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THE SYNTHESIS OF 6-DEOXYANTHRACYCLINONES: (±)α-CITROMYCINONE AND (±)4-DEMETHOXY-6-DEOXYDAUNOMYCINONE

JOHN S. SWENTON,* D. KEITH ANDERSON,[1a] CHARLES E. COBURN and ANTHONY P. HAAG[1b]
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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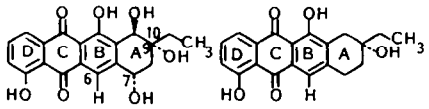
Abstract—Two synthetic approaches have been explored to prepare 6-deoxyanthracyclinones in general and α-citromycinone in particular. The first approach employed as starting materials 1,4,5-trimethoxynaphthalene and the Diels–Alder product from butadiene and maleic anhydride. The key step was the regioselective carbon acylation of 4-hydroxy-1,5-dimethoxynaphthalene with the half-ester acid chloride of *cis*-4,5-dicarboxycyclohexene. The resulting product was converted to 7,10-dideoxy-α-citromycinone; however, even the C-7—OH group required for glycosylation could not be introduced satisfactorily into this product. The second strategy employed as the key step the coupling of a highly functionalized metallated quinol equivalent with the monoketal of a benzocyclobutenedione. This route gave (±)-α-citromycinone and (±)-4-demethoxy-6-deoxydaunomycinone in quantities suitable for biological testing.

Introduction and Overview

While the syntheses of anthracyclinone aglycons having the 6,11-dihydroxyl[2] and the 6-hydroxyl[3] functionality have been extensively investigated, much less research has focused on aglycons having only the 11-hydroxyl functionality in the B-ring, the 6-deoxyanthracyclinones.[4–6] Several challenging synthetic targets have this B-ring substitution pattern;[7] and it has been hypothesized that anthracyclines from aglycons with this substitution pattern may show reduced cardiotoxicity.[8] Synthetically, α-citromycinone, **1**, is one of the most challenging of the 6-deoxyanthracyclinones. This aglycon, which was isolated in low yield (< 1%) from a fermentation broth by Brockmann,[9] became our prime synthetic objective.

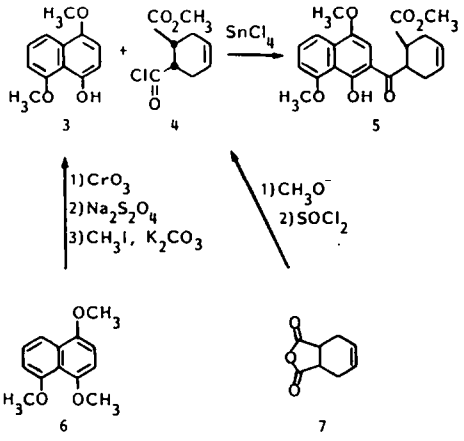


1 **2**

Our initial synthetic strategy to 6-deoxyanthracyclinones was to prepare tetracyclic precursors such as **2** regiospecifically and then to convert these systems to the desired A-ring substitution pattern using chemistry developed in the rhodomycinones. It was not appreciated at the time how unreliable these procedures were, especially for introduction of the 7-OH group.[10] While a usable regiospecific synthesis of **2** was developed, the 7-OH group required for glycosylation could never be satisfactorily introduced. However, this chemistry could be very useful for 6-deoxyanthracyclinone synthesis if an efficient method for introduction of the A-ring substituents could be developed. Our second approach used the 1,4-dipole-metallated *p*-quinol strategy[11] outlined in Scheme 1 and resulted in a synthesis of the title compounds in acceptable amounts for biological testing.

A classical approach to 6-deoxyanthracyclinones

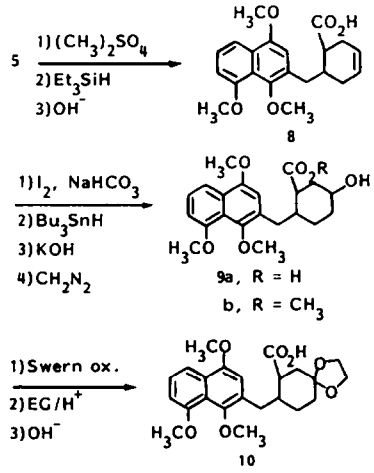
The general strategy for preparation of **2** was regiospecific Friedel–Crafts coupling of the naphthol **3** with an appropriate acid chloride. The requisite naphthol was prepared from 1,4,5-trimethoxynaphthalene, **6**,[12] by a sequence of Jones oxidation to juglone methyl ether, sodium dithionite reduction to the corresponding hydroquinone, and selective methylation of the 1-hydroxyl group. When **6** (55 g) was reacted as above without purification of intermediates, **3** (33 g) was obtained in 64% overall yield.



3 **4** **5** **6** **7**

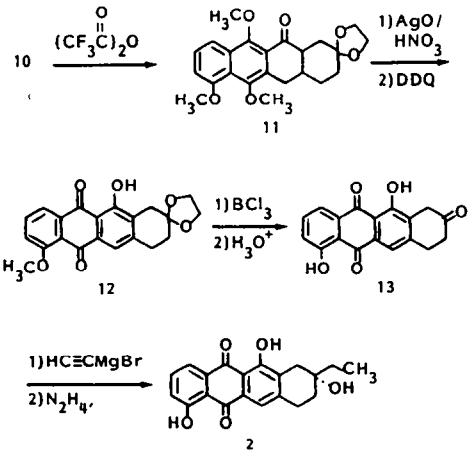
The key coupling step was regiospecific C-acylation of **3**. This chemistry was examined first with **4** which could be easily prepared from commercially available **7**.[13] While most Friedel–Crafts catalysts examined gave predominantly O-acylation, titanium tetrachloride and stannic chloride catalyzed reactions gave the desired C-acylated product **5** in 55% and 65% yields,[14] respectively. Some O-acylated product was noted in both reactions but was not quantified. Under the reaction conditions, the O-acylated product produced no **5**, but rather the cleavage product **3**. Thus, the C-acylated product obtained in these reactions does not appear to derive from Fries Rearrangement of an initial O-acylation product.

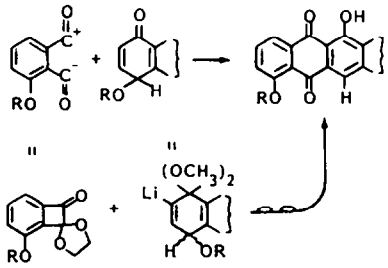
The coupling product **5** was then methylated, the ketone reduced with triethylsilane, and the ester hydrolyzed to afford **8** (94% overall). The required oxygen functionality, at what is eventually to be C-9, was introduced via a sequence of iodolactonization, reduction, and hydrolysis. While the conversion of **5** to



9a required six steps, no intermediates needed to be rigorously purified and **9a** could be obtained in 86% overall yield from **5** on a 20-gram scale. It is fortunate that the intermediates did not require purification since some epimerization occurred during the methylation step with dimethyl sulfate and purification of the individual compounds in the sequence was attendant with considerable loss of material.[16] Finally, **9a** was esterified with diazomethane, and the resulting ester **9b** was converted to **10**.

The final steps in the synthesis of the tetracyclic framework were trifluoroacetic anhydride cyclization and aromatization of the B-ring. The intramolecular Friedel–Crafts reaction occurred smoothly with no complications from the Hayashi rearrangement. However, the aromatization (**11** → **12**) could only be effected in good yield by silver oxide oxidation to the quinone followed by dehydrogenation with Pd-C in xylene or preferably with dichlorodicyanobenzoquinone and lutidine. This gave the tetracyclic **12** as golden crystals. Demethylation of **12** with accompanying ketal hydrolysis furnished **13** in 85% yield which was identical with an authentic sample.[17] Reaction of **13** with an excess of ethynyl magnesium bromide gave the ethynyl carbinol in 41% overall yield. Enolization of the ketone apparently contributed to the low yield since some **13** was always recovered from the reaction. The reduction of the acetylene to the desired Et group could be effected either by hydrogenation using rhodium on





Scheme 1. 1,4-Dipole-metallated *p*-quinol approach to 6-deoxyanthracyclinones.

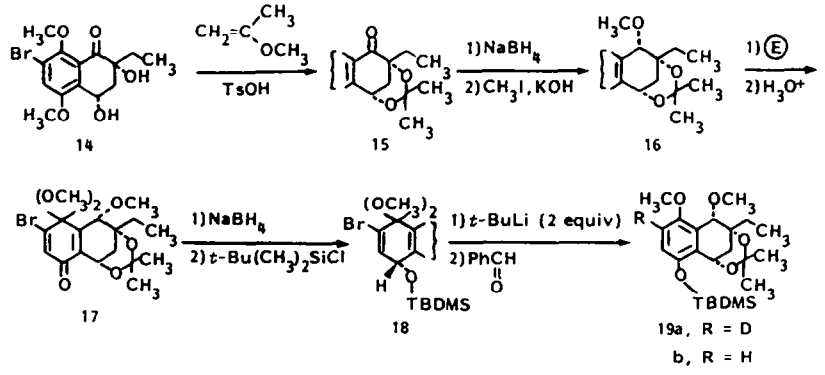
alumina as catalyst (90%) or diimide under carefully controlled conditions. Unfortunately, all efforts to introduce the 7- and 10-OH groups via the bromination/solvolysis sequence gave reaction mixtures containing at a minimum three compounds possessing the 6-deoxyanthracyclinone chromophore in low overall yield.[6a] Thus, this synthetic approach was abandoned in favor of one in which the requisite functionality was already present in the A-ring prior to assembling the tetracyclic system.

The 1,4-dipole-metallated quinol strategy to 6-deoxyanthracyclinones

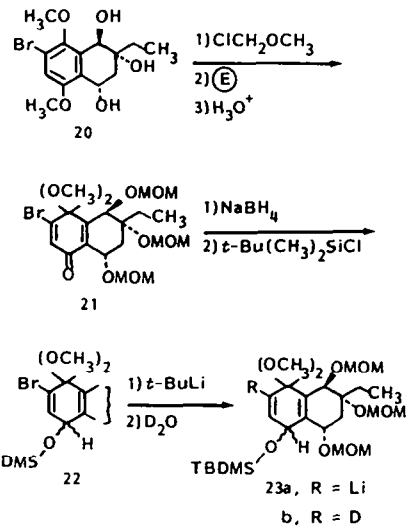
We noted several years ago the advantages of synthetic approaches to anthracyclinones which did not require A-ring functionalization of the tetracyclic ring system.[18] The convergent approach outlined in Scheme 1 incorporates this philosophy and requires fragments which would serve as the CD- and AB-ring precursors. While the benzocyclobutenedione monoketal, **24**,[11,18b] used in our rhodomycinone synthesis would serve as the 1,4-dipole equivalent, no known system was available for the metallated *p*-quinol equivalent. However, a metallated derivative of **18** might serve this purpose; thus, its synthesis was explored.

