water by means of a Dean-Stark apparatus. Removal of the solvent in vacuo left the crude enamine which was mixed with 1,3-propane dithiotosylate (1.93 g, 4.7 mmol) and triethylamine (5 mL) in acetonitrile (80 mL), and the mixture was refluxed for 4 h. After evaporation of solvent in vacuo, the residue was extracted with methylene chloride, washed with 3% HCl and 5% $NaHCO_3$, and dried over Na_2SO_4. Removal of the solvent in vacuo left an orange-red caramel (2.13 g) which on silica gel column chromatography followed by recrystallization from methyl alcohol afforded **25** (1.27 g, 65%) as pale yellow needles [mp 202.5–204 °C; IR ν_{max} (Nujol) 2800–2700, 1680 cm^{-1}; NMR δ 6.60 (1 H, s), 6.52 (1 H, s), 3.84 (6 H, s); MS *m/e* 419 (M^+), 232, 205, 191. Anal. Calcd for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34; S, 15.28. Found: C, 62.68; H, 7.08; N, 3.24; S, 15.46.] and the isomeric **26** (0.18 g, 9.2%) as pale yellow needles [mp 225.5–227 °C; IR ν_{max} (Nujol) 2800–2700, 1680 cm^{-1}; NMR δ 6.57 (1 H, s), 6.54 (1 H, s), 3.84 (6 H, s); MS *m/e* 419 (M^+), 232, 205, 191. Anal. Calcd for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34; S, 15.28. Found: C, 62.71; H, 6.84; N, 3.22; S, 15.29.].

1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-[2,2-(propane-1,3-dithio)ethyl]-2*H*-benzo[*a*]quinolizine-2-acetic Acid Methyl Ester (28). To a solution of **25** (0.073 g, 0.17 mmol) in a mixture of *tert*-butyl alcohol (2 mL) and tetrahydrofuran (2 mL) was added KOH (65 mg, 1 mmol), and the mixture was heated at 60 °C for 3 h with stirring. After cooling, the reaction mixture was acidified with concentrated hydrochloric acid and then treated with ethereal diazomethane. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with methylene chloride, washed with water, and dried over K_2CO_3. The solvent was evaporated in vacuo to leave **28** (0.075 g, 94%) as amorphous powder: IR ν_{max} (neat) 2850–2700, 1720 cm^{-1}; NMR δ 6.70 (1 H, s), 6.62 (1 H, s), 3.90 (6 H, s), 3.70 (3 H, s); MS *m/e* 451 (M^+), 205, 149. Anal. Calcd for $C_{23}H_{33}NO_4S_2$: C, 61.16; H, 7.37; N, 3.10; S, 14.20. Found: C, 60.94; H, 7.22; N, 3.13; S, 14.00.

3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Methyl Ester (29). A suspension of W-2 Raney nickel (ca. 3 mL) and **28** (0.447 g, 1 mmol) in methyl alcohol (42 mL) was refluxed for 20 h. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography followed by recrystallization from petroleum ether to give **29** (0.32 g, 92.4%) as colorless prisms: mp 77–78.5 °C (lit.[17] mp 78.9–79.2 °C); IR ν_{max} (neat) 2850–2700, 1720 cm^{-1}; NMR δ 6.65 (1 H, s), 6.56 (1 H, s), 3.84 (6 H, s), 3.72 (3 H, s), 0.92 (3 H, collapsed t, J = 7.0 Hz); MS *m/e* 347 (M^+), 246, 205, 191.

Acknowledgment. We thank Professor T. Kametani, Pharmaceutical Institute, Tohoku University, for the gift of 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline and also Mr. K. Kawamura, Mrs. C. Koyanagi, and Miss K. Mushiake, Pharmaceutical Institute, Tohoku University, for spectral measurements and microanalyses.

Registry No.—**2,** 65910-27-2; **3** HCl, 19779-81-8; **4,** 67237-59-6; **5,** 67237-60-9; **5** HCl, 67237-61-0; **6,** 67237-62-1; **7,** 1798-09-0; **8,** 67237-63-2; **9,** 67237-64-3; **10,** 1860-59-9; **11,** 67237-65-4; **12** HCl, 67237-66-5; **13** HCl, 67237-67-6; **14,** 1199-31-1; **16,** 3382-18-1; **17,** 15357-92-3; **18,** 65341-27-7; **20,** 19778-10-0; **20** HCl, 19778-11-1; **22,** 67237-68-7; **23,** 67237-69-8; **24,** 65378-14-5; **25,** 65341-28-8; **26,** 65341-29-9; **28,** 65341-30-2; **29,** 3332-90-9; 3-methoxybenzyl cyanide, 19924-43-7; 2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; formalin, 50-00-0; 2-(4-benzyloxy-3-methoxyphenyl)ethylamine, 22231-61-4; 1,3-propane dithiotosylate, 3866-79-3.

References and Notes

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Studies on Total Synthesis of the Olivomycins

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Studies directed toward total synthesis of olivin (**4**), the aglycon of the olivomycin antitumor antibiotics, are described. The key aldehyde **23,** containing the tricyclic nucleus of olivin, has been prepared in 14 steps from 3,5-dimethoxybenzyl chloride. Methods for construction of the olivin hydroxy ketone side chain were also investigated. Attempted addition of trianion **24** to simple aldehydes was unsuccessful. Cyclohexanecarboxaldehyde, a model for aldehyde **23,** was converted to dithiane **36,** which in two steps was transformed to ketone **38.** Hydroxylation of **38** with *m*-CPBA via a kinetic enolate and trimethylsilyl ether **39** produced a single acyloin, having either structure **40** or **42.**

The olivomycins are a group of antitumor antibiotics first isolated in 1962 from a strain of *Actinomyces olivoreticuli*.[2] The crude antibiotic was subsequently found to be a mixture of three components, olivomycin A, B, and C.[3] Extensive chemical studies led to assignment of absolute stereostructures **1, 2,** and **3,** respectively, to these compounds.[4] The olivomycin antibiotics differ from each other only in the nature of the sugar moieties, and upon hydrolysis all three compounds afford the same aglycon, olivin (**4**). The chromomycins[5] and mithramycins[6] are closely related groups of antitumor antibiotics which differ from the olivomycins in the nature of the carbohydrate residues. In addition both contain a methyl group at the C-7 position of the aglycon. Hydrolysis of the chromomycins and mithramycins affords an aglycon,

