cooled to −78 °C. D-Selectride (1*M* in THF, 3 mL) was added and stirring was continued for 2 h at −78 °C. The reaction was quenched by adding HOAc/H_2O (1/1, 5 mL). After warming to room temperature, the solvents were evaporated and the residue was dissolved in EtOH (10 mL) and treated with 1 N HCl (10 mL) with sitrring overnight at room temperature. The solvents were gain evaporated, and the residue was dissolved in H_2O which was washed with petroleum ether twice and then extracted with $CHCl_3$/*i*-PrOH (4/1) four times. The latter extracts were dried (Na_2SO_4) and evaporated to give **5e** (164 mg, 90%): mp 115–116 °C from $CHCl_3$; ^1H NMR (acetone-d_6) δ 0.97 (d, 3 H, *J* = 7 Hz), 3.20 (m, 1 H), 3.45–3.85 (m, 2 H), 4.03 (m, 1 H), 6.03 (d, 1 H, *J* = 8 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H).

This material was identical with the minor component obtained from the $NaBH_4$ reduction of **3d**.

(*R*)-2-(*N*-(Phenylsulfonyl)amino)hexanoic Acid (6a). To PtO_2 (120 mg), reduced by shaking under H_2 (50 psi) for 15 min in H_2O (15 mL), was added primary alcohol **5a** (200 mg, 0.78 mol), and oxygen was passed through the mixture at 55 °C for 20 h. The mixture was filtered, $NaHCO_3$ was added to the filtrate until it was faintly alkaline, and the aqueous solution was washed with EtOAc and then acidified (6 N HCl) to pH 2. The acidic solution was extracted with EtOAc, and the extracts were dried and evaporated to give **6a** (152 mg, 72%): mp 97–99 °C from CH_2Cl_2/*n*-hexane; ^1H NMR δ 0.83 (t, 3 H, *J* = 7 Hz), 1.22 (m, 4 H), 1.67 (m, 2 H), 3.93 (m, 1 H), 5.39 (d, 1 H, *J* = 10 Hz), 7.4–7.75 (m, 3 H), 7.8–8.0 (m, 2 H); IR (nujol) 3330, 1710 cm^{-1}; $[\alpha]^{20}_D$ −4.2° (*c* 0.6, MeOH). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.1; H, 6.3; N, 5.2. Found: C, 53.0; H, 6.3; N, 5.1.

(*R*)-2-(*N*-(Phenylsulfonyl)amino)-1,7-heptanedioic acid (6b) was prepared similarly to **6a** using reduced PtO_2 (200 mg), H_2O (30 mL), O_2, and diol **5b** (300 mg, 1.04 mmol) at 60 °C for 48 h. The product was obtained as an oil and was not further purified (240 mg, 73%): ^1H NMR (acetone-d_6) δ 1.1–1.9 (m, 6 H), 2.23 (t, 2 H, *J* = 7 Hz), 3.93 (m, 1 H), 6.7 (d, 1 H, *J* = 10 Hz), 7.4–7.7 (m, 3 H), 7.8–8.0 (m, 2 H).

(*R*)-2-(*N*-(Phenylsulfonyl)amino)-3-(3,4-dimethoxyphenyl)propionic Acid (6c). The oxidation of **5c** was performed at 55 °C for 5.5 h to give **6c** (55%) plus recovered educt (25%). Acid **6c** had mp 173–174 °C from EtOAc/petroleum ether: ^1H NMR (acetone-d_6) δ 2.93 (m, 2 H), 3.71 (s, 3 H), 3.77 (s, 3 H), 4.12 (m, 1 H), 6.70 (m, 3 H), 7.47 (m, 3 H), 7.67 (m, 2 H); IR (nujol) 3325, 1765 cm^{-1}; $[\alpha]^{20}_D$ +6.8° (*c* 1, MeOH). Anal. Calcd for $C_{17}H_{19}NO_6S$: C, 55.9; H, 5.2; N, 3.8. Found: C, 55.7; H, 5.2; N, 3.7.

(2*R*,3*R*)-2-(*N*-(Phenylsulfonyl)amino)-3-hydroxybutanoic Aicd (6d). Diol **5d** was oxidized for 24 h at 55 °C as above. The yield of pure, crystalline acid **6d** was 55%: mp 175–177 °C from EtOAc/petroleum ether; ^1H NMR (5% Me_2SO-d_6 in $CDCl_3$) δ 1.17 (d, 3 H, *J* = 6.5 Hz), 3.83 (dd, 1 H, J_1 = 3.7 Hz, J_2 = 8.6 Hz), 4.01 (m, 1 H), 4.2–5.6 (s, 2 H), 6.29 (d, 1 H, *J* = 8.8 Hz), 7.5 (m, 3 H), 7.85 (m, 2 H), $[\alpha]^{23}_D$−16.8° (*c* 1.6, MeOH). Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.3; H, 5.1; N, 5.4. Found: C, 46.5; H, 5.1; N, 5.4.

These properties are identical with those of **6d** prepared from commercial D-allothreonine and phenylsulfonyl chloride under Schotten–Bauman conditions.

D-Norleucine (7a). A mixture of **6a** (90 mg, 0.33 mmol), phenol (90 mg), and 48% HBr (1.2 mL) was refluxed for 30 min. After cooling the mixture, it was washed with EtOAc and evaporated to a residue which was purified by ion exchange chromatography on Dowex AG-1, X-8, 50–100 mesh, OH^-. After loading the column and washing it with H_2O, the amino acid was eluted with 1 N HOAc in 80% yield (35 mg): mp 299–301 °C dec (lit.[15] mp 301 °C dec); $[\alpha]^{15}_D$ −20.1° (*c* 0.8, 6 N HCl) [lit.[15] $[\alpha]^{20}_D$ −22.4° (*c* 4.7, 6 N HCl)].

Table I

amino acid	acyl derivative[a]	HPLC conditions[b]
7a	A	NP (EtOAc/isooctane, 18/32)
7b	B	RP (H_2O/MeOH, 50/50)
7c	B	RP (H_2O/MeOH, 50/50)
7d	B	RP (H_2O/CH_3CN, 85/15)

[a] A is α-Methoxy-α-(trifluoromethyl)phenylacetyl, B is *N*-(phenylsulfonyl)prolyl. [b] NP is normal phase, RP is reversed phase.

D-α-Aminopimelic Acid (7b). Phenylsulfonyl derivative **6a** was deblocked with HBr/phenol as above to give **7b** in 66% yield: mp 218–220 °C from aqueous EtOH; $[\alpha]^{20}_D$ −20.5° (*c* 1, 5 N HCl) [lit.[16] $[\alpha]^{26}_D$ −21.0 (*c*, 1, 5 N HCl)]. Anal. Calcd for $C_7H_{13}NO_4$: C, 48.0; H, 7.5; N, 8.0. Found: C, 47.85; H, 7.39; N, 7.83.

D-Dopa [D-3-(3,4-Dihydroxyphenyl)alanine, 7c] was prepared by deblocking **6c** with HBr/phenol by refluxing for 1 h in 62% yield: mp 275–276 °C dec (lit.[17] mp 276–278 °C dec); $[\alpha]^{20}_D$ +12.1° (*c* 1, 1 N HCl) [lit.[17] $[\alpha]^{11}_D$ +13.0° (*c* 5, 1 N HCl)].

D-Allothreonine (7d). To **6d** (150 mg, 0.58 mmol) dissolved in liquid NH_3 was added Na until a blue color persisted for 5 min, then NH_4Cl was added to quench the blue color. After evaporating the NH_3, the residue was purified by ion exchange as above and crystallized from H_2O/ethanol: yield, 59 mg (86%); mp 268–270 °C (lit.[18] mp 272–273 °C dec); $[\alpha]^{22}_D$ −8.8° (*c* 1, H_2O) [lit.[18] $[\alpha]^{25}_D$ −9.1° (*c* 3.9, H_2O)].

Determination of Optical Purities. Each amino acid was converted to its methyl ester with methanolic HCl. The esters were then *N*-acylated with either *N*-(phenylsulfonyl)prolyl chloride[14] or α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[28] When racemic N-acylating agents were used the resulting diastereomeric derivatives were shown to be separable by analytical HPLC. When optically pure N-acylating agents were used, HPLC showed that >99% of only one diastereomer was present (the limits of detection). Table I shows the specific acylated derivatives and HPLC conditions used in each case.

***N*-(Phenylsulfonyl)-L- or *N*-(Phenylsulfonyl)-D,L-proline.** L- or D,L-proline (2.87 g, 25 mmol) was dissolved in 50 mL of 1 N NaOH (0.05 mol) and phenylsulfonyl chloride (4.41 g, 3.19 mL, 25 mmol) was added dropwise at room temperature. After being stirred for 5 h, the mixture was acidified with 2 N HCl to pH 2 and extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated to give 4.0 g (62%) of a white solid: mp 84–86 °C; ^1H NMR δ 1.9 (m, 2 H), 2.2 (m, 2 H), 3.4 (m, 2 H), 4.7 (t, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.8; H, 5.1; N, 5.5. Found: C, 52.1; H, 5.2; N, 5.4.