Reaction of **14**[19] with 2-methoxypropene using acid catalysis afforded **15** in quantitative yield, protecting both hydroxyl groups. Reduction of **15** with sodium borohydride followed by methylation of the resulting alcohol gave **16** in 90% overall yield from **14**. While **16** possessed the incorrect stereochemistry at the eventual C-10 of α-citromycinone, its ease of preparation prompted further study of this chemistry. Furthermore, it appeared that epimerization at this position could be effected via methods already developed for the rhodomycinones. Anodic oxidation and hydrolysis of **16** furnished the crystalline monoketal **17** in 75% yield. Sodium borohydride reduction of **17** afforded a crystalline alcohol in 93% yield which was protected as its *t*-butyldimethylsilyl ether.[20] The metallation chemistry of **18** was not ideal. Metallation followed by addition of deuterium oxide afforded **19a** with only 50–60% deuterium incorporation. Addition of benzaldehyde to metallated **18** afforded no detectable addition product and a 30% yield of benzyl alcohol in addition to **19b**. These preliminary results indicated that **18** would not serve as a viable metallated *p*-quinol precursor.

While the above work was being performed, routes which employed **20** were also being explored. This triol, also available from **14**,[19] had the advantage of having



the correct A-ring functionality and thus would not require an epimerization step after the tetracyclic ring system was formed. Protection of the hydroxyl groups as methoxymethyl (MOM) ethers and standard electrolysis/hydrolysis furnished the crystalline monoketal **21**. Sodium borohydride reduction of **21** produced a difficultly separable mixture of epimeric



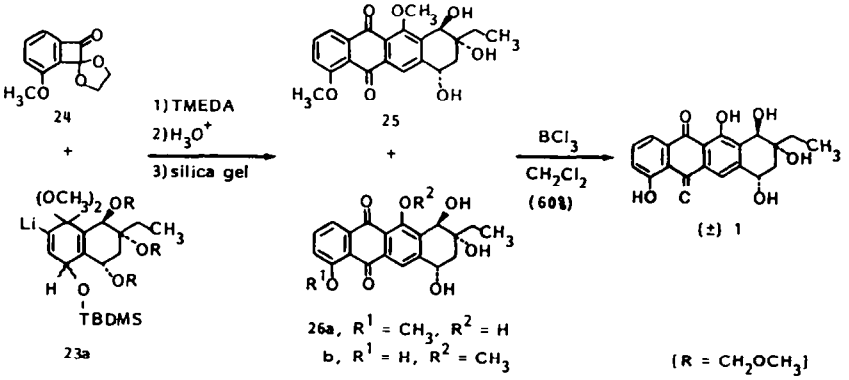
alcohols in excellent yield which were directly silylated with *t*-butyldimethylsilyl chloride. The resulting mixture of epimeric *t*-butyldimethylsilyl ethers was used for the metallation studies. The metal halogen exchange reactions of **22** were studied with methyl, sec-butyl, and *t*-butyllithium in several solvent systems. In contrast to the results with **18**[21] two equivalents of *t*-butyllithium in tetrahydrofuran at −90° gave an acceptable metal halogen exchange reaction, judging from quenching reactions with deuterium oxide (the aromatizated product from **23b** was obtained with more than 90% incorporation of deuterium).

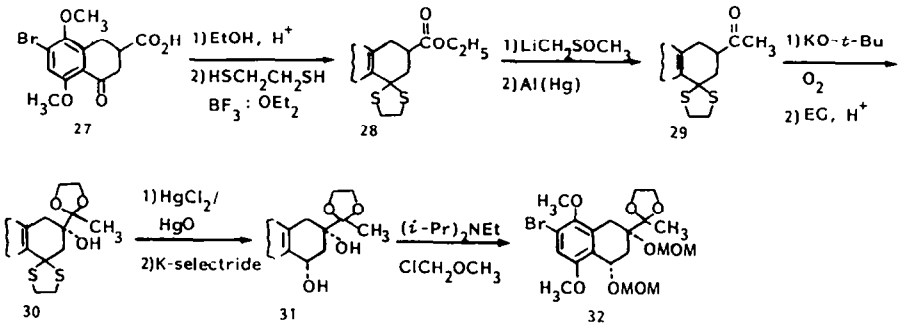
The stage was then set for the coupling of **23a** with **24**. Reaction of the lithium compound **23a** with **24** initially produced a low yield of a mixture of coupling products. The coupling reaction was improved by addition of tetramethylethylenediamine, and acid hydrolysis of the reaction mixture gave a difficultly separable mixture of **25** and **26** in 40% yield. Only **25** was obtained pure, and no additional attempts to isolate **26** pure were made after it was established that both **25** and **26** afforded **1** on reaction with boron trichloride. We favor **26a** as the structure of this second product; however, **26b** cannot be rigorously excluded.

While no authentic sample of α-citromycinone was available, a comparison of the high-field region of the ^{1}H-NMR spectrum of our synthesized material with that of α_2-rhodomycinone leaves no doubt that the A-ring stereochemistry is correct.[4] Furthermore, the ultraviolet and mass spectra reported for α-citromycinone are in good agreement with those recorded for **1**.[4] Thus, the structure assigned to α-citromycinone has been prepared in eight steps from **20** in 8% overall yield.

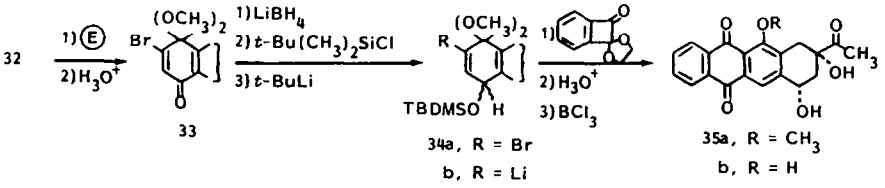
The synthesis of (±)*4-demethoxy-6-deoxydaunomycinone*

With a workable route to 6-deoxyanthracyclinones, a system with the A-ring functionality of daunomycinone was desired for biological testing. Using chemistry developed in the rhodomycinone series,[22] the corresponding bromo system, **32**, was prepared as outlined in Scheme 2. The anodic oxidation/hydrolysis





Scheme 2. Synthesis of AB-ring segment of 4-demethoxy-6-deoxydaunomycinone.



cleanly furnished the monoketal **33**. Reduction of **33** with lithium borohydride again afforded a mixture of epimeric alcohols. Protection of the hydroxyl group of the alcohols with t-butyldimethylsilyl chloride was much more difficult than in the previously discussed system. The rate of this silylation was markedly improved when 4-dimethylaminopyridine was added as catalyst. Metal halogen exchange of **34a** was complete in three minutes at −78° using two equivalents of t-butyllithium, and the resulting lithium reagent was reacted with benzocyclobutenedione monoketal. After hydrolysis of the crude coupling reaction, a 30% yield of a 15:1 mixture of two tetracyclic coupling products was isolated. As observed in the α-citromycinone synthesis, this mixture of products was converted to racemic 4-demethoxy-6-deoxydaunomycinone, **35b**, when reacted with boron trichloride. The low yield in the coupling reaction was disappointing and it was thought that perhaps only one of the epimeric t-butyldimethylsilyl ethers was undergoing the reaction successfully. It was possible to obtain in about 95% purity both epimeric alcohols from the lithium borohydride reduction of **33** since they crystallized in different forms and could therefore be separated by hand. However, when each of these enriched alcohols was silylated and coupled with the benzocyclobutenedione monoketal, nearly identical yields (31% and 35%) of coupling products resulted. Thus, the low yield in the coupling step is not due to the low reactivity of one of the epimeric silyl ethers.

Summary

A usable route to 6-deoxyanthracyclinones has been developed employing as a key step the coupling of a fully functionalized, protected AB-ring segment with a CD-ring portion. The yield in the coupling step is modest, but the method has been used to produce up to one-half gram of the racemic material for coupling with glycons and biological testing. Only recently has the C-7-oxygen substituent been introduced directly into tetracyclic ring systems of 6-deoxyanthracyclinones. The bromination/solvolysis sequence was used to prepare **35** in 23% yield[5a] and 6-deoxycarminomycinone in unreported yield.[5c] Since the difficulty of introducing the hydroxyl group at C-7 is now appreciated,[10] two other strategies[5b,d] which introduce the 7-OH group earlier in the synthetic sequence have been used to prepare 6-deoxyanthracyclinones.

EXPERIMENTAL[23]

5-Methoxy-1,4-naphthoquinone

To a vigorously stirred 5° soln of 1,4,5-trimethoxynaphthalene (64 g, 0.29 mol) in acetone (2 l) was added dropwise Jones reagent (115 ml, 2.67 M chromic acid in 8 N H_2SO_4) over 25 min (temp was maintained below 10° during the addition). The cooling bath was then removed, the mixture was stirred for 20 min, and then isopropyl alcohol (35 ml) was added. After 15 min the mixture was filtered, and the ppt was saved. The filtrate was concentrated *in vacuo*, diluted with water (3.5 l), and then filtered to give 18.6 g of orange solid, m.p. 177–180°. The previously filtered material was added to the filtrate, and the resulting solid was filtered to afford 27.5 g of orange-yellow solid, m.p. 175–181°. The combined solid was recrystallized from abs EtOH to afford 39.9 g (72%) of 5-methoxy-1,4-naphthoquinone, m.p. 181–183° (lit.[24] 189°).

1,5-*Dimethoxy-4-naphthol*, **3**

A mixture of 5-methoxy-1,4-dimethoxynaphthoquinone (10 g, 0.05 mol), sodium dithionite (37 g, 0.21 mol), Et_2O (2.5 l), and water (600 ml) was vigorously shaken. This mixture was combined with three other identical runs, and the colorless organic phase was separated and worked up in the usual manner to afford 35.7 g (89%) of the crude hydroquinone. This material, K_2CO_3 (130 g), and CH_3I (29.3 ml, 0.47 mol) were slurried with dry acetone (2.5 l), and the soln was heated to reflux for 48 hr. The progress of the reaction could be conveniently monitored by VPC (1 ft × 1/8 in. column of 3% SE-30 on 140–160 Chrm G at 155°). The mixture was cooled, filtered, and concentrated *in vacuo*, and the residue was worked up in the usual manner to afford, after trituration with cold Et_2O, 33.3 g (78% overall) of the title compound, m.p. 148–150° (lit.[25] 155–156°).

Compound **5**. To a stirred mixture of **3** (56.8 g, 0.28 mol) in dry CH_2Cl_2 (1.4 l) was added $SnCl_4$ (34.6 ml, 0.30 mol) via syringe.

