108.4, 60.2, 39.8, 38.0, 14.2; IR (neat) 3080, 1719, 1672 cm^{-1}.

Ethyl 5-Methylene-2-oxocyclohexane-1-carboxylate (65). A solution of 54.2 mg (0.250 mmol) of **41** in 2 mL of HOAc was stirred with 0.1665 g (2.55 mmol) of zinc dust for 4.5 h under nitrogen at room temperature. Excess zinc was removed by filtration, and the residue was washed with CH_2Cl_2. Water (50 mL) was added to the filtrate, the organic layer was removed, and the aqueous layer was extracted twice with 20-mL portions of CH_2Cl_2. The organic layers were combined, neutralized with 25 mL of saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure to give 43.5 mg (95.4%) of **65**[19] as a 4:1 mixture of enol and keto forms, respectively.

Data for the enol form of **65**: ^1H NMR δ 12.21 (s, 1), 4.85 (d, 1, J = 1.3), 4.80 (d, 1, J = 1.3), 4.23 (q, 2, J = 7.1), 2.97 (br d, 2, J = 1.3), 2.44–2.33 (m, 4), 1.32 (t, 3, J = 7.1); ^{13}C NMR δ 172.2, 171.5, 143.3, 109.5, 96.8, 60.3, 30.8, 30.4 (2), 14.3; IR (neat) 3074 (w), 1747 (m), 1720 (m), 1656 (s), 1619 (s) cm^{-1}.

Acknowledgment. We thank the National Institutes of Health (Grant GM-30528) for generous financial support and Dr. Steven A. Kates for carrying out preliminary experiments.

Registry No. **1**, 30414-57-4; **2**, 59529-68-9; **3**, 117369-82-1; **4**, 117369-83-2; **5**, 117369-84-3; **6**, 117369-85-4; **7**, 117369-86-5; **8**, 117369-87-6; **9**, 117369-88-7; **10**, 88681-86-1; **11**, 117369-89-8; **12**, 117369-90-1; **13**, 117369-91-2; **14**, 56028-92-3; **15**, 13163-77-4; **16**, 119-36-8; **17**, 22717-57-3; **17** (ethyl ester), 34265-58-2; **18**, 4670-56-8; **19**, 23287-26-5; **20**, 5628-60-4; **21**, 117369-92-3; **22**, 117369-93-4; **23**, 17504-13-1; **24**, 117369-94-5; **25**, 4906-69-8; **26**, 4068-78-4; **27**, 54815-88-2; **28**, 59604-96-5; **29**, 117-99-7; **40** (isomer 1), 117369-98-9; **40** (isomer 2), 117370-14-6; **41**, 117369-99-0; **45**, 117370-00-0; **46**, 117370-01-1; **47**, 117370-02-2; **51a**, 117369-96-7; **51b**, 62343-95-7; **53a**, 117370-03-3; **53b**, 117370-06-6; **55**, 117370-04-4; **56a**, 117370-05-5; **56b**, 117370-08-8; **58a**, 46174-31-6; **59**, 117370-07-7; **60**, 117369-97-8; **61** (isomer 1), 117370-09-9; **61** (isomer 2), 117370-10-2; **63** (isomer 1), 117370-11-3; **63** (isomer 2), 117370-12-4; **64**, 117370-13-5; **65**, 50635-46-6; $H_2C{=}CHCH_2Br$, 106-95-6; $H_2C{=}C(CH_3)CH_2Br$, 3017-69-4; (E)-$H_3CCH{=}C(CH_3)CH_2Br$, 57253-30-2; $H_2C{=}C(Ph)CH_2Br$, 3360-53-0; $H_2C{=}C(Cl)CH_2Br$, 4860-96-2; 1-bromomethylcyclohexene, 37677-17-1; methyl acetoacetate, 105-45-3; methyl 3-oxopentanoate, 30414-53-0; methyl chloroacetoacetate, 4755-81-1; methyl 4-phenyl-3-oxobutanoate, 37779-49-0; 1-phenylpentane-2,4-dione, 3318-61-4; 4-methyl-5-hexen-2-one, 61675-14-7; 4-phenyl-5-hexen-2-one, 50552-30-2; 1-acetyl-2-vinylcyclohexane, 117369-95-6; acrolein, 107-02-8; methacrolein, 78-85-3.

