The pentane solution was poured into ice-cold, saturated, aqueous NH_4Cl, after which 25 mL of 12 M aqueous H_2SO_4 was added. The layers were separated, and the aqueous layer was washed with pentane. The organic layers were combined, dried with Na_2SO_4, and rotary evaporated. The major product, 9-ethyl-*cis*-2-decalone (**19**),[20] was collected by thin-layer chromatography (hexane): IR (CCl_4) 1715 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 0.79 (t, 3, J = 7 Hz), 1.03–2.63 (m, 17); ^{13}C NMR ($CDCl_3$) δ 6.57, 21.55, 24.51, 26.76, 27.63, 31.51, 32.93, 37.37, 37.60, 40.66, 46.80, 212.64.

Desilylation of 9-[(Trimethylsilyl)ethynyl]-*cis*-2-decalone To Form 9-Ethynyl-*cis*-2-decalone (18). To 0.44 g (1.80 mmol) of 9-[(trimethylsilyl)ethynyl]-*cis*-2-decalone in 12 mL of DMF were added several spatula tips full of $(CH_3CH_2)_4NF$. The reaction mixture was allowed to stir overnight and was worked up by the addition of hexane and water. The hexane layer was washed with water and rotary evaporated to give 0.25 g (80% yield) of 9-ethynyl-*cis*-2-decalone (**18**): IR (CCl_4) 2110 (C≡C), 3310 cm^{-1} (≡CH); ^1H NMR (CCl_4) 1.24–2.51 (m, 15), 2.13 (s, 1, ≡CH); mol wt calcd 176.120 109, found 176.117 565.

Reduction of 9-Ethynyl-*cis*-2-decalone (18) to 9-Ethyl-*cis*-2-decalone (19). To a small amount of 5% Pd on charcoal in 10 mL of anhydrous methanol was added 0.14 g (0.82 mmol) of **18** in 5 mL of methanol. The apparatus was filled with H_2 and gas uptake was measured by means of a buret. After 6.5 h the reaction mixture was filtered to remove the Pd/C and rotary evaporated to give a quantitative yield of 9-ethyl-*cis*-2-decalone (**19**):[20] IR (CCl_4) 1715 cm^{-1} (CO); ^1H NMR (CCl_4) δ 0.79 (t, 3, J = 7 Hz), 1.03–2.63 (m, 17); ^{13}C NMR ($CDCl_3$) δ 6.59, 21.57, 24.52, 26.76, 27.63, 31.54, 32.94, 37.37, 37.60, 40.69, 46.81, 212.63.

Acknowledgment. The authors acknowledge generous support for this work provided by the National Institutes of Health (Grant No. HL 22612, to R.T.H. as a Postdoctoral Fellow and to D.B.C. as a NCI Fellow) and by the National Science Foundation (Grant No. CHE 76-02130). They also thank Hoffmann-LaRoche, Inc., for elemental analyses, J. Larrabee and T. F. Murray for Raman spectra, and Professor B. B. Snider for helpful comments and suggestions.

Registry No. **7**, 66529-94-0; **8**, 66529-95-1; **9**, 66529-96-2; **10**, 66529-97-3; **11**, 54125-18-7; **12**, 66529-98-4; **13**, 66529-99-5; **14**, 66530-00-5; **15**, 66530-01-6; **16**, 66530-02-7; **17**, 73838-35-4; **18**, 73838-36-5; **19**, 32980-04-4; **20a**, 73838-37-6; **20b**, 71120-86-0; **20c**, 73838-38-7; **20e**, 73838-39-8; **20f**, 73838-40-1; **21b**, 73838-41-2; **21c**, 73838-42-3; **21e**, 73838-43-4; **22**, 73838-44-5; **23**, 66530-05-0; **24**, 73838-45-6; **25a**, 73838-46-7; **25b**, 73890-06-9; **26a** (epimer 1), 73838-47-8; **26b** (epimer 1), 73890-08-1; 3,3-dimethyl-1-butyne, 917-92-0; 1-hexyne, 693-02-7; ethynyltrimethylsilane, 1066-54-2; ethyne, 74-86-2; 2-cyclopenten-1-one, 930-30-3; 2-cyclohexen-1-one, 930-68-7; 4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone, 1196-55-0; 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3*H*)-naphthalenone, 826-56-2; 4-(cumyloxy)-2-cyclopenten-1-one, 65457-77-4; bis(2,4-pentanedionato-*O*,*O'*)nickel, 3264-82-2; diisobutylaluminum hydroxide, 1191-15-7; dimethyl(neohexynyl)aluminum, 66530-03-8; 3-(trimethylsiloxy)-1-octyne, 73061-39-9; 1-octyn-3-ol, 818-72-4; 3-(*tert*-butyldimethylsiloxy)-1-octyne, 60134-93-2; 3-((triethylsilyl)oxy)-1-octyne, 73838-48-9; 3-((triphenylmethyl)oxy)-1-octyne, 52418-74-3; triphenylmethyl chloride, 76-83-5; 3-acetoxy-1-octyne, 54315-33-2; diisobutylaluminum chloride, 1179-25-5; dimethylaluminum chloride, 1184-58-3; 3-(*tert*-butyldimethylsiloxy)-1-octynyllithium, 60134-82-9; **26a** (epimer 2), 73890-07-0; **26b** (epimer 2), 73890-09-2; hexanol, 66-25-1; 2,2,7,7-tetramethyl-3,5-octadiyne, 6130-98-9.

Anthra[1,2-*b*]pyran Antibiotics: Total Synthesis of *O*-Methylkidamycinone

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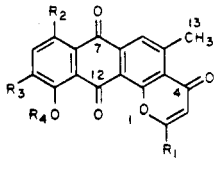
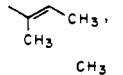
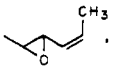
Received March 10, 1980

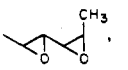
A regiospecific total synthesis of *O*-methylkidamycinone (**1d**) is described. Ethyl 2-methoxy-6-methylbenzoate (**6a**) was transformed to 7-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**7c**) which was converted to an anion and condensed with methyl crotonate to afford methyl 3-methyl-1,4,8-trimethoxynaphthoate (**8a**) after methylation. The 3-methyl group of **8a** was brominated, and the introduced bromine was displaced with sodium thiophenoxide to give **8c** which was oxidized to the corresponding sulfoxide **8d**. The anion of sulfoxide **8d** was condensed with 3-penten-2-one to furnish 2-acetyl-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (**9a**). The dilithium anion of **9a** was prepared and condensed with tiglaldehyde to afford (2′*E*,4′*E*)-2-(4′-methylhexa-2′,4′-dienoyl)-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (**13**). Cyclization and dehydrogenation of **13** with selenium dioxide afforded (1′*E*)-5-methyl-2-(1′-methyl-1′-propenyl)-7,11,12-trimethoxy-4*H*-anthra[1,2-*b*]pyran-4-one (**15**). Oxidative cleavage of the 7,12-dimethoxy groups of **15** completed the construction of **1d**.

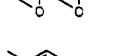
Kidamycin (**1a**),[2] pluramycin A (**1b**),[3] hedamycin (**1c**),[4] and indomycins[5] are members of a family of structurally similar anticancer antibiotics which have been isolated from various streptomyces species. Those antibiotics for which complete structures have been established have an



1a R_1 =  , R_2 = angolosamine, R_3 = N,N-dimethylvancosamine, R_4 = H

1b R_1 =  , R_2 = angolosamine, R_3 = N,N-dimethylvancosamine, R_4 = H

1c R_1 =  , R_2 = angolosamine, R_3 = N,N-dimethylvancosamine, R_4 = H

1d R_1 =  , $R_2 = R_3 = H$, $R_4 = CH_3$

anthra[1,2-*b*]pyran nucleus substituted with the amino sugars angolosamine and *N*,*N*-dimethylvancosamine at the 8- and 10-positions, respectively. The structural diversity of the antibiotics is due to the variety of unsaturated chains

(1) Recipient of a Research Career Development Award (CA 00486) from the National Cancer Institute of the National Institutes of Health (1978–1983).

(2) Hata, T.; Umezawa, I.; Komiyama, K.; Asano, K.; Kanda, N.; Fujita, H.; Kono, M. *Prog. Antimicrob. Anticancer Chemother., Proc. Int. Congr. Chemother.* **1970**, *1*, 81. Kanda, N. *J. Antibiot.* **1971**, *24*, 599; **1972**, *25*, 557. Furukawa, M.; Itai, A.; Iitaka, Y. *Tetrahedron Lett.* **1973**, 1065. Furakawa, M.; Iitaka, Y. *Ibid.* **1974**, 3289. Furukawa, M.; Hayakawa, I.; Ohta, G.; Iitaka, Y. *Tetrahedron* **1975**, *31*, 2989.

