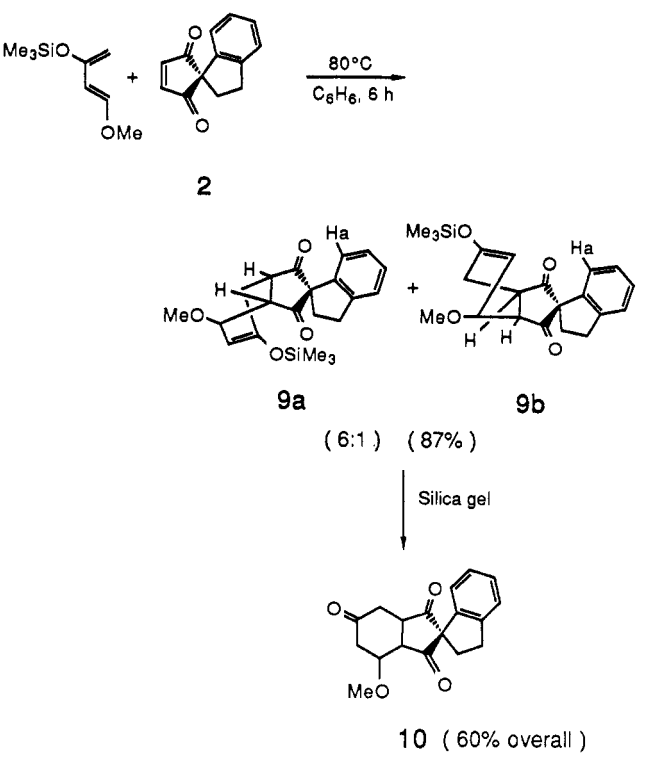
As anticipated, the Diels–Alder cycloaddition of 1,3-butadiene with 2 afforded adducts 7 and 8 (5:1) in a 75% yield (eq 2). The structural assignments given 7 and 8



(eq. 2)

(5:1) (75%)

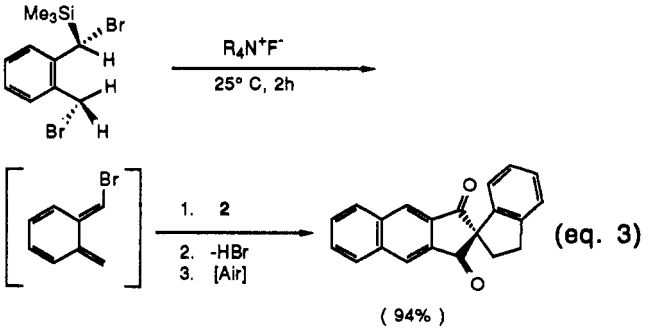
Scheme II



10 (60% overall)

are consistent with those given to the same pair of diastereomers prepared by an alternative method.[2f] The assigned stereochemistry[2f] of 7 and 8 is based upon the assumption that 1,2-carbonyl migrations are stereospecific reactions that proceed with inversion of configuration at the migration terminus (eq 1).[2q] The Diels–Alder reaction of dienophile 2 with Danishefsky's diene[8] in benzene under an argon atmosphere also afforded a mixture of diastereomers **9a** and **9b** (87%) in 6 h (Scheme II). The trimethylsilyl group (^{1}H NMR, 0.23 ppm) was lost upon chromatographic workup on silica gel, affording 1,3,5-trione 10 as a mixture of stereoisomers (mp 185–186 °C) in 60% yield. As one would anticipate, the "electron-rich" diene underwent a Diels–Alder cycloaddition with 2 at a reduced temperature and reaction time in comparison to 1,3-butadiene. Reaction of the more hindered diene with dienophile 2 afforded a 6:1 ratio of diastereomers **9a** and **9b**, which is consistent with the assumption that the two reactants will approach each other from the least sterically hindered direction.

In a preliminary report we described the room-temperature Diels–Alder cycloaddition reaction of dienophile 2 with an *o*-quinodimethane intermediate (eq 3). *o*-



(eq. 3)

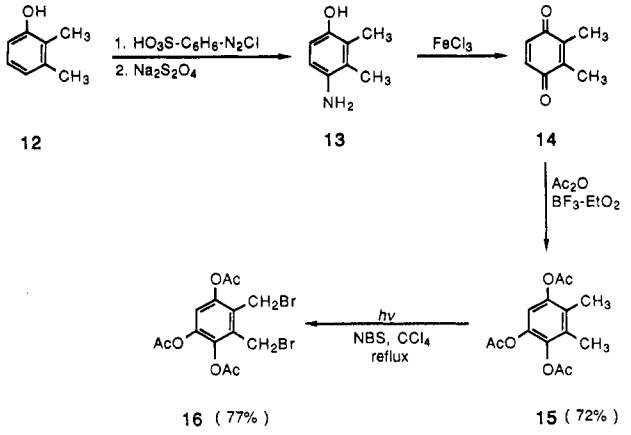
(94%)

Quinodimethane derivatives are very reactive in the

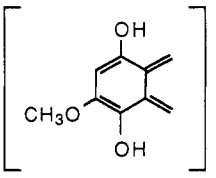
(7) Reetz, M. T.; Giannis, A. *Synth. Commun.* **1981**, *11*, 315.

(8) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Organic Synthesis*; Stevens, R. V., Ed.; Wiley: New York, 1983; Vol. 61, p 147.

Scheme III



Diels–Alder reaction because of the restoration of aromaticity upon cycloaddition. These diene intermediates have been utilized extensively for the synthesis of polycyclic ring systems that are otherwise difficult to prepare.[9] Intrigued by the ease of reaction of dienophile **2** with this highly reactive intermediate (eq 3), we turned our attention to the development of an *o*-quinodimethane derivative with latent functionality, that could potentially introduce the required oxygen functionality in **1**. We looked at possible precursors to the oxygen functionalized diene **11** and chose the dihalide **16**. Our approach to this compound is shown in Scheme III. Following the procedure of Nilsson,[10]



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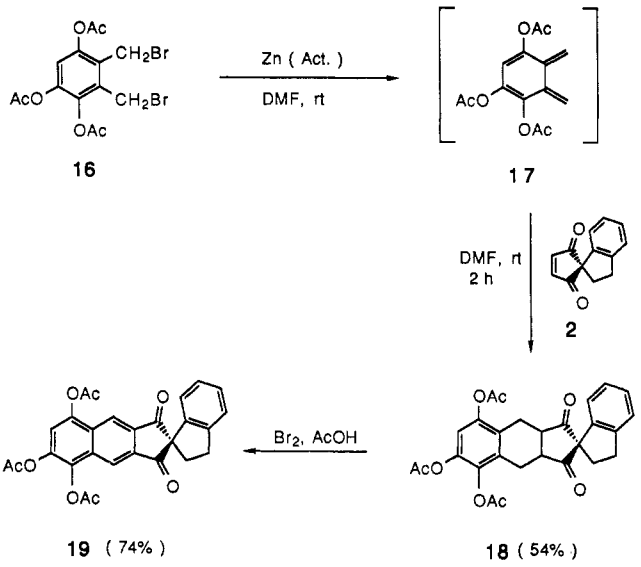
phenol **12** was coupled with diazotized sulfanilic acid, and the red azo compound was reduced with sodium dithionite to the aminophenol **13**. Aminophenol **13** was converted to 2,3-dimethylbenzoquinone (**14**) by reaction with ferric chloride and concentrated hydrochloric acid. At this point, we wanted to introduce the third oxygen functionality into quinone **14**, which could later be transformed into the methoxy group that is present in fredericamycin A. Treatment of **14** with boron trifluoride etherate, with acetic anhydride as the solvent, effected the Thiele[11] reaction, which afforded the triacetoxy derivative **15** in a 72% yield after recrystallization. Light-catalyzed NBS bromination of **15** afforded (77%) the corresponding α,α'-dibromo derivative **16**.

Our attention then turned to seeking a reagent that would be compatible with the carbonyl groups in the dienophile **2** and suitable for the generation of *o*-quinodimethane intermediate **17** (Scheme IV). We chose activated zinc[12] to generate *o*-quinodimethane **17** in situ, which readily afforded adduct **18** upon Diels–Alder cycloaddition with dienophile **2** (Scheme IV). Reaction of

Scheme IV



dienophile **2** and zinc (freshly activated) in *N,N*-dimethylformamide with substituted *o*-(α,α'-dibromo)xylene **16** at room temperature afforded spiro dione **18** in 54% yield. The *o*-(α,α'-dibromo)xylene **16** was added to the dienophile to avoid dimerization of the highly reactive *o*-quinodimethane intermediate **17**. Diels–Alder adduct **18** was aromatized with bromine and acetic acid, prior to attempting to introduce the remaining two oxygens of the quinone portion of fredericamycin A. Several attempts were made to oxidize the middle ring of **19** with chromium trioxide in an 80% acetic acid solution. Unfortunately, we recovered only **19** after workup. The inability to readily oxidize the 4- and 9-positions of **19** is attributed to deactivation by the carbonyl groups of the adjacent cyclopentane ring.

