31 (9.0 mg, 0.02 mmol) in acetic anhydride (5 mL) in a sealed tube was heated at 270 °C (bath temperature) for 2 h. After removal of low volatiles under vacuum, the residue was chromatographed on a silica gel column (AcOEt–hexane, 1:8 v/v) to give **32** (8.0 mg, 85%): $[\alpha]^{30}_D$ −36.1° (*c* 0.72, $CHCl_3$); IR (film) 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.10 to 0.15 (m, 6 H), 0.84 (s, 3 H), 0.86 (s, 3 H), 0.88 (s, 3 H), 1.02–1.83 (m, 5 H), 2.02 (s, 3 H), 2.08–2.68 (m, 1 H), 2.70–4.40 (m, 8 H), 4.54–4.75 (m, 1 H), 4.85–5.03 (m, 1 H), 5.03–5.24 (m, 2 H), 7.35 (s, 5 H); MS, *m/e* 475 (M^+), 91 (100). Anal. Calcd for $C_{26}H_{41}NO_5Si$: C, 65.65; H, 8.69; N, 2.94. Found: C, 65.68; H, 8.74; N, 3.03.

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-isopropenylpyrrolidine (34). A mixture of **32** (55 mg, 0.12 mmol) and K_2CO_3 (32 mg, 0.23 mmol) in methanol (1.5 mL) was stirred at room temperature for 1 h. After the mixture was diluted with CH_2Cl_2 and water, the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated in vacuo to leave crude **33** (51 mg), which was used immediately.

To a stirred solution of **33** (51 mg) in THF (1.5 mL) was added 1 N *n*-Bu_4NF–THF solution (0.22 mL, 0.22 mmol) at 0 °C, and the mixture was stirred at room temperature for 40 min. After the mixture was diluted with ether and water, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to leave a colorless oil, which was chromatographed on a silica gel column (AcOEt–hexane, 2:1 v/v) to give **34** (35.8 mg, 92%): $[\alpha]^{30}_D$ −43.3° (*c* 0.56, $CHCl_3$); IR (film) 3400, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95–1.74 (m, 2 H), 1.64 (br s, 3 H), 1.94–2.42 (m, 1 H), 2.64 (br s, 2 H, exchangeable), 2.61–2.96 (m, 1 H), 3.24–3.95 (m, 7 H), 4.58 (br s, 1 H), 4.82 (br s, 1 H), 5.07 (s, 2 H), 7.28 (s, 5 H); MS, *m/e* 319 (M^+), 91 (100); calcd for $C_{18}H_{25}NO_4$ 319.1783, found 319.1769.

1-(Benzyloxycarbonyl)kainic Acid (35). To a stirred solution of **34** (32 mg, 0.1 mmol) in acetone (1 mL) was added 8 N Jones reagent (0.125 mL, 1.00 mmol) at 0 °C, and the stirring was continued at the same temperature for 5 min. The mixture was then raised to room temperature (10 min) and, after the addition of water (five drops), stirred for 90 min at the same temperature. The excess oxidant was quenched by addition of 2-propanol (0.5 mL), and the mixture was diluted with ether and water. The organic layer was separated, and the aqueous layer was further extracted with ether. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated in vacuo to leave the diacid **35** (34 mg): IR (film) 3100, 2950, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (br s, 3 H), 1.94–2.58 (m, 2 H), 2.67–4.00 (m, 4 H), 4.18–4.56 (m, 1 H), 4.56–4.82 (m, 1 H), 4.96 (br s, 1 H), 5.05–5.27 (m, 2 H), 7.14–7.50 (m, 5 H), 7.50–8.07 (br s, 2 H, exchangeable); MS, *m/e* 347 (M^+), 91 (100); calcd $C_{18}H_{21}NO_6$ 347.1369, found 347.1362.

1-(Benzyloxycarbonyl)kainic Acid Dimethyl Ester (36). A solution of **35** (34 mg) in methanol (1 mL) was treated with an excess of ethereal diazomethane. After the excess diazomethane was blown off, the reaction mixture was evaporated to leave an oily residue, which was chromatographed on a silica gel column (AcOEt–hexane, 1:4 v/v) to give **36** (23 mg, 61% overall) as a colorless oil: $[\alpha]^{30}_D$ −25.2° (*c* 1.03, $CHCl_3$); IR (film) 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 1.16–1.92 (m, 1 H), 1.69 (s, 3 H), 2.25 (d, *J* = 3.4 Hz, 1 H), 2.32 (s, 1 H), 2.56–3.23 (m, 2 H), 3.23–4.03 (m, 7 H), 4.16–4.34 (m, 1 H), 4.57–4.82 (m, 1 H), 4.82–5.00 (m, 1 H), 5.00–5.32 (m, 2 H), 7.18–7.52 (m, 5 H); MS, *m/e* 375 (M^+), 91 (100); calcd for $C_{20}H_{25}NO_6$ 375.1682, found 375.1697.

(−)-Kainic acid (1). A mixture of **36** (141 mg, 0.38 mmol) and 38% NaOH (3.4 mL) in MeOH (2 mL) was refluxed for 14 h. After being cooled, the mixture was diluted with CH_2Cl_2 and water. The aqueous layer was separated and washed with CH_2Cl_2. The aqueous layer was then filtered through two separate columns of ion-exchange resin [Amberlite IRA-45 (OH^- form), H_2O then 1 N HCO_2H and Amberlite CG-120 (H^+ form), H_2O] to give a colorless solid, which was recrystallized from aqueous MeOH to give **1** (32.4 mg, 40%) as colorless needles: mp 243–244 °C dec (lit.[15] mp 250–252 °C dec); $[\alpha]^{27}_D$ −14.2° (*c* 0.23, H_2O) [lit.[15] $[\alpha]^{20}_D$ −14° (*c* 1, H_2O)]; IR (Nujol) 3500, 3130, 2600, 1680, 1600 cm^{-1}; ^1H NMR (D_2O δ 1.76 (s, 3 H), 2.20–2.57 (m, 2 H), 2.80–3.82 (m, 4 H), 4.11 (d, *J* = 3.6 Hz, 1 H).

1-(Benzyloxycarbonyl)kainic Acid Dimethyl Ester (36) from Natural Kainic Acid (1). To a stirred solution of natural **1** (103 mg, 0.48 mmol) in a mixture of 2 N NaOH (0.85 mL) and dioxane (0.36 mL) was added benzyl chlorocarbonate (90%, 0.09 mL, 0.57 mmol) at 0 °C, and the mixture was stirred for 10 min at the same temperature and for 5 h at room temperature. After the mixture was diluted with ether and water, the aqueous layer was separated. The aqueous layer was then made acidic by addition of concentrated HCl and extracted with CH_2Cl_2. The extract was washed (brine), dried ($MgSO_4$), and evaporated to give the crude carbamate **35** (157 mg) as an amorphous solid, which was used immediately.

A stirred solution of the crude **35** (157 mg) in MeOH (3 mL) was treated with an excess of ethereal diazomethane. After the excess diazomethane was blown off, the solution was evaporated in vacuo to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt–hexane, 1:4 v/v) to give **36** (145 mg, 80%) as a colorless oil: $[\alpha]_D$ −26.0° (*c* 1.03, $CHCl_3$). Spectral data were in all respects identical with those of the synthetic material.

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-isopropenylpyrrolidine (34) from Natural Kainic Acid (1). To a stirred solution of **36** [238 mg, 0.63 mmol, obtained from natural kainic acid (**1**)] in THF (5 mL) was added $LiAlH_4$ (30 mg, 0.79 mmol) portionwise at 0 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was treated with 28% NH_4OH at 0 °C to decompose the excess hydride and the mixture, after being stirred for 8 h, was filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated in vacuo to leave a pale yellow oil, which was chromatographed on a silica gel column (AcOEt–hexane, 2:1 v/v) to give **34** (152 mg, 75%) as a colorless oil: $[\alpha]^{29}_D$ −46.5° (*c* 0.56, $CHCl_3$). Spectral data were in all respects identical with those of the synthetic material.

Acknowledgment. We are greatly indebted to Dr. Kyosuke Nomoto, Suntory Institute for Bioorganic Research, for providing natural (−)-kainic acid. We thank the Ministry of Education, Science and Culture, Japan, for generous support of this research.

(15) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.

Synthesis of (±)-Fredericamycin A

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Contribution from the Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167. *Received February 25, 1988*

Abstract: The synthesis of (±)-fredericamycin A (**1**) and supporting studies are reported with full experimental detail. Model studies on the construction of the parent spiro system (**25**) from dimethyl phthalate and the anion of indene are described. Preparation of synthons for the upper (**59**) and lower (**82**) units of **1** and investigations into controlling the regiochemistry of their coupling are delineated. The regiospecific union of **59** and **82** and the elaboration of the resulting product (**86**) into **1** are presented.

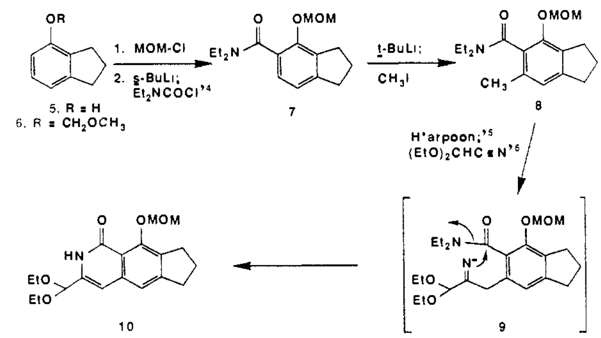
In 1981 scientists at the Frederick Cancer Research Center in Frederick, Maryland, reported the isolation[1] of a red substance with promising activity[2] in a variety of in vitro anticancer screens. The structure of the substance, appropriately christened fre-

(1) 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*, 1389–1401.

(2) Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *34*, 1402–1407.

0002-7863/88/1510-6471$01.50/0

Scheme I

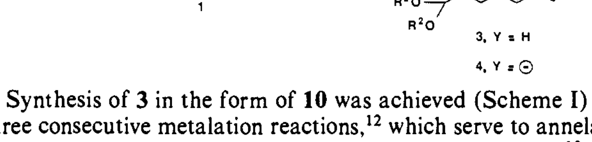


dericamycin A, was determined to be **1** by X-ray crystallographic analysis.[3] In vivo studies[2] on the biological activity of **1** confirmed the chemotherapeutic potential of fredericamycin A: **1** substantially increases long-term survival of mice inoculated with Ehrlich carcinoma [T/C (i.e., percent treated versus control) = 295], Meth-A-fibrosarcoma (T/C = 242), and P388 leukemia cells (T/C = 200); **1** also reduces CD8F mammary tumor size by more than 90%. Unlike many clinically employed antineoplastic agents, fredericamycin A does not show mutagenicity in the Ames test.[2]

The exceptional biological activity of fredericamycin A has established it as an important new lead compound for the chemotherapy of human cancers. That fact, coupled with the entirely unprecedented skeletal framework[4] found in **1** has stimulated considerable interest in fredericamycin A[8] and its synthesis.[9] A brief communication from this laboratory[10] recently outlined the first, and to date only, total synthesis of (±)-fredericamycin A. We now describe that synthesis in full detail.

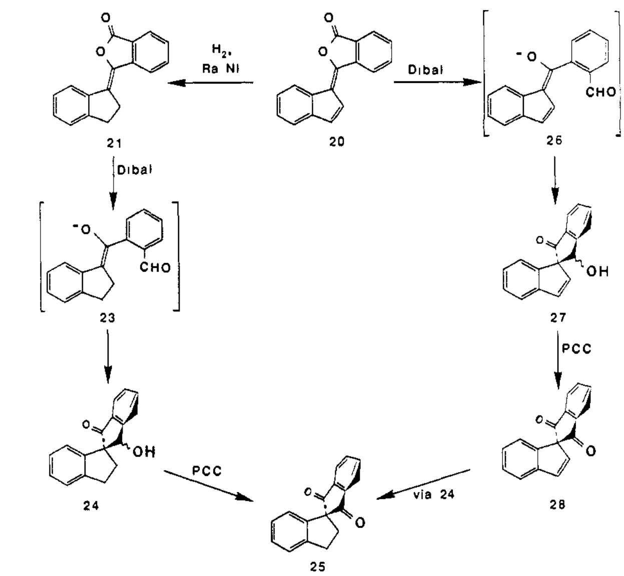
The basic synthetic strategy (eq 1) was to first construct synthons for the top and bottom units of **1** and to then effect their coupling in conjunction with elaboration of the spiro center. The latter operation was envisaged to commence with acylation of **4** by **2**, it being anticipated that lateral metalation[11] of **3** would afford **4**.