This was followed by addition of **4** (57.1 g, 0.28 mol), and the orange-brown mixture was stirred for 2 hr at room temp. The reaction was slowly quenched with ice water (300 ml), and the organic phase was separated. After extraction with sat $NaHCO_3$ aq (300 ml) and back extraction with CH_2Cl_2 (100 ml), the combined organic phase was worked up as usual to give a deep orange amorphous residue. Crystallization of this material from CH_3OH/CH_2Cl_2 gave 67.3 g (65%) of **5**: m.p. 165–167°; IR 3280 (br, m), 2915 (m), 1735 (s), 1650 (s), 1620 (s), 1605 (s), 1510 (m), 1460 (s), 1405 (s), 1390 (s), 1200 (s), 1155 (s), 1080 (s); ^{1}H-NMR (60 MHz) 11.33 (s, 1H), 7.73 (dd, J = 8, 1 Hz, 1H), 7.45 (dd, J = 8, 8 Hz, 1H), 7.02 (s, 1H), 6.90 (dd, J = 8, 1 Hz, 1H), 5.70 (s, 2H), 4.03 (s, 3H), 3.93 (s, 3H), 3.60 (s, 3H), 3.0–3.3 (m, 2H), 2.4–2.7 (m, 4H); ^{13}C-NMR 203.8, 174.2, 158.0, 152.8, 147.6, 131.3, 128.5, 125.4, 125.1, 116.4, 116.1, 115.6, 106.8, 104.4, 56.4, 55.9, 51.5, 45.2, 40.0, 26.8, 26.0. (Found: C, 67.85; H, 5.99. Calc for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99%).

Conversion of **5** *to* **8** *without purification of intermediates*

A stirred soln of **5** (23.5 g, 0.06 mol), K_2CO_3 (44 g, 5 equiv), $(CH_3)_2SO_4$ (30 ml, 5 equiv), in dry acetone (600 ml) was heated to reflux for 11.5 hr. The mixture was then filtered, and the filtrate was worked up as usual. The crude product contained appreciable $(CH_3)_2SO_4$ which was removed at 0.1 torr. A sample of the resulting product was purified by silica gel chromatography (20–30% E/H as eluant). The resulting colorless oil was a mixture of diastereomers as judged by ^{13}C- and ^{1}H-NMR; IR (film) 2940 (m), 2840 (m), 1730 (s), 1670 (s), 1612 (m), 1597 (s), 1509 (m), 1415 (s), 1370 (s), 1270 (s), 1205 (s), 1080 (s), 820 (s), 760 (s). (Found: C, 68.60; H, 6.42. Calc for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29%).

This crude material was dissolved in trifluoroacetic acid (150 ml), the soln was cooled in ice, and triethylsilane (25.6 ml, 2.5 equiv) was added slowly. After addition was complete, the maroon mixture was stirred at room temp for 1.5 hr, and the trifluoroacetic acid and excess triethylsilane were distilled at room temp (0.2 torr). The residue was dissolved in CH_2Cl_2 (200 ml) and washed with water (50 ml) and then with sat $NaHCO_3$ aq. After back extraction with CH_2Cl_2 (50 ml), the organic phase was worked up as usual. Purification of a portion of the material by preparative TLC (40% E/H as eluant) gave a colorless gum: IR (film) 2920 (s), 1730 (s), 1601 (s), 1580 (s), 1511 (s), 1450 (s), 1416 (s), 1365 (s), 1267 (s), 1075 (s), 1019 (m), 758 (m); exact mass calc for $C_{22}H_{26}O_5$ *m/e* 370.178010, obsd 370.178815.

The crude ester was dissolved in cold CH_3OH (500 ml), 20% aqueous KOH (280 ml) was added, and the mixture was stirred for 24 hr at room temp. After concentration *in vacuo*, the aqueous mixture was diluted with water (1 l) and extracted with ether (2 × 100 ml). Acidification of the aqueous phase with conc HCl and extraction with CH_2Cl_2 (3 × 100 ml) gave 21.2 g of brown solid (94% over three steps). A sample of pure **8** was obtained by silica gel chromatography (10–40% Et_2O/H as eluant) followed by recrystallization from Et_2O/C_6H_{12}: m.p. 156–158°; IR 3500–2400 (br, s), 1730 (s), 1603 (s), 1585 (m), 1517 (s), 1420 (s), 1378 (s), 1270 (s), 1080 (s), 1020 (m), 820 (s), 770 (s); ^{1}H-NMR (60 MHz) 9.9 (br s, 1H), 7.80 (dd, J = 8, 1.5 Hz, 1H), 7.26 (dd, J = 8, 8 Hz, 1H), 6.83 (dd, J = 8, 1.5 Hz, 1H), 6.63 (s, 1H), 5.66 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.72 (s, 3H), 2.8 (br s, 4H), 2.4 (br s, 2H), 2.1 (br s, 2H); ^{13}C-NMR 180.9, 155.6, 151.2, 147.8, 129.6, 127.9, 126.0, 125.0, 124.6, 120.8, 114.8, 107.7, 107.0, 62.1, 56.2, 55.7, 42.2, 35.6, 31.3, 28.7, 25.3. (Found: C, 70.67; H, 6.81. Calc for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79%).

Iodolactonization of **8**

The crude acid from above (21.2 g, 0.06 mol) was dissolved in 5% $NaHCO_3$ (1.4 l). The soln formed from KI (54.4 g, 0.30 mol), I_2 (15.12 g, 0.06 mol), and water (35 ml) was added to the rapidly stirred soln of **8**. After stirring for 2.5 hr in the dark, the heterogeneous mixture was extracted with CH_2Cl_2 (3 × 150 ml), and the organic phase was washed with 10% $Na_2S_2O_3$ aq until the violet color was removed. Concentration gave 28.0 g (97%) of the iodolactone as a brown solid foam. A pure sample was obtained by silica gel chromatography (15% Et_2O/H as eluant) as a white solid: m.p. 110–116°; IR 2930 (m), 1778 (s), 1602 (s), 1581 (m), 1510 (s), 1463 (s), 1450 (s), 1418 (s), 1372 (s), 1270 (s), 1080 (s), 1018 (m); ^{1}H-NMR (60 MHz) 7.86 (dd, J = 8, 1 Hz, 1H), 7.36 (dd, J = 8, 8 Hz, 1H), 6.90 (dd, J = 8, 1 Hz, 1H), 6.80 (s, 1H), 4.7–4.9 (m, 1H), 4.4–4.5 (m, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.80 (s, 3H), 2.1–2.8 (m, 8H); ^{13}C-NMR 176.6, 155.5, 151.2, 147.8, 128.1, 127.6, 125.2, 120.7, 114.9, 108.2, 106.8, 80.2, 62.2, 56.1, 55.8, 41.8, 37.0, 35.8, 34.9, 34.6, 23.1. (Found: C, 52.41; H, 4.84. Calc for $C_{21}H_{23}O_5I$: C, 52.30; H, 4.81%).

Compound **9a**. To the crude iodolactone (28 g, 0.06 mol) in benzene (300 ml) were added tri-n-butylstannane (16.4 ml, 0.06 mol) and azobisisobutyronitrile (20 mg). The mixture was heated to reflux for 16 hr, concentrated *in vacuo*, diluted with Et_2O (300 ml), and then stirred with 1 M KF (200 ml). The white ppt was filtered, and the organic phase was worked up as usual to yield 24.9 g of crude lactone as a brown gum. A sample was purified by silica gel chromatography (50% Et_2O/H as eluant) to yield the mixture of pure diastereomers: m.p. 93–104°; IR 2930 (m), 1770 (s), 1602 (s), 1580 (m), 1512 (m), 1465 (m), 1455 (m), 1420 (s), 1375 (s), 1275 (s), 1135 (s), 1080 (s), 965 (m); exact mass calc for $C_{21}H_{24}O_5$ *m/e* 356.1623, obsd 356.1629.

The crude lactone (24.9 g) containing inorganic impurities was dissolved in CH_3OH (250 ml), and 10% KOH aq (180 ml) was slowly added. After stirring for 4 hr at room temp, the CH_3OH was removed *in vacuo*, and the aqueous soln was extracted with Et_2O (2 × 70 ml) and then acidified with conc HCl to afford 20.4 g (94% over two steps) of hydroxy acid **9a**. A pure sample of **9a** was obtained by crystallization from EtOAc/CH_3OH: m.p. 202–203°; IR 3600–2400 (br m), 1712 (s), 1601 (s), 1582 (m), 1511 (m), 1462 (m), 1451 (m), 1414 (s), 1367 (s), 1268 (s), 1075 (s), 758 (m); ^{1}H-NMR (60 MHz, DMSO-d_6) 7.72 (dd, J = 8, 1 Hz, 1H), 7.33 (dd, J = 8, 8 Hz, 1H), 6.97 (dd, J = 8, 1 Hz, 1H), 6.73 (s, 1H), 3.90 (s, 6H), 3.65 (s, 3H), 2.3–3.0 (m, 3H), 1.3–2.0 (m, 7H); exact mass calc for $C_{21}H_{26}O_6$ *m/e* 374.172924, obsd 374.173468.

Compound **9b**. Finely powdered hydroxy acid **9a** (20.4 g, 0.55 mol) was slurried with EtOAc (400 ml) and treated with diazomethane in Et_2O until a yellow color persisted. After quenching the reaction with HOAc (1 ml), workup as usual afforded 21.8 g of tan foam. Slow recrystallization from Et_2O gave 13.6 g, m.p. 119–122°, of ester. Chromatography of the mother liquors on silica gel (50–80% Et_2O/H as eluant) and recrystallization gave an additional 2.7 g of crystalline product, total 16.3 g (77%). Analytically pure material was obtained by recrystallization from Et_2O/C_6H_{12}: m.p. 122–125°; IR 3410 (m), 2920 (s), 1725 (s), 1598 (s), 1577 (m), 1508 (s), 1448 (s), 1418 (s), 1365 (s), 1260 (s), 1160 (m), 1070 (s), 993 (m); ^{1}H-NMR (60 MHz) 7.76 (dd, J = 8, 1 Hz, 1H), 7.27 (dd, J = 8, 8Hz, 1H), 6.83 (dd, J = 8, 1 Hz, 1H), 6.60 (s, 1H), 4.00 (br s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 2.5–2.8 (m, 3H), 1.9 (br s, 3H), 1.5 (br s, 4H); ^{13}C-NMR 175.7, 155.5, 151.1, 147.7, 129.4, 127.8, 125.5, 124.9, 114.7, 107.4, 106.9, 68.5, 62.0, 56.1, 55.6, 55.1, 44.3, 37.1, 32.6, 30.8, 30.6, 24.7. (Found: C, 67.87; H, 7.29. Calc for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27%).

Compound **10**. To a mixture of dry CH_2Cl_2 (350 ml) and oxalyl chloride (8.0 ml, 0.09 mol) at −60°, DMSO (14.2 ml, 0.2 mol) was added dropwise. The soln was stirred for 5 min, and then **9b** (16.2 g, 0.04 mol) in CH_2Cl_2 (30 ml) was added over 10 min. The soln was stirred at −20° for an additional 15 min, and then Et_3N (29 ml, 0.21 mol) was added slowly. After stirring at room temp for 1 hr, water (50 ml) was added, and the soln was acidified with 10% HCl. Workup afforded a crude product which was used directly in the next step. A pure sample of the diastereomeric esters was obtained by silica gel chromatography (30–70% Et_2O/H as eluant) as an amorphous gum: IR 3005 (m), 2940 (m), 1730 (s), 1601 (s), 1581 (m), 1510 (m), 1463 (m), 1451 (m), 1415 (s), 1370 (s), 1268 (s), 1194 (m), 1168 (m), 1078 (s); exact mass calc for $C_{22}H_{26}O_6$ *m/e* 386.172924, obsd 386.173529.

