$C_{22}H_{36}Br_2$). An analytical sample was prepared by recrystallization from hexane. Anal. Calcd for $C_{22}H_{36}Br_2$: C, 57.39; H, 7.83; Br, 34.78. Found: C, 57.97; H, 7.96; Br, 34.35.

The product mixture (rf values 0.5 (**2a**) and 0.4 (**2b**) by analytical TLC, eluent hexane) was subjected to HPLC, using 3% ethyl acetate-hexane (v/v) as eluent. This procedure resulted in the isolation of pure **2a** in addition to unidentified decomposition products of the other isomer. After recrystallization from benzene, **2a** had mp 203-205 °C dec. ^{1}H NMR δ 1.04-1.47 (multiplet of doublets, 24 H, $CH(CH_3)_2$), 2.06 (d, 3 H, J = 6.98 Hz, $CHBrCH_3$), 2.15 (d, 3 H, J = 7.35 Hz, $CHBrCH_3$), 3.62-3.79 (m, 3 H, $CH(CH_3)_2$), 4.46 (septet, 1 H, J = 7.19 Hz, $CH(CH_3)_2$), 6.07 (q, 1 H, J = 7.32 Hz, $CHBrCH_3$), 6.89 (q, 1 H, J = 6.99 Hz, $CHBrCH_3$). See also Figure 6. ^{13}C NMR δ 21.50, 22.49, 22.59, 22.71, 22.77, 23.16, 23.37 ($CH(CH_3)_2$), 26.17, 26.71 ($CHBrCH_3$), 27.81, 28.19 ($CH(CH_3)_2$), 47.49, 47.73 ($CHBrCH_3$), 139.04, 140.41, 144.67, 147.81, 148.11, 149.23 (aromatic carbons).

Both diastereomers decompose slowly in $CHCl_3$ or CH_2Cl_2 solutions, and more rapidly in tetrachloroethene or on exposure to light. They are relatively stable in CCl_4 or hydrocarbon solutions, but repeated recrystallization of the mixture invariably resulted in preferential decomposition of **2b**.

Dipole moments were determined for two solutions of mixtures of **2a** and **2b** in benzene at room temperature.[42] Mixtures containing 64 and 84% of **2a** had μ = 2.92 and 2.81 D, respectively. The calculated dipole moments of **2a** and **2b** are therefore 2.72 and 3.25 D, respectively.[43]

Acknowledgment. We thank Mary W. Baum for technical assistance, Alberto Gutierrez and Roman Gancarz for stimulating discussions, the Grace Chemical Company for a Fellowship to J.S., the National Science Foundation for support of this work.

(42) We thank Professor E. N. DiCarlo for these measurements.

(43) Dipole moments calculated by the empirical force field method (MM2) are 1.71 and 3.45 D for (1'*RS*,2'*SR*)- and (1'*RS*,2'*RS*)-**2**, respectively.

Total Synthesis of (±)-Granaticin

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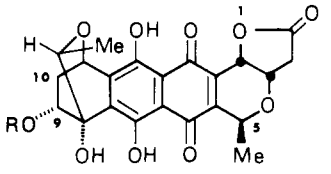
Abstract: A 20-step total synthesis of (±)-granaticin from tetralone **8** is described. Conversion of **8** to allylic alcohol **15** followed by a catalytic osmylation afforded triol **16** in a highly stereoselective manner, which was then cyclized to benzooxabicycle **18** through the agency of benzylic bromination with NBS. The intermediate **18** was efficiently converted to cyanophthalide **22**, and its annulation with 5-*tert*-butoxy-2-furfurylideneacetone afforded naphthyl ketone **25**. Reduction of **25** to a carbinol and subsequent pyranocyclization provided a diastereomeric mixture of hexacyclic compounds, **26a,b** and **27a,b**, which could be separated by HPLC. The predominant isomers **26a** and **26b**, whose structures were determined by X-ray crystallography and NMR spectroscopy, were subjected to two-step *O*-demethylation (oxidation with ceric ammonium nitrate to dimethoxy-1,4-naphthoquinones and subsequent treatment with $AlCl_3$-Et_2S) to provide (±)-granaticin (**1**) and its diastereomer **30**, respectively.

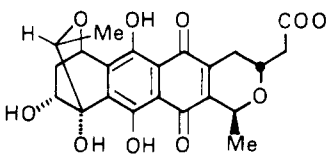
The antibiotic granaticin (**1**) was first isolated in 1957 from the culture of *Streptomyces olivaceus*[1a] and since has been detected in a number of other actinomycetes along with granaticin B (**2**),[1b] the α-L-rhodinoside of **1**, and dihydrogranaticin (**3**).[1c-e,2] Granaticin is highly active against Gram-positive bacteria and protozoa and exhibits some activity against P-388 lymphocytic leukemia in mice (T/C 166% at 1.5 mg/Kg) and cytotoxicity against KB cells (ED_{50} 1.6 μg/mL).[1d,3] The glycoside **2** shows a distinct inhibition of various transplanted tumors in rodents after intraperitoneal application.[4] Granaticin has been reported to inhibit RNA synthesis in bacteria by the failure to charge leucyl-*t*RNA.[5a] The cytotoxicity of **1** is attributed to inhibition of ribosomal RNA maturation.[5b]

A novel feature of the molecular structure of **1**, which had been determined by a combination of chemical degradations and an X-ray crystallographic analysis in 1968,[6] is the attachment of two



1, R = H

2, R =



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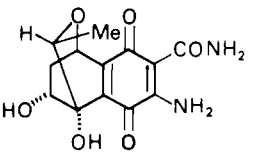

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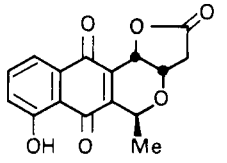

5

oxygen-containing heterocycles at each side of the naphthazarin ring. These residues, the 2-oxabicyclo[2.2.2]oct-5-ene system

(1) (a) Corbaz, R.; Ettlinger, L.; Gäumann, E.; Kalvoda, J.; Keller-Schierlein, W.; Kradolfer, F.; Manukian, B. K.; Neipp, L.; Prelog, V.; Reusser, P.; Zähner, H. *Helv. Chim. Acta* **1957**, *40*, 1262-1269. (b) Barcza, S.; Brufani, M.; Keller-Schierlein, W.; Zähner, H. *Ibid.* **1966**, *49*, 1736-1740. (c) Pyrek, J. St.; Mordarski, M.; Zamojski, A. *Arch. Immunol. Ther. Exp.* **1969**, *17*, 827-832. (d) Chang, C.-j.; Floss, H. G.; Soong, P.; Chang, C.-t. *J. Antibiot.* **1975**, *28*, 156. (e) Pyrek, J. St.; Achmatowicz, O., Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673-680.

(2) *The Merck Index*, 10th ed.; Windholz, M.; Budavari, S.; Blumetti, R. F.; Otterbein, E. S., Eds.; Merck & Co., Inc.: NJ, 1983; p 4408.

(3) Krzywy, T.; Mordarski, M.; Orlowska, B.; Tkaczowa, A. *Arch. Immunol. Ther. Exp.* **1969**, *17*, 63-71.

(4) Sethi, M. L. *J. Pharm. Sci.* **1977**, *66*, 130-132 (footnote 1).

(5) (a) Ogilvie, A.; Wiebauer, K.; Kersten, W. *Biochem. J.* **1975**, *152*, 511, 517. (b) Heinstein, P. *J. Pharm. Sci.* **1982**, *71*, 197-200.

(6) (a) Keller-Schierlein, W.; Brufani, M.; Barcza, S. *Helv. Chim. Acta* **1968**, *51*, 1257-1268. (b) Brufani, M.; Dobler, M. *Ibid.* **1968**, *51*, 1269-1275.