(eq 1)



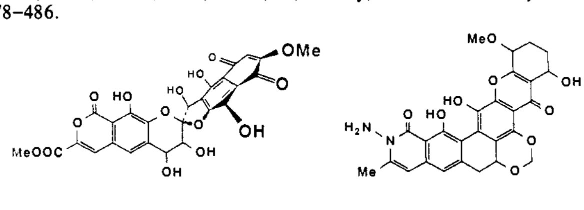
Synthesis of **3** in the form of **10** was achieved (Scheme I) by three consecutive metalation reactions,[12] which serve to annelate the pyridone ring onto the methoxymethyl (MOM) ether[13] (**6**)

Scheme II



(3) (a) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478–4479. (b) Full paper: Misra, R.; Pandey, R. C.; Hilton, B. D.; Roller, P. P.; Silverton, J. V. *J. Antibiot.* **1987**, *40*, 786–802.

(4) Of known natural products, DK-7814-A (i) and its congeners[5] appear structurally most closely related to **1**. A small family of xanthone–isoquinolone antibiotics[6] (e.g., albofungin,[7] ii) share a number of structural features with **1**. The biosynthesis of fredericamycin A has been investigated: Byrne, K. M.; Hilton, B. D.; White, R. J.; Misra, R.; Pandey, R. C. *Biochemistry* **1985**, *24*, 478–486.



(5) Daiichi Seiyako Co., Ltd. Jpn Kokai Tokkyo Koho JP 82-32,286, 1982, Feb 20; *Chem. Abstr.* **1982**, *97*, 36008*a*.

(6) For a leading reference, see: Nakagawa, A.; Omura, S.; Kushida, K.; Shimizu, H.; Lukacs, G. *J. Antibiot.* **1987**, *40*, 301–308.

(7) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N.; Omelchenko, V. N.; Onoprienko, V. V.; Petrenko, G. I.; Popravko, S. A. *Tetrahedron Lett.* **1972**, 1751–1754.

(8) *Chem. Eng. News.* **1982**, Aug 16, p 27; **1983**, Sept 19, pp 36–37; **1986**, Dec 8, pp 30–31.

(9) For reports from other laboratories describing methods for the synthesis of synthons for the top or bottom units of **1** and/or model studies on the construction of its spiro ring system, see: (a) Rama Rao, A. V.; Reddy, D. R.; Deshpande, V. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1119–1120. (b) Parker, K. A.; Koziski, K. A., Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181–2182. (c) Kende, A. S.; Ebetino, F. H.; Ohta, T. *Ibid.* **1985**, *26*, 3063–3066. (d) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Ibid.* **1985**, *26*, 4723–4724. (e) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Ibid.* **1985**, *26*, 4725–4726. (f) Braun, M.; Veith, R. *Ibid.* **1986**, *27*, 179–182. (g) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1986**, *51*, 749–752. (h) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878–880. (i) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835–3838. (j) Acharya, K. R.; Puranik, V. G.; Tavle, S. S.; Guru Row, T. N. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 334–336. (k) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1986**, *27*, 1983–1986. (l) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183–188. (m) Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *Ibid.* **1987**, *52*, 1339–1342. (n) Ciufolini, M. A.; Brown, M. E. *Tetrahedron Lett.* **1987**, *28*, 171–174. (o) Rama Rao, A. V.; Reddy, D. R.; Annapurna, G. S.; Deshpande, V. H. *Ibid.* **1987**, *28*, 451–454. (p) Rama Rao, A. V.; Sreenivasan, N.; Reddy, D. R.; Deshpande, V. H. *Ibid.* **1987**, *28*, 455–458. (q) Mehta, G.; Subrahmanyam, D. *Ibid.* **1987**, *28*, 479–480. (r) Rama Rao, A. V.; Reddy, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 574–575. (s) Clive, D. L. J.; Sedgeworth, J. *J. Heterocycl. Chem.* **1987**, *24*, 509–511.

(10) Kelly, T. R.; Ohashi, N.; Armstrong-Chong, R. J.; Bell, S. H. *J. Am. Chem. Soc.* **1986**, *108*, 7100–7101.

(11) See, inter alia: (a) Gilman, H.; Morton, J. W., Jr. *Org. React.* (*N.Y.*) **1954**, *8*, 258–304 (see especially pp 260 and 278). (b) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, England, 1974; p 30. (c) Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514–3517. (d) Harmon, T. E.; Shirley, D. A. *Ibid.* **1974**, *39*, 3164–3165. (e) Ludt, R. E.; Crowther, G. P.; Hauser, C. R. *Ibid.* **1970**, *35*, 1288–1296. (f) Vaulx, R. L.; Jones, F. N.; Hauser, C. R. *Ibid.* **1964**, *29*, 1387–1391. (g) Cabiddu, S.; Melis, S.; Piras, P. P.; Sotgiu, F. *J. Organometal. Chem.* **1979**, *178*, 291–300. (h) Beak, P.; Tse, A.; Hawkings, J.; Chen, C.-W.; Mills, S. *Tetrahedron* **1983**, *39*, 1983–1989. (i) Footnote 8 in Watanabe, M.; Sahara, M.; Furukawa, S.; Billedeau, R.; Snieckus, V. *Tetrahedron Lett.* **1982**, *23*, 1647–1650. See also ref 12 and 13.

(12) For reviews, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1–360. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312. See also *Tetrahedron Symposia-in-Print No. 9*; Newkome, G. R., Ed.; *Tetrahedron* **1983**, *39*, 1955–2091.

(13) For a leading reference to the use of MOM ethers as directing groups in ortho lithiation, see: Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031–2042.

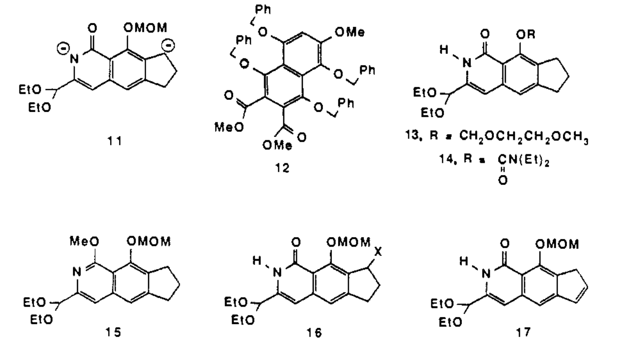
(14) Snieckus, V. *Heterocycles* **1980**, *14*, 1649–1676.

(15) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582–584.

(16) Compare: Poindexter, G. S. *J. Org. Chem.* **1982**, *47*, 3787–3788.

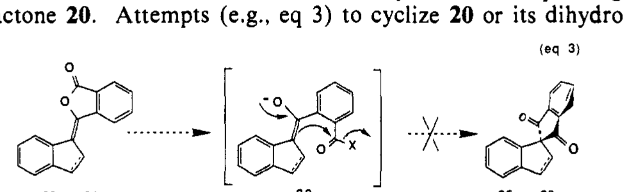
of commercially available 4-indanol (**5**). The sequence in Scheme I routinely affords **10** in multigram batches in 52% overall yield. Each metalation reaction does require, however, individualized reaction conditions.

It had been our hope that the proximity of the MOM group in **10** would facilitate lateral metalation at the adjacent benzylic position and that the resulting anion (**11**) could be acylated by a molecule such as **12**, thereby incorporating the upper unit of **1** and setting the stage for elaboration of the spiro center. Unfortunately, despite exhaustive efforts we were unable to achieve the desired deprotonation of **10** to **11**. Neither substitution of other putative directing groups such as $CH_2OCH_2CH_2OMe$[17] and $C(=O)NEt_2$[18] as in **13** and **14** for the MOM group nor use of isoquinoline **15** in place of isoquinolone **10** led to the desired metalation. Attempts to carry the benzylic anion forward in a latent form (**16**, X = Br or $SnMe_3$) fell victim to the instability of intermediates.



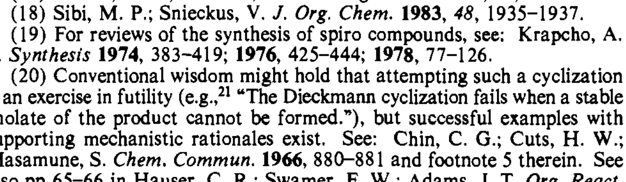
With an eye toward enhancing the acidity of the benzylic proton in **10**, we envisioned replacing indan **10** with indene **17**. Before doing so, however, it seemed prudent to determine whether the basic strategy (eq 1) for constructing[19] the spiro system was feasible. Model studies affirmed our expectations. Thus (eq 2),

(eq 2)



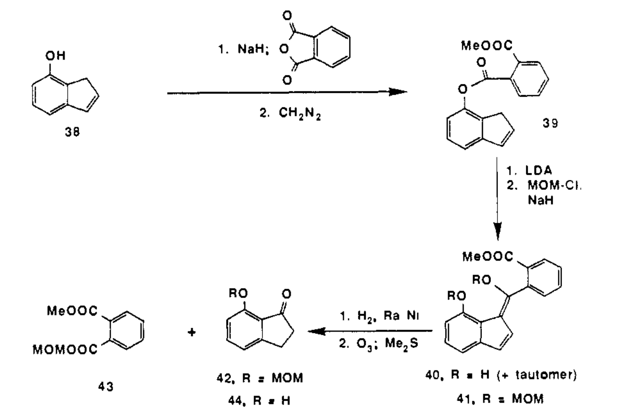
the indene anion (**18**) is smoothly acylated by dimethyl phthalate. The resulting product, nominally enol ester **19**, exists as a mixture of tautomers/isomers. Although this mixture can be separated, it is easier to convert the mixture directly to the corresponding lactone **20**. Attempts (e.g., eq 3) to cyclize **20** or its dihydro

(eq 3)



derivative **21** directly to the spiro diketone system under either basic[20] (e.g., methoxide: via **22**, X = OMe) or acidic[22] conditions

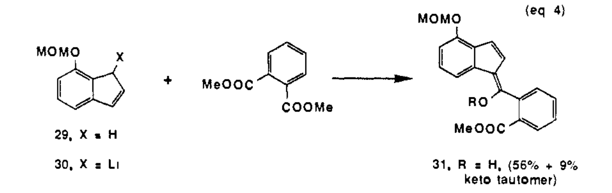
Scheme III



failed. On the other hand (Scheme II), Dibal reduction of dihydro lactone **21** followed by an in situ aldol condensation provides[23] the spiro system as a stereoisomeric mixture of ketols **24**, which can be oxidized to the desired spiro diketone **25** in good overall yield. A similar sequence with **20** as starting material affords the unsaturated spiro diketone **28**, which can be converted to **25** via **24** (hydrogenation of the indene double bond in **28** is accompanied by reduction[24] of one of the carbonyls).

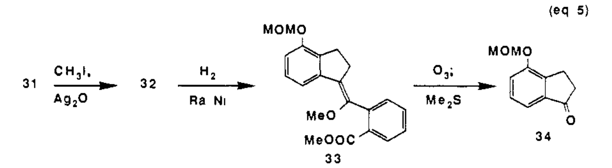
The use of an indene (eq 2) in place of an indan provided a solution to our metalation difficulties, but a Sisyphean complication soon surfaced. For inherent in the use of an indenyl anion is the possibility of reaction at either terminus of the allylic anion system. And acylation (eq 4) of the unsymmetrical MOMO-substituted

(eq 4)



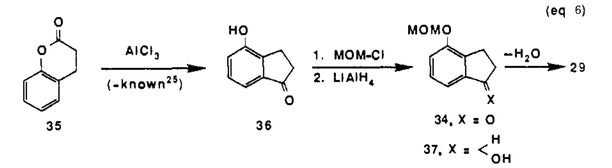
indene **29**, although proceeding in satisfactory yield, provided exclusively the undesired regioisomer **31**. The structure of **31** was established by degradation (eq 5) to indanone **34**, an authentic

(eq 5)



sample of which was prepared independently by the sequence given in eq 6. The starting indene (**29**) was prepared as also shown in eq 6.

(eq 6)



Efforts to overcome the regiochemical debacle of eq 4 by exploiting the presence of the MOM group in **30** to direct (e.g., via metal ion complexation) the phthalate to the desired position in **30** were fruitless. But a conceptionally similar stratagem (Scheme III), involving attachment of the acylating group to the phenolic

(17) Ellison, R. A.; Kotsonis, F. M. *J. Org. Chem.* **1973**, *38*, 4192–4196.

(18) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935–1937.

(19) For reviews of the synthesis of spiro compounds, see: Krapcho, A. P. *Synthesis* **1974**, 383–419; **1976**, 425–444; **1978**, 77–126.

(20) Conventional wisdom might hold that attempting such a cyclization is an exercise in futility (e.g.,[21] "The Dieckmann cyclization fails when a stable enolate of the product cannot be formed."), but successful examples with supporting mechanistic rationales exist. See: Chin, C. G.; Cuts, H. W.; Masamune, S. *Chem. Commun.* **1966**, 880–881 and footnote 5 therein. See also pp 65–66 in Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React. (N.Y.)* **1954**, *8*, 59–196 and references therein.

(21) See p 26 in Schaefer, J. P.; Bloomfield, J. J. *Org. React. (N.Y.)* **1967**, *15*, 1–203.