Seeking a method in which we could introduce oxygen in the middle ring of the quinone portion of fredericamycin A by a Diels–Alder cycloaddition reaction, we examined the possibility of using 3-cyano-1(3*H*)-isobenzofuranone as a diene precursor. The literature contains a number of reports of cyclophthalides (3-cyano-1(3*H*)-isobenzofuranones) undergoing 1,4-additions to enones in a Michael fashion but is devoid of any examples of cyanophthalides being added to dienophiles under Diels–Alder reaction conditions. Morrow and Swenton[13] have annulated a highly functionalized quinone monoketal with a substituted cyanophthalide anion in their synthesis of adriamycin derivatives. More recently, Yoshii et al.[14] utilized an acyclic cyanophthalide anion in an annulation reaction with 5-*tert*-butoxy-2-furfurylideneacetone in their synthesis of (±)-granaticin. In both of these syntheses the functionalized cyanophthalide anions have been added to enones in a Michael fashion, followed by addition of the resulting enolate anion of the intermediate to the carbonyl, with ring opening and subsequent loss of cyanide. Utilizing Hauser's[15] 1,4-dipolar equivalent **20**, Parker[2b] has reported the synthesis of 2,2-dimethyl-4,9-dihydroxy-1*H*-benz[*f*]-indene-1,3(2*H*)-dione (**21**, eq 4). In an analogous manner, annulation of 3-cyano-1(3*H*)-isobenzofuranone (**22**) to ene dione **2** would provide the three contiguous rings of the quinone half of **1**, as well as the introduction of the appropriate oxygen functionality to the middle ring. Anionic

(9) (a) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609. (b) Ardecky, R. J.; Dominguez, D.; Cava, M. P. *J. Org. Chem.* **1982**, *47*, 409. (c) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992. (d) Kerdesky, F. A. J.; Cava, M. P. *J. Am. Chem. Soc.* **1978**, *100*, 3635. (e) Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1959**, *81*, 6458.

(10) Nilsson, J. L. G.; Sievertsson, H.; Selander, H. *Acta Pharm. Suec.* **1968**, *5*, 215.

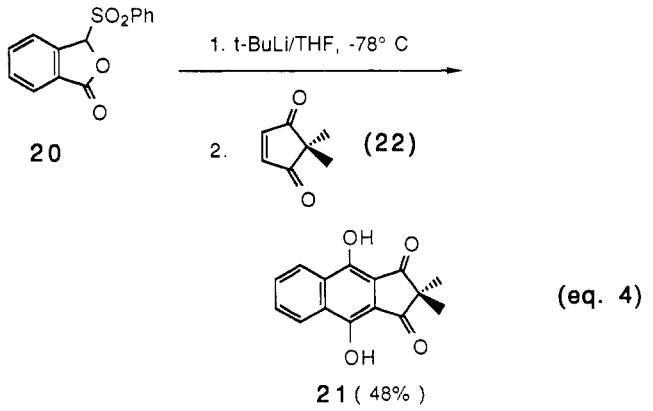
(11) Katsuhara, J. *J. Org. Chem.* **1967**, *32*, 797.

(12) Alder, K.; Fremery, M. *Tetrahedron* **1961**, *14*, 190.

(13) Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 713.

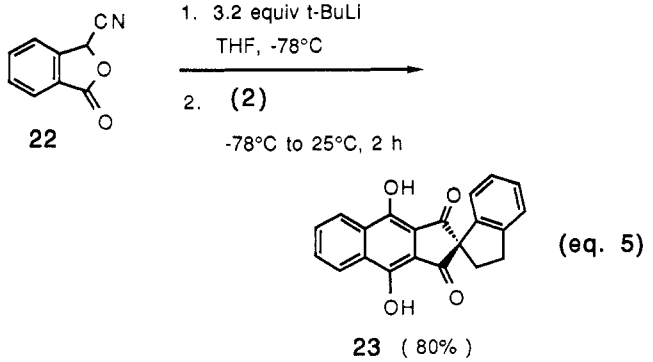
(14) Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *J. Am. Chem. Soc.* **1987**, *109*, 3402.

(15) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378.



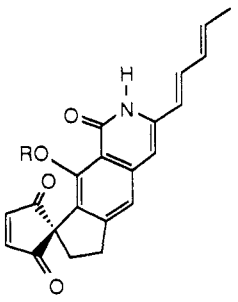
(eq. 4)

addition of cyanophthalide[16] (**22**) to enedione **2** afforded an 80% yield of spiro dione **23** as a white crystalline material (eq 5). Even though the addition of the lithium



(eq. 5)

enolate of cyanophthalide to **2** is a well-behaved reaction that proceeds in high yield, we felt that the use of *tert*-butyllithium could ultimately cause problems when added to ene dione **25** in the final stages of a total synthesis of **1**. As a result, we deemed it advisable to develop a Diels–Alder route under neutral reaction conditions that would allow the preparation of the quinone portion of fredericamycin A.



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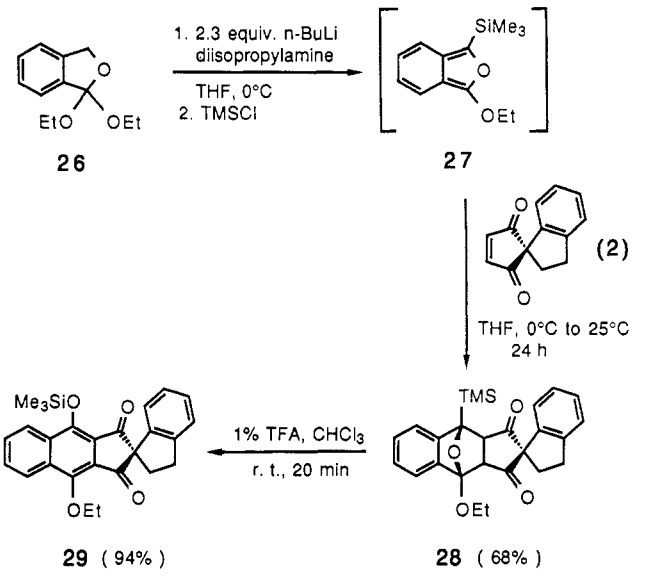
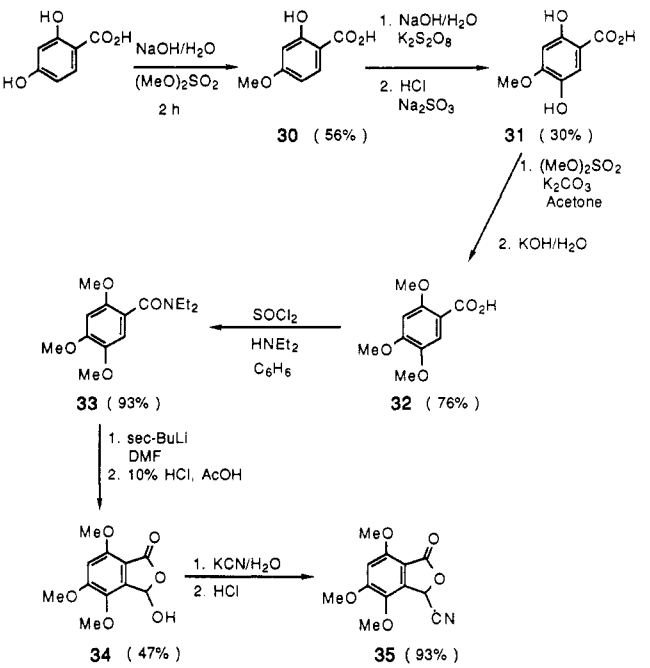
Rickborn et al.[17] have recently reported the first example of an alkoxyisobenzofuran–aryne cycloaddition. 1-Ethoxy-3-(trimethylsilyl)isobenzofuran (**27**) was generated in situ and shown to undergo Diels–Alder reactions with substituted benzynes (arynes). Utilization of the transient 1-ethoxyisobenzofuran in a cycloaddition reaction with enedione **2** would establish the credibility of this Diels–Alder route to the quinone portion of fredericamycin A. Reaction of **27** with dienophile **2** afforded bridgehead trimethylsilylated ketal **28** (Scheme V). Thus, treatment

Scheme V



Scheme VI



of 1,1-diethoxyphthalan[18] (**26**) and diisopropylamine in tetrahydrofuran at 0 °C with *n*-butyllithium resulted in a yellow solution. The mixture was stirred at 0 °C for an additional hour to ensure complete anion generation, and the anion was quenched with chlorotrimethylsilane. A solution of **27** in tetrahydrofuran was then added to dienophile **2**. The mixture was warmed to room temperature and stirred for 24 h. Concentration and purification by flash chromatography on silica gel with 20% ether in hexane, with 1% triethylamine to neutralize the column, afforded Diels–Alder adduct **28** in 68% yield. Catalytic trifluoroacetic acid cleavage of **28** at the ketal center, followed by facile Brook rearrangement, afforded **29** in a 94% yield.