***N*-(Phenylsulfonyl)-L- or *N*-(Phenylsulfonyl)-D,L-propyl Chloride.** A solution of 1.27 g (5 mmol) of *N*-(phenylsulfonyl)-L- or *N*-(phenylsulfonyl)-D,L-proline in 10 mL of dry CH_2Cl_2 with 1.0 mL (11 mmol) of oxalyl chloride and 2 drops of DMF was stirred for 1 h at room temperature. Volatile solvents were removed on the rotary evaporator and the residue was dissolved in benzene, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to give 1.15 g (62%) of the acid chloride as a low melting solid: ^1H NMR δ 1.90 (m, 2 H), 2.20 (m, 2 H), 3.40 (m, 2 H), 4.70 (t, 1 H), 7.60 (m, 3 H), 7.9 (m, 2 H).

Regiospecific Total Syntheses of (±)-Aklavinone and (±)-ε-Pyrromycinone from a Common Synthon

Frank M. Hauser*[1] and Dipakranjan Mal

Contribution from the Department of Chemistry & Biochemical Sciences, Oregon Graduate Center, Beaverton, Oregon 97006. *Received May 23, 1983*

Abstract: The preparation and use of the cyclohexenone **10** as a common intermediate for regiospecific total synthesis of both (±)-aklavinone (**1a**) and (±)-ε-pyrromycinone (**2a**) is described.

Aklavinone (**1a**) and pyrromycinone (**2a**) are the parent aglycons of two extensive families of glycosidically derived anthracycline antibiotics possessing significant anticancer activity.[2,3] Aklavin (**1b**), which has rhodosamine as the sugar residue, was

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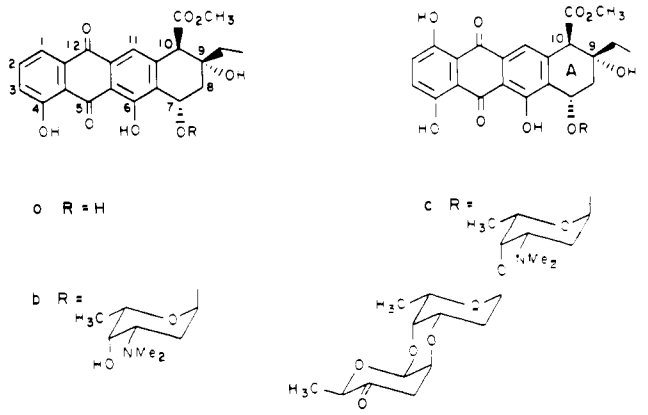
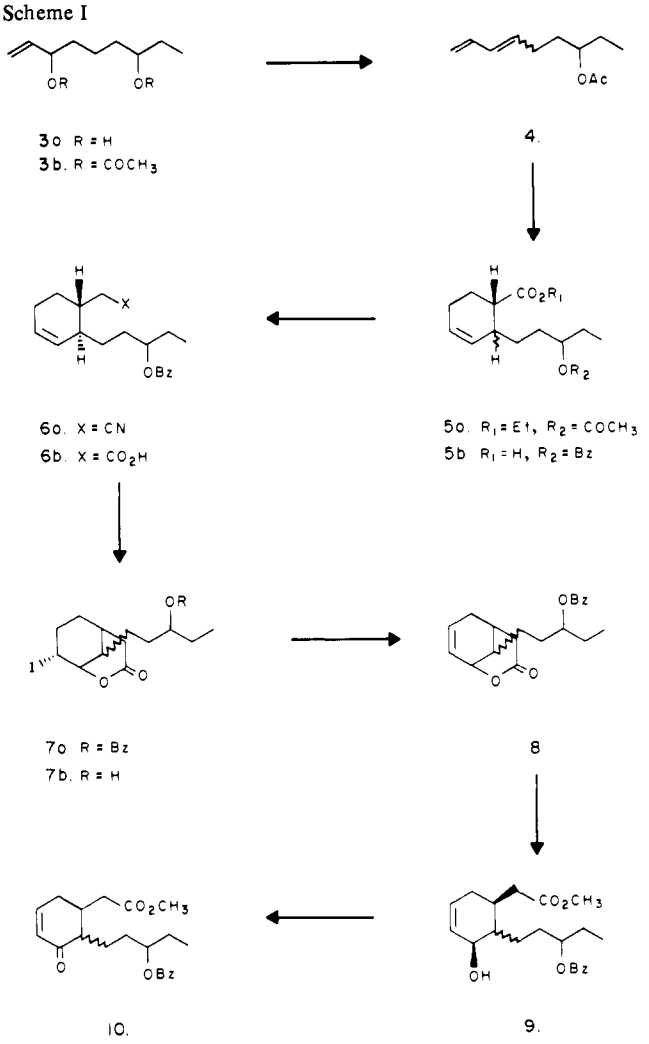


for many years the only antibiotic known to be derived from aklavinone (**1a**).[3] Beginning in 1975, Oki et al. published a series of papers describing the isolation, characterization, and biological activity of seven new antibiotics with **1a** as the aglycon.[4] One of these, aclacinomycin A (**1c**) is presently undergoing clinical evaluation since it has been found to have substantial anticancer activity while being less toxic than the clinically useful rhodomycin, daunorubicin.[4,5]

Because of its important biological activity, there has been considerable interest in the total synthesis of aclacinomycin (**1c**). Five total syntheses of the aglycon (**1a**),[6-10] one of the trisaccharide fragment,[11] and the chemical coupling of **1a** with the sugar moiety have been reported.[12] Further impetus for synthesis of the aglycon has been the finding by Oki et al.[13] that microbiological transformation of (±)-aklavinone to **1c** can be achieved.

Eleven pyrromycinone (**2a**) derived anthracyclines are presently known.[2-4] As in the aklavinone series, the earliest member to be fully characterized was the rhodosamine conjugated antibiotic, pyrromycin (**2b**).[3] Subsequent work by several groups led to the isolation and structure elucidation of cinerubins A[14] (**2c**) and B,[15]

Scheme I



musettamycin,[16] marcellomycin,[16] rudolformycin,[17] rhodoirubins[18] A, B and G, and two unnamed glycosides.[4b,c] With the exception of aclacinomycin Y, pyrromycinone derived anthracycline antibiotics exhibit greater in vitro activity than aclacinomycins but are less effective in vivo.[2b,4c] Of potential importance is the finding that cinerubicin A (**2c**) is effective against certain cancers which are resistant to daunorubicin and other anticancer agents.[19] In spite of the impressive biological activity of this class of anthracycline antibiotics, there has been no total synthesis of pyrromycinone (**2a**).

In this paper we describe total syntheses of both (±)-aklavinone (**1a**) and (±)-ε-pyrromycinone (**2a**) from a common synthon, the cyclohexenone **10**. The synthetic plan is shown in Scheme II and has as key elements our recent adaptation of the phthalidesulfone annelation[20] to convergent, regiospecific preparation of polycyclic aromatic systems.[21] Since initial selection of the phthalidesulfone

(1) Recipient of a Career Development Award, 1978–1983, from the National Cancer Institute of the National Institutes of Health (Grant No. CA 00486).

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(3) For a review of the isolation and structure elucidation of the anthracyclinones, see: Brockmann, H. *Fortschr. Chem. Org. Naturst.* **1963**, *21*, 121.

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establishes the functionalization of the final product, construction of virtually any hydroxylation pattern in the C-ring of anthraquinones and the D-ring of anthracyclines is possible. This versatile facet of the methodology was exploited to regiospecifically fashion the tricyclic intermediates **12** and **18** from the phthalidesulfones **11** and **17** and the single cyclohexenone **10**. The cyclohexenone **10** contributes the latent functionalization necessary for fabrication of the A-ring. Highly stereoselective terminal ring construction was achieved using a metal templated intramolecular aldol cyclization.