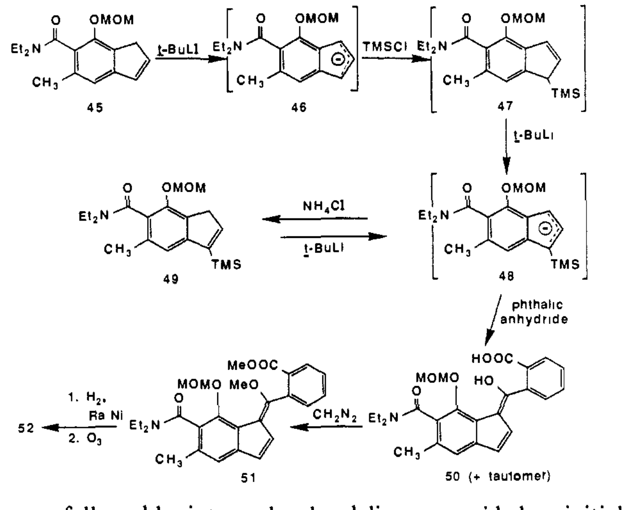
(22) See, inter alia, Loewenthal, H. J. E. *Proc. Chem. Soc., London* **1960**, 355. Kos, Y.; Loewenthal, H. J. E. *J. Chem. Soc.* **1963**, 605–611. Gerlach, H.; Muller, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1030–1031. Mitra, R. B.; Kulkarni, G. H.; Khanna, P. N. *Synthesis*, **1977**, 415–417.

(23) A similar reduction/aldol sequence has been reported: Holland, H. L.; MacLean, D. B.; Rodrigo, R. G. A.; Manske, R. F. H. *Tetrahedron Lett.* **1975**, 4323–4326. We thank Prof. Rodrigo for bringing the similarity of this reaction to our attention.

(24) Compare ref 9c.

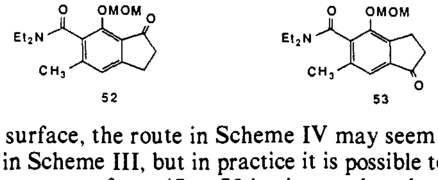
(25) Loudon, J. D.; Razdan, R. K. *J. Chem. Soc.* **1954**, 4299–4304.

Scheme IV



oxygen followed by intramolecular delivery, provided an initial solution to the regiochemical problem; the regiochemistry assigned to **40** was confirmed by degradation to **42**, which was shown to be identical with an authentic sample of **42** prepared by methoxymethylation of the known[26] 7-hydroxyindanone **44**.

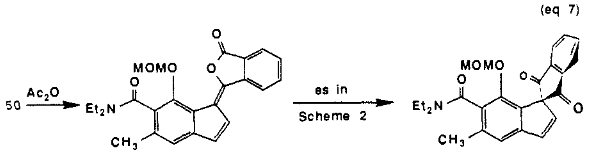
Despite the regiochemical merits of the intramolecular acyl transfer in Scheme III, the overall yield of the conversion of **38** to **40** is only modest. Furthermore, a sequence patterned after that in Scheme III would add an undesirable number of additional steps to the synthesis of fredericamycin A itself. Consequently, an alternative rejoinder to the regiochemical difficulty was sought. Indeed, the seeds of such a response were present within the initially adverse regiochemical behavior exhibited by indenyl anions such as **30** (eq 4). For, as illustrated with the more advanced model system shown in Scheme IV, reaction of anion **46** with TMS-Cl follows the same regiochemical course, giving indenylsilane **47**,[27] which, in turn, can be deprotonated to **48**. In contrast to **46**, which is acylated at the undesired end of the allylic system, acylation of **48** occurs at the desired site, presumably because the steric bulk of the trimethylsilyl group in anion **48** hinders approach to the TMS-bearing carbon atom. Upon aqueous acid workup, the TMS group in the acylation product is cleaved; the resulting material **50**, a mixture of tautomers, is most conveniently purified after conversion to the ester dienol ether **51** with diazomethane. That **51** is the regioisomer depicted was established by degradation to **52**, which was shown to be different from an authentic sample of **53** (which would have been produced had acylation of **48** taken the alternative regiochemical course).



52 53

On the surface, the route in Scheme IV may seem no shorter than that in Scheme III, but in practice it is possible to carry out the whole sequence from **45** to **50** in situ, so that the conversion of **45** to **50** is effectively a one-pot operation. In addition, **50** can be converted (eq 7) to the spiro dione **55**.

(eq 7)

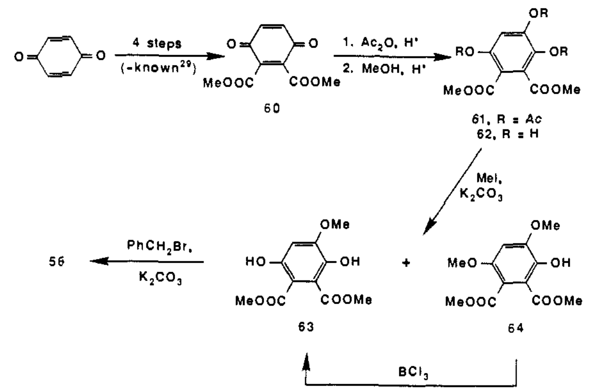


54 55

(26) Wagatsuma, S.; Higuchi, S.; Itoh, H.; Nakano, T.; Naoi, Y.; Sakai, K.; Matsui, T.; Takahashi, Y.; Nishi, A.; Sano, S. *Org. Prep. Proced. Int.* **1973**, *5*, 65–70.

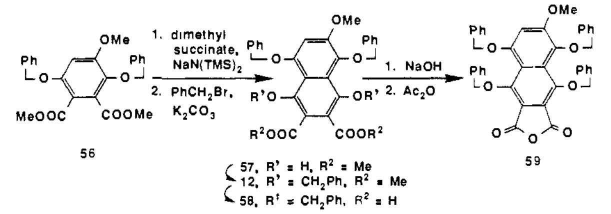
(27) Model studies indicated that establishing regiochemistry by electrophilic acylation of allyl silanes such as **47** was not a viable strategy in our hands.

Scheme V



Having both a solution to the assembly of the spiro center and a means for controlling regiochemistry in hand, we turned from model studies to the synthesis of fredericamycin A itself. Synthesis of naphthalene anhydride **59**, the synthon for the upper half of **1**, proceeds via phthalate **56** (eq 8). Condensation[28] of **56** with

(eq 8)



dimethyl succinate and benzylation of the crude product (→ **12**) followed by hydrolysis to diacid **58** and anhydride formation afford **59**.

Initially, phthalate **56** was obtained as shown in Scheme V. The known quinone diester **60** was prepared by a modification of literature procedures.[29] Thiele acetoxylation[30] of **60** followed by transesterification of the resulting triacetate **61** with acidic methanol affords phthalate **62**. The latter contains three phenolic hydroxyl substituents, but since the reactivity of two of them is attenuated by hydrogen bonding to adjacent carbomethoxy groups, **62** can be selectively monomethylated to **63**.[31a] A lesser amount of a dimethyl ether, tentatively formulated as **64**,[31b] is also obtained, but **64** can be selectively demethylated to **63** with BCl_3, by again exploiting the adjacency[32] of a carbomethoxy group. Benzylation of **63** provides **56**.

The sequence in Scheme V is operationally straightforward, but it is relatively lengthy and hazardous (as usually run, the first step[29b] employs upwards of 100 g of potassium cyanide). A shorter and safer alternative is the Diels–Alder-based route[33,34] in eq 9,

(28) Compare, inter alia, Homeyer, A. H.; Wallingford, V. H. *J. Am. Chem. Soc.* **1942**, *64*, 798–801.

(29) (a) Ansell, M. F.; Nash, B. W.; Wilson, D. A. *J. Chem. Soc.* **1963**, 3028–3036. (b) Jackman, L. M. *Adv. Org. Chem.* **1960**, *2*, 360.

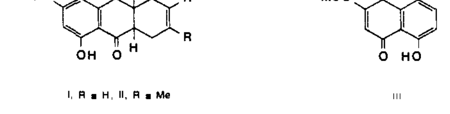
(30) For a review, see: McOmie, J. F. W.; Blatchly, J. N. *Org. React. (N.Y.)* **1972**, *19*, 199–277.

(31) (a) For a recent report of a similarly conceived synthesis of **56**, see: Keith, D. D. *Tetrahedron Lett.* **1985**, *26*, 5907–5910. (b) We have not rigorously excluded the possibility that the dimethyl ether is dimethyl 6-hydroxy-3,4-dimethoxyphthalate rather than **64**.[31a]

(32) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, 4153–4159.

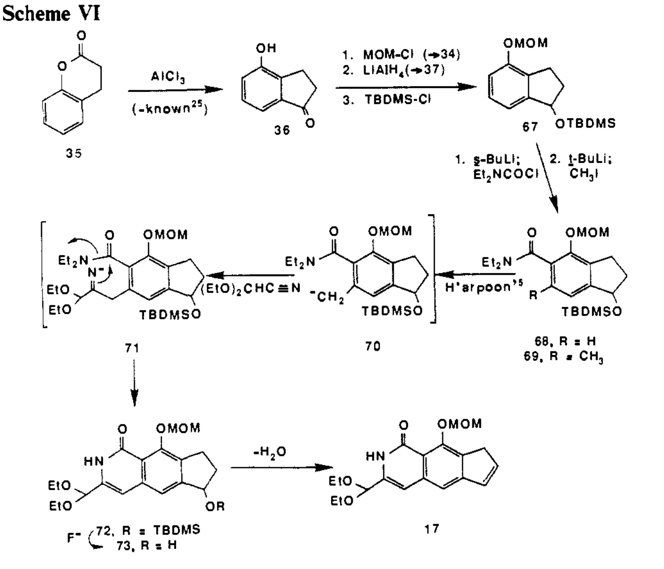
(33) Compare Pelter, A.; Al-Bayati, R.; Lewis, W. *Tetrahedron Lett.* **1982**, *23*, 353–356. We thank Prof. Pelter for helpful discussions.

(34) Attempts to prepare **58** by elaboration (e.g., benzylation and oxidation) of i or ii, the Diels–Alder adducts of naphthopurpurin methyl ether (Kelly, T. R. *Tetrahedron Lett.* **1978**, 1387–1390) and, respectively, butadiene and 2,3-dimethylbutadiene, were unsuccessful.



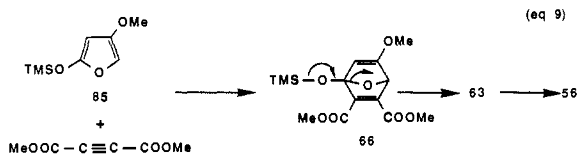
i, R = H, ii, R = Me iii

Scheme VI



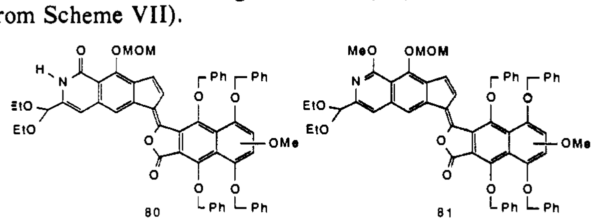
which gives **56** in 59% overall yield without purification of intermediates.

(eq 9)



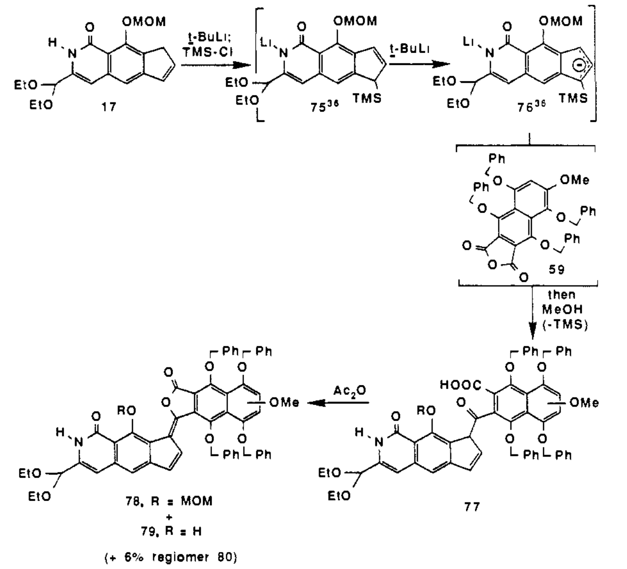
Fabrication of **17**, the indenyl counterpart of **10**, was accomplished as indicated in Scheme VI. A modification of the literature[25] procedure for rearrangement of dihydrocoumarin (**35**) to hydroxyindanone **36** raises the yield from 47% to 88%. Conversion to the MOM ether **34**, reduction of the ketone, and silylation of the resulting carbinol **37** give **67**. As before (Scheme I), annelation of the pyridone ring is achieved by three successive metalation reactions. Silyl ether cleavage and dehydration with *o*-nitrophenyl selenocyanate[35] then provide **17**. The overall yield of **17** from dihydrocoumarin **35** is 33%; both indene **17** and anhydride **59** can be prepared in multigram batches.