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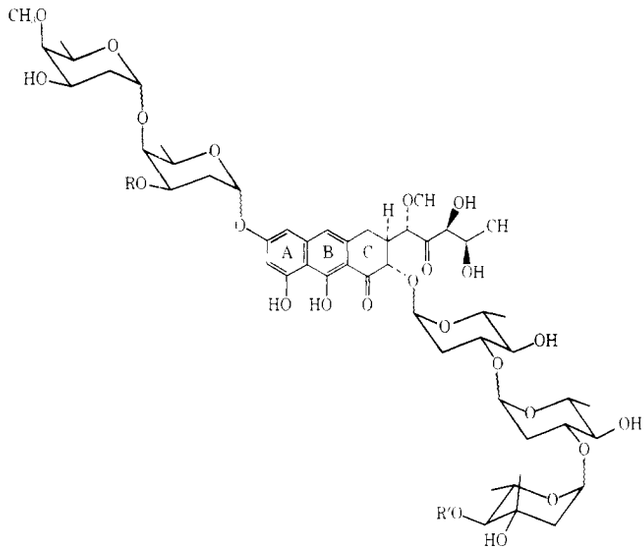
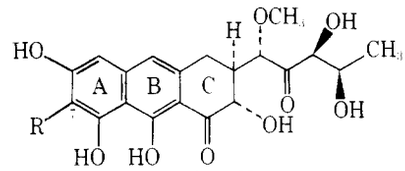


1, R = CH_3CO; R′ = $(CH_3)_2CHCO$
2, R = CH_3CO; R′ = CH_3CO
3, R = H; R′ = $(CH_3)_2CHCO$

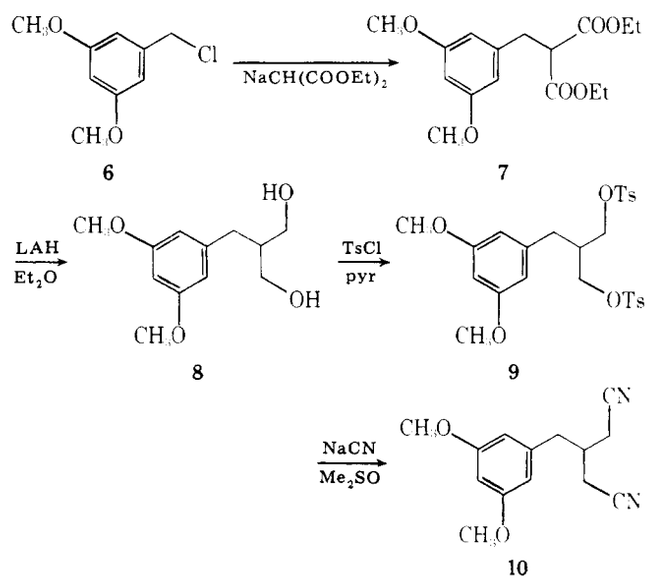


4, R = H
5, R = CH_3

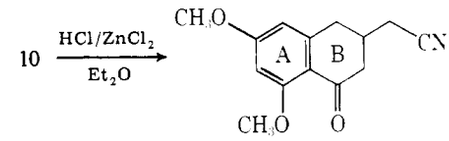
chromomycinone (**5**). The olivomycins, as well as the chromomycins and mithramycins, are currently being evaluated clinically in human cancer chemotherapy.[7]

We are presently attempting to develop a total synthesis of olivin (**4**) and ultimately a synthesis of the olivomycins. Described in this paper are synthetic studies which hopefully will lead to the preparation of olivin, and which with minor modification should also produce chromomycinone (**5**).

Our strategy for construction of the tricyclic nucleus of olivin involves sequential annulation of nonaromatic B and C rings on to a preformed A ring, followed by B-ring aromatization. Thus, readily available chloride **6**[8] was alkylated with sodiodiethyl malonate (93% yield) and the resulting product **7** was reduced to diol **8** with lithium aluminum hydride (95%).

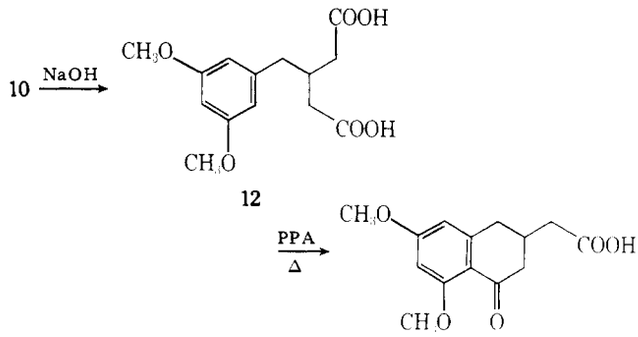


Diol **8** was then transformed via ditosylate **9** to dinitrile **10**. Intramolecular Hoesch condensation[9] of dinitrile **10**



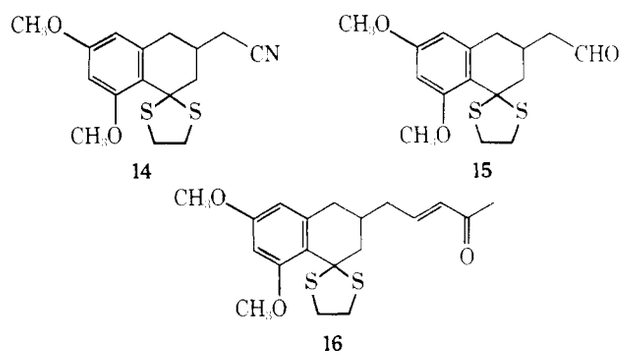
11

(ZnCl/HCl), followed by hydrolysis of the intermediate imine, provided bicyclic ketone **11** in good yield. An alternative but longer and less attractive route to the bicyclic system involved the basic hydrolysis of dinitrile **10** to the diacid **12** which was cyclized with polyphosphoric acid to ketoacid **13**.[10]



12 **13**

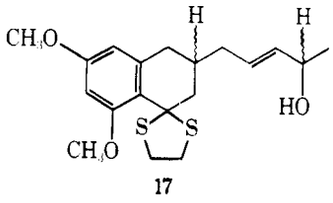
A number of attempts were then made to convert ketonitrile **11** into the corresponding ethylene ketal, but **11** was recovered unchanged in all of these reactions. However, treatment of **11** with ethane dithiol/BF_3 etherate produced a stable crystalline thioketal **14** (90%).[11] Reduction of **14** with Dibal yielded aldehyde **15** (90%), and condensation of this aldehyde with di-



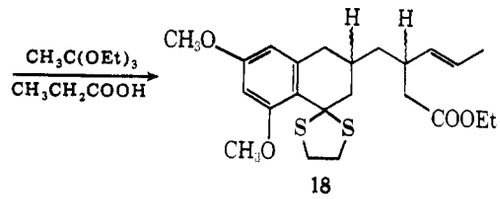
14 **15** **16**

methylphosphonoacetone (sodium hydride/benzene) afforded the trans-α,β-unsaturated ketone **16** (90%).[12] Reduction of **16** with either lithium aluminum hydride or Dibal gave an inseparable mixture of diastereomeric alcohols **17**, which cleanly underwent the Johnson modification[13] of the Claisen rearrangement (triethyl orthoacetate/propionic acid) to afford esters **18**, again as an inseparable diastereomeric mixture (50%). Cleavage of the dithiolane group of **18** was best effected with methyl iodide in wet methanol,[14] giving ketoesters **19**. Base-catalyzed cyclization of ketoester **19** afforded the tricyclic diketones **20** (or a tautomer[15]).