The crude ketone (16 g, 0.04 mol), ethylene glycol (30 ml), and *p*-toluenesulfonic acid (50 mg) in benzene (150 ml) were heated at reflux for 3 hr with azeotropic removal of water. After quenching the reaction with 5% $NaHCO_3$, workup as usual

afforded the crude ketal which was used directly in the next step. A pure sample of the ketal was obtained by recrystallization from CH_3OH: m.p. 111.5–113.5°; IR 3000 (s), 1740 (s), 1605 (s), 1580 (s), 1505 (m), 1460 (s), 1450 (s), 1410 (s), 1360 (s), 1290 (s), 1270 (s), 1190 (s), 1075 (s), 1040 (s), 883 (m), 760 (s); ^{1}H-NMR (60 MHz, CCl_4) 7.80 (dd, J = 8, 1 Hz, 1H), 7.13 (dd, J = 8, 8 Hz, 1H), 6.70 (dd, J = 8, 1 Hz, 1H), 6.47 (s, 1H), 3.87 (s, 6H), 3.80 (s, 4H), 3.64 (s, 3H), 3.60 (s, 3H), 2.2–2.9 (m, 5H), 1.5–2.0 (m, 5H). (Found: C, 66.87; H, 7.06. Calc for $C_{24}H_{30}O_7$: C, 67.01; H, 7.03%).

To the crude ketal in CH_3OH (500 ml) was added 20% KOH aq, and the slurry was stirred overnight at room temp. Concentration and dilution with water (200 ml) was followed by washing the aqueous phase with Et_2O (50 ml). Acidification of the aqueous material and workup as usual afforded 18.0 g of a tan solid from which 15 g of **10** was obtained by slow crystallization from Et_2O/H. A pure sample of **10** was obtained by recrystallization from CH_2Cl_2/Et_2O: m.p. 173–174°; IR 3600–2400 (br m), 2950 (s), 1730 (s), 1602 (s), 1583 (m), 1518 (s), 1422 (s), 1376 (s), 1276 (s), 1195 (s), 1080 (s), 1022 (m), 863 (m); ^{1}H-NMR (60 MHz) 10.26 (br s, 1H), 7.80 (dd, J = 8, 1 Hz, 1H), 7.28 (dd, J = 8, 8 Hz, 1H), 6.85 (dd, J = 8, 1 Hz, 1H), 6.61 (s, 1H), 3.96 (s, 7H), 3.90 (s, 3H), 3.73 (s, 3H), 2.4–3.2 (m, 5H), 1.6–2.2 (m, 5H); ^{13}C-NMR 180.0, 155.6, 151.3, 147.8, 129.5, 127.9, 125.0, 120.8, 114.8, 108.8, 107.2, 107.1, 64.3 (2C), 62.1, 56.2, 55.7, 44.3, 36.5, 33.0, 31.0, 28.8, 25.3; exact mass calc for $C_{23}H_{28}O_7$ *m/e* 416.183488, obsd 416.184424.

Compound **11**. A mixture of **10** (26.5 g, 0.06 mol), trifluoroacetic anhydride (45 ml), and trifluoroacetic acid (45 ml) was stirred at room temp for 1 hr. The resulting red-brown soln was poured into ice (900 ml), and the mixture was extracted with CH_2Cl_2 (3 × 180 ml). The organic phase was washed with $NaHCO_3$ (180 ml) and worked up to yield a yellow-orange foam. This crude material was dissolved in a mixture of benzene (530 ml), ethylene glycol (18 ml), and *p*-toluenesulfonic acid and heated at reflux for 2 hr with azeotropic removal of water. Workup as for **10** gave 16.9 g of **11** after recrystallization from CH_2Cl_2. The analytical sample showed: m.p. 209–211°; IR 2930 (m), 1685 (s), 1606 (m), 1575 (s), 1566 (s), 1395 (m), 1361 (s), 1345 (s), 1264 (s), 1088 (s), 1074 (s), 1058 (s), 950 (s), 772 (m); ^{1}H-NMR (200 MHz) 7.93 (dd, J = 8, 1 Hz, 1H), 7.41 (dd, J = 8, 8 Hz, 1H), 6.98 (dd, J = 8, 1 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 4.2–3.9 (m, 4H), 3.80 (s, 3H), 3.52 (dd, J = 17.1, 4.0 Hz, 1H), 2.65–2.35 (structured m, 3H), 2.2–1.6 (m, 6H); ^{13}C-NMR 198.6, 155.7, 154.3, 148.8, 131.1, 130.6, 126.1, 123.5, 122.2, 117.1, 109.2, 108.9, 64.4 (2C), 62.8, 61.3, 56.4, 50.9, 37.5, 34.7, 34.2, 31.3, 30.7. (Found: C, 68.90; H, 6.58. Calc for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58%).

Compound **12**. To a vigorously stirred slurry of finely powdered **11** (14.8 g, 0.037 mol) in acetone (500 ml) was added silver (II) oxide (22.2 g, 0.18 mol) and 40% aqueous HNO_3 (27 ml). After 10 min the mixture was filtered and partitioned between water (600 ml) and EtOAc (600 ml). Workup afforded a crude orange foam which was immediately dissolved in benzene (1.6 l). To the benzene soln was added dichlorodicyanobenzoquinone (10.2 g, 0.05 mmol) and 2,6-lutidine (5.2 ml). The soln was heated to reflux for 2 hr, cooled to room temp, and filtered. After concentration the residue was dissolved in CH_2Cl_2 (600 ml), and the organic layer was washed with cold 10% HCl (120 ml). Workup and recrystallization from CH_2Cl_2/CH_3OH gave 8.7 g (64%) of **12** as yellow-orange crystals: m.p. 205–206.5°; IR 2942 (m), 2884 (m), 2845 (m), 1670 (s), 1629 (s), 1583 (s), 1431 (s), 1371 (s), 1280 (s), 1140 (s), 1066 (s), 922 (m), 830 (m); ^{1}H-NMR (60 MHz) 12.7 (s, 1H), 7.91 (dd, J = 8, 2 Hz, 1H), 7.64 (dd, J = 8, 8 Hz, 1H), 7.49 (s, 1H), 7.26 (dd, J = 8, 2 Hz, 1H), 4.03 (s, 4H), 4.00 (s, 3H), 3.09 (obscured t, J = 6 Hz, 2H), 2.97 (s, 2H), 1.97 (t, J = 6 Hz, 2H); ^{13}C-NMR 188.0, 181.7, 160.4, 145.8, 135.6, 134.8, 132.0, 129.7, 119.4 (2C), 118.3, 112.7, 107.5, 64.7 (2C), 56.6, 33.4, 31.1, 29.3 (2C); UV ($CHCl_3$) λ_{max} nm (log ε) 260 (4.6), 266 (4.6), 287 (4.2), 399 (4.1), 412 (4.1), 435 (4.0). (Found: C, 69.16; H, 5.10. Calc for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95%).

Compound **13**. The ketal **12** (2.6 g, 7.1 mmol) in CH_2Cl_2 (200 ml) at −25° was treated dropwise with BCl_3 (50 ml of a 1 M soln in CH_2Cl_2). After 1 hr, water (10 ml) was added, and the mixture was shaken vigorously with water (200 ml) to ensure complete hydrolysis of the borate esters. The aqueous layer was extracted with CH_2Cl_2 (2 × 300 ml), and the crude product was recrystallized from $CHCl_3$ to give 1.75 g (80%) of **13**: m.p. 249–250°; IR 1724 (s), 1635 (s), 1603 (s), 1574 (m), 1453 (m), 1374 (s), 1306 (s), 1268 (s), 1233 (s), 1180 (s), 803 (m); ^{1}H-NMR (300 MHz) 13.02 (s, 1H), 12.65 (s, 1H), 7.85 (dd, J = 7.6, 1.2 Hz, 1H), 7.73 (s, 1H), 7.70 (dd, J = 8.5, 7.6 Hz, 1H), 7.33 (dd, J = 8.5, 1.2 Hz, 1H), 3.68 (s, 2H), 3.24 (t, J = 6.7 Hz, 2H), 2.67 (t, J = 6.7 Hz, 2H); exact mass calc for $C_{18}H_{12}O_5$ *m/e* 308.068466, obsd 308.067666.

Compound **2**. A soln of ethynyl Grignard[26] was prepared from EtMgBr (9.3 ml of a 1.9 M Et_2O soln, 18 mmol) and acetylene in THF (150 ml). A soln of **13** (0.54 g) in THF (400 ml) was added to the Grignard soln over 0.5 hr. The deep maroon mixture was stirred for 7 hr at room temp and poured into cold NH_4Cl (200 ml), and the organic layer was extracted with EtOAc (200 ml). Workup afforded 0.59 g of brown solid which was chromatographed on silica gel (CH_2Cl_2 as eluant) to afford 0.14 g (25%) of recovered **13** and 0.24 g (41%) of the ethynyl alcohol **2**. Recrystallization from CH_2Cl_2/CH_3OH gave an analytical sample: m.p. 219.5–221.5°; IR 3420 (br m), 3285 (m), 2100 (w), 1625 (s), 1602 (s), 1572 (m), 1476 (m), 1451 (s), 1420 (s), 1389 (s), 1330 (s), 1314 (s), 1265 (s), 1054 (s), 901 (m), 778 (s); ^{1}H-NMR (300 MHz) 13.10 (s, 1H), 12.71 (s, 1H), 7.83 (dd, J = 7.5, 1.8 Hz, 1H), 7.67 (dd, J = 7.5, 7.5 Hz, 1H), 7.63 (s, 1H), 7.31 (d, J = 7.5 Hz, 1H), 3.20 (AB q, J = 18.3 Hz, Δν = 70.9 Hz, 2H), 3.12–3.15 (m, 2H), 2.51 (s, 1H), 2.15 (t, J = 6.7 Hz, 2H). (Found: C, 71.52; H, 4.36. Calc for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22%).