Deprotonation of **17**, silylation (→ **75**), in situ deprotonation (→ **76**), acylation, and desilylation to **77** can be achieved in one pot (Scheme VII); lactonization of the crude product, nominally **77** (which is actually a mixture of tautomers/double bond isomers), affords a ca. 1:1 mixture of **78** and **79** in 33% total yield (67% based on unrecovered **17**), contaminated by a small amount (6%) of the undesired regioisomer **80**. The partial cleavage of the MOM ether in the sequence in Scheme VII could not be circumvented, and reattachment of the MOM group (**79** → **78**) could not be accomplished. This lability of the MOM group was not observed in the model series (Scheme IV and eq 7) or in the formation of undesired regioisomer **80** (i.e., if TMS-Cl is omitted from Scheme VII).



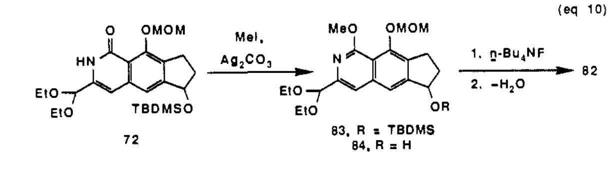
MOM lactone **78** (but not phenol lactone **79**) can be carried forward to fredericamycin A (compare Schemes VIII and IX), but substantially better yields and complete regiospecificity can be realized by enlisting isoquinoline **82** in place of isoquinolone **17**.

Scheme VII



Thus isoquinoline **82**, available either directly (83%) from **17** by sonicating a mixture of **17** and CH_3I/Ag_2CO_3 in benzene[37] or, preferably, as shown in eq 10 (86% overall yield), can be

(eq 10)

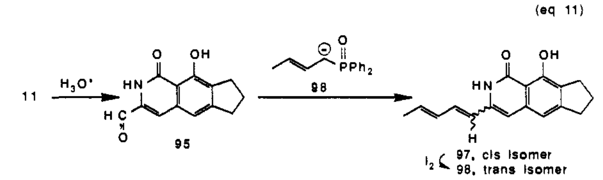


converted (Scheme VIII) to the spiro hexacyclic ring system of fredericamycin A by deployment of a sequence of operations analogous to those used in eq 2 and Scheme II. Conversion of **82** to silyl anion **85**, coupling with anhydride **59**, and lactonization provide **86** (omission of the TMS group in **85** in Scheme VIII results in almost complete regiochemical reversal: undesired lactone **81** is produced in 93% yield). Dibal reduction of **86** to **87** and in situ aldol condensation afford **88**, apparently as a mixture of the four possible diastereomers. Oxidation of **88** to **89** eliminates the diastereomeric element and furnishes **89** in an overall yield of 40% from **82**.

Hydrogenation of **89** over Pd/C (Scheme IX) serves to not only saturate the indene double bond and cleave the four benzyl ethers (but not the benzylic acetal) but also sets the stage for oxidation of the pale yellow hydrogenation product **90** to the deep red naphthopurpurin **91** merely upon opening of the reaction vessel to the air, giving **91** in 78% overall yield from **89**. Hydrolysis of the more (relative to the MOM acetal[39]) labile benzylic acetal moiety gives aldehyde **92**.

Appendence of the pentadienyl side chain of fredericamycin A onto **92** proved troublesome. In model studies (eq 11) with aldehyde **95** and the Horner reagent **96**[40] the side chain could be introduced in good yield. A 1:1 mixture of geometric isomers

(eq 11)

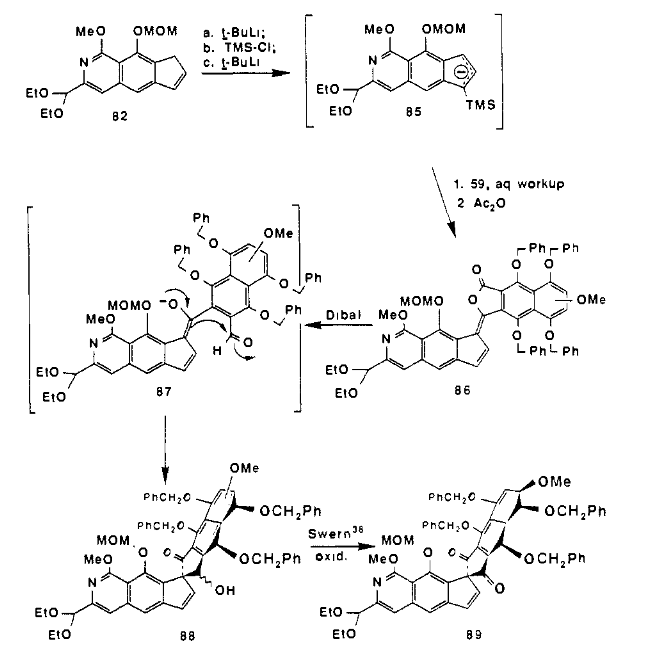


(35) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
(36) The pyridone may be O- or N-silylated.
(37) Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040–4044.
(38) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
(39) In general, when the heterocyclic system is in the form of an isoquinoline, the benzylic acetal is hydrolyzed in preference to the MOM group with aqueous acid; when the heterocyclic system is in the form of an isoquinolone, the MOM group is usually more labile to aqueous acid than the benzylic acetal.
(40) Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2386–2390.

97 and 98 is produced, but this mixture can be isomerized to essentially pure 98 with iodine.[41] Unfortunately, 95 proved an imperfect model for 92, since reaction of 92 with 96 gave an intractable mixture of products. Substitution of ylide 93[42] for the Horner reagent 96 served to overcome this difficulty, furnishing the desired 94. As expected,[42b] 94 is produced as a mixture of isomers in which the trans,trans and cis,trans stereoisomers are apparently the major components, but it proved possible to isomerize this mixture almost entirely to the thermodynamically favored and natural trans,trans isomer by treatment with iodine. This isomerization is most conveniently conducted in conjunction with cleavage of the MOM and isoquinoline methyl ethers; the one-pot isomerization/double deprotection serves to complete the synthesis of (±)-fredericamycin A. The synthetic (±)-1 so obtained was shown to be identical, except for properties dependent on optical activity, with natural fredericamycin A by the usual battery (UV, NMR, TLC, and HPLC) of analytical methods.

The sequences developed in the course of this synthesis are now being applied to the preparation of analogues designed to probe the mechanism of action of fredericamycin A. The results of those studies will be reported in due course.

Scheme VIII



Experimental Section[53]

Dimethyl 6-Methoxy-1,4,5,8-tetrakis(phenylmethoxy)-2,3-naphthalenedicarboxylate (12). A solution of 2.15 g (4.15 mmol) of naphthoquinol 57 in 200 mL of dry acetone under argon was stirred with anhydrous potassium carbonate (5.8 g) and benzyl bromide (6.0 mL, 50 mmol) at room temperature overnight. The suspension was then filtered through Celite, washing with acetone, and concentrated under reduced pressure. The excess benzyl bromide was removed under high vacuum at ~40 °C, leaving a pale yellow solid. Recrystallization from benzene (15 mL)/petroleum ether (22 mL) afforded 2.38 g (82%) of the tetrabenzyl ether 12 as colorless needles, mp 150–151 °C: IR (Nujol) ν 1745, 1705 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.75 (3 H, s), 3.77 (3 H, s), 3.80 (3 H, s), 4.83 (2 H, s), 5.05 (2 H, s), 5.07 (2 H, s), 5.11 (2 H, s), 6.82 (1 H, s), 7.15–7.70 (20 H, m). Anal. Calcd for $C_{43}H_{38}O_9$: C, 73.91; H, 5.48. Found: C, 73.85; H, 5.53.

3-(Diethoxymethyl)-2,8-dihydro-9-(methoxymethoxy)-1*H*-cyclopent[*g*]isoquinolin-1-one (17). To a stirred solution of alcohol 73 (5.57 g, 15.3 mmol) and *o*-nitrophenyl selenocyanate[35] (4.53 g, 19.9 mmol) in 50 mL of THF under argon was added tri-*n*-butylphosphine (4.96 mL, 19.9 mmol) dropwise, over ~5 min, so that the temperature of the reaction mixture did not exceed 45 °C. The reaction was stirred at room temperature for 1 h, after which time TLC indicated complete formation of the bright yellow selenide. The reaction was then cooled to 0 °C, and a 30% solution of hydrogen peroxide (4.0 mL, 40 mmol) was added dropwise. The reaction was allowed to slowly warm to room temperature over a period of 2 h (at ~10 °C the reaction became somewhat exothermic). The mixture was then diluted with ether, washed with saturated sodium chloride (5×), and dried (Na$_2$SO$_4$) and the solvent was removed. The crude product was partially purified by flash column chromatography on silica, eluting first with petroleum ether/EtOAc (2:1, then 1:1) and then with neat EtOAc to give 5.5 g of partially purified indene 17 as an orange solid. Recrystallization from ethyl acetate/heptane gave 17 (4.31 g, 82%) as tan needles, mp 123.5–124.0 °C: IR (CHCl$_3$) ν 3380, 1644 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.28 (6 H, t, *J* = 7 Hz), 3.55–3.75 (6 H, m), 3.67 (3 H, s), 5.28 (2 H, s), 5.38 (1 H, s), 6.55 (1 H, s), 6.79 (1 H, dt, *J* = 2 and 5 Hz), 6.89 (1 H, dt, *J* = 2 and 5 Hz), 7.32 (1 H, s), 8.60 (1 H, br s). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.05. Found: C, 65.97; H, 6.65; N, 4.03.

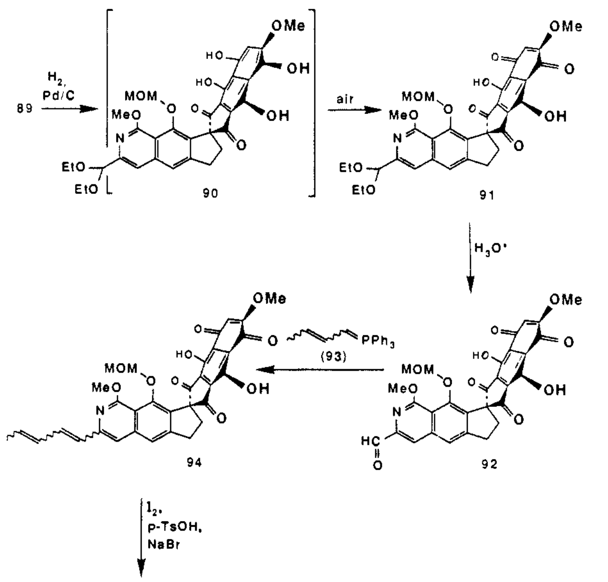
Preparative-Scale Synthesis of 2,3-Dihydro-4-(methoxymethoxy)-1*H*-inden-1-one (34). Chloromethyl methyl ether (9.1 mL, 0.12 mol) was added over 5 min to an ice-cold stirred solution of 15.0 g (0.10 mol) of 4-hydroxyindanone (36) and 21.2 mL (0.12 mmol) of *N*,*N*-diisopropylethylamine in 250 mL of THF. The ice bath was removed, and the reaction was stirred at room temperature for 2 days. Further chloromethyl methyl ether (3 mL) and *N*,*N*-diisopropylethylamine (11 mL) were added, and the reaction mixture was stirred for another 24 h. The reaction was then quenched with 1 M HCl and extracted with ether (300 mL); the ether extract was washed successively with 1 M NaOH (1×) and saturated NaCl (2×) dried (Na$_2$SO$_4$), and the solvent was evaporated under reduced pressure. The resulting tan oil was purified by Kugelrohr distillation (140 °C/0.5 Torr), affording 34 as a colorless solid (19.0 g, 97%), which was used without further purification in subsequent reactions. An analytical sample, mp 51–52 °C, was obtained by recrystallization from heptane: IR (CHCl$_3$) ν 1710, 1605 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.60–2.75 (2 H, m), 3.00–3.15 (2 H, m), 3.50 (3 H, s), 5.27 (2 H, s), 7.25–7.43 (3 H, m). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.40.

2,3-Dihydro-4-hydroxy-1*H*-inden-1-one (36). A mixture of 300 g of AlCl$_3$, 60 g of NaCl, and 51.3 mL (0.40 mol) of dihydrocoumarin was heated with mechanical stirring at 200–210 °C for 1 h and then quenched with ice and concentrated HCl. The precipitate was collected and washed with H$_2$O and EtOH. Recrystallization from absolute EtOH (~3 L) gave a first crop of 47.0 g (77.2%) of 36 as colorless crystals, mp 244–246 °C (lit.[25] mp 239–240 °C). Concentration of the mother liquor and collection of additional crops of 36 gave a total yield of 88%.