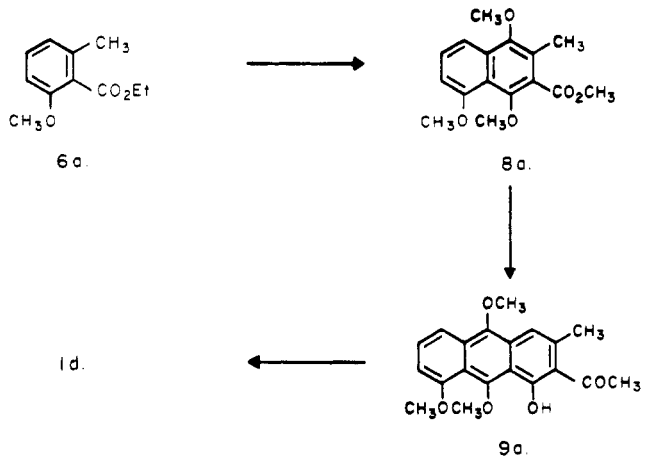
(3) Kondo, S.; Miyamoto, M.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 1143. Séquin, U.; Ceroni, M.; *Helv. Chim. Acta* **1978**, *61*, 2241.

(4) Séquin, U.; Bedford, C. T.; Chung, S. K.; Scott, A. I. *Helv. Chim. Acta* **1977**, *60*, 896. Séquin, U. *Tetrahedron* **1978**, *34*, 761. Séquin, U.; Furukawa, M. *Ibid.* **1978**, *34*, 3623. Ceroni, M.; Séquin, U. *Tetrahedron Lett.* **1979**, 3703. Zehnder, M.; Séquin, U.; Nadig, H. *Helv. Chim. Acta* **1979**, *62*, 2525.

(5) Brockmann, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 481.

0022-3263/80/1945-3061$01.00/0

Scheme I



attached to the 2-position of the nucleus. The important biological activity of this family of antibiotics makes these substances attractive subjects for synthetic study.

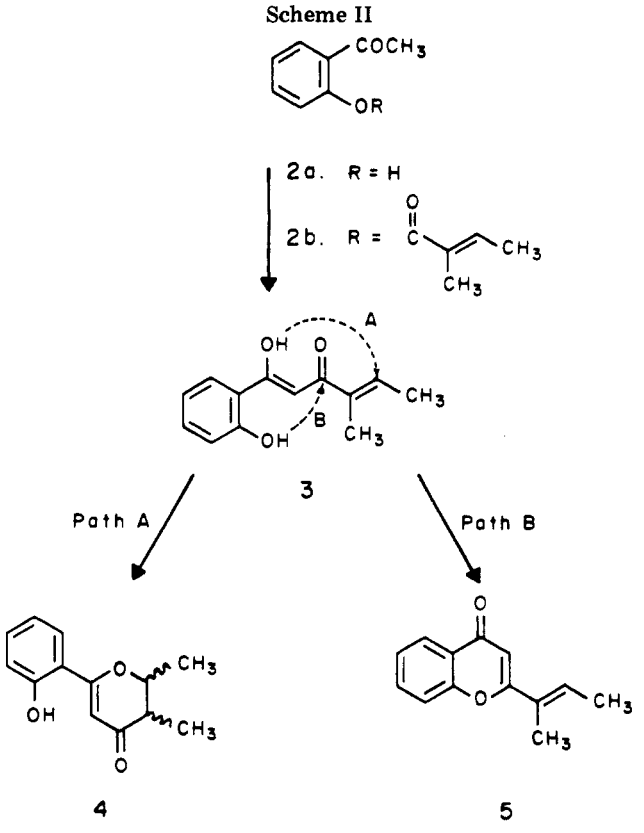
In a series of recent communications,[6-9] we have reported the development of general synthetic methods which can be used to synthesize complex natural polycyclic aromatic systems while maintaining absolute control over the regiochemistry of introduced functionalities. We report here the details of the application of these concepts to the total synthesis of the aglycone[10] *O*-methyl ether **1d** of kidamycin (**1a**).[11]

Scheme I presents an outline of our planned synthesis of *O*-methylkidamycinone (**1d**). The progressive construction strategy[6] and adjunct annelation methods[7] would be used to regiospecifically transform ethyl 2-methoxy-6-methylbenzoate (**6a**) first to naphthalene **8a** and then to the selectively protected anthracene intermediate **9a**. Final synthesis of **1d** would be accomplished by fashioning the terminal pyrone fragment from the ortho phenolic and acetyl functionalities of anthracene **9a** and oxidatively cleaving the 7,12-dimethoxy groups.

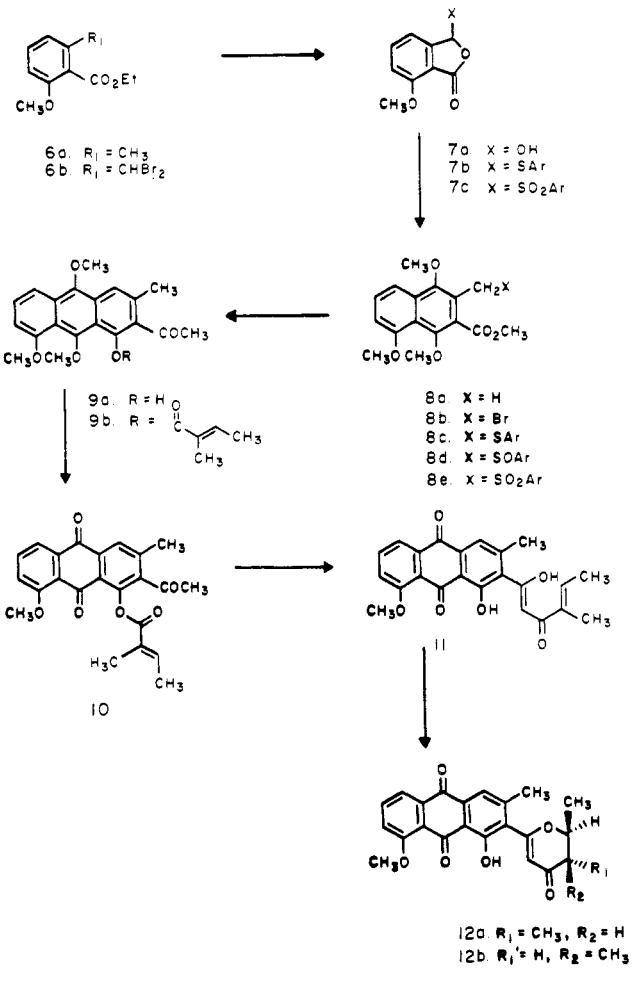
While numerous methods exist for fashioning 4*H*-1-benzopyran-4-ones from ortho phenolic and acetyl functionalities on an aromatic ring,[12] only a few preparations of 2-styryl-substituted benzopyrones[13-15] and none for either 2-vinyl- or 2-alkyl-substituted vinylbenzopyrones have been described. The absence of literature precedent for stereospecifically constructing the vinylpyrone moiety found in kidamycin (**1a**) led us to test the preparation of this fragment prior to undertaking the synthesis of anthracene intermediate **9a**.

The reaction sequence shown in Scheme II, modeled after the Baker–Venkataraman route[14,16] for constructing

Scheme II



Scheme III



benzopyrones, was investigated. Acylation of *o*-hydroxyacetophenone (**2a**) with tigloyl chloride in pyridine af-

(6) Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1977**, *99*, 4533.
(7) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1977**, *42*, 4155.
(8) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.
(9) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596.
(10) Rather than defining an aglycone as the nonsugar portion resulting from hydrolysis of a molecule, we have here defined aglycone as the nonsugar portion which when coupled or condensed with a sugar provides the parent substance. This definition of aglycones broadly encompasses those substances which have C-sugar residues.
(11) A preliminary account describing portions of this work has been published. Hauser, F. M.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 1628.
(12) Ellis, G. P. "Chemistry of Heterocyclic Compounds: Chromenes, Chromanones and Chromones"; Wiley: New York, 1977; Vol. 31. Elderfield, R. C. "Heterocyclic Compounds"; Wiley: New York, 1951; Vol 2. Dean, F. M. "Naturally Occurring Oxygen Ring Compounds"; Butterworths: London, 1963.
(13) Chekravarti, D. *J. Indian Chem. Soc.* **1931**, *8*, 129. Heibron, I. M.; Barnes, H.; Morton, R. A. *J. Chem. Soc.* **1923**, *123*, 2566.
(14) Baker, W. *J. Chem. Soc.* **1933**, 1381.
(15) Cheema, U. S.; Gulati, K. C.; Venkataraman, K. *J. Chem. Soc.* **1932**, 925.

forded tigloate ester **2b** which on treatment with sodium hydride in dioxane gave diketone intermediate **3**.[17]

