measured 2θ values for 30 moderate angle reflections. A crystal density of approximately 1.2 g/cm^3 indicated that two molecules of composition $C_{25}H_{38}O_5$ formed the asymmetric unit ($Z = 8$). All diffraction maxima with $2\theta \leq 112°$ were collected on a computer controlled four-circle diffractometer using graphite monochromated Cu Kα X-rays (1.541 78 Å) and 2θ-θ scans. A total of 3792 reflections were measured in this manner, and 2467 of the 3539 unique reflections were judged observed ($|F_o| \geq 4.0\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. No corrections were deemed necessary for absorption or decomposition. The structure was solved routinely using the SHELXTL system of programs. Full-matrix least-squares refinements with anisotropic heavy atoms and fixed, isotropic and riding hydrogens have converged to a standard crystallographic residual of 5.54%. Additional crystallographic information is available and is described in the paragraph at the end of this paper.

Absolute Configuration of Trunculin C Methyl Ester (3). A solution of trunculin C methyl ester (4.2 mg) in methanol (0.5 mL) containing 5% palladium on carbon catalyst (2 mg) was stirred under an atmosphere of hydrogen at room temperature for 1.5 h. The catalyst was removed by filtration, and the solvent was evaporated to obtain the 3,6-diol 7 (3.7 mg): ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 1 H, J = 7.9 Hz, H-16), 7.05 (br d, 1 H, J = 7.9 Hz, H-15, 6.88 (br s, 1 H, H-13), 3.73 (dd, 1 H, J = 10.4, 6.1 Hz, H-7), 3.71 (s, 3 H, OMe), 3.66 (m, 1 H, H-3), 2.57 (m, 2 H, H-11), 2.56 (dq, 1 H, J = 7.2, 7.2 Hz, H-2), 2.30 (s, 3 H, Me-23), 1.78-2.00 (m, 3 H), 1.58-1.65 (m, 4 H), 1.45 (s, 3 H, Me-24), 1.21 (d, 3 H, J = 7.2 Hz, Me-19), 1.20 (s, 3 H, Me-20), 1.06 (d, 3 H, J = 6.8 Hz, Me-22), 0.99 (s, 3 H, Me-21); CIMS m/z 419 (MH^+, 10), 401 ($MH^+ - H_2O$, 100).

A solution of 14% 2-phenylbutyric acid in pyridine (60.7 mg) was added to the 3,6-diol 7 (3.7 mg), and the solution was stirred at 25 °C for 24 h. The excess anhydride was destroyed by addition of water (2.5 mL), and the resulting suspension was titrated against 0.005 N sodium hydroxide solution using phenolphthalein as indicator. The volume of base consumed was 9.3 mL and the percentage of esterification was 94%. The ester was removed by extraction with ethyl acetate, the aqueous phase was acidified with dilute hydrochloric acid and the partially resolved 2-phenylbutyric acid was extracted with benzene. The optical rotation, measured in methanol solution, indicated an excess of (+)-2-phenylbutyric acid with an optical yield of 12%. This result requires a 3R absolute configuration for trunculin C methyl ester (3).

Conversion of Trunculin D Methyl Ester (4) into Trunculin C Methyl Ester (3). A small crystal of p-toluenesulfonic acid was added to a solution of trunculin D methyl ester (4, 5 mg) in dry benzene (0.2 mL), and the solution was warmed to 55 °C for 40 min. The cooled solution was passed through a short column of silica gel, and the solvent was evaporated to obtain trunculin C methyl ester (3, 2.8 mg), which was identified by comparison of the TLC behavior and NMR spectrum with those of authentic material.

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Supplementary Material Available: Tables of crystal data, fractional coordinates, interatomic distances, interatomic angles, and thermal parameters (11 pages). Ordering information is given on any current masthead page.

Synthesis and Preliminary Evaluation of the Fredericamycin A ABCDE Ring System

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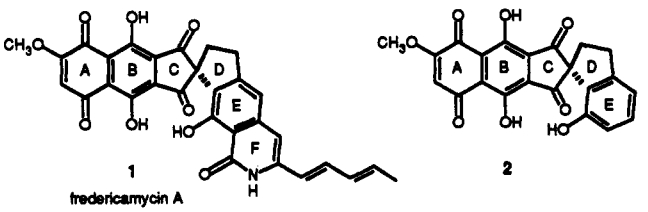
A concise preparation of **2** constituting the fully functionalized fredericamycin A ABCDE ring system is detailed and is based on the implementation of a regiospecific, intermolecular alkyne-chromium carbene complex benzannulation reaction for introduction of the AB ring system and a facile aldol closure for introduction of the spirocyclic CD ring system. Chemical and preliminary biological comparisons of **2** with fredericamycin are described.

Fredericamycin A (1, NSC-305263), a quinone antitumor antibiotic[1] isolated from *Streptomyces griseus*[2] bearing a unique spiro[4.4]nonene central to its structure, has been shown to possess potent in vitro cytotoxic activity and confirmed in vivo antitumor activity. The biological properties of fredericamycin A have been suggested to be derived from inhibition of RNA and protein synthesis through the nondiscriminant oxidative damage of DNA and/or through effective inhibition of DNA processing



enzymes including topoisomerase I and II.[1,3-5] Thus, since the establishment of the fredericamycin A structure that required a single-crystal X-ray structure determination[6] after extensive spectroscopic studies failed to resolve tautomeric structures,[3] it has remained the subject of continued biological[5] and extensive synthetic efforts[6] al-

(1) In vitro and in vivo activity: Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *34*, 1402. Von Hoff, D. D.; Cooper, J.; Bradley, E.; Sandbach, J.; Jones, D.; Makuch, R. *Am. J. Med.* **1981**, *70*, 1027. Water-soluble potassium salt: Misra, R. *J. Antibiot.* **1988**, *41*, 976. Derivatives: Yokoi, K.; Hasegawa, H.; Narita, M.; Asaoka, T.; Kukita, K.; Ishizeki, S.; Nakajima, T. Jpn. Patent 152468, 1985; *Chem. Abstr.* **1986**, *104*, 33948j. Mechanism of action: Hilton, B. D.; Misra, R.; Zweier, J. L. *Biochemistry* **1986**, *25*, 5533. Biosynthesis: Byrne, K. M.; Hilton, B. D.; White, R. J.; Misra, R.; Pandey, R. C. *Biochemistry* **1985**, *24*, 478.

(2) 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.

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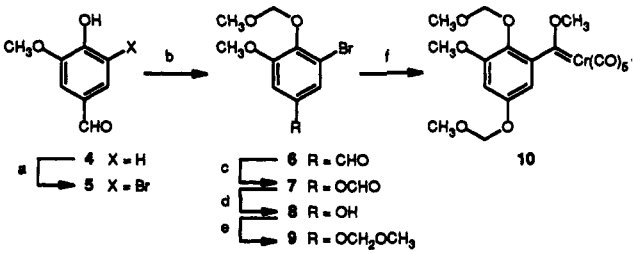
0022-3263/91/1956-2115$02.50/0

Scheme I[a]



[a] Key: (a) Br_2, HOAc, 25 °C, 0.5 h;[15] (b) 1.5 equiv of CH_3OCH_2Cl, 0.1 equiv of Bu_4NI, 1.1 equiv of NaH, DMF, 25 °C, 24 h, 91%; (c) 1.5 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 16 h; (d) 10% aqueous KOH, CH_3OH, 25 °C, 12 h, 85% from **6**; (e) 1.5 equiv of CH_3OCH_2Cl, 0.1 equiv of Bu_4NI, 1.1 equiv of NaH, DMF, 25 °C, 72 h, 71%; (f) 1.1 equiv of BuLi, Et_2O, −78 °C, 0.25 h; 1.0 equiv of $Cr(CO)_6$, −78 to +25 °C, 2.5 h; 1.5 equiv of $(CH_3)_3OBF_4$, CH_2Cl_2, 0–25 °C, 1.5 h, 78%.

though to date this includes only one completed total synthesis.[7]

In continued efforts on the development of an alternative, covergent total synthesis of fredericamycin A and in efforts to provide agents necessary to address the origin of its cytotoxic and antitumor properties, herein we provide full details of a preparation of **2** constituting the fully functionalized fredericamycin A ABCDE ring system and a key partial structure of the natural product. The approach employed in the preparation of **2** extends our prior efforts[8,9] and rests on the implementation of a regiospecific, intermolecular alkyne–chromium carbene complex benzannulation reaction[10–14] (AB ring introduction) employing alkyne **11**,[9] the use of the functionalized Fischer chromium carbene complex **10**, and a simple aldol closure for introduction of the spiro[4.4]nonene (CD ring system). Since **2** constitutes an advanced fredericamycin A partial structure lacking only the functionalized F ring, the comparative chemical and preliminary biological evaluations of **2** are described.