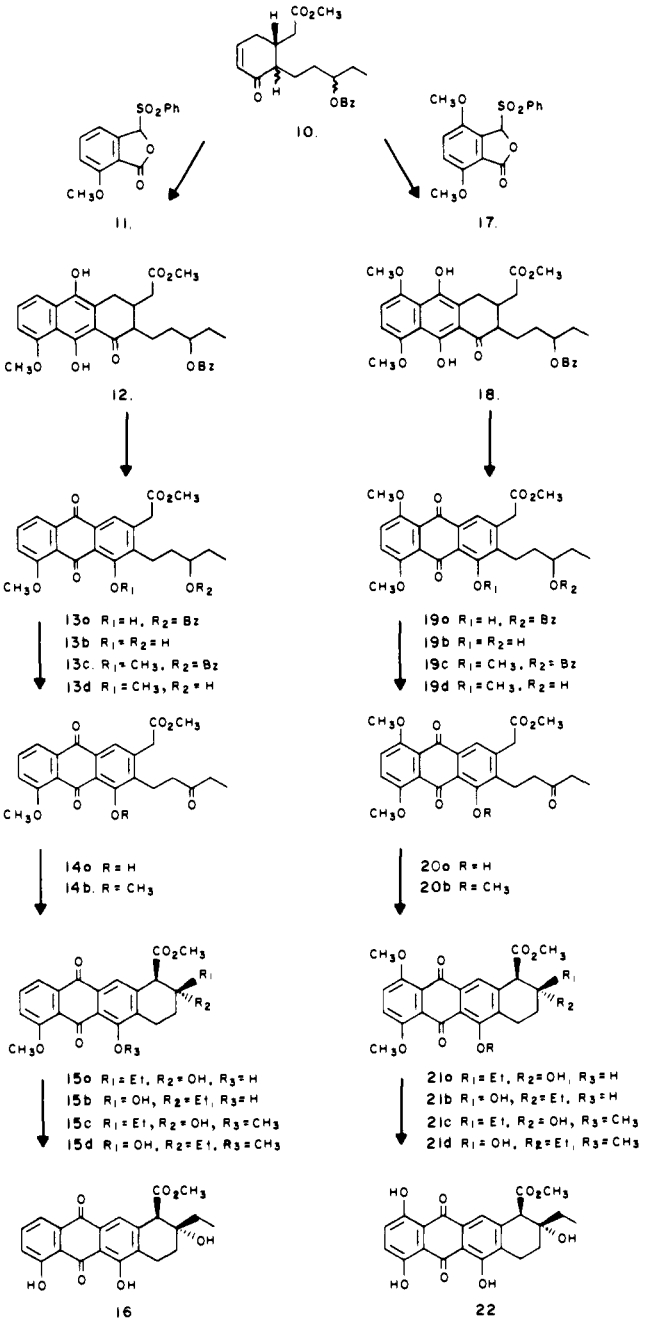
Synthesis of the Cyclohexenone 10. Cyclohexenone **10**, which serves as a synthon for the A and B rings of both aglycons, was selectively prepared as shown in Scheme I. Treatment of the diacetate derivative **3b** of the known alcohol **3a**[22] with a catalytic amount of palladium acetate and triphenylphosphine in refluxing dioxane led to chemospecific elimination of the allylic acetoxy group.[23] The resultant diene acetate **4** was isolated as a 78:22 mixture of *E* and *Z* isomers. The *E* isomer selectively underwent Diels–Alder reaction with ethyl acrylate (150 °C, sealed tube) to regiospecifically form **5a**. The adduct was shown by capillary GC/MS to be a 58:42 mixture of geometric isomers and was isolated by distillation on a large scale in 92% yield based on *E* diene. Although **5** and subsequent intermediates were mixtures of geometric isomers, the entire product was used since the sp^3 centers were converted to planar sp^2 hybridized carbons at a later stage in the synthesis (i.e., **12** to **13** and **18** to **19**).

In order to provide for subsequent selective manipulation of the alcohol moiety, **5a** was hydrolyzed (NaOH, EtOH), then chemospecifically benzylated (NaH, BzBr, THF, Δ) to give the benzyl ether product **5b** in 83% overall yield. Because moderate amounts of material (25–50 g) were involved, an experimentally nonhazardous[24] reaction sequence was employed to homologate **5b** to the acetic acid derivative **6b**. Reduction of **5b** (LAH, Et_2O) followed by mesylation (MsCl, Py) of the resultant alcohol intermediate and then displacement of the mesylate group with cyanide (NaCN, DMF, room temperature, 24 h; 100 °C, 24 h) gave the nitrile **6a**. The polarity of **6a** was such that its purification could be achieved by a simple filtration through silica gel. Hydrolysis of **6a** (NaOH, EtOH) completed the homologation sequence and furnished the acid **6b** in 91% yield from **5b**.

The use of the acetic acid appendage to guide the regiospecific transformation of the 3,4-olefinic entity in **6b** to an unsaturated enone fragment initially met with difficulty. Attempted iodolactonization of **6b** to **7a** in a biphasic system consisting of methylene chloride and an aqueous solution of sodium bicarbonate, potassium iodide, and iodine failed to go to completion even after several days. Moreover, protracted reaction times led to other products.[25]

In contrast, treatment of **6b** with iodine (2 equiv) in acetonitrile[26] led to rapid and complete reaction; however, beside the desired iodolactones **7a**, the hydroxy lactones **7b** resulting from cleavage of the benzyl group were also produced. Addition of collidine to scavenge the in situ generated hydrogen iodide stopped the debenzylation side reaction and the iodolactones **7a** were routinely isolated in 83% yield.

Scheme II



Dehydrohalogenation of **7a** with DBU in benzene quantitatively furnished the unsaturated bicyclic lactones **8**. Hydrolysis of the lactone mixture with sodium hydroxide followed by chemospecific methylation of the carboxyl functionality with methyl iodide and DBU in acetonitrile[27] gave the hydroxy ester **9** in 96% yield from **8**.[28] Because of its tendency to relactonize, **9** was directly oxidized with Swern's reagent[29] (ClCOCOCl, Me_2SO, Et_3N) to ketone **10** (85%).

After the conditions for effecting the individual steps were established, the reaction sequence to the cyclohexenone **10** was repeated several times on a moderate scale. The average overall yield of **10** from the olefinic diol **3a** was routinely 28%.

Synthesis of (±)-Aklavinone (1a) and (±)-ε-Pyrromycinone (2a). The use of cyclohexenone **10** as a precursor to both

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(22) A modification of the procedure reported by Saucy et al. permitted preparation of **3a** in a single flask. Saucy, G.; Borer, R.; Fürst, A. *Helv. Chim. Acta* **1971**, *54*, 218.

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(24) The application of the Wolff rearrangement to homologate the acid was precluded since large quantities of diazomethane would have been required.

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(28) Attempted methanolysis of the olefinic lactone **8** with a catalytic amount of sodium methoxide in methanol gave an equilibrium mixture of the hydroxy ester **9** and starting material.

(29) Mancuso, A. J.; Huang, S.-L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2840.

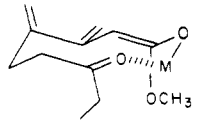
(±)-aklavinone (**1a**) and (±)-ε-pyrromycinone (**2a**) is shown in Scheme II. For the preparation of intermediates to (±)-aklavinone (**1a**), **10** was condensed with the lithium *tert*-butoxide generated anion of the methoxyisobenzofuranone **11**.[20,21] After methanolysis[30] of the tetrahydronaphthacenone **12**, concurrent aromatization of the B ring and oxidation of the hydroquinone moeity were achieved using oxygen in DMF[31] (100 °C, 12 h). The regiospecifically constructed anthraquinone **13a** was obtained in 80–85% overall yield for the two-step process.

In order to provide appropriate functionalization for construction of the A ring through intramolecular aldol cyclization, deprotection of the latent alcohol residue in **13a** and subsequent oxidation to a ketone were required. Hydrogenolysis of **13a** (10% Pd/C, H_2, EtOH, HCl; 95%) and oxidation of the resultant alcohol **13b** ($PyHCrO_3Cl$,[32] CH_2Cl_2; 93%) gave the ketone **14a**.[33] The methyl ether derivative **14b** was analogously prepared after first methylating **13a**.

Construction of the A ring through triton B promoted aldol cyclization of an intermediate similar to **14** was first reported by Krohn.[34] While our work was in progress, Boeckman and Sum[10] published a synthesis of (±)-aklavinone (**1a**) in which triton B in methanol–methylene chloride was employed to cyclize the demethylated and 6-ethyl ether derivative of **14a**. The use of potassium carbonate to effect a similar cyclization in a more complex system was reported in a synthesis of (±)-aklavinone (**1a**) by Kishi et al.[7]

Intramolecular aldol cyclization of **14a** with triton B in 5:1 methanol–methylene chloride at −30 °C gave a 96% yield of diastereoisomers **15a** and **15b** in a 1:1 ratio. Under these same conditions, Boeckman and Sum[10] reported that the ethyl ether derivative of **14a** gave a ratio of approximately 4:1. On the basis of this result, we examined the methyl ether derivative **14b** and likewise noted enhanced formation of the desired isomer **15c**. However, repeated attempts using this base solvent system never produced a ratio of **15c** to **15d** better than 2:1. In the course of this study we found that direct measurement of the isomer ratios by ^1H NMR was distorted because of the overlap of absorptions. Accurate determination of the ratios was performed by isolating the isomers which were readily separated by chromatography.[35]

Recent reports of successful metal-templated stereoselective intramolecular cyclizations[36,37] prompted us to consider this method as a means of enhancing the production of **15c**. Although steric interactions develop between the ethyl and carbomethoxy groups, the transition state geometry resulting from the reaction of the *E* enolate was expected to be that shown below. This geometry would produce the desired diastereoisomer **15c**.