Aromatization of the B ring of **20** could be effected by chloranil to give the desired tricyclic ketone **21** as a crystalline solid. Ultimately, the O-methyl groups of **21** will have to be removed for synthesis of olivin, but in order to continue with some model studies we decided to prepare the trimethyl ether **22**. Methylation of the chelated hydroxyl group of **21** proved difficult, and attempts to use methyl iodide or dimethyl sulfate in conjunction with various bases for formation of ether **22** were generally discouraging. However, treatment of phenol **21** with methyl fluorosulfonate and potassium *tert*-butoxide in glyme gave ether **22** in good yield.[16] Cleavage of alkene **22** with osmium tetroxide/periodate afforded keto aldehyde **23**.



17



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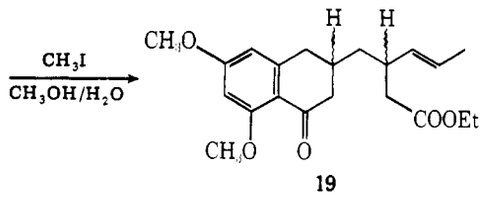

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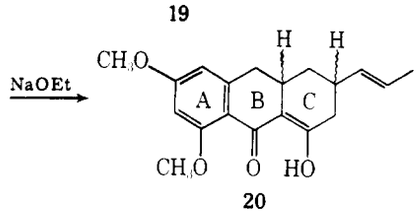

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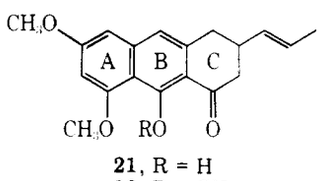
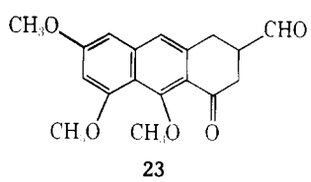
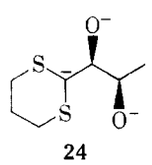


21, R = H
22, R = CH_3



23

With the key aldehyde **23** now in hand, it was our intention to couple it with trianion **24**.[17] This anion should be available by deprotonation of dithiane diol **25**, which we prepared from readily available methyl *threo*-2,3-dihydroxybutyrate (**26**)[18] as described below.



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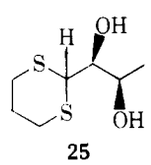

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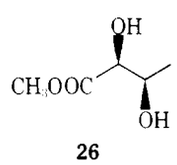
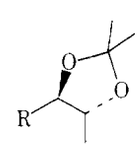
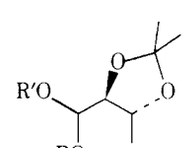


26

Ester **26** on treatment with acetone/$CuSO_4$/*p*-TsOH was converted to acetonide **27a**. Reduction of **27a** with Dibal, followed by either aqueous or methanolic quench, produced either the hydrate **28** or hemiacetal **29**, respectively. Although hydration of an aldehyde such as **27b** is not without precedent,[19] we felt it would be prudent to confirm the structures assigned to **28** and **29** by synthesizing them via an alternative route.

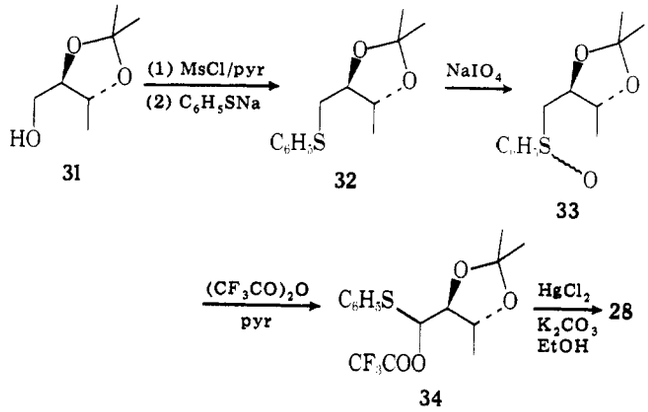


27a, R = $COOCH_3$
b, R = CHO



28, R = R′ = H
29, R = CH_3; R′ = H
30, R = CH_3; R′ = $COCH_3$

Reduction of ester **27a** with lithium aluminum hydride afforded alcohol **31** (93%) which on treatment with mesyl chloride/pyridine followed by sodium thiophenoxide gave sulfide **32**. Oxidation of **32** with sodium periodate yielded a



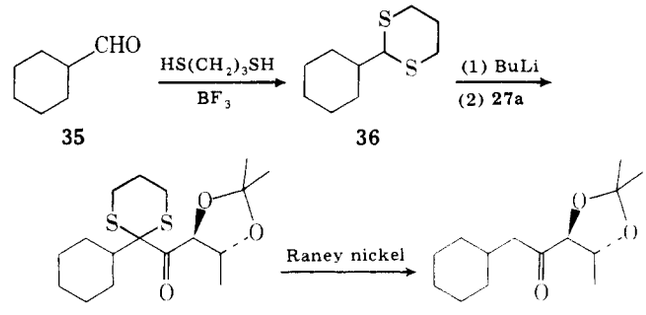
31 32 33

34

1/1 mixture of diasteromeric sulfoxides **33**. A Pummerer rearrangement of these sulfoxides was effected with trifluoroacetic anhydride/pyridine to give trifluoroacetate **34**, which upon mercury(II)-catalyzed hydrolysis was converted to hydrate **28**, identical to material prepared by Dibal reduction of ester **27a**, followed by an aqueous quench.

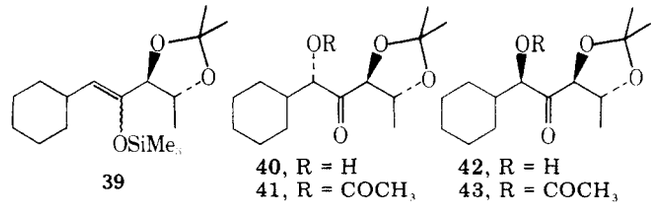
Conversion of hemiacetal **29** to dithane **25** was effected in 73% yield with 1,3-propanedithiol/boron trifluoride etherate. Compound **25** could be successfully deprotonated with 3-equiv of *n*-butyllithium (as evidenced by a D_2O quench yielding C-deuterated **25**) but attempted addition of trianion **24** to some simple aldehydes was disappointing. In general, only low yields of addition products could be isolated, and therefore this approach to construction of the olivin side chain was abandoned.

Using cyclohexanecarboxaldehyde (**35**) as a model for aldehyde **23** we have investigated an alternative sequence for synthesis of this side chain. Aldehyde **35** was converted to dithiane **36** by standard means,[20] and after metallation with *n*-butyllithium was acylated with ester **27a** to produce **37**. Raney nickel desulfurization of **37** afforded ketone **38**.