Synthesis of the Fredericamycin A ABCDE Ring System. Conversion of vanillin (**4**) to 5-bromovanillin (**5**)[15] followed by protection of the phenol as its methoxymethyl ether provided **6** (Scheme I). Baeyer–Villiger oxidation of **6** employing *m*-chloroperbenzoic acid followed by immediate hydrolysis of the resulting formate **7** without intermediate purification provided phenol **8**. Protection of the free phenol of **8** as its methoxymethyl ether provided **9** in an overall sequence[16] amenable to the large-scale preparation of the Fischer chromium carbene complex **10**. The conversion of **9** to the Fischer chromium carbene complex **10** was accomplished most effectively in one step through *n*-butyllithium metalation (−78 °C) and trap of the aryllithium reagent with hexacarbonylchromium followed by direct O-alkylation of the lithium acylmetalate with trimethyloxonium tetrafluoroborate in methylene chloride to provide **10** (78% from **9**). This direct O-methylation of the lithium acylmetalate proved more covenient than intermediate generation of the organic soluble tetra-*n*-butylammonium salt through cation exchange with Bu_4NBr (92% after purification by chromatography) and subsequent O-methylation with methyl trifluoromethanesulfonate (63% overall).[17,18]

In agreement with observations made in preliminary efforts,[8,9] the benzannulation reaction of **10** with the functionalized alkyne **11**[9] proceeded best in heptane (0.1 M in alkyne) in the presence of acetic anhydride (1.5 equiv)[9,13] under reaction conditions that do *not* acylate the product phenol and provided **12** (48%) as the exclusive isolable reaction product[19] (Scheme II). The product **12** proved to be a single cyclization regioisomer and a 3–4.5:1 mixture of diastereomers.[20] Consistent with past obser-

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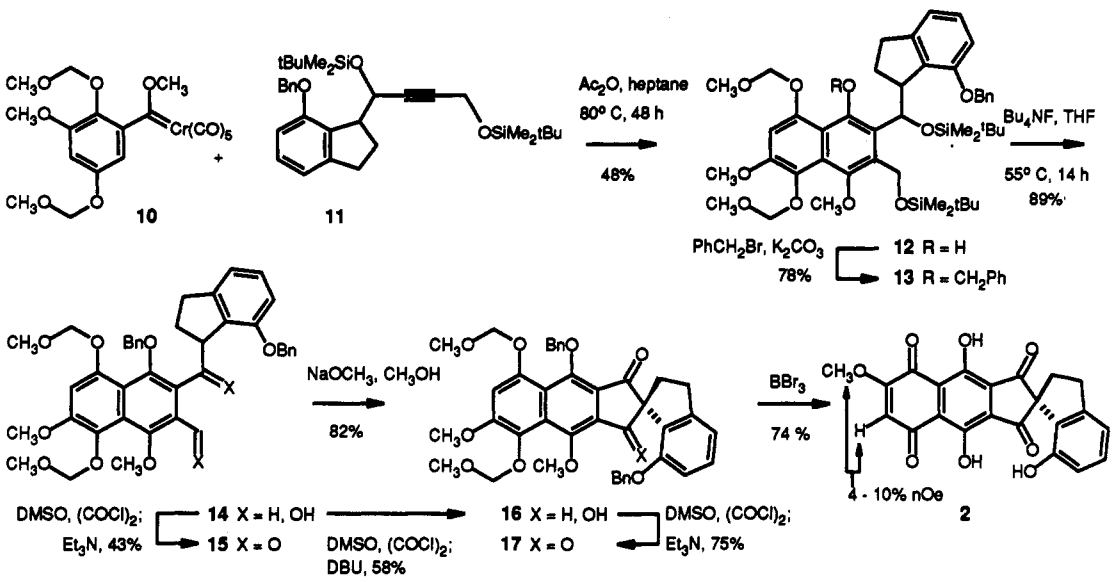
(16) Efforts to convert **5** to **9** directly through (1) 5% aqueous H_2O_2, 1 N NaOH, 24 h, 25 °C (55% purified), (2) CH_3OCH_2Cl, K_2CO_3, DMF, catalytic Bu_4NI, 60 °C, 24 h (ca. 20%) with or without purification of the intermediate hydroquinone proved less satisfactory than the approach detailed in Scheme I. See: Reference 18. Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.

(17) For the tetra-*n*-butylammonium salt: ^1H NMR ($CDCl_3$, 470 MHz) δ 6.31 (1 H, m), 6.19 (1 H, m), 5.12 (2 H, s, OCH_2O), 4.95 (2 H, s, OCH_2O), 3.78 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3), 3.42 (3 H, s, OCH_3), 3.20 (8 H, bs, $N(CH_2)_4$), 2.78–0.99 (28 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 315.64 (e, carbene C), 228.32 (e, CO_{trans}), 221.44 (e, CO_{cis}), 155.85 (e), 153.21 (e), 152.78 (e), 130.58 (o), 101.39 (e, OCH_2O), 99.88 (o), 98.30 (e, OCH_2O), 94.89 (e), 76.88 (e, $N(CH_2)_4$), 58.70 (o, OCH_3), 56.92 (o, OCH_3), 55.62 (o, OCH_3), 23.79 (e, $(CH_2)_4$), 19.47 (e, $(CH_2)_4$), 13.42 (o, $(CH_3)_4$). Alternative efforts to methylate the tetra-*n*-butylammonium salt included $(CH_3)_3OBF_4$ (61%), CH_3I/DMF (0%), CH_2N_2/CH_3OH (0%), CH_3COCl followed by CH_3OH/CH_2Cl (8%), and *p*-TsCl followed by CH_3OH/CH_2Cl_2 (0%).

(18) Initial attempts to employ 2,5-bis(benzyloxy)-3-bromo-1-methoxybenzene proved much less successful due to an effective intramolecular protonation of the resulting aryllithium reagent from the proximal C-2 benzyloxy benzylic center. For similar observations, see: Cross, B. E.; Zammitt, L. J. *Tetrahedron* **1976**, *32*, 1587.

Scheme II



vations this may be attributed to the modest steric differences in the alkyne α substituents that dictate the regioselectivity of the initial [2 + 2] chromium metallocyclobutene adduct, preferentially placing the alkyne large substituent ortho to the phenol in the benzannulation product **12**. More subtle is the overall effect of the alkyne structure on the success of the benzannulation reaction of (2,5-dialkoxyaryl)chromium carbene complexes such as **10**. As detailed in the observations of Semmelhack and coworkers,[14] the facility with which the benzannulation reaction of such complexes proceed with propargylic substrates is substantially diminished relative to that of simple arylchromium carbene complexes although the use of bulky alcohol protecting groups favors naphthol formation over competitive side reactions. This subtle but important contribution to the success of the benzannulation reaction of **10** through employment of the bis-α,α-[(*tert*-butyldimethylsilyl)oxy]alkyne **11** coupled with the use of the modified reaction conditions[9] proved necessary for significant generation of **12**.[12b] In contrast to our prior observations, the conduct of the benzannulation reaction with complete consumption of alkyne **11** required use of an excess of the arylchromium carbene complex **10** (1.5–2.5 equiv), suggesting a nonproductive consumption of **10** under the prescribed reaction conditions.

Subsequent protection of the free phenol of the benzannulation product **12** as the benzyl ether was accomplished cleanly under mild basic conditions (78%) without competitive elimination of *tert*-butyldimethylsilanol. Deprotection of the primary and secondary benzylic alcohols was effectively accomplished through treatment of **13** with tetra-*n*-butylammonium fluoride,[21] provided diol **14** (89%), and set the stage for introduction of the spirocyclic CD ring system. After considerable effort, oxidation of diol **14** under Swern oxidation conditions[22] provided the keto aldehyde **15** cleanly but only under the specified reaction conditions. The success of the Swern oxidation of **14** proved critically dependent on the reaction conditions in which the activation of both alcohols through formation of the bisalkoxysulfonium salt (15 min, –64 °C) preceded introduction of triethylamine and base-catalyzed elimination of dimethyl sulfide with formal oxidation of the primary and secondary alcohols.[23] Conventional alternatives to the Swern oxidation procedure[24,25] did not serve to improve the conversion of **14** to **15**. Keto aldehyde **15** closed cleanly to the spirocyclic keto alcohol **16** (82%) upon exposure to sodium methoxide, providing the functionalized spiro[4.4]nonene subunit, and completed the assemblage of the carbon skeleton of the fredericamycin A ABCDE ring system. In the extensive efforts to optimize the conversion of diol **14** to the sensitive keto aldehyde **15** under Swern and related oxidation procedures employing the use of alternative bases to triethylamine, trace or substantial amounts of the subsequent aldol adduct **16** were detected in the oxidation reaction products. This proved most prominent if the mixtures were left for a sustained period of time in the presence of a strong base including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Given

(19) Under more vigorous reaction conditions, products derived from the in situ elimination of *tert*-butyldimethylsilanol from **12** with generation of an unstable orthoquinomethide were observed in related reactions; see ref 9.