Magnesium methoxide and the propanoxides of titanium and zirconium were selected for study because of their ability to strongly coordinate oxygen centers.[36,37] Treatment of **14b** with either zirconium or titanium propanoxides failed to give any reaction. On the other hand, reaction of **14b** with excess magnesium methoxide gave the desired results and reproduceably furnished a 3.5 to 1 (78:22) ratio of **15c** to **15d**.

Observations of the reaction by TLC disclosed notable contrast to those conducted with either triton B or potassium carbonate. The magnesium methoxide cyclization of **14b** proceeded slowly and required 5 h to go to completion. Whereas both **15c** and **15d** were immediately evident on addition of triton B or potassium carbonate to **14b**, only **15c** was observed after 10 min of reaction with magnesium methoxide. Approximately 10% of the isomer **15d** was present at 50% reaction.

The conversion of **15c** to (±)-aklavinone (**1a**) was routine. Demethylation of **15c** to (±)-7-deoxyaklavinone (**16**) was achieved in 98% yield using aluminum chloride in methylene chloride. A procedure reported by Kende,[6] involving homolytic bromination (Br_2, AIBN, CCl_4) followed by solvolysis in THF–water, was employed to transform **16** to (±)-aklavinone (**1a**). The melting point and ^1H NMR of our synthetic material were identical with the several published values for (±)-aklavinone.

A reaction sequence paralleling the construction of (±)-aklavinone (**1a**) was employed to prepare pyrromycinone (**2a**). Condensation of the anion of dimethoxyphthalide sulfone **17**[38] with cyclohexenone **10**, followed by methanolysis (MeOH/HCl) and then aromatization in DMF under oxygen (100 °C, 8 h) furnished the anthraquinone **19a** in 86% overall yield. Debenzylation of **19a** (5% Pd/C, H_2) MeOH; 88% yield) and oxidation of the resultant alcohol **19b** with pyridinium chlorochromate[32] in methylene chloride gave the ketone **20a** (96% yield). Intramolecular aldol cyclization of the phenol **20a** and of the methyl ether derivative **20b** gave results identical with those obtained in the aklavinone series. Triton B promoted cyclization of the phenol **14a** and the methyl ether **14b** gave ratios of 1:1 (**15a**:**15b**) and 2:1 (**15c**:**15d**), respectively. As before, magnesium methoxide produced the isomers **21c** and **21d** in a 78:22 ratio.

Demethylation of **21c** ($AlCl_3$, CH_2Cl_2, room temperature; 24 h gave (±)-7-deoxypyrromycinone (**22**) in 96% yield. Homolytic bromination of **22** (Br_2, AIBN, CCl_4) followed by solvolysis in THF–water furnished pure (±)-ε-pyrromycinone (**2a**) after recrystallization.[40] The TLC behavior and ^1H NMR spectrum of our synthetic material was identical with an authentic sample of (±)-ε-pyrromycinone (**2a**) which was obtained by hydrolyzing pyrromycin (**1a**), generously provided by Dr. Terrance Doyle of Bristol Laboratories.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a JEOL-FX-90Q spectrometer and were determined in $CDCl_3$. Carbon and hydrogen analyses were performed by Galbraith Laboratories.

Preparative TLC chromatography was performed on a chromatotron (Harrison Research) using rotors coated to 4-mm thickness (silica gel 60 PF-254 manufactured by E. Merck and Co.) Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

3,7-Dihydroxy-1-nonene (3a). A modification of the procedure reported by Saucy et al.[22] was employed to accomplish a one-pot preparation of this material.

To a well-stirred solution of glutaraldehyde (40.0 g) in dry THF (400 mL) under N_2 at −78 °C was added dropwise ethylmagnesium bromide (0.3 mol), prepared from ethyl bromide (0.42 mol) and magnesium (0.4

(30) A small amount (~10%) of the *tert*-butyl ester product is formed in the condensation reaction through trans esterification and methanolysis converts this minor product back to the methyl ester.

(31) We have found this reaction to be general. Hauser, F. M.; Prasanna, S., unpublished work.

(32) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.

(33) A sample and the ^1H NMR spectrum of this product were generously provided by Dr. Boeckman. A comparison of the spectra and the TLC behavior showed they were identical.

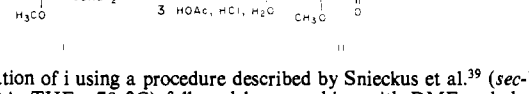
(34) Krohn, K. *Tetrahedron Lett.* **1981**, *22*, 3219.

(35) Cyclizations were performed on a 100 to 200 mg scale and the combined yields of isolated material were >95%.

(36) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.

(37) For a recent review of metal-templated intermolecular aldol reactions, see: Mukaiyama, T. "Organic Reactions"; Wiley: New York, 1982; Vol. 28, Chapter 3.

(38) 4,7-Dimethoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**2**) was prepared from *N*,*N*-diethyl-2,5-dimethoxybenzamide (i) as shown below.



Metalation of i using a procedure described by Snieckus et al.[39] (*sec*-BuLi, TMEDA, THF, −78 °C) followed by quenching with DMF and then hydrolysis (HOAc, HCl, H_2O, Δ) furnished the crude 3-hydroxyisobenzofuranone ii. Replacement of the 3-hydroxyl in ii (PhSH, TsOH, Δ; 55% from i) and then oxidation (H_2O_2, HOAc, room temperature, 18 h; 94%) furnished **2**.

(39) deSilva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.

(40) The 7-hydroxy epimer of **2a** was not observed.

mol) in THF (400 mL). The cooling bath was then removed and the reaction was stirred at ambient temperature overnight. A solution of vinylmagnesium bromide (0.4 mol, 308.0 mL, 1.3 molar in THF) was added next. The mixture was refluxed for 4 h, then cooled to room temperature, and quenched with saturated ammonium chloride solution (400 mL). The organic layer was separated and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic layers were washed with water (100 mL) and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to furnish a colorless syrupy liquid which upon distillation gave 42.0 g (65%) of the diol **3a**: bp 105–110 °C (0.6 mm) [lit.[22] bp 96–98 (0.3 mm)]; ^{1}H NMR δ 6.1–5.6 (m, 1 H), 5.3–5.0 (m, 2 H), 4.2–4.0 (m, 1 H), 3.7–3.4 (m, 1 H), 2.1 (s, br, 2 H), 1.7–1.2 (m, 8 H), 0.92 (t, 3 H, J = 7.5 Hz).

3,7-Diacetoxy-1-nonene (3b). A mixture of the diol **3a** (45.4 g, 0.29 mol), acetic anhydride (137 mL, 1.45 mol), and pyridine 250 mL) was heated on a steam bath for 24 h. Workup in the usual manner furnished 65.3 g (94%) of the diacetate **3b** with bp 81–87 °C (0.04 mm); ^{1}H NMR δ 5.95–5.14 (m, 1 H), 5.4–5.0 (m, 3 H), 4.79 (quintet, 1 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 1.8–1.0 (m, 8 H), and 0.88 (t, 3H, J = 7.0 Hz); mass spectrum, m/z 242 ($M^{+\cdot}$).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.54; H, 8.99.

7-Acetoxynona-1,3-diene (4). A mixture of diacetate **3b** (20.0 g, 82.6 mmol), triphenylphosphine (2.2 g, 8.4 mmol), and palladium acetate (0.2 g, 0.89 mmol) in freshly distilled dioxane (40 mL) was heated at reflux for 1 h.[23] Dioxane was removed under reduced pressure and the residue was fractionated to give 12.3 g (82%) of diene **4** with bp 110–120 °C (119 mm). This product was shown to be a 76:24 mixture of E and Z isomers by capillary GC. ^{1}H NMR δ 6.8–4.6 (m, 6 H), 2.35–1.9 (m, 2 H), 2.04 (s, 3 H), 1.8–1.3 (m, 4 H), 0.88 (t, 3 H, J = 7 Hz); mass spectrum, m/z 182 ($M^{+\cdot}$).

Ethyl 2-(3-Acetoxypent-1-yl)cyclohex-3-ene-1-carboxylate (5a). A glass bomb charged with ethyl acrylate (36 g, 0.36 mol), diene **4** (33.0 g, 0.18 mol), and hydroquinone (0.6 g) was heated at 155 °C for 24 h. The bomb was cooled to room temperature, and the contents distilled to give 7.0 g of unreacted Z diene **4** and 36.7 g (72%) of the adduct **5a**. This product was shown by GC analysis to be a 40:60 mixture of cis and trans isomers: bp 110–120 °C (0.3 mm); ^{1}H NMR δ 5.80–5.40 (m, 2 H), 4.75 (quintet, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 2.8–1.7 (m, 4 H), 2.1 (s, 3 H), 1.7–1.3 (m, 8 H), 1.26 (t, 3 H, J = 7.0 Hz) and 0.87 (t, 3 H, J = 7 Hz); mass spectrum, m/z 282 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.89, H, 9.12.