2,3-Dihydro-4-(methoxymethoxy)-1*H*-inden-1-ol (37). To a stirred suspension of lithium aluminum hydride (1.48 g, 39 mmol) in ca. 100 mL of anhydrous ether was slowly added a solution of 15.0 g (78.8 mmol) of 34 in 50 mL of ether under an argon atmosphere at 0 °C. The reaction mixture was stirred at 0 °C to room temperature for 20 min and then recooled to 0 °C, and 12.6 g (39 mmol) of sodium sulfate decahydrate was cautiously added to the reaction mixture.[45] The suspension was stirred for 0.5 h and then MgSO$_4$ was added, and, following a further

(41) Zechmeister, L. *Fortschr. Chem. Org. Naturstoffe* **1960**, *18*, 223–349.
(42) (a) Bohlmann, F.; Mannhardt, H.-J. *Chem. Ber.* **1956**, *89*, 1307–1315. (b) Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1828–1845 (note footnote 2).
(43) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2926.
(44) Mozingo, R.; Adkins, H.; Richards, L. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 181–183. The catalyst was measured as described in footnote 8.
(45) On very large-scale reactions, addition of the ketone (34) to a vigorously stirred suspension of lithium aluminum hydride frequently gave a brown gum. If this occurred the following workup procedure was used. The reaction was slowly quenched by the addition of 1 M hydrochloric acid, diluted with ether, and stirred for 0.5 h until all the aluminum salts were dissolved. The organic phase was washed with 1 M HCl (1×) and saturated NaCl (2×) and dried (Na$_2$SO$_4$), and the solvent was removed to give a brown solid.
(46) Prepared as in footnote 3 in Arndt, F.; Noller, C. R.; Bergsteinsson, I. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 165–167.
(47) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561–562.
(48) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 2198–2208.
(49) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385–391.
(50) Chromatography of the mother liquors generally provides an additional ~10% of 57. Under somewhat different conditions, yields of up to 61% have been obtained for the conversion of 56 to 57, but the procedure given here is consistently reproducible.
(51) Corey, E. J.; Ventakeswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
(52) On small-scale reactions (≤3 g) the product (69) isolated from the reaction mixture is essentially pure. However, on medium and large scale reactions, some loss (10–30%) of the silyl protecting group is sometimes observed, and the product is contaminated with some of the corresponding hydroxy compound. The presence of this hydroxy compound appears to have no effect on the next reaction.
(53) Also see the supplementary material.

Scheme IX



5 min, the mixture was filtered through a pad of Celite. The solvent was then removed to afford alcohol **37** (14.6 g, 96%) as a pale yellow solid, which could be used without further purification.

An analytical sample of alcohol **37**, mp 69.5–70.0 °C, was obtained as fluffy white needles on recrystallization from heptane: IR ($CHCl_3$) ν 3590, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (1 H, br s), 1.90–2.01 (1 H, m), 2.44–2.55 (1 H, m), 2.72–2.83 (1 H, m), 3.00–3.10 (1 H, m), 3.48 (3 H, s), 5.20 (2 H, s), 5.24 (1 H, t, J = 6 Hz), 6.99 (1 H, d, J = 8 Hz), 7.08 (1 H, d, J = 8 Hz), 7.21 (1 H, t, J = 8 Hz). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.89; H, 7.51.

Dimethyl 4-Methoxy-3,6-bis(phenylmethoxy)phthalate (56). (a) By Benzylation of 63. A solution of 5.50 g (21.5 mmol) of quinol **63** in 150 mL of dry acetone was stirred at room temperature with 21 g of anhydrous potassium carbonate and 15.3 mL (129 mmol) of benzyl bromide under argon for 15 h. The solution was then diluted with 200 mL of ether and filtered through Celite, and the solvent was evaporated under reduced pressure. The excess benzyl bromide was removed under high vacuum (40–50 °C). The pale yellow oily crystalline residue was recrystallized from ether/petroleum ether to afford 8.50 g (91%) of dibenzyl ether **56** as chunky colorless rhombs, mp 149–150 °C. The mother liquor was purified by flash column chromatography on silica, eluting with 1:3 EtOAc/petroleum ether, affording an additional 0.63 g (7%) of **56** for a total yield of 98%: IR (Nujol) ν 1739, 1714 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.80 (3 H, s), 3.84 (6 H, s), 4.98 (2 H, s), 5.15 (2 H, s), 6.59 (1 H, s), 7.30–7.50 (10 H, m). Anal. Calcd for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 68.68; H, 5.42.

(b) From Furan 65. A solution of 1.06 g (5.69 mmol) of furan **65**[33] in 1 mL of CH_2Cl_2 was added dropwise over 5 min to a solution of dimethyl acetylenedicarboxylate (0.81 g, 5.7 mmol) in 4 mL of CH_2Cl_2, affording a pale orange reaction mixture. The reaction was stirred at room temperature for 3 h, after which time the color had changed to a light yellow. A mixture of methanol/formic acid (1:1, 10 mL) was added, and the reaction mixture was heated at 50–60 °C for 2 h; the reaction mixture was then poured into 150 mL of ether, twice washed with water, and dried (Na_2SO_4), and the solvent was evaporated. The resulting oily solid was dissolved in acetone (50 mL) and treated with benzyl bromide (3.7 mL, 31 mmol) and anhydrous potassium carbonate at room temperature under an argon atmosphere overnight. The solution was then filtered through Celite, and the solvent was evaporated. The excess benzyl bromide was removed under high vacuum (40–45 °C) to afford an oily crystalline residue. Purification by flash column chromatography on silica (EtOAc/petroleum ether, 1:3) afforded dibenzyl ether **56** (1.46 g, 59%) identical in all respects with a sample prepared by method **a**.

Dimethyl 1,4-Dihydroxy-6-methoxy-5,8-bis(phenylmethoxy)-2,3-naphthalenedicarboxylate (57). Sodium bis(trimethylsilyl)amide (1 M in THF, Aldrich, 73.8 mL, 73.8 mmol) was added to a stirred solution of phthalate **56** (6.44 g, 14.8 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone[49] (8.92 mL, 73.8 mmol) in 50 mL of THF, all at ice-bath temperature under an atmosphere of argon. To this pale yellow mixture was added via a syringe pump dimethyl succinate (4.83 mL, 36.9 mmol) over a period of 80 min, while the reaction mixture was maintained at ice-bath temperature. As the reaction proceeded the initially yellow solution went a deep orange color and became very viscous. The solution was stirred for a further 30 min before acidifying with 1 M HCl (→ pH 3~4). The yellow solution was extracted with EtOAc (~500 mL), and the EtOAc extract was washed successively with saturated NaCl (2×) and water (1×). Following drying (Na_2SO_4) and evaporation of the solvent, an oily yellow solid was obtained. Recrystallization from ethyl acetate (40 mL) at 0 °C overnight afforded quinol **57** as fluffy yellow microneedles (3.07 g, 40%[50]): ^1H NMR ($CDCl_3$) δ 3.89 (3 H, s), 3.91 (3 H, s), 3.93 (3 H, s), 5.08 (2 H, s), 5.23 (2 H, s), 6.80 (1 H, s), 7.20–7.80 (10 H, m), 10.48 (1 H, s), 11.11 (1 H, s).

6-Methoxy-4,5,8,9-tetrakis(phenylmethoxy)naphtho[2,3-*c*]furan-1,3-dione (Anhydride 59). To a vigorously stirred solution of diester **12** (6.80 g, 9.73 mmol) in THF (90 mL) and methanol (45 mL) at room temperature was added a solution of 3.12 g of sodium hydroxide in 6 mL of water. The reaction mixture was stirred at 55–60 °C for 1 h before being cooled back to room temperature. The volatiles were then removed under reduced pressure, and water (300 mL) was added. The solution was cooled to ice-bath temperature and concentrated HCl (20 mL) was added. After 20 min at 0 °C, the crystals were collected by suction filtration, washed with water, and dried over P_2O_5 under vacuum to afford 6.5 g of diacid **58**.

To the crude diacid was added 25 mL of acetic anhydride, and the mixture was stirred at 145 °C for 20 min. The reaction mixture was allowed to cool slowly to room temperature, which resulted in the formation of yellow needles. To the resultant suspension was added ether/petroleum ether (1:1, 60 mL), and the mixture was cooled at 0 °C for 1 h. Filtration gave yellow needles of the anhydride **59** (6.06 g, 94% based on diester **12**). Recrystallization from 1,2-dichloroethane provided an analytical sample, mp 166–168 °C dec: IR (Nujol) ν 1830, 1771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (3 H, s), 4.84 (2 H, s), 5.17 (2 H, s), 5.18 (2 H, s), 5.27 (2 H, s), 6.93 (1 H, s), 7.20–7.52 (20 H, m). Anal. Calcd for $C_{41}H_{32}O_8$: C, 75.45; H, 4.94. Found: C, 75.47; H, 4.96.

Dimethyl 3,6-Dioxo-1,4-cyclohexadiene-1,2-dicarboxylate (60). (a) 3,6-Dihydroxyphthalonitrile. This was prepared from *p*-benzoquinone (132 g, 1.22 mol) and potassium cyanide (110 g) by the method of Jackman et al.;[29b] 66 g (67% of theory) was obtained following recrystallization from water, mp ≥225 °C dec (lit[29b] 230 °C dec).

(b) Dimethyl 3,6-Dihydroxyphthalate. 3,6-Dihydroxyphthalonitrile (25 g, 0.16 mol) was added to 160 g of potassium hydroxide in 160 mL of water at room temperature under argon. The solution was boiled for 1 h before being allowed to cool to room temperature. The reaction was then cooled to ice-bath temperature and cautiously acidified with 20% sulfuric acid (1000 mL), taking care to prevent the reaction from becoming too vigorous. The solution was then extracted with ethyl acetate (10 × 150 mL); the EtOAc extracts were combined, dried (Na_2SO_4), and evaporated to afford a cream-colored solid residue of crude 3,6-dihydroxyphthalic acid. This acid, 1200 mL of dry methanol, and 64 mL of boron trifluoride etherate were boiled under argon for 15 h. The reaction mixture was then concentrated under reduced pressure to a volume of ~200 mL and extracted with ether (3 × 150 mL). The combined extracts were washed successively with saturated $NaHCO_3$ (2×) and water (2×) and dried (Na_2SO_4); the solvent was removed to afford 19.3 g (55% overall from 3,6-dihydroxyphthalonitrile) of dimethyl 3,6-dihydroxyphthalate as a colorless solid, mp 140–141 °C (lit[29a] mp 140–143 °C): IR (Nujol) ν 1715, 1700 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (6 H, s), 7.09 (2 H, s), 8.80 (2 H, br s).

(c) Dimethyl 3,6-Dioxo-1,4-cyclohexadiene-1,2-dicarboxylate (60). Silver(II) oxide (Alfa, 94%; 3.77 g, 28.6 mmol) was added to a stirred solution of 5.89 g (26.0 mmol) of dimethyl 3,6-dihydroxyphthalate in 20 mL of CH_2Cl_2 over a period of 5 min. Following 10 min of stirring at room temperature, the reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure to afford quinone **60** (5.83 g, 100%) as pale yellow needles, mp 149–152 °C (lit[29a] mp 155.5–157 °C): IR (Nujol) ν 1755, 1740, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (6 H, s), 6.86 (2 H, s).

Dimethyl 3,4,6-triacetoxyphthalate (61).[31a] To a magnetically stirred mixture of 12.3 g (54.9 mmol) of quinone diester **60** in acetic anhydride (210 mL) under argon was slowly added boron trifluoride etherate (36 mL). The solution was warmed to 55–60 °C and maintained at that temperature for 8 h, after which time the resulting reaction mixture was poured into ice/water (2 L) and stirred for 1 h. The solution was extracted with EtOAc (2 × 100 mL), and the combined extracts were washed with NaCl (3×) and dried (Na_2SO_4). Evaporation of solvent and other volatiles under reduced pressure afforded a viscous residue. Trituration with ether (100 mL) and cooling in an ice bath for 1 h afforded triacetate **61** (17.5 g, 87%) following filtration. Recrystallization from chloroform/petroleum ether yielded colorless prisms, mp 125–126 °C: IR (Nujol) ν 1780, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (9 H, s), 3.84 (6 H, s), 7.25 (1 H, s). Anal. Calcd for $C_{16}H_{16}O_{10}$: C, 52.18; H, 4.38. Found: C, 52.23; H, 4.43.

Dimethyl 3,4,6-Trihydroxyphthalate (62).[31a] Triacetate **61** (3.63 g, 9.86 mmol) was suspended in 90 mL of dry MeOH and cooled to ice bath temperature. Dry HCl gas was bubbled slowly into the solution for 40 min; following this the ice bath was removed and the reaction mixture was stirred for a further 1.5 h. The solvent was removed under reduced pressure to afford a colorless solid residue (2.4 g, 100%) of trihydroxyphthalate **62**, which normally was used without further purification. An analytically pure sample of **62**, mp 161–162 °C, was prepared by recrystallization from water: IR (Nujol) ν 3350 (br), 1695, 1678 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.85 (3 H, s), 3.90 (3 H, s), 6.10 (1 H, br s), 6.65 (1 H, s), 8.55 (1 H, br s), 9.70 (1 H, br s). Anal. Calcd for $C_{10}H_{10}O_7$: C, 49.59; H, 4.16. Found: C, 49.41; H, 4.15.