(20) Both diastereomers convert to a single keto aldehyde **15**, confirming the diastereomeric assignment although both benzannulation regioisomers and all diastereomers potentially derived from the reaction of **10** with **11** would ultimately provide **2**.

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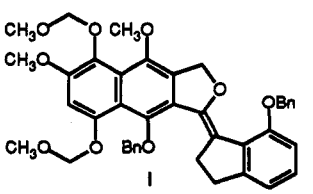
(22) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(23) In instances of incomplete activation of both alcohols, **i** was isolated as a major byproduct (0–42%). For **i**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40–6.68 (14 H, m), 5.11–4.80 (10 H, m), 3.96 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.37 (3 H, s, OCH_3), 3.20–2.69 (3 H, m), 2.03 (1 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.10 (e), 152.09 (e), 150.67 (e), 147.93 (e), 147.08 (e), 145.71 (e), 138.72 (e), 137.67 (e), 135.37 (e), 133.13 (e), 131.67 (e), 130.47 (e), 128.90 (o), 128.70 (o), 128.68 (o), 128.59 (o), 128.35 (o), 128.34 (o), 128.29 (o), 128.21 (o), 128.05 (o), 127.97 (o), 126.86 (e), 120.64 (e), 117.77 (o), 109.45 (o), 103.77 (o), 101.14 (e), 99.34 (o), 97.43 (e), 83.53 (o), 75.79 (e, OCH_2Ph), 70.09 (e, OCH_2Ph), 63.57 (o, OCH_3), 60.71 (e), 57.93 (o, OCH_3), 56.98 (o, OCH_3), 56.53 (o, OCH_3), 46.11 (o), 32.86 (e, CH_2), 25.18 (e, CH_2).

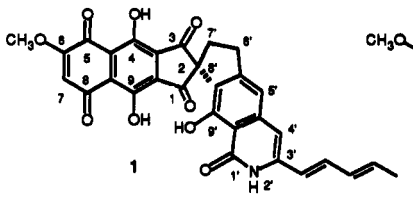


i

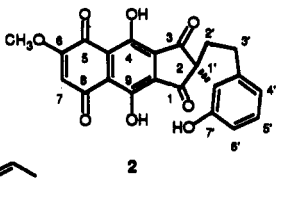
(24) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670. Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1972**, *42*, 4339.

(25) Similar to observations detailed in prior studies,[9] conventional oxidation reagents [MnO_2, PDC (10–20% **15**), $Ba(MnO_4)_2$, and PCC] provided predominately the lactone (ca. 30% unoptimized) derived from primary alcohol oxidation and subsequent oxidation of the resulting hemiacetal.

Table I. ^{1}H NMR Spectroscopic Data for 1[3] and 2 (300 MHz, ppm)



1



2

signal	2			1[3]	assignment 2/1
	$CDCl_3$	$CDCl_3$ + 1% CF_3CO_2D[a]	DMSO-d_6	$CDCl_3$	
1	13.21 (s)		13.13 (s)	13.19 (s)	C-9 OH/C-9 OH (C-9′ OH)[b]
2	12.57 (s)		12.21 (s)	12.56 (s)	C-4 OH/C-4 OH
3		8.82 (bs)	9.53 (s)	12.12 (s)	C-7′ OH/C-9′ OH (C-9 OH)[b]
4	7.14 (m)	7.17 (m)	7.08 (m)		C-5′ H/–
5	6.94 (d, J = 8.0 Hz)	6.94 (d, J = 7.5 Hz)	6.78 (d, J = 7.2 Hz)		C-4′ H/–
6	6.47 (d, J = 8.0 Hz)	6.49 (d, J = 7.9 Hz)	6.48 (m)		C-6′ H/–
7	6.31 (s)	6.37 (s)	6.58 (s)	6.30 (s)	C-7 H/C-7 H
8	4.02 (s)	4.03 (s)	3.97 (s)	4.00 (s)	OCH_3/OCH_3
9	3.28 (t, J = 7.3 Hz)	3.27 (t, J = 7.1 Hz)	3.14 (m)	3.32 (t, J = 7.5 Hz)	C-3′ H_2/C-6′ H_2
10	2.53 (t, J = 7.3 Hz)	2.53 (t, J = 7.1 Hz)	2.36 (m)	2.55 (t, J = 7.5 Hz)	C-2′ H_2/C-7′ H_2

[a] $CDCl_3$ + 1% CH_3CO_2H (500 MHz) additionally listed in the Experimental Section. [b] Original assignments taken from ref 3.

the sensitive nature of keto aldehyde **15**, we elected to optimize the Swern oxidation of **14** employing DBU under reaction conditions that would subsequently promote the aldol closure of **15** to **16** in situ. Thus, treatment of **14** with the Swern reagent derived from activation of dimethyl sulfoxide with oxalyl chloride at −78 °C for 2 h required to permit activation of the primary and secondary alcohols followed by treatment with DBU (−78 to +25 °C, 6 h) provided **16** *directly from 14 in 58% overall yield.* Oxidation of **16** under Swern conditions[22] provided dione **17** (74%) without detection of a competitive retro aldol reaction.[26] A single-step deprotection procedure employing boron tribromide (5 equiv) at low temperature served admirably to remove the two phenol methoxymethyl ethers, the two phenol benzyl ethers, and the activated C-4 methyl ether, leaving intact the required C-6 methyl ether. Subsequent workup accompanied by air oxidation of the hydroquinone provided **2** (74% overall yield), which displayed chemical properties remarkably similar to those of fredericamycin A. In addition to the comparable spectroscopic properties with fredericamycin A (**1**) that support the selective deprotection leaving intact the C-6 methyl ether, unambiguous confirmation of the assigned structure **2** was derived from observation of a strong positive NOE (4–10%) between the quinone hydrogen and the methyl ether. Thus, **2** has been prepared from readily accessible starting materials (**10** and **11**[9]) in 11% overall yield. Of the key six steps, only two contain carbon–carbon bond forming reactions and the remaining four steps constitute functional group interconversions or protecting group introduction/removal.

Chemical and Preliminary Biological Comparison of Fredericamycin A and 2. The comparison of the spectroscopic properties of fredericamycin A[3] (**1**) and **2** are summarized in Tables I and II and exhibit an excellent correlation between the ^{1}H NMR and ^{13}C NMR spectra. In addition, **2** exhibits the same pH dependence on the appearance of the UV spectrum that is observed for fredericamycin A[3] (Figure 1 and eq 1). Like fredericamycin A, **2** exhibits a characteristic intense red color at acidic pH (λ_{max} = 506 nm) and exhibits a strong bathochromic shift and an intense blue color at basic pH (λ_{max} = 732 nm). This behavior is reversible and exhibits an isosbestic point at 557 nm. The red (acidic) form exhibits significantly better solubility properties in aprotic organic solvents, the basic form is freely soluble in aqueous solutions, and the acidic form appears to be more stable to storage.[27]

(26) MnO_2, PDC (44%), and PCC (35%) proved less satisfactory.