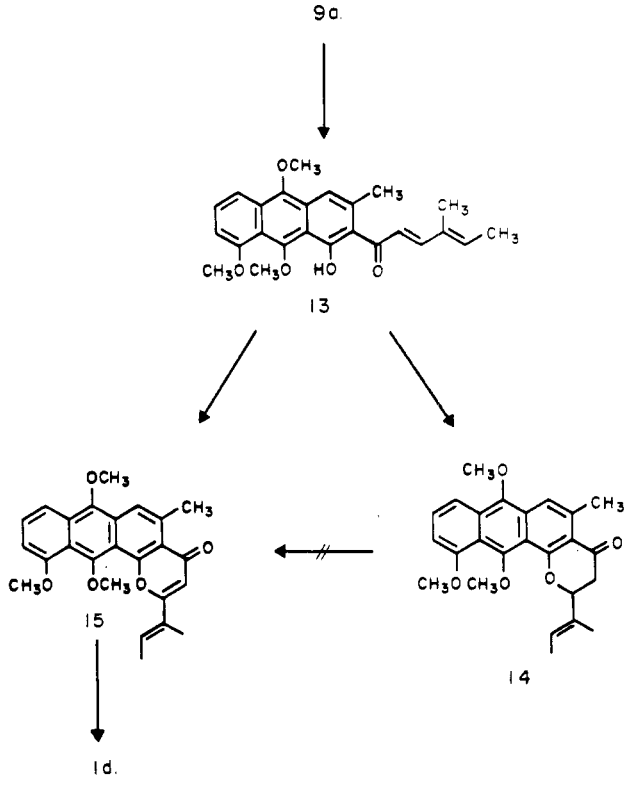
Two modes of cyclization are possible for **3**. Conjugate addition of the enol hydroxyl to the terminal vinyl fragment (path A) would give the phenyl substituted pyrone **4**, while condensation of the phenolic group with the β-ketone followed by dehydration (path B) would provide the vinyl-substituted benzopyrone **5**. Heating diketone **3** in acetic acid containing sodium acetate furnished a single product in 75% overall yield from **2a**. The ^{1}H NMR spectrum of the product was consistent with the vinyl-substituted benzopyrone structure **5**. In addition, formation of **5** from **3** did not result in loss of the stereochemical integrity of the vinyl fragment.

Construction of the vinylpyrone moiety having been demonstrated, synthesis of the anthracene intermediate **9a** was undertaken (Scheme III). The transformation of methyl 2-methoxy-6-methylbenzoate (**6a**) to methyl 3-methyl-1,4,8-trimethoxy-2-naphthoate (**8a**) necessitated the preparation of intermediate (phenylsulfonyl)isobenzofuranone **7c**. Dibromination of the 6-methyl group of **6a** in dilute carbon tetrachloride with *N*-bromosuccinimide afforded dibromomethyl benzoate **6b** which in turn was hydrolyzed in hydrochloric acid–acetic acid to 3-hydroxyisobenzofuranone **7a** in 80% overall yield.[18] The toluenesulfonic acid catalyzed condensation of **7a** with benzenethiol[19] in benzene with azeotropic removal of water gave 3-thiophenyl-1(3*H*)-isobenzofuran-1-one (**7b**).[20] Both *m*-chloroperbenzoic acid[21] in methylene chloride and hydrogen peroxide in acetic acid[22] were equally effective oxidants for converting (thiophenyl)isobenzofuranone **7b** to the corresponding sulfone **7c**. However, use of the latter reagent had the advantage that a less tedious workup was required.

The vested regiochemistry of isobenzofuranone **7c** was now exploited to achieve regiospecific construction of naphthoate **8a**. The anion of **7c**, formed with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), was condensed with methyl crotonate at −78 °C, and the product was methylated with dimethyl sulfate and potassium carbonate in acetone to give methyl 3-methyl-1,4,8-trimethoxynaphthoate (**8a**) in 83% yield.

For the conversion of naphthoate **8a** to anthracene **9a**, it was necessary to prepare intermediate sulfoxide **8d** which was efficiently accomplished in three steps. Selective monobromination of the 3-methyl group of **8a** with NBS in carbon tetrachloride furnished bromomethyl product **8b**, which in turn was converted to thiophenylated product **8c** on treatment with sodium thiophenoxide in refluxing ethanol. The overall yield of sulfide **8c** from naphthoate **8a** was 89%. Both sodium periodate in tetrahydrofuran–water[23] and *m*-chloroperbenzoic acid in methylene chloride at −78 °C[24] could be used to convert

Scheme IV



sulfide **8c** to sulfoxide **8d**. The periodate oxidation gave **8d** as the sole product in quantitative yield, but took 3 days to go to completion. The *m*-chloroperbenzoic acid oxidation could be conducted in 1 h, and although a small amount (9%) of sulfone **8e** was produced, it was readily separated by slug chromatography.

Transformation of **8d** to anthracene **9a** was achieved by converting **8d** to an anion with LDA at −78 °C followed by condensation with 3-penten-2-one. For aromatization of the terminal ring, the reaction mixture was warmed to room temperature and then heated to reflux to eliminate phenylsulfinic acid from the initial adduct.[8] The yield of regiospecifically constructed, selectively protected anthracene **9a** was 71%.

Construction of the vinylpyrone fragment from the phenolic and acetyl functionalities of **9a** was initiated next by using the sequence developed earlier for this purpose. Acylation of **9a** with tigloyl chloride gave tigloate ester **9b**. Attempted transfer of the tigloyl moiety to the acetyl functionality led to consumption of **9b** without production of any identifiable product. The reaction failure was attributed to the lability of the 9,10-dimethoxy groups, and this was subsequently proven when quinone **10**, derived by oxidative demethylation of **9b** with cupric bromide,[25] was smoothly transformed to diketone **11** upon treatment with excess sodium hydride in tetrahydrofuran. The presence of a vinyl absorption δ 8.60 in the ^{1}H NMR spectrum of **11** indicated that diketone **11** was totally in the enol form.[17]

In contrast to the result obtained in the model study, treatment of diketone **11** with sodium acetate in acetic acid afforded alternate epimeric cyclization products **12a** and

(16) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1936**, 1767.

(17) Only one of the tautomeric forms is shown.

(18) This procedure was adapted from a preparation of 3,7-dihydroxy-1(3*H*)-isobenzofuranone. Eliel, E. L.; Rivard, D. E.; Burgstahler, A. W. *J. Org. Chem.* **1953**, *18*, 1679.

(19) Wheeler, D. D.; Young, D. C.; Erley, D. S. *J. Org. Chem.* **1957**, *22*, 547.

(20) An alternate preparation of **7b** was recently developed. Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H. *Synthesis* **1980**, 72.

(21) Brown, D. J.; Ford, P. W. *J. Chem. Soc. C* **1969**, 2720. Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1970**, *35*, 2106.

(22) Schöberl, A.; Wagner, S. "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Georg Thieme-Verlag: Stuttgart, 1955; Vol. IX, pp 227–243.

(23) Johnson, C. R.; Keiser, J. E. *Org. Synth.* **1966**, *46*, 78.

(24) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109. Johnson, C. R.; Diefenbach, H.; Keiser, J. E.; Sharp, J. C. *Tetrahedron* **1969**, *25*, 5649. Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(25) The oxidative demethylation of 9,10-dimethoxyanthracene with cupric bromide appears to be general, and further study of the reaction is in progress.

12b in 76 and 22% yields, respectively. From their individual ^{1}H NMR spectra, the structures of **12a** and **12b** were determined. The presence of doublets in both spectra at ca. δ 1.25 and 1.55, corresponding to two methyl groups adjacent methine protons, demonstrated the involvement and loss of integrity of the tigloyl moiety. Additional supporting spectral assignments were singlets appearing at δ 5.60 and 13.28 which correspond to the olefinic proton of the newly formed pyrone ring[26] and the hydrogen-bonded phenolic absorption, respectively. The large coupling constant (J_{AB} = 12 Hz) for the protons at δ 2.53 ($COCHCH_3$) and 4.44 ($OCHCH_3$) in the spectrum of **12a** permitted assignment of the configuration of the methyl groups as trans, while the smaller coupling constant (J_{AB} = 3.4 Hz) of the corresponding protons in the spectrum of **12b** allowed assignment of the configuration of that isomer as cis.

The sequence shown in Scheme IV, which follows another classical route for constructing benzopyrones,[12] was investigated. Unlike the previous sequence, only one conjugate-addition cyclization was possible, and that would provide a dihydropyrone fragment. Attempted preparation of dienone intermediate **13** by condensation of anthracene **9a** with tiglaldehyde employing an alcoholic sodium hydroxide medium failed. A successful preparation of dienone **13** in 75% yield was readily achieved by initially converting anthracene **9a** to its dilithium anion with LDA in THF and then condensing the anion with tiglaldehyde at −78 °C. The large coupling constant (J = 15 Hz) of the olefinic protons at δ 6.98 and 6.40 in the ^{1}H NMR spectrum permitted the assignment of a trans configuration to the newly formed olefinic linkage.