2-[3-(Benzyloxy)pent-1-yl]cyclohex-3-ene-1-carboxylic acid (5b). A stirred solution of the Diels–Alder adduct **5a** (34 g, 0.12 mol), ethanol (200 mL), and aqueous potassium hydroxide (33.6 g, 0.6 mol, in 170 mL water) was heated at reflux for 16 h. The ethanol was removed under reduced pressure and the aqueous solution was acidified with concentrated hydrochloric acid at 0 °C and then repeatedly extracted with ether (5 × 200 mL). The combined organic phases were washed with brine (200 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield essentially pure hydroxy acid in quantitative yield. This substance was used without further purification. ^{1}H NMR δ 6.3 (broad, 2 H, exchangeable in D_2O), 5.90–5.5 (m, 2 H), 3.9–3.4 m, 1 H), 3.0–1.1 (m, 12 H), 0.93 (t, 3 H, J = 7.0 Hz).

To a stirred suspension of sodium hydride (7.4 g, 50% in mineral oil, 150 mmol) in dry THF (200 mL) under N_2 was slowly added a solution of the hydroxy acid (13.0 g, 61.3 mmol) in dry THF (100 mL). The mixture was stirred at room temperature for 1 h, then benzyl bromide (36.4 mL, 300 mmol) was added, and the reaction was heated at reflux for 3 h. The mixture was cooled in an ice bath and water (100 mL) was added dropwise to destroy excess sodium hydride. The aqueous layer was separated and washed with ether (50 mL, discarded) to remove excess benzyl bromide and mineral oil. The water layer was then acidified with hydrochloric acid (12 N, 20 mL), and extracted with ether (5 × 200 mL). The combined organic layers were washed with brine (100 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to obtain 15.3 g (83%) of the benzyl ether acid **5b**: ^{1}H NMR δ 7.31 (s, 5 H), 5.9–5.4 (m, 2 H), 4.48 (s, 2 H), 3.5–3.1 (m, 1 H), 2.8–1.1 (m, 12 H), 0.9 (t, 3 H, J = 7.2 Hz); mass spectrum, m/z 302 ($M^{+\cdot}$).

2-[2-(3-(Benzyloxy)pent-1-yl)cyclohex-3-en-1-yl]acetonitrile (6a). A solution of the acid **5b** (14.5 g, 48 mmol) in anhydrous ether (200 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (2.3 g, 60 mmol) also in anhydrous ether (200 mL). The reaction was heated at reflux for 1 h, then cooled in an ice bath. Water (2.3 mL), aqueous sodium hydroxide solution (15%, 2.3 mL), and water (7.0 mL) were successively added to destroy the excess hydride reagent. The aluminate precipitate was filtered and the cake washed with ether (100 mL). The filtrate was dried ($MgSO_4$), filtered, and evaporated in vacuo to give 13.4 g (97%) of the corresponding alcohol as an oil. A sample (1 g) was chromatographed on silica gel to give 0.98 g of the alcohol as a mixture of cis and trans isomers (GC): ^{1}H NMR δ 7.32 (s, 5 H), 5.8–5.5 (m, 2 H), 4.50 (s, 2 H), 3.7–3.4 (m, 2 H), 3.4–3.2 (m, 1 H), 2.3–1.7 (m, 3 H), 1.7–1.1 (m, 9 H), 0.92 (t 3 H, J = 7 Hz); mass spectrum, m/z 288 ($M^{+\cdot}$).

Methanesulfonyl chloride (3.7 mL, 47.4 mmol) was added to a stirred solution of the above alcohol (10.5 g, 36.5 mmol) in pyridine (15 mL) over a period of 5 min. The mixture was stirred at room temperature for 1 h and then worked up in the usual manner to give the crude mesylate (13.4 g): ^{1}H NMR δ 7.32 (s, 5 H), 5.8–5.4 (m, 2 H), 4.48 (s, 2 H), 4.3–4.0 (m, 2 H), 3.48–3.1 (m, 1 H), 3.0–2.8 (m, 3 H), 2.4–1.1 (m, 12 H), 0.91 (t, 3 H, J = 7 Hz).

A mixture of the mesylate (13.5 g, 36.5 mmol), sodium cyanide (3.6 g, 73 mmol), and sodium iodide (1.0 g) in dimethylformamide (100 mL) was heated on a steam bath for 24 h. The reaction was cooled, then poured into water (250 mL), and extracted with ether (3 × 200 mL). The combined ether extracts were washed with water (100 mL) and brine (3 × 100 mL), then dried ($MgSO_4$), filtered, and concentrated to give 11.0 g of an oil. This material was chromatographed on silica gel (250 g, CH_2Cl_2 as solvent) to give 10.0 g (92%) of pure nitrile **6a**: ^{1}H NMR δ 7.33 (s, 5 H), 5.8–5.4 (m, 2 H), 4.50 (AB quartet, 2 H, J = 12 Hz), 3.5–3.15 (m, 1 H), 2.4–1.0 (m, 14 H), 0.92 (t, 3 H, J = 7.4 Hz); mass spectrum, m/z 297 ($M^{+\cdot}$).

2-[2-(3-(Benzyloxy)pent-1-yl)cyclohex-3-en-1-yl]acetic acid (6b). A mixture of the nitrile **6a** (25.3 g, 83.3 mmol) and potassium hydroxide (18.7 g, 333 mmol) in ethanol (100 mL) and water (20 mL) was heated at reflux for 4 days. The ethanol was removed at reduced pressure and replaced with water (100 mL). The basic solution was extracted with ether (50 mL) which was discarded. The aqueous phase was then acidified with hydrochloric acid (12 N, 30 mL) and extracted with ether (5 × 200 mL). The combined ether extracts were washed with brine (5 × 50 mL), then dried ($MgSO_4$), filtered, and concentrated to furnish 25.0 g (95%) of the acid **6b** as an oil: ^{1}H NMR δ 7.32 (s, 5 H), 5.8–5.4 (m, 2 H), 4.55 (s, 2 H), 3.5–3.1 (m, 1 H), 2.5–1.1 (m, 14 H), 0.92 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 316 ($M^{+\cdot}$).

9-[3-(Benzyloxy)pent-1-yl]-8-iodo-6-oxabicyclo[3.3.1]non-3-one (7a). To a solution of the unsaturated acid **6b** (8.0 g, 25.3 mmol) in acetonitrile (150 mL) was added collidine (3.7 mL, 27.8 mmol) followed by iodine (14.14 g, 55.7 mmol), and the mixture was stirred at room temperature for 24 h. Benzene (250 mL) was added to the mixture and the solution was transferred to a separatory funnel and successively washed with sodium thiosulfate solution (10%, 2 × 50 mL), water (50 mL), and brine (3 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a light brown viscous oil which was filtered through a short column of silica gel (100 g, CH_2Cl_2) to give 9.0 g (81%) of iodolactones **7a**. A sample (1.0 g) of the iodolactone mixture was chromatographed (silica gel 50 g, methylene chloride) to obtain the individual isomers.

Data for the less polar isomer: TLC R_f 0.6 (methylene chloride–ethyl acetate, 9:1); ^{1}H NMR δ 7.33 (s, 5 H), 5.7–5.3 (m, 4 H), 3.35 (s, br, 1 H), 3.0–2.3 (m, 2 H), 2.2–1.75 (m, 3 H), 1.75–1.2 (m, 9 H), 0.92 (t, 3 H, J = 7 Hz); mass spectrum, m/z 442 ($M^{+\cdot}$). Data for the more polar isomer: TLC R_f 0.5 (methylene chloride–ethyl acetate, 9:1); ^{1}H NMR δ 7.33 (s, 5 H), 5.8–5.35 (m, 4 H), 3.45 (quintet, 1 H, J = 7.0 Hz), 3.05–2.4 (m, 2 H), 2.2–1.8 (m, 6 H), 1.8–1.3 (m, 6 H), 0.94 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 442 ($M^{+\cdot}$).

9-[2-(Benzyloxy)pent-1-yl]-6-oxabicyclo[3.3.1]non-6-en-3-one (8). To a stirred solution of the iodolactones **7a** (8.5 g, 19.2 mmol) in dry benzene (100 mL) under nitrogen was added DBU (8.8 g, 57.6 mmol), and the mixture was heated at reflux for 5 h. The resulting mixture was partitioned between ether (100 mL) and water (100 mL). The layers were separated, and the aqueous solution was further extracted with ether (2 × 50 mL). The combined organic phases were washed with hydrochloric acid (4 N, 25 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to furnish 5.8 g (96%) of the unsaturated bicyclic lactones **8** as a colorless oil: ^{1}H NMR δ 7.32 (s, 5 H), 6.1–6.8 (m, 2 H), 4.7–4.3 (m, 3 H), 3.5–3.1 (m, 1 H), 2.95–1.2 (m, 12 H), 0.93 (t, 3 H, J = 7.2 Hz); mass spectrum, m/z 314 ($M^{+\cdot}$).