Table II. ^{13}C NMR Spectroscopic Data for 1[3] and 2 ($CDCl_3$, 150 MHz, ppm)

signal	2	1	assignment 2/1
1	201.3	199.2	C-1/C-1
2	200.8	199.0	C-3/C-3
3	189.0	188.7	C-8/C-8
4	183.6	183.3	C-5/C-5
5	161.6	161.2	C-6/C-6
6	153.3	155.6	C-7′/C-9′
7	151.0	153.5	C-C3′/C-C6′
8	150.9	153.2	C-4/C-4
9	149.1	152.6	C-9/C-9
10	136.8	136.9	C-C3/C-C3
11	135.1	136.7	C-C1/C-C1
12	131.2	108.3	C-6′/C-C9′
13	131.1	141.1	C-5′/C-C5′
14	126.8	124.6	C-C2/C-C2
15	118.6	118.2	C-C5/C-C5
16	118.0	118.2	C-C8/C-C8
17	113.5	113.0	C-7/C-7
18	111.2	111.0	C-4′/C-5′
19	65.7	64.7	C-2/C-2
20	57.7	57.4	OCH_3/OCH_3
21	35.8	34.8	C-2′/C-7′
22	32.6	32.9	C-3′/C-6′

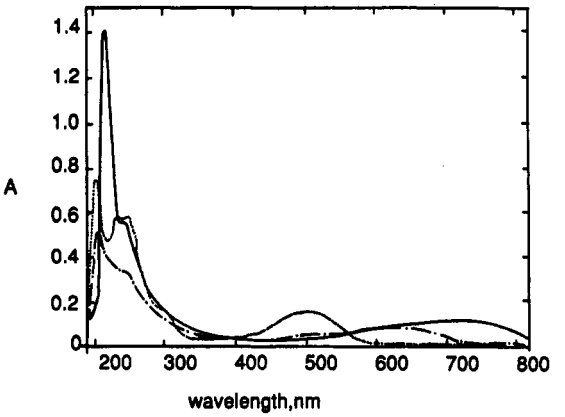
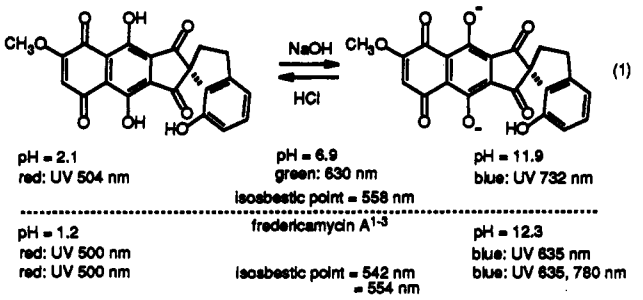
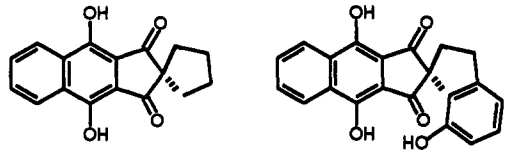


Figure 1. UV spectrum of **2** (2.1×10^{-5} M) in H_2O: —, pH 11.9 (0.01 N NaOH); –·–, pH 6.9 (0.025 M KH_2PO_4–0.025 M Na_2HPO_4); ···, pH 2.1 (0.1 N HCl).



The ability for fredericamycin A to inhibit the catalytic function of topoisomerase I and II at concentrations relevant to the in vitro cytotoxic potency of the agents has suggested that this may constitute a site of action for the agent.[4] Nonetheless, the inherent, albeit nondiscriminate, activity of quinones mediated through the hydroquinone/quinone redox interconversion has been suggested to be responsible for the properties of 1[1-3] although to date it has not been possible to estimate the effective concentration (potency) at which this may prove relevant. Consequently, the comparable evaluations of 2 (IC_{50}, L1210 and B16 in vitro cytotoxic activity; inhibition of topoisomerase I and II catalytic activity)[4] were conducted, and the results are summarized in Table III along with those derived from the evaluation of 1[4] and 18 and 19.[9] The



18 19

agents 18 and 19 proved inactive, and 2 proved to be 100× less potent than fredericamycin A in the cytotoxic assays and inactive in the topoisomerase I and II inhibition assays at concentrations where the partial activity of 1 would prove perceptible. Since 2 possesses in vitro cytotoxic activity at the level of simple quinones,[28] one interpretation of these results is that 2 embodies the nondiscriminate cytotoxic properties associated with the quinone unit of fredericamycin A but lacks structural features necessary for potent expression of the quinone properties (discriminate quinone activity) or for observation of more selective and potent sites of action pertinent to the natural product (topoisomerase I and/or II inhibition). These and additional questions will be addressed with the preparation of more advanced analogues of 1 incorporating elements of the fredericamycin F ring system based on the synthesis of 2 detailed herein.

Experimental Section

5-Bromo-3-methoxy-4-(methoxymethoxy)benzene-1-carboxaldehyde (6). A solution of 5[15] (28.30 g, 107.6 mmol) and tetra-*n*-butylammonium iodide (3.98 g, 10.8 mmol) in *N,N*-dimethylformamide (160 mL) at 0 °C was treated with sodium hydride (60% dispersion in mineral oil, 4.70 g, 118.3 mmol). The resulting reaction mixture was stirred for 10 min at ambient temperature, recooled to 0 °C, and treated with chloromethyl methyl ether (12.30 g, 161.4 mmol). The reaction mixture was stirred at ambient temperature for 24 h, diluted with water (300 mL), and extracted with ethyl acetate (2 × 200 mL). The combined extracts were washed with 10% aqueous sodium bicarbonate (300 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 16 cm × 4 cm, 10–15% EtOAc–hexane gradient eluant) afforded 26.91 g (29.59 g theoretical, 91%) of 6 as a white solid: mp 45–46 °C (hexane:EtOAc = 3:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (1 H, s, CHO), 7.65 (1 H, d, J = 1.7 Hz, aromatic), 7.37 (1 H, d, J = 1.6 Hz, aromatic), 5.28 (2 H, s, OCH_2O), 3.91 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.71 (o, CHO), 153.70 (e), 148.70 (e), 133.12 (e), 128.75 (o), 117.97 (e), 110.18 (o), 98.73 (e, OCH_2O), 58.10 (o, OCH_3), 56.25 (o, OCH_3); IR (KBr) ν_{max} 2974, 2836, 1683, 1588, 1568, 1465, 1423, 1393, 1279, 1148, 1043 cm^{-1}; EIMS, *m/e* (relative intensity) 276/274 (M^+, 4/4), 246/244 (1/1, M^+ - HCHO), 94 (2), 77 (1), 45 (base, CH_2OCH_3); CIMS (2-methylpropane), *m/e* 279/277 (M^+ + H, base); EIHRMS, *m/e* calcd for $C_{10}H_{11}BrO_4$ 273.9841, found 273.9840.

Anal. Calcd for $C_{10}H_{11}BrO_4$: C, 43.80; H, 4.02. Found: C, 43.98; H, 3.95.

5-Bromo-3-methoxy-4-(methoxymethoxy)phenol (8). A solution of 6 (15.00 g, 54.6 mmol) in methylene chloride (100 mL) was treated with *m*-chloroperbenzoic acid (16.60 g, 81.9 mmol). The resulting reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate (500 mL), washed with 10% aqueous sodium bicarbonate (2 × 500 mL), and dried (Na_2SO_4). Concentration in vacuo afforded formate 7 that was carried to the next step without purification. A solution of crude formate in methanol (60 mL) was treated with 10% aqueous potassium hydroxide (33 mL). The resulting reaction mixture was stirred for 12 h (25 °C), diluted with water (200 mL), neutralized with 10% aqueous hydrochloric acid (33 mL), and extracted with ethyl acetate (2 × 300 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 16 cm × 40 cm, 20% EtOAc–hexane eluant) afforded 12.15 g (14.35 g theoretical, 85%) of 8 as a colorless oil. The conversion of 6 (14.4–97.9 mmol) to 8 was routinely achieved in 81–91% yield (two steps): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.78 (1 H, bs, aromatic), 6.53 (1 H, bs, aromatic), 5.86 (1 H, s, OH), 5.04 (2 H, s, OCH_2O), 3.78 (3 H, s, OCH_3), 3.43 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.87 (e), 147.56 (e), 138.54 (e), 111.80 (o, CH), 107.87 (e, CBr), 100.85 (o, CH), 95.38 (e, OCH_2O), 56.35 (o, OCH_3), 56.04 (o, OCH_3); IR (film) ν_{max} 3376, 2942, 1606, 1586, 1490, 1468, 1432, 1196, 1154, 1042, 976 cm^{-1}; EIMS, *m/e* (relative intensity) 264/262 (M^+, 3/3), 234 (3), 217 (3), 183 (M^+ - Br, 5), 77 (1), 45 (base); CIMS (2-methylpropane), *m/e* 265/263 (M^+ + H, base); EIHRMS, *m/e* (relative intensity) calcd for $C_9H_{11}BrO_4$ 261.9841, found 261.9840.

