2531-80-8; **11b**, 29329-26-8; **11c**, 82892-06-6; **11d**, 72511-04-7; **11e**, 18197-78-9; **13**, 82892-07-7; **14**, 82892-08-8; **15**, 82892-09-9; *syn*-**16**, 82892-10-2; *anti*-**16**, 82892-11-3; **17**, 82892-12-4; **19**, 82892-16-8; **21**, 82892-13-5; 2,2-dinitropropane, 595-49-3; 2-(2-guanidinoethyl)-1,3-dioxolane picrate, 82892-15-7; *S*-methylisothiourea, 2986-19-8; nitroethane–lithium, 28735-55-9; 2-nitropropane–lithium, 3958-63-2; 1-(methoxyoxalyl)imidazole, 72030-76-3; *p*-nitrobenzyl chloride, 100-14-1; 2-(2-chloro-2-nitroethyl)-2-chloro-1,3-dioxolane, 82892-17-9.

Development of a Strategy for Convergent Total Synthesis of the Aureolic Acid Antitumor Antibiotics[1,2]

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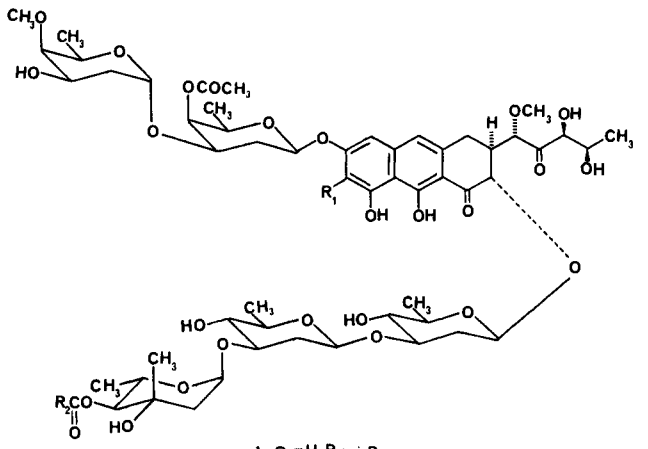
Received February 18, 1982

It has been found that condensation of an *o*-toluate carbanion with a 3-alkoxycyclohexen-2-one will produce the dihydroanthracenone system found in olivin (**3**) and chromomycinone (**4**), the aglycons of the aureolic acids. Several examples of this reaction are described, leading to synthesis of model aromatic systems **17**, **18**, **21**, **23**, **24**, and **26**. A route to compound **34**, having the complete carbon framework and most of the functionality of olivin, has been developed which uses the above type of condensation as the critical step.

The aureolic acids are a class of structurally related compounds produced by several varieties of *Streptomyces* and *Actinomyces*.[3,4] A few of these metabolites such as olivomycin A (**1**) and chromomycin A_3 (**2**), are clinically

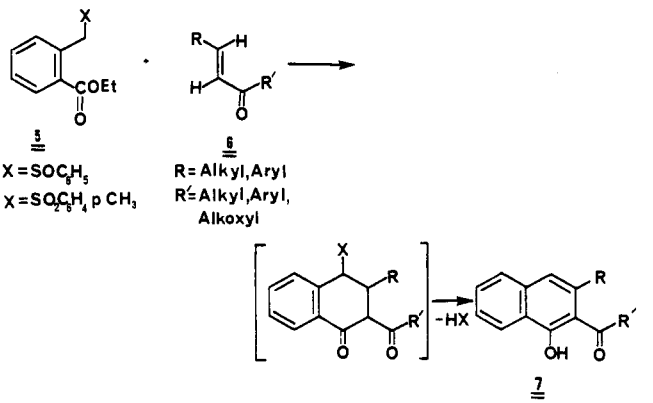


1 R_1=H, R_2= *i*-Pr
2 R_1=CH_3, R_2=CH_3

effective antitumor agents. Aureolic acid itself (also known as mithramycin) has been approved in the United States for treatment of testicular cancers.[5] However, these compounds have not found wide applicability in chemotherapy due to their high toxicities, although an attempt has been made recently to produce semisynthetic analogues of **1** having more favorable therapeutic properties.[4b]

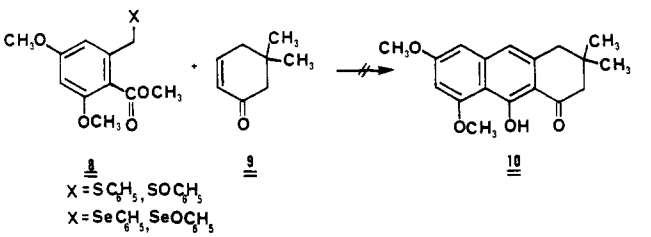
From a structural standpoint, the aureolic acids are all comprised of a complex tricyclic aglycon attached to disaccharide and trisaccharide moieties. The compounds in the olivomycin subgroup of aureolic acids all contain olivin (**3**)[6] as the aglycon. Metabolites designated as chromomycins have chromomycinone (**4**)[7] as the aglycon unit. Mithramycin also contains chromomycinone but is distinct