Supplementary Material Available: Experimental procedures and spectroscopic data for all compounds not described in the Experimental Section (8 pages). Ordering information is given on any current masthead page.

A Concise Synthesis of *d,l*-Methylenomycin A and *d,l-epi*-Methylenomycin A

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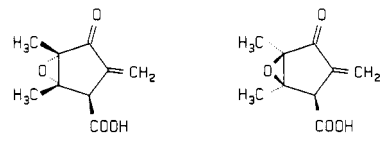
Received May 12, 1988

A cationic cyclopentaannelation reaction that was developed in our laboratories has been applied to the synthesis of *d,l*-methylenomycin A, a fungal metabolite that has been isolated from a strain of *Streptomyces violaceoruber*. The efficiency of the key reaction makes a very short total synthesis possible. A synthesis of *d,l-epi*-methylenomycin A has also been accomplished.

The synthesis of cyclopentanoids continues to be the focus of much research.[2] The isolation and structure elucidation of unusual cyclopentanoid natural products and the continuing interest in polyquinane chemistry accounts for this research activity. The family of methylenomycin antibiotics were isolated by Haneishi and coworkers from a *Streptomyces* strain.[3] Methylenomycin A is effective against Lewis lung carcinoma in mice.[4] Methylenomycin A and methylenomycin B are active against Gram-positive and Gram-negative bacteria and are cytotoxic in the KB assay.[3,5] The unprecedented structure of these fungal metabolites led to a flurry of synthetic activity that culminated in several successful total syntheses.[6] A cationic cyclopentaannelation reaction that was discovered in our laboratories offers an extremely straightforward and direct entry to these compounds.[7] We have reported the synthesis of some of the simpler members of this class of compounds, methylenomycin B, *d,l*-desepoxy-4,5-didehydromethylenomycin A, and *d,l*-desdihydroxy-4,5-didehydroxanthocidin.[8] We now report the total synthesis of *d,l*-methylenomycin A (**1**) and *d,l-epi*-methylenomycin A (**2**).



1 2

The retrosynthesis for **1** and **2** leads to tertiary alcohol **4** via *d,l*-desepoxy-4,5-didehydromethylenomycin A (**3**).

(1) Fellow of the Alfred P. Sloan Foundation, 1987–1989.

(2) This area has been reviewed extensively: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1–20. Ramaiah, M. *Synthesis* **1984**, 529–570. Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876. Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442.

(3) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386–392. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *Ibid.* **1974**, *27*, 393–399.

(4) Terahara, A.; Haneishi, T.; Arai, M. *Heterocycles* **1979**, *13*, 353–371.

(5) Tius, M. A.; Patterson, G. M.; Astrab, D. P. *J. Antibiot.* **1985**, *38*, 1061–1067.

(6) Total syntheses of methylenomycin A: (a) Jernow, J.; Tautz, W.; Rosen, P.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 4210–4212. (b) Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3904–3913. (c) Takahashi, Y.; Isobe, K.; Hagiwara, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1981**, 714–715.

(7) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1984**, *25*, 1539–1542.

(8) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438–3442.