5-Bromo-3-methoxy-1,4-bis(methoxymethoxy)benzene (9). A solution of 8 (6.83 g, 26.0 mmol) and tetra-*n*-butylammonium iodide (0.96 g, 2.6 mmol) in *N,N*-dimethylformamide (50 mL) at 0 °C was treated with sodium hydride (60% dispersion in mineral oil, 1.14 g, 28.6 mmol). The resulting reaction mixture was stirred at ambient temperature for 0.5 h before the addition of chloromethyl methyl ether (2.96 mL, 39.0 mmol). The reaction mixture was stirred for 72 h (25 °C), diluted with water (200 mL), and extracted with ethyl acetate (2 × 150 mL). The combined extracts

Table III. In Vitro Cytotoxic Activity and Enzyme Inhibition Studies

agent	IC_{50} L1210, B16; μg/mL[a]	IC_{50} topoisomerase I,[b] μM	IC_{50} topoisomerase II,[c] μM	DNA strand breaks[d]
1[e]	0.03, 0.05	4.4	7.4	no (100 μM)
2	2, 2	>50	>50	no (100 μM)
18	>10, >10	nt	nt	nt
19	>10, >10	nt	nt	nt

[a] Inhibitory concentration for 50% cell growth relative to untreated controls.[28] [b] Concentration for 50% inhibition of topoisomerase I catalytic activity (relaxation of supercoiled pUC18 DNA), 0% inhibition for 2 at 50 μM.[4] [c] Concentration for 50% inhibition of topoisomerase II activity (decatenation of kDNA networks), 0% inhibition by 2 at 50 μM.[4] [d] Agent-induced topoisomerase I or II DNA single-strand breaks in L1210 cells (1 h, 37 °C) with 10, 25, and 100 μM agent; no breaks detected with 1 or 2.[4] [e] Topoisomerase I and II inhibition by 1 taken from ref 4.

(27) The exposure of 2 to aqueous base in the presence of air promotes the relatively rapid decomposition of the agent. In contrast, 2 has proven stable in the presence of acid and we have found that storage of 2 in the presence of a trace amount of acetic acid (red form) substantially prolongs its storage lifetime.

(28) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918 and references cited therein.

were washed with 10% aqueous sodium bicarbonate (200 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 16 cm × 20 cm, 10% EtOAc–hexane eluant) afforded 5.69 g (7.97 g theoretical, 71%) of **9** as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.86 (1 H, s, aromatic), 6.57 (1 H, s, aromatic), 5.10 (2 H, s, OCH_2O), 5.08 (2 H, s, OCH_2O), 3.81 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 3.46 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.32, 153.91, 138.39, 117.76 (CH), 111.72 (CH), 101.56 (CBr), 98.78 (OCH_2O), 95.00 (OCH_2O), 58.00 (OCH_3), 56.15 (OCH_3), 56.10 (OCH_3); IR (film) ν_{max} 2958, 2904, 1600, 1572, 1488, 1466, 1156, 1012 cm^{-1}; EIMS, *m/e* (relative intensity) 308/306 (M^+, 17/17), 277/275 (17, $M^+ - OCH_3$), 263/261 (2, $M^+ - CH_2OCH_3$), 227 (26, $M^+ - Br$), 77 (2), 65 (2), 45 (base); CIMS (2-methylpropane), *m/e* 309/307 ($M^+ + H$, base); EIHRMS, *m/e* calcd for $C_{11}H_{15}BrO_5$ 306.0102, found 306.0099.

Anal. Calcd for $C_{11}H_{15}BrO_5$: C, 43.14; H, 4.90. Found: C, 43.15; H, 4.66.

Pentacarbonyl[methoxy[2,5-bis(methoxymethoxy)-3-methoxyphenyl]methylene]chromium (10). A solution of **9** (0.36 g, 1.2 mmol) in ether (5 mL) at −78 °C was treated with *n*-butyllithium (2.5 M, 0.51 mL, 1.3 mmol). The resulting reaction mixture was stirred for 15 min[29] and then treated with hexacarbonylchromium (0.26 g, 1.2 mmol). The cooling bath was removed, and the reaction mixture was allowed to warm to ambient temperature over 2.5 h providing a deep red solution. The reaction mixture was concentrated in vacuo, diluted with methylene chloride (5 mL), and treated at 0 °C with trimethyloxonium tetrafluoroborate (0.26 g, 1.8 mmol). The resulting reaction mixture was allowed to warm to ambient temperature over 1.5 h, filtered through Florisil (ether, 20 mL), and concentrated in vacuo. Flash chromatography (SiO_2, 4.5 cm × 30 cm, 5–20% EtOAc–hexane gradient elution) afforded 0.42 g (0.54 g theoretical, 78%) of **10** as a deep red oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 6.56 (1 H, d, J = 2.2 Hz, aromatic), 6.13 (1 H, d, J = 2.2 Hz, aromatic), 5.13 (2 H, s, OCH_2O), 5.04 (2 H, bs, OCH_2O), 4.37 (3 H, bs, OCH_3), 3.84 (3 H, s, OCH_3), 3.51 (3 H, s, OCH_3), 3.47 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 315.89 (e, $C_{carbene}$), 224.91 (e, CO_{trans}), 216.14 (e, CO_{cis}), 154.12 (e), 152.93 (e), 130.24 (e), 118.02 (o, CH), 107.29 (o, CH), 101.73 (o, OCH_3), 99.01 (e, OCH_2O), 96.40 (e, $CC_{carbene}$), 95.19 (e, OCH_2O), 66.47 (o, $C_{carbene}OCH_3$), 57.52 (o, OCH_3), 56.11 (o, OCH_3); IR (film) ν_{max} 2958, 2064 (sharp), 1936, 1846, 1592, 1460 cm^{-1}; EIMS, *m/e* (relative intensity) 462 (M^+, 6), 378 (22, $M^+ - 3$ CO), 350 (6, $M^+ - 4$ CO), 322 (53, $M^+ - 5$ CO), 292 (38), 239 (35), 52 (base, Cr^+); CIMS (2-methylpropane), *m/e* 463 ($M^+ + H$, 14), 271 (base, $M^+ + H - Cr(CO)_5$); EIHRMS, *m/e* calcd for $C_{18}H_{18}CrO_{11}$, 462.0254, found 462.0259. The methoxymethyl ether adjacent to the chromium carbene exhibits broadened ^1H NMR signals due to hindered rotation (−40 to +25 °C) that sharpen upon warming (60 °C), and notable is the fact that the complex is stable as the pentacarbonylchromium complex.

5,8-Bis(methoxymethoxy)-1,7-dimethoxy-2-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-[1-[7′-(phenylmethoxy)-1′-indanyl]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-naphthalenol (12). A solution of **10** (1.71 g, 3.70 mmol), **11** (0.95 g, 1.78 mmol), and acetic anhydride (0.25 mL, 2.7 mmol) in heptane (18 mL) under argon was warmed at 55 °C for 48 h. The cooled reaction mixture was diluted with ether (80 mL) and filtered through Florisil, and the filtrate was concentrated in vacuo. Flash chromatography (SiO_2, 30 cm × 7 cm, 5–15% EtOAc–hexane eluant) afforded 0.715 g (1.48 g theoretical, 48%) of **12** as a 4.4:1 mixture of diastereomers (3–4.4:1) as a light yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 9.90 and 9.24 (1 H, s, OH), 7.27–6.42 (18 H, m, aromatic), 5.46–4.01 (19 H, m), 3.95 and 3.93 (3 H, s, OCH_3), 3.89–3.71 (1 H, m), 3.67 and 3.65 (3 H, s, OCH_3), 3.62 and 3.60 (3 H, s, OCH_3), 3.57 and 3.46 (3 H, s, OCH_3), 3.36–3.09 (2 H, m), 2.87–2.75 (2 H, m), 2.59–2.49 (2 H, m), 2.15–2.03 (2 H, m), 0.92 and 0.83 (9 H, s, $OSiC(CH_3)_3$), 0.81 and 0.73 (9 H, s, $OSiC(CH_3)_3$), 0.18 and 0.17 (3 H, s, $OSiCH_3$), 0.02 and −0.05 (3 H, s, $OSiCH_3$), −0.07 and −0.16 (3 H, s, $OSiCH_3$), −0.20 and −0.46 (3 H, s, $OSiCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.85 (e), 156.27 (e), 152.07 (e), 151.70 (e), 151.50 (e), 151.32 (e), 150.37 (e), 149.98 (e), 148.33 (e), 147.88 (e), 147.22 (e), 145.46 (e), 138.72 (e), 137.85 (e), 134.95 (e), 134.73 (e), 134.67 (e), 134.15 (e), 132.26 (e), 129.93 (e), 129.12 (o), 128.68 (o), 128.65 (o), 128.45 (o), 128.18 (o), 127.59 (o), 127.44 (o), 127.43 (o), 127.14 (o), 126.97 (o), 126.87 (o), 126.83 (o), 126.79 (o), 124.62 (e), 124.32 (e), 124.00 (e), 119.64 (e), 117.80 (o), 117.62 (o), 115.97 (e), 112.71 (e), 109.79 (o), 107.56 (o), 104.73 (o), 101.38 (o), 100.97 and 99.36 (e, OCH_2O), 98.28 and 96.65 (e, OCH_2O), 75.20 and 70.67 (o, CHO(TBDMS)), 69.99 and 69.67 (e, OCH_2Ph), 63.37 and 63.00 (o, OCH_3), 57.81 and 56.85 (o, OCH_3), 57.50 and 55.83 (e, CH_2O(TBDMS)), 56.69 and 56.35 (o, OCH_3), 56.15 and 56.13 (o, OCH_3), 49.55 and 49.19 (o, CHAr), 32.53 and 31.91 (e, CH_2Ar), 31.82 and 28.84 (e, CH_2CH_2Ar), 26.46 and 26.00 (o, 3 C, $OSiC(CH_3)_3$), 25.96 and 25.94 (o, 3 C, $OSiC(CH_3)_3$), 23.32 and 22.86 (e, $OSiC(CH_3)_3$), 18.73 and 18.09 (e, $OSiC(CH_3)_3$), −4.69 and −5.00 (o, 2 C, $OSiCH_3$), −5.23 and −5.62 (o, 2 C, $OSiCH_3$); IR (film) ν_{max} 3394, 2930, 2856, 1610, 1590, 1464, 1384, 1348, 1254, 1216, 1154, 1128, 1062, 1004, 974 cm^{-1}; FABMS (glycerol), *m/e* (relative intensity) 834 (M^+, 4), 611 (base), 463 (18), 403 (32), 303 (33), 275 (21), 271 (19), 223 (33); FABHRMS (*m*-nitrobenzyl alcohol, $M^+ + H$), *m/e* calcd for $C_{46}H_{66}O_{10}Si_2$ 835.4273, found 835.4198.