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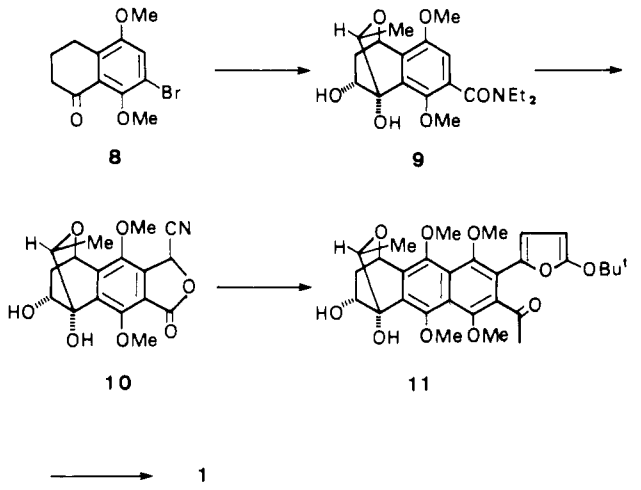
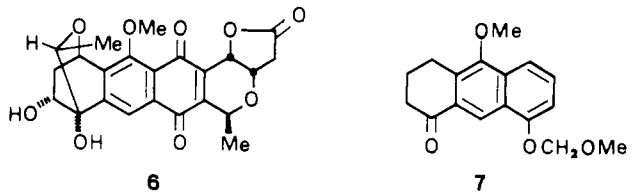
Scheme I



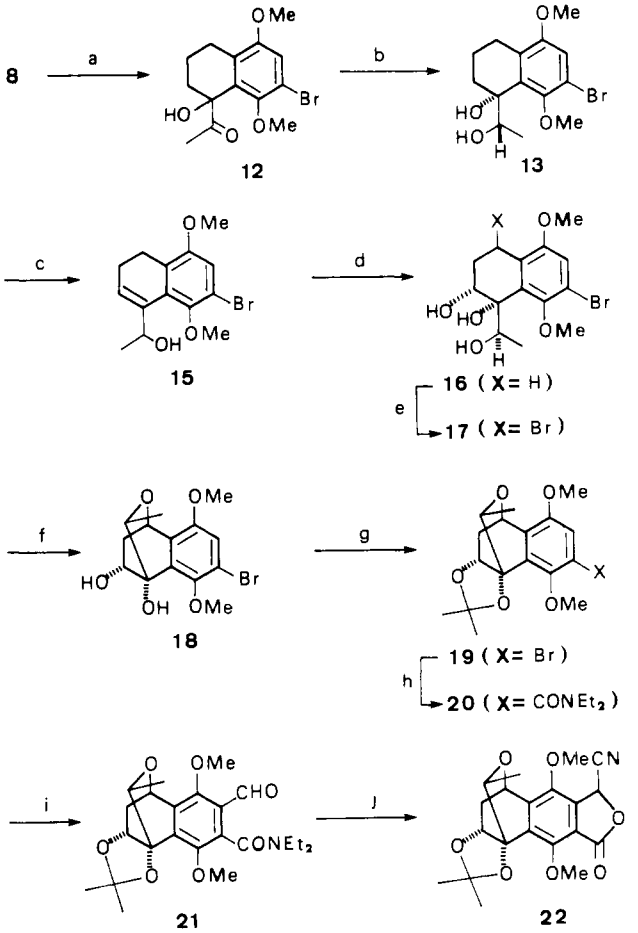
derived from a *C*-glycoside[7] and the pyrano-γ-lactone ring, are the same as those found with sarubicin A (U 58431) (**4**)[8] and nanaomycin D[9a] (**5**, the enantiomer of kalafungin[10]), respectively. Our own interest in **1** as a synthetically challenging target led us to embark on a program directed toward its total synthesis in mid 1981. To date we have developed a highly stereoselective synthetic method for construction of the oxabicyclic ring system[11] and achieved the first total synthesis of (±)-**4**.[12] We then progressed very recently to a synthesis of the granaticin analogue **6**[13] from



the anthracenone **7** which was prepared from 1,8-dihydroxyanthraquinone (chrysazin). However, all attempts at the transformation of **6** into **1** were unsuccessful due to sensitivity of the oxabicycle to conventional *O*-demethylation methods. Our continued efforts focussed on a modified strategy have now yielded the first total synthesis of (±)-**1**, which is the subject of this article.

The synthetic plan, which utilizes the tetralone **8** as starting material, involves the key transformations outlined in Scheme I: (1) a highly stereoselective synthesis[11] of the 5,6-benzo-2-oxabicyclo[2.2.2]oct-5-ene derivative **9**; (2) transformation of **9** into the tetracyclic cyanophthalide **10** and subsequent annulation[14,15b] with 5-*tert*-butoxy-2-furfurylideneacetone[16] leading to the intermediate **11**; (3) formation of the pyrano-γ-lactone ring according to the method of Kraus.[15]

Scheme II[a]



[a] (a) CH_2=C(OMe)Li, THF, −60 °C; HCl-MeOH (90%); (b) $NaBH_4$, 2-propanol (ca. 100%); (c) Ac_2O, pyridine; $SOCl_2$, pyridine; KOH-MeOH (65%); (d) $Me_3N(O)$, catalytic OsO_4, *tert*-butyl alcohol-H_2O, 60 °C (65%); (e) NBS, CCl_4, AIBN, 40 °C; (f) $AgClO_4$, THF (65% from **16**); (g) CH_2=C(OMe)Me, camphorsulfonic acid, THF, room temperature (97%); (h) *n*-BuLi, THF, −100 °C; ClCONEt$_2$, −70 °C (90%); (i) *t*-BuLi, THF, −75 °C; DMF, 0 °C (96%); (j) Me_3SiCN, KCN-18-crown-6, CH_2Cl_2; HOAc, room temperature; CH_2=C(OMe)Me, camphorsulfonic acid, THF, room temperature (84%).

Results and Discussion

Reaction of **8**[17] with lithiated methyl vinyl ether[18] followed by brief acid-treatment of the reaction product afforded α-ketol **12** in 90% yield (Scheme II).[19] This material was then reduced with sodium borohydride to afford diol **13** as a 1:9 mixture of diastereomers.[20] Regioselective dehydration of **13** to allylic alcohol

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(14) (a) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263–2266. (b) Li, T.; Wu, Y. *J. Am. Chem. Soc.* **1981**, *103*, 7007–7009. (c) Li, T.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741–3744. (d) Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 637–639. (e) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318–325. (f) Freskos, J. N.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1985**, 658–659.

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(18) Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125–7127.

(19) All compounds are racemic. One enantiomer corresponding to **1**[6] is depicted for graphic simplicity.

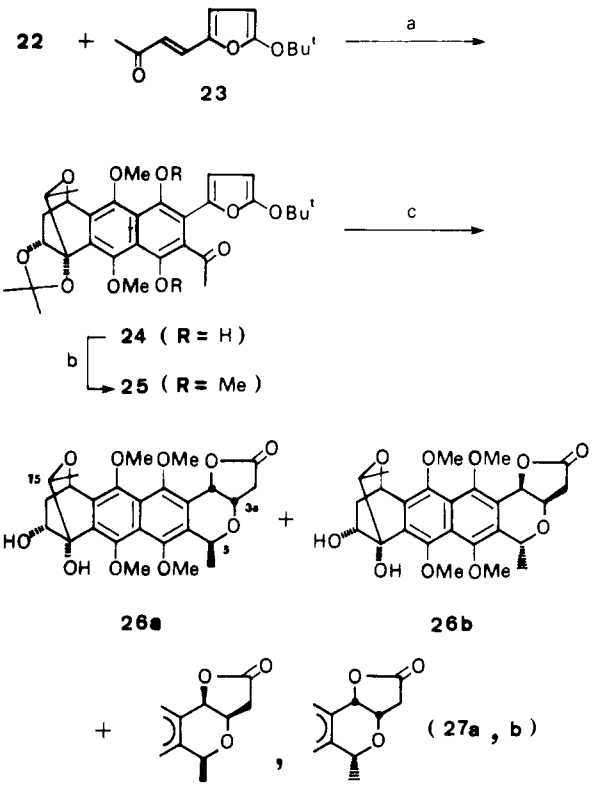
15 was first attempted by use of acid catalysts (e.g., trifluoroacetic acid or camphorsulfonic acid in dichloromethane or benzene).[11b] However, the yields of **15** were unacceptable (<20%) due to concomitant formation of 1-acetyltetralone and 1-ethylnaphthalene derivatives in considerable amounts. Therefore, we turned to utilization of the following conventional three-step reaction: formation of monoacetate **14**, dehydration of **14** with thionyl chloride in the presence of pyridine, and hydrolysis of the resultant allylic acetate, affording **15** in 65% yield from **13**. Catalytic osmylation of **15** using trimethylamine *N*-oxide as a cooxidant[22] and in aqueous *tert*-butyl alcohol at 60 °C produced a 25:1 mixture of the triol **16** and its 1′-epimer in 80% yield.[21] The pure (1*R**,2*R**,1′*R**) diastereomer **16** was readily obtained by recrystallization of the mixture from *i*-Pr_2O-AcOEt in 65% yield from **15**. Transformation of **16** into the oxabicycle **18** was nicely achieved according to the technique that we had previously established.[11] Thus, treatment of **16** in dry carbon tetrachloride (1.5×10^{-2} M) with *N*-bromosuccinimide at 40 °C in the presence of azobisisobutyronitrile (AIBN) afforded the benzylic bromination product **17** (contaminated with a small amount of cyclized product **18**), which on treatment with 1 equiv of silver perchlorate in THF at room temperature afforded **18** in 60–67% chromatographed yields. The stereochemistry of **18** as depicted in Scheme II was determined by ^{1}H NMR spectroscopy. Resonance of the methyl protons on the oxabicycle was observed at 0.86 ppm (d, J = 6.2 Hz), indicating a shielding by the benzene ring, to which the methyl group is projecting.[11a] Replacement of the bromine atom in **18** with the *N*,*N*-diethylcarbamoyl group was carried out on its acetonide **19** by sequential treatment with 1 equiv of *n*-butyllithium at −100 °C and 3 equiv of diethylcarbamoyl chloride (−70 °C to room temperature) to afford **20** in 90% yield from **18**.