To a vigorously stirred soln of the ethynyl alcohol (0.097 g, 0.29 mmol), hydrazine hydrate (1.2 ml, 2.5 mmol), HOAc (2 drops), sat $CuSO_4$ aq (2 drops), and THF (10 ml) was added sodium periodate (0.62 g, 2.9 mmol) in water (3 ml) over a period of 1 hr. The reaction was exothermic, and a cold bath was employed to keep the temp near 25°. The mixture was then diluted with water (20 ml) and extracted with EtOAc (3 × 20 ml). Workup and purification by preparative TLC on silica gel (1% CH_3OH/CH_2Cl_2 as eluant) gave 0.078 g (80%) of **2**. Two recrystallizations from CH_2Cl_2/CH_3OH afforded an analytical sample: m.p. 162.0–163.5°; IR 3400 (br, s), 2970 (s), 2920 (s), 1621 (s), 1600 (s), 1478 (m), 1420 (s), 1390 (s), 1338 (s), 1319 (s), 1272 (s), ^{1}H-NMR (300 MHz) 13.07 (s, 1H), 12.70 (s, 1H), 7.81 (d, J = 7.3 Hz, 1H), 7.65 (dd, J = 8.5, 7.5 Hz, 1H), 7.61 (s, 1H), 7.28 (d, J = 8.5 Hz, 1H), 3.49 (s, 1H), 3.21–3.10 (m, 1H), 2.95–2.84 (m, 1H), 2.92 (d, J = 18.5 Hz, 1H), 2.73 (d, J = 18.5 Hz, 1H), 1.96–1.89 (m, 1H), 1.79–1.73 (m, 1H), 1.70 (q, J = 7.3 Hz, 2H), 1.07 (t, J = 7.3 Hz, 3H); UV ($CHCl_3$) λ_{max} nm (log ε) 432 (4.0), 294 (4.0), 284 (4.0), 266 (4.4), 259 (4.4); exact mass calc for $C_{20}H_{18}O_5$ *m/e* 338.115413, obsd 338.115998.

Compound **16**. A soln of **15** (1.5 g, 3.9 mmol) in CH_3OH (70 ml) was treated with $NaBH_4$ (0.73 g, 19.2 mmol) at 0°. Standard workup afforded 1.5 g (quantitative) of a white solid. Recrystallization from Et_2O/PE gave colorless crystals, m.p. 121–122.5°: IR 2960 (m), 2940 (m), 1465 (s), 1435 (m), 1400 (m), 1380 (m), 1365 (m), 1295 (m), 1240 (s), 1195 (m), 1115 (s), 1070 (m), 1035 (m), 970 (m); ^{1}H-NMR (CCl_4) 6.83 (s, 1H), 5.03 (dd, J = 3, 4 Hz, 1H), 4.43 (d, J = 9 Hz, 1H, forms singlet with D_2O), 3.90 (s, 3H), 3.80 (s, 3H), 2.9 (d, J = 9 Hz, 1H, disappears with D_2O), 2.33 (dd, J = 14, 4 Hz, 1H), 1.8 (q, J = 7 Hz, 2H), 1.47 (dd, J = 14, 3 Hz, 1H, with higher field component overlapped by singlet), 1.40 (s, 3H), 1.10 (s, 3H), 0.97 (t, J = 7 Hz, 3H, overlapped by singlet). (Found: C, 52.35; H, 6.01. Calc for $C_{17}H_{23}O_5Br$: C, 52.72; H, 5.99%).

A soln of powdered KOH (2.25 g, 34 mmol) in DMSO (22 ml) at room temp was treated with the above product (3.3 g, 8.5 mmol), followed immediately by CH_3I (1.1 ml, 17.6 mmol). After 30 min, workup as usual afforded 3.2 g of pale yellow solid which was recrystallized from Et_2O/PE to give 2.71 g (80%) of white crystals, m.p. 91–92°: IR (CCl_4) 2960 (m), 2940 (m), 1570 (m), 1460 (s), 1430 (m), 1395 (m), 1380 (m), 1365 (m), 1295 (m), 1230 (s), 1190 (s), 1135 (s), 1095 and 1085 (s, br), 1035 (m), 970 (m); ^{1}H-NMR (CCl_4) 6.93 (s, 1H), 5.03 (unresolved dd,

appears as t, J = 4 Hz, 1H), 4.15 (s, 1H), 3.83 (s, 6H), 3.60 (s, 3H), 2.23 (dd, J = 14, ~4 Hz, 1H), 1.90 (q, J = 7 Hz, 2H), 1.45 (dd, J = 14, ~4 Hz, 1H, partially obscured by singlet), 1.37 (s, 3H), 1.00 (s, 3H overlapped by triplet), 0.97 (t, J = 7 Hz, 3H). (Found: C, 53.90; H, 6.46. Calc for $C_{18}H_{25}O_5Br$: C, 53.87; H, 6.28%).

Compound **17**. A soln of **16** (1.25 g, 3.1 mmol) in 2% methanolic KOH (60 ml) was anodically oxidized in a standard H cell at a potential of 1.4–1.6 V *vs* a Pt electrode at 0–10°. Standard workup gave 1.34 g (93%) of an off-white solid suitable for use in the next step. Recrystallization of the sample from Et_2O/PE gave the pure bisketal, m.p. 129–131°: IR (CCl_4) 2990 (m), 2970 (m), 2940 (m), 2840 (m), 1460 (m), 1380 (m), 1370 (m), 1310 (m), 1245 (m), 1190 (m), 1150 (s), 1135 (s), 1090 (vs), 1075 (vs), 910 (m); ^{1}H-NMR 6.77 (s, 1H), 4.80 (dd, J = 4, 3 Hz, 1H), 3.70 (s, 3H), 3.63 (s, 1H), 3.40 (s, 3H), 3.33 (s, 3H), 3.27 (s, 3H), 3.13 (s, 3H), 2.53 (dd, J = 14, 4 Hz, 1H), 2.30–1.65 (m, 2H), 1.55 (dd, with higher field component obscured by singlet, J = 14, 3 Hz, 1H), 1.55 (s, 3H), 1.35 (s, 3H), 0.97 (t, J = 8 Hz, 3H). (Found: C, 51.71; H, 6.73. Calc for $C_{20}H_{31}BrO_7$: C, 51.84; H, 6.75%).

The crude bisketal (1.49 g, 3.2 mmol) in 1:1 acetone/THF (40 ml) was treated with 20% aqueous HOAc (20 ml) and stirred for 49 hr at room temp. Workup followed by recrystallization from Et_2O/PE gave 1.09 g (81%) of **17** as colorless crystals, m.p. 166–167.5°: IR 2980 (m), 2960 (m), 2940 (br, m), 2830 (m), 1655 (s), 1610 (m), 1375 (s), 1340 (m), 1290 (m), 1275 (m), 1260 (m), 1245 (s), 1185 (s), 1140 (s), 1080 (vs), 1040 (s), 990 (m), 880 (m); ^{1}H-NMR 7.00 (s, 1H), 4.95 (t, J = 4 Hz, 1H), 3.76 (s, 1H), 3.73 (s, 3H), 3.30 (s, 3H), 3.20 (s, 3H), 2.50 (dd, J = 15, 4 Hz, 1H), 2.35–1.60 (m, 2H), 1.55 (dd, J = 15, 4 Hz, 1H, higher field component overlapped by singlet), 1.53 (s, 3H), 1.27 (s, 3H), 0.97 (t, J = 7 Hz, 3H). (Found: C, 51.73; H, 6.02. Calc for $C_{18}H_{25}O_6Br$: C, 51.81; H, 6.04%).

Compound **18**. A −20° soln of **17** (0.34 g, 0.8 mmol) in CH_3OH (15 ml) was treated with $NaBH_4$ (60 mg, 1.6 mmol). After stirring for 1 hr, acetone (1 ml) was added, and the reaction was worked up as usual to give 0.32 g (96%) of the alcohol. Recrystallization from Et_2O/PE gave the analytical sample, m.p. 111–113°: IR (CCl_4) 3500 (m), 2990, 2960, and 2940 (overlapping, m), 2830 (m), 1460 (m), 1380 (m), 1370 (m), 1350 (m), 1240 (m), 1225 (m), 1210 (m), 1195 (m), 1140 (s), 1090 (vs), 1025 (m), 1015 (m), 995 (m); ^{1}H-NMR (CCl_4) 6.67 (d, J = 4 Hz, 1H), 4.50–4.33 (unresolved m, 1H), 4.33–4.20 (t, collapses to doublet with D_2O, J = 4 Hz, 1H), 3.53 and 3.50 (overlapping singlets, 4H), 3.25 (d, disappears with D_2O, J ≃ 3 Hz, 1H), 3.10 (s, 3H), 3.00 (s, 3H), 2.27 (dd, J = 4, 13.5 Hz, 1H), 2.15–1.55 (multiplet, overlapped by dd, 2H), 1.55 (dd, J = 13.5, ~4 Hz, 1H), 1.40 (s, 3H), 1.25 (s, 3H), 0.87 (t, J = 8 Hz, 3H). (Found: C, 51.29; H, 6.49. Calc for $C_{18}H_{27}O_6Br$: C, 51.56; H, 6.49%).

A soln of the crude alcohol from above (220 mg, 0.53 mmol) in dry DMF (3 ml) was treated with imidazole (0.36 g, 5.3 mmol) and t-butyldimethylsilyl chloride (0.4 g, 2.6 mmol), and the mixture was stirred at room temp for 24 hr. After quenching the reaction with $NaHCO_3$ (15 ml), workup as usual gave 0.27 g (97%) of **18** as a white solid. Recrystallization from Et_2O/PE gave 0.21 g (75%) of analytically pure material, m.p. 133–135°: IR (CCl_4) 2930 (s), 2860 (m), 2830 (m), 1465 (m), 1380 (m), 1365 (m), 1255 (m), 1240 (m), 1210 (m), 1195 (m), 1145 (s), 1090 (vs), 1040 (s), 1000 (m), 875 (m), 830 (m); ^{1}H-NMR (CCl_4) 6.47 (d, J = 4 Hz, 1H), 4.40 (dd, J = 3.5, 2.5 Hz, 1H), 4.10 (unresolved m, 1H), 3.57 (s, 3H), 3.50 (m, 1H), 3.13 (s, 3H), 3.00 (s, 3H), 2.17 (dd, J = 12.5, 3.5 Hz, 1H), 1.97–1.60 (highly structured m, 2H), 1.40 (dd, obscured by singlet, J = 12.5, ~2.5 Hz, 1H), 1.37 (s, 3H), 1.27 (s, 3H), 0.90 (s overlapped by t, 12H), 0.17 and 0.15 (overlapping singlets, 6H). (Found: C, 54.03; H, 7.75. Calc for $C_{24}H_{41}O_6BrSi$: C, 53.72; H, 7.70%).