5,8-Bis(methoxymethoxy)-4,6-dimethoxy-3-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-(phenylmethoxy)-2-[1-[7′-(phenylmethoxy)-1′-indanyl]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]naphthalene (13). A solution of **12** (0.23 g, 0.28 mmol), potassium carbonate (0.39 g, 2.80 mmol), and tetra-*n*-butylammonium iodide (0.10 g, 0.28 mmol) in acetone (0.90 mL) was treated with benzyl bromide (0.10 mL, 0.84 mmol), and the resulting reaction mixture was warmed at 55 °C for 64 h. The solution was diluted with 25% EtOAc–hexane (20 mL) and passed through Florisil, and the filtrate was concentrated in vacuo. Flash chromatography (SiO_2, 30 cm × 5 cm, 10–15% EOAc–hexane eluant) afforded 201 mg (259 mg theoretical, 78%) of **13** as a 3.2:1 mixture of diastereomers (3–4.4:1) as a light yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.48–6.46 (26 H, m, aromatic), 6.17 (2 H, m), 5.72 (2 H, m), 5.44 (2 H, m), 5.12–4.30 (18 H, m), 4.04 and 3.97 (3 H, s, OCH_3), 3.71 and 3.70 (3 H, s, OCH_3), 3.69 and 3.61 (3 H, s, OCH_3), 3.23 and 3.20 (3 H, s, OCH_3), 3.01 (2 H, m), 2.73 (6 H, m), 2.11 (2 H, m), 0.94 and 0.90 (9 H, s, $OSiC(CH_3)_3$), 0.84 and 0.83 (9 H, s, $OSiC(CH_3)_3$), 0.50 and 0.18 (3 H, s, $OSiCH_3$), 0.16 and 0.09 (3 H, s, $OSiCH_3$), 0.04 and −0.01 (3 H, s, $OSiCH_3$), −0.04 and −0.43 (3 H, s, $OSiCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) 157.22 (e), 156.41 (e), 153.36 (e), 152.94 (e), 152.89 (e), 152.60 (e), 150.41 (e), 148.78 (e), 148.12 (e), 147.85 (e), 147.90 (e), 140.39 (e), 139.20 (e), 138.87 (e), 137.60 (e), 137.40 (e), 136.57 (e), 134.61 (e), 133.85 (e), 133.73 (e), 133.08 (e), 132.94 (e), 132.72 (e), 131.34 (e), 129.23 (o), 129.03 (o), 128.81 (o), 128.78 (o), 128.72 (o), 128.68 (o), 128.67 (o), 128.54 (o), 128.50 (o), 128.46 (o), 128.44 (o), 128.21 (o), 128.17 (o), 128.14 (o), 128.11 (o), 127.98 (o), 127.41 (o), 127.15 (o), 126.93 (o), 126.52 (o), 126.49 (o), 126.06 (o), 125.43 (e), 125.04 (e), 119.71 (e), 118.51 (e), 118.14 (o), 117.73 (o), 111.01 (o), 108.89 (o), 103.10 (o, 2 C), 101.05 (e, two carbons, OCH_2O), 75.39 and 75.11 (e, OCH_2O), 74.60 and 74.36 (e, OCH_2Ph), 72.13 and 69.92 (o, OCH_3), 70.16 and 69.82 (e, OCH_2Ph), 63.60 and 63.42 (o, CHO(TBDMS)), 57.86 and 57.71 (o, 2 C, OCH_3), 57.51 and 55.60 (e, CH_2O(TBDMS)), 57.17 and 57.09 (o, CH_3), 49.83 and 49.51 (o, CHAr), 31.06 and 30.51 (e, CH_2Ar), 30.30 and 29.92 (e, CH_2CH_2Ar), 26.54 and 26.40 (o, $OSiCCH_3$), 26.36 and 26.35 (o, 3 C, $OSiC(CH_3)_3$), 26.10, 26.08 (o, 3 C, $OSiC(CH_3)_3$), 18.85 (e, $OSiC(CH_3)_3$), 18.79 (e, 2 C, $OSiC(CH_3)_3$), 18.28 (e, $OSiC(CH_3)_3$), −4.58 and −4.81 (o, $OSiCH_3$), −4.98 (o, 2 C, $OSiCH_3$), −5.18 and −5.23 (o, $OSiCH_3$), −5.36 and −5.41 (o, $OSiCH_3$); IR (film) ν_{max} 2954, 2930, 2856, 1734, 1606, 1586, 1344, 1154, 1062 cm^{-1}; EIMS, *m/e* (relative intensity) 701 (6, $M^+ - C_{16}H_{15}O$), 525 (2), 367 (2), 332 (1), 223 (9), 181 (3), 175 (2), 147 (2), 115 (2), 91 (base), 75 (15); FABHRMS, (*m*-nitrobenzyl alcohol), *m/e* calcd for $C_{37}H_{57}O_9Si_2$ (fragmentation, $M^+ - C_{16}H_{15}O$) 701.3541, found 701.3570.

5,8-Bis(methoxymethoxy)-4,6-dimethoxy-3-(1-hydroxymethyl)-2-[1-hydroxy-1-[7′-(phenylmethoxy)-1′-indanyl]-methyl]-1-(phenylmethoxy)naphthalene (14). A solution of **13** (0.12 g, 0.13 mmol) in tetrahydrofuran (4 mL) was treated with a solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1 M, 0.51 mL, 0.51 mmol) under nitrogen, and the resulting reaction mixture was warmed at 55 °C for 14 h. The solvent was removed in vacuo. Flash chromatography (SiO_2, 15 cm × 5 cm, 15–35% EtOAc–hexane eluant) afforded 79 mg (89 mg theoretical, 89%) of **14** as a light yellow foam. Major diastereomer: ^1H NMR

(29) Longer reaction times lead to diminished yields of product.

($CDCl_3$, 300 MHz) δ 7.37–7.05 (10 H, m, aromatic), 6.83 (3 H, m, aromatic), 6.46 (1 H, d, J = 8.1 Hz, aromatic), 5.27 (1 H, bs), 5.05 (1 H, d, J = 5.9 Hz), 4.97 (1 H, d, J = 5.9 Hz), 4.81 (1 H, d, J = 7.0 Hz), 4.76 (1 H, d, J = 7.0 Hz), 4.62 (3 H, m), 4.26 (3 H, bs), 4.00 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.24 (3 H, s, OCH_3), 3.02 (1 H, m), 2.75 (2 H, m), 2.51 (1 H, m), 2.11 (1 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.16 (e), 189.01 (e), 188.38 (e), 187.51 (e), 186.38 (e), 184.08 (e), 169.84 (e), 167.23 (e), 160.16 (e), 159.19 (e), 157.72 (e), 155.56 (o), 155.33 (o), 154.98 (o, 2 C), 154.78 (o, 2 C), 154.06 (o, 2 C), 153.37 (o), 152.17 (o, 2 C), 149.69 (e), 138.74 (o), 138.42 (e), 125.59 (o), 118.15 (o), 113.00 (e, OCH_2O), 108.16 (e, OCH_2O), 75.12 (e, OCH_2Ph), 68.58 (o, OCH_3), 66.20 (e, OCH_2Ph), 55.89 (o, OCH_3), 47.79 (o, OCH_3), 46.41 (o, OCH_3), 45.94 (e, CH_2OH), 45.78 (o, CHOH), 36.95 (o, CHAr), 7.11 (e, CH_2Ar), 5.82 (e, CH_2Ar). Minor diastereomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–6.43 (14 H, m), 5.26–4.29 (11 H, m), 3.91 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.67 (6 H, s, OCH_3), 3.00 (1 H, m), 2.78 (2 H, m), 2.51 (1 H, m), 2.11 (1 H, m); IR (film) ν_{max} 3384, 2938, 1606, 1588, 1454, 1348, 1152, 1052, 1018, 974 cm^{-1}; EIMS, m/e (relative intensity) 588 (1), 455 (16), 337 (8), 275 (5), 223 (15), 91 (base), 77 (2); CIMS, m/e (relative intensity) 697 (M^+ + H, 1), 253 (base); EIHRMS, m/e calcd for $C_{41}H_{44}O_{10}$ 696.2935, found 696.2940.