Transformation of the amide **20** into cyanophthalide **22**, which is the second key stage in our synthetic plan (Scheme I), was begun with introduction of a formyl group onto the free position of the aromatic ring. When compound **20** was treated with 3 equiv of *tert*-butyllithium (−80 to 0 °C) and then with 4 equiv of *N*,*N*-dimethylformamide, there was obtained aldehyde **21** in 96% yield based on 47% recovered starting material. Use of lesser amounts of the lithiation reagent resulted in a dramatic decrease in product yield. Next, compound **21** was allowed to react with trimethylsilyl cyanide in the presence of KCN-18-crown-6 complex in dichloromethane (ca. 10 min),[23] and the resultant (*O*-trimethylsilyl)cyanohydrin was, without purification, kept in acetic acid at room temperature for 12 h. By extractive workup followed by exposure of the product to 2-methoxypropene, there was obtained the cyanophthalide **22** in 84% yield as a 1:1 diastereomeric mixture. This method for the synthesis of cyanophthalides from *O*-formyl-*N*,*N*-diethylbenzamides has advantage over the reported methods[24] because of the mildness of the reaction conditions as well as the higher yields obtainable. Additional examples to show the generality of this improved procedure will be reported elsewhere.

With the key intermediate **22** in hand, we proceeded with Kraus' benzannulation[14] of **22** by using 5-*tert*-butoxy-2-furfurylideneacetone (**23**)[16] as a Michael acceptor (Scheme III).[19] After extensive investigation of the reaction conditions, the following procedure was found to be best in terms of product yield and reproducibility of the reaction. Treatment of **22** with 3.3 equiv of $LiCH_2SOCH_3$ in THF in the presence of 3.0 equiv of *tert*-butyl alcohol and then with 3.3 equiv of **23** (−78 to 25 °C) provided naphthyl ketone **24** in 87% yield. *O*-Methylation of **24** with dimethyl sulfate and potassium carbonate in refluxing acetone proceeded smoothly to afford **25** in 77% yield.

The pyrano-γ-lactone annulation with **25** according to a modification[16] of the Kraus protocol[15] was now commenced by reduction of the ketone functionality with lithium aluminum hydride. A carbinol product obtained in quantitative yield was subjected to exposure to 1 equiv of *p*-toluenesulfonic acid in acetonitrile (0 °C, ca. 20 min), and the resulting γ-naphthylbutenolide intermediate[15] was, immediately after extractive isolation, treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at −10 °C. By this sequence of reactions, there was obtained a mixture of four pyrano-γ-lactones bearing the granaticin skeleton. The mixture was cleanly separated by preparative high-performance chromatography (10μ silica gel) to afford **26a** (32%), **26b** (26%), **27a** (4.7%), and **27b** (2.9%) in the overall yields

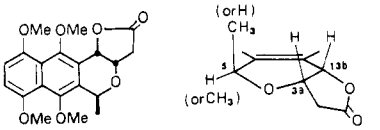
Scheme III[a]



[a] (a) $LiCH_2SOMe$-*t*-BuOH, THF, −78 °C to room temperature (87%); (b) Me_2SO_4, K_2CO_3, acetone, reflux (77%); (c) $LiAlH_4$, Et_2O, −15 °C; TsOH, MeCN, 0 °C; DBU, PhMe, −10 °C (**26a**, 32%; **26b**, 26%; **27a,b**, 7.6%).

Table I. ^{1}H NMR (270 MHz) Data of the Pyrano-γ-lactone Portion of **26a,b**, **27a,b**, and Compound A

	δ ppm ($CDCl_3$)			
compd	C(13b)–H	C(3a)–H	C(5)–H	C(5)–CH_3
26a	5.59	4.77	5.40	1.60
26b	5.59	4.77	5.39	1.58
27a	5.64	4.39	5.06	1.74
27b	5.62	4.41	5.15	1.76
A	5.59	4.73	5.36	1.55



A

Partial structures of 26a and its C(5)-epimer

(20) The major and less polar isomer was assigned a (1*R**,1′*S**) configuration as depicted in the scheme based on a cyclic model for the α-ketol system in the hydride reduction. Brown's acetoxymercuration–demercuration on the 1-hydroxy-1-vinyl derivative of 7-bromo-5,8-dimethoxytetralone produced (1*R**,1′*R**)-diol as a major product.

(21) For rationalization of the stereochemical outcome, see: ref 12a, footnote 16.

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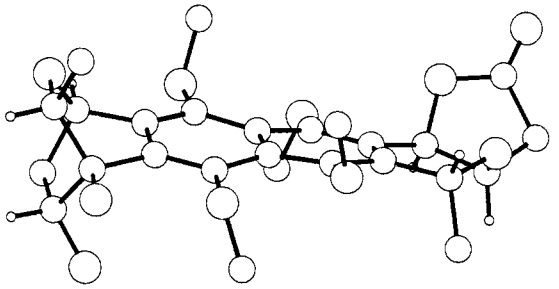


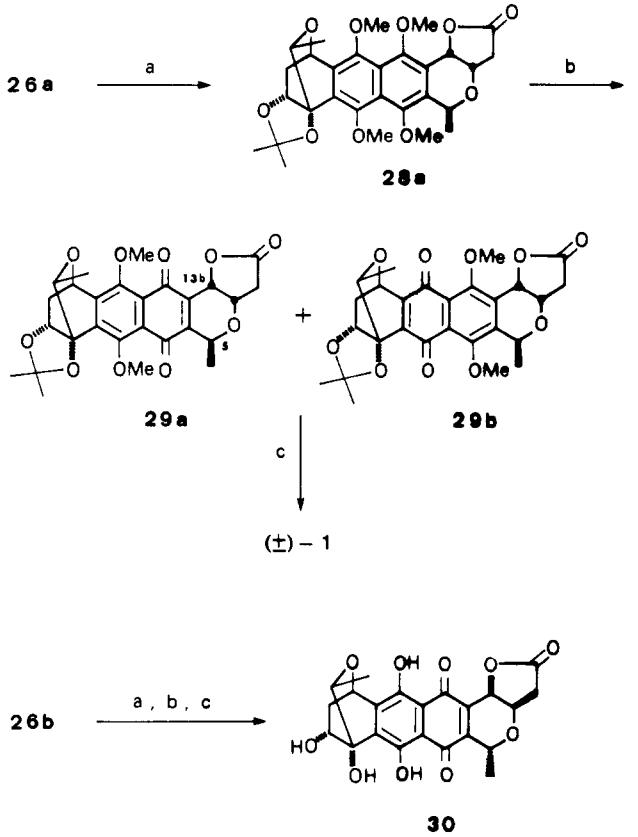
Figure 1. Perspective drawing of compound **26b**.

indicated in parentheses.[25] Assignment of the major two isomers **26a,b** to 3a,5-trans and the minor two **27a,b** to 3a,5-cis stereochemistry, respectively, was made on the basis of 270-MHz ^{1}H NMR analysis. Significant differences in the chemical shifts of C(3a)–H and C(5)–H, which support the stereochemical assignments, are listed in Table I together with the data of a reference compound A.[16] Differentiation between **26a** and **26b** was made by X-ray crystallography of **26b**, the isomer which gave crystals suitable for the analysis. The perspective drawing of **26b** is given in Figure 1.

Conversion of the tetramethoxynaphthalene nucleus of **26a** to a naphthazarin system, the final stage in the total synthesis, was initiated by oxidative *O*-demethylation. The 1,2-diol group, which is sensitive toward oxidation, was protected as the acetonide **28a** (Scheme IV).[19] This substance, obtained in 97% yield, was treated with ceric ammonium nitrate[26] in acetonitrile to afford an inseparable mixture of regioisomeric naphthoquinones **29a** and **29b** (ratio, 5:1) in quantitative yield. The major isomer was assigned structure **29a** on the basis of significant upfield shifts of the H-13b and H-5 resonances on the pyran ring compared to those for **28a** (0.27 and 0.41 ppm, respectively).[9b,13] Separation of the isomers, however, is of no consequence since, on ensuing *O*-demethylation, they should give the same product due to the tautomeric nature of the naphthazarin system.[27]

At this point we encountered difficulties in *O*-demethylation of **29a**. Initial attempts employing boron halides (e.g., BBr_3, BBr_3–Me_2S complex,[28] BCl_3) resulted in complete destruction of the oxabicycle to give a complex mixture of products.[29] Attempted nucleophilic demethylation with lithium methylthiolate led instead to reaction at the γ-lactone, not unexpectedly;[30] oxidative demethylation with AgO[31] was also unsuccessful. Success was finally realized with the use of 6 molar equiv of $AlCl_3$–Et_2S complex[32,33] in dichloromethane at ambient temperature to furnish a water-soluble aluminum complex;[32] from its carmine aqueous solution there was obtained essentially pure (±)-granaticin, in 82% yield from **28a**, after extraction with chloroform under acidic conditions. The synthetic (±)-**1** was identical with a sample of natural granaticin in the ^{1}H NMR and UV spectra and R_f values (TLC). The diastereomer **30** was also prepared in a similar yield from **26b** by employing the same sequence of reactions and was readily distinguishable from **1** by TLC by using KH_2PO_4 impregnated silica gel (R_f: **1**, 0.38; **30**, 0.28; with AcOEt). However, the ^{1}H NMR spectra of both compounds (270 MHz) were quite similar; the resonance signals different from each other in more than 0.01 ppm were only those of C(5)–Me, C(10)–H*endo*, and C(9)–OH [Δ(**1**–**30**) +0.02, +0.03, and ca. −0.05 ppm, respectively].