Scheme I

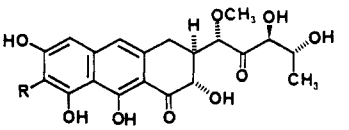


5 X=SOC_6H_5, X=$SO_2C_6H_4$ p CH_3
6 R=Alkyl,Aryl; R'=Alkyl,Aryl, Alkoxyl
7

Scheme II



8 X=SC_6H_5, SOC_6H_5; X=SeC_6H_5, $SeOC_6H_5$
9
10



3 R=H
4 R=CH_3

(1) A portion of this work has appeared in communication form: Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 3593.
(2) Taken in part from the Ph.D. thesis of J.H.D., submitted to The Pennsylvania State University, 1981.
(3) For a review see: Slavik, M.; Carter, S. K. In "Advances in Pharmacology and Chemotherapy"; Academic Press: New York, 1975; pp 1–30.
(4) See also: (a) Skarbek, J. D.; Brady, L. R. *Lloydia* **1975**, *38*, 369. (b) Kumar, V.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1980**, *23*, 376 and references cited.
(5) Calabresi, P.; Parks, R. E. In "The Pharmacological Basis of Therapeutics", 5th ed; Goodman, L. S., Gilman, A., Eds.; Macmillan: New York, 1975; p 1251.
(6) Bakhaeva, G. P.; Berlin, Y. A.; Chuprunova, D. A.; Kolosov, M. N.; Peck, G. Y.; Piotrovich, L. A.; Shemyakin, M. M.; Vasina, I. A. *J. Chem. Soc., Chem. Commun.* **1967**, 10 and references cited.
(7) Harada, N.; Nakanishi, K.; Tatsuoka, S. *J. Am. Chem. Soc.* **1969**, *91*, 5896 and references cited.

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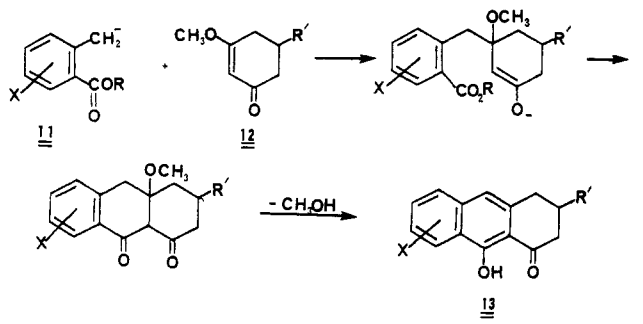
Scheme III



by virtue of having a different set of sugar residues than those found in the chromomycins.

Despite the fact that these aglycons have quite novel and challenging structures, little work has appeared to date on synthesis of **3** and **4**.[8-10] During the past few years we have been attempting to devise a convergent, stereoselective approach to total synthesis of both olivin and chromomycinone.[1,8] In this paper we describe an efficient route to the tricyclic framework of both aglycons which we expect will ultimately be used in total syntheses of these compounds.

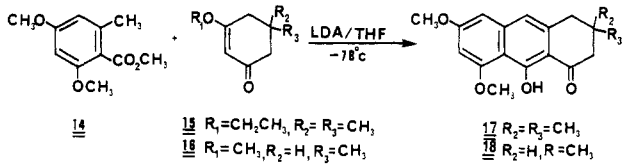
Our original plan for synthesis of the ring system present in **3** and **4** was based upon work published independently by Hauser and Rhee[11] and by van Leusen and co-workers[12] in 1978. Both groups found that naphthalene systems such as **7** could be produced by base-promoted condensation of sulfur-substituted toluate esters **5** with acyclic Michael acceptors **6** (Scheme I).

Analogously, we attempted to combine the sulfur and selenium compounds **8**[14] with cyclohexenone **9** to produce the olivin model **10** (Scheme II), but these condensations proved uniformly disappointing. In general, the cyclohexenone was destroyed, and the aromatic unit was recovered unchanged in these experiments.

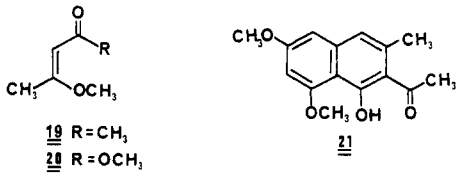
Since polymerization of cyclohexenone **9** appeared to be a problem in the proposed condensation, we considered the possibility of using the β-methoxy enone **12** in its place. We anticipated that compound **12**, being a vinylogous ester, would be less prone to self-condensation than **9**. Since **12** is in a higher oxidation state than **9**, it was obvious that any condensation leading to the proposed tricyclic system must employ an aromatic stabilized carbanion in an oxidation state lower than that of **8**. Thus, we reasoned that the simple *o*-toluate carbanion **11** might react with β-methoxy enone **12** to directly afford the desired aglycon system **13** as outlined in Scheme III.

Although dianions derived from some *o*-toluic acids were prepared and C-alkylated several years ago,[15] at the beginning of this research program toluate ester carbanions **11** were unknown. Since then, we have found and described how such species can be generated in certain cases and subsequently can be sulfenylated or selenated to prepare compounds of type **8**.[14] From these studies, it appears critical that an alkoxyl group be ortho to the ester substituent in order to prevent rapid toluate self-condensation to produce an isocoumarin.[14] It must be mentioned that during the course of this work, Staunton and coworkers reported the use of the carbanion derived from methyl dimethylorsellinate in some condensations related to those described below.[16]

In fact, it has proven possible to execute the chemistry shown in Scheme III. Specifically, orsellinate **14**[17] was

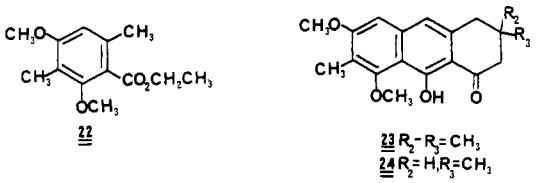


deprotonated with LDA in THF at −20 °C and was condensed with β-alkoxy enones **15**[18a] and **16**[18b] at −78 °C to afford the highly fluorescent tricyclic olivin-like ketones **17** (64%) and **18** (57%), respectively. Interestingly, the strong green fluorescence characteristic of **17** and **18** appears instantaneously upon acidification, showing that the entire condensation sequence occurs at this point, and not, for example, during the subsequent workup procedure. Similarly, condensation of **14** with the acyclic methoxy enone **19**[18c] gave the known[19] acetyl naphthalene **21** (50%).