The intramolecular cyclization of dienone **13** to dihydroanthra[1,2-*b*]pyran **14** proved surprisingly difficult. The use of acetic acid–water, pyridine–benzene,[27,28] and sodium methoxide in methanol,[29,30] mediums effective for the cyclization of phenolic chalcones to dihydrobenzopyrones, all failed to give the product. Ultimately, two different sets of conditions were found to effect cyclization. Addition of 1 equiv of potassium hydroxide to a methanolic solution of **13** with stirring for *exactly* 5 min afforded a 10% yield of dihydroanthra[1,2-*b*]pyran **14**. A higher yield and experimentially less tedious method for preparing **14** was to reflux anthradienone **13** in methanolic sodium acetate solution[31] for 2 days. A 35% yield of **14** was obtained with reisolation of 41% of the starting material. Neither longer reaction times nor variations in the reaction conditions had an appreciable positive effect on the composition of the product mixture. The ^{1}H NMR spectrum of **14** provided conclusive evidence for the structure assignment. An ABX coupling pattern was observed for the hydrogens α to the carbonyl group of the pyrone, and the hydrogen at the 2-position was a multiplet at δ 4.97. By far the most striking feature of the spectrum was the appearance of the 13-methyl group at δ 2.78 due to its proximity to and coplanarity with the deshielding cone of the pyrone carbonyl group.

Direct dehydrogenation of dihydroanthrapyran **14** to anthrapyran **15** with dichlorodicyanobenzoquinone (DDQ) or selenium dioxide[32] failed and resulted in the formation of numerous products, with no single compound predominating. An attempt to dehydrogenate **14** by monobrominating the methylene group α to the carbonyl function and then dehydrohalogenating was terminated. Under all the conditions tried for monobromination,[33] complex product mixtures were observed.

An alternate plan for introducing the unsaturation was undertaken. The planned approach was to complex the olefinic moiety of **13** with an electrophilic reagent, thereby simultaneously achieving ring closure through neighboring participation of the phenolic moiety and introduction of elements of the electrophile α to the carbonyl group. Concurrent or subsequent elimination of the introduced electrophile portion would accomplish dehydrogenation and give anthrapyrone **15**.[34] Attempts to achieve this goal by treating **13** with iodine in pyridine, with palladium acetate[35] in acetic acid, or with dichlorodicyanobenzoquinone in benzene gave complex reaction mixtures. The successful cyclization–dehydrogenation of **13** to **15** was finally achieved in 27% yield, with reisolation of 50% of **13**, by refluxing **13** with selenium dioxide[36] in *tert*-amyl alcohol for 16 h. The use of longer reaction times and/or larger amounts of selenium dioxide gave lower yields, and other mediums such as benzene, toluene, methanol, ethanol, *tert*-butyl alcohol, and, surprisingly, even *n*-amyl alcohol failed to give the product.

The final transformation, oxidative cleavage of the 7,12-dimethoxy groups present in **15**, was accomplished in 83% yield by silver oxide oxidation in dilute nitric acid[37] to give *O*-methylkidamycinone (**1d**).

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 621 spectrophotometer and are expressed in reciprocal centimeters. Ultraviolet spectra were run on a Cary 15 (Varian) ultraviolet–visible spectrophotometer and are expressed in nanometers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Varian Model HA-100 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained with a CEC Du Pont Model 21-110B or a Du Pont Model 21-491B spectrometer at an ionizing voltage of 70 eV. Carbon and hydrogen analyses were performed by Galbraith Laboratories.

Analytical thin-layer chromatography (TLC) was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. with 5% ethyl acetate–dichloromethane as the eluent. Preparative TLC

(26) The olefinic proton α to the carbonyl group of 1(4*H*)-benzopyran-4-ones normally appears at much lower field as a singlet in the region between δ 7.0 and 6.0. Dreyer, D. L.; Bertell, D. J. *Tetrahedron* **1967**, *23*, 4607.

(27) Dutta, C. P.; Roy, L. K. P. *Indian J. Chem.* **1975**, *13*, 425.

(28) Compound **13** was unstable under the reaction conditions. Oxidative demethylation occurred, affording the anthraquinone analogue of **13** (mp 140–142 °C) in 56% yield. Prior refluxing of the reaction medium to exhaust dissolved oxygen and then conducting the reaction under a nitrogen atmosphere gave an identical result.

(29) von Auwers, K.; Lämmerhirt, E. *Justus Liebigs Ann. Chem.* **1920**, *421*, 1.

(30) Refluxing **13** with sodium methoxide in methanol afforded 1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (mp 109–110 °C), a derivative of chrysophanol. Demethylation of the product (HBr) followed by air oxidation gave chrysophanol identical with an authentic sample.

(31) Stermitz, F. R.; Adamovics, J. A.; Geigert, J. *Tetrahedron* **1975**, *31*, 1593.

(32) Subrahmanyan, K.; Rao, J. M.; Rao, K. V. J. *Indian J. Chem., Sect. A* **1977**, *15B*, 105.

(33) Attempted bromination of **14** with NBS and phenyltrimethylammonium perbromide gave complex product mixtures. Reaction of **14** with cupric bromide gave the quinone analogue of **13**.

(34) This approach has been used previously to prepare benzopyran-4-ones.

(35) Kasahara, A.; Izumi T.; Ooshima, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2526.

(36) Selenium dioxide has been extensively exploited to directly convert chalcones to falvones. Ahmad, S.; Wagner, H.; Razag, S. *Tetrahedron* **1978**, *34*, 1593. Mahal, H. S.; Rai, H. S.; Venkataraman, K. *J. Chem. Soc.* **1935**, 866. Matsuura, S.; Kunii, T.; Matsuura, A. *Chem. Pharm. Bull.* **1973**, *21*, 2757. Seshadri, T. R.; Sharma, P. *Indian J. Chem.* **1973**, *11*, 338.

(37) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227. Hammer, R. N.; Kleinberg, J. *Inorg. Synth.* **1953**, *4*, 12.

chromatographics were performed on 20 × 20 cm precoated silica gel GF plate (layer thickness 0.25 cm) manufactured by Analtech, Inc. Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230 mesh ASTM.

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH), and dioxane was dried by distillation from calcium hydride. Solvents were reagent grade and were not usually purified prior to use.

Solutions of lithium diisopropylamide were prepared by addition of *n*-butyllithium (Aldrich Chemical Co.) to a stirred solution of diisopropylamine in tetrahydrofuran under nitrogen at 0 °C.

(1′*E*)-2-(1′-Methyl-1′-propenyl)-4*H*-1-benzopyran-4-one (5). A mixture of *o*-hydroxyacetophenone (**2a**; 1.16 g, 8.53 mmol), tigloyl chloride, and pyridine (6 mL) was heated at reflux overnight. The resulting dark brown solution was poured into cold 10% aqueous HCl (200 mL) and the mixture then extracted with dichloromethane (2 × 150 mL). The combined dichloromethane extracts were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give **2b** as a brown oil which was used without purification in the next step: ^1H NMR (CCl_4) δ 1.89 (d, J = 7 Hz, 3 H, =CHC**H**$_3$), 1.93 (s, 3 H, C=CC**H**$_3$), 2.42 (s, 3 H, COC**H**$_3$), 6.93–7.54 (m, 3 H, Ar H), 7.62 (dd, J = 7 and 2 Hz, 1 H, Ar H). Tigloate ester **2b** (1.86 g, 8.55 mmol), dioxane (50 mL), and 50% NaH (1.00g, 21 mmol) were heated on a steam bath for 3 h. The resulting dark solution was cooled and then quenched with glacial acetic acid. The solvent was removed, and the residue was dissolved in ethyl acetate (200 mL). The solution was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to furnish diketone **3** as an oil: ^1H NMR (CCl_4) δ 1.88 (d, J = 7 Hz, 3 H, =CHC**H**$_3$), 2.55 (s, 3 H, C=CC**H**$_3$), 6.28 (s, 1 H, C**H**=COH), 6.68–6.98 (m, 2 H, Ar H), 7.36 (t, J = 7 Hz, 1 H, Ar H), 7.60 (d, J = 7 Hz, 1 H, Ar H), 11.89 (s, 1 H, ArO**H**), 12.08 (s, 1 H, CH=CO**H**); mass spectrum, m/e 218 ($M^{+\cdot}$), 203, 263, 121. A mixture of the diketone **3** obtained above, glacial acetic acid (30 mL), and excess sodium acetate (3–4 g) was heated on a steam bath for 7 h. The acetic acid was evaporated at reduced pressure to give an oil, which was dissolved in ethyl acetate (200 mL). The ethyl acetate extract was washed with water, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and evaporated to give a brown oil. Further purification was accomplished by column chromatography (100 g, silica gel, CH_2Cl_2 to 10% EtOAc–CH_2Cl_2) to furnish 0.95 g (75% overall yield from **2a**) of **5** as a colorless oil: ^1H NMR (CCl_4) δ 1.88 (d, J = 7 Hz, 3 H, =CHC**H**$_3$), 1.90 (s, 3 H, =CC**H**$_3$), 6.14 (s, 1 H, C=CH), 6.64 (q, J = 7 Hz, 1 H, =C**H**CH$_3$), 7.16–7.66 (m, 3 H, Ar H), 8.04 (d, J = 7 Hz, 1 H, Ar H); mass spectrum, m/e 200 ($M^{+\cdot}$), 185, 120.