Compound **21**. A magnetically stirred soln of **20** (2.40 g, 6.92 mmol) in CH_2Cl_2 (30 ml) was treated with diisopropylethylamine (6.9 ml, 39.6 mmol) and chloromethyl methyl ether (5.5 ml, 72 mmol), and the resulting soln was refluxed for 24 hr under N_2. (A calculation error in stoichiometry led to insufficient base being employed in this reaction. Undoubtedly, the yield would be much improved had the amine been used in amounts equivalent to the chloro ether.) The mixture was cooled and poured into sat $NaHCO_3$ aq (60 ml) and was worked up as usual to yield 3.0 g of a dark orange oil. The product was purified by flash chromatography on silica gel (5 × 15 cm, 15% EtOAc/PE as eluant) to afford 2.10 g (63%) of a colorless oil: IR (CCl_4) 2940 (m), 2890 (m), 1465 (m), 1440 (m), 1400 (m), 1230 (m), 1150 (s), 1130 (m), 1115 (m), 1090 (m), 1035 (vs), 960 (m), 920 (m); ^{1}H-NMR 7.00 (s, 1H), 5.0–4.3 (m, 8H), 3.77 (s, 6H), 3.43 (s, 3H), 3.27 (s, 3H), 3.20 (s, 3H), 2.20 (m, 2H), 1.80 q, J = 7.5 Hz, 2H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C-NMR 155.1, 149.6, 132.2, 125.9, 116.6, 115.0, 98.8, 95.5, 91.0, 76.7, 69.8, 68.9, 61.7, 56.3, 56.2, 55.7, 55.4, 32.6, 27.1, 6.4; exact mass calc for $C_{20}H_{31}O_8{}^{79}Br$ *m/e* 478.1203, obsd 478.1218.

To the cathode compartment of a standard H-cell apparatus was added 2% KOH/CH_3OH (60 ml), and to the anode compartment were added the blocked triol from above (2.0 g, 4.18 mmol) and 2% KOH/CH_3OH (60 ml). Oxidation was performed at a potential range of 1.5–1.6 V (initial current 0.45 A) *vs* a Pt reference electrode at −5 to −0° for 4.25 hr. Chips of dry ice were added to the contents of the anode compartment until the soln was slightly basic, the solvent was then removed *in vacuo* at room temp, and the residue was worked up to afford 1.92 g (85%) of the crude bisketal as a tan oil. This material was utilized without further purification.

A magnetically stirred soln of crude bisketal (1.6 g, 2.96 mmol) in a mixture of $(CH_3)_2CO$/THF (30:30 ml) was treated with 20% aqueous AcOH (30 ml) and was stirred at room temp. After 12 hr, the mixture was poured into sat $NaHCO_3$ aq (50 ml), and the organic solvents were removed *in vacuo*. Workup yielded 1.43 g of an orange oil. Chromatography on neutral activity III alumina (2 × 25 cm column, 20% Et_2O/PE as eluant) proceeded as follows: 180 ml, nil; 20 ml, 42 mg of two unidentified impurities; 120 ml, 1.02 g (71%) of the monoketal **21** as a white solid, m.p. 100–101.5°; IR (CCl_4) 2940 (m), 2890 (m), 1670 (s), 1655 (shoulder), 1270 (m), 1185 (m), 1150 (s), 1135 (s), 1090 (vs), 1030 (vs), 1005 (shoulder), 925 (m); ^{1}H-NMR (CCl_4) 6.90 (s, 1H), 5.00–4.30 (m, 7H), 4.15 (s, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 3.27 (s, 3H), 3.20 (s, 3H), 3.07 (s, 3H), 2.07 (d, J = 4 Hz, 2H), 1.73 (q, J = 7.5 Hz, 2H), 1.03 (t, J = 7.5 Hz, 3H). (Found: C, 48.48; H, 6.34. Calc for $C_{20}H_{31}O_9Br$: C, 48.49; H, 6.31%).

Compound **22**. A magnetically stirred soln of **21** (790 mg, 1.61 mmol) in CH_3OH (30 ml) was cooled to −20° (ethylene glycol/dry ice) and treated with $NaBH_4$ (246 mg, 6.48 mmol). After stirring for 3 hr at −20°, the reaction was quenched with acetone (1 ml) and allowed to warm to 0° over 30 min. The cold mixture was treated with ice water (50 ml), followed by several small chips of dry ice to lower the pH of the mixture. Workup gave 780 mg (98%) of a tan oil which was a 2.5:1 mixture of diastereomeric alcohols which was used without further purification.

A magnetically stirred soln of the crude mixture of alcohols (500 mg, 1.01 mmol) in DMF (6.0 ml) was treated with imidazole (690 mg, 10.1 mmol) and t-butyldimethylsilyl chloride (770 mg, 5.09 mmol) at room temp. After stirring for 78 hr the reaction was quenched and worked up to afford 584 mg (95%) of a mixture of silyl ethers in a ratio of ~2.5:1. This material can be chromatographed on neutral activity III alumina with very little decomposition. However, since the epimers cannot be separated in this way, the crude epimeric mixture was generally used without further purification.

Compound **25**. A magnetically stirred soln of crude product from above (497 mg, 0.813 mmol of epimeric mixture) in dry THF (7.5 ml) under a dry argon atm was treated with a soln of t-BuLi in pentane (0.89 ml of a 1.9 M soln, 1.69 mmol) at −78°, then after 25 min was treated with tetramethylethylenediamine (0.79 ml, 5.25 mmol), and stirred for an additional 5 min. A soln of **24** (0.34 g, 1.62 mmol) in dry THF (0.8 ml) was added, and the mixture was stirred for 5 min at −78°. The mixture was allowed to warm to −61° ($CHCl_3$/dry ice) and stirred for an additional 25 min. Warming to room temp over 15 min was followed by heating to reflux for 3 hr. The cooled soln was quenched with CH_3OH (1 ml) and

concentrated *in vacuo*. The residue was worked up as usual to yield 500 mg of an orange foam. This crude coupling product was immediately hydrolyzed by a mixture of THF (10 ml), water (4 ml), and conc HCl (1.5 ml) at room temp for 55 hr. The hydrolysis mixture was quenched by sat $NaHCO_3$ aq (5 ml) and worked up as usual to afford 433 mg of a dark orange oil. This oil was purified by flash chromatography using a silica gel column (6 in. × 0.75 in., 4% CH_3OH/CH_2Cl_2 as eluant). Elution proceeded as follows: 120 ml of 4% CH_3OH/CH_2Cl_2, 180 mg of unidentified impurities; 150 ml of 4% CH_3OH/CH_2Cl_2, 122.3 mg of a mixture of **25** and **26**; 100 ml of 20% CH_3OH/CH_2Cl_2, 100 mg of unidentified impurities. The total yield of **25** and **26** was 40%. Compounds **25** and **26** were very difficult to separate and, therefore, were utilized as a mixture in the next step. A pure sample of **25** showed: m.p. 148–151° (dec) IR 3420 (br, s), 2920 (m), 1670 (s), 1585 (s), 1445 (m), 1340 (m), 1270 (s), 1220 (m), 1150 (s), 1055 (m), 1020 (m), 990 (m), 695 (m); ^{1}H-NMR 8.15 (s, 1H), 7.81 (dd, J = 7.8, 1.5 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.8, 1.5 Hz, 1H), 4.85 (m, 1H), 4.75 (s, 1H), 3.95 (s, 6H), 3.05 (br s, 1H), 2.54 (br s, disappears with D_2O, 1H), 2.12 (d, J = 3.2 Hz, 2H), 1.78 (q, J = 7.6 Hz, 2H), 1.05 (t, J = 7.6 Hz, 3H). The mass spectrum of **25** showed the M^+-18, M^+-36, and M^+-72 peaks which are distinctive of these systems. An acceptable combustion analysis could not be obtained for this compound.

(±)-α-*Citromycinone* **1**

A magnetically stirred soln of **25** (16 mg, 0.04 mmol) in dry CH_2Cl_2 (2 ml) under N_2 was treated with a soln of BCl_3 in CH_2Cl_2 (0.40 ml of a 1 M soln, 0.40 mmol) at −78°. After stirring for 2 hr at −78°, the reaction was quenched with CH_3OH (3 ml) and allowed to warm to room temp. Workup gave 15 mg of a yellow solid which was recrystallized from $CH_3OH/CHCl_3$ to give 12 mg (80%) of (±)-**1** as yellow crystals: m.p. 220–222° (w/decomp); IR 3400 (broad s), 1630 (s), 1605 (s), 1575 (m), 1475 (m), 1455 (s), 1385 (s), 1330 and 1310 (s, doublet), 1255 (vs), 1130 (m), 1085 (m), 1035 (m); ^{1}H-NMR (pyridine-d_6) 8.35 (s, 1H), 7.87 (dd, J = 7.3, 1.5 Hz, 1H), 7.62 (obscured by solvent), 5.59 (s, 1H), 5.28 (unresolved dd, 1H), 2.80 (dd, J = 5, ~14 Hz, 1H), 2.48 (d, J = ≃14 Hz, 1H), 2.25 (structured m, 2H), 1.36 (t, J = 17.3 Hz, 3H); UV (C_6H_{12}) 435 nm (log ε 3.92), 417 nm (log ε 3.92). The mass spectrum showed the M^+-18, M^+-36, and M^+-72 peaks reported by Brockmann for the originally isolated sample of α-citromycinone. For details of other spectroscopic and analytical data see reference 4.

Ethyl 1,2,3,4-*tetrahydro*-7-*bromo*-5,8-*dimethoxy*-4-*oxo*-2-*naphthoate*, **27**.[11,27]

Yield 99%, m.p. 135.5–136.3°; IR 1740 (s), 1730 (m), 1680 (s), 1560 (m), 1465 (m), 1280 (m), 1255 (m), 1225 (m), 1200 (m), 1090 (m), 1025 (m), 1020 (m); ^{1}H-NMR 1.25 (t, J = 7.5 Hz, 3H), 2.73–3.50 (m, 5H), 3.80 (s, 3H), 3.88 (s, 3H); 4.18 (q, J = 7.5 Hz, 2H), 7.08 (s, 1H); exact mass calc for $C_{15}H_{17}O_5{}^{79}Br$ *m/e* 356.0260, obsd 356.0273.

Ethyl 1,2,3,4-*tetrahydro*-7-*bromo*-5,8-*dimethoxy*-4-*oxo*-2-*naphthoate cyclic* 4-(*ethylene mercaptole*), **28**.[27]

Yield 92%, m.p. 139–140°; IR 1725 (vs), 1465 (s), 1440 (s), 1380 (s), 1285 (s), 1235 (s), 1210 (s), 1090 (s), 1030 (s); ^{1}H-NMR 1.30 (t, J = 7.0 Hz, 3H), 2.15–3.73 (m, 9H), 3.73 (s, 3H), 3.88 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 6.98 (s, 1H); ^{13}C-NMR 174.0, 155.3, 148.1, 131.9, 127.6, 116.3, 115.5, 64.5, 60.6, 60.1, 56.5, 47.9, 42.0, 41.3, 39.8, 27.2, 14.2; exact mass calc for $C_{17}H_{21}O_4S_2{}^{79}Br$ *m/e* 432.0065, obsd 432.0045.