35 36 37 38

This ketone can be deprotonated kinetically with LDA, followed by silylation to afford a silyl enol ether **39**.[21] Without complete characterization, **39** was treated with *m*-chloro-



39 40, R = H; 41, R = $COCH_3$ 42, R = H; 43, R = $COCH_3$

perbenzoic acid in methylene chloride and after acidic workup only a *single* stereoisomeric α-hydroxy ketone was obtained.[22] This acyloin has either structure **40** or **42**, but we are unable to distinguish between these two possibilities by simple spectral means.[23] The acyloin was further characterized by conversion to a single acetate (either **41** or **43**) with acetic anhydride/pyridine (single sharp $COCH_3$ in the ^1H NMR).

We anticipate that it should be possible to convert an acyloin such as this to the corresponding methyl ether with in-

version if **42** or with retention if **40**.[23] This work is in progress, and the chemistry described in this paper will be used in the synthesis of olivin.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on either a Perkin-Elmer 137 or 197 spectrometer. NMR spectra were taken at 60 MHz on Varian A60A or Perkin-Elmer R-12 spectrometers; 100-MHz spectra were recorded on a Varian XL-100 instrument. All NMR spectra were taken in deuteriochloroform unless otherwise noted. NMR spectra (270 MHz) were obtained on a Bruker HX instrument at Yale University on a facility supported by NIH grant PR00798. Low-resolution mass spectra were obtained on a CEC 21-104 instrument. High-resolution mass spectra were obtained on a CEC 21-110B spectrometer at MIT under NIH grant PR-00317. Elemental analyses were done by Microtech Laboratories, Skokie, Ill. E.M. Merck Silica Gel 60 (0.05–0.20 mm) was used for column chromatography and Silica Gel PF_{254} was used for both analytical and preparative TLC.

Diethyl 3,5-Dimethoxybenzylmalonate (7). Sodium metal (55 g, 2.39 mol) was dissolved in 900 mL of absolute ethanol and diethyl malonate (225 g, 1.4 mol) was added over a 30-min period at 60 °C. A solution of 3,5-dimethoxybenzyl chloride (**6**) (130 g, 0.69 mol)[8] in 400 mL of absolute ethanol was added over 1 h at 70–75 °C with stirring. The mixture was refluxed overnight and the alcohol was distilled off. The residue was treated with 3% hydrochloric acid and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was distilled to provide diester **7**: bp 160–5 °C (0.1 mm) (200 g, 93%); NMR δ 1.20 (6 H, t, J = 9 Hz), 3.15 (2 H, d, J = 6 Hz), 3.75 (6 H, s), 4.18 (4 H, q, J = 9 Hz), 6.35 (3 H, s).

2-(3,5-Dimethoxybenzyl)-1,3-propanediol (8). Diester **7** (100 g, 0.32 mol) in 425 mL of dry THF was slowly added over 3 h to a slurry of lithium aluminum hydride (50 g) in dry THF (1.2 L). The mixture was stirred at room temperature overnight and excess $LiAlH_4$ was destroyed by slow addition of 100 mL of ethyl acetate, followed by 50 mL of saturated NH_4Cl. The solid precipitate was removed by filtration and washed with ethyl acetate. The combined organic phase was evaporated in vacuo and the residual oil was taken up in ether, washed with H_2O, and dried ($MgSO_4$) to afford 69 g (95%) of a colorless viscous oil which slowly crystallized upon standing: mp 32–34 °C; IR (film) 3450 and 1600 cm^{-1}; NMR δ 1.20 (1 H, m), 2.5 (2 H, br, s), 2.60 (2 H, d, J = 3 Hz), 3.8 (10 H, m), 6.38 (3 H, s).

2-(3,5-Dimethoxybenzyl)-1,3-propanediol Ditosylate (9). Diol **8** (66 g, 0.29 mol) was dissolved in 200 mL of dry pyridine and the resulting solution was cooled to 0 °C. *p*-Toluenesulfonyl chloride (166 g, 0.87 mol) was added at such a rate that the temperature was maintained between 0 and 10 °C. The mixture was stirred in ice for 4 h and stored in a refrigerator overnight. The mixture was poured onto ice and extracted with ether. The organic layer was thoroughly washed with dilute HCl and water, dried over $MgSO_4$, and evaporated to afford a white solid. Recrystallization from ether/chloroform gave 126 g (91%) of crystals: mp 87–88 °C; IR ($CHCl_3$) 1600 and 1460 cm^{-1}; NMR δ 1.20 (1 H, t), 2.41 (8 H, br s), 3.71 (6 H, s), 3.91 (4 H, d, J = 5 Hz), 6.10 (2 H, d, J = 2 Hz), 6.30 (1 H, d, J = 2 Hz), 7.33 (4 H, d, J = 9 Hz), 7.75 (4 H, d, J = 9 Hz).

Anal. Calcd for $C_{26}H_{30}O_8S_2$: C, 58.44; H, 5.61. Found: C, 58.37; H, 5.69.

3-(3,5-Dimethoxybenzyl)glutaronitrile (10). To a solution of 65 g (0.12 mol) of ditosylate **9** in 200 mL of Me_2SO was added over 30 min a suspension of 20 g of sodium cyanide in 100 mL of Me_2SO with stirring at room temperature. After stirring at room temperature for 3 h, the mixture was heated on a steam bath for 1 h, poured onto ice, and extracted with ether. After drying ($MgSO_4$) and evaporation a white crystalline solid (28 g, 86%) was isolated. Recrystallization from CH_2Cl_2/hexane gave an analytical sample: mp 52–53 °C; IR ($CHCl_3$) 2250 and 1600 cm^{-1}; NMR δ 1.20 (1 H, t), 2.53 (4 H, d, J = 2 Hz), 2.80 (2 H, d, J = 6 Hz), 3.83 (6 H, s), 6.41 (3 H, s).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.87; H, 6.55. Found: C, 68.85; H, 6.50.

1-Oxo-3,4-dihydro-6,8-dimethoxy-(2*H*)-naphthalene-3-acetonitrile (11). Dinitrile **10** (31 g, 0.12 mol) was dissolved in 700 mL of dry ether and 30 g of fused zinc chloride was added. Hydrogen chloride gas was passed through the mixture for 1.5 h. The ether was evaporated and the residue was refluxed with 100 mL of water for 2 h. On cooling a solid precipitated was collected, dried, and recrystallized from methylene chloride to afford 29 g (93%) of crystals: mp 144–145 °C; IR ($CHCl_3$) 2250, 1685, and 1600 cm^{-1}; NMR δ 2.46 (5 H, m), 2.93 (2 H, m), 3.86 (6 H, s), 6.35 (2 H, s).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.50; H, 5.93.