However, the related ester **20** could not be successfully combined with the orsellinate carbanion.

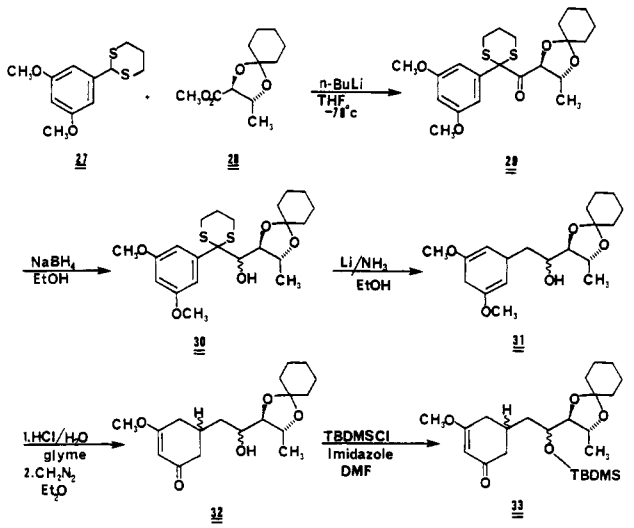
The method also serves for preparation of the chromomycinone system. Toluate **22**,[20] under reaction conditions similar to those mentioned above, condensed with β-alkoxy enones **15** and **16**, giving tricyclics **23** and **24**, respectively, in modest yields.[21]



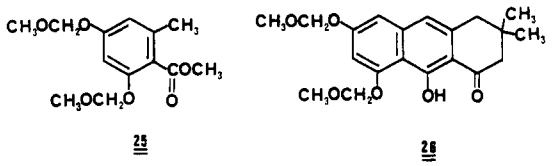
We anticipate that methyl protection of the aglycon A-ring phenols will not be practical in our eventual total

(8) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.
(9) Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1172.
(10) Thiem, J.; Wessel, H.-P. *Tetrahedron Lett.* **1980**, 3571; *Liebigs Ann. Chem.* **1981**, 2216.
(11) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. Cf. also: Hauser, F. M.; Subbarao, P. *Ibid.* **1982**, *47*, 383 and references cited therein.
(12) Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron Lett.* **1978**, 2213.
(13) For some other related approaches to linear aromatic systems see: Park, K. A.; Kallmerten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5881. Kende, A. S.; Rizzi, J.; Riemer, J. *Tetrahedron Lett.* **1979**, 1201. Kraus, G. A.; Sugimoto, H. *Ibid.* **1978**, 2263. Broom, N. J.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162.
(14) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H. *Synthesis* **1980**, 72.
(15) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.
(16) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1978**, 406. Evans, G. E.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *Ibid.* **1979**, 205. Leeper, F. J.; Staunton, J. *Ibid.* **1979**, 206.
(17) Sargent, M. V.; Vogel, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1986. Santesson, J. *Acta Chem. Scand.* **1970**, *24*, 3373. Nicollier, G.; Rebetez, M.; Tabacchi, R.; Gerlach, H.; Thalmann A. *Helv. Chim. Acta* **1978**, *61*, 2899.
(18) (a) Gannon, W. F.; House, H. O. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, p 539. (b) Cf.: Gompper, R. *Chem. Ber.* **1960**, *93*, 187. (c) Awang, D. V. C. *Can. J. Chem.* **1971**, *49*, 2672. Compound **19** was an *E*/*Z* mixture.
(19) Shibata, S.; Morashita, E.; Raneda, M.; Kimura, Y.; Takido, M.; Takahashi, S. *Chem. Pharm. Bull.* **1969**, *17*, 454.
(20) Elix, J. A.; Norfolk, S. *Aust. J. Chem.* **1975**, *28*, 1113.
(21) Compound **22** seems to be more prone to self-condensation than does orsellinate **14**. The only characterizable product, other than the desired one, in any of these condensations is the isocoumarin.

Scheme IV



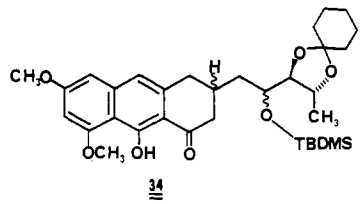
synthesis. Thus, bis(methoxymethyl) derivative **25** was prepared from methyl orsellinate and was found to react with enone **15** under the above experimental conditions to form **26** (55%).



In view of the promising results with these simple model systems, we next turned our attention to construction of a tricyclic framework containing all of the carbon atoms and most of the functionality of olivin (**3**). The requisite β-methoxy enone **33** was prepared as shown in Scheme IV.