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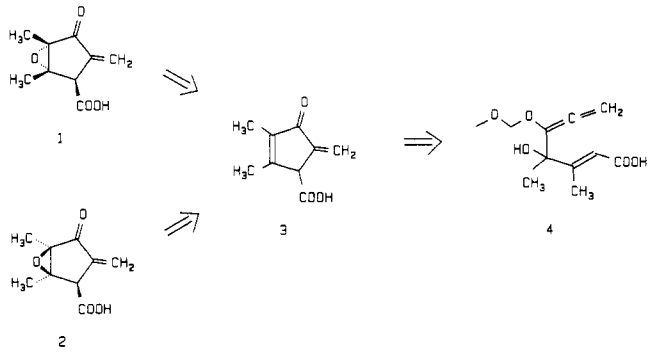
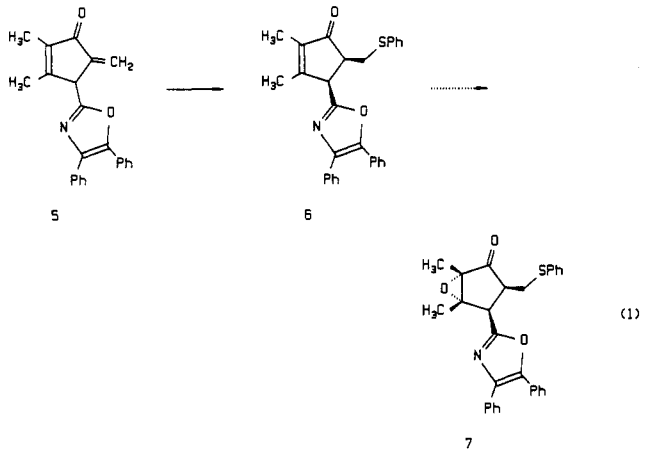
Since the electron-withdrawing carboxy group in **4** was expected to retard the cationic cyclization reaction,[8] a carboxylic acid equivalent was used instead. The 4,5-

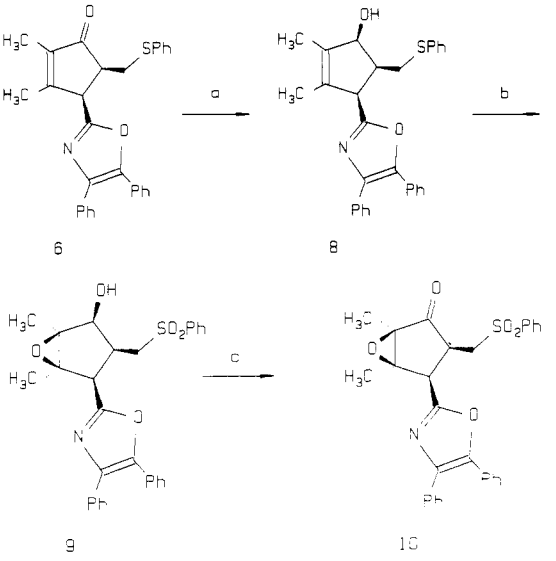


diphenyloxazole group that has been developed by Wasserman as a photoremovable carboxy group equivalent[9] was an attractive candidate, since it was known[8] to tolerate the cyclization conditions. Cyclopentenone **5**[8] (eq 1) appeared to be an attractive precursor to both **1** and **2**. The introduction of the epoxy group into **5** requires the protection of the reactive *exo*-methylene group. The treatment of **5** with a small excess of thiophenol in the presence of triethylamine in tetrahydrofuran (THF) at 0 °C provided enone **6** in 90% yield (eq 1). The large diphenyloxazole