4-(3,5-Dimethoxybenzyl)glutaric Acid (12). Dinitrile **10** (3.8 g, 1.56 mmol), 50 mL of 5% sodium hydroxide, and 50 mL of ethylene glycol monomethyl ether were refluxed for 18 h. The solvent was evaporated in vacuo and the residue was dissolved in water and washed with ether. The aqueous layer was acidified with HCl, extracted with ethyl acetate, and dried ($MgSO_4$). Upon evaporation of the solvent 4.16 g (94%) of oily diacid **12** was isolated. A sample crystallized from ethyl acetate/hexane had mp 128–130 °C: IR (film) 2500–3500, 1710, and 1600 cm^{-1}; NMR δ 2.1–2.5 (7 H, m), 3.75 (6 H, s), 6.3 (3 H, s).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.36; H, 6.34.

1-Oxo-3,4-dihydro-6,8-dimethoxy-(2*H*)-naphthalene-3-acetic Acid (13). To 1.8 g of polyphosphoric acid heated on a steam bath was added 30 mg of diacid **12**. The mixture was heated for 20 min and cooled. Ice water was added and the mixture was swirled until the PPA had dissolved. Extraction with ether gave only 5 mg of **13**, but filtration of the aqueous phase afforded another 15 mg. The two solid crops were combined to afford a total of 72% of **13**, mp 209–211 °C. An analytical sample crystallized from methanol had mp 214–216 °C: NMR (Me_2SO-d_6) δ 2.5 (7 H, m), 3.80 (3 H, s), 3.87 (3 H, s), 6.5 (2 H, s).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.49; H, 5.81.

3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′(2′*H*)-naphthalene]-1-acetonitrile (14). Ketone **11** (10 g, 0.04 mol) was dissolved in 150 mL of methylene chloride and 6 g (0.06 mol) of 1,2-ethanedithiol was added, followed by 1 mL of boron trifluoride etherate. The solution was stirred at room temperature overnight and 50 mL of 5% sodium hydroxide was added. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to afford 12 g (90%) of white crystals. An analytical sample was recrystallized from methylene chloride/hexane: mp 148–149 °C; IR ($CHCl_3$) 1600, 1580, and 1460 cm^{-1}; NMR δ 2.48 (5 H, m), 2.96 (2 H, m), 3.48 (4 H, m), 3.76 (3 H, s), 3.88 (3 H, s), 6.20 (1 H, d, J = 2 Hz), 6.36 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{16}H_{19}NO_2S_2$: C, 59.81; H, 5.91; S, 19.95. Found: C, 59.87; H, 5.68; S, 19.95.

3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′(2′*H*)-naphthalene]-3′-acetaldehyde (15). Nitrile **14** (10 g, 0.031 mol) was dissolved in dry benzene (225 mL) and the solution was cooled to 10 °C. Diisobutylaluminum hydride (37 mL of a 1 M solution in hexane, 0.037 mol) was added dropwise under nitrogen while maintaining the temperature below 10 °C. The solution was stirred for 4 h at 10 °C and dilute HCl was added. The benzene layer was separated, washed with water, dried ($MgSO_4$), and evaporated in vacuo to afford 9 g (90%) of an amorphous solid which appeared pure by TLC analysis: IR ($CHCl_3$) 1720, 1600, and 1580 cm^{-1}; NMR δ 2.40 (7 H, m), 3.35 (4 H, m), 3.65 (3 H, s), 3.75 (3 H, s), 6.15 (1 H, d, J = 2 Hz), 6.30 (1 H, d, J = 2 Hz), 10.05 (1 H, s).

5-(3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′-(2′*H*)-naphthalen]-3′-yl)-3-penten-2-one (16). A slurry of sodium hydride (5 g of 50% in mineral oil) in 60 mL of dry benzene was treated with 10 g (0.06 mol) of dimethyl phosphonoacetone in 60 mL of dry benzene slowly with stirring. The mixture was stirred for 30 min at room temperature and a solution of aldehyde **15** (9 g, 27 mmol) in 100 mL of benzene was added dropwise. The mixture was stirred overnight and 20 mL of water was added. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to afford a white solid. Recrystallization from benzene/hexane gave 9 g (90%) of crystals: mp 112–113 °C; IR ($CHCl_3$) 1670, 1600, and 1580 cm^{-1}; NMR δ 2.10 (9 H, m), 3.35 (4 H, m), 3.62 (3 H, s), 3.75 (3 H, s), 5.99–6.25 (4 H, m).

Anal. Calcd for $C_{19}H_{24}O_3S_2$: C, 62.64; H, 6.58. Found: C, 62.71; H, 6.60.

5-(3′,4′-Dihydro-6′,8′-dimethoxyspiro[1,3-dithiolane-2,1′-(2′*H*)-naphthalen]-3′-yl)-3-penten-2-ol (17). Ketone **16** (9.5 g, 26 mmol) was dissolved in 200 mL of dry benzene and cooled to 10 °C. Diisobutylaluminum hydride (40 mL of a 1 M solution in hexane, 39 mmol) was added slowly while maintaining the temperature below 10 °C. The mixture was stirred at 10 °C for 4 h and dilute HCl was added. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (200 g) with benzene/ethyl acetate (9/1) to afford the alcohols **17** as a gummy solid (3.3 g, 60%): IR ($CHCl_3$) 3450, 1600, and 1580 cm^{-1}; NMR δ 1.27 (3 H, d, J = 6 Hz), 2.13 (8 H, m), 3.50 (4 H, m), 3.78 (3 H, s), 3.90 (3 H, s), 5.70 (2 H, m), 6.26 (1 H, d, J = 2 Hz), 6.41 (1 H, d, J = 2 Hz).

Ethyl 3′,4′-Dihydro-6′,8′-dimethoxy-β-1-propenylspiro[1,3-dithiolane-2,1′(2′*H*)-naphthalene]-1-butanoate (18). A mixture of alcohols **17** (5.1 g, 13 mmol), 21 mL of triethyl orthoacetate, and

70 μL of propionic acid was heated at 135–140 °C for 5 h while a slow stream of nitrogen was flushed through the system to remove ethanol. The reaction mixture was evaporated in vacuo and the residue was chromatographed on 100 g of silica gel eluting with benzene/ethyl acetate (9/1) to afford esters **18** as a gummy solid (3 g, 50%): IR ($CHCl_3$) 1740, 1600, and 1580 cm^{-1}; NMR δ 1.26 (3 H, t, J = 7 Hz), 1.64 (3 H, d, J = 5 Hz), 2.36–2.03 (7 H, m), 3.50 (4 H, m), 3.76 (3 H, s), 3.88 (3 H, s), 4.15 (2 H, q, J = 7 Hz), 5.68 (2 H, m), 6.23 (1 H, d, J = 2 Hz), 6.43 (1 H, d, J = 2 Hz).