Ester **28**,[22] synthesized in two steps from methyl crotonate, was combined with the carbanion derived from dithiane **27** to afford crystalline ketone **29** in 52% yield.[23] Reduction of **29** with ethanolic sodium borohydride produced a 70:30 mixture of epimeric alcohols **30** (98%). Since this new chiral center is of no importance to the synthesis, no attempt was made to effect a stereoselective carbonyl reduction.

Lithium/ammonia reduction of **30** served to both reductively cleave the dithiane group and reduce the aromatic ring, affording bis-enol ether **31**. Although the dithiane reduction is not specifically precedented, it is well-known that various benzylic oxygen substituents are reductively removed during Birch reductions.[24] Immediate hydrolysis of the air-sensitive bis-enol ether with aqueous HCl in glyme gave the corresponding diketone, which without characterization was methylated with diazomethane,[18b] yielding β-methoxy enone **32** as an inseparable, complex mixture of stereoisomers as evidenced by ^{13}C NMR. It was not possible to establish the ratios of the various stereoisomers by ^1H NMR. Protection of the alcohol function of **32** as its *tert*-butyldimethylsilyl ether was done by the standard method, giving **33**.[25] Condensation of β-methoxy enone **33** with orsellinate **14** by using 1 equiv of LDA at −78 °C gave tricyclic ketone **34** as a mixture of stereoisomers in even better yield (75%) than was obtained in the simpler model reactions described above.



In this work we have demonstrated that the condensation of toluate carbanions with β-alkoxycyclohexenones provides an efficient route to the olivin (**3**) and chromomycinone (**4**) ring systems. Considerable progress has been made to date in our laboratories in applying this methodology to total synthesis of the aureolic acid aglycons, and this work will be the subject of future publications.

Experimental Section

Melting points were taken on a Thomas-Hoover Uni-melt capillary melting point apparatus equipped with a calibrated therometer. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 197 spectrophotometer. Proton magnetic resonance spectra (60 MHz) were recorded on either a Varian A60-A or an EM-360 NMR spectrometer. ^1H NMR (200 MHz) spectra were obtained on a Bruker WP 200 Fourier transform spectrometer and at 360 MHz on a Bruker WM 360 spectrometer. Chemical shifts are reported in δ units with tetramethylsilane as an internal standard. Unless otherwise indicated, spectra were recorded at 60 MHz. Carbon-13 nuclear magnetic resonance spectra were obtained on a Varian CFT-20 NMR spectrometer with a 10-mm probe for samples larger than 60 mg and a microprobe for sample sizes from 10 to 20 mg. Mass spectra were routinely recorded at 70 eV by electron impact on an Associated Electrical Industries, Ltd., MS-902 double-focusing mass spectrometer. Combustion analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL.

Anhydrous tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide. Diisopropylamine was distilled from calcium hydride and stored over 4-Å molecular sieves. Glyme was distilled from $LiAlH_4$.

Analytical and preparative thin-layer chromatography were done on silica gel 60 PF-254 (E. M. Merck) or aluminum oxide PF-254 Type T (E. M. Merck). Visualization was effected by basic aqueous permanganate spray. Liquid column chromatography was carried out by using 70–230-mesh silica gel 60 (E. M. Merck) or 80–200-mesh basic alumina (Brockman Activity I, Fisher) as the stationary phase. Flash chromatography was performed as described[26] by using silica gel 60 H (E. M. Merck).

3,3-Dimethyl-3,4-dihydro-9-hydroxy-6,8-dimethoxy-1-(2*H*)-anthracenone (17). A solution of 0.60 mL of diisopropylamine (4.4 mmol) and 2.6 mL of *n*-butyllithium (1.6 M in hexane, 4.2 mmol) in dry THF (5 mL) was stirred under a nitrogen atmosphere at −20 °C for 20 min, and was cooled to −78 °C. A solution of ester **14** (0.252 g, 1.2 mmol)[17] in dry THF (3 mL) was added, and the mixture was allowed to stir for 10 min. β-Ethoxy enone **15** (0.201 g, 1.20 mmol) dissolved in dry THF (5 mL) was added over a 5-min period. The solution was allowed to warm slowly to room temperature and was stirred for 10 min. The reaction mixture was diluted with 5% HCl and diethyl ether. The organic phase was washed twice with water and dried with anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (50 g) with chloroform as the eluant to afford 0.232 g (64%) of the tricyclic ketone **17**: mp 157–159 °C; ^1H NMR ($CDCl_3$) 15.45 (s, 1 H), 6.79 (s, 1 H), 6.54 (d, 1 H, J = 2.0 Hz), 6.42 (d, 1 H, J = 2.0 Hz), 3.96 (s, 3 H), 3.88 (s, 3 H), 2.76 (s, 2 H), 2.52 (s, 2 H), 1.05 (s, 6 H); ^{13}C NMR ($CDCl_3$) 203.49 (s), 165.59 (s), 161.96 (s), 161.19 (s), 141.93 (s), 138.54 (s), 116.49 (d), 110.26 (s), 109.72 (s), 98.81 (d), 97.68 (d), 56.00 (q), 55.28 (q), 51.83 (t), 43.66 (t), 32.73 (s), 27.92 (q);

(22) Miyamoto, M.; Morita, K.; Kawamatsu, Y.; Kawashima, K.; Nakanishi; K. *Tetrahedron* **1967**, *23*, 411.
(23) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357.
(24) Pinder, A. R.; Smith, H. *J. Chem. Soc.* **1954**, 113. Birch, A. J.; Subba Rao, G. S. R. *Aust. J. Chem.* **1970**, *23*, 1641.
(25) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

IR ($CHCl_3$) 3025, 2965, 1620 cm^{-1}; mass spectrum, *m/e* 300 (B, M^+), 285 ($M^+ - CH_3$), 244 ($M^+ - C_4H_8$).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.95; H, 6.77.