Scheme IV[a]



[a] (a) CH_2=C(OMe)Me, camphorsulfonic acid, THF, 25 °C (97%); (b) ceric ammonium nitrate, MeCN, 25 °C (ca. 100%, **29a**/**29b** = 5); (c) $AlCl_3$–Et_2S, CH_2Cl_2, room temperature; 1% HCl (82% from **28a**).

In summary, we have achieved the first total synthesis of racemic granaticin, in 20 steps from tetralone **8** (ca. 2% overall yield), which features stereocontrolled syntheses of the oxabicycle and pyrano-γ-lactone systems and an efficient use of a cyanophthalide annulation.

Experimental Section[34]

1-Acetyl-7-bromo-1-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (12). A stirred solution of methyl vinyl ether (19.3 g, 0.33

(25) The suffix a refers to the less polar isomer. No stereostructural assignment for **27a** and **27b** has been made.

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(29) Although the first indication of the desired *O*-demethylation was obtained in the reaction of BBr_3 with the corresponding hydroquinones (CH_2Cl_2, −80 to −50 °C), the unacceptable yields of (±)-**1** (<15%) could not be improved, the serious side reactions being again a competitive attack of the reagent on the oxabicycle.

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(34) **General.** Infrared spectra were recorded on a Jasco IRA-1 grating spectrometer. Proton NMR spectra were obtained at 270 MHz (with a JEOL GX-270), unless otherwise indicated as 60 MHz (with a JEOL PMX-60). Chemical shifts in $CDCl_3$ solution are reported in δ values in parts per million relative to tetramethylsilane as an internal standard. Mass spectra (EI) were obtained on a JEOL JMS-D-300 spectrometer with a JMA-1000 data processing system. Liquid chromatography under medium and high pressures was carried out with UVILOG Model ALPC-100 and Waters Model 6000A chromatographs by using Fuji-Davison BW-200 silica gel (150–325 mesh) and Kusano 10μ silica gel, respectively. KH_2PO_4 coated silica gel for column chromatography was obtained by treating E. Merck silica gel 60 (230–400 mesh) with 1% aqueous KH_2PO_4 followed by drying at 130 °C.[1e,35] Dry solvents and reagents were obtained by using standard procedures. Anhydrous magnesium sulfate was used for drying organic solvent extracts unless otherwise noted, and removal of the solvents was performed with a rotary evaporator and finally under high vacuum. Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Elemental combustion analyses were performed by M. Ogawa of the Instrument Center of this university.

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mol) in dry THF (300 mL) under nitrogen was cooled to −75 °C, and a pentane solution of *t*-BuLi (1.36 M, 117 mL, 0.16 mol) was added over 2 min. The orange mixture was allowed to warm to 0 °C, and then stirring at the same temperature was continued for 1.5 h. The resulting colorless solution was cooled to −75 °C again, and, after addition of a solution of **8**[17] (28.5 g, 0.10 mol) in dry THF (150 mL) during 5 min, the reaction mixture was stirred at −60 to −70 °C for 30 min, when the starting material was not detected by TLC. After quenching at −60 °C by addition of saturated aqueous NH_4Cl (500 mL), the mixture was extracted with ether (200 mL × 3). The combined ether extracts were washed with brine (200 mL × 3), dried, and concentrated in vacuo to give a viscous oil (34.0 g). This material was dissolved in methanol (475 mL), and the solution was treated with 2% HCl (4.5 mL) at 20 °C for 40 min. After addition of saturated aqueous $NaHCO_3$ (50 mL), the bulk of the methanol was removed in vacuo, and the residue was extracted with AcOEt (200 mL × 3). After washing with water and drying, the organic extract was concentrated in vacuo. The residual solid dissolved in benzene was filtered through a column of silica gel (60 g) to give **12** (29.7 g, 90%) as a pale yellow solid. An analytical sample was obtained by recrystallization from *i*-Pr_2O–hexane to give colorless cubes, mp 101–102 °C: IR (KBr) 3420, 2950, 1720, 1705 cm^{-1}; ^1H NMR δ 2.08 (3 H, s), 3.73, 3.83 (each 3 H, s), 4.53 (1 H, s), 6.97 (1 H, s); MS, *m/e* 330, 328 (M^+), 287, 285 (base peak), 272, 270. Anal. Calcd for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.21. Found: C, 50.96; H, 5.33.

7-Bromo-1-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (15). To a stirred solution of **12** (26.9 g, 81.8 mmol) in 2-propanol (520 mL) at 20 °C was added a solution of $NaBH_4$ (19.2 g, 0.51 mol) in water (350 mL). After 4 h, the mixture was cooled with ice–water and acidified by addition of 10% HCl. The mixture was extracted with AcOEt (200 mL × 3) after removal of the bulk of 2-propanol in vacuo. The combined extracts were concentrated in vacuo, and a solution of the residual oil in methanol (400 mL) was treated with 20% NaOH (340 mL) at 20 °C for 1.5 h. The resulting suspension was concentrated in vacuo to remove the bulk of methanol and extracted with dichloromethane (200 mL × 3). The combined extracts were washed with water, dried, and concentrated in vacuo to give crude diol **13** as a white solid (27.8 g) [^1H NMR (60 MHz) (major diastereomer)[20] δ 1.10 (3 H, d, *J* = 6.5 Hz), 3.80, 3.96 (each 3 H, s), 6.93 (1 H, s); (minor isomer)[20] 0.95 (1 H, d, *J* = 6.5 Hz), 3.80, 3.96 (each 3 H, s), 4.48 (1 H, q, *J* = 6.5 Hz), 6.93 (1 H, s)]. This material dissolved in pyridine (50 mL) was treated with acetic anhydride (28 mL) overnight at room temperature. The monoacetate **14** (29.9 g, a white solid) obtained after the usual workup was used for the next step without purification. The major isomer could be isolated by recrystallization from *i*-Pr_2O, mp 105–106 °C (65% yield from **12**): ^1H NMR (60 MHz) δ 1.37 (3 H, d, *J* = 7 Hz), 1.77 (3 H, s), 3.80 (3 H, s), 4.08 (3 H, s), 4.73 (1 H, s), 5.33 (1 H, q, *J* = 7 Hz), 6.96 (1 H, s).

A portion of the crude **14** (11.2 g, 30 mmol) in dry pyridine (33 mL) was stirred and cooled with ice–water, and to the solution was added $SOCl_2$ (2.7 mL, 37 mmol) dropwise. After 20 min, the resulting pale yellow suspension was treated with crushed ice and then with 10% HCl (350 mL), and the whole was extracted with AcOEt (100 mL × 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ and water (100 mL × 2), dried, and concentrated in vacuo to give a pale red oil (10.9 g). This material (crude *O*-acetate of **15**) was refluxed with 5% methanolic KOH (120 mL) for 1 h. The mixture was extracted with AcOEt after dilution with brine (300 mL). The extract was washed with brine (200 mL × 2), dried, and concentrated in vacuo. The residual oil was subjected to chromatography (silica gel, 145 g; elution with 1:9 AcOEt–benzene) to give **15** (6.26 g, 65% from **13**) as a solid, which was recrystallized from *i*-Pr_2O to give colorless needles, mp 120–121 °C: IR (KBr) 3430, 1560 cm^{-1}; ^1H NMR δ 1.37 (3 H, d, *J* = 6.2 Hz), 1.83–2.33 (2 H, m), 2.33–2.73 (3 H, m), 3.70, 3.80 (each 3 H, s), 5.07 (1 H, qm, *J* = ca. 6 Hz), 6.40 (1 H, tm, *J* = ca. 5 Hz), 6.97 (1 H, s); MS, *m/e* 314, 312 (M^+), 296, 294 (base peak), 281, 279. Anal. Calcd for $C_{14}H_{17}O_3Br$: C, 53.69; H, 5.47. Found: C, 53.63; H, 5.47.