Dimethyl 3,6-Dihydroxy-4-methoxyphthalate (63)[31a] **and Dimethyl 3-Hydroxy-4,6-dimethoxyphthalate (64).**[31a,b] Triacetate **61** (7.49 g, 20.3 mmol) was suspended in dry MeOH (150 mL) and treated with gaseous HCl as described above to afford 4.91 g of crude trihydroxyphthalate **62** as a colorless solid. This crude **62** was then dissolved in 100 mL of dry acetone under an argon atmosphere, and 2.95 g (21.3 mmol) of anhydrous potassium carbonate and 10 mL of methyl iodide were added. The reaction was stirred at 4 °C for 3 days in the dark, after which time further potassium carbonate (0.50 g) was added and the solution was stirred for an additional 24 h. The resulting brown solution was filtered through Celite, washing thoroughly with ether, to afford a creamy tan solid after evaporation of the solvent. Flash column chromatography on silica, eluting with 1:3 EtOAc/petroleum ether, afforded three fractions. The first fraction consisted of 1.54 g (28%) of dimethyl ether **64**,[31b] mp 86.5–88.0 °C (from EtOAc/petroleum ether), as a colorless solid: ^{1}H NMR (CDCl$_3$) δ 3.78 (3 H, s), 3.88 (3 H, s), 3.90 (3 H, s), 3.93 (3 H, s), 6.52 (1 H, s), 11.16 (1 H, s).

The second fraction yielded 3.06 g (59%) of monomethyl ether **63** as a colorless solid. An analytically pure sample, mp 149–151 °C, was prepared by recrystallization from CH$_2$Cl$_2$: IR (Nujol) ν 3420, 1738, 1670, 1630 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.88 (3 H, s), 3.92 (6 H, s), 6.16 (1 H, br s), 6.52 (1 H, s), 10.74 (1 H, br s). Anal. Calcd for $C_{11}H_{12}O_7$: C, 51.57; H, 4.72. Found: C, 51.30; H, 4.94.

The most polar fraction was trihydroxyphthalate **62** (0.22 g, 4%).

Selective Demethylation of Dimethyl Ether 64[31] **to 63.** A solution of boron trichloride (1 M in hexanes, 68 mL, 68 mmol) was added over 5 min to a stirred solution of 8.70 g (32.2 mmol) of dimethyl ether **64** in 250 mL of CH$_2$Cl$_2$ at −78 °C, all under an argon atmosphere. Following a further 15 min of stirring at −78 °C, the reaction mixture was allowed to warm to room temperature over a 20-min period. The solution was quenched with saturated NH$_4$Cl, and the organic layer was washed with water (2×), dried (Na$_2$SO$_4$), and concentrated to afford the monomethyl ether **63** (8.1 g, 98%), which was identical with a sample of **63** prepared directly by monomethylation of **62**.

1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dihydro-4-(methoxymethoxy)-1*H*-indene (67). To a solution of 20.8 g (0.31 mmol) of imidazole[51] and 28.4 g (0.15 mol) of alcohol **37** in ~50 mL of *N*,*N*-dimethylformamide was added over 10 min 23.1 g (0.15 mol) of *tert*-butyldimethylsilyl chloride (the reaction becomes warm). The mixture was then stirred at room temperature overnight (2 h was generally sufficient time for complete reaction), diluted with ether, washed with saturated sodium chloride (4×), and dried (Na$_2$SO$_4$). The solvent was removed in vacuo to give silyl ether **67** (45.9 g, 100%), which was used without further purification. An analytical sample was obtained as a colorless oil by preparative TLC on silica, eluting with petroleum ether/EtOAc (15:1): bp (Kugelrohr distillation) 125 °C (0.05 Torr); IR (CHCl$_3$) ν 1598 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.15 (3 H, s), 0.17 (3 H, s), 0.95 (9 H, s), 1.86–2.00 (1 H, m), 2.36–2.50 (1 H, m), 2.63–2.74 (1 H, m), 2.97–3.06 (1 H, m), 3.47 (3 H, s), 5.19 (2 H, s), 5.26 (1 H, t, J = 7 Hz), 6.94 (1 H, d, J = 7 Hz), 6.98 (1 H, d, J = 7 Hz), 7.18 (1 H, t, J = 7 Hz). Anal. Calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15. Found: C, 66.36; H, 9.39.

1-[(*tert*-Butyldimethylsilyl)oxy]-*N*,*N*-diethyl-2,3-dihydro-4-(methoxymethoxy)-1*H*-indene-5-carboxamide (68). To a stirred solution of 23.1 g (75 mmol) of **67** in 600 mL of THF at −78 °C was added a solution of *sec*-butyllithium (1.4 M in cyclohexane, 60 mL, 84 mmol), all under an argon atmosphere. After 1 h 10.5 mL (86.3 mmol) of freshly distilled diethylcarbamoyl chloride was added to the cloudy orange solution, and the reaction mixture was stirred overnight, while being allowed to warm to room temperature. Solid NaHCO$_3$ was added to the reaction mixture, and the mixture was then stirred at room temperature for 1 h to destroy any excess diethylcarbamoyl chloride. The mixture was then decanted from the NaHCO$_3$, diluted with ether, quenched with 1 M HCl, washed once with saturated NH$_4$Cl and then with saturated NaCl, and dried. After the solvent was removed, the crude product was purified by liquid chromatography (Waters Prep LC 500A, silica), eluting with 20:1 petroleum ether/EtOAc to give unreacted starting ether **67** (4.2 g, 18%). The polarity of the solvent was then increased to 4:1 petroleum ether/EtOAc to remove an unknown byproduct. Finally amide **68** (18.6 g, 63.1%) was eluted with 2:1 petroleum ether/EtOAc. An analytical sample of **68** was obtained as a viscous colorless oil by preparative TLC on silica with petroleum ether/EtOAc as eluant and Kugelrohr distillation (bp 180 °C/0.01 Torr): IR (CHCl$_3$) ν 1620 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.17 (6 H, br s), 0.95 (9 H, s), 1.03 (3 H, t, J = 7 Hz), 1.23 (3 H, t, J = 7 Hz), 1.80–2.90 (4 H, m), 3.05–3.30 (2 H, m), 3.30–3.55 (2 H, m), 3.50 (3 H, s), 5.05 (2 H, s), 5.24 (1 H, t, J = 6 Hz), 7.08 (2 H, s). Anal. Calcd for $C_{22}H_{37}NO_4Si$: C, 64.82; H, 9.15; N, 3.44. Found: C, 64.54; H, 9.23; N, 3.32.

1-[(*tert*-Butyldimethylsilyl)oxy]-*N*,*N*-diethyl-2,3-dihydro-4-(methoxymethoxy)-6-methyl-1*H*-indene-5-carboxamide (69). To a stirred solution of 18.1 g (44 mmol) of amide **68** in 400 mL of THF at −78 °C was added a solution of *tert*-butyllithium (1.7 M in pentane, 34 mL, 58 mmol), all under argon. Following 15 min of stirring, methyl iodide (3.6 mL, 58 mmol) was added to the mixture, and the reaction mixture was stirred at −78 °C for a further 15 min and then at room temperature for 5–10 min. The reaction mixture was quenched with 1 M HCl, diluted with ether, washed with 1 M HCl (1×) and saturated NaCl, and dried (Na$_2$SO$_4$). The solvent was removed to afford 18.6 g (100%) of the crude **69**, which was used in the next step without further purification.[52] An analytical sample was obtained as an extremely viscous colorless oil by preparative TLC on silica, eluting with 2:1 petroleum ether/EtOAc: bp (Kugelrohr distillation) 200 °C/(0.1 Torr); IR (CHCl$_3$) ν 1622 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.18 (3 H, s), 0.20 (3 H, s), 0.98 (9 H, s), 1.04 (3 H, t, J = 7 Hz), 1.26 (3 H, t, J = 7 Hz), 1.70–3.00 (4 H, m), 2.25 (3 H, s), 3.13 (2 H, q, J = 7 Hz), 3.51 (3 H, s), 3.56 (2 H, q, J = 7 Hz), 4.97–5.05 (2 H, AB system), 5.05–5.30 (1 H, m), 6.90 (1 H, s). Anal. Calcd for $C_{23}H_{39}NO_4Si$: C, 65.52; H, 9.32; N, 3.32. Found: C, 65.44; H, 9.53; N, 3.30.

6-[(*tert*-Butyldimethylsilyl)oxy]-3-(diethoxymethyl)-2,6,7,8-tetrahydro-9-(methoxymethoxy)-1*H*-cyclopent[*g*]isoquinolin-1-one (72). A solution of *n*-butyllithium (1.55 M in hexane, 48.0 mL, 75 mmol) was added slowly to a stirred solution of 12.7 mL (75 mmol) of 2,2,6,6-tetramethylpiperidine in 250 mL of THF at 0 °C under an argon atmosphere. The solution was stirred for 5 min at 0 °C, cooled to −78 °C, and then stirred for a further 5 min. To this was added at −78 °C a solution of 18.5 g (44 mmol) of methyl amide **69** in 50 mL of THF, and the resulting blood-red solution was stirred for 15 min at −78 °C. Diethoxyacetonitrile (Chemical Dynamics Corporation, 10.6 mL, 77 mmol) was then added, and the reaction mixture was stirred for a further 10 min at −78 °C, followed by 5 min at room temperature. The reaction mixture was quenched with 1 M HCl and diluted with ether; the organic phase was washed with saturated NH$_4$Cl (1×) and saturated NaCl (2×) and dried (Na$_2$SO$_4$). The solvent was removed to give 28 g (>100%) of a mixture of crude silyloxy pyridone **72** and the deprotected[52] hydroxy pyridone **73**. This mixture was normally used without purification. A small amount of pyridone **72** was purified by flash column chromatography on silica, eluting with 1:1 petroleum ether/EtOAc, to give a colorless solid: ^{1}H NMR (CDCl$_3$) δ 0.18 (3 H, s), 0.21 (3 H, s), 0.98 (9 H, s), 1.27 (6 H, t, J = 7 Hz), 1.90–2.05 (1 H, m), 2.42–2.54 (1 H, m), 2.76–2.92 (1 H, m), 3.18–3.28 (1 H, m), 3.53–3.74 (4 H, m), 3.61 (3 H, s), 5.20 and 5.21 (2 H, 2 d, J = 7 Hz), 5.28 (1 H, t, J = 6 Hz), 5.35 (1 H, s), 6.52 (1 H, s), 7.20 (1 H, s), 8.56 (1 H, br s).

3-(Diethoxymethyl)-2,6,7,8-tetrahydro-6-hydroxy-9-(methoxymethoxy)-1*H*-cyclopent[*g*]isoquinolin-1-one (73). To a solution of the above mixture of pyridones **72** and **73** in 200 mL of THF at 0 °C was added a solution of *n*-Bu$_4$NF (Aldrich, 1 M in THF, 26 mL, 26 mmol); the ice bath was then removed, and the reaction mixture was stirred at room temperature for 1 h. The mixture was then diluted with ether, washed with saturated NaCl (3×), dried (Na$_2$SO$_4$), and the solvent was removed. The resulting yellow solid was purified by recrystallization from benzene to give 5.6 g of alcohol **73**. The mother liquor was purified by flash column chromatography on silica, eluting with 2:1 petroleum ether/EtOAc followed by EtOAc to afford an additional 6.0 g of alcohol **73** (total yield of 78% overall for the three steps from amide **68**). An analytical sample of **73**, mp 151.0–153.0 °C, was obtained as fine white needles after recrystallization from benzene: IR (CHCl$_3$) ν 3380, 1647 cm^{-1}; ^{1}H NMR (CDCl$_3$, 80 MHz) δ 1.26 (6 H, t, J = 7 Hz), 1.70–3.30 (4 H, m), 3.40–3.80 (4 H, m), 3.60 (3 H, s), 5.17 (2 H, s), 5.33 (1 H, s), 5.20–5.40 (1 H, m), 6.42 (1 H, s), 7.28 (1 H, s), 8.60 (1 H, br s). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.79; H, 7.10; N, 3.62.