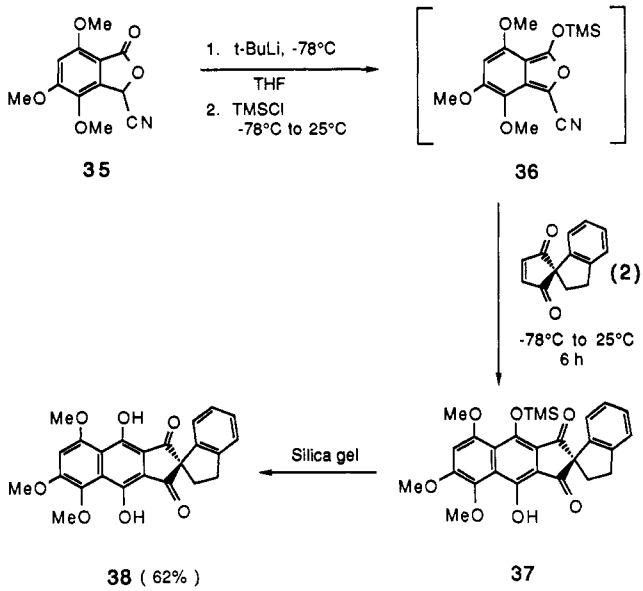
Since we have established that spiro enedione **2** was reactive toward isobenzofuran **27** it now remained to prepare the precursor leading to the fully oxygenated

(16) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.

(17) (a) Mirsadeghi, S.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 787. (b) Pollart, D. J.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 792.

(18) (a) Contreras, L.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2573. (b) Contreras, L.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2580.

Scheme VII



isobenzofuran. With the isolation of **28**, we felt that with the proper manipulation of this methodology we could introduce all five remaining oxygens of the quinone portion in one step. The synthesis of isobenzofuranone **35**, which contains the remaining five oxygens needed to completely functionalize the quinone portion of fredericamycin A, is outlined in Scheme VI. Selective methylation of commercially available 2,4-dihydroxybenzoic acid was accomplished with 20% sodium hydroxide and dimethyl sulfate. Elbs persulfate oxidation converted **30** to 2,5-dihydroxy-4-methoxybenzoic acid (**31**) in modest yield. Methylation of **31** under standard conditions and saponification afforded commercially available 2,4,5-trimethoxybenzoic acid (**32**) in 76% yield. Treatment of **32** with thionyl chloride in benzene afforded a 98% yield of crude 2,4,5-trimethoxybenzoyl chloride which was converted to *N,N*-diethyl-2,4,5-trimethoxybenzamide (**33**) in 93% yield, using diethylamine in benzene. Selective ortho-lithiation[19] of **33** and subsequent trapping with *N,N*-dimethylformamide resulted in *N,N*-diethyl-6-formyl-2,4,5-trimethoxybenzamide, which upon treatment with 10% hydrochloric acid in acetic acid afforded 3-hydroxy-4,5,7-trimethoxy-1-(3*H*)-isobenzofuranone (**34**). Treatment of **34** with potassium cyanide in water, followed by concentrated hydrochloric acid, afforded isobenzofuranone **35** in 93% yield.

Diels–Alder cycloaddition of isobenzofuran[20] **36**, generated in situ, and enedione **2** afforded, after flash chromatography, the desired model spiro adduct **38** in 62% yield (Scheme VII). In a typical reaction sequence, **35** in tetrahydrofuran at −78 °C was treated with 1.0 equiv of a *tert*-butyllithium solution. The solution was stirred at −78 °C for 30 min before 1.2 equiv of chlorotrimethylsilane was added, and the mixture was warmed to room temperature. To the reaction mixture at −78 °C a solution of dienophile **2** (1.1 equiv) in tetrahydrofuran was added. The resulting red solution was warmed to room temperature and stirred for 6 h to afford crude **37**. The trimethylsilyl group (^{1}H NMR, 0.18 ppm) was lost upon chromatographic workup on silica gel using hexane–ethyl acetate (1:1). Recrystallization (chloroform–hexane) of the chromatographed product afforded crystalline **38** in 62% yield.

This Diels–Alder cycloaddition reaction has allowed us to successfully introduce the seven oxygens of the quinone portion of fredericamycin A. Selective demethylation of **38** will produce 4,9-dihydro-6-methoxy-spiro[2*H*-benz[*f*]-indene-2,1′-indan]-1,3,5,8-tetrone.[21] The application of this synthon to the total synthesis of fredericamycin A is presently under way.

Experimental Section

General Procedures. All moisture-sensitive reactions were conducted in flame- or oven-dried apparatus under a positive pressure of argon. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. All solvents were dried and purified before use when required.

1,2-Bis[(trimethylsilyl)oxy]cyclobutene (3). Via the procedure of Bloomfield,[6] cyclobutene **3** was prepared in a 75% yield: bp 74 °C (7 mm); ^{13}C NMR ($CDCl_3$) 120.1, 26.0, 0.314 ppm; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 18 H), 1.98 (s, 4 H); IR (neat) 1719, 1311, 1252, 878, 847 cm^{-1}.

1,1-Bis(ethylthio)indan (4). Stannic chloride (19 mL, 0.16 mol) was added dropwise over a 30-min period to a solution of 1-indanone (73.9 g, 0.56 mol) and ethanethiol (83.8 mL, 1.13 mol) in methylene chloride (500 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then allowed to warm to −40 °C before being poured into a saturated solution of sodium bicarbonate (700 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 500 mL). The combined organic extracts were washed with water (3 × 1 L), saturated aqueous sodium chloride (2 × 800 mL), and dried ($MgSO_4$). Concentration resulted in an oil, which was further purified by column chromatography on silica gel with hexane and ethyl acetate (19:1) to afford, after trituration from pentane, 98.9 g (74%) of **4** as a white crystalline material: mp 31–33 °C; ^{13}C NMR ($CDCl_3$) 144.4, 142.4, 127.9, 126.1, 125.1, 123.7, 66.1, 43.0, 30.3, 24.8, 13.8 ppm; ^{1}H NMR ($CDCl_3$) δ 1.15–1.20 (SCH_2CH_3, t, J = 15.0 Hz, 6 H), 2.43–2.68 (m, 6 H), 2.97–3.02 (t, J = 15.0 Hz, 2 H), 7.19–7.25 (m, 3 H), 7.31–7.34 (t, J = 9.0 Hz, 1 H); IR (neat) 3068, 3037, 2968 (vs), 2927 (vs), 2869, 1472 (s), 1455 (s), 1447, 1374, 1258, 1152, 1057, 1030, 1022, 976, 876, 810, 765 (vs), 741, 735 cm^{-1}.

2-[1-(Ethylthio)indan-1-yl]-2-[(trimethylsilyl)oxy]cyclobutanone (5). To a solution of 23.8 g (0.10 mol) of 1,1-bis(ethylthio)indan (**4**) in methylene chloride (100 mL) at −60 °C was added 37.0 mL (0.30 mol) of boron trifluoride etherate. After the addition of the Lewis acid, 25.4 g (0.11 mol) of cyclobutene **3** in methylene chloride (40 mL) was added dropwise. The mixture was allowed to warm to −40 °C and stirred for 1 h. The reaction mixture was poured at −40 °C into a saturated solution of sodium bicarbonate (400 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3 × 200 mL). The combined organic phases were washed with water (2 × 400 mL) and saturated sodium chloride solution (1 × 400 mL) and dried ($MgSO_4$). Concentration of the organic phase resulted in an oil, which was purified by flash chromatography on silica gel with hexane and ethyl acetate (29:1) to afford 19.7 g (59%) of **5**: ^{13}C NMR ($CDCl_3$) 211.4, 145.0, 142.5, 127.8, 126.1, 125.2, 124.6, 99.0, 63.5, 42.1, 34.9, 31.3, 26.0, 24.0, 13.9, 1.34 ppm; ^{1}H NMR ($CDCl_3$) δ 0.031 ($Si(CH_3)_3$, s, 9 H), 1.03–1.08 (SCH_2CH_3, t, J = 15.0 Hz, 3 H), 2.01–2.12 (m, 1 H), 2.20–2.31 (m, 3 H), 2.65–2.85 (m, 4 H), 2.93–2.98 (t, J = 15.0 Hz, 2 H), 7.17–7.22 (m, 3 H),

(19) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(20) Generation and ^{1}H NMR spectral characterization of intermediate **34**: to dimsyl anion in deuteriated dimethyl sulfoxide at −78 °C was added a solution of **33** in deuteriated dimethyl sulfoxide. After the mixture was stirred at −78 °C for 10 min, chlorotrimethylsilane was added. The reaction mixture was stirred at −78 °C for 30 min before being allowed to warm to room temperature. The ^{1}H NMR spectrum of this solution indicated complete loss of **33** and the formation of 3-cyano-4,5,7-trimethoxy-1-[(trimethylsilyl)oxy]isobenzofuran (**34**). ^{1}H NMR spectra indicated the presence of a silane resonance at 0.188 ppm, the downfield shift of the aromatic proton, and the disappearance of the resonance associated with the proton attached to the carbon bearing the cyanide. No attempt was made to isolate this very unstable isobenzofuran. Our spectral data for **34** is in good agreement with that reported by Pollart and Rickborn[17b] for 1-ethoxy-3-(trimethylsilyl)isobenzofuran.