(1*R,2*R**)-7-Bromo-1-[(*R**)-1-(hydroxyethyl)]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol (16).** To a stirred solution of **15** (9.39 g, 30.0 mmol) in *t*-BuOH (90 mL) and water (27 mL) were added $Me_3N(O)$ dihydrate (3.33 g, 30.0 mmol) and OsO_4 (ca. 10 mg), and the mixture was heated at 60 °C for 9 h, during which time an additional amount of the *N*-oxide (1.67 g, 15 mmol) was added every hour. The resulting dark brown mixture was cooled and, after treatment with a solution of $NaHSO_3$ (23 g) in water (300 mL) for 10 min, extracted with AcOEt (150 mL × 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 145 g; elution with 1:4 AcOEt–benzene) to afford a solid (8.38 g, 80%): a 25:1 mixture of **16** and its diastereomer as determined by integration of the C-methyl doublets at 0.98 and 1.06 ppm in the 270-MHz ^1H NMR spectrum. Pure **16** (6.73 g, 65%) was obtained by recrystallization of the mixture from *i*-Pr_2O–AcOEt as a white solid, mp 109–110 °C: IR (KBr) 3450 cm^{-1}; ^1H NMR δ 0.98 (3 H, d, *J* = 6.6 Hz, C-Me), 1.8–2.0 (2 H, m, H-3), 2.43 (1 H, ddd, *J* = 18.1, 8.4, 6.2 Hz, H-4), 2.87 (1 H, dt, *J* = 18.1, 6.1 Hz, H-4), 3.78, 3.94 (each 3 H, s, OMe), 4.19 (1 H, dd, *J* = 8.4, 3.9 Hz, H-2), 4.54 (1 H, br s, OH), 4.77 (1 H, q, *J* = 6.6 Hz, H-1′), 6.95 (1 H, s, H-6). MS, *m/e* 348, 346 (M^+), 285 (base peak), 283. Anal. Calcd for $C_{14}H_{19}O_5Br$: C, 48.43; H, 5.52. Found: C, 48.50; H, 5.45.

(1*R,2*R**,4*S**,10*R**)-7-Bromo-5,8-dimethoxy-10-methyl-1,2,3,4-tetrahydro-4,1-(epoxymethano)naphthalene-1,2-diol (18).** A solution of **16** (1.74 g, 5.00 mmol) and cyclohexene oxide (1.0 mL) in dry CCl_4 (340 mL) was stirred and warmed to 40 °C with a sunlamp under constant bubbling with nitrogen gas, and to the mixture were added *N*-bromosuccinimide (recrystallized from water and powdered, 0.93 g, 5.22 mmol) and AIBN (150 mg). After 25 min, the reaction mixture was cooled with ice–water and washed with 1% aqueous $NaHSO_3$ (100 mL) and brine. The organic layer was dried and concentrated in vacuo. The residue (crude **17**) was dissolved in dry THF (30 mL), and the solution was treated with $AgClO_4$ (1.04 g, 5.00 mmol) at room temperature for 15 min before addition of brine (50 mL). The mixture was extracted with AcOEt (50 mL × 3). The combined organic extracts were washed with brine, dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 80 g; elution with 1:2 AcOEt–hexane) to give **18** (1.12 g, 65%) as a viscous oil: IR (film) 3450 cm^{-1}; ^1H NMR δ 0.86 (3 H, d, *J* = 6.2 Hz, Me-10), 1.43 (1 H, dt, *J* = 14.5, 1.8 Hz, H*endo*-3), 2.63 (1 H, br s, OH), 2.70 (1 H, ddd, *J* = 14.5, 8.8, 3.7 Hz, H*exo*-3), 3.77 (1 H, q, *J* = 6.2 Hz, H-10), 3.80, 3.94 (each 3 H, s, OMe), 4.00 (1 H, dd, *J* = 8.8, 1.8 Hz, H-2), 5.13 (1 H, dd, *J* = 3.7, 1.8 Hz, H-4), 5.70 (1 H, s, OH), 7.04 (1 H, s, H-6); MS, *m/e* 346, 344 (M^+), 302, 300 (base peak). Anal. Calcd for $C_{14}H_{17}O_5Br$: C, 48.71; H, 4.96. Found: C, 48.74; H, 5.03.

Acetonide 19. 2-Methoxypropene (4.4 mL, 46 mmol) was added to a cooled (0 °C) solution of **18** (5.02 g, 14.6 mmol) and camphorsulfonic acid (85 mg) in dry THF (75 mL). After being kept at room temperature for 1 h, the mixture was treated with crushed ice and then with saturated aqueous $NaHCO_3$ (20 mL) and brine (100 mL) before extraction with AcOEt. The organic extract was dried and concentrated in vacuo to give **19** as a pale yellow solid (5.44 g, 97%). Recrystallization from hexane afforded pure **19** as colorless needles (4.99 g in two crops, 89%), mp 144–145 °C: ^1H NMR δ 0.81 (3 H, d, *J* = 6.2 Hz, Me-10), 1.49 (1 H, dd, *J* = 12.8, 6.2 Hz, H*endo*-3), 1.55, 1.63 (each 3 H, s, acetonide Me), 2.74 (1 H, ddd, *J* = 12.8, 9.2, 5.1 Hz, H*exo*-3), 3.78, 3.80 (each 3 H, s, OMe), 4.01 (1 H, q, *J* = 6.2 Hz, H-10), 4.26 (1 H, dd, *J* = 9.2, 6.2 Hz, H-2), 5.25 (1 H, d, *J* = 5.1 Hz, H-4), 7.07 (1 H, s, H-6); MS, *m/e* 386, 384 (M^+), 342, 340, 284, 282 (base peak). Anal. Calcd for $C_{17}H_{21}O_5Br$: C, 53.00; H, 5.49. Found: C, 53.15; H, 5.49.

(1*R,2*R**,4*S**,10*R**)-1,2-(Isopropylidenedioxy)-5,8-dimethoxy-10-methyl-1,2,3,4-tetrahydro-4,1-(epoxymethano)naphthalene-7-*N*,*N*-diethylcarboxamide (20).** A stirred solution of **19** (2.51 g, 6.52 mmol) in dry THF (65 mL) under nitrogen was cooled to −100 °C, and a 1.5 M hexane solution of *n*-BuLi (4.66 mL, 7.17 mmol) was added dropwise over 1 min. Three minutes after the addition was completed, Et_2NCOCl (2.65 g, 19.6 mmol) was introduced, and the mixture was allowed to warm to −70 °C over 20 min and then kept at −70 ± 5 °C for 30 min before stirring at room temperature for 1.5 h. The resulting pale yellow solution was extracted with AcOEt (50 mL × 3) after addition of saturated aqueous $NaHCO_3$ (60 mL) and water (120 mL). The combined extracts were washed with brine, dried, and concentrated in vacuo. The solid residue (2.85 g) was recrystallized from hexane to give **20** (2.01 g) as colorless plates, mp 161–162 °C. Chromatography of the mother liquor (silica gel, 25 g; elution with 1:2 AcOEt–hexane) furnished an additional amount of **20** (357 mg, combined yield of 90%): IR (KBr) 1630 cm^{-1}; ^1H NMR δ 0.83 (3 H, d, *J* = 6.2 Hz, Me-10), 1.06, 1.27 (each 3 H, t, *J* = 7.1 Hz, CH_2Me), 1.52 (1 H, dd, *J* = 12.8, 6.2 Hz, H*endo*-3), 1.55, 1.59 (each 3 H, s, acetonide Me), 2.75 (1 H, ddd, *J* = 12.8, 9.2, 5.1 Hz, H*exo*-3), 3.20 (2 H, q, *J* = 7.1 Hz, CH_2Me), 3.42, 3.74 (each 1 H, dq, *J* = 14.1, 7.1 Hz, $CHHMe$), 3.74, 3.80 (each 3 H, s, OMe), 4.00 (1 H, q, *J* = 6.2 Hz, H-10), 4.26 (1 H, dd, *J* = 9.2, 6.2 Hz, H-2), 5.29 (1 H, d, *J* = 5.1 Hz, H-4), 6.71 (1 H, s, H-6); MS, *m/e* 405 (M^+), 361, 303, 231 (base peak). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.44; H, 7.98; N, 3.67.