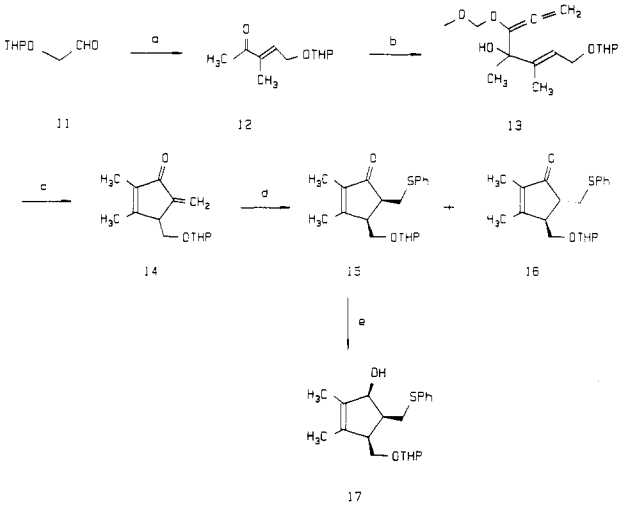
group was expected to direct the epoxidation from the opposite face of the ring. In the event, exposure of **6** to hydrogen peroxide or *tert*-butyl hydroperoxide and base under a variety of conditions failed to produce detectable quantities of epoxy ketone **7**. The complex nature of the reaction mixture suggested that an alternative approach be followed. Enone **6** was reduced stereospecifically to alcohol **8** in over 90% yield with diisobutylaluminum hydride (DIBAL–*n*-butyllithium "ate" complex (Scheme I).[10] The epoxidation of the allylic alcohol with an excess of *m*-chloroperoxybenzoic acid in dichloromethane at 0 °C was straightforward and led to epoxy sulfone **9**. Further oxidation of **8** with Jones reagent in acetone produced epoxy ketone **10** in 60% yield. The conversion of **9** to *d,l-epi*-methylenomycin A requires that the diphenyloxazole group be unmasked and that elimination of the phenyl sulfone take place. Exposure of **10** to singlet oxygen in dichloromethane followed by treatment with aqueous potassium carbonate gave a complex mixture of products.[9]

Scheme I[a]



[a] (a) 1.1 equiv of (*n*-Bu)(*i*-Bu)$_2$AlHLi, THF, −78 °C, 90%; (b) 4 equiv *m*-CPBA, CH_2Cl_2, 0 °C, 75%; (c) Jones reagent, acetone, 0 °C, 60%.

Scheme II[a]



[a] (a) 1.2 equiv of $(EtO)_2POCH(CH_3)COCH_3$, 1.2 equiv of LDA, −78 to 0 °C, 60–65%; (b) 4.0 equiv of α-lithio-α-(methoxymethoxy)allene, THF/ether (1/1), −78 °C, 75%; (c) 5.0 equiv of $(CF_3CO)_2O$, 6.0 equiv of 2,6-lutidine, CH_2Cl_2, −20 °C, 75%; (d) 1.1 equiv of PhSH, 1.5 equiv of Et_3N, THF, 0 °C, 85%; (e) 1.2 equiv of (*n*-Bu)(*i*-Bu)$_2$AlHLi, THF, −78 °C, 85–90%.

The 4,5-diphenyloxazole group that had served so well as a masked carboxylic acid equivalent in our synthesis of the desepoxy[8] series appeared to be incompatible with the new reaction sequence. The 4,5-diphenyloxazole group was substituted for a more robust and servicable carboxylic acid equivalent.