3,3,7-Trimethyl-3,4-dihydro-9-hydroxy-6,8-dimethoxy-1-(2*H*)-anthracenone (23). A solution of 0.4 mL of diisopropylamine (2.9 mmol) and 2.0 mL of *n*-butyllithium (1.4 M in hexane, 2.8 mmol) in dry THF (20 mL) was stirred under a nitrogen atmosphere at −20 °C for 20 min and cooled to −78 °C. A solution of ester **22** (0.60 g, 2.5 mmol)[20] in dry THF (2 mL) was added, and the mixture was allowed to stir for 10 min. β-Ethoxy enone **15** (0.47 g, 2.8 mmol) dissolved in dry THF (2 mL) was added over a 5-min period. The solution was allowed to warm slowly to room temperature and was then stirred for 10 min. The reaction mixture was then diluted with 5% HCl and diethyl ether. The organic phase was washed twice with water and dried with anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was allowed to crystallize overnight. The resulting 173 mg of crystalline product was washed with diethyl ether and collected by filtration. The mother liquor was concentrated and chilled to yield an additional 80 mg of tricyclic **23**: total yield 253 mg (32%); mp 197–199 °C; ^1H NMR ($CDCl_3$) 14.92 (s, 1 H), 6.73 (s, 1 H), 6.62 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.71 (s, 2 H), 2.50 (s, 2 H), 2.21 (s, 3 H), 1.02 (s, 6 H); IR ($CHCl_3$) 2950, 1610, 1517 cm^{-1}.

The following compounds were prepared by using the procedure outlined in the above two experiments. All compounds were initially purified by flash chromatography on silica gel[27] with 20% ethyl acetate/CCl_4.

18: 57% yield; recrystallized from methylene chloride/hexane, mp 155–156 °C; ^1H NMR ($CDCl_3$, 360 MHz) 15.43 (s, 1 H), 6.83 (s, 1 H), 6.55 (d, 1 H, J = 2.1 Hz), 6.42 (d, 1 H, J = 2.1 Hz), 3.99 (s, 3 H), 3.91 (s, 3 H), 2.98 (m, 1 H), 2.84 (ddd, 1 H, J = 1.89, 3.58, 16.8 Hz), 2.69 (ddd, 1 H, J = 1.89, 10.52, 15.71 Hz), 2.62 (dd, 1 H, J = 10.98, 17.09 Hz), 2.36 (m, 1 H), 1.13 (d, 3 H, J = 6.4 Hz); IR (KBr) 3025, 2950, 1610 cm^{-1}; mass spectrum, *m/e* (relative intensity) 287 ($M^+ + 1$, 17.9), 286 (M^+, 100), 271 ($M^+ - CH_3$, 1.2), 257 (14.7), 244 (20.6), 299 (10.4), 226 (25.3).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.49; H, 6.44.

21: 50% yield; recrystallized from methylene chloride/hexane, mp 97–98 °C (lit.[19] mp 98–99 °C); ^1H NMR ($CDCl_3$, 360 MHz) 9.80 (s, 1 H), 6.97 (br d, 1 H, J = 0.81 Hz), 6.60 (d, 1 H, J = 2.3 Hz), 6.42 (d, 1 H, J = 2.3 Hz), 4.02 (s, 3 H), 3.88 (s, 3 H), 2.62 (s, 3 H), 2.36 (d, 3 H, J = 0.81 Hz); IR (KBr) 3350, 3010, 2925, 1630 cm^{-1}; mass spectrum, *m/e* (relative intensity) 261 ($M^+ + 1$, 8.1), 260 (M^+, 49.9), 245 ($M^+ - CH_3$, 100), 230 ($M^+ - 2CH_3$, 31).

24: 36% yield; recrystallized from methylene chloride/hexane, mp 160–162 °C; ^1H NMR (360 MHz) 14.97 (s, 1 H), 6.88 (s, 1 H), 6.78 (s, 1 H), 3.94 (s, 3 H), 3.86 (s, 3 H), 2.98 (m, 1 H), 2.78 (ddd, 1 H, J = 1.95, 3.66, 16.93 Hz), 2.65 (dd, 1 H, J = 10.67, 15.5 Hz), 2.42 (dd, 1 H, J = 11.28, 16.78 Hz), 2.31 (m, 1 H), 2.26 (s, 3 H), 1.15 (d, 2 H, J = 6.1 Hz); IR (KBr) 3050, 2975, 1610 cm^{-1}; mass spectrum, *m/e* (relative intensity) 301 ($M^+ + 1$, 2), 300 (M^+, 10), 285 ($M^+ - CH_3$, 6.2), 240 (8.2), 84 (59), 49 (100).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.73; H, 6.73.