7-Methoxy-3-hydroxy-1(3*H*)-isobenzofuranone (7a). A mixture of ethyl 2-methoxy-6-methylbenzoate (**6a**; 8.5 g, 43.8 mmol) and *N*-bromosuccinimide (16.13 g, 90.7 mmol) in CCl_4 (800 mL) was heated at reflux under N_2 with irradiation by a sunlamp for 30 min. A catalytic amount of benzoyl peroxide was added, and heating was continued with irradiation. The course of the reaction was followed by ^1H NMR. The stepwise disappearance of the aromatic methyl and methylene absorptions at δ 2.26 and 3.89, respectively, and the concomitant appearance of a singlet at δ 6.76 indicated the reaction was complete. Usually, 12–24 h were required to complete the dibromination of **6a**. The reaction mixture was cooled in an ice bath and then filtered to remove succinimide. Evaporation of the solvent furnished crude dibromo compound **6b**, which was not purified but was hydrolyzed directly: ^1H NMR (CCl_4) δ 1.39 (t, J = 8 Hz, 3 H, CH_2CH_3), 3.81 (s, 3 H, OCH_3), 4.37 (q, J = 8 Hz, 2 H, OCH_2), 6.76 (s, 1 H, $CHBr_2$), 6.80 (d, J = 8 Hz, 1 H, Ar H), 7.37 (t, J = 8 Hz, 1 H, Ar H), 7.56 (d, J = 8 Hz, 1 H, Ar H). A mixture of the dibromomethyl benzoate **6b** (15 g, 42.6 mmol) from above, 9% HCl (160 mL), and enough acetic acid to make the mixture homogeneous was heated at reflux for 12 h. The solution was evaporated to dryness under reduced pressure, and the residue was dissolved in ethyl acetate (350 mL). The ethyl acetate solution was extracted repeatedly with saturated aqueous $NaHCO_3$ (3 × 150 mL), and the combined sodium bicarbonate extracts were acidified with 10% aqueous HCl. The organic material was extracted with ethyl acetate (350 mL) and washed with water and brine. The ethyl acetate solution was dried ($MgSO_4$), filtered, and evaporated to give 6.31 g of **7a** as a colorless solid (80% yield). A sample was recrystallized from water: mp 152–154 °C; ^1H NMR (acetone-d_6) δ 3.93 (s, 3 H, OCH_3), 6.54 (d, J = 8 Hz, 1 H, CHO**H**), 6.82 (d, J = 8 Hz, 1 H, CHOH), 7.14 (d, J = 8 Hz, 1 H, Ar H), 7.18 (d, J = 7 Hz, 1 H, Ar H), 7.70 (t, J = 8 Hz, 1 H, Ar H).

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H 4.47. Found: C, 60.04; H, 4.51.

7-Methoxy-3-(phenylthio)-1(3*H*)-isobenzofuranone (7b). A mixture of 7-methoxy-3-hydroxy-1(3*H*)-isobenzofuranone (**7a**; 6.13 g, 34 mmol), benzenethiol (4.89 g, 44.5 mmol), and benzene (400 mL) was heated at reflux with a catalytic amount of *p*-toluenesulfonic acid for 3 h. The water generated in the reaction was azeotropically removed by using a Dean–Stark apparatus. The benzene was evaporated under reduced pressure, and the residual oil was dissolved in ethyl acetate (300 mL) and washed successively with water, saturated aqueous $NaHCO_3$, and brine. The ethyl acetate solution was dried ($MgSO_4$), filtered, and evaporated to furnish a pale yellow solid which was purified by column chromatography (100 g of silica gel, CH_2Cl_2) to give 6.67 g (72%) of **7b** as a white powder: mp 126–127 °C; ^1H NMR (acetone-d_6) δ 3.88 (s, 3 H, OCH_3), 6.88 (s, 1 H, PhSCH), 7.12 (t, J = 8 Hz, 1 H, Ar H), 7.24–7.60 (m, 6 H, Ar H), 7.72 (t, J = 8 Hz, 1 H, Ar H).

Anal. Calcd for $C_{15}H_{12}SO_3$: C, 66.16; H 4.44. Found: C, 66.23; H, 4.40.

7-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (7c). Two methods were employed to oxidize sulfide **7b** to sulfone **7c**.

Method A. To a solution of 7-methoxy-3-phenylthio-1-(3*H*)-isobenzofuranone (**7b**; 6.67g, 24.5 mmol) in dichloromethane (300 mL) was added *m*-chloroperbenzoic acid (10.9 g, 54 mmol), and the mixture was stirred at room temperature overnight. The solid *m*-chlorobenzoic acid was removed by filtration, and the filtrate was washed with aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give a colorless powder which was recrystallized from acetone–hexanes to furnish 7.30 g (96%) of **7c** as colorless needles: mp 176–177 °C; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H, OCH_3), 6.10 (s, 1 H, ArCH), 7.04 (d, J = 8 Hz, 1 H, Ar H), 7.40–7.92 (m, 7 H, Ar H); mass spectrum, m/e 304 ($M^{+\cdot}$), 163.

Anal. Calcd for $C_{15}H_{12}SO_5$: C, 59.20; H, 3.97. Found: C, 59.17; H, 4.00.

Method B. A mixture of sulfide **7b** (5.5 g, 20.19 mmol) and acetic acid (60 mL) in a beaker (400 mL) was heated on a steam bath until the solid dissolved. The solution was cooled to room temperature and hydrogen peroxide (6 mL, 30%, 69.76 mmol) was added. The solution was again heated on the steam bath until the reaction began to effervesce. At this point, the steam bath was shut off, and the reaction proceeded exothermically. Partial crystallization of the reaction occurred as the reaction cooled to room temperature. Water (250 mL) was added to complete the precipitation of **7c** which was collected by filtration, washed with water, and dried. Recrystallization (acetone-hexanes) afforded 6.02 g (98%) of pure sulfone **7c**.

Methyl 3-Methyl-1,4,8-trimethoxy-2-naphthoate (8a). To a stirred solution of LDA at −78 °C, prepared from diisopropylamine (2.73 g, 27 mmol), dry THF (50 mL), and *n*-BuLi (16.9 mL of a 1.6 M solution, 27 mmol) under N_2 at 0 °C, was added a slurry of sulfone **7c** (4.00 g, 13.1 mmol) in THF (40 mL), and the mixture was stirred at −78 °C for 15 min. Methyl *trans*-2-butenoate (3.16 g, 31.6 mmol) was added to the deep yellow anion solution. The cooling bath was immediately removed, and the mixture was brought to room temperature. After the mixture was stirred for 2 h, it was heated at reflux for an additional 2 h. The reaction mixture was acidified with glacial acetic acid, and the THF was removed under reduced pressure. The residue was dissolved in ethyl acetate (400 mL) and washed with water, aqueous sodium dithionite (2 g/50 mL of H_2O), and brine. The organic extract was dried ($MgSO_4$), filtered, and evaporated to give a brown solid.

The crude product was dissolved in acetone (250 mL) and heated under reflux with dimethyl sulfate (9.5 g, 38.4 mmol) and anhydrous K_2CO_3 (10.0 g, 72.4 mmol) overnight. Inorganic material was removed by filtration, and the filtrate was evaporated to give a brown oil which was dissolved in ether (300 mL) and treated with triethylamine (10 mL). After being allowed to stand for 30 min, the ether solution was washed with water, aqueous

HCl (10%), and brine, dried ($MgSO_4$), filtered, and evaporated to give an oil which was further purified by column chromatography (100 g of silica gel, CH_2Cl_2) to furnish 3.16 g (83%) of **8a** as a colorless oil: ^1H NMR (CCl_4) δ 2.29 (s, 3 H, $ArCH_3$), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.74 (d, J = 8 Hz, 1 H, Ar H), 7.29 (t, J = 8 Hz, 1 H, Ar H), 7.59 (d, J = 8 Hz, 1 H, Ar H).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.23; H 6.27.

Methyl 3-(Bromomethyl)-1,4,8-trimethoxy-2-naphthoate (8b). A mixture of methyl 3-methyl-1,4,8-trimethoxy-2-naphthoate (**8a**; 3.12 g, 10.76 mmol), *N*-bromosuccinimide (2.04 g, 11.0 mmol), and carbon tetrachloride (300 mL) was heated at reflux for 30 min while being irradiated with a sunlamp. A catalytic amount of benzoyl peroxide was added, and the mixture was heated at reflux with irradiation for an additional 1.5 h. The reaction mixture was refrigerated and then filtered to remove succinimide. The filtrate was evaporated under reduced pressure to give a solid which was further purified by column chromatography (100 g of silica gel, 5% EtOAc–CH_2Cl_2) to furnish 3.33 g (84%) of **8b** as a light yellow solid: mp 84–87 °C; ^1H NMR (CCl_4) δ 3.80 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.73 (s, 3 H, CH_2Br), 6.81 (d, J = 8 Hz, 1 H, Ar H), 7.33 (t, J = 8 Hz, 1 H, Ar H), 7.60 (d, J = 8 Hz, 1 H, Ar H).