1,2,3,4-*Tetrahydro*-7-*bromo*-5,8-*dimethoxy*-4-*oxo*-2-*acetylnaphthalene cyclic* 4-(*ethylene mercaptole*), **29**.[27]

Yield 84%, m.p. 134.5–136.0°; IR 1710 (vs), 1570 (m), 1470 (s), 1445 (m), 1430 (m), 1425 (m), 1390 (m), 1370 (m), 1230 (s), 1085 (s), 1045 (m), 1025 (m); ^{1}H-NMR 2.28 (s, 3H), 2.43–3.73 (m, 9H), 3.73 (s, 3H), 3.85 (s, 3H), 6.98 (s, 1H); ^{13}C-NMR 209.1, 155.4, 148.2, 132.1, 127.7, 116.4, 115.5, 65.0, 60.0, 56.5, 47.8, 47.6, 42.0, 41.3, 28.3, 26.5; exact mass calc for $C_{16}H_{19}O_3S_2{}^{79}Br$ *m/e* 401.9959, obsd 401.9997.

1,2,3,4-*Tetrahydro*-7-*bromo*-5,8-*dimethoxy*-4-*oxo*-2-*acetyl*-2-*hydroxynaphthalene*-4-(*ethylene mercaptole*)

Yield 71%, m.p. 146.5–147.0°; IR 3480 (m), 2930 (m), 1710 (s), 1695 (m), 1570 (m), 1465 (s), 1450 (m), 1430 (m), 1415 (m), 1390 (m), 1355 (m), 1220 (s), 1065 (s); ^{1}H-NMR 2.33 (s, 3H), 2.60 (s, 1H), 2.70 (s, 1H), 3.00 (s, 2H), 3.20–3.70 (highly structured m, 4H), 3.70 (s, 3H), 3.80 (s, 1H, disappears with D_2O), 3.83 (s, 3H), 7.00 (s, 1H); ^{13}C-NMR 211.7, 155.3, 148.7, 130.2, 126.7, 116.9, 115.8, 77.4, 61.8, 60.2, 56.6, 50.3, 42.0, 40.9, 33.3, 24.7; exact mass calc for $C_{16}H_{19}O_4S_2{}^{79}Br$ *m/e* 417.9908, obsd 417.9912.

1,2,3,4-*Tetrahydro*-7-*bromo*-5,8-*dimethoxy*-4-*oxo*-2-*acetyl*-2-*hydroxy*-*naphthalene cyclic* 4-(*ethylene mercaptole*), *cyclic* 2-(*ethyleneglycol ketal*), **30**.[27]

Yield 94%, m.p. 143.5–144.3°; IR 3490 (m), 1465 (s), 1370 (m), 1230 (m), 1100 (m), 1065 (s), 1035 (m), 1020 (m); ^{1}H-NMR 1.43 (s, 3H), 2.60 (s, 2H), 2.10 (s, 1H), 2.83 (s, 1H), 3.05 (s, 1H), 3.18–3.63 (highly structured m, 4H), 3.73 (s, 3H), 3.85 (s, 3H), 4.03 (s, 4H), 6.98 (s, 1H); ^{13}C-NMR 155.2, 148.9, 131.3, 127.8, 116.5, 115.4, 111.6, 74.6, 65.6 (2C), 62.7, 60.1, 56.6, 48.5, 41.9, 40.8, 31.5, 19.0; exact mass calc for $C_{18}H_{23}O_5S_2{}^{79}Br$ *m/e* 462.0170, obsd 462.0191.

1,2,3,4-*Tetrahedry*-7-*bromo*-5,8-*dimethoxy*-4-*oxo*-2-*acetyl*-2-*hydroxynaphthalene cyclic* 4-(*ethyleneglycol ketal*).[27]

Yield 85%, m.p. 153.0–153.8°; IR 3410 (m), 1690 (s), 1560 (s), 1475 (s), 1230 (s), 1090 (s), 1065 (vs); ^{1}H-NMR (80 MHz) 1.40 (s, 3H), 2.81 (m, 2H), 3.18 (m, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 4.04 (s, 4H), 7.06 (s, 1H). The compound was not analyzed due to possible instability problems.

cis-1,2,3,4-*Tetrahydro*-7-*bromo*-5,8-*dimethoxy*-2-*acetyl*-2,4-*dihydroxynaphthalene cyclic* 4-(*ethyleneglycol ketal*), **31**.[27]

Yield 90%, m.p. 194–195°; IR 3440 (s), 3310 (s), 1465 (s), 1430 (s), 1405 (s), 1330 (s), 1225 (s), 1110 (s), 1085 (s), 1055 (s), 1040 (s), 1020 (s), 890 (s); ^{1}H-NMR 1.43 (s, 3H), 1.88 (dd, J = 2.3, 7.5 Hz, 1H), 2.35 (d of t, J = 2.0, 14.3 Hz, 1H), 2.95 (AB, J = 18 Hz, Δν = 36 Hz, the downfield wing shows an additional splitting, J = 2Hz, 2H), 3.38 (s, disappears with D_2O, 1H), 3.75 (s, 3H), 3.83 (s, 3H), 4.03 (s, 4H), 5.08 (m, collapses to dd with D_2O, J = 2, 4.5 Hz, 1H), 6.95 (s, 1H); exact mass calc for $C_{16}H_{21}O_6{}^{79}Br$ *m/e* 388.0522, obsd 388.0512.

Compound **32**. A soln of the diol, **31** (2.35 g, 6.0 mmol), chloromethylmethyl ether (9.2 ml, 0.12 mol), diisopropylethyl amine (22.2 ml, 0.13 mol) in CH_2Cl_2 (95 ml) was heated to reflux for 36 hr. Workup gave 3.13 g of an orange oil which was flash chromatographed on silica gel using 15% EtOAc/PE as eluant. There was obtained 2.79 g (97%) of the protected diol as an oil: IR (neat) 2940 (s), 2890 (s), 1580 (s), 1470 (s), 1440 (s), 1410 (s), 1375 (s), 1230 (s), 1150 (s), 1100 (s), 1030 (s); ^{1}H-NMR 1.38 (s, 3H), 1.88 (dd, J = 4.5, 15.4 Hz, 1H), 2.53 (unresolved dd, J = 15.4 Hz, 1H), 3.10 (s, 1H), 3.20 (s, overlapping with 3.23 signal, 1H), 3.23 (s, 3H), 3.40 (s, 3H), 3.78 (s, 6H), 3.78–4.08 (m, 4H), 4.60–5.15 (highly structured m, 5H), 6.90 (s, 1H); ^{13}C-NMR 147.8, 142.3, 127.4, 120.2, 111.7, 108.4, 108.0, 92.4, 88.9, 76.3, 64.9, 62.6, 62.3, 58.0, 53.6, 53.4, 53.3, 31.9, 26.7, 18.3. In spite of the apparent purity of this material an acceptable combustion analysis could not be obtained and a parent peak was not observed in the mass spectrum.

Compound **33**. Anodic oxidation of 3.15 g (6.6 mmol) of **32** in 2% KOH/CH_3OH (60 ml) and workup essentially as described for **20** gave 3.44 g (97%) of a light yellow oil which was dissolved in a mixture of THF (50 ml), $(CH_3)_2CO$ (50 ml), and 20% aqueous HOAc (50 ml) and stirred for 1.5 hr at 35°. Workup as for reaction of **16** and recrystallization of the product from Et_2O/H gave 2.49 g (78%) of monoketal **33**: m.p. 147.0–147.5°; IR 1665 (s), 1650 (s), 1190 (m), 1150 (m), 1100 (s), 1080 (s), 1070 (s), 1040 (s), 1025 (s); ^{1}H-NMR 1.43 (s, 3H), 1.75 (dd, J = 5.6, 15 Hz, 1H), 2.45 (dd, obscured by 2.50 signal, J = 15 Hz, 1H), 2.50 (s, 1H), 2.73 (s, 1H), 3.10 (s, 3H), 3.22 (s, 3H), 3.35 (s, 3H), 3.45 (s, 3H), 3.75–4.15 (m, 4H), 4.63–4.70 (m, 3H),

5.00 (AB, J = 4.6 Hz, Δν = 7.6 Hz, 2H), 6.95 (s, 1H); ^{13}C-NMR 181.4, 151.3, 145.3, 137.2, 136.3, 112.2, 97.7, 97.2, 92.8, 78.1, 66.7, 65.7, 64.5, 56.3, 55.9, 51.1, 31.4, 29.1, 18.8, one carbon not observed. (Found: C, 48.71; H, 5.97. Calc for $C_{20}H_{29}O_9Br$: C, 48.69; H, 5.92%).

Compound **34a**. To the monoketal, **33**, (2.3 g, 4.7 mmol) in toluene (60 ml) at 0° was added lithium borohydride (0.15 g, 7.0 mmol). After reaction for 12 hr at room temp, the reaction was quenched by addition of $(CH_3)_2CO$ (5 ml) and 5% NaOH (2 ml). Standard workup afforded 2.06 g (90%) of a mixture of diastereomeric alcohols as a white solid which was used directly in the next step. A portion of the above material (0.5 g, 1 mmol), imidazole (0.68 g, 10.1 mmol), t-butyldimethylsilyl chloride (0.76 g, 5.1 mmol), and 4-dimethylaminopyridine (0.025 g, 0.2 mmol) in DMF (15 ml) was heated at 45° for 6 days. Workup as for reaction of **21** and chromatography on Activity III neutral alumina (7% EtOAc/H as eluant) gave 0.49 g (80%) of a mixture of silyl ethers, **34a**, which was used directly in the next step. (Found: C, 51.12; H, 7.37. Calc for $C_{26}H_{45}O_9BrSi$: C, 51.23; H, 7.44%).

Compound **35a**. To a −78° mixture of the epimeric silyl ethers, **34a** (1.0 g, 1.64 mmol) in THF (13 ml) was added dropwise 1.81 ml (3.45 mmol) of 1.9 M t-BuLi. After 3 min, tetramethylethylenediamine (1.64 ml, 10.8 mmol) was added, and after an additional 5 min, benzocyclobutenedione monoethylene glycol ketal (0.578 g, 3.28 mmol) in THF (5 ml) was added. The dark red mixture was warmed to room temp over 1 hr and then heated to reflux for 4 hr. Workup gave 1.43 g of a crude red-orange oil which was dissolved in a mixture of $(CH_3)_2CO$ (20 ml), water (8 ml), and conc HCl (2.8 ml). The soln was stirred for 36 hr at room temp and worked up essentially as for reaction of **23a** to yield 0.96 g of red-orange oil. Flash chromatography of this material on silica gel using 7–10% EtOAc/H as eluant gave first 1-hydroxy-4-methoxy-6-acetylnaphthalene: m.p. 189.0–190.5°; IR 3200 (br, s), 1650 (s), 1625 (s), 1595 (m), 1460 (m), 1435 (m), 1365 (s), 1345 (m), 1280 (s), 1235 (m), 1100 (s), 1040 (m), 800 (m); ^{1}H-NMR (300 MHz) 2.75 (s, 3H), 3.99 (s, 3H), 5.12 (s, 1H), 6.79 (AB, J = 8.22 Hz, Δν = 52.5 Hz, 2H), 8.13 [AB J = 8.8 Hz, Δν = 33.0 Hz (the right wing is meta coupled to 8.86 signal, J = 1.7 Hz), 2H], 8.86 (d, J = 1.7 Hz, 1H); exact mass calc for $C_{13}H_{12}O_3$ *m/e* 216.0786, obsd 216.0763.