26: 55% yield (oil); ^1H NMR ($CDCl_3$, 360 MHz) 15.08 (s, 1 H), 6.86 (d, 1 H, J = 2.13 Hz), 6.85 (s, 1 H), 6.76 (s, 1 H, J = 2.2 Hz), 5.36 (s, 3 H), 5.27 (s, 3 H), 3.60 (s, 3 H), 3.51 (s, 3 H), 2.78 (s, 2 H), 2.55 (s, 2 H), 1.07 (s, 6 H); IR (film) 3025, 2960, 1615 cm^{-1}; mass spectrum, *m/e* (relative intensity) 361 ($M^+ + 1$, 3.1), 360 (M^+, 14.9) 328 (11.4), 298 (4.5).

Preparation of Methoxymethyl-Protected Orsellinate 25. To a solution of methyl orsellinate[17] (1.00 g, 5.48 mmol) in 25 mL of diisopropylethylamine was added chloromethyl methyl ether (1.54 g, 18.2 mmol) at 0 °C. The mixture was warmed to room temperature, stirred for 8 h, and evaporated to dryness in vacuo. The residue was dissolved in methylene chloride, and the solution was washed with 5% HCl, followed by brine. The organic extract was dried ($MgSO_4$) and evaporated in vacuo. The crude product was chromatographed on 20 g of silica gel, eluting with 15% ethyl acetate/hexane to give 1.40 g (93%) of **25** as a colorless oil: ^1H NMR ($CDCl_3$) 6.45 (br d, 2 H, J = 2 Hz), 6.55 (br d, 2 H, J = 2 Hz), 5.1 (s, 4 H), 3.8 (s, 3 H), 3.4 (s, 3 H), 2.25 (s, 3 H); IR (film) 2950, 1730, 1600 cm^{-1}; mass spectrum, *m/e* (relative intensity) 271 ($M^+ + 1$, 0.7), 270 (M^+, 17.1), 239 (17.5), 193 (39.2), 120 (6.2), 45 (100).

2-(3,5-Dimethoxyphenyl)-*m*-dithiane (27). To a magnetically stirred solution of 0.90 g (5.4 mmol) of 3,5-dimethoxybenzaldehyde in chloroform (5 mL) was added 0.55 mL (5.5 mmol) of 1,3-propanedithiol. Anhydrous hydrogen chloride was bubbled through the solution for 5 min, and the solution was allowed to stand for 30 min. The mixture was diluted with chloroform (10 mL) and water (15 mL), the layers were separated, and the organic phase was washed successively with 5% sodium hydroxide (2 × 15 mL) and water (10 mL). The solution was dried with anhydrous sodium sulfate, and the solvent was removed in vacuo to yield 1.35 g of crystalline product which was recrystallized from methanol to give 1.08 g (78%) of colorless dithiane **27**: mp 94–95 °C; ^1H NMR ($CDCl_3$) 6.63 (d, 2 H, J = 2.2 Hz), 6.37 (t, 1 H, J = 2.2 Hz), 5.08 (s, 1 H), 3.76 (s, 6 H), 2.8–3.2 (m, 4 H), 1.8–2.3 (m, 2 H); IR (CCl_4) 2900, 1600 cm^{-1}; mass spectrum, *m/e* 256 (B, M^+), 182 ($M^+ - C_3H_6S$).

Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.25; H, 6.29. Found: C, 56.67; H, 6.29.

Preparation of Ester (28). To a magnetically stirred solution of 100 g (1.0 mol) of methyl crotonate in 160 mL of *tert*-butyl alcohol, 160 mL of water, and 100 mL of 30% hydrogen peroxide was added over a 2-h period approximately 20 mg of osmium tetraoxide dissolved in 20 mL of *tert*-butyl alcohol. The reaction temperature was maintained at 25–30 °C with an ice bath. After heat evolution had ceased, the reaction mixture was allowed to stir at room temperature for 6 h. To the resulting green-black mixture was added 8 mL of 30% hydrogen peroxide, and the mixture was stirred overnight. Saturated sodium bisulfite solution was added *until a negative peroxide test was obtained.* The mixture was evaporated to dryness in vacuo, and the green residual oil was distilled at reduced pressure (90 °C, 0.08 torr), affording 58.2 g (47%) of diol: ^1H NMR ($CDCl_3$) 3.8–4.3 (m, 2 H), 3.80 (s, 3 H), 3.71 (s, 2 H, OH), 1.26 (d, 3 H, J = 6.2 Hz); IR (film) 3450, 2990, 2960, 1740 cm^{-1}.

A mixture of 27.23 g (0.203 mol) of the above diol, 1 g of *p*-toluenesulfonic acid, 30 g (0.19 mol) of anhydrous copper sulfate, 22 g (0.25 mol) of cyclohexanone, and 150 mL of dry methylene chloride was stirred for 24 h at room temperature. An additional 10 g (0.062 mol) of anhydrous copper sulfate was added, and the mixture was stirred for 20 h longer. The mixture was filtered, and the filtrate was evaporated in vacuo. The remaining oil was distilled under reduced pressure to give unreacted cyclohexanone (25 °C, 0.1 torr), followed by ketal **28** (85 °C, 0.14 torr): 38.72 g (89%); ^1H NMR ($CDCl_3$) 3.8–4.3 (m, 2 H), 3.76 (s, 3 H), 1.5–1.8 (m, 10 H), 1.41 (d, 3 H, J = 5.8 Hz); IR (film) 2940, 1765, 1740, 1130 cm^{-1}.