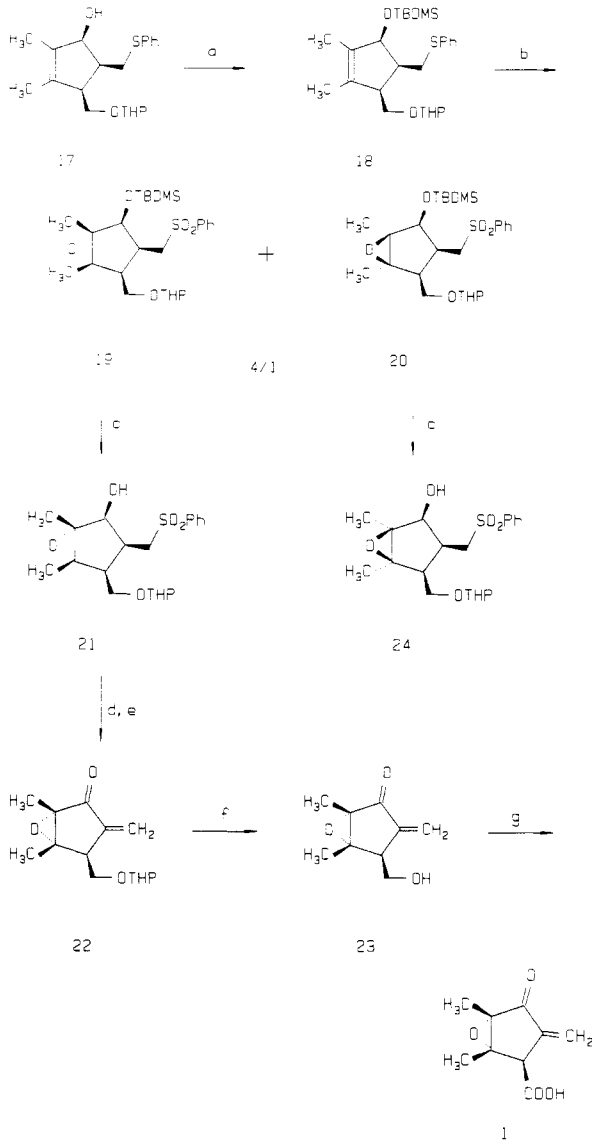
The ozonolysis of allyl tetrahydropyranyl ether produced aldehyde **11**, which was converted to enone **12** in 60–65% yield by treatment with the lithio anion of diethyl 2-oxo-1-methylpropylphosphonate in THF as a single geometrical isomer (Scheme II). The addition of α-lithio-α-(methoxymethoxy)allene[11] to **12** at −78 °C produced **13** in 75% yield. Treatment of a dichloromethane solution of **13** with

(9) Wasserman, H. H.; Gambale, R. J.; *J. Am. Chem. Soc.* **1985**, *107*, 1423–1424. For a review, see: Wasserman, H. H.; Lipshutz, B. H. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; Chapter 9.

(10) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717–1724.

(11) (a) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chem. Pays-Bas* **1968**, *87*, 916–924. (b) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746–7747. (c) Reich, H. J.; Kelly, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 1119–1120.

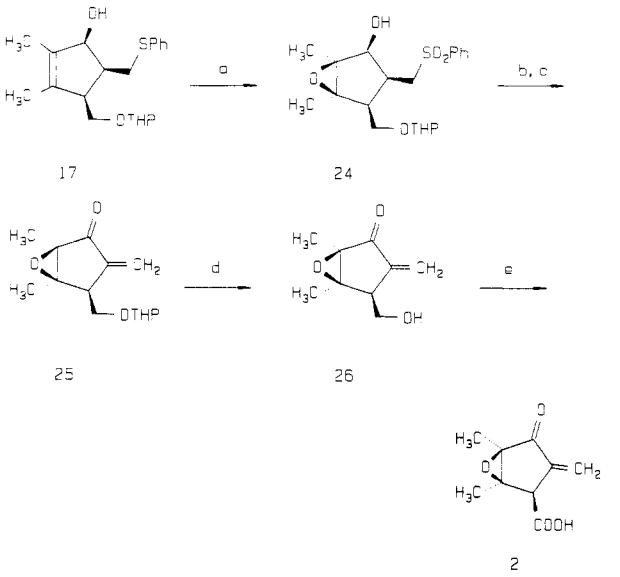
Scheme III[a]



[a] (a) 3 equiv of *tert*-butyldimethylsilyl chloride, 6 equiv of imidazole, DMF, 25 °C, 85%; (b) 5 equiv of *m*-CPBA, CH_2Cl_2, 0 °C, 80%; (c) 2 equiv of *n*-Bu_4NF, THF, 25 °C, 85%; (d) Swern oxidation; (e) 2 equiv of DBU, THF, 25 °C, 85% for two steps; (f) 3% aqueous HCl, THF, 25 °C, 80%; (g) Jones reagent, acetone, 0 °C, 80%.