Methyl 3-[(Phenylthio)methyl]-1,4,8-trimethoxy-2-naphthoate (8c). To a solution of sodium ethoxide, prepared by dissolving sodium (0.23 g, 9.93 mmol) in absolute ethanol (75 mL), was added benzenethiol (1.24 g, 10.93 mmol), and the mixture was stirred for 10 min. A solution of **8b** (3.33 g, 9.02 mmol) in THF (50 mL) was added to the thiophenoxide solution which was then heated at reflux overnight. The resulting dark solution was acidified with 10% aqueous HCl, and the ethanol was removed under reduced pressure. The deposited material was dissolved in ethyl acetate (200 mL), and the extract was washed successively with 10% NaOH, 10% HCl, water, and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated to give a brown oil, which upon chromatographic separation (110 g of silica gel, CH_2Cl_2 to 5% EtOAc–CH_2Cl_2) furnished 3.42 g (75%) of **8c** as a light yellow solid. Recrystallization of the material from ethanol provided colorless needles: mp 91–92 °C; ^1H NMR (CCl_4) δ 3.78 (s, 6 H, 2 OCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.34 (s, 2 H, $PhSCH_2$), 6.76 (d, J = 8 Hz, 1 H, Ar H), 7.08–7.44 (m, 6 H, Ar H), 7.56 (d, J = 8 Hz, 1 H, Ar H).

Anal. Calcd for $C_{22}H_{22}SO_5$: C, 66.31; H, 5.57. Found: C, 66.31; H, 5.58.

Methyl 3-[(Phenylsulfinyl)methyl]-1,4,8-trimethoxy-2-naphthoate (8d). Sulfoxide **8d** was prepared from sulfide **8c** by oxidation with either sodium metaperiodate (method A) or *m*-chloroperbenzoic acid (method B).

Method A. To a solution of sulfide **8c** (3.4 g, 8.55 mmol) in methanol was added an aqueous solution of $NaIO_4$ (2.38 g, 11.1 mmol, in 50 mL of H_2O). The mixture was stirred at room temperature for 3 days at which time TLC analysis indicated that the starting material was consumed.

The insoluble inorganic material was removed by filtration, and the solid was washed with methanol. The filtrate and methanol washings were combined and evaporated under reduced pressure to give a residue which was dissolved in ethyl acetate (200 mL). The ethyl acetate solution was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give a solid which was purified by column chromatography (100 g of silica gel, 10–15% EtOAc–CH_2Cl_2) to give 3.36 g (95%) of **8d** as colorless crystals: mp 114–116 °C; ^1H NMR (CCl_4) δ 3.83 (s, 3 H, OCH_3), 3.93 (s, 6 H, 2 OCH_3), 3.95 (s, 3 H, OCH_3), 4.08 (d, J = 13 Hz, 1 H, C**H**(H)SOPh), 4.40 (d, J = 13 Hz, 1 H, CH(**H**)SOPh), 6.83 (d, J = 7 Hz, 1 H, Ar H), 7.30–7.70 (m, 7 H, Ar H); mass spectrum, m/e 414 ($M^{+\cdot}$).

Method B. To a solution of **8c** (5.24 g, 13.2 mmol) in dichloromethane (300 mL), cooled to −78 °C, was added *m*-chloroperbenzoic acid (2.70 g, 13.2 mmol). The mixture was maintained at −78 °C for 30 min and then slowly brought to room temperature. An additional quantity (270 mg) of *m*-chloroperbenzoic acid was added to the mixture since a substantial amount of the starting material had not reacted. The reaction mixture was stirred for another 5 min at room temperature and was then quenched with aqueous $NaHSO_3$ solution (2 g in 75 mL of H_2O). TLC analysis of the reaction mixture indicated a small amount of less polar sulfone **8e** (R_f 0.31) had formed along with the desired sulfoxide **8d** (R_f 0.16). The dichloromethane layer was separated from the aqueous layer and then washed successively with aqueous $NaHCO_3$, water, and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated to give a foam, which furnished upon chromatographic separation (100 g of silica gel, 5–30% EtOAc–CH_2Cl_2) 4.80 g (88%) of **8d** and 0.51 g (9%) of methyl 3-[(phenylsulfonyl)methyl]-1,4,8-trimethoxy-2-naphthoate (**8e**). Compound **8d**, prepared by this procedure, was identical with the sample prepared by method A. Recrystallization of **8e** from acetone–hexanes provided colorless plates: mp 142–143 °C; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.84 (s, 2 H, SO_2CH_2), 6.90 (dd, J = 7 and 2 Hz, 1 H, Ar H), 7.27–7.60 (m, 6 H, Ar H), 7.79 (dd, J = 7 and 2 Hz, 1 H, Ar H).

2-Acetyl-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (9a). To a stirred solution of LDA at −78 °C, prepared from diisopropylamine (1.69 g, 16.7 mmol), THF (40 mL), and *n*-BuLi (10.3 mL of a 1.6 M solution, 16.5 mmol) under N_2 at 0 °C for 15 min, was added a solution of sulfoxide **8d** (3.0 g, 7.24 mmol) in THF (40 mL). To the resulting brown anion solution was added 3-penten-2-one (1.8 g, 21.4 mmol), with THF washing. The reaction was stirred at −78 °C for 15 min, was brought to room temperature, and after 2.5 h was heated at reflux overnight. The brown-red reaction mixture was acidified with glacial acetic acid, and the THF was removed under reduced pressure to give an oil which was dissolved in ethyl acetate (200 mL). The ethyl acetate solution was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to furnish an oil. The oil gave, upon chromatographic separation (100 g of silica gel, CH_2Cl_2), 3.4 g (71%) of **9a** as a yellow solid. Compound **9a** was unstable at room temperature. Recrystallization from acetone–hexanes provided analytically pure **9a** as brown crystals: mp 132–134 °C; IR (Nujol) 2940, 2860, 1700, 1630, 1554 cm^{-1}; UV (EtOH) λ_{max} 267 nm; ^1H NMR (CCl_4) δ 2.43 (s, 3 H, $ArCH_3$), 2.59 (s, 3 H, $COCH_3$), 3.96 (s, 6 H, 2 OCH_3), 3.99 (s, 3 H, OCH_3), 6.66 (d, J = 8 Hz, 1 H, Ar H), 7.25 (t, J = 8 Hz, 1 H, Ar H), 7.39 (s, 1 H, Ar H); mass spectrum, m/e 340 ($M^{+\cdot}$), 325, 311.

Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92; Found: C, 70.68; H, 6.07.

(2′*E*)-2-Acetyl-3-methyl-1-[(2′-methyl-2′-butenoyl)oxy]-8,9,10-trimethoxyanthracene (9b). A mixture of **9a** (140 mg, 0.41 mmol), excess tigloyl chloride (350 mg, 3.38 mmol), and pyridine (10 mL) was stirred under N_2 at room temperature overnight. The reaction was poured into cold aqueous 10% HCl (150 mL) and then extracted with ethyl acetate (150 mL). The ethyl acetate solution was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a foam. The crude product was purified by column chromatography (75 g of silica gel, CH_2Cl_2 to 5% EtOAc–CH_2Cl_2) to furnish 170 mg (80%) of ester **9b** as a brown solid. Recrystallization of the material from hexanes provided yellow needles: mp 161–163 °C; ^1H NMR (CCl_4) δ 1.90 (d, J = 7 Hz, 3 H, =CHC**H**$_3$), 1.99 (s, 3 H, =CC**H**$_3$), 2.30 (s, 6 H, $ArCH_3$ and $COCH_3$), 3.64 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.56 (d, J = 7 Hz, 1 H, Ar H), 7.08 (q, J = 7 Hz, 1 H, =C**H**CH$_3$), 7.15 (t, J = 8 Hz, 1 H, Ar H), 7.68 (d, J = 8 Hz, 1 H, Ar H), 7.83 (s, 1 H, Ar H); mass spectrum, m/e 422 ($M^{+\cdot}$), 407, 340, 325.

(2′*E*)-2-Acetyl-8-methoxy-3-methyl-1-[(2′-methyl-2′-butenoyl)oxy]anthraquinone (10). To a solution of **9b** (160 mg, 0.38 mmol) in THF (30 mL) was added cupric bromide (223 mg, 0.76 mmol), and the mixture was heated at reflux for 3.5 h. The inorganic material was removed by filtration, and the filtrate was evaporated to dryness. The resulting residue was dissolved in ethyl acetate (50 mL), washed with water and brine, dried (Na_2SO_4), filtered, and evaporated to give a brown solid, which was further purified by column chromatography (10 g of silica gel, CH_2Cl_2 to 5% EtOAc–CH_2Cl_2) to furnish 114 mg (77%) of **10** as a yellow solid. Recrystallization of the product from benzene–petroleum ether (bp 30–65 °C) or acetone–hexanes provided pure **10** as yellow plates: mp 179–181.5 °C; ^1H NMR ($CDCl_3$) δ 1.97 (d, J = 7 Hz, 3 H, =CHC**H**$_3$), 2.06 (s, 3 H, CC**H**$_3$), 2.43 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $COCH_3$), 3.96 (s, 3 H, OCH_3), 7.17 (q, J = 7 Hz, 1 H, C**H**CH$_3$), 7.30 (d, J = 7 Hz, 1 H, Ar H),

7.64 (d, J = 7 Hz, 1 H, Ar H), 7.87 (d, J = 7 Hz, 1 H, Ar H), 8.01 (s, 1 H, Ar H); mass spectrum, m/e 392 ($M^{+\cdot}$), 348, 333, 310, 295.