2-(3,5-Dimethoxyphenyl)-*m*-dithian-2-yl *trans*-3-Methyl-1,4-dioxaspiro[4.5]dec-2-yl Ketone (29). A magnetically stirred solution of 13.65 g (53.3 mmol) of dithiane **27** in THF (100 mL) was cooled to −20 °C under a nitrogen atmosphere, and 40.0 mL of *n*-butyllithium (1.6 M in hexane, 64.0 mmol) was added. The solution was stirred at −20 °C for 20 min and cooled to −78 °C. A solution of 34.0 g (158.8 mmol) of ester **28** in THF (50 mL) was cooled to −78 °C in a dry ice/acetone-jacketed addition funnel and was added quickly to the lithiated dithiane solution. The resulting solution was stirred for 1.5 h at −78 °C and quenched with water (40 mL), and the mixture was diluted with diethyl ether (100 mL) and water (100 mL). The organic phase was washed with water (2 × 100 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo to give a colorless oil, which was carefully distilled (85 °C, 0.14 torr) to afford unreacted ester **28** (20.3 g). The residue was chromatographed on silica gel (900 g) with $CHCl_3$ as the eluant, giving ketone **29** (12.3 g, 52%). An analytical sample of **29** was recrystallized from hexane: mp 110–113 °C; ^1H NMR ($CDCl_3$) 6.79 (d, 2 H, J = 2.2 Hz), 6.51 (t, 1 H, J = 2.2 Hz), 3.9–4.5 (m, 2 H), 3.82 (s, 6 H), 2.6–3.0 (m, 4 H), 1.8–2.2 (m, 2 H), 1.3–1.8 (m, 10 H), 1.08 (d, 3 H, J = 5.5 Hz); IR (film) 2940, 2860, 1715, 1600 cm^{-1}; mass spectrum, *m/e* 438 (M^+), 255 (B, $M^+ - C_{10}H_{15}O_3$).

Anal. Calcd for $C_{22}H_{30}O_5S_2$: C, 60.24; H, 6.89. Found: C, 60.24; H, 6.89.

(2*R,3*R**)-α-[2-(3,5-Dimethoxyphenyl)-*m*-dithian-2-yl]-3-methyl-1,4-dioxaspiro[4.5]decane-2-methanol (30).** To a magnetically stirred solution of 10.9 g (24.9 mmol) of dithiane ketone **29** in absolute ethanol (125 mL) was added 3.8 g (100

mmol) of $NaBH_4$. The solution was stirred for 10 h and was carefully diluted with saturated ammonium chloride solution (20 mL). The mixture was evaporated in vacuo until most of the ethanol was removed, and the residue was diluted with diethyl ether (100 mL) and water (100 mL). The organic phase was washed with water (2 × 50 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to yield 10.7 g (98%) of a colorless 70:30 mixture of diastereomeric alcohols **30** of sufficient purity for the next step: ^1H NMR (200 MHz, $CDCl_3$) 7.241, 7.236 (d's, 2 H, J's = 2.21 Hz), 6.415 (t, 1 H, J = 2.21 Hz), 3.813 (s, 6 H), 3.7–4.2 (m, 3 H), 3.003 (d, 1 H, J = 11.03 Hz, OH), 2.6–3.0 (m, 4 H), 1.8–2.2 (m, 2 H), 1.4–1.7 (m, 10 H), 1.298, 1.145 (d's, 3 H, J's = 6.07 Hz); IR (film) 3520, 2950, 2870, 1600 cm^{-1}; mass spectrum, m/e 440 (M^+), 397 ($M^+ - C_2H_3O$), 255 (B, $M^+ - 185$).

(2*R,3*R**)-α-[(3,5-Dimethoxy-2,5-cyclohexadien-1-yl)-methyl]-3-methyl-1,4-dioxaspiro[4.5]decane-2-methanol (31).** A three-necked, 250-mL, round-bottomed flask equipped with a dry ice/acetone condenser, anhydrous ammonia inlet, glass stopper, and a glass-coated magnetic stirring bar was flushed with nitrogen and charged with 2.50 g (5.68 mmol) of dithiane alcohols **30** dissolved in diethyl ether (5 mL) and ethanol (5 mL). Stirring was begun, and about 150 mL of liquid ammonia was condensed into the flask. Lithium shot was added slowly to the solution until a blue color persisted and was then added as necessary to maintain the blue color for 1 h. The ammonia was allowed to evaporate, and the residue was diluted with diethyl ether (100 mL) and water (100 mL). [**Caution**: the entire extractive workup must be done in a fume hood since 1,3-propanedithiol is a product of the reaction.] The organic phase was washed with 5% sodium hydroxide (2 × 30 mL) and water (2 × 30 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to afford dienol ether **31** as a colorless oil which was used directly in the next step: ^1H NMR ($CDCl_3$) 4.71 (m, 1 H), 4.58 (m, 1 H), 3.54 (s, 6 H), 2.9–4.3 (m, 5 H), 2.76 (d, 2 H, J = 6.2 Hz), 1.3–2.4 (m, 12 H), 1.28 (d, 3 H, J = 5.8 Hz); IR (film) 3480, 2940, 2860, 1695, 1660, 1150 cm^{-1}; mass spectrum, m/e 338 (M^+), 295 ($M^+ - C_2H_3O$), 183 (B, $M^+ - C_9H_{15}O_2$).