trifluoroacetic anhydride and 2,6-lutidine at −20 °C produced the desired cyclopentenone in 75% yield. This represents an appreciable improvement over the 50% yield that had been achieved by using methanesulfonyl chloride and triethylamine in THF.[8] Trifluoroacetic anhydride in the presence of 2,6-lutidine should be considered the reagent of choice for inducing the cationic cyclopentaannelation reaction. The selective protection of the reactive *exo*-methylene group in **14** was carried out as for **5**, by exposure to thiophenol in the presence of triethylamine in THF. A 4.5:1 mixture of two diastereomers **15** and **16** was isolated in 85% combined yield. The two thiophenoxy enones were easily separable by flash chromatography[12] on silica gel. The stereochemical identity of the two products was proven by nuclear Overhauser experiments on the corresponding unprotected alcohols. Enone **15** was reduced to allylic alcohol **17** with DIBAL–*n*-butyllithium

Scheme IV[a]



[a] (a) 3 equiv of *m*-CPBA, CH_2Cl_2, 0 °C, 75%; (b) 2 equiv of $(COCl)_2$, 4 equiv of DMSO, 10 equiv of Et_3N, CH_2Cl_2, −78 to 0 °C; (c) 2 equiv of DBU, THF, 25 °C, 90% for two steps; (d) 3% aqueous HCl, THF, 25 °C, 90%; (e) Jones reagent, acetone, 0 °C, 60–70%.

"ate" complex in 85–90% yield. Allylic alcohol **17** is the precursor to both **1** and **2**.

For completion of the methylenomycin A synthesis, epoxidation of allylic alcohol **17** must be directed to take place at the face of the molecule opposite to the alcohol. The *tert*-butyldimethylsilyl ether[13] **18** was converted to a 4:1 mixture of diastereomeric epoxy sulfones **19** and **20** in 91% combined yield (Scheme III). The separation of the diastereomers by flash chromatography was straightforward. The assignment of stereochemistry was done on the basis of the ^1H NMR spectra of the corresponding desilylated alcohols. Alcohol **24** was also prepared by direct epoxidation of **17** (Scheme IV). The conclusive proof of structure was provided by converting **19** to methylenomycin A (**1**) and **20** to *epi*-methylenomycin A (**2**). Desilylation of **19** with tetra-*n*-butylammonium fluoride in THF provided epoxy alcohol **21**, which was subjected to Swern oxidation[14] followed by immediate treatment with DBU in THF to provide enone **22** in 75–85% overall yield. Hydrolytic removal of the tetrahydropyranyl protecting group followed by Jones oxidation provided *d,l*-methylenomycin A (**1**) in 65% yield over two steps. The purification of the crude product was accomplished by dissolving in aqueous sodium bicarbonate, washing with ether, and acidifying with 3% aqueous HCl. Extraction with dichloromethane produced crystalline *d,l*-methylenomycin A, which was spectroscopically identical with a sample of the natural product provided by Dr. Tatsuo Haneishi of Sankyo Co.

The synthesis of *epi*-methylenomycin A (**2**) follows the same logic and is summarized in Scheme IV. Desilylation of the minor isomer **20** provided epoxy alcohol **24**. Alternatively, **24** could be prepared by exposure of **17** to an excess of *m*-chloroperoxybenzoic acid. Swern oxidation[14] followed by treatment of the crude product with DBU in THF provided epoxy enone **25** in 80–85% yield. Hydrolytic removal of the protecting group followed by Jones

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(13) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(14) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

oxidation provided d,l-epi-methylenomycin A (2) in 60–70% yield.[15]

A concise synthesis of d,l-methylenomycin A and its diastereomer has been described. The cationic cyclopentaanelation reaction assembles the methylenomycin carbon skeleton in an extremely efficient way. The structural features of the methylenomycins are found in a number of interesting natural products so further applications of this methodology will be forthcoming.