(21) Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 223.

(22) Smith, L. I.; Tess, W. H. *J. Am. Chem. Soc.* **1944**, *66*, 1523.

7.36–7.40 (m, 1 H); IR (neat) 2964, 2931, 1786 (vs), 1263, 1253 (s), 1173, 1053, 979, 895, 876, 844 (vs), 753 cm^{-1}; MS (70 eV) calcd for $C_{18}H_{26}O_2SSi$ 334.1422, found 334.1420.

Spiro[cyclopentane-1,1′-indan]-2,5-dione (6). To a solution of 8.7 g (26 mmol) of cyclobutanone **5** in benzene (100 mL) was added 7.8 g (28 mmol) of mercuric chloride. The reaction mixture was allowed to reflux for 15 min before being cooled and filtered through a coarse sintered-glass funnel containing Celite. The organic layer was washed with 10% hydrochloric acid solution (1 × 50 mL), water (2 × 50 mL), and saturated sodium chloride solution (1 × 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 4.89 g (94%) of spiro-[cyclopentane-1,1′-indan]-2,5-dione. Recrystallization from hexane and ethyl acetate yielded 4.73 g (91%) of **6** as a white solid: mp 107–108 °C; ^{13}C NMR ($CDCl_3$) 213.0, 144.8, 140.8, 128.3, 126.9, 125.4, 122.4, 69.8, 35.5, 32.8, 31.6 ppm; ^1H NMR ($CDCl_3$) δ 2.37–2.42 (t, J = 7.5 Hz, 2 H), 2.82–2.95 (m, 2 H), 2.95–3.09 (m, 2 H), 3.14–3.19 (t, J = 7.5 Hz, 2 H), 6.89–6.91 (d, 1 H), 7.12–7.17 (t, J = 7.5 Hz, 1 H), 7.20–7.25 (dt, J = 7.2 Hz, J^2 = 0.9 Hz, 1 H), 7.27–7.30 (d, 1 H); IR (KBr) 3071, 3021, 2980, 2949, 2936, 2920, 2853, 1717 (vs), 1478, 1456, 1412, 1271, 1258, 1194, 1111, 995, 772 (s) cm^{-1}; MS (70 eV) calcd for $C_{13}H_{12}O_2$ 200.0837, found 200.0837. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.87; H, 5.89.

Spiro[3-cyclopentene-1,1′-indan]-2,5-dione (2). To a solution of 4.3 g (22 mmol) of spiro dione **6** in glacial acetic acid (100 mL) at room temperature was added 1.10 mL (22 mmol) of bromine. The reaction mixture was allowed to stir for 1 h and then poured into water (100 mL). The aqueous layer was extracted with methylene chloride (3 × 100 mL), and the combined extracts were washed with water (1 × 300 mL), saturated sodium bicarbonate solution (2 × 200 mL), and saturated sodium chloride solution (1 × 200 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel using hexane and ethyl acetate (9:1) yielded 2.95 g (68%) of **2** as a yellow crystalline material: mp 80–81 °C (hexane); ^{13}C NMR ($CDCl_3$) 204.2, 150.2, 145.5, 140.2, 128.5, 126.9, 125.2, 122.2, 63.2, 31.9, 31.7 ppm; ^1H NMR ($CDCl_3$) δ 2.41–2.46 (t, J = 7.3 Hz, 2 H), 3.23–3.28 (t, J = 7.6 Hz, 2 H), 6.79–6.82 (d, 1 H), 7.12–7.15 (t, J = 7.4 Hz, 1 H), 7.24–7.28 (dt, J^1 = 7.5 Hz, J^2 = 1.1 Hz, 1 H), 7.33–7.35 (d, 1 H), 7.51 (s, 2 H); IR (KBr) 3062, 2977, 2961, 2945, 2865, 1700 (vs), 1672 (s), 1478 (s), 1458, 1327, 1284 (s), 1257, 1214, 863, 836, 789, 750 (s) cm^{-1}; MS (70 eV) calcd for $C_{13}H_{10}O_2$ 198.0681, found 198.0684.

3a,4,7,7a-Tetrahydrospiro[2*H*-indene-2,1′-indan]-1,3-dione (7, 8). Dienophile **2** (500 mg, 2.5 mmol), 1,3-butadiene (406 mg, 7.5 mmol), and benzene (3 mL) were placed in a glass tube and sealed under vacuum. The reaction mixture was heated for 20 h at 120 °C. After the sealed tube had been allowed to cool to room temperature, it was cooled to −78 °C before being opened. The reaction mixture was concentrated to give a mixture of **7** (83%) and **8** (17%) by ^1H NMR. Distillation afforded 470 mg (75%), bp 144–160 °C (0.075 mmHg), of a mixture of **7** (51%) and **8** (18%). Attempts to separate **7** from **8** by recrystallization failed. Further purification was carried out by trituration with pentane and ether at −78 °C. **7**: mp 110–112 °C (lit.[2f] mp 111–112 °C); ^{13}C NMR ($CDCl_3$) 214.8, 145.0, 141.7, 128.4, 127.0, 126.1, 125.6, 122.3, 68.7, 45.5, 33.6, 32.2, 21.7 ppm; ^1H NMR ($CDCl_3$) δ 2.23–2.42 (m, 4 H), 2.36–2.40 (t, J = 7.5 Hz, 2 H), 3.16–3.21 (t, J = 7.5 Hz, 2 H), 3.31–3.41 (m, 2 H), 5.78–5.80 (t, J = 2.1 Hz, 2 H), 6.93–6.95 (d, 1 H), 7.08–7.13 (t, J = 7.5 Hz, 1 H), 7.17–7.21 (t, J = 6.0 Hz, 1 H), 7.25–7.28 (d, 1 H); IR (KBr) 3035, 2938, 2848, 1763, 1721 (vs), 1660, 1478, 1222 (s), 1205, 1187, 779, 780, 659 cm^{-1}. **8**: ^{13}C NMR ($CDCl_3$) 215.3, 146.3, 140.2, 128.5, 127.1, 126.2, 124.8, 124.2, 68.9, 45.0, 39.2, 31.5, 21.4 ppm; ^1H NMR ($CDCl_3$) δ 2.31–2.33 (m, 2 H), 2.34–2.39 (t, J = 8.0 Hz, 2 H), 2.48–2.55 (m, 2 H), 3.06–3.11 (t, J = 7.5 Hz, 2 H), 3.28–3.33 (m, 2 H), 5.82–5.83 (t, J = 1.5 Hz, 2 H), 6.85–6.87 (d, 1 H), 7.10–7.18 (t, J = 12.0 Hz, 1 H), 7.19–7.23 (dt, J^1 = 6.0 Hz, J^2 = 1.5 Hz, 1 H), 7.26–7.30 (d, 1 H); IR (KBr) 3034, 2942, 2901, 2826, 1766, 1726 (vs), 1662, 1483, 1283 (s), 1199, 1184, 1146, 782, 699 cm^{-1}; MS (70 eV) calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1155.

3a,4,6,7a-Tetrahydro-7-methoxyspiro[2*H*-indene-2,1′-indan]-1,3,5-trione (10). To a solution of 400 mg (2 mmol) of spiro[3-cyclopentene-1,1′-indan]-2,5-dione (**2**) in benzene (2 mL) at 25 °C was added 520 mg (3 mmol) of Danishefsky's[8] diene. The reaction mixture was refluxed for 6 h before being allowed to cool to room temperature. Concentration yielded 520 mg (70%) of impure dione **9**: ^1H NMR ($CDCl_3$) δ 0.229 (s, 9 H), 2.35–2.60 (m, 4 H), 3.12–3.32 (m, 4 H), 3.66 (s, 3 H), 4.17–4.21 (m, 1 H), 5.55–5.59 (d, 1 H), 6.85–6.88 (d, 1 H), 7.07–7.12 (t, 1 H), 7.26–7.32 (t, 1 H), 7.55–7.60 (d, 1 H). Purification by flash chromatography on silica gel with hexane and ethyl acetate (2:1) afforded 358 mg (60%) of trione **10**: mp 178–179 °C (hexane–ethyl acetate); ^{13}C NMR ($CDCl_3$) 214.2, 210.8, 205.8, 145.4, 141.3, 128.4, 126.8, 125.7, 122.1, 78.8, 69.4, 56.5, 51.1, 43.4, 41.5, 35.0, 32.7, 31.7 ppm; ^1H NMR ($CDCl_3$) δ 2.39–2.69 (m, 4 H), 2.83–2.90 (dd, J^1 = 20.4 Hz, J^2 = 3.3 Hz, 1 H), 3.14–3.32 (m, 7 H), 3.62–3.71 (dt, J^1 = 6.0 Hz, J^2 = 3.0 Hz, 1 H), 4.23–4.26 (q, J = 3.0 Hz, 1 H), 6.86–6.88 (d, 1 H), 7.09–7.14 (t, J = 9.0 Hz, 1 H), 7.19–7.24 (t, J = 9.0 Hz, 1 H), 7.27–7.31 (d, 1 H); IR (KBr) 3072, 2990, 2930, 2882, 2834, 1727 (vs), 1725 (vs), 1721 (vs), 1698, 1478, 1454, 1290 (s), 1246 (s), 1194, 1002 (s), 982, 754 (s) cm^{-1}; MS (70 eV) calcd for $C_{18}H_{18}O_4$ 298.1204, found 298.1204.