Continued elution gave a mixture of **35a** and **35b** (0.174 g, 30%) from which a pure sample of **35a** was isolated: m.p. 190.5–191.3°; IR 1700 (m), 1675 (s), 1586 (m), 1335 (m), 1270 (m), 1255 (m), 1070 (m); ^{1}H-NMR (200 MHz) 2.28 (d separated by 2.3 Hz, 2H), 2.40 (s, 3H), 3.07 (AB, J = 17.9 Hz, Δν = 31.5 Hz, 2H), 3.88 (s, 3H), 3.96 (d, disappears with D_2O, J = 10.1 Hz, 1H), 4.45 (s, disappears with D_2O, 1H), 4.91–4.96 (m, collapses to t with D_2O, J = 3.4 Hz, 1H), 7.73–7.78 (highly structured m, 2H), 8.20–8.26 (m, 3H); exact mass calc for $C_{21}H_{18}O_6$ *m/e* 366.1006, obsd 366.1055.

Compound **35b**. To a −78° soln of a mixture of **35a** and **35b** (0.12 g, 0.32 mmol) in CH_2Cl_2 (20 ml) was added BCl_3 (2.6 ml of a 1 M soln), the mixture stirred for 2 hr at −78°, and then the reaction was quenched with CH_3OH. Workup essentially as described for **1** and chromatography on silica gel 6% EtOAc/CH_2Cl_2 as eluant) gave a mixture of **34a** and **34b** (0.024 g) and **35b** (0.080 g, 89% corrected for recovered **34a**), m.p. 208.5–209.5° (lit.[25] m.p. 206.0–208.0°). This material showed spectroscopic properties and TLC behavior identical with a sample supplied by Dr. Penco of Farmitalia Drug Co.

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[1a]Taken in part from the Ph.D. Thesis of D. K. Anderson, The Ohio State University, 1982; [b]Taken in part from the Ph.D. Thesis of A. P. Haag, The Ohio State University, 1981.

[2a]For reviews of work in this area see: *Anthracycline Antibiotics* (Edited by H. S. El Khadem) Academic Press, New York (1982); F. Arcamone, *Doxorubicin: Anticancer Antibiotics*. Academic Press, New York (1981); [b]For refs to earlier work see T. R. Kelly, J. Vaya and L. Ananthasubramanian, *J. Am. Chem. Soc.* **102**, 5983 (1980).

[3a]B. A. Pearlman, J. M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki and Y. Kishi, *J. Am. Chem. Soc.* **103**, 4248 (1981); [b]P. N. Confalone and G. Pizzolato, *Ibid.* **103**, 4251 (1981); [c]A. S. Kende and J. P. Rizzi, *Ibid.* **103**, 4247 (1981); [d]J. Yadav, P. Corey, C. Hsu, K. Perlman and C. Sih, *Tetrahedron Letters* **22**, 811 (1981); [e]S. D. Kimball, D. R. Walt and F. Johnson, *J. Am. Chem. Soc.* **103**, 1561 (1981); [f]R. K. Boeckman, Jr. and F.-W. Sum, *Ibid.* **104**, 4604 (1982) and refs cited; [g]J. G. Bauman, R. B. Barber, R. D. Gless and H. Rapoport, *Tetrahedron Letters* **21**, 4777 (1980); [h]J. P. Gesson, J. C. Jacquesy and M. Mondon, *Ibid.* **21**, 3351 (1980); [i]A. S. Kende and J. P. Rizzi, *Ibid.* **22**, 1779 (1981); [j]Z. Ahmed and M. P. Cava, *Ibid.* **22**, 5239 (1981); [k]T.-t. Li and Y. L. Wu, *J. Am. Chem. Soc.* **103**, 7007 (1981); [l]A. V. Rama Rao, V. H. Deshpande and N. L. Reddy, *Tetrahedron Letters* **23**, 775 (1982); [m]K. Krohn and B. Sarstedt, *Angew. Chem.* **22**, 875 (1983).

[4]A preliminary report on the total synthesis of α-citromycinone has appeared: D. K. Anderson, C. E. Coburn, A. P. Haag and J. S. Swenton, *Tetrahedron Letters* **24**, 1329 (1983).

[5]Two papers report syntheses of 6-deoxyanthracyclinones which have the 7-OH group. [a]S. Penco, F. Angelucci, F. Arcamone, M. Ballabio, G. Barchielli, G. Franceschi, G. Franchi, A. Suarato and E. Vanotti, *J. Org. Chem.* **48**, 405 (1983); [b]R. K. Boeckman and S. H. Cheon, *J. Am. Chem. Soc.* **105**, 4113 (1983); [c]F. Angelucci, F. Arcamone, G. Barchielli, A. Suarto, E. Vanotti and S. Penco, *J. Chem. Soc.* Chem. Commun. 530 (1984); [d]F. M. Hauser and D. Mal, *J. Am. Chem. Soc.* **106**, 1862 (1984).

[6]Synthetic routes to the 6-deoxyanthracyclinone ring system have also been reported: [a]A. S. Kende, J. P. Gesson and T. P. Demuth, *Tetrahedron Letters* **22**, 1667 (1981); [b]J. P. Gesson, J. C. Jacquesy and M. Mondon, *Ibid.* **22**, 1337 (1981); [c]K. Krohn and B. Behnke, *Ibid.* **23**, 395 (1982); [d]P. N. Preston, T. Winwick and J. D. Morley, *J. Chem. Soc.* Chem. Commun. 307 (1984).

[7]H. Brockmann, *Fortschr. Chem. Org. Naturst.* **21**, 121 (1963); R. H. Thompson, *Naturally Occurring Quinones* Chap. 6. Academic Press: New York (1971).

[8]D. M. S. Wheeler, *Cancer Chemother. Rpts. Pt. 1* **59**, 258 (1975).

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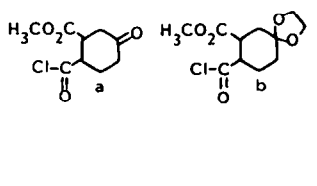
[10]For a discussion, see ref. 2*a*, pp. 188–190, and accompanying paper: J. S. Swenton, J. Freskos, G. W. Morrow and T. A. Sercel, *Tetrahedron* **40**, 4625 (1984).

[11]For the use of this type of strategy in rhodomycinone synthesis, see: J. S. Swenton, D. K. Anderson, D. K. Jackson and L. Narasimhan, *J. Org. Chem.* **46**, 4825 (1981).

[12]D. K. Jackson and J. S. Swenton, *Synth. Commun.* **7**, 333 (1977).

[13]*Chem. Abstracts* **49**, 5329e (1955); I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk S.S.S.R., Otdel, Khim. Nauk*, 329 (1954).

[14]The C-acylation observed between **3** and **4** is dramatically substrate dependent. Attempted C-acylation of **a** and **b** with **3** and $SnCl_4$ afforded primarily O-acylation products. It appears that the double bond of **4** is important for observing C-acylation. The intramolecular interaction of this double bond with the acylium ion could influence the softness of the cation and thus the C vs. O alkylation ratio. Such an interaction between a double bond and a carbonium ion has



precedent in the Lewis acid catalyzed rearrangements of γ,Δ unsaturated aldehydes.[15]

[15] R. C. Cookson and S. A. Smith, *Chem. Commun.* 145 (1979); J. E. Baldwin and M. Lusch, *J. Org. Chem.* **44**, 1923 (1979).

[16] The stereochemistry for the major product in the series **8–10** is undoubtedly *cis* since if **10** is formed in refluxing base solution, the ratio of diastereomers changes with predominance of what would reasonably be assigned as the *trans* isomer.

[17] We wish to thank Professor A. Kende for an authentic sample of **13**.

[18] [a]J. S. Swenton and P. W. Raynolds, *J. Am. Chem. Soc.* **100**, 6188 (1978); [b]D. K. Jackson, L. Narasimhan and J. S. Swenton, *Ibid.* **101**, 3989 (1979).

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[20] E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.* **94**, 6190 (1972); K. K. Ogilvie and D. Iwacha, *Tetrahedron Letters* 317 (1973).

[21] The difference in the metallation and functionalization chemistry of **18** *vs* **22** under seemingly identical conditions remains unexplained; however, it may be related to the different solvation of the organolithium species via the hydroxyl protecting groups.

[22] See accompanying paper.

[23] The following abbreviations have been used throughout the Experimental: n-BuLi, $CHCl_3$, cyclohexane (C_6H_{12}), DMF, DMSO, EtOH, ether Et_2O, hexanes (H), HCl, lithium diisopropylamide (LDA), CH_3OH, CH_2Cl_2, petroleum ether (PE), THF. All m.ps below 220° were taken with a Thomas–Hoover capillary m.-p. apparatus and are uncorrected. Measurements with standard samples indicate that the reported m.ps are probably 1–2° lower than the correct value. M.ps greater than 220° were recorded on a hot-stage apparatus. IR spectra were taken primarily on a Perkin–Elmer Model 283B grating spectrometer with some spectra being recorded on a Perkin–Elmer Infracord spectrometer. ^{1}H-NMR spectra were recorded at 90 MHz in $CDCl_3$ unless otherwise noted. Apparent multiplicities are reported, and in some cases, signals reported as triplets are in fact closely spaced doublet of doublets. ^{13}C-NMR spectra (TMS ref) were recorded on a Bruker WP-80 instrument at 20 MHz in $CDCl_3$. The 200- and 300-MHz ^{1}H-NMR spectra were recorded by Mr. C. Engelman and Dr. G. Larson. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronics MS-9 double-focusing mass spectrometer. Ultraviolet spectra were recorded on a Carey Model 15 instrument. The maxima are reported in nanometers with the extinction coefficients in parentheses. Tetrahydrofuran was freshly distilled from benzophenone/sodium prior to use. All other solvents used for reactions were freshly dried and distilled. All reactions were run under nitrogen or argon atmosphere. Analytical samples were analyzed by Scandinavian Microanalytical Laboratory. Aluminum oxide and silica gel were from E. Merck Co. "Workup as usual" consisted of extraction of the product (CH_2Cl_2 or Et_2O), drying over calcium sulfate or sodium sulfate, and concentration *in vacuo* followed by drying under vacuum.

[24] R. H. Thomson, E. Race and F. M. Rowe, *J. Chem. Soc.* 350 (1947).

[25] N. F. Hayes and R. H. Thomson, *J. Chem. Soc.* 904 (1955).

[26] A. S. Kende, J. E. Mills and Y. Tsay, U.S. Patents 4,021,457 (1977) and 4,070,382 (1978).

[27] The experimental procedure is essentially identical to that for the unbrominated compound except compound **29** was prepared using dimsyl lithium. Since this is described in detail in the accompanying paper, only the yield and spectroscopic data of the compound are reported herein.