Anal. Calcd for $C_{41}H_{44}O_4$: C, 70.69, H, 6.32. Found: C, 70.63; H, 6.59.

5,8-Bis(methoxymethoxy)-4,6-dimethoxy-2-[1-oxo-1-[7′-(phenylmethoxy)-1′-indanyl]methyl]-1-(phenylmethoxy)-naphthalene-3-carboxaldehyde (15). A solution of oxalyl chloride (18 μL, 0.21 mmol) in methylene chloride (0.8 mL) at −64 °C was treated with dimethyl sulfoxide (32 μL, 0.45 mmol). The resulting solution was stirred for 5 min, treated with **14** (66 mg, 0.09 mmol) in methylene chloride (0.8 mL), and further stirred at −64 °C for 15 min. Following the addition of triethylamine (0.13 mL, 0.94 mmol), the reaction mixture was stirred for 5 min (−64 °C) and the cooling bath was removed. The solution was allowed to warm to room temperature over a period of 20 min. The reaction mixture was quenched with the addition of 10% aqueous hydrochloric acid (1 mL), diluted with water (50 mL), and extracted with ether (2 × 25 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 25 cm × 5 cm, 10–25% EtOAc–hexane eluant) afforded 28 mg (65 mg theoretical, 43%) of **15** as a light yellow foam: ^1H NMR ($CDCl_3$, 200 MHz) δ 10.23 (1 H, s, CHO), 7.33–6.81 (13 H, m, aromatic), 6.47 (1 H, d, J = 8.1 Hz, aromatic), 5.01–4.62 (8 H, m), 4.40 (1 H, m, C*H*HPh), 3.97 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.67 (3 H, s, OCH_3), 3.27 (3 H, s, OCH_3), 3.17 (1 H, m, C*H*HAr), 2.93 (1 H, m, CH*H* Ar), 2.79 (1 H, m, C*H*HCH_2Ar), 2.22 (1 H, m, CH*H*CH_2Ar); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 205.42 (e, CO), 190.22 (o, CHO), 158.25 (e), 156.18 (e), 151.97 (e), 151.91 (e), 148.72 (e), 148.54 (e), 138.42 (e), 137.50 (e), 136.21 (e), 129.97 (e), 129.90 (e), 129.14 (o), 128.55 (o), 128.45 (o), 128.42 (o), 128.28 (o), 127.75 (o), 127.63 (o), 127.61 (o), 127.48 (o), 127.45 (o), 126.87 (o), 126.03 (e), 125.82 (e), 120.73 (e), 117.89 (o), 109.43 (o), 106.83 (o), 101.25 (e, OCH_2O), 97.68 (e, OCH_2O), 69.55 (e, 2 C, OCH_2Ph), 65.29 (o, CHAr), 58.10 (o, OCH_3), 56.89 (o, OCH_3), 56.66 (o, OCH_3), 56.69 (o, OCH_3), 32.53 (e, CH_2Ar), 29.67 (e, CH_2CH_2Ar); IR (film) ν_{max} 3426, 2934, 1734, 1718, 1700, 1684, 1654, 1648, 1636, 1606 1588, 1458, 1346 cm^{-1}; CIMS (2-methylpropane), m/e 693 (M^+ + H, 1), 92 ($C_7H_8^+$, base); CIHRMS, m/e calcd for $C_{41}H_{40}O_{10}$ 693.2700, found 693.2700.

2,3-Dihydro-7-(phenylmethoxy)-1*H*-indene-1-spiro-2′-[5′,8′-bis(methoxymethoxy)-4′,6′-dimethoxy-3′-hydroxy-9′-(phenylmethoxy)-2′*H*-benz[*f*]inden-1′-one] (16) from 15. A solution of **15** (28 mg, 0.04 mmol) in methanol (1 mL) was treated with sodium methoxide (25% solution in methanol, 8 μL, 0.04 mmol), and the reaction mixture was warmed at 65 °C for 5.5 h. The cooled reaction mixture was concentrated in vacuo. Flash chromatography (SiO_2, 19 cm × 3 cm, 20% EtOAc–hexane eluant) afforded 23 mg (28 mg theoretical, 82%) of **16** (1:1 mixture of diastereomers) as a light yellow foam: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.67–6.70 (28 H, m, aromatic), 5.77 (1 H, bs, CHO*H*), 5.43–4.86 (17 H, m), 4.54 (2 H, m, C*H*OH), 4.03 and 4.04 (3 H, s, OCH_3), 3.92 and 3.79 (3 H, s, OCH_3), 3.69 and 3.68 (3 H, s, OCH_3), 3.42 (6 H, s, OCH_3), 3.20–2.03 (8 H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 204.61 and 204.39 (e, CO), 155.64 (e), 155.33 (e), 155.22 (e), 154.75 (e), 153.51 (e), 153.44 (e), 152.67 (e), 152.56 (e), 149.16 (e), 148.92 (e), 148.66 (e), 147.94 (e), 140.68 (e), 140.41 (e), 138.19 (e), 138.10 (e), 137.10 (e), 136.71 (e), 134.73 (e), 134.17 (e), 134.08 (e), 130.86 (e), 130.56 (e), 130.31 (o), 130.00 (e), 129.92 (o), 129.27 (o), 128.70 (o, 2 C), 128.52 (o), 128.45 (o), 128.43 (o), 128.34 (o), 128.32 (o), 128.10 (o), 128.01 (o), 127.82 (o), 127.74 (o), 127.69 (o), 127.67 (o), 127.55 (o), 127.23 (o), 127.07 (o), 126.92 (o), 126.85 (o), 125.03 (o), 123.52 (e), 123.23 (e), 120.17 (e), 119.97 (e), 118.59 (o), 118.09 (o), 110.22 (o), 109.57 (o), 103.13 (o), 102.96 (o), 101.31 and 101.12 (e, OCH_2O), 97.35 (e, 2 C, OCH_2O), 77.25 (e, 2 C, OCH_2Ph), 75.02 and 74.95 (o, CHOH), 70.46 and 69.76 (e, OCH_2Ph), 67.92 and 66.80 (e, spiro carbon), 63.64 and 62.29 (o, OCH_3), 58.04 and 58.00 (o, OCH_3), 57.95 and 56.80 (o, OCH_3), 56.68 and 56.60 (o, OCH_3), 39.48 and 33.08 (e, CH_2Ar), 32.27 and 31.94 (e, CH_2CH_2Ar); IR (film) ν_{max} 3472, 2936, 1718, 1602, 1454, 1342, 1264, 1154, 1026, 738, 698 cm^{-1}; CIMS (2-methylpropane), m/e 693 (M^+ + H, weak), 419 (base); EIHRMS, m/e calcd for $C_{41}H_{40}O_{10}$ 692.2621, found 692.2691.

16 from 14. A solution of oxalyl chloride (60 μL, 0.69 mmol) in methylene chloride (12 mL) at −78 °C was treated with dimethyl sulfoxide (85 μL, 1.20 mmol), and the resulting solution was stirred for 15 min (−78 °C). A solution of **14** (0.12 g, 0.17 mmol) in methylene chloride (0.5 mL) was added, and the mixture was stirred at −78 °C for 2 h. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 0.38 mL, 2.57 mmol) was added, and the cooling bath was allowed to warm to room temperature over 5.5 h. The mixture was quenched with the addition of water, further diluted with water (100 mL), and extracted with ether (2 × 50 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 30 cm × 5 cm, 15–25% EtOAc–hexane eluant) afforded 68.5 mg (119 mg theoretical, 58%) of **16** as a 1.8:1 mixture of diastereomers.