(1*R,2*R**,4*S**,10*R**)-6-Formyl-1,2-(isopropylidenedioxy)-5,8-dimethoxy-10-methyl-1,2,3,4-tetrahydro-4,1-(epoxymethano)naphthalene-7-*N*,*N*-diethylcarboxamide (21).** A stirred solution of **20** (710 mg, 1.75 mmol) in dry THF (15 mL) under nitrogen was cooled to −80 °C, and a 1.5 M pentane solution of *t*-BuLi (3.4 mL, 5.3 mmol) was added dropwise over 1 min. After being kept at −75 ± 5 °C for 1 h, the mixture was allowed to warm to 0 °C and treated with dry DMF (0.54 mL, 7.0 mmol) for 15 min. After addition of brine (30 mL) to the reaction mixture, the whole was extracted with AcOEt (20 mL × 3). The com-

bined extracts were washed with brine, dried, and concentrated in vacuo to give a pale yellow oil. This material was subjected to chromatography (silica gel, 70 g; elution with 1:1 AcOEt–hexane) to give, in the order of elution, recovered **20** (344 mg, 47%) and **21** (390 mg, 51%) as a viscous oil: IR (film) 1690, 1630 cm^{-1}; ^1H NMR δ 0.88 (3 H, d, J = 6.1 Hz, Me-10), 1.02, 1.32 (each 3 H, t, J = 7.1 Hz, CH_2Me), 1.55 (1 H, dd, J = 13.2, 4.9 Hz, H*endo*-3), 1.56, 1.58 (each 3 H, s, acetonide Me), 2.84 (1 H, ddd, J = 13.2, 9.3, 4.9 Hz, H*exo*-3), 3.05, 3.61 (each 2 H, q, J = 7.1 Hz, CH_2Me), 3.80, 3.89 (each 3 H, s, OMe), 4.07 (1 H, q, J = 6.1 Hz, H-10), 4.31 (1 H, dd, J = 9.3, 6.4 Hz, H-2), 5.24 (1 H, d, J = 4.9 Hz, H-4), 10.29 (1 H, s, CHO); MS, m/e 433 (M^+), 404, 302 (base peak). Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.58; H, 7.27; N, 3.30.

(5*R,7*R**,8*R**,11*R**)-3-Cyano-7,8-(isopropylidenedioxy)-4,9-dimethoxy-11-methyl-5,6,7,8-tetrahydro-5,8-(epoxymethano)-3*H*-naphtho[2,3-*c*]furan-1-one (22).** Trimethylsilyl cyanide (175 μL, 1.35 mmol) was added to a stirred solution of **21** (390 mg, 0.90 mmol) and KCN–dicyclohexyl-18-crown-6 complex (7 mg) in dry dichloromethane (2.5 mL) at 0 °C under nitrogen. After 10 min, the reaction mixture was concentrated in vacuo. The residue was dissolved in AcOH (1.2 mL), and the solution was kept at room temperature overnight. Saturated aqueous $NaHCO_3$ (50 mL) was added to the solution, and the whole was extracted with AcOEt (10 mL × 3). The combined extracts were washed with water, dried, and concentrated in vacuo. The residue was dissolved in dry THF (1.5 mL) and treated with 2-methoxypropene (0.17 mL) and camphorsulfonic acid (ca. 2 mg) at room temperature for 1 h. The reaction mixture, which showed a single spot on TLC (R_f 0.61, 1:39 MeOH–$CHCl_3$), was subjected to standard workup to give a pale yellow oil. Chromatography of this material (silica gel, 22 g; elution with 1:4 AcOEt–hexane) afforded **22** (291 mg, 84%) as a white foam (ca. 1:1 distereomeric mixture) [IR (film) 1790 cm^{-1}; MS, m/e 387 (M^+), 343, 285. Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.20; H, 5.50; N, 3.69]. One crystalline diastereomer was obtained by recrystallization from i-Pr_2O (8.6 mg from 30 mg of the mixture) as colorless needles: mp 168–172 °C; ^1H NMR δ 0.78 (3 H, d, J = 6.2 Hz, Me-11), 1.57, 1.62 (each 3 H, s, acetonide Me), 1.63 (1 H, dd, J = 13.2, 6.4 Hz, H*endo*-6), 2.89 (1 H, ddd, J = 13.2, 9.3, 5.3 Hz, H*exo*-6), 3.98, 3.99 (each 3 H, s, OMe), 4.08 (1 H, q, J = 6.2 Hz, H-11), 4.29 (1 H, dd, J = 9.3, 6.4 Hz, H-7), 5.26 (1 H, d, J = 5.3 Hz, H-5), 6.05 (1 H, s, H-3); MS, m/e 387 (M^+), 343, 285.

(1*R,2*R**,4*R**,12*R**)-7-Acetyl-6-(5-*tert*-butoxy-2-furyl)-1,2-(isopropylidenedioxy)-5,8,9,10-tetramethoxy-12-methyl-1,2,3,4-tetrahydro-4,1-(epoxymethano)anthracene-1,2-diol (25).** A 1.5 M hexane solution of *n*-BuLi (0.81 mL, 1.24 mmol) was injected over 0.5 min to a stirred solution of dry dimethyl sulfoxide (88 μL) in dry THF (1.2 mL) at −10 °C under nitrogen, and the cloudy mixture was allowed to warm to 0 °C over 30 min. After addition of *t*-BuOH (105 μL), stirring of the reaction mixture was continued for 30 min. The resulting pale yellow solution was cooled to −78 °C, and there were added a solution of **22** (146 mg, 0.38 mmol) in dry THF (0.6 mL) and, 15 min later, a solution of **23** (258 mg, 1.24 mmol) in dry THF (0.6 mL). The reaction mixture was allowed to warm to −10 °C over 40 min and then kept at room temperature for 4 h. The resulting deep red suspension was treated with 8% aqueous KH_2PO_4 (30 mL) and extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine (20 mL × 2), dried, and concentrated in vacuo. The residue was subjected to chromatography (silica gel, 15 g; elution with 1:4 AcOEt–hexane) to give **24** (186 mg, 87%) as a reddish oil: ^1H NMR δ 0.90 (3 H, d, J = 6.2 Hz, Me-12), 1.39 (9 H, s, CMe_3), 1.57 (1 H, dd, J = 13.0, 6.6 Hz, H-3), 1.58, 1.66 (each 3 H, s, acetonide Me), 2.60 (3 H, s, COMe), 2.87 (1 H, ddd, J = 13.0, 9.4, 5.3 Hz, H-3), 3.95, 3.98 (each 3 H, s, OMe), 4.11 (1 H, q, J = 6.2 Hz, H-12), 4.37 (1 H, dd, J = 9.4, 6.6 Hz, H-2), 5.27 (1 H, d, J = 5.3 Hz, H-4), 5.60 (1 H, d, J = 3.3 Hz, furyl H), 6.93 (1 H, d, J = 3.3 Hz, furyl H), 9.84 (1 H, s, OH), 10.02 (1 H, s, OH).

A solution of **24** (173 mg, 0.30 mmol) in dry acetone (3.5 mL) was stirred under nitrogen and refluxed after addition of anhydrous K_2CO_3 (340 mg) and dimethyl sulfate (0.12 mL, 1.2 mmol). After 2 h, additional amounts of K_2CO_3 and Me_2SO_4 (1.2 and 0.6 mmol, respectively) were introduced, and refluxing was continued for 30 min. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in benzene (2 mL), and the solution was treated with triethylamine (0.4 mL) overnight. The mixture was evaporated in vacuo, and the residue was subjected to chromatography (silica gel, 6 g; elution with 1:9 AcOEt–hexane) to give **25** (140 mg, 77%) as a pale yellow oil. An analytical sample was obtained by crystallization from hexane, mp 160–162 °C: IR (KBr) 1710 cm^{-1}; ^1H NMR δ 0.84 (3 H, d, J = 6.2 Hz, Me-12), 1.41 (9 H, s, CMe_3), 1.59 (3 H, s, acetonide Me), 1.64 (1 H, dd, J = 13.0, 6.6 Hz, H-3), 1.69 (3 H, s, acetonide Me), 2.60 (3 H, s, COMe), 2.88 (1 H, ddd, J = 13.0, 9.4, 5.3 Hz, H-3), 3.72, 3.74, 3.78, 3.80 (each 3 H, s, OMe), 4.10 (1 H, q, J = 6.2 Hz, H-12), 4.36 (1 H, dd, J = 9.4, 6.6 Hz, H-2), 5.41 (1 H, d, J = 4.9 Hz, H-4), 5.61 (1 H, d, J = 3.3 Hz, furyl H), 6.90 (1 H, d, J = 3.3 Hz, furyl H); MS, m/e 597 ($M^+ + 1$), 582, 540 (base peak). Anal. Calcd for $C_{33}H_{40}O_{10}$: C, 66.43; H, 6.76. Found: C, 66.61; H, 6.71.