3-(Diethoxymethyl)-1-methoxy-9-(methoxymethoxy)-8*H*-cyclopent[*g*]isoquinoline (82). (a) From 17. Silver carbonate (1.82 g, 6.59 mmol) and methyl iodide (1.0 mL, 16 mmol) were added to a solution of 474 mg (1.32 mmol) of isoquinolone **17** in 20 mL of benzene and sonicated in a 150-W Branson Bransonic 32 ultrasonic cleaning bath under an atmosphere of argon for 5 days (the bath attains a temperature of ~50 °C). The suspension was then filtered through Celite, which was washed with benzene; the combined filtrate and wash were evaporated under reduced pressure. The resulting oil was purified by flash column chromatography on silica, eluting with 1:5 EtOAc/petroleum ether, to afford 410 mg (83%) of isoquinoline **82** as a colorless oil, which crystallized on standing. An analytical sample, mp 66–67 °C, was obtained upon recrystallization from petroleum ether at −4 °C: IR ($CDCl_3$) ν 1632, 1618 (sh), 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (6 H, t, *J* = 7 Hz), 3.64 (2 H, apparent t, *J* = 2 Hz), 3.66 (3 H, s), 3.66–3.82 (4 H, m), 4.12 (3 H, s), 5.19 (2 H, s), 5.49 (1 H, s), 6.73 and 6.90 (2 × 1 H, each apparent dt, *J* = 2 and 5 Hz), 7.49 (1 H, s), 7.51 (1 H, s). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.91. Found: C, 66.62; H, 7.03; N, 3.94.

(b) From 72. Silver carbonate (12.1 g, 43.9 mmol) and methyl iodide (2.74 mL, 44.0 mmol) were added to a solution of isoquinolone **72** (4.20 g, 8.79 mmol) in benzene (80 mL) under an atmosphere of argon. Following sonication (see part **a** above) in the dark for 6 days, the suspension was filtered through Celite, washing with benzene, and concentrated to afford an oily tan solid. The residue was purified by filtering through a 2-in. plug of silica, eluting with 1:3 EtOAc/petroleum ether to yield the isoquinoline **83** (4.18 g, 97%) as a colorless oil, which was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 0.14 (3 H, s), 0.16 (3 H, s), 0.94 (9 H, s), 1.20 and 1.21 (6 H, 2 overlapping t, *J* = 7 Hz), 1.82–1.95 (1 H, m), 2.35–2.45 (1 H, m), 2.76–2.87 (1 H, m), 3.15–3.24 (1 H, m), 3.54–3.69 (4 H, m), 3.55 (3 H, s), 4.04 (3 H, s), 5.05 (2 H, s), 5.25 (1 H, t, *J* = 7 Hz), 5.42 (1 H, s), 7.39 (1 H, s), 7.40 (1 H, s).

To the isoquinoline **83** (4.18 g) in 10 mL of THF at ice-bath temperature was added a solution of *n*-Bu_4NF (1 M in THF, 8.54 mL, 8.54 mmol, Aldrich). The cooling bath was removed, and the reaction was stirred for a further 2 h under argon. The solution was then poured into ether; the ether layer was washed with saturated NaCl (2×), dried (Na_2SO_4), and evaporated to afford a pale tan solid. The solid was purified by filtering through a 2-in. plug of silica, eluting with 1:1 EtOAc/petroleum ether to afford the alcohol **84** (3.04 g, 94%) as a colorless crystalline solid. An analytical sample, mp 118.5–119 °C, was obtained from ether/petroleum ether as fluffy colorless needles: IR ($CDCl_3$) ν 3600, 1637, 1617, 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 and 1.29 (6 H, 2 overlapping t, *J* = 7 Hz), 1.90 (1 H, d, *J* = 7 Hz), 1.91–2.05 (1 H, m), 2.52–2.60 (1 H, m), 2.94–3.05 (1 H, m), 3.25–3.35 (1 H, m), 3.61–3.77 (4 H, m), 3.64 (3 H, s), 4.21 (3 H, s), 5.14 (2 H, s), 5.34 (1 H, apparent q, *J* = 7 Hz), 5.48 (1 H, s), 7.47 (1 H, s), 7.58 (1 H, s). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.49; H, 7.16; N, 3.73.

Alcohol **84** (1.45 g, 3.84 mmol) was dehydrated by the method previously described for dehydration of **73** to **17**. Purification by flash column chromatography on silica, eluting with 1:9 EtOAc/petroleum ether, afforded 1.30 g (94%) of isoquinoline **82**, identical with material prepared by procedure a.

Regiochemically Controlled Coupling of 82 and 59. 3-[3-(Diethoxymethyl)-1-methoxy-9-(methoxymethoxy)-8*H*-cyclopent[*g*]isoquinolin-8-ylidene]-6(and 7)-methoxy-4,5,8,9-tetrakis(phenylmethoxy)naphtho[2,3-c]furan-1(3*H*)-one (86). A solution of *tert*-butyllithium (1.51 M in pentane, 1.80 mL, 2.72 mmol) was added dropwise to a stirred solution of 465 mg (1.29 mmol) of isoquinoline **82** in 15 mL of THF at −78 °C, all under an argon atmosphere. After 5 min, chlorotrimethylsilane (167 μL, 1.32 mmol) was added to the resultant deep red solution, and stirring was continued for a further 15 min. A solution of 844 mg (1.29 mmol) of anhydride **59** in 80 mL of THF at −78 °C was then added over 10 min to the orange/tan silyl indenyl anion (**85**) solution, and stirring was continued at −78 °C for 45 min. Sodium bis(trimethylsilyl)amide (1 M in THF, 1.29 mL, 1.29 mmol, Aldrich) was then added, and stirring was continued for a further 10 min. A mixture of acetic acid (1 mL) and methanol (30 mL) was added, the cold bath was removed, and the orange solution was allowed to warm to room temperature over 20 min. The reaction was then poured into saturated NH_4Cl solution and extracted into ether (150 mL); the ether extract was washed with saturated NaCl (2×) and dried (Na_2SO_4), and the solvent removed to afford a pale yellow residue. The residue was dissolved in 100 mL of THF and treated with 5 g of sodium acetate and 5 mL of acetic anhydride, resulting in immediate formation of a deep orange color. Following stirring at room temperature for 5 min, solid K_2CO_3 (10 g) was added and the solution was stirred for a further 30 min. The orange solution was then poured into ether (200 mL), washed successively with water (2×) and saturated NaCl (2×), dried (Na_2SO_4), and evaporated under reduced pressure, affording a dark orange residue. Purification by flash column chromatography on silica, eluting with 1:4 EtOAc/petroleum ether, afforded 1.04 g (81%) of lactone **86** as a rich orange film. The lactone **86** was a ∼3:2 mixture of (methoxy) regioisomers by ^1H NMR spectroscopy: IR ($CDCl_3$) ν 1770, 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (6 H, t, *J* = 7 Hz), 3.48 and 3.49 (3 H, 2 s), 3.69–3.80 (4 H, m), 3.85 and 3.87 (3 H, 2 s), 4.14 and 4.15 (3 H, 2 s), 4.70–5.30 (8 H, m), 5.22 (2 H, br s), 5.50 (1 H, s), 6.71 and 6.75 (1 H, 2 d, *J* = 5 Hz), 6.85 and 6.95 (1 H, 2 s), 7.04 (1 H, s), 7.00–7.61 (21 H, m), 7.91 and 7.94 (1 H, 2 d, *J* = 5 Hz).

3′-(Diethoxymethyl)-3-hydroxy-1′,6(and 1′,7)-dimethoxy-9′-(methoxymethoxy)-4,5,8,9-tetrakis(phenylmethoxy)spiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinolin]-1(3*H*)-one (88). A solution of diisobutylaluminum hydride (Aldrich, 1 M in toluene, 665 μL, 0.66 mmol) was added dropwise over 1 min to a deep-orange solution of lactone **86** (429 mg, 0.43 mmol) in CH_2Cl_2 (15 mL) at −78 °C under an argon atmosphere. Following stirring for 20 min, the resultant light orange solution was quenched with acetic acid/dichloromethane (1:9, 2 mL) and allowed to warm to ∼0 °C over 10 min. Potassium carbonate (5 g) was added, and stirring was continued for a further 30 min at ice-bath temperature, resulting in the initially orange solution turning a bright yellow. The reaction was poured into ether (100 mL); the ether layer was washed successively with 0.05 M HCl (2×) and saturated NaCl (2×), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was filtered through a 2-in. plug of silica, eluting with ether, to afford on removal of solvent a light yellow foam of the alcohol **88** as a diastereomeric mixture by ^1H NMR spectroscopy. The alcohol (**88**) was used without further purification in the next reaction. TLC showed the alcohol mixture (R_f 0.33, 1:1 ether/petroleum ether) as a bright lemon-lime colored fluorescent spot under long-wave UV light: IR ($CDCl_3$) ν 3530 (br), 1725, 1605, 1583 cm^{-1}.

3′-(Diethoxymethyl)-1′,6-dimethoxy-9′-(methoxymethoxy)-4,5,8,9-tetrakis(phenylmethoxy)spiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]-isoquinoline]-1,3-dione (89). Oxalyl chloride (380 μL, 4.35 mmol) was added dropwise to a stirred solution of dimethyl sulfoxide (620 μL, 8.74 mmol) in CH_2Cl_2 (10 mL) at −78 °C, all under an atmosphere of argon. After 15 min a solution of the alcohol **88** (from above) in CH_2Cl_2 (5 mL with a further 2 mL of rinses) was added dropwise over 5 min. Following 15 min of stirring, triethylamine (1.22 mL, 8.75 mmol) was added and stirring was continued for another 5 min before the solution was allowed to warm to room temperature (10 min). The reaction was then quenched with water and extracted into CH_2Cl_2; the CH_2Cl_2 extract was washed with water (2×), dried (Na_2SO_4), and concentrated. The yellow/tan oil was purified by flash column chromatography on silica, eluting with 1:1 ether/petroleum ether, to afford the spiro diketone **89** (213 mg, 50% overall from **86**) as an unstable yellow-orange solid: IR ($CDCl_3$) ν 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (6 H, t, *J* = 7 Hz), 2.95 (3 H, s), 3.60–3.75 (4 H, m), 3.86 (3 H, s), 4.04 (3 H, s), 4.82 (1 H, d, *J* = 10 Hz), 4.93 (1 H, d, *J* = 10 Hz), 4.98 (2 H, s), 5.10–5.40 (6 H, m), 5.49 (1 H, s), 6.39 (1 H, d, *J* = 5 Hz), 6.94 (1 H, s), 7.10 (1 H, d, *J* = 5 Hz), 7.12–7.60 (20 H, m), 7.50 (1 H, s), 7.55 (1 H, s).

3′-(Diethoxymethyl)-6′,7′-dihydro-4,9-dihydroxy-1′,6-dimethoxy-9′-(methoxymethoxy)spiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-1,3,5,8-tetrone (91). A solution of tetrabenzyl ether **89** (178 mg, 0.18 mmol) in ethanol/acetic acid (10:1, 55 mL) was stirred over 10% palladium on activated carbon (Aldrich, 100 mg) for 4 h under 1 atm of hydrogen. The solution was then opened to the air and stirred for a further 1 h, resulting in the initially pale yellow solution turning deep red. The reaction was filtered through a plug of Celite and concentrated to afford a black crystalline residue of the acetal quinone **91** (105 mg, 98%): IR ($CDCl_3$) ν 1745 (sh), 1720, 1700, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (6 H, t, *J* = 7 Hz), 2.55 (2 H, apparent t, *J* = 7 Hz), 2.99 (3 H, s), 3.41 (2 H, apparent t, *J* = 7 Hz), 3.60–3.75 (4 H, m), 4.02 (6 H, br s), 4.82 (2 H, s), 5.46 (1 H, s), 6.31 (1 H, br s), 7.44 (1 H, s), 7.50 (1 H, s), 12.60 and 13.20 (2 H, 2 br s). This material was used in the next step without further purification.

1,3,5,6′,7′,8-Hexahydro-4,9-dihydroxy-1′,6-dimethoxy-9′-(methoxymethoxy)-1,3,5,8-tetraoxospiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-3′-carboxaldehyde (92). The acetal quinone **91** from above (105 mg) in 20 mL each of acetone and THF was stirred with 35 mL of 0.015 M HCl for 2 h at room temperature. The solution was added to 50 mL of 1:1 ether/EtOAc; the organic layer was separated, washed with water (2×), and filtered through cotton wool to give a red crystalline residue after evaporation of the solvent. Recrystallization from CH_2Cl_2/EtOAc afforded 71 mg (71% overall from **89**) of aldehyde **92**, mp 174–175.5 °C dec: IR ($CDCl_3$) ν 1755, 1723, 1710, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (2 H, apparent t, *J* = 7 Hz), 2.99 (3 H, s), 3.50 (2 H, apparent t, *J* = 7 Hz), 4.01 (3 H, s), 4.11 (3 H, s), 4.83 (2 H, s), 6.32 (1 H, s), 7.66 (1 H, s), 7.88 (1 H, s), 10.01 (1 H, s), 12.58 (1 H, s), 13.22 (1 H, s). Anal. Calcd for $C_{29}H_{21}NO_{11}\cdot H_2O$: C, 60.31; H, 4.01; N, 2.42. Found: C, 60.28; H, 3.88; N, 2.26.