2,3-Dihydro-7-(phenylmethoxy)-1*H*-indene-1-spiro-2′-[5′,8′-bis(methoxymethoxy)-4′,6′-dimethoxy-9′-(phenylmethoxy)-2′*H*-benz[*f*]indene-1′,3′-dione] (17). A solution of oxalyl chloride (26 μL, 0.30 mmol) in methylene chloride (6.9 mL) at −78 °C was treated with dimethyl sulfoxide (35 μL, 0.50 mmol), and the resulting solution was stirred for 15 min (−78 °C). A solution of **16** (69 mg, 0.10 mmol) in methylene chloride (3 mL) was added, and the mixture was stirred at −78 °C for 1 h. Triethylamine (69 μL, 0.50 mmol) was added, the cooling bath was removed, and the solution was allowed to warm to room temperature over a period of 40 min. The mixture was quenched with the addition of water, further diluted with water (100 mL), and extracted with ether (2 × 50 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 25 cm × 5 cm, 15–20% EtOAc–hexane eluant) afforded 51 mg (68 mg theoretical, 75%) of **17** as a colorless foam: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65–6.62 (14 H, m, aromatic), 5.07 (4 H, m), 4.95 (1 H, d, J = 9.6 Hz, OC*H*HPh), 4.75 (2 H, s), 4.64 (1 H, d, J = 9.6 Hz, OCH*H*Ph), 4.07 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.70 (3 H, s, OCH_3), 3.43 (3 H, s, OCH_3), 3.31 (2 H, m, CH_2Ar), 2.53 (2 H, m, CH_2CH_2Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.47 (e, CO), 200.34 (e, CO), 154.67 (e), 154.14 (e), 153.77 (e), 151.89 (e), 150.70 (e), 148.84 (e), 137.60 (e), 137.25 (e), 136.25 (e), 130.67 (e), 130.48 (e), 130.38 (o), 128.96 (o), 128.79 (o), 128.70 (o), 128.59 (o), 128.48 (o), 128.41 (o), 128.11 (o), 128.00 (o), 127.81 (e), 127.55 (o), 127.30 (o), 125.64 (e), 122.44 (e), 117.89 (o), 109.01 (o), 105.31 (o), 101.46 (e, OCH_2O), 97.23 (e, OCH_2O), 69.89 (e, 2 C, OCH_2Ph), 66.91 (e, spiro carbon), 62.98 (o, OCH_3), 57.99 (o, OCH_3), 56.83 (o, OCH_3), 56.70 (o, OCH_3), 35.53 (e, CH_2Ar), 32.95 (e, CH_2CH_2Ar); IR (film) ν_{max} 3418, 2936, 1702, 1592, 1460, 1342, 1266, 1154, 1048 cm^{-1}; EIMS, m/e (relative intensity) 690 (M^+, 1), 523 (4), 477 (3), 388 (2), 91 (base), 45 (62); CIMS (2-methylpropane), m/e 691 (M^+ + H, 95), 92 (base); CIHRMS, m/e calcd for $C_{41}H_{38}O_{10}$ 691.2543, found 691.2536.

2′,3′-Dihydro-7′-hydroxy-6-methoxy-1*H*-indene-1′-spiro-2-[4,9-dihydroxy-2*H*-benz[*f*]indene-1,3,5,8-tetrone] (2). A solution of **17** (13 mg, 0.02 mmol) in methylene chloride (1 mL) at −78 °C was treated with a solution of boron tribromide in methylene chloride (Aldrich; 1 M; 96 μL, 0.10 mmol), and the reaction mixture turned red upon the addition. The solution was stirred at −78 °C for 40 min, quenched with the addition of water (2 mL), diluted with 10% aqueous hydrochloric acid (5 mL), and extracted with ether (2 × 5 mL). The combined ether extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 6 cm × 3 cm, ethyl acetate:methylene chloride:acetic acid = 20:20:1 (eluant)) afforded 5.8 mg (7.8 mg the-

oretical, 74%) of **2** as a dark red solid: mp >250 °C (CH_2Cl_2:hexane = 1:1); ^1H NMR ($CDCl_3$ + 1 drop of AcOH, 500 MHz) δ 13.18 (1 H, s, C-9 OH), 12.54 (1 H, s, C-4 OH), 7.10 (1 H, m, C-5′ H), 6.91 (1 H, d, J = 7.6 Hz, C-4′ H), 6.45 (1 H, d, J = 7.9 Hz, C-6′ H), 6.29 (1 H, s, C-7 H), 4.02 (3 H, s, OCH_3), 3.26 (2 H, t, J = 7.3 Hz, C-3′ H), 2.51 (2 H, t, J = 7.3 Hz, C-2′ H); ^{13}C NMR ($CDCl_3$ + 1 drop of CF_3CO_2D, 150 MHz) δ 201.31 (CO, C-1), 200.79 (CO, C-3), 189.02 (CO, C-8), 183.59 (CO, C-5), 161.55, 153.34, 150.99, 150.95, 149.07, 136.79, 135.13, 131.21, 131.11, 126.77, 118.58, 117.99, 113.49, 111.23, 65.72 (spiro carbon), 57.73 (OCH_3), 35.81 (CH_2), 32.63 (CH_2): IR (KBr) ν_{max} 3442, 2950, 1748, 1714, 1612, 1420, 1294 cm^{-1}; UV (H_2O) λ_{max}, nm (ε) (pH 11.9) 732 (7480), 250 (33 120), (pH 6.9) 630 (5670), 246 (20 980, sh), (pH 2.1) 504 (7540), 296 (7960 sh), 250 (27 780), 234 (28 820); EIMS, m/e (relative intensity) 406 (M^+, 38), 390 (7, $M^+ - CH_4$), 375 (4, $M^+ - OCH_3$), 363 (7), 275 (6), 247 (5), 91 (base), 77 (40), 57 (68); CIMS (2-methylpropane), m/e 409 ($M^+ + H + 2$ H, base, hydroquinone form); FABHRMS (glycerol, $M^+ + H + 2H$), m/e calcd for $C_{22}H_{16}O_8$ 409.0923, found 409.0922.

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Supplementary Material Available: Table summarizing the results of a study of the benzannulation of **10** and **11** and ^1H NMR spectra of **12**, **13**, **15–17**, and **2** (7 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis of S-1452, an Orally Active Potent Thromboxane A_2 Receptor Antagonist

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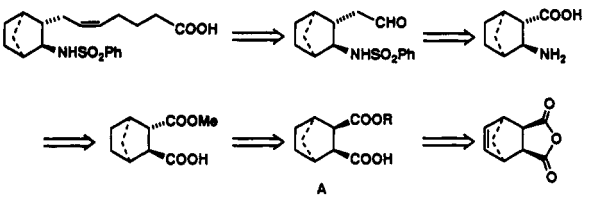
An efficient and extremely practical enantioselective fission of pro-chiral bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride was applied to the asymmetric synthesis of the potent and orally active thromboxane A_2 (TXA_2) receptor antagonist, S-1452. The lithium salt of (*R*)-(−)-benzylmandelate was employed as a chiral ligand, giving a crystalline key intermediate **3** of which the chemical purity was 100.0% after crystallization. Epimerization and the methanolysis process of **3** afforded the half ester **4**, which was transformed into S-1452.

Introduction

TXA_2 is a very potent inducer of human platelet aggregation and vascular smooth muscle contraction and has been considered to be an important endogenous mediator of circulatory disorders including angina pectoris, thrombosis, and asthma. Therefore, TXA_2 receptor antagonists may be very important compounds for the treatment of such diseases.[1] Among the number of TXA_2 receptor antagonists, S-145, *dl*-(5*Z*)-7-(3-*endo*-(phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-*exo*-yl)heptenoic acid, has proved to be a very potent and novel therapeutic agent having long lasting biological activity.[2] Initially, S-145 had been developed as a racemate, and later the difference of biological activity and binding affinity to TXA_2/PGH_2 receptor between the *d* isomer and *l* isomer has been studied extensively.[3] The *d* isomer was found to be several to 20 times more potent than the *l* isomer, exhibiting higher binding affinity to the receptor. Although the potent *d* isomer can be synthesized by the use of the classical optical resolution method,[4] a practical large-scale synthesis of the *d* isomer became necessary for further development.

Chart I. Retrosynthesis of S-1452



Recently, S-1452, calcium (1*R*,2*S*,3*S*,4*S*)-(5*Z*)-7-(((phenylsulfonyl)amino)bicyclo[2.2.1]hept-2-yl)hept-5-enoate, has been established as being suitable as a chemically stable and orally active compound.[5] We therefore tried to develop a new method to produce S-1452 with high optical purity on a large scale. As shown in Figure 1, S-1452 has a structure analogous to prostaglandin H_2[6] except that the ω-side chain is modified to the (phenylsulfonyl)amino group and the nuclear oxygens to carbons. Thus, it would be desirable to obtain optically active

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