(3a*R,5*R**,8*R**,9*S**,11*S**,13b*R**,15*S**)-8,9-Dihydroxy-6,7,12,13-tetramethoxy-5,15-dimethyl-3,3a,5,8,9,10,11,13b-octahydro-11,8-(epoxymethano)-2*H*-furo[3,2-*b*]anthra[2,3-*d*]pyran-2-one (26a) and Its Diastereomers 26b and 27a,b.** A solution of **25** (319 mg, 0.53 mmol) in dry ether (5 mL) was added to a stirred suspension of $LiAlH_4$ (31 mg, 0.82 mmol) in dry ether (5 mL) at −15 °C. After continued stirring at the same temperature for 10 min, the reaction was quenched by addition of wet ether (5 mL). The ether layer was washed with brine, dried, and concentrated in vacuo to give the corresponding carbinol as a pale yellow oil (318 mg, 99%) which was homogeneous on TLC (R_f 0.56, 1:2 AcOEt–hexane). This material was dissolved in dry acetonitrile (5.3 mL), and the solution was treated at 0 °C with a solution of *p*-toluenesulfonic acid in acetonitrile (0.5 M, 1.1 mL) for 20 min. After neutralization with an aqueous $NaHCO_3$, the reaction mixture was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue was dissolved in dry toluene (9.5 mL) after azeotropic drying with toluene, and to the solution cooled at −10 °C was added DBU (80 μL, 0.53 mmol). After stirring at the same temperature for 30 min, the mixture was diluted with AcOEt (30 mL), washed with brine, dried, and concentrated in vacuo. The residue, which showed two major spots on TLC (R_f 0.38 and 0.26, 1:2 AcOEt–hexane), was subjected to chromotography (Merck 9385 silica gel, 15 g; elution with 1:1 AcOEt–hexane) to obtain mixtures of **26a** and **27a** and of **26b** and **27b**. These two portions of the diastereomeric mixture were separately subjected to HPLC (a Kusano CIG column packed with 10μ silica gel, 22 × 300 mm; elution with 1:1 AcOEt–hexane) to afford **26a** (86 mg, 32%) and **27a** (12 mg, 4.7%) and **26b** (68 mg, 26%) and **27b** (8 mg, 2.9%), respectively; relative retention times on the HPLC = 1.00 (**27a**), 1.03 (**26a**), 1.70 (**26b**), 2.40 (**27b**).

Compound 26a: colorless small needles from acetone–AcOEt, mp 278–280 °C; IR (KBr) 1785 cm^{-1}; ^1H NMR δ 0.98 (3 H, d, J = 6.0 Hz, Me-15), 1.60 (d, J = 6.8 Hz, Me-5; overlapped with H*endo*-10 and OH), 2.72 (1 H, d, J = 17.6 Hz, H-3), 2.83 (1 H, ddd, J = 14.5, 9.0, 3.7 Hz, H*exo*-10), 2.99 (1 H, dd, J = 17.6, 4.9 Hz, H-3), 3.80, 3.84, 3.88 (each 3 H, s, OMe), 3.91 (1 H, q, J = 6.0 Hz, H-15), 3.97 (3 H, s, OMe), 4.09 (1 H, dd, J = 9.0, 2.4 Hz, H-9), 4.77 (1 H, br s, H-3a), 5.27 (1 H, dd, J = 3.7, 1.6 Hz, H-11), 5.41 (1 H, br, H-5), 5.59 (1 H, br s, H-13b), 6.66 (1 H, br s, OH); MS, m/e 502 (M^+, base peak), 458, 149. Anal. Calcd for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.08; H, 6.03.

Compound 26b: colorless cubes from AcOEt, mp 250–251 °C; IR (KBr) 1770 cm^{-1}; ^1H NMR δ 0.90 (3 H, d, J = 6.0 Hz, Me-15), 1.58 (d, J = 6.8 Hz, Me-5; overlapped with H*endo*-10 and OH), 2.72 (1 H, d, J = 17.5 Hz, H-3), 2.89 (1 H, ddd, J = 14.5, 9.0, 3.5 Hz, H*exo*-10), 3.00 (1 H, dd, J = 17.5, 4.9 Hz, H-3), 3.80, 3.81 (each 3 H, s, OMe), 3.88 (1 H, q, J = 6.2 Hz, H-15), 3.90, 3.98 (each 3 H, s, OMe), 4.13 (1 H, dd, J = 9.1, 2.6 Hz, H-9), 4.77 (1 H, br s, H-3a), 5.28 (1 H, dd, J = 3.7, 1.6 Hz, H-11), 5.39 (1 H, br s, H-5), 5.59 (1 H, br s, H-13b), 6.54 (1 H, br, OH); MS, m/e 502 (M^+, base peak), 458, 149. Anal. Calcd for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 61.90; H, 6.04.

Compound 27a (not crystallizable): ^1H NMR δ 0.90 (3 H, d, J = 6.1 Hz, Me-15), 1.61 (1 H, dt, J = 14.3, 1.6 Hz, H-10), 1.74 (3 H, d, J = 6.2 Hz, Me-5), 2.56 (1 H, d, J = 2.4 Hz, HO-9), 2.78 (1 H, d, J = 17.2 Hz, H-3), 2.85 (1 H, ddd, J = 14.3, 9.4, 3.8 Hz, H-10), 2.94 (1 H, dd, J = 17.2, 4.1 Hz, H-3), 3.71, 3.86 (each 3 H, s, OMe), 3.89 (1 H, q, J = 6.1 Hz, H-15), 3.91, 4.00 (each 3 H, s, OMe), 4.12 (1 H, ddd, J = 9.4, 2.4, 1.6 Hz, H-9), 4.39 (1 H, dd, J = 4.1, 2.4 Hz, H-3a), 5.06 (1 H, q, J = 6.2 Hz, H-5), 5.26 (1 H, dd, J = 3.8, 1.6 Hz, H-11), 5.64 (1 H, d, J = 2.4 Hz, H-13b), 6.61 (1 H, s, HO-8); MS, m/e 502 (M^+, base peak), 458, 443, 440, 425.

Compound 27b (not crystallizable): ^1H NMR δ 1.00 (3 H, d, J = 6.3 Hz, Me-15), 1.57 (1 H, dt, J = 14.7, 2.0 Hz, H-10), 1.76 (3 H, d, J = 6.2 Hz, Me-5), 2.60 (1 H, br s, HO-9), 2.79 (1 H, d, J = 17.3 Hz, H-3), 2.86 (1 H, ddd, J = 14.7, 9.1, 3.8 Hz, H-10), 2.94 (1 H, dd, J = 17.3, 4.2 Hz, H-3), 3.70, 3.81, 3.89 (each 3 H, s, OMe), 3.91 (1 H, q, J = 6.3 Hz, H-15), 3.99 (3 H, s, OMe), 4.10 (1 H, dd, J = 9.1, 2.0 Hz, H-9), 4.40 (1 H, dd, J = 4.2, 2.4 Hz, H-3a), 5.05 (1 H, q, J = 6.2 Hz, H-5), 5.30 (1 H, dd, J = 3.8, 2.0 Hz, H-11), 5.62 (1 H, d, J = 2.4 Hz, H-13b), 6.80 (1 H, s, HO-8); MS, m/e 502 (M^+, base peak), 458, 443, 440, 425.

Acetonide 28a. Reaction of **26a** (35.5 mg, 0.07 mmol) with 2-methoxypropene (68 μL) and a catalytic amount of camphorsulfonic acid in THF (3 mL) at room temperature for 1 h afforded **28a** (36.8 mg, 97%) after the usual extractive workup followed by chromatography (silica gel, 2 g; elution with 1:4 AcOEt–hexane): colorless needles from i-Pr_2O–CH_2Cl_2, mp 265–268 °C: ^1H NMR δ 0.84 (3 H, d, J = 6.2 Hz, Me-15), 1.59 (3 H, d, J = 6.7 Hz, Me-5), 1.59, 1.69 (each 3 H, s, acetonide Me), 1.66 (1 H, dd, J = 13.0, 6.5 Hz, H-10), 2.72 (1 H, d, J = 17.5 Hz, H-3),

2.86 (1 H, ddd, J = 13.0, 9.4, 5.1 Hz, H-10), 2.99 (1 H, dd, J = 17.5, 4.8 Hz, H-3), 3.75, 3.79, 3.81, 3.95 (each 3 H, s, OMe), 4.11 (1 H, q, J = 6.2 Hz, H-15), 4.36 (1 H, dd, J = 9.4, 6.5 Hz, H-9), 4.75 (1 H, dd, J = 4.8, 2.8 Hz, H-3a), 5.37 (1 H, q, J = 6.7 Hz, H-5), 5.41 (1 H, d, J = 5.1 Hz, H-11), 5.59 (1 H, d, J = 2.8 Hz, H-13b); MS, m/e 542 (M^+), 440 (base peak), 425. Anal. Calcd for $C_{29}H_{34}O_{10}$: C, 64.20; H, 6.32. Found: C, 64.45; H, 6.23.