2,3-Dimethylbenzoquinone (14). By use of the procedure of Nilsson,[10] 2,3-dimethylbenzoquinone (**14**) was prepared in a 62% yield: mp 55 °C (lit.[21] mp 57–58 °C); ^{13}C NMR ($CDCl_3$) 187.0, 140.7, 136.0, 11.9 ppm; ^1H NMR ($CDCl_3$) δ 2.03 (s, 6 H), 6.72 (s, 2 H); IR (KBr) 3305, 3271, 3058, 2959, 2931, 1764, 1655, 1635, 1603, 1311, 1138, 1065, 834 cm^{-1}.

1,2,5-Triacetoxy-3,4-dimethylbenzene (15). To a solution of 19.7 g (0.14 mol) of 2,3-dimethylbenzoquinone (**14**) in acetic anhydride (200 mL) at 0 °C was added 34.4 mL (0.28 mol) of boron trifluoride etherate. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into water (500 mL) and extracted with methylene chloride (3 × 150 mL). The methylene chloride layer was then removed under reduced pressure to afford 32.6 g (83%) of crude 3,4,6-triacetoxy-*o*-xylene (**15**) as a white solid. Recrystallization of the solid from hexane and ethyl acetate afforded 30.3 g (77%) of **15**: mp 88–89 °C; ^{13}C NMR ($CDCl_3$) 168.7, 168.0, 146.3, 140.1, 138.6, 131.7, 127.6, 114.5, 20.7, 20.5, 20.2, 13.2, 12.8 ppm; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.11 (s, 3 H), 2.24 (s, 3 H), 2.29 (s, 3 H), 2.30 (s, 3 H), 6.83 (s, 1 H); IR (KBr) 2999, 2933, 1775, 1760, 1478, 1372, 1190, 1085, 922, 910 cm^{-1}; MS (70 eV) calcd for $C_{14}H_{16}O_6$ 280.0947, found 280.0951.

1,2,5-Triacetoxy-3,4-bis(bromomethyl)benzene (16). A mixture of 2.8 g (10 mmol) of 3,4,6-trimethoxy-*o*-xylene (**15**), 3.74 g of *N*-bromosuccinimide, and 5 mg of benzoyl peroxide in refluxing carbon tetrachloride (50 mL) was irradiated (GE sunlamp) for 1 h. Filtration of the reaction mixture afforded the product and succinimide. The solid was dissolved in methylene chloride (75 mL) and washed with a 3% sodium hydroxide solution (1 × 50 mL). The organic layer was then washed with water (2 × 50 mL) and a saturated sodium chloride solution (1 × 50 mL) and dried ($MgSO_4$). Concentration resulted in a white solid, which was recrystallized from hexane and ethyl acetate to afford 3.6 g (82%) of the bis(bromomethyl) derivative **16**: mp 170–172 °C; ^{13}C NMR ($CDCl_3$) 168.0, 167.1, 146.8, 143.0, 138.9, 131.2, 126.8, 118.9, 21.9, 21.7, 20.8, 20.6, 20.2 ppm; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 2.26 (s, 3 H), 2.26 (s, 3 H), 4.54 (CH_2Br, s, 4 H), 7.19 (s, 1 H); IR (KBr) 3095, 3047, 1772 (vs), 1761 (vs), 1471, 1431, 1366, 1321, 1209 (vs), 1182 (vs), 1155 (s), 1088, 1019, 961, 911, 889, 855, 764 cm^{-1}.

5,6,8-Triacetoxy-3a,4,9,9a-tetrahydrospiro[2*H*-benz[*f*]-indene-2,1′-indan]-1,3-dione (18). To a solution of 350 mg (1.8 mmol) of dione **2** and 208 mg (3.2 mmol, 2.0 equiv) of zinc (freshly activated) in *N,N*-dimethylformamide (2 mL) at room temperature was added a solution of 717 mg (1.5 mmol, 1.2 equiv) of dibromoxylene **16** in *N,N*-dimethylformamide (10 mL) dropwise over a 10-min period. The reaction mixture was stirred at room temperature for 2 h and then poured into a beaker containing ice water (50 mL). The resulting pink precipitate was collected by filtration. The precipitate was dissolved in ethyl acetate (50 mL), and any insoluble impurities were removed by filtration. The ethyl acetate was removed under reduced pressure, and the crude crystalline product was ground up in a beaker containing water. The product, which is insoluble in water, was then collected by filtration, dissolved in chloroform (40 mL), and dried ($MgSO_4$). The drying agent was removed by filtration through a medium sintered-glass filter containing Celite (to remove any remaining traces of zinc). Concentration yielded 624 mg (84%) of crude **18**, which was further purified by recrystallization with chloroform, ether, and

hexane (2:1:4) to afford 403 mg (54%) of 1,3-dione **18** as an orange crystalline material: mp 178 °C dec; ^{13}C NMR ($CDCl_3$) 214.36, 214.40, 168.6, 167.7, 144.9, 144.6, 140.9, 137.3, 131.3, 128.2, 127.2, 126.7, 125.5, 122.0, 115.5, 71., 45.7, 45.6, 31.8, 22.9, 22.4, 20.5, 20.3, 20.1, 20.0 ppm; ^1H NMR ($CDCl_3$) δ 2.06–2.12 (m, 3 H), 2.32 (s, 3 H), 2.308 (s, 3 H), 2.312 (s, 3 H), 2.88 (br, 3 H), 3.05–3.10 (t, J = 15.0 Hz, 2 H), 3.51 (br, 2 H), 6.91 (s, 1 H), 7.05–7.10 (t, J = 15.0 Hz, 1 H), 7.15–7.24 (m, 3 H); IR (KBr) 3069, 2930, 2854, 1774 (s), 1721 (s), 1624, 1600, 1479, 1435, 1372 (m), 1195 (vs), 1182 (vs), 1087, 1017, 892, 751 cm^{-1}; MS (70 eV) calcd for $C_{27}H_{24}O_8$ 476.1471, found 476.1465.

5,6,8-Triacetoxyspiro[2*H*-benz[*f*]indene-2,1′-indan]-1,3-dione (19). To a solution of 214 mg (0.45 mmol) of 1,3-dione **18** in acetic acid (10 mL) was added 52 μL (1.00 mmol) of bromine over a 5-min period. The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a beaker containing water (25 mL) and was extracted with methylene chloride (3 × 25 mL). The combined organic extracts were washed with a saturated sodium sulfate solution (1 × 40 mL), a saturated sodium bicarbonate solution (1 × 40 mL), water (2 × 40 mL), and a saturated sodium chloride solution 1 × 40 mL) and dried ($MgSO_4$). Concentration and recrystallization from hexane and ethyl acetate afforded 160 mg (75%) of spiro dione **19** as a yellow crystalline material: mp 105–110 °C dec; ^{13}C NMR ($CDCl_3$) 201.6, 201.4, 168.4, 167.7, 167.3, 154.6, 154.3, 146.9, 145.7, 140.6, 137.4, 128.4, 127.2, 126.9, 125.23, 125.19, 122.9, 122.8, 122.4, 118.7, 116.5, 64.0, 32.0, 21.7, 20.7, 20.5, 20.3 ppm; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 2.35 (s, 3 H), 2.51 (s, 3 H), 2.41–2.45 (t, J = 12.0 Hz, 2 H), 3.20–3.24 (t, J = 11.9 Hz, 2 H), 6.57–6.65 (d, 1 H), 6.75–6.73 (d, 1 H), 7.00–7.11 (m, 2 H), 7.20–7.24 (t, J = 12.0 Hz, 1 H), 7.29–7.35 (t, J = 18.1 Hz, 1 H), 8.62–8.70 (d, 1 H); IR (KBr) 3070, 3024, 2938, 2858, 1776 (s), 1746, 1701 (s), 1630, 1479, 1461, 1372, 1245, 1210 (s), 1193 (s), 1176 (vs), 1138, 1016, 937, 887, 750 cm^{-1}; MS (70 eV) calcd for $C_{27}H_{20}O_8$ 472.1158, found 472.1163.