Ethyl 1-Oxo-3,4-dihydro-6,8-dimethoxy-β-1-propenylnaphthalene-3-butyrate (19). Thioketal **18** (0.93 g, 2 mmol) was dissolved in 30 mL of methanol containing 5% water and 2 mL of methyl iodide was added.[14] The solution was refluxed overnight, the solvent was evaporated, and the residue was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to afford a gum which was chromatographed on 25 g of silica gel eluting with benzene/ethyl acetate (95/5). A gummy product (0.49 g, 50%) was obtained which appeared pure by TLC: IR ($CHCl_3$) 1720, 1660, and 1600 cm^{-1}; NMR δ 1.26 (3 H, t, J = 7 Hz), 1.63 (3 H, d, J = 6 Hz), 2.81–2.16 (6 H, m), 4.15 (2 H, q, J = 7 Hz), 5.45 (2 H, m), 6.40 (2 H, d, J = 2 Hz).

3,4,4a,10-Tetrahydro-6,8-dimethoxy-3-(1-propenyl)-1,9(2*H*,9a*H*)-anthracenedione (20). Ketoester **19** (250 mg, 0.7 mmol), 7 mL of dry toluene, 5 μL of ethanol, and 38 mg (0.79 mmol) of a 50% oil dispersion of sodium hydride were refluxed under nitrogen for 5.5 h. The mixture was diluted with ether and washed with 3% HCl and saturated $NaHCO_3$. The combined aqueous fraction was back extracted twice with CH_2Cl_2 and the organic extracts were combined and dried ($MgSO_4$). Upon evaporation of solvent 205 mg of crude material was obtained. This residue was dissolved in about 4 mL of hot benzene. Hexane was added and the mixture was slowly cooled to room temperature and stored at −20 °C overnight. The solid which formed was collected and dried to give 105 mg of **20,** mp 135–145 °C. Preparative TLC of the recrystallization residue (10% ether/CH_2Cl_2) gave an additional 38 mg of **20.** Total yield: 143 mg (64%); NMR δ 6.41 (2 H, m), 3.92 (3 H, s), 3.85 (3 H, s), 2.62 (4 H, m), 2.48–2.2 (2 H, m), 2.4–1.7 (4 H, m), 1.65 (1.5 H, d, J = 8 Hz), 1.58 (1.5 H, d, J = 8 Hz); IR ($CHCl_3$) 1600 cm^{-1}; λ_{max} (CH_3OH) 347, 280 nm (ε 14 000, 4800).

1,2,3,4-Tetrahydro-5,7-dimethoxy-10-hydroxy-4-oxo-3-propenylanthracene (21). Diketone **20** (0.23 g, 0.7 mmol) and chloranil (0.24 g, 1 mmol) were dissolved in 20 mL of dry benzene and heated at reflux for 48 h under nitrogen. The solvent was removed and the residue was chromatographed on 5 g of silica gel. Elution with benzene gave unconsumed chloranil and elution with benzene/ethyl acetate (95/5) provided **21.** Recrystallization from benzene/hexane gave 0.11 g (50%) of **21:** mp 127–128 °C; IR ($CHCl_3$) 3400, 1620, and 1605 cm^{-1}; NMR δ 1.70 (3 H, d, J = 5 Hz), 2.75–2.95 (5 H, m), 3.96 (3 H, s), 4.08 (3 H, s), 5.75 (2 H, m), 6.61–6.91 (3 H, m), 15.15 (1 H, s); mass spectrum (70 eV), m/e (rel intensity) 312 (M^+, 12), 270 (12), 245 (8), 57 (100).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.72; H, 6.40. Found: C, 72.92; H, 6.78.

1,2,3,4-Tetrahydro-5,7,10-trimethoxy-4-oxo-3-propenylanthracene (22). Phenol **21** (280 mg, 0.9 mmol) and potassium *tert*-butoxide (112 mg, 1.34 mmol) in 1 mL of 1,2-dimethoxyethane was treated with 105 mg (0.92 mmol) of methyl fluorosulfonate. The mixture was stirred for 30 min at room temperature and an additional 20 mg (0.18 mmol) of methyl fluorosulfonate was added. The mixture was stirred for 5 min longer, diluted with methylene chloride, washed with 5% sodium hydroxide and brine, and dried over $MgSO_4$. Evaporation of the solvent yielded 300 mg of crude product which was chromatographed on 10 g of silica gel, eluting with 5% ether/methylene chloride to afford 250 mg (85%) of crystalline ether **22** along with 5 mg of unreacted phenol **21.** Recrystallization of **22** from ether yielded light orange prisms: mp 138–139 °C; IR ($CHCl_3$) 1675, 1615, and 1560 cm^{-1}; NMR δ 1.65 (3 H, d, J = 5 Hz), 2.3–3.2 (5 H, m), 3.92 (6 H, s), 3.95 (3 H, s), 5.40–5.60 (2 H, m), 6.44 (1 H, br s), 6.58 (1 H, d, J = 2 Hz), 7.19 (1 H, s).

Anal. Calcd for $C_{20}H_{22}O_4$: m/e 326.1516. Found: m/e 326.1519.

1,2,3,4-Tetrahydro-5,7,10-trimethoxyl-4-oxo-3-formylanthracene (23). To a solution of 21 mg (0.065 mmol) of alkene **22** in 2 mL of dioxane/water (3/1) was added 2 mg of osmium tetroxide and the mixture was stirred for 30 min. Sodium metaperiodate (65 mg, 0.3 mmol) was added in portions over a 5-h period. The reaction mixture was diluted with methylene chloride and washed with saturated sodium sulfite, 5% sodium hydroxide, and brine. The organic layer was dried ($MgSO_4$) and evaporated to yield 11 mg (55%) of a red gum, which was further purified by preparative TLC developing with ethyl acetate: NMR δ 2.8–3.4 (5 H, m), 3.90 (6 H, s), 3.94 (3 H, s), 6.44 (1 H, d, J = 2 Hz), 6.58 (1 H, d, J = 2 Hz), 7.23 (1 H, s), 9.76 (1 H, s); IR (film) 1720, 1680, 1620, and 1560 cm^{-1}; mass spectrum m/e (rel intensity) 314 (100), 285 (27), 257 (22), 165 (29), 147 (60).

Methyl *trans*-2,2,5-Trimethyl-1,3-dioxolane-4-carboxylate (27a). Diol **26** (12.5 g, 108 mmol), 300 mg of *p*-toluenesulfonic acid, and 3 g of anhydrous cupric sulfate in 50 mL of acetone were stirred at room temperature for 14 h. The mixture was filtered and evaporated. The residue was dissolved in ether and washed with 5% sodium hydroxide and brine and dried with $MgSO_4$. Evaporation of the solvent in vacuo, followed by distillation (22 °C (0.08 mm)), afforded 7.7 g (47%) of acetonide **27a:** IR (film) 1760 and 1735 cm^{-1}; NMR δ 1.4–1.98 (9 H, m), 3.8 (3 H, s), 4.4–4.05 (2 H, m).