Methyl 2-[6-(Benzyloxy)pent-1-yl)-1-hydroxycyclohex-2-en-5-yl]-acetate (9). A solution of potassium hydroxide (1.4 g, 35 mmol) in methanol–water (1:1, 25 mL) was added to the lactone **8** (5.5 g, 17.5 mmol) and the resulting mixture was heated on a steam bath overnight. Water (10 mL) was added and the methanol was removed under reduced pressure. The aqueous solution was acidified with hydrochloric acid (7.0 mL, 6 N) at 0 °C and then extracted with ether (5 × 100 mL). The combined ether extracts were washed with water (10 mL) and brine (2 × 25 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give 5.5 g (95%) of the corresponding acid: ^{1}H NMR δ 7.31 (s, 5 H), 6.5 (s, br, 2 H), 5.69 (s, br, 2 H), 4.5 (AB quartet, 2 H, J = 12 Hz), 4.3–4.1 (m, 1 H), 3.48–3.05 (m, 1 H), 2.5–1.2 (m, 12 H), 0.91 (t, 3 H, J = 7.1 Hz); mass spectrum, m/z 314 ($M^{+\cdot}$ – 18). Due to the tendency of this

compound to relactonize, it was used in the next step without further purification.

A mixture of the hydroxy acid (5.5 g, 16.6 mmol) and DBU (3 mL, 20 mmol) in acetonitrile (60 mL) was stirred for 15 min, and then iodomethane (2.5 mL, 40 mmol) was added.[27] The reaction was continued for 16 h at room temperature, then diluted with ether (200 mL). The ether solution was transferred to a separatory funnel and successively washed with cold hydrochloric acid (6 N, 20 mL), water (25 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated to give 5.5 g of the ester **9** as a light yellow oil. This product was used in the next step without further purification. A small amount (0.5 g) of this material was purified through a silica gel column to furnish a TLC homogeneous ester (0.49 g): ^1H NMR δ 7.32 (s, 5 H), 5.7 (br, s, 2 H), 4.50 (AB quartet, 2 H, J = 12.0 Hz), 4.3–4.1 (m, 1 H), 3.65 (s, 3 H), 3.5–3.15 (m, 1 H), 2.5–1.2 (m, 12 H), 0.92 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 346 ($M^{+\cdot}$).

Methyl [6-(3-(Benzyloxy)pent-1-yl)-1-oxo-2-cyclohexen-5-yl]acetate (10). Dimethyl sulfoxide (2.27 mL, 32.0 mmol) was added dropwise to a cold (−78 °C) magnetically stirred solution of oxalyl chloride (1.8 mL, 21.0 mmol) in methylene chloride (25 mL) under nitrogen and the mixture stirred for 10 min. To this solution was added the alcohol **9** (5.5 g, 16 mmol) in methylene chloride (25 mL). After 45 min, triethylamine was added to the reaction which was allowed to warm to room temperature over 1 h. Saturated bicarbonate (50 mL) and methylene chloride (50 mL) were added to the reaction and the methylene chloride layer was separated. The aqueous layer was further extracted with methylene chloride (2 × 50 mL). The combined organic phases were washed with brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give a light brown oil. Chromatography (silica gel, CH_2Cl_2) of the material afforded 4.5 g (82%) of pure unsaturated ketone **10** as a colorless oil: ^1H NMR δ 7.32 (s, 5 H), 7.0–6.62 (m, 1 H), 6.1–5.8 (m, 1 H), 4.49 (s, 2 H), 3.67 (s, 3 H), 3.5–3.2 (m, 1 H), 2.9–2.0 (m, 6 H), 1.9–1.2 (m, 6 H), 0.91 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 344 ($M^{+\cdot}$).

Methyl 2-[3-(3-(Benzyloxy)pent-1-yl)-4-hydroxy-5-methoxyanthraquinon-2-yl]acetate (13a). A magnetically stirred solution of lithium *tert*-butoxide (16.5 mmol) was initially prepared by adding *n*-butyllithium (12.7 mL, 16.5 mmol of 1.3 molar solution) to *tert*-butyl alcohol (1.58 mL, 16.8 mmol) in THF (50 mL) at 0 °C under nitrogen. This solution was cooled to −78 °C and the (phenylsulfonyl)isobenzofuranone **11** (1.7 g, 5.6 mmol) was added as a solid in one portion and the mixture was stirred for 10 min to generate a slurry of the anion. A solution of the enone **10** (2.5 g, 7.27 mmol) in THF (10 mL) was then rapidly added. The cooling bath was immediately removed and the reaction was allowed to come to room temperature for 1 h, then refluxed for 15 min. A number of striking color changes were observed as the reaction proceeded. Upon addition of enone **10**, the deep yellow to orange-yellow color of the initial anion slurry became a much deeper orange as the anion dissolved. As the reaction warmed, a clear deep red solution formed and finally a red precipitate.

The reaction was cooled in an ice bath and hydrochloric acid (4 N, 5 mL) was added. The fluorescent yellow solution was transferred to a separatory funnel and extracted with ethyl acetate (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give impure **12** as a yellow solid. Analysis of a TLC showed a major and minor product (~9:1) of similar R_f. A small sample (~100 mg) was separated using a chromatotron. The major product was the desired methyl ester **12**: ^1H NMR δ 14.93 (s, 1 H), 14.73 (s, 1 H), 7.6 (d, 1 H, J = 7.5 Hz), 7.48 (t, 1 H, J = 7.5 Hz), 7.24 (s, 5 H), 6.81 (d, 1 H, J = 7.5 Hz), 4.44 (s, 2 H), 3.98 (s, 3 H), 3.64 (s, 3 H), 3.5–3.0 (m, 1 H), 3.0–2.1 (m, 6 H), 1.8–1.4 (m, 6 H), 0.91 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 506 ($M^{+\cdot}$).

The minor component was identified as the *tert*-butyl ester from its mass spectrum which gave m/z 548 for the parent ion and M − 44 as the base peak. This material, on heating at 50 °C for 1 h in methanol saturated with hydrogen chloride gas, quantitatively gave the methyl ester **12**.

The initially received condensation product was dissolved in methanol (200 mL) and dry hydrogen chloride was injected for 1 min. The reaction mixture was heated at reflux for 2 h at which point analysis of a TLC showed complete conversion of *tert*-butyl ester to the methyl ester **12**. The methanol was evaporated at reduced pressure and the residue was taken up in DMF and heated at 70 °C for 5 h under an oxygen atmosphere. The reaction was poured into water (200 mL) and repeatedly extracted with ethyl acetate (5 × 200 mL). The combined organic extracts were washed with brine (5 × 200 mL), then dried, filtered, and evaporated at reduced pressure to give impure **13a**. Chromatography of this product on silica gel (100 g, CH_2Cl_2) gave 2.25 g (80%) of pure quinone **13a**: mp 115–116 °C; ^1H NMR δ 13.40 (s, 1 H), 7.96 (d, 1 H, J = 7.5 Hz), 7.72 (t, 3 H, J = 7.5 Hz), 7.63 (s, 1 H), 7.38–7.25 (m, 6 H), 4.56 (s, 2 H), 4.07 (s, 3 H), 3.77 (s, 2 H), 3.68 (s, 3 H), 3.52 (quintet, 1 H), 2.87 (t, 2 H, J = 8.0 Hz), 1.98–1.4 (m, 4 H), 0.96 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 502 ($M^{+\cdot}$).

Anal. Calcd for $C_{30}H_{30}O_7$: C, 71.70; H, 6.01. Found: C, 71.50; H, 5.94.

Methyl [3-(3-(Benzyloxy)pent-1-yl)-4,5-dimethoxyanthraquinon-2-yl]acetate (13c). A mixture of **13a** (1.41 g, 2.8 mmol), dimethyl sulfate (1.86 mL, 19.8 mmol), and potassium carbonate (2.7 g, 19.7 mmol) in dry acetone (60 mL) was heated at reflux for 8 h, then cooled, and filtered. The filtrate was concentrated in vacuo, the residue was taken up in ethyl acetate (50 mL), and triethylamine (6 mL) was added. The mixture was allowed to react at room temperature for 0.5 h and then poured into hydrochloric acid solution (4 N, 25 mL). The aqueous layer was separated and further extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The yellow residue was recrystallized (benzene–hexane) to give 1.32 g (91%) of the pure methyl ether **13c** with mp 77–79 °C: ^1H NMR δ 7.87 (s, 1 H), 7.84 (d, 1 H, J = 7.5 Hz), 7.64 (t, 1 H, J = 7.9 Hz), 7.35–7.29 (m, 6 H), 4.57 (s, 2 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.78 (s, 2 H), 3.68 (s, 3 H), 3.45 (m, 1 H), 2.84 (t, broad, 2 H), 1.9–1.4 (m, 4 H), 0.96 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 516 ($M^{+\cdot}$).

Anal. Calcd for $C_{31}H_{32}O_7$: C, 72.07; H, 6.24. Found: C, 71.03, H, 6.19.