Anal. Calcd for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.36; H, 5.12.

(2′*E*)-2-[(2′,3′-Dihydro-2′,3′-dimethyl-4-oxo-4*H*-pyran-6′-yl]-1-hydroxy-8-methoxy-3-methylanthraquinone (12a) and *Z* Isomer 12b. To a stirred solution of **10** (43 mg, 0.11 mmol) in THF (3 mL) was added excess NaH (50%, 50 mg), and the resulting brown mixture was heated at reflux for 5 h. TLC analysis of the reaction indicated that the starting material was consumed with formation of a single product, less polar than the starting ester. The reaction mixture was cooled to 0 °C and quenched with glacial acetic acid. The organic material was extracted with ethyl acetate (100 mL), washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to furnish 40 mg (93%) of **11** as an orange solid. Since the material obtained appeared to undergo air oxidation, it was immediately used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3 H, $=CCH_3$), 1.91 (d, J = 7 Hz, 3 H, $=CHCH_3$), 2.47 (s, 3 H, $ArCH_3$), 4.06 (s, 3 H, OCH_3), 6.10 (s, 1 H, $CH=COH$), 6.87 (q, J = 7 Hz, 1 H, $=CHCH_3$), 7.36 (d, J = 7 Hz, 1 H, Ar H), 7.60 (s, 1 H, Ar H), 7.73 (t, J = 7 Hz, Ar H), 7.89 (d, J = 7 Hz, 1 H, Ar H), 12.89 (s, 1 H, ArOH); mass spectrum, m/e 392 ($M^{+\cdot}$), 377, 309, 295. To a suspension of β-diketone **11** (37 mg, 0.094 mmol) in glacial acetic acid (2 mL) was added sodium acetate (200 mg, 2.4 mmol). The mixture was then heated overnight on an oil bath at 100–115 °C. TLC analysis of the reaction mixture indicated that two new products had formed and that the starting material was consumed. The resulting yellow reaction mixture was cooled to room temperature and then diluted with ethyl acetate (50 mL). The ethyl acetate solution was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give an orange residue. Chromatographic separation (75 g of silica gel, CH_2Cl_2) of the crude product furnished 28 mg (75%) of **12a** and 8 mg (22%) of **12b** both as orange solids. Recrystallization of the materials from acetone–hexanes provided pure samples. For **12a**: mp 228–230 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 3 H, $OCHCH_3$), 1.55 (d, J = 7 Hz, 3 H, $COCHCH_3$), 2.43 (s, 3 H, $ArCH_3$), 2.53 (dt, J = 12 and 6 Hz, 1 H, $OCHCH_3$), 4.04 (s, 3 H, OCH_3), 4.44 (dt, J = 12 and 6 Hz, 1 H, $COCHCH_3$), 5.59 (s, 1 H, C=CHCO), 7.34 (d, J = 8 Hz, 1 H, Ar H), 7.59 (s, 1 H, Ar H), 7.70 (t, J = 8 Hz, 1 H, Ar H), 7.92 (d, J = 8 Hz, 1 H, Ar H), 13.28 (s, 1 H, ArOH); mass spectrum, m/e 392 ($M^{+\cdot}$). For **12b**: mp 194–196 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 7 Hz, 3 H, $OCHCH_3$), 1.49 (d, J = 7 Hz, 3 H, $COCHCH_3$), 2.46 (s, 3 H, $ArCH_3$), 2.50 (dt, J = 3.4 and 6 Hz, 1 H, $OCHCH_3$), 4.07 (s, 3 H, OCH_3), 4.84 (dt, J = 3.4 and 6 Hz, 1 H, $COCHCH_3$), 5.54 (s, 1 H, C=CHCO), 7.34 (d, J = 8 Hz, 1 H, Ar H), 7.62 (s, 1 H, Ar H), 7.74 (t, J = 8 Hz, 1 H, Ar H), 7.96 (d, J = 8 Hz, 1 H, Ar H), 13.28 (s, 1 H, ArOH); mass spectrum, m/e 392 ($M^{+\cdot}$).

(2′*E*,4′*E*)-1-Hydroxy-3-methyl-2-(4′-methylhexa-2′,4′-dienoyl)-8,9,10-trimethoxyanthracene (13). Lithium diisopropylamide was prepared by stirring a mixture of diisopropylamine (173 mg 1.71 mmol), THF (7 mL), and n-BuLi (1 mL of a 1.6 M solution, 1.6 mmol) under N_2 at 0 °C for 15 min. To the pale, greenish yellow solution, cooled to −78 °C, was added a solution of **9a** (253 mg, 0.74 mmol) in THF (7 mL), and the mixture was stirred at −78 °C for 5 min. To the dark red anion solution was added tiglaldehyde (173 mg, 2.06 mmol), and the reaction mixture was brought to room temperature. The resulting red solution was stirred at room temperature for 4 h and then acidified with glacial acetic acid. The THF was removed under reduced pressure, and the residual mixture was dissolved in ethyl acetate (100 mL), which was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give a red foam. Purification of crude dienone **13** was accomplished by column chromatography (15 g of silica gel, benzene to 15% EtOAc–CH_2Cl_2) to yield 227 mg (75%) of **13** as a red-brown solid. Recrystallization of the material from acetone–hexanes gave pure **13** as yellow-orange needles: mp 154–155.5 °C; UV (EtOH) λ_{max} 228 nm (ϵ 14 000), 262 (82 000), 293 (3200), 387 (10 600), 418 (6000); ^{1}H NMR (CCl_4) δ 1.80 (d, J = 7 Hz, 3 H, $=CHCH_3$), 1.85 (s, 3 H, $=CCH_3$), 2.48 (s, 3 H, $ArCH_3$), 3.94 (s, 3 H, OCH_3), 3.97 (s, 6 H, 2 OCH_3), 5.86 (q, J = 7 Hz, 1 H, $=CHCH_3$), 6.40 (d, J = 15 Hz, 1 H, $COCH=CH$), 6.65 (d, J = 8 Hz, 1 H, Ar H), 6.98 (d, J = 15 Hz, 1 H, $COCH=CH$), 7.23 (t, J = 8 Hz, 1 H, Ar H), 7.74 (d, J = 8 Hz, 1 H, Ar H), 10.36 (s, 1 H, ArOH); mass spectrum, m/e 406 ($M^{+\cdot}$), 391, 310, 295.

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.69; H, 6.55.

(1′*E*)-5-Methyl-2-(1′-methyl-1′-propenyl)-7,11,12-trimethoxy-2,3-dihydro-4*H*-anthra[1,2-*b*]pyran-4-one (14). Methanolic sodium acetate (method A) and methanolic potassium hydroxide (method B) were employed to cyclize **13** to **14**.

Method A. To a solution of **13** (127 mg, 0.31 mmol) in methanol (20 mL) was added aqueous sodium acetate (240 mg in 2 mL of H_2O), and the mixture was heated at reflux under N_2 for 40 h. TLC analysis of the reaction during this period showed that a highly fluorescent compound, less polar than the starting material, had formed along with several other minor components and that a substantial amount of unreacted starting material remained. Since further heating did not alter the extent of reaction, the solution was cooled and diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give a pale yellow oil, which upon chromatographic separation (35 g of silica gel, CH_2Cl_2) furnished 44 mg (35%) of **14** as an orange solid and 52 mg (41%) of unreacted starting material. The recovered starting material was transformed to provide an additional 19 mg of **14**, which increased the total yield of the cyclized product to 50%. Recrystallization of the product from benzene–petroleum ether (bp 30–65 °C) furnished pure **14** as an orange solid: mp 129–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (d, J = 7 Hz, 3 H, $=CHCH_3$), 1.92 (s, 3 H, $=CCH_3$), 2.64 (dd, J = 16 and 4 Hz, 1 H, $COCH_e$), 2.78 (s, 3 H, $ArCH_3$), 3.06 (dd, J = 16 and 14 Hz, 1 H, $COCH_a$), 3.85 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.97 (dd, J = 14 and 4 Hz, 1 H, $OCHCH_2$), 5.82 (q, J = 7 Hz, 1 H, $CHCH_3$), 6.76 (d, J = 8 Hz, 1 H, Ar H), 7.40 (d, J = 8 Hz, 1 H, Ar H), 7.49 (s, 1 H, Ar H), 7.80 (d, J = 8 Hz, 1 H, Ar H); mass spectrum, m/e 406 ($M^{+\cdot}$), 391, 324, 310.