6′,7′-Dihydro-4,9-dihydroxy-1′,6-dimethoxy-9′-(methoxymethoxy)-3′-(1,3-pentadienyl)spiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-1,3,5,8-tetrone (94). Solid *trans*-2-butenyltriphenylphosphonium bromide[42] (250 mg, 0.63 mmol) was stirred with a magnetic bead under an argon atmosphere for 30 min to generate a fine powder. THF (10 mL) was added, the resulting suspension was cooled to ice-bath temperature, and a solution of *n*-butyllithium (2.30 M, 273 μL, 0.63 mmol) was added dropwise; the resulting orange solution was stirred for a further 1 h to give a solution calculated to be 0.063 M in ylide **93**.

To a stirred solution of 25 mg (0.040 mmol) of aldehyde **92** in 5 mL of THF at −78 °C was added dropwise 2.20 mL (0.138 mmol) of the ylide solution. The resultant green solution was stirred for 10 min before being quenched with methanol (10 mL) and warmed to room temperature (15 min). Acetic acid (3 mL) was added, and the solution was poured into water and extracted with ether; the ether extract was dried (Na_2SO_4) and concentrated. The residue was filtered through a 1-in. plug of silica, eluting with 1:2 $EtOAc/CH_2Cl_2$, to afford after concentration a red residue. Flash column chromatography on silica, eluting with 1:4 $EtOAc/CH_2Cl_2$, gave a major red band consisting of a mixture of the four possible diene isomers **94** (5.5 mg, 21%); the two major components were apparently the trans,trans and cis,trans isomers and were present in a ~2:1 ratio as estimated by ^1H NMR: ^1H NMR ($CDCl_3$, two major isomers) δ 1.87 (3 H, dd, *J* = 1.5 and 7 Hz), 2.54 (2 H, apparent t, *J* = 7 Hz), 2.99 and 3.00 (3 H, 2 s), 3.38 and 3.39 (2 H, 2 overlapping apparent t, *J* = 7 Hz), 4.02 (3 H, s), 4.09 (3 H, s), 4.83 and 4.84 (2 H, 2 s), 5.80–6.70 (4 H, m), 6.31 (1 H, s), 6.98 and 7.07 (1 H, 2 s), 7.38 and 7.41 (1 H, 2 s), 12.60 (1 H, br s), 13.23 (1 H, s).

(±)-Fredericamycin A (1). (a) By Deprotection of Diene Isomer Mixture 94. The isoquinoline diene mixture **94** (4.9 mg, 0.010 mmol), *p*-toluenesulfonic acid (50 mg), and anhydrous NaBr (120 mg) in 5 mL of CH_3OH were boiled for 1.5 h. The solution was poured into ethyl acetate, washed with water (4×), filtered through cotton wool, and concentrated to afford a deep red residue. The residue was washed with ether several times to remove any residual sulfonic acid, leaving a dark red residue, which was filtered through a 1-in. plug of silica with chloroform/methanol/acetic acid (87:3:3) and concentrated to give a dark red solid (4.1 mg, 93%). HPLC and ^1H NMR showed the solid to be Fredericamycin A and its cis,trans isomer (~2:1) by comparison with an authentic sample. Isomer-free (±)-**1** was obtained by HPLC on a 4.6 × 250 mm reversed-phase 5 μm C_{18} bonded phase silica column (ODS-Hypersil, Shandon Southern Inc.). The column was developed by elution beginning with methanol/water/acetic acid (70:30:1) as solvent and changing (gradient) over 30 min to methanol/acetic acid (100:1) at a flow rate of 1 mL/min. The pure (±)-**1** so obtained was identical (^1H NMR, UV, HPLC, TLC) with an authentic sample of natural[3b] fredericamycin A by direct comparison.

(b) By Deprotection and Simultaneous Isomerization of Dienes 94. A solution of anhydrous sodium bromide (100 mg), *p*-toluenesulfonic acid (20 mg), **94** (4.6 mg, 0.01 mmol), and a small crystal of iodine were boiled in 3 mL of CH_3OH for 20 min. At this point TLC indicated that deprotection was complete; however, some decomposition was taking place so that reaction was stopped. Following workup as previously outlined, fredericamycin A (2.2 mg, 53%) was obtained containing ~ 10% of the undesired isomeric impurity. Pure (±)-**1** was secured by HPLC as described in part **a**.

2,6,7,8-Tetrahydro-9-hydroxy-1-oxo-(1*H*)-cyclopent[*g*]isoquinoline-3-carboxaldehyde (95). Methyl amide **8** (1.19 g, 4.08 mmol) was reacted as outlined for the preparation of quinolone **10**. The reaction mixture containing crude **10** (as its anion) was worked up by quenching with 1 M HCl (15 mL) and stirring at room temperature overnight (12 h). The solution was extracted with CH_2Cl_2 (4 × 50 mL), and the extracts were washed with water (2×), dried (Na_2SO_4), and concentrated. The oily tan solid was washed well with ether/petroleum ether (1:1) to afford 0.80 g (85%) of aldehyde **95** as a pale tan solid. An analytical sample, mp 263–264 °C dec, was obtained from CH_2Cl_2/MeOH as pale tan microneedles: ^1H NMR ($CDCl_3$) δ 2.18 (2 H, quintet, *J* = 7 Hz), 3.03 (4 H, q, *J* = 7 Hz), 7.11 (1 H, s), 7.13 (1 H, d, *J* = 15 Hz), 8.80 (1 H, br s), 9.53 (1 H, s), 12.45 (1 H, s). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.83; H, 4.55; N, 5.86.

(*Z*,*E*)- and (*E*,*E*)-2,6,7,8-Tetrahydro-9-hydroxy-3-(1,3-pentadienyl)-1*H*-cyclopent[*g*]isoquinolin-1-one (97 and 98). A solution of sodium bis(trimethylsilyl)amide (Aldrich, 1 M in THF, 0.64 mL, 0.64 mmol) was added dropwise to a stirred solution of 55 mg (0.22 mmol) of *trans*-crotyldiphenylphosphine oxide (**96**)[40] in THF at 0 °C under an atmosphere of argon. After 15 min a solution of 47 mg (0.21 mmol) of aldehyde **95** in 5 mL of THF was added over 3 min via cannula; the reaction mixture was allowed to warm to room temperature and stirred for a further 1 h. The solution was then diluted with ether, washed with saturated NH_4Cl (2×) and saturated NaCl (2×), dried (Na_2SO_4), and concentrated to afford a pale tan residue of the dienes **97** and **98** (46 mg, 84%) as a 1:1 mixture of *E* and *Z* isomers about the newly generated olefinic bond as judged by ^1H NMR: ^1H NMR ($CDCl_3$, partial) δ 1.86 and 1.89 (3 H, 2 overlapping dd, *J* = 1 and 6 Hz).

Isomerization of 97 to 98. To a boiling solution of 21 mg of the 1:1 mixture of dienes **97** and **98** in 3 mL of MeOH containing 100 mg of anhydrous NaBr and 20 mg of *p*-toluenesulfonic acid in 3 mL of MeOH was added a small crystal of iodine; the resulting solution was boiled for 15 min. Following cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed successively with saturated sodium thiosulfate (2×), saturated $NaHCO_3$ (2×), and water (2×) and dried (Na_2SO_4). The solvent was evaporated to afford a pale tan solid residue of essentially pure trans,trans diene **98**: ^1H NMR ($CDCl_3$) δ 1.86 (3 H, dd, *J* = 1 and 6 Hz), 2.11 (2 H, quintet, *J* = 7 Hz), 2.95 (4 H, apparent q, *J* = 7 Hz), 5.98–6.24 (3 H, m), 6.37 (1 H, s), 6.72 (1 H, ddd, *J* = 1, 10 and 15 Hz), 6.82 (1 H, s), 9.74 (1 H, br s), 12.41 (1 H, s); mass spectrum, m/e (relative intensity) 268 (14), 267 (72, M^+), 266 (13), 253 (18), 252 (100), 238 (15), 234 (12).

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Registry No. (±)-**1**, 104438-52-0; (±)-*cis,trans*-**1**, 115887-67-7; **5**, 1641-41-4; **6**, 104422-92-6; **7**, 115757-83-0; **8**, 115757-84-1; **10**, 104422-93-7; **12**, 104422-99-3; **13**, 115757-88-5; **14**, 115757-92-1; **15**, 115757-93-2; **17**, 104422-96-0; **19**, 115757-94-3; (±)-**19** (ketone), 115757-95-4; **20**, 115757-96-5; **21**, 115757-97-6; (±)-*cis*-**24**, 115757-99-8; (±)-*trans*-**24**, 115757-98-7; **25**, 95033-81-1; (±)-*cis*-**27**, 115758-01-5; (±)-*trans*-**27**, 115758-02-6; **28**, 115758-00-4; **29**, 115758-03-7; **31**, 115796-79-7; (±)-**31** (ketone), 115758-04-8; **32**, 115758-05-9; **33**, 115758-06-0; **34**, 115757-63-6; **35**, 119-84-6; **36**, 40731-98-4; (±)-**37**, 115757-64-7; **38**, 2059-92-9; **39**, 115758-07-1; **40**, 115758-08-2; **41**, 115758-09-3; **42**, 115758-10-6; **43**, 115758-11-7; **44**, 6968-35-0; **45**, 115758-14-0; **49**, 115758-15-1; **50**, 115758-16-2; **51**, 115758-17-3; **52**, 115758-20-8; **53**, 115758-21-9; **54**, 115758-22-0; **55**, 115758-24-2; **55** ((±)-*cis*-ketol), 115758-23-1; **55** ((±)-*trans*-ketol), 115757-65-8; **56**, 104422-97-1; **57**, 104422-98-2; **58**, 115757-66-9; **59**, 104423-00-9; **60**, 77220-15-6; **60** (quinol diacid), 3786-46-7; **60** (quinol), 7474-92-2; **61**, 105518-06-7; **62**, 103548-64-7; **63**, 103548-65-8; **64**, 103577-13-5; **65**, 82204-15-7; (±)-**67**, 115757-67-0; (±)-**68**, 115757-68-1; (±)-**69**, 115757-69-2; (±)-**72**, 115757-70-5; (±)-**73**, 115757-61-4; (±)-**73** (*o*-nitrophenyl selenide), 115757-62-5; **78** (6-methoxy), 115758-27-5; **78** (7-methoxy), 115758-28-6; **79** (6-methoxy), 115758-25-3; **79** (7-methoxy), 115758-26-4; **80** (6-methoxy), 115758-29-7; **80** (7-methoxy), 115758-30-0; **81** (6-methoxy), 115758-31-1; **81** (7-methoxy), 115758-32-2; **82**, 104423-02-1; (±)-**83**, 115757-71-6; (±)-**84**, 115757-72-7; **86** (6-methoxy), 115757-89-6; **86** (7-methoxy), 115796-78-6; (±)-*cis*-**88** (6-methoxy), 115757-75-0; (±)-*trans*-**88** (6-methoxy), 115757-74-9; (±)-*cis*-**88** (7-methoxy), 115758-34-4; (±)-*trans*-**88** (7-methoxy), 115758-33-3; (±)-**89**, 104423-03-2; (±)-**91**, 104423-04-3; (±)-**92**, 104423-05-4; (±)-(*E*,*E*)-**94**, 115757-76-1; (±)-(*Z*,*E*)-**94**, 115757-77-2; (±)-(*E*,*Z*)-**94**, 115757-79-4; (±)-(*Z*,*Z*)-**94**, 115757-78-3; **95**, 115757-80-7; **97**, 115757-81-8; **98**, 115757-82-9; **99a**, 115757-85-2; **99b**, 115757-86-3; **100a**, 115757-86-3; **100b**, 115757-90-9; **101a**, 115757-87-4; **101b**, 115757-91-0; (±)-**102**, 115758-12-8; (±)-**102** (*o*-nitrophenyl selenide), 115758-13-9; **103**, 115758-18-4; **104**, 115758-19-5; MeOCOC≡CCOOMe, 762-42-5; $MeOCO(CH_2)_2COOMe$, 106-65-0; Et_2NCOCl, 88-10-8; $(EtO)_2CHCN$, 6136-93-2; (*E*)-$CH_3CH{=}CHCH_2PPh_3^+Br^-$, 39741-81-6; (*E*)-$CH_3CH{=}CHCH_2P(O)Ph_2$, 17668-60-9; $MeOCOC_6H_4$-*o*-COOMe, 131-11-3; 3,6-dihydroxyphthalonitrile, 4733-50-0; indene, 95-13-6; phthalic anhydride, 85-44-9.

Supplementary Material Available: The Experimental Section of this paper provides details of the preparation and characterization of compounds most directly related to the synthesis of **1**. The supplementary material contains general experimental considerations and experimental details relating to the synthesis and characterization of all other compounds mentioned in the Discussion section (29 pages). Ordering information is given on any current masthead page.