Methyl [4,5-Dimethoxy-3-(3-hydroxypent-1-yl)anthraquinon-2-yl]-acetate (13d). A mixture of ester **13c** (250 mg, 48 mmol), hydrochloric acid (12 N, 2 drops), and Pd/C (10%, 25 mg) in methanol (50 mL) was hydrogenolyzed at room temperature under 22 psi for 1 h. The mixture was filtered to remove the catalyst, and the filtrate was poured into brine (100 mL) and extracted with methylene chloride (3 × 50 mL). The methylene chloride extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give an orange residue which was recrystallized (benzene–hexane) to give 195 mg (95%) of **13d** with mp 126–129 °C: ^1H NMR δ 7.89 (s, 1 H), 7.84 (d, 1 H, J = 8.0 Hz), 7.63 (t, 1 H, J = 8.0 Hz), 7.30 (d, 1 H, J = 8 Hz), 4.00 (s, 3 H), 3.98 (s, 3 H), 3.83 (s, 2 H), 3.71 (s, 3 H), 3.48 (m, 1 H), 2.91 (t, 2 H, J = 7.2 Hz), 2.16 (s, broad, 1 H), 1.8–1.3 (m, 4 H), 0.93 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 426 ($M^{+\cdot}$).

Methyl [4-Hydroxy-3-(3-hydroxypent-1-yl)-5-methoxyanthraquinon-2-yl]acetate (13b). This compound was prepared in the manner similar to the foregoing experiment. Thus, benzyl ether **13a** (0.2 g) was hydrogenolyzed to give 146 mg (89%) of the alcohol **13b**: ^1H NMR δ 13.56 (s, 1 H), 7.95 (dd, 1 H, J = 8.0 Hz, J = 1.0 Hz), 7.72 (t, 1 H, J = 8.0 Hz), 7.67 (s, 1 H), 7.34 (dd, 1 H, J = 8.0 Hz, J = 1.0 Hz), 4.07 (s, 3 H), 3.82 (s, 2 H), 3.72 (s, 3 H), 3.70–3.3 (m, 1 H), 2.94 (t, 2 H, J = 7.8 Hz), 1.85–1.2 (m, 4 H), 0.93 (t, 3 H, J = 7.0 Hz).

Methyl [4,5-Dimethoxy-3-(3-oxopent-1-yl)anthraquinon-2-yl]acetate (14b). To a vigorously stirred suspension of pyridinium chlorochromate (0.6 g, 2.8 mmol) in dry methylene chloride (40 mL) was added a solution of alcohol **13d** (0.32 g, 0.75 mmol) in methylene chloride (20 mL).[32] The reaction was stirred at room temperature for 3 h, then diluted with methylene chloride (20 mL), filtered and evaporated. The residue was taken up in methylene chloride and filtered through a short column of silica gel (25 g) to remove residual chromium salts. The eluant was evaporated to give 0.31 g (97%) of pure **21** as light yellow solid with mp 142–145 °C: ^1H NMR δ 7.86 (s, 1 H), 7.82 (d, 1 H, J = 8.1 Hz), 7.64 (t, 1 H, J = 8.1 Hz), 7.30 (d, 1 H, J = 8.1 Hz), 4.01 (s, 3 H), 3.95 (s, 3 H), 3.86 (s, 2 H), 3.71 (s, 3 H), 2.97 (t, 2 H, J = 7.0 Hz), 2.77 (t, 2 H, J = 7.0 Hz), 2.41 (q, 2 H, J = 7.0 Hz), 1.06 (t, 3 H, J = 7.0 Hz); mass spectrum m/z 424 ($M^{+\cdot}$).

Anal. Calcd for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70. Found: C, 67.60; H, 5.60.

Methyl [4-Hydroxy-5-methoxy-3-(3-oxopent-1-yl)anthraquinon-2-yl]-acetate (14a). Oxidation of alcohol **13b** (20 mg, 0.049 mmol) with pyridinium chlorochromate, according to the preceding procedure, yielded 17 mg of **14a** (85%) with mp 225 °C dec: ^1H NMR δ 13.39 (s, 1 H), 7.94 (dd, 1 H, J = 8.0 Hz, J = 1.0 Hz), 7.14 (t, 1 H, J = 8.0 Hz) 7.33 (dd, 1 H, J = 8.0 Hz, J = 1.0 Hz), 4.06 (s, 3 H), 3.87 (s, 2 H), 3.70 (s, 3 H), 2.90 (m, 4 H), 2.53 (d, 1 H, J = 7.0 Hz), 2.35 (d, 1 H, J = 7.0 Hz), 1.05 (t, 3 H, J = 7.5 Hz).

10(*R*,*S*)-(Methoxycarbonyl)-4,6-dimethoxy-9(*R*,*S*)-ethyl-9(*R*,*S*)-hydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (15c) and 10(*R*,*S*)-(Methoxycarbonyl)-4,6-dimethoxy-9(*SR*)-ethyl-9(*S*,*R*)-hydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (15d). To a magnetically stirred solution of magnesium methoxide (0.6 g, 7 mmol) in methanol (50 mL) at room temperature was added in one portion keto ester **14b** (0.3 g, 0.7 mmol), and the mixture was stirred under nitrogen atmosphere for 5 h at room temperature. The reaction was quenched with hydrochloric acid (10 mL, 3 N) and partitioned between brine (50 mL) and methylene chloride (100 mL). The phases were separated, and the

aqueous layer was extracted with methylene chloride (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid. This material was chromatographed on silica gel (50 g, ether:hexane:methylene chloride, 1:1:2) to furnish 210 mg of **15c** and 60 mg of **15d** (combined yield, 90%).

Data for **15c**: mp 193–197 °C; ^{1}H NMR δ 7.84 (dd, 1 H, J = 1 Hz, J = 8.1 Hz), 7.83 (s, 1 H), 7.64 (t, 1 H, J = 8.1 Hz), 7.3 (dd, 1 H, J = 1 Hz, J = 8.1 Hz), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.96 (s, 1 H), 3.71 (s, 3 H), 3.18–2.9 (m, 2 H), 2.4–2.1 (m, 1 H), 2.1–1.8 (m, 1 H), 1.7–1.5 (m, 3 H), 1.07 (t, 3 H, J = 7.5 Hz); mass spectrum, m/z 424 ($M^{+\cdot}$).

Anal. Calcd for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70. Found: C, 67.71; H, 5.63.

Data for **15d**: mp 138–140 °C; ^{1}H NMR δ 7.84 (dd, 1 H, J = 1.0 Hz, J = 8.0 Hz), 7.76 (s, 1 H), 7.64 (t, 1 H, J = 8.0 Hz) 7.30 (dd, 1 H, J = 1.0 Hz, J = 8.0 Hz), 4.01 (s, 3 H), 3.97 (s, 3 H), 3.92 (s, 1 H), 3.85 (s, 3 H), 3.2–2.85 (m, 2 H), 2.45–2.1 (m, 1 H), 1.9–1.4 (m, 4 H), 0.99 (t, 3 H, 7.0 Hz).

Cyclization of Keto Ester 14a with Triton B. To a well-stirred solution of keto ester **14a** (8.0 mg, 0.02 mmol) in methanol–methylene chloride (1.0 mL, 2:1) under nitrogen at −20 °C was added a solution of Triton B in methanol (40%, 0.067 mL). After the resulting solution was stirred at this temperature for 8 h, it was quenched with dilute hydrochloric acid solution (2 N, 1.5 mL). The reaction was poured in methylene chloride (10 mL) and washed with brine (20 mL). The organic layers were dried ($MgSO_4$), filtered, and evaporated to give a yellow solid which was chromatographed to furnish an inseparable mixture of **15a** and **15b** (7.6 mg, 96%). Examination of this mixture by its ^{1}H NMR indicated that it consisted of **15a** and **15b** in approximately a 1:1 ratio, as judged by their characteristic chemical shifts of methoxycarbonyl methyl groups.

(±)-7-Deoxyaklavinone (16). To a well-stirred solution of **15c** (100 mg) in methylene chloride (50 mL) was added aluminum chloride (200 mg) and the resulting mixture was stirred under nitrogen at room temperature for 2 h. The reaction was quenched with hydrochloric acid (6 N, 10 mL) and allowed to stand overnight at room temperature. The phases were separated, and the aqueous layer was again extracted with methylene chloride (50 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. This was recrystallized (methylene chloride–hexane) to yield 90 mg (97%) of **16**: mp 207–209 °C (lit.[10] mp 209–211 °C). The spectral characteristics of this product were in full agreement with those reported for an authentic sample.

Methyl 2-[3-(3-(Benzyloxy)pent-1-yl)-5,8-dimethoxy-4-hydroxyanthraquinon-2-yl]acetate (19a). This compound was prepared in a manner analogous to that employed for quinone **13a**. Condensation of 4,7-dimethoxy-3-phenylsulfonylisobenzofuranone (**17**)[38] (2.6 g, 7.8 mmol) with the cyclohexenone **10** (3.5 g, 10.1 mmole) gave, after chromatography, 3.4 g (82%) of pure quinone **19a** with mp 128–130 °C: ^{1}H NMR δ 13.1 (s, 1 H), 7.54 (s, 1 H), 7.35–7.32 (m, 6 H), 7.26 (s, 1 H), 4.55 (s, 2 H), 4.00 (s, 3 H), 3.98 (s, 3 H), 3.76 (s, 2 H), 3.67 (s, 3 H), 3.6–3.2 (m, 1 H), 2.84 (t, 2 H, J = 8.3 Hz), 1.9–1.4 (m, 4 H), 0.95 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 532 ($M^{+\cdot}$).