5-[2-Hydroxy-2-[(2*R,3*R**)-3-methyl-1,4-dioxaspiro[4.5]-dec-2-yl]ethyl]-3-methoxy-2-cyclohexen-1-one (32).** The dienol ether **31** obtained in the above experiment was dissolved in glyme (which had been purged of oxygen by bubbling nitrogen through it for 30 min) and stirred under a nitrogen atmosphere. A 3.6% solution of hydrochloric acid (20 mL, which was purged of oxygen in the same manner) was added, and the mixture was stirred at room temperature for 50 min. The reaction mixture was diluted with dichloromethane (100 mL) and brine (50 mL). The aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic fractions were dried with Na_2SO_4. The solvent was removed in vacuo to afford the β-diketone as a colorless oil.

This material was treated with 50 mL of ethanolic etheral diazomethane solution (~0.45 M, 22 mmol). The solution was allowed to partially evaporate at room temperature in a fume hood and the remaining solvent was removed in vacuo. The residue was chromatographed on silica gel (75 g) with ethyl acetate as the eluant to afford 1.05 g (57% based on dithiane alcohols **30** of inseparable oily β-methoxy enone **32** stereoisomers: ^1H NMR ($CDCl_3$, 60 MHz) 5.39 (s, 1 H), 3.71 (s, 3 H), 3.2–4.2 (m, 3 H), 1.9–2.8 (m, 6 H), 1.4–1.7 (m, 12 H), 1.29 (d, 3 H, J = 5.8 Hz); IR (film) 3430, 2940, 1650, 1605 cm^{-1}; mass spectrum, m/e 324 (M^+), 281 ($M^+ - C_2H_3O$), 125 (B, $M^+ - C_{11}H_{19}O_3$).

5-[2-(*tert*-Butyldimethylsiloxy)-2-[(2*R,3*S**)-3-methyl-1,4-dioxaspiro[4.5]dec-2-yl]ethyl]-3-methoxy-2-cyclohexen-1-one (33).** To a solution of 97.5 mg (0.657 mmol) of *tert*-butyldimethylsilyl chloride and 88 mg (1.31 mmol) of imidazole in 1.0 mL of dry DMF was added 70.0 mg (0.216 mmol) of enone alcohol **32**. The solution was allowed to stand at room temperature for 20 h. Diethyl ether (5 mL) was added to the solution, causing imidazole to precipitate. The reaction mixture was filtered, and the filtrate was concentrated to approximately a 2-mL volume. This solution was placed directly on a 20 cm × 20 cm × 1 mm silica gel preparative thin-layer chromatography plate. The plate was eluted with ethyl acetate, affording 85.4 mg (90%) of enone silyl ether **33**: ^1H NMR ($CDCl_3$, 60 MHz) 5.45 (s, 1 H), 3.5–4.2 (m, 3 H), 3.74 (s, 3 H), 2.1–2.5 (m, 4 H), 1.4–1.8 (m, 13 H), 1.33, 1.30 (d's, 3 H, J's = 6.0 Hz), 0.90 (s, 9 H), 0.10 (s, 6 H); IR (film) 2950, 2870, 1665, 1620, 1225 cm^{-1}; mass spectrum, m/e 438 (M^+), 423 ($M^+ - CH_3$), 395 ($M^+ - C_2H_3O$), 381 ($M^+ - C_4H_9$), 283 (B, $M^+ - C_9H_{15}O_2$).

3-[2-(*tert*-Butyldimethylsiloxy)-2-[(2*R,3*S**)-3-methyl-1,4-dioxaspiro[4.5]dec-2-yl]ethyl]-3,4-dihydro-9-hydroxy-6,8-dimethoxy-1(2*H*)-anthracenone (34).** To a magnetically stirred solution of 148 mg (0.705 mmol) of methyl 4,6-dimethoxy-*o*-toluenecarboxylate (**14**) and THF (3 mL), cooled to −78 °C under a nitrogen atmosphere, was added 0.87 mL of lithium diisopropylamide solution (0.81 M in THF, 0.71 mmol). The solution was stirred for 15 min, during which time a deep orange color developed. To this orsellinate anion solution was added 277 mg (0.633 mmol) of β-methoxy enone **33** dissolved in THF (1 mL). The reaction mixture was stirred for 4 min at −78 °C and was then warmed to room temperature. After the solution was stirred for 10 min at room temperature, 25 mL of 5% hydrochloric acid was added, and the reaction mixture was extracted with 30 mL of diethyl ether. The organic phase was washed with water (2 × 30 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was chromatographed on 50 g of Florisil with $CHCl_3$ as the eluant to yield 278 mg (75% based on β-methoxy enone **33**) of the tricyclic **34**: ^1H NMR ($CDCl_3$, 60 MHz) 15.26 (s, 1 H), 6.77 (s, 1 H), 6.49 (d, 1 H, J = 2.2 Hz), 6.36 (d, 1 H, J = 2.2 Hz), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.3–3.9 (m, 3 H), 2.2–3.0 (m, 4 H), 1.4–1.9 (m, 13 H), 1.30 (d, 3 H, J = 5.8 Hz), 0.87 (s, 9 H), 0.09 (s, 6 H); IR (film) 2935, 2855, 1625, 1610, 1585 cm^{-1}; mass spectrum, m/e 584 (B, M^+), 569 ($M^+ - CH_3$), 541 ($M^+ - C_2H_3O$), 527 ($M^+ - C_4H_9$), 429 ($M^+ - C_9H_{15}O_2$).

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