Method B. To a solution of **13** (30 mg, 0.074 mmol) in methanol (5 mL) was added a 2% KOH solution (6.2 mg, 0.11 mmol), and the resulting red mixture was heated on a steam bath for 5 min. The reaction mixtures was then quenched immediately with glacial acetic acid and diluted with ethyl acetate (50 mL). The ethyl acetate layer was separated, washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give a deep red residue. The residue was chromatographically separated (25 g of silica gel, CH_2Cl_2) to yield 3.0 mg (10%) of **14**. No starting material was recovered from the column separation. The product obtained was identical with that prepared by method A.

(1′*E*)-5-Methyl-2-(1′-methyl-1′-propenyl)-7,11,12-trimethoxy-4*H*-anthra[1,2-*b*]pyran-4-one (15). To a solution of o-hydroxy dienone **13** (472 mg, 1.16 mmol) in *tert*-amyl alcohol (10 mL) was added SeO_2 (192 mg, 1.73 mmol), and the mixture was heated under N_2 at 60–70 °C overnight. The resulting dark product was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure to give a dark residue. Chromatographic separation (50 g of silica gel, CH_2Cl_2 to 10% EtOAc–CH_2Cl_2) of the residue yielded 129 mg (27%) of **15** as a yellow solid, 47 mg (10%) of **14**, 56.8 mg (13%) of the quinone analogue of **13**, and 236 mg (50%) of the unreacted starting material **13**. The recovered starting material was transformed to give an additional 26 mg (total yield of 33%) of **15**. Recrystallization of the chromatographed sample of **13** from ethanol provided yellow needles: mp 150.5–152.5 °C; UV (EtOH) λ_{max} 245 nm (ϵ 33 000), 264 (78 000), 295 (17 000), 390 (9800); ^{1}H NMR ($CDCl_3$) δ 1.98 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.02 (s, 3 H, CCH_3), 2.98 (s, 3 H, $ArCH_3$), 3.88 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 6.46 (s, 1 H, COCH), 6.84 (d, J = 8 Hz, 1 H, Ar H), 7.80 (s, 1 H, Ar H), 7.88 (d, J = 8 Hz, 1 H, Ar H); mass spectrum, m/e 404 ($M^{+\cdot}$), 389, 309, 295.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.25; H, 5.89. Found: C, 74.28; H, 5.98.

(1′*E*)-11-Methoxy-5-methyl-2-(1′-methyl-1′-propenyl)-4*H*-anthra[1,2-*b*]pyran-4,7,12-trione (1d). To a solution of **15** (336 mg, 0.83 mmol) in dioxane (50 mL) was added AgO (415 mg, 3.35 mmol), forming a suspension which was stirred at room temperature. To the stirred mixture was added 4 N HNO_3 until the silver oxide completely dissolved. The resulting colorless solution was stirred for 5 min and then diluted with a mixture of $CHCl_3$ and H_2O (4:1) (200 mL). The organic layer was washed with water

and brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 314 mg of a yellow solid. Recrystallization of the solid material from dichloromethane–hexanes (three times) provided 258 mg (93%) of analytically pure **1d** as yellow needles: mp 251–252 °C; UV (EtOH) λ_{max} 216 nm (ϵ 27 000), 237 (33 800), 268 (28 000), 320 (5900), 384 (7500); ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H, CCH_3), 2.04 (d, J = 7 Hz, $CHCH_3$), 2.98 (s, 3 H, $ArCH_3$), 4.05 (s, 3 H, OCH_3), 6.35 (s, 1 H, COCH), 7.20–7.50 (m, 1 H, CH_3CH), 7.44 (d, J = 8 Hz, 1 H, Ar H), 7.91 (s, 1 H, Ar H); mass spectrum, m/e 374 ($M^{+\cdot}$), 295, 266.

Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 73.50; H, 4.95.

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Registry No. 1d, 73713-33-4; **2a**, 118-93-4; **2b**, 73713-34-5; **3**, 73713-35-6; **5**, 73713-36-7; **6a**, 6520-83-8; **6b**, 73713-37-8; **7a**, 73713-38-9; **7b**, 73318-26-0; **7c**, 65131-09-1; **8a**, 70151-05-2; **8b**, 70151-06-3; **8c**, 70151-07-4; **8d**, 70151-08-5; **8e**, 73713-39-0; **9a**, 70151-09-6; **9b**, 73713-40-3; **10**, 73713-41-4; **11**, 73713-42-5; **12a**, 70151-11-0; **12b**, 70151-12-1; **13**, 73713-43-6; **14**, 73713-44-7; **15**, 73713-45-8; tigloyl chloride, 35660-94-7; *N*-bromosuccinimide, 128-08-5; benzenethiol, 108-98-5; methyl *trans*-2-butenoate, 623-43-8; 3-penten-2-one, 625-33-2; tiglaldehyde, 497-03-0; *tert*-amyl alcohol, 75-85-4.

East Indian Sandalwood Oil. 2.[1] Stereoselective Synthesis of (±)-Epi-β-santalene and (±)-Epi-β-santalol[‡2]

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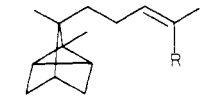
Acid-catalyzed rearrangement of γ-lactone **6** in the presence of acetonitrile provides a mixture of amide acids, which are readily separated as their ethyl esters **18–20**. The major product **18**, when subjected to fragmentation, provides esters **21** and **22** (92% and 8%, respectively). The structure of **21** has been confirmed by its conversion, via aldehyde **23**, to (±)-epi-β-santalene (**8**). Similarly, the structure of **22** has been confirmed by its conversion to (±)-α-santalene (**3**). (±)-Epi-*cis*-β-santalol (**9**), (±)-epi-*trans*-β-santalol (**10**), and (±)-dihydroepi-β-santalol (**11**) have also been prepared via aldehyde **23**.

Introduction

The oil which is obtained by steam distilling the heartwood of East Indian sandalwood trees is used in large quantities by the fragance industry for its sweet woody tenacious odor. α-Santalol (**1**) and β-santalol (**2**) account for up to 90% of the oil and are generally considered to be responsible for its main odor character. Many minor components of the oil have been identified, and undoubtedly some of them contribute to the overall odor character. α-Santalene (**3**), β-santalene (**4**), and dihydro-β-santalol (**5**) are all reported to have tenacious woody odors. Our previous synthesis of (±)-β-santalene and (±)-β-santalol from racemic camphene relied on the acid-catalyzed rearrangement of γ-lactone **6** to the δ-lactone **7**. Further investigation of this rearrangement in the presence of aliphatic nitriles has provided additional support for the mechanism proposed earlier and has resulted in the synthesis of (±)-epi-β-santalene (**8**) and the first syntheses of (±)-epi-*cis*-β-santalol (**9**), (±)-epi-*trans*-β-santalol (**10**), and (±)-dihydroepi-β-santalol (**11**).



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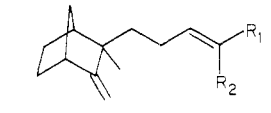
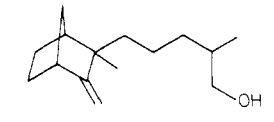
3, R = CH_3



2, R_1 = CH_3; R_2 = CH_2OH
4, R_1 = R_2 = CH_3



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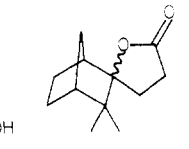

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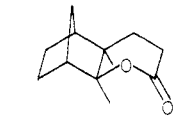

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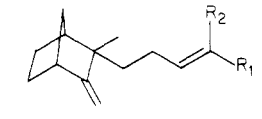
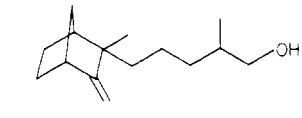


8, R_1 = R_2 = CH_3
9, R_1 = CH_3; R_2 = CH_2OH
10, R_1 = CH_2OH; R_2 = CH_3



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Discussion

We were interested in determining what effect the addition of aliphatic nitriles to the acid-catalyzed rearrangement of γ-lactone **6** would have on the equilibrium mixture of carbocations depicted in Scheme I and in particular whether the Ritter[3] adduct corresponding to cation **17** could be obtained preferentially. In the event, sulfuric acid catalyzed rearrangement of **6** in the presence of acetonitrile gave a mixture of amide acids. Esterification (ethanol, *p*-toluenesulfonic acid) gave a mixture of one major and two minor products, which were readily separated by preparative high-performance LC. Spectral data and mechanistic considerations suggested structures **18–20** for the three unknowns. The major product, when heated with *p*-toluenesulfonyl chloride in pyridine, gave a mixture

[‡] Dedicated to the memory of Dr. Ernest Guenther.

(1) Christenson, P. A.; Willis, B. J. *J. Org. Chem.*, **1979**, *44*, 2012.
(2) Part of this work was adumbrated at the 178th American Chemical Society Meeting, Division of Agricultural and Food Chemistry, Washington D.C., Sept 9, 1979, Paper No. 46.
(3) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

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