α-Methoxy-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-methanol (29). Diisobutylaluminum hydride (4.7 mL of a 1 M solution in hexane) was added over 5 min to a solution of 0.72 g (4.1 mmol) of ester **27a** in 15 mL of ether at −78 °C. The mixture was stirred for 30 min and 2.5 mL of methanol was added. The reaction mixture was warmed to room temperature and stirred for 2 h. The mixture was filtered and the filter cake was washed thoroughly with ether. Evaporation of the solvent afforded 0.61 g (85%) of hemiacetal **29:** IR (film) 3435 and 1080 cm^{-1}; NMR δ 1.3 (3 H, d, J = 7 Hz), 1.4 (6 H, s), 3.5 (3 H, s), 3.7–4.7 (3 H, m); CI mass spectrum (isobutane), m/e (rel intensity) 145 (100), 115 (10), 101 (15).

Hemiacetal **29** (110 mg, 0.635 mmol) was stirred with 12 mL of acetic anhydride in 1 mL of anhydrous pyridine for 2 h at room temperature. The mixture was diluted with ether, washed with 3% HCl, 5% NaOH, and brine, dried ($MgSO_4$), and evaporated to afford 51 mg of an oil. Bulb-to-bulb distillation (80 °C (2 mm)) gave 40 mg (34%) of pure acetate **30:** IR (film) 1750 and 1090 cm^{-1}; NMR δ 1.35–1.45 (9 H, m), 2.20 (3 H, s), 3.55 (3 H, s), 3.75 (1 H, m), 4.2 (1 H, m).

***trans*-2,2,5-Trimethyl-1,3-dioxolane-4-methanol (31).** Ester **27** (2 g, 11.3 mmol) in 10 mL of ether was added dropwise to a slurry of 0.46 g (11.3 mmol) of lithium aluminum hydride in 30 mL of dry ether. The mixture was cooled and water was cautiously added. The mixture was filtered and the filter cake was thoroughly washed with ether. The combined filtrate was evaporated to afford 1.55 g (93%) of alcohol **31:** IR (film) 3450 cm^{-1}; NMR δ 1.25 (3 H, d, J = 4 Hz), 1.35 (6 H, s), 2.4–2.8 (1 H, br s, OH), 3.5–4.1 (2 H, m).

***trans*-4-Phenylthiomethyl-2,2,5-trimethyl-1,3-dioxolane (32).** To a solution of 0.144 g (1.46 mmol) of triethylamine and 0.145 g (1 mmol) of alcohol **31** in 1.5 mL of methylene chloride cooled to 0 °C was added dropwise 0.135 g (1.2 mmol) of methanesulfonyl chloride. The reaction mixture was stirred at 0 °C for 15 min and warmed to room temperature. The mixture was diluted with methylene chloride and washed with 3% hydrochloric acid, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), and evaporated to afford 164 mg (75%) of mesylate. This material was added to a solution of sodium thiophenoxide (formed from 43 mg (2.9 mmol) of sodium metal and 0.32 g (2.9 mmol) of thiophenol) in 2 mL of absolute ethanol and stirred at room temperature overnight. The ethanol was evaporated and the residue was dissolved in ether, washed with 5% NaOH and brine, dried ($MgSO_4$), and evaporated to afford 135 mg (78% based on mesylate) of crude sulfide **32:** IR (film) 3100 and 1590 cm^{-1}; NMR δ 1.35 (3 H, d, J = 6 Hz), 1.40 (6 H, s), 3.15 (2 H, m), 3.65–4.0 (2 H, m), 7.35 (5 H, m).

Preparation of Sulfoxides 33. Sulfide **32** (1.11 g, 4.7 mmol) was stirred for 22 h with 1.44 g (6.8 mmol) of sodium metaperiodate in 10 mL of methanol. The mixture was filtered and evaporated. The residue was dissolved in ether and washed with 5% NaOH and brine, dried ($MgSO_4$), and evaporated. The residue was rapidly chromatographed on 20 g of silica gel in ether to remove some residue of diphenyl disulfide affording 0.96 g (73%) of a 1:1 mixture of diastereomeric sulfoxides **33:** IR (film) 3100, 1590, and 1040 cm^{-1}. Samples of pure sulfoxide isomers were separated by chromatography on activity III alumina eluting with ether/methylene chloride (1/1). More polar diastereomer: NMR δ 1.28 (3 H, d, J = 6 Hz), 1.42 (3 H, s), 1.46 (3 H, s), 2.8–3.1 (2 H, m), 3.6–4.4 (2 H, m). Less polar diastereomer: NMR δ 1.22 (3 H, d, J = 6 Hz), 1.35 (3 H, s) 1.40 (3 H, s), 2.9–3.1 (2 H, m), 3.4–4.4 (2 H, m).

α-Hydroxy-*trans*-2,2,5-trimethyl-1,3-dioxoline-4-methanol (28). Trifluoroacetic anhydride (79 mg, 0.35 mmol) was added to a solution of 69 mg (0.27 mmol) of sulfoxides **33** in 1 mL of benzene and the solution was stirred at room temperature for 5 min. Pyridine (0.05 mL, 6.2 mmol) was added and the mixture was stirred for an additional 20 min. The mixture was diluted with ether, washed with 3% HCl, 5% NaOH, and brine, dried ($MgSO_4$), and evaporated to afford 72 mg (84%) of oily trifluoroacetate **34:** IR (film) 3100, 1795, and 1595 cm^{-1}; NMR δ 1.3–1.5 (9 H, m), 3.8–4.5 (2 H, m), 6.3 (1 H, m), 7.35 (5 H, m).

The trifluoroacetate **34** was stirred with 69 mg of mercuric chloride and 56 mg of potassium carbonate in 2 mL of 95% ethanol at room temperature overnight. The solvent was removed in vacuo and the

residue was taken up in methylene chloride and filtered. Evaporation of the solvent gave 25 mg (78%) of hydrate **28**. This material was identical to a sample prepared by an aqueous workup of a Dibal reduction of ester **27a**: IR (film) 3450 and 1090 cm^{-1}; NMR δ 1.2 (3 H, s), 1.42 (6 H, s), 3.2–4.7 (3 H, m).

***threo*-2,3-Dihydroxy-3-(1,3-dithian-2-yl)-propane (25).** Hydrate **28** (200 mg, 1.13 mmol) was stirred at room temperature with 0.35 g (3.3 mmol) of 1,3-propanedithiol and 0.02 mL of BF_3·etherate in 5 mL of methylene chloride for 14 h. The solvent was removed in vacuo and the residue was chromatographed on 10 g of silica gel, eluting first with methylene chloride to remove 1,3-propanedithiol and 2,2-dimethyl-1,3-dithane, then with ether/methylene chloride (10/90) to remove minor products, and finally with ether/methylene chloride (20/80) to afford 155 mg (73%) of dithiane **25**: IR (film) 3450 cm^{-1}; NMR δ 1.25 (3 H, d, J = 8 Hz), 2.1 (2 H, m), 2.5–3.0 (6 H, m), 3.60 (1 H, dd, J = 4, 8 Hz), 3.9–4.4 (1 H, m).