4,9-Dihydroxyspiro[2*H*-benz[*f*]indene-2,1′-indan]-1,3-dione (23). To a solution of 100 mg (0.63 mmol) of 3-cyano-1-(3*H*)-isobenzofuranone[16] (**22**) in THF (5 mL) at −78 °C was added 1.11 mL (1.89 mmol, 3 equiv) of a 1.7 M *tert*-butyllithium solution dropwise over a 5-min period. The reaction mixture was stirred at −78 °C for 10 min, in which time the solution turned a dark red color. To the mixture was added a solution of 125 mg (0.63 mmol) of dione **2** in THF (5 mL). The solution turned from a dark red to a very dark green color upon complete addition of the dienophile. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h before being quenched with water (10 mL) and acidified to pH ~1 with concentrated hydrochloric acid. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with a saturated sodium chloride solution (1 × 50 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography on silica gel using hexane and ethyl acetate (3:1) afforded, after recrystallization (chloroform–hexane), 167 mg (80%) of dihydroxy spiro dione **23** as a white crystalline material: mp 246–248 °C dec; ^{13}C (DMSO-d_6) 200.8, 146.6, 145.1, 142.5, 130.0, 129.7, 127.9, 126.7, 124.8, 124.3, 122.9, 115.8, 67.9, 32.0, 31.5 ppm; ^1H NMR (acetone-d_6) δ 2.57–2.62 (t, J = 7.3 Hz, 2 H), 3.25–3.30 (t, J = 7.3 Hz, 2 H), 6.87–6.90 (d, 1 H), 7.08–7.13 (t, J = 7.3 Hz, 1 H), 7.24–7.28 (t, J = 7.3 Hz, 1 H), 7.37–7.40 (d, 1 H), 7.88–7.91 (m, 2 H), 8.47–8.50 (m, 2 H), 9.52 (br, 2 H); IR (KBr) 3369, 3067, 2923, 2850, 1708 (s), 1680 (vs), 1615, 1477, 1473, 1351, 1319 (s), 1261, 1254, 1222, 1204, 1029, 1013 (s), 920, 777, 748, 662, 654 cm^{-1}; MS (70 eV) calcd for $C_{21}H_{14}O_4$ 330.0892, found 330.0888.

1,1-Diethoxyphthalan (26). 1,1-Diethoxyphthalan (**26**) was prepared in a 49% yield by the procedure of Contreras and MacLean.[18a] Physical data: bp 65 °C (0.2 mm) [lit.[12a] bp 60 °C (0.1 mm)]; ^{13}C NMR ($CDCl_3$) 139.9, 129.5, 127.7, 123.7, 122.5, 121.0, 70.5, 58.6, 15.0 ppm; ^1H NMR ($CDCl_3$) δ 1.17–1.22 (t, J = 7.2 Hz, 6 H), 3.35–3.46 (m, 2 H), 3.59–3.70 (m, 2 H), 5.09 (s, 2 H), 7.24–7.26 (d, 1 H), 7.33–7.46 (m, 3 H); IR (neat) 2977, 2932, 2898, 2871, 1463, 1364, 1358, 1300 (s), 1262 (vs), 1128 (vs), 1050, 1032, 1015 (s), 968 (s), 763 cm^{-1}; MS (70 eV) calcd for $C_{12}H_{16}O_3$ 209.1178 (M + 1), found 209.1181.

4-Ethoxy-4,9-epoxy-3a,9a-dihydro-9-(trimethylsilyl)spiro[2*H*-benz[*f*]indene-2,1′-indan]-1,3-dione (28). By use of a modification of a procedure of Rickborn,[17] a solution of 210 mg (1.01 mmol) of 1,1-diethoxyphthalan (**26**) and 17 μL (0.12 mmol) of diisopropylamine in THF (5 mL) at 0 °C was added to 317 μL (2.50 mmol) of *n*-butyllithium solution. The reaction mixture was allowed to stir at 0 °C for 1 h to ensure complete anion generation. A solution of chlorotrimethylsilane (317 μL, 2.50 mmol) in THF (2 mL) was added dropwise to the reaction mixture. After complete addition of the chlorotrimethylsilane solution, 200 mg (1.01 mmol) of spiro[3-cyclopentene-1,1′-indan]-2,5-dione (**2**) in tetrahydrofuran (5 mL) was added dropwise over a 5-min period. The ice bath was removed, and the mixture was stirred for 24 h at room temperature. To the reaction mixture was added ether (100 mL), and the resulting organic phase was washed with pH 7 buffer (3 × 40 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography on silica gel using 20% ether in hexane with 1% triethylamine afforded 80 mg (68%) of epoxy dione **28** as a viscous clear oil: ^{13}C NMR (acetone-d_6) 204.1, 201.8, 147.3, 145.2, 142.8, 140.3, 131.2, 130.5, 128.9, 126.3, 125.9, 125.2, 122.4, 121.3, 73.5, 69.3, 63.5, 58.5, 53.7, 45.3, 31.9, 31.4, 15.1, 0.621 ppm; ^1H NMR (acetone-d_6) δ 0.37 (s, 9 H), 1.18–1.23 (t, J = 7.2 Hz, 3 H), 2.53–2.58 (t, J = 7.3 Hz, 2 H), 3.23–3.28 (t, J = 7.3 Hz, 2 H), 3.32–3.39 (m, 3 H), 3.48–3.53 (d, 1 H), 6.89–6.92 (d, 1 H), 7.09–7.14 (t, J = 7.3 Hz, 1 H), 7.22–7.27 (t, J = 7.3 Hz, 1 H), 7.39–8.16 (m, 5 H); IR (neat) 3032, 2940, 2904, 2845, 1714 (s), 1710 (s), 1685 (vs), 1616, 1474, 1452, 1355, 1320, 1270, 1254, 1219, 1270, 1178, 1036, 1015 (s), 991, 869 (s), 777, 754 cm^{-1}; MS (70 eV) calcd for $C_{26}H_{28}SiO_4$ 432.1749, found 432.1743.

4-Ethoxy-9-[(trimethylsilyl)oxy]spiro[2*H*-benz[*f*]-indene-2,1′-indan]-1,3-dione (29). To a stirred solution of 50 mg (0.12 mmol) of epoxy dione **28** in methylene chloride (2 mL) at room temperature was added 1 μL (0.01 mmol) of trifluoroacetic acid. The reaction mixture was stirred for 30 min and concentrated. The resulting product was purified by recrystallization from ethyl acetate and hexane to afford 49 mg (94%) of (trimethylsilyl)oxy dione **29**: mp 198–200 °C; ^{13}C NMR (acetone-d_6) 203.7, 202.3, 154.3, 151.6, 146.3, 146.1, 132.5, 131.7, 130.6, 129.5, 129.1, 128.7, 126.3, 125.7, 125.2, 122.3, 121.6, 120.3, 65.4, 58.2, 31.7, 31.2, 15.3, 0.669 ppm; ^1H NMR (acetone-d_6) δ 0.35 (s, 9 H), 1.16–1.21 (t, J = 7.2 Hz, 3 H), 2.55–2.59 (t, J = 6.9 Hz, 2 H), 3.40–3.47 (m, 4 H), 6.85–6.88 (d, 1 H), 7.16–7.21 (t, J = 7.3 Hz, 1 H), 7.23–7.28 (t, J = 7.3 Hz, 1 H), 7.59–7.78 (m, 5 H), 7.95–7.80 (t, J = 7.3 Hz, 1 H), 8.34–8.37 (d, 1 H); IR (KBr) 3058, 2995, 2956, 2851, 1708 (s), 1700 (s), 1682 (vs), 1614, 1593, 1476, 1445, 1340, 1270, 1249, 1173, 1076, 1023 (s), 1001, 969, 776, 748 cm^{-1}; MS (70 eV) calcd for $C_{26}H_{26}SiO_4$ 430.1593, found 430.1595.

2-Hydroxy-4-methoxybenzoic Acid (30). To a solution of 15.4 g (0.1 mol) of 2,4-dihydroxybenzoic acid in 20% sodium hydroxide (50 mL) was added 10.41 mL (0.11 mol) of dimethyl sulfate. The resulting orange solution was stirred at room temperature for 2 h before being neutralized with concentrated hydrochloric acid. The mixture was extracted with ether (3 × 100 mL), and the aqueous layer was acidified to pH ~1 with concentrated hydrochloric acid, resulting in a white precipitate. The precipitate was collected by filtration, washed with water, and dried (under vacuum). Recrystallization from ethanol and water afforded 9.2 g (56%) of acid **30** as a white flocculant material: mp 157–159 °C; ^{13}C NMR (acetone-d_6) 172.5, 166.9, 165.3, 132.6, 107.9, 106.0, 101.5, 55.9 ppm; ^1H NMR (acetone-d_6) δ 3.84 (s, 3 H), 6.44–6.51 (m, 2 H), 7.77–7.80 (d, 1 H), 11.38 (br, 2 H); IR (KBr) 3050–2554 (br), 1649 (vs), 1624 (vs), 1576, 1504, 1465, 1436 (s), 1384, 1360, 1316, 1261 (vs), 1250 (s), 1226, 1205, 1176, 1150 (s), 1095, 1025, 966, 962, 841, 780, 715, 693, 627 cm^{-1}.