Anal. Calcd for $C_{31}H_{32}O_8$: C, 69.91; H, 6.06. Found: C, 69.85; H, 6.17.

Methyl [3-(3-(Benzyloxy)pent-1-yl)-4,5,8-trimethoxyanthraquinon-2-yl]acetate (19c). The methyl ether **19c** was prepared using the procedure described for **13c**. From the anthraquinone **19a** (1.15 g, 2.16 mmol) there was obtained 1.1 g (93%) of the methyl ether **19c** with mp 83–85 °C: ^{1}H NMR δ 7.75 (s, 1 H), 7.34 (s, 6 H), 7.24 (s, 1 H), 4.56 (s, 2 H), 3.95 (s, 9 H), 3.76 (s, 2 H), 3.67 (s, 3 H), 3.6–3.2 (m, 1 H), 2.81 (t, 2 H, J = 8 Hz), 1.9–1.4 (m, 4 H), 0.95 (t, 3 H, J = 7.0 Hz); mass spectrum, m/e 546 ($M^{+\cdot}$).

Anal. Calcd for $C_{32}H_{34}O_8$: C, 70.31; H, 6.27. Found: C, 70.50; H, 6.46.

Methyl [3-(3-Hydroxypent-1-yl)-4,5,8-trimethoxyanthraquinon-2-yl]-acetate (19d). The benzyl ether **19c** (1.1 g) was hydrogenolyzed as described for the preparation of **13d** to yield 0.86 g (93%) of the alcohol **19d** with mp 145–146 °C: ^{1}H NMR δ 7.78 (s, 1 H), 7.35 (s, 1 H), 7.24 (s, 1 H), 3.96 (s, 3 H), 3.95 (s, 6 H), 3.81 (s, 2 H), 3.70 (s, 3 H), 3.48 (m, 1 H), 2.89 (t, 2 H, J = 8.0 Hz), 2.08 (s, 1 H), 1.8–1.3 (m, 4 H), 0.92 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 456 ($M^{+\cdot}$).

Anal. Calcd for $C_{25}H_{28}O_8$: C, 65.78; H, 6.18. Found: C, 65.53; H, 6.32.

Methyl [5,8-Dimethoxy-4-hydroxy-3-(3-hydroxypent-1-yl)anthraquinon-2-yl]acetate (19b). As described for **13d**, the alcohol **19b** (0.22 g, 88%) was obtained by hydrogenolysis of **19a** (0.3 g, 0.56 mmol): mp 161–162 °C; ^{1}H NMR δ 13.29 (s, 1 H), 7.59 (s, 1 H), 7.36 (s, 2 H), 4.02 (s, 3 H), 3.99 (s, 3 H), 3.82 (s, 2 H), 3.71 (s, 3 H), 3.5 (m, 1 H), 2.92 (m, 2 H), 1.90–1.30 (m, 4 H), 0.93 (t, 3 H, J = 7.5 Hz).

Methyl [3-(3-Oxypent-1-yl)-4,5,8-trimethoxyanthraquinon-2-yl]acetate (20b). This product was prepared by using the procedure employed for the preparation of **14b**. From the alcohol **19d** (0.85 g, 1.86 mmol) there was obtained 0.83 g (93%) of the keto ester **20b** with mp 111–114 °C: ^{1}H NMR δ 7.75 (s, 1 H), 7.26 (s, 2 H), 3.96 (s, 9 H), 3.83 (s, 2 H), 3.70 (s, 3 H), 3.2–2.56 (m, 4 H), 2.4 (q, 2 H, J = 7.0 Hz), 1.05 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 454 ($M^{+\cdot}$).

Anal. Calcd for $C_{25}H_{26}O_8$: C, 66.07; H, 5.77. Found: C, 65.80; H, 5.71.

Methyl [5,8-Dimethoxy-4-hydroxy-3-(3-oxopent-1-yl)anthraquinon-2-yl]acetate (20a). When the procedure described in the preparation of **14b** was followed, the alcohol **19b** (0.16 g, 0.36 mmol) was oxidized to give 0.153 g (96%) of keto ester **20a** with mp 213–215 °C: ^{1}H NMR δ 13.12 (s, 1 H), 7.55 (s, 1 H), 7.36 (s, 2 H), 4.02 (s, 3 H), 3.99 (s, 3 H), 3.86 (s, 2 H), 3.7 (s, 3 H), 2.93 (m, 4 H), 2.50 (d, 1 H, J = 7.0 Hz), 2.36 (d, 1 H, J = 7.0 Hz), 1.05 (t, 3 H, J = 7.5 Hz).

10(R,S)-(Methoxycarbonyl)-9(R,S)-ethyl-9(R,S)-hydroxy-7,8,9,10-tetrahydro-1,4,6-trimethoxy-5,12-naphthacenedione (21c) and 10(R,S)-(Methoxycarbonyl)-(S,R)-ethyl-9(S,R)-hydroxy-7,8,9,10-tetrahydro-1,4,6-trimethoxy-5,12-naphthacenedione (21d). Keto ester **20b** (0.2 g, 0.44 mmol) was cyclized with magnesium methoxide (0.38 g, 4.4 mmol) in a manner identical with that employed for the preparation of **15c** and **15d**. After the usual workup of the reaction, chromatographic separation furnished **21c** (156 mg) and **21d** (28 mg). The combined yield was 92%.

Data for **21c**: mp 180–183 °C; ^{1}H NMR δ 7.73 (s, 1 H), 7.26 (s, 2 H), 3.98 (s, 3 H), 3.95 (s, 7 H), 3.70 (s, 3 H), 3.15–2.87 (m, 2 H), 2.4–2.05 (m, 1 H), 2.0–1.8 (m, 1 H), 1.65–1.45 (m, 3 H), 1.05 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 454 ($M^{+\cdot}$).

Data for **21d**: mp 193–195 °C; ^{1}H NMR δ 7.66 (s, 1 H), 7.26 (s, 2 H), 3.96 (s, 9 H), 3.90 (s, 1 H), 3.83 (s, 3 H), 3.2–2.8 (m, 2 H), 2.4–2.0 (m, 1 H), 1.9–1.4 (m, 4 H), 0.98 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 454 ($M^{+\cdot}$).

Cyclization of Keto Ester 20a with Triton B. In a manner silimar to the one described for **14a**, the keto ester **20a** (20 mg, 0.045 mmol) was cyclized with a solution of Triton B (40%, 0.2 mL) at 0 °C for 4 h. The product isolated after chromatography (silica gel, ethyl acetate–methylene chloride, 1:5) was found to be an inseparable mixture, approximately 1:1, of **21a** and **21b** (as judged from the ^{1}H NMR spectrum).

(±)-ε-7-Deoxypyrromycinone (22). The methyl ether **21c** (100 mg, 0.22 mmol) was demethylated with aluminum chloride in the same manner as in the case of **16** to give 85 mg (94%) of **22** with mp 215 °C dec: ^{1}H NMR δ 13.00 (s, 1 H), 12.6 (s, 1 H), 12.26 (s, 1 H), 7.69 (s, 1 H), 7.27 (s, 2 H), 3.94 (s, 1 H), 3.73 (s, 3 H), 3.12–2.8 (m, 2 H), 2.4–2.0 (m, 1 H), 2.0–1.82 (m, 1 H), 1.65–1.4 (m, 3 H), 1.08 (t, 3 H, J = 7.0 Hz); mass spectrum, m/z 412 ($M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{20}O_8$: C, 64.08; H, 4.89. Found: C, 63.98; H, 5.04.

(±)-ε-Pyrromycinone (2a). To a stirred hot solution of (±)-ε-7-deoxypyrromycinone (**22**) (50 mg, 0.12 mmol) in carbon tetrachloride (50 mL) containing AIBN (5 mg) was added dropwise a solution of bromine (40 mg, 0.25 mmol) in carbon tetrachloride (25 mL). The mixture was heated at reflux for 2 h and then evaporated to dryness under reduced pressure. The residue was taken up in tetrahydrofuran–water (10 mL, 1:1), stirred for 2 h at room temperature, and then extracted with methylene chloride (3 × 25 mL). The organic phases were successively washed with sodium bicarbonate solution (10 mL) and brine (20 mL), then dried ($MgSO_4$), filtered, and evaporated to give a solid. Chromatography (silica gel, methylene chloride) of this material afforded 50 mg (96%) of ε-pyrromycinone **2a**, mp 203–205 °C. This synthetic material was identical in all respects (IR, NMR, MS) with an authentic sample prepared from pyrromycin.

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