***trans*-(2-Cyclohexyl-1,3-dithian-2-yl)(2,2,5-trimethyl-1,3-dioxolan-4-yl)methanone (37).** n-Butyllithium (7.4 mL of a 2.2 M solution in hexane, 15.5 mmol) was added to a −20 °C solution of 3 g (14.5 mmol) of cyclohexyl dithiane **36** in 60 mL of dry THF.[20] The mixture was stirred for 1.5 h at −20 °C and cooled to −78 °C and 3 g (17 mmol) of ester **27a** was added dropwise. After stirring for 1 h, the mixture was warmed to room temperature and was evaporated in vacuo. Ether and water were added to the residue and the organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on 120 g of silica gel in CH_2Cl_2/hexane (1/1) to afford 3 g (60%) of a waxy solid. A sample recrystallized from hexane had mp 70–72 °C: IR (film) 1705 cm^{-1}; NMR δ 1.1–2.1 (13 H, m), 1.35 (3 H, d, J = 6 Hz), 1.42 (3 H, s), 1.48 (3 H, s), 2.4–2.65 (4 H, m), 3.15 (1 H, dt, J = 12, 2 Hz), 4.35 (1 H, m), 4.58 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{17}H_{28}O_3S_2$: C, 59.29; H, 8.19. Found: C, 59.68; H, 8.37.

***trans*-2-Cyclohexyl-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)-ethanone (38).** Thioketal **37** (300 mg, 0.87 mmol) was stirred 30 min at room temperature with 5 g of freshly prepared Raney nickel (activity W-2) in 10 mL of absolute ethanol. The reaction mixture was filtered and evaporated in vacuo to 180 mg of crude ketone **38** which was purified by bulb-to-bulb distillation (85 °C (0.1 mm)) and then by chromatography on silica gel eluting with methylene chloride to afford 120 mg (60%) of pure ketone: IR (film) 1705 cm^{-1}; NMR δ 0.9–2.1 (11 H, m), 1.38 (3 H, d, J = 7 Hz), 1.45 (6 H, s), 2.55 (2 H, d, J = 7 Hz), 3.9–4.4 (2 H, m).

[4α,5β]-2-Cyclohexyl-2-hydroxy-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)ethanone (40 or 42). A solution of lithium diisopropylamide was formed at −20 °C by addition of 0.21 mL (0.34 mmol) of 1.6 M n-butyllithium to a solution of 36 mg (0.355 mmol) of diisopropylamine in 2 mL of THF. The solution was cooled to −70 °C and 50 mg (0.21 mmol) of ketone **38** in 0.5 mL of dry hexane was added dropwise over a 3-min period. The solution was stirred for 30 min and 0.15 mL (1.2 mmol) of chlorotrimethylsilane was added. The mixture was warmed to room temperature and poured onto aqueous sodium bicarbonate. The mixture was extracted with methylene chloride, and the organic phase was dried ($MgSO_4$) and evaporated to yield 55 mg (88%) of crude silylenol ether **39**: IR (film) 1665, 1245, and 840 cm^{-1}; δ 0.28 (9 H, s), 1.0–2.5 (11 H, m), 1.45, (3 H, d, J = 6 Hz), 1.70 (6 H, s), 3.7–4.3 (2 H, m), 4.78 (1 H, d, J = 10 Hz).

This material in 2 mL of dry hexane was cooled to −20 °C and treated with 40 mg (0.23 mmol) of purified m-chloroperbenzoic acid. The reaction mixture was stirred for 1 h during which time the flask was warmed to +10 °C. The mixture was diluted with aqueous sodium sulfate and extracted with methylene chloride. The organic phase was washed with 3% HCl, saturated sodium bicarbonate, and brine, dried with $MgSO_4$, and evaporated to give 40 mg (79%) of crude acyloin. Preparative TLC of this material eluting with methylene chloride gave 25 mg (50%) of pure acyloin as a colorless oil: IR (film) 3450 and 1710 cm^{-1}; NMR (270 MHz) δ 1.0–2.5 (1 H, m), 1.36 (3 H, d, J = 6 Hz), 1.39 (3 H, s), 1.40 (3 H, s), 3.94 (1 H, dq, J = 8, 6 Hz), 4.04 (1 H, d, J = 8 Hz), 4.20 (1 H, br s).

[4α,5β]-2-Cyclohexyl-2-acetoxy-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)ethanone (41 or 43). Ketoalcohol **40** or **42** (5 mg, 0.02 mmol) was stirred at room temperature for 12 h with excess acetic anhydride in 0.5 mL of dry pyridine. The mixture was diluted with methylene chloride, washed with 3% HCl and saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated to give 5 mg (86%) of acetate: IR (film) 1740 and 1725 cm^{-1}; NMR δ 1.0–2.2 (11 H, m), 1.42–1.52 (9 H, m), 2.12 (3 H, s), 3.9–4.3 (2 H, m), 5.02 (1 H, d, J = 4 Hz).

Anal. Calcd for $C_{16}H_{26}O_5$: m/e 298.1780. Found: m/e 298.1777.

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Registry No.—**6,** 6652-32-0; **7,** 5859-68-7; **8,** 67194-88-1; **9,** 67194-89-2; **10,** 67194-90-5; **11,** 67194-91-6; **12,** 67194-92-7; **13,** 41651-06-3; **14,** 67194-93-8; **15,** 67194-94-9; **16,** 67194-95-0; *erythro*-**17,** 67194-96-1; *threo*-**17,** 67194-97-2; *erythro*-**18,** 67208-76-8; *threo*-**18,** 67194-98-3; *erythro*-**19,** 67194-99-4; *threo*-**19,** 67194-69-8; **20,** 67195-00-0; **21,** 67195-01-1; **22,** 67195-02-2; **23,** 67195-03-3; **25,** 67195-04-4; **26,** 5057-95-4; **27a,** 63640-49-3; **28,** 67195-05-5; **29,** 67195-06-6; **30,** 67226-41-9; **31,** 67195-07-7; **32,** 67195-08-8; **33** isomer 1, 67195-09-9; **33** isomer 2, 67252-86-2; **34,** 67195-10-2; **36,** 56698-00-1; **37,** 67195-11-3; **38,** 67195-12-4; **39,** 67195-13-5; **40** or **42,** 67195-14-6; **41** or **43,** 67195-15-7; diethyl malonate, 105-53-3; p-toluenesulfonyl chloride, 98-59-9; 1,2-ethanedithiol, 540-63-6; dimethylphosphonoacetone, 4202-14-6.

References and Notes

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(23) We hope to make a stereochemical correlation with natural olivin when we have actually attached the side chain to aldehyde **23.**