2,5-Dihydroxy-4-methoxybenzoic Acid (31). To a solution of 10.0 g (59.5 mmol) of acid **30** and 8.0 g (200 mmol) of sodium hydroxide in water (90 mL) at 10 °C was added a solution of 17.0 g (62.9 mmol) of potassium persulfate in water (300 mL) over a 4-h period. The reaction mixture was then allowed to warm to room temperature and was stirred for 24 h, resulting in a purple solution. The mixture was neutralized with 1 N hydrochloric acid and extracted with ether (3 × 150 mL). The combined organic extracts were washed with a saturated sodium chloride solution (1 × 250 mL) and dried ($MgSO_4$). Concentration and recrystallization from ethanol and water afforded 3.21 g (30%) of acid **31** as colorless rectangular rods: mp 200–202 °C dec (lit.[23] mp

(23) Rajagopalan, S.; Seshadri, T. R.; Varadarajan, S. Proc. *Indian Acad. Sci.* **1949**, *30A*, 265.

201 °C dec); ^{13}C NMR (DMSO-d_6) 172.0, 159.5, 157.6, 135.2, 121.8, 103.6, 100.1, 55.8 ppm; ^1H NMR (DMSO-d_6) δ 3.79 (s, 3 H), 6.50 (s, 1 H), 7.84 (s, 1 H), 11.30 (br, 1 H); IR (KBr) 3599, 3543, 3400–2553 (br), 1680 (s), 1626 (s), 1507, 1424, 1272 (s), 1239 (s), 1219 (vs), 1193 (vs), 1159 (s), 1050 (vs), 881, 801, 705, 606 cm^{-1}.

2,4,5-Trimethoxybenzoic Acid (32). To 3.00 g (16.3 mmol) of acid **31** and 7.2 g (52 mmol) of potassium carbonate in refluxing acetone (100 mL) was added 4.6 mL (49 mmol) of dimethyl sulfate. The reaction mixture was stirred for 3 h at 56 °C and was then filtered through a coarse sintered-glass funnel containing Celite (washing with acetone) to remove the inorganic salts. The organic phase was washed with a saturated sodium chloride solution (1 × 100 mL) and dried ($MgSO_4$). Concentration gave a brown solid (methyl 2,4,5-trimethoxybenzoate) suitable for use in the next step.

The crude product was added to a 5% potassium hydroxide solution (100 mL) and refluxed for 0.5 h. After cooling, the saponified mixture was acidified to pH ~1 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with a saturated sodium chloride solution (1 × 100 mL) and dried ($MgSO_4$). Concentration and recrystallization from benzene and petroleum ether afforded 2.61 g (76%) of 2,4,5-trimethoxybenzoic acid (**32**) as colorless needles: mp 143–144 °C (Aldrich Chemical Co., mp 144–145 °C); ^{13}C NMR ($CDCl_3$) 165.3, 154.4, 153.7, 144.0, 114.5, 109.0, 96.3, 57.2, 56.2 ppm; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3 H), 3.98 (s, 3 H), 4.08 (s, 3 H), 6.59 (s, 1 H), 7.59 (s, 1 H), 10.73 (s, 1 H); IR (KBr) 3246 (br), 2967, 2963, 2835, 1710 (vs), 1614 (s), 1521, 1480, 1443, 1419, 1361, 1287, 1268, 1235, 1213 (s), 1170, 1044, 1021 (s), 876, 841, 826 cm^{-1}; MS (70 eV) calcd for $C_{10}H_{12}O_5$ 212.0684, found 212.0681.

***N,N*-Diethyl-2,4,5-trimethoxybenzamide (33).** To a solution of 10.0 g (47 mmol) of 2,4,5-trimethoxybenzoic acid (**32**) in benzene (100 mL) at room temperature was added 8.6 mL (118 mmol) of thionyl chloride dropwise over a 10-min period. The reaction mixture was stirred at room temperature for 2 h, while vigorous gas evolution occurred. The green solution was then stirred overnight, resulting in a yellow solution. The solvent and excess thionyl chloride were removed by distillation, resulting in a white solid. The solid was dried under vacuum to afford 10.6 g (98%) of crude 2,4,5-trimethoxybenzoyl chloride suitable for use in the next step.

To a solution of the crude benzoyl chloride in benzene (100 mL) at 0 °C was added 9.8 mL (94 mmol) of diethylamine dropwise over a 10-min period. The evolution of gas was observed as the benzoyl chloride dissolved, resulting in a viscous orange-brown colored solution. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 12 h. The mixture was washed with 1 N hydrochloric acid (2 × 100 mL) and a saturated sodium chloride solution (1 × 100 mL) and dried ($MgSO_4$). Concentration and recrystallization from ethyl acetate and hexane afforded 11.64 g (93%) of benzamide **33** as a white crystalline material: mp 74–75 °C (lit.[2m] mp 73–74 °C); ^{13}C NMR ($CDCl_3$) 168.3, 150.0, 149.5, 143.2, 118.2, 111.3, 97.7, 56.45, 56.36, 55.9, 42.7, 38.7, 13.8, 12.7 ppm; ^1H NMR ($CDCl_3$) δ 1.03–1.08 (t, J = 7.1 Hz, 3 H), 1.23–1.26 (t, J = 7.1 Hz, 3 H), 3.16–3.23 (q, J = 7.1 Hz, 2 H), 3.56 (br, 2 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 3 H), 6.53 (s, 1 H), 6.76 (s, 1 H); IR (KBr) 2971, 2935, 2848, 1626 (vs), 1216 (s), 1517 (s), 1475 (s), 1456, 1428, 1390, 1335, 1283 (s), 1212 (vs), 1151, 1037, 1023 (s), 857, 831, 807 cm^{-1}; MS (70 eV) calcd for $C_{14}H_{21}NO_4$ 267.1471, found 267.1464.

3-Hydroxy-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (34). By use of a modification of a reported procedure,[24] a mixture of 5.00 g (19 mmol) of *N,N*-diethyl-2,4,5-trimethoxybenzamide (**33**) and 3.2 mL (21 mmol) of *N,N,N',N'*-tetramethylethylenediamine in THF (30 mL) were cooled to −78 °C. To the solution was added 16.2 mL (21 mmol, 1.3 M) of a *sec*-butyllithium solution dropwise with vigorous stirring over a 20-min period, followed by 45 min of stirring at −78 °C. To the cloudy yellow solution was added 6.4 mL (83 mmol) of *N,N*-dimethylformamide via syringe. The solution was stirred for 30 min at −78 °C, warmed to room temperature, and stirred for 18 h. Water (50 mL) was added, and the solution was acidified to pH ~1 with concentrated hydrochloric acid. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were concentrated at reduced pressure to give a yellow residue. The residue was dissolved in methylene chloride (100 mL) and washed with 1 N hydrochloric acid (1 × 50 mL) and water (1 × 50 mL) and dried over calcium sulfate. Concentration afforded *N,N*-diethyl-6-formyl-2,4,5-trimethoxybenzamide as an orange oil suitable for use in the next step.

The oil was dissolved in acetic acid (100 mL), and 10% aqueous hydrochloric acid (100 mL) was added. The mixture was refluxed for 18 h, and the solvent was removed in vacuo at 40–45 °C. The resulting red residue was taken up in ethyl acetate (100 mL), and water was added (100 mL). The mixture was filtered, and the solid product was saved. The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 75 mL). The organic layer was extracted with saturated aqueous sodium bicarbonate solution (3 × 50 mL). The basic layer was cooled to 0 °C, carefully acidified to pH ~1 with concentrated hydrochloric acid, and extracted with ethyl acetate (3 × 75 mL). This combined organic layer was washed with a saturated sodium chloride solution (1 × 125 mL) and dried ($MgSO_4$). Concentration resulted in a red-brown solid, which was combined with the filtered product and recrystallized (ethyl acetate–hexane) to afford 215 mg (47%) of 3-hydroxy-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (**34**) as a white crystalline material: mp 215–216 °C; ^{13}C NMR (DMSO-d_6) 165.4, 158.8, 154.6, 140.3, 137.2, 105.1, 99.2, 94.6, 60.5, 56.6, 56.2 ppm; ^1H NMR (acetone-d_6) δ 3.83 (s, 3 H), 3.93 (s, 3 H), 3.99 (s, 3 H), 6.54–6.57 (d, 1 H), 6.73–6.75 (d, 1 H), 6.84 (s, 1 H); IR (KBr) 3462 (s), 3095, 3014, 2997, 2953, 2845, 1774 (vs), 1625, 1608, 1516 (s), 1448, 1438, 1360, 1340, 1321, 1248, 1238 (s), 1121, 1153, 1053 (s), 1016, 970, 953, 938, 853, 841, 770 cm^{-1}; MS (70 eV) calcd for $C_{11}H_{12}O_6$ 240.0634, found 240.0630.