Acetonide 28b. This compound was prepared from **26b** by using the same procedure as described above for **28a**: colorless needles from AcOEt-*i*-Pr_2O, mp 198 °C dec: ^1H NMR δ 0.77 (3 H, d, J = 6.2 Hz, Me-15), 1.60 (3 H, s, acetonide Me), 1.61 (3 H, d, J = 6.6 Hz, Me-5), 1.61 (1 H, dd, J = 12.9, 6.6 Hz, H-10), 1.72 (3 H, s, acetonide Me), 2.72 (1 H, d, J = 17.6 Hz, H-3), 2.90 (1 H, ddd, J = 12.9, 9.4, 5.2 Hz, H-10), 3.01 (1 H, dd, J = 17.6, 4.9 Hz, H-3), 3.71, 3.78, 3.81, 3.96 (each 3 H, s, OMe), 4.09 (1 H, q, J = 6.2 Hz, H-15), 4.37 (1 H, dd, J = 9.4, 6.6 Hz, H-9), 4.84 (1 H, dd, J = 4.9, 2.9 Hz, H-3a), 5.42 (1 H, d, J = 5.2 Hz, H-11), 5.55 (1 H, q, J = 6.6 Hz, H-5), 5.66 (1 H, d, J = 2.9 Hz, H-13b). Anal. Calcd for $C_{29}H_{34}O_{10}$: C, 64.20; H, 6.32. Found: C, 64.13; H, 6.35.

(±)-Granaticin (1). A stirred solution of **28a** (21.7 mg, 0.04 mmol) in acetonitrile (4 mL) at 25 °C was titrated with a 18% aqueous solution of ceric ammonium nitrate by dropwise addition of the reagent at ca. 5-s intervals. When a transient blue-black color was not observed after a 10-drop addition, the reaction mixture was diluted with water (20 mL) and extracted with AcOEt (10 mL × 3). The combined extracts were washed with water (10 mL × 2), dried, and concentrated in vacuo to give a 5:1 mixture of **29a** and **29b** as a yellow solid which was essentially homogeneous on TLC (R_f 0.28, 1:1 AcOEt–hexane): ^1H NMR (major isomer) δ 0.85 (d, J = 6.2 Hz, Me-15), 1.61 (d, J = 6.6 Hz, Me-5), 1.56, 1.61 (each s, acetonide Me), 2.67 (d, J = 17.8 Hz, H-3), 2.97 (dd, J = 17.8, 5.3 Hz, H-3), 3.88, 3.90 (each s, OMe), 4.08 (q, J = 6.2 Hz, H-15), 4.30 (dd, J = 9.2, 6.4 Hz, H-9), 4.68 (dd, J = 5.3 3.3 Hz, H-3a), 4.96 (q, J = 6.6 Hz, H-5), 5.32 (d, J = 3.3 Hz, H-13b), 5.33 (d, J = 4.8 Hz, H-11).

To a stirred solution of the quinone mixture in dry dichloromethane (2 mL) at 0 °C was added a dichloromethane solution (1.0 mL) containing $AlCl_3$ (0.24 mmol) and Et_2S (0.95 mmol). After being kept at the same temperature for 10 min and then at room temperature for 50 min, the deep purple reaction mixture was poured onto an ice-cold 1% HCl, and phases were separated. The aqueous layer was warmed at 50 °C for 1 min and extracted with chloroform (10 mL × 2). This extraction procedure was repeated 9 times. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to furnish a deep red solid (14.5 mg, 82%), which was essentially homogeneous on TLC. An analytical sample was obtained by chromatography (KH_2PO_4-treated silica gel, 1:99 MeOH–$CHCl_3$): deep red crystals from benzene, mp 215–216 °C (dec); R_f 0.38 (AcOEt), 0.51 ($CHCl_3$–MeOH = 9:1) with silica gel thin-layer impregnated with 1% KH_2PO_4;[1e] IR ($CHCl_3$) 3580, 3450, 1790, 1610, 1565 cm^{-1}; UV λ_{max} (EtOH) 223 (ϵ 37 400), 290 (ϵ 5600), 490 (ϵ 4000), 529 (ϵ 5800), 570 (ϵ 6300), 593 (ϵ 5800), 640 (ϵ 4900) nm; UV λ_{max} (EtOH–HCl) 222 (ϵ 37 200), 282 (ϵ 9100), 495 (ϵ 7900), 525 (ϵ 8900), 568 (ϵ 5600) nm; ^1H NMR δ 1.03 (3 H, d, J = 6.2 Hz, Me-15), 1.56 (1 H, dt, J = 14.5, ca. 2 Hz, H*endo*-10), 1.59 (3 H, d, J = 6.9 Hz, Me-5), 2.63 (1 H, d, J = 2.2 Hz, HO-9), 2.73 (1 H, ddd, J = 14.5, 8.4, 3.6 Hz, H*exo*-10), 2.73 (1 H, d, J = 17.6 Hz, H-3), 2.99 (1 H, dd, J = 17.5, 5.1 Hz, H-3), 3.80 (1 H, q, J = 6.2 Hz, H-15), 4.02 (1 H, dd, J = 8.4, 2.0 Hz, H-9), 4.75 (1 H, dd, J = 5.1, 2.9 Hz, H-3a), 5.20 (1 H, dd, J = 3.6, 1.8 Hz, H-11), 5.23 (1 H, q, J = 6.9 Hz, H-5), 5.34 (1 H, d, J = 2.9 Hz, H-13b), 6.36 (1 H, s, HO-8), 12.79 (1 H, s, OH), 12.89 (1 H, s, OH); MS, m/e 446 (M^+ + 2), 444 (M^+), 402, 400 (base peak), 384, 382, 368, 367.

(3a*R,5*R**,8*S**,9*R**,11*R**,13b*R**,15*R**)-7,8,9,12-Tetrahydroxy-5,15-dimethyl-6,13-dioxo-3,3a,5,6,8,9,10,11,13,13a-decahydro-11,8-(epoxymethano)-2*H*-furo[2,3-*b*]anthra[2,3-*d*]pyran-2-one (30).** Oxidative *O*-demethylation of **28b** (21.7 mg, 0.04 mmol) with ceric ammonium nitrate as described above for **28a** afforded a 1:4 mixture of regioisomeric naphthoquinones: MS, m/e 514 (M^+ + 2), 512 (M^+), 468 (base peak), 410, 395, 351; ^1H NMR (major isomer) δ 0.87 (d, J = 6.2 Hz, Me-15), 1.52 (d, J = 6.7 Hz, Me-5), 1.56, 1.62 (each s, acetonide Me), 2.69 (d, J = 17.8 Hz, H-3), 2.97 (dd, J = 17.8, 5.1 Hz, H-3), 3.87, 3.89 (each s, OMe), 4.30 (dd, J = 9.2, 6.4 Hz, H-9), 4.67 (dd, J = 5.1, 3.1 Hz, H-3a), 5.08 (q, J = 6.7 Hz, H-5), 5.26 (d, J = 3.1 Hz, H-13b), 5.35 (d, J = 4.9 Hz, H-11). The crude quinone mixture was subjected to *O*-demethylation by using the same procedure as described above to give essentially homogeneous **30** (15.2 mg, 86%). This material was purified by chromatography (KH_2PO_4-treated silica gel, 15 g; elution with 1:2 AcOEt–benzene): deep red crystals from benzene (10.2 mg, 57%), mp 200–205 °C dec; R_f 0.28 (AcOEt), 0.51 ($CHCl_3$–MeOH = 9:1); IR ($CHCl_3$) 3580, 3450, 1790, 1610, 1565 cm^{-1}; UV λ_{max} (EtOH) 223 (ϵ 33 900), 290 (ϵ 5700), 489 (ϵ 2800), 529 (ϵ 4800), 570 (ϵ 6100), 595 (ϵ 6100), 639 (ϵ 5200) nm; UV λ_{max} (EtOH–HCl) 222 (ϵ 33 500), 280 (ϵ 6500), 494 (ϵ 6500), 525 (ϵ 7300), 566 (ϵ 4400) nm; ^1H NMR δ 1.04 (3 H, d, J = 6.3 Hz, Me-15), 1.53 (1 H, dt, J = 14.5, 1.8 Hz, H*endo*-10), 1.57 (3 H, d, J = 6.9 Hz, Me-5), 2.68 (1 H, br, HO-9), 2.73 (1 H, d, J = 17.6 Hz, H-3), 2.74 (1 H, ddd, J = 14.5, 8.3, 3.7 Hz, H*exo*-10), 2.99 (1 H, dd, J = 17.6, 5.1 Hz, H-3), 3.80 (1 H, q, J = 6.3 Hz, H-15), 4.03 (1 H, dd, J = 8.3, 1.8 Hz, H-9), 4.75 (1 H, dd, J = 5.1, 2.9 Hz, H-3a), 5.20 (1 H, dd, J = 3.7, 1.8 Hz, H-11), 5.23 (1 H, q, J = 6.9 Hz, H-5), 5.34 (1 H, d, J = 2.9 Hz, H-13b), 6.36 (1 H, s, HO-8), 12.79, 12.88 (each 1 H, s, OH); MS, m/e 446 (M^+ + 2), 444 (M^+), 402, 400, 382 (base peak), 367.

Acknowledgment. We are indebted to Dr. M. Shiro of Shionogi Research Laboratories, Osaka, for X-ray crystallographic determination of compound **26b** and Dr. H. H. Peter of Ciba-Geigy Ltd., Switzerland, for supplying a sample of natural granaticin.