3-Cyano-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (35). To a mixture of 550 mg (2.3 mmol) of 3-hydroxy-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (**34**) and 1.79 g (27.5 mmol, 12 equiv) of potassium cyanide was added water (30 mL). The solution was stirred in a well-vented hood at room temperature for 15 min to effect a homogeneous clear orange solution, and concentrated hydrochloric acid (20 mL) was added. The mixture was allowed to stand at room temperature for 3 h, and the resulting precipitated product was filtered and vacuum-dried to afford 533 mg (93%) of 3-cyano-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (**35**) as a tan crystalline material: mp 129–130 °C; ^{13}C NMR (acetone-d_6) 165.2, 160.7, 157.0, 137.3, 136.9, 115.6, 103.9, 100.5, 63.5, 60.9, 57.2, 56.9 ppm; ^1H NMR (acetone-d_6) δ 3.91 (s, 3 H), 3.9 (s, 3 H), 4.07 (s, 3 H), 6.40 (s, 1 H), 6.94 (aromatic, s, 1 H); IR (KBr) 3088, 2990, 2950, 2938, 2856, 1788 (s), 1776 (vs), 1629, 1609, 1515 (s), 1473, 1440, 1357 (s), 1338, 1272, 1247, 1234 (s), 1207 (s), 1182, 1152, 1091, 1067, 1028 (vs), 1017 (vs), 1003 (s), 964, 840, 762 cm^{-1}; MS (70 eV) calcd for $C_{12}H_{11}NO_5$ 249.0637, found 249.0640. Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.67; H, 4.35; N, 5.46.

4,9-Dihydroxy-5,6,8-trimethoxyspiro[2*H*-benz[*f*]indene-2,1'-indan]-1,3-dione (38). To a solution of 50 mg (0.20 mmol) of 3-cyano-4,5,7-trimethoxy-1(3*H*)-isobenzofuranone (**35**) in THF (2 mL) at −78 °C was added 130 μL (0.20 mmol) of an *n*-butyllithium solution over a 2-min period. The mixture was stirred at −78 °C for 30 min before 31 μL (0.24 mmol, 1.2 equiv) of chlorotrimethylsilane was added. The orange reaction mixture was then warmed to room temperature and stirred for 5 min, before cooled to −78 °C. To the mixture at −78 °C was added a solution of 44 mg (0.22 mmol, 1.1 equiv) of spiro dione **2** in THF (2 mL) over a 5-min period. The resulting red solution was warmed to room temperature (resulting in a green solution) and stirred for 6 h. To the reaction mixture was added ethyl acetate (10 mL) and water (10 mL), and the phases were separated. The organic phase was washed with water (2 × 5 mL) and a saturated sodium chloride solution (1 × 5 mL) and dried ($MgSO_4$). ^1H NMR ($CDCl_3$) of the crude reaction mixture indicated the presence of a (trimethylsilyl)oxy resonance at 0.18 ppm, which was lost upon chromatographic workup. Purification by flash chromatography on silica gel using hexane and ethyl acetate (2:1) afforded 51 mg (62%) of **38** as a tan crystalline material: mp 168–171 °C dec; ^{13}C NMR ($CDCl_3$) 201.2, 201.1, 154.6, 153.2, 146.5, 145.2, 143.0, 140.6, 131.2, 130.3, 129.8, 127.9, 126.3, 124.8, 124.4, 119.3, 118.9,

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116.2, 65.7, 57.1, 56.4, 56.3, 31.8, 32.9 ppm; ^{1}H NMR ($CDCl_3$) δ 2.56–2.61 (t, J = 7.2 Hz, 2 H), 3.27–3.22 (t, J = 7.2 Hz, 2 H), 4.01 (s, 3 H), 4.07 (s, 3 H), 4.10 (s, 3 H), 6.78–6.80 (s, 1 H), 6.87 (s, 1 H), 7.04–7.09 (t, 1 H), 7.18–7.23 (t, 1 H), 7.31–7.33 (d, 1 H), 10.40 (br, 1 H), 10.70 (s, 1 H); IR (KBr) 3372, 3069, 3020, 2925, 2856, 1709 (s), 1688 (vs), 1620, 1478, 1470, 1322 (s), 1260, 1253, 1208 (s), 1197 (s), 1172 (vs), 1012 (s), 789, 749 cm^{-1}; MS (70 eV) calcd for $C_{24}H_{20}O_7$ 420.1203, found 420.1199.

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Registry No. 1, 80455-68-1; **2**, 105365-18-2; **3**, 17082-61-0; **4**, 100020-34-6; 4 (ketone), 83-33-0; **5**, 116664-59-6; **6**, 116664-60-9; (±)-**7**, 116698-30-7; (±)-**8**, 116698-31-8; (±)-**9a**, 116664-61-0; (±)-**9b**, 116698-32-9; (±)-**10** (isomer 1), 116664-62-1; (±)-**10** (isomer 2), 116698-33-0; **14**, 526-86-3; **15**, 5091-02-1; **16**, 116664-63-2; **18**, 116664-64-3; (±)-**19**, 116664-65-4; (±)-**22**, 116664-66-5; **23**, 116664-67-6; **26**, 70103-17-2; (±)-**28**, 116664-68-7; (±)-**29**, 116669-32-0; **30**, 2237-36-7; **31**, 5981-37-3; **32**, 490-64-2; **32** (Me ester), 20029-76-9; **32** (acid chloride), 42833-66-9; **33**, 105518-12-5; **33** (6-formyl deriv), 105518-13-6; (±)-**34**, 116664-69-8; (±)-**35**, 116664-70-1; (±)-**38**, 116664-71-2; CH_2=CHCH=CH_2, 106-99-0; 2,4-$(OH)_2C_6H_3CO_2H$, 89-86-1; Danishefsky diene, 54125-02-9.

Acid-Catalyzed Transformations of the Heliangolide 15-Hydroxyacetylleptocarpin[1]

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Acid-catalyzed transformations of the natural heliangolide 15-hydroxyacetylleptocarpin (1) were carried out. Treatment with perchloric acid afforded three elimination products: the dihydropyran **2**, its acetate **3**, and the germacratrienolide **4**. BF_3·OEt_2 catalysis gave **5**, derived from a pinacolic rearrangement followed of hemiketalization. In all these cases, the 1(10)-epoxide promoted the reaction. Allylic chloride **7** was obtained by treatment of **1** with $SOCl_2$. Mechanisms explaining the characterized reaction products are proposed.

The acid-catalyzed cyclizations of germacrolides (*trans,trans*-1(10),4-germacradienolides) and their 1(10)- and 4(5)-epoxy derivatives have been extensively investigated because of interest in their biogenesis, the reaction mechanisms and the transformation products.[2] The reactions afford eudesmanolides, elemanolides, and guaianolides as the main products, and in some cases xanthanolides[3,4] and cyclobutane derivatives[3] have also been obtained. Few acid-catalyzed studies have been performed on the geometric isomers of germacranolides.[5] However, cyclization of heliangolides (1(10)-*trans*,4-cis-germacradienolides) gave cadinanolides[6,7] and eudesmanolides[7] in low yield.[8]

The present work deals with the acid-catalyzed transformations of the heliangolide 15-hydroxyacetylleptocarpin (**1**),[9] which yields products of functional groups transformations and rearrangements. The expected cadinanolides or eudesmanolides were not observed.

Treatment of **1** with perchloric acid in acetone for 1 h gave a mixture of compounds **2–4**. The major product **2**, mp 162–164 °C, analyzed for $C_{20}H_{24}O_6$ (elemental analysis and mass spectrometry), indicated that a $C_2H_4O_2$ unit was lost in the reaction. Its IR spectrum showed the presence of hydroxyl (3540 cm^{-1}), an α,β-unsaturated γ-lactone (1755 cm^{-1}), and double bonds (1640 cm^{-1}). ^{1}H NMR spin decoupling experiments established the sequence from H-5 to H-9 and corresponded to the arrangement in **1**. Major differences are (a) the one-proton multiplet at δ 5.85, (b) an additional AB system of an oxymethylene group, overlapping with the AB system corresponding to H-15, and (c) the C-10 methyl resonance of the starting material was no longer present. The ^{13}C NMR spectrum of **2** confirmed the presence of an additional trisubstituted double bond and the additional oxymethylene group, indicating the presence of a Δ^3-dihydropyran ring. Addition of trichloroacetyl isocyanate (TAI) induced a paramagnetic shift (Δδ 1.16) in the signal of H-15, thus establishing that C-15 beared the primary allylic alcohol.[10] These data led to the deduction of structure **2**.

X-ray crystallographic analysis of **2** confirmed the proposed structure. Figure 1 is a computer-perspective drawing of the solved structure, and details of this analysis are included in the Experimental Section. The tricyclic structure **2** adopts the chair–boat conformation representative of the heliangolides,[11] although it is qualitatively more rigid than that of the starting material.

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