Experimental Section

All reactions were performed in flame-dried glass apparatus equipped with rubber septa under a static nitrogen or argon atmosphere. Alkyllithiums were titrated according to the procedure of Watson and Eastham.[16] Thin-layer chromatography was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash chromatography was performed on Brinkmann silica gel (0.040–0.063 mm) using mixtures of ethyl acetate and hexane. Melting points (uncorrected) were reported for all crystalline products. All other products were isolated as clear, colorless oils.

Proton nuclear magnetic resonance spectra were recorded at 300 MHz on a Nicolet NT-300 spectrometer (Oxford magnet). NMR data are reported in ppm from $CHCl_3$ (7.24 ppm). Infrared spectra were recorded on a Nicolet 5MX FT spectrometer or on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were recorded on a Varian MAT-311 or on a VG-70SE spectrometer. Elemental analyses were performed by Desert Analytics, Tucson, AZ 85717.

Cyclopentenone 14. To a solution of tertiary alcohol **13** (0.30 g, 1.01 mmol) and 2,6-lutidine (0.64 g, 6.00 mmol) in 15 mL of dichloromethane was added neat trifluoroacetic anhydride (1.05 g, 5.00 mmol) at −20 °C under an atmosphere of dry nitrogen over a period of 15 min. After 30 min at −20 °C the reaction was quenched with 5 mL of cold, saturated aqueous sodium bicarbonate. The product was extracted into ether, and the ethereal layer was washed with water and brine and was dried over Na_2SO_4. Solvent evaporation followed by flash chromatography on silica gel (15% ethyl acetate and 0.1% triethylamine in hexane) provided 180 mg of cyclic enone **14** as a mixture of tetrahydropyranyl diastereomers (76% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1 H), 5.46 (s, 1 H), 4.60 (m, 1 H), 4.00–3.00 (m, 5 H), 2.07 (s, 3 H), 1.77 (s, 3 H), 1.73–1.40 (m, 6 H); IR (neat) 2950, 2875, 1695, 1632 cm^{-1}; mass spectrum, m/e (relative intensity) 236 (M^+), 122, 85 (100).

(Phenylthio)cyclopentanone 15. To a solution of enone **14**[8] (0.44 g, 1.86 mmol) in 7 mL of THF were added triethylamine (0.28 g, 2.78 mmol) and thiophenol (0.22 g, 2.05 mmol) sequentially at 0 °C. The temperature of the solution was allowed to rise to 25 °C over a 45-min period. Stirring was continued for an additional hour and the reaction was quenched by addition of 6 mL of water. Following ether extraction, the organic phase was washed with water and brine and was dried over $MgSO_4$. Concentration of the organic phase produced a mixture of cis enone **15** and trans enone **16**. The diasteromeric phenylthio enones were separated by flash chromatography on silica gel with 10% ethyl acetate in hexane containing 0.1% triethylamine to produce 450 mg (70% yield) of **15** and 100 mg (15% yield) of **16**.

15 (THP diastereomers): ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 4.56 and 4.40 (two m, 1 H), 3.95 (dt, J = 10.2, 4.7 Hz, 1 H), 3.75 and 3.61–3.37 (m, 4 H), 2.96–2.81 (m, 2 H), 2.59 (m, 1 H), 2.04 (s, 3 H), 1.69 (s, 3 H), 1.75–1.38 (m, 6 H); IR (neat) 2939, 2868, 1697, 1647, 1581, 1479, 1437, 1385, 1348, 1325, 1275, 1259, 1199, 1188, 1153, 1134, 1074, 1032 cm^{-1}; mass spectrum, m/e (relative intensity) 346 (M^+), 262, 245 (M^+ − OTHP), 244, 135, 85 (100), calcd for $C_{20}H_{26}SO_3$ 346.1602, found 346.1572.

16 (THP diastereomers): ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 4.55 and 4.43 (two m, 1 H), 4.12 and 4.04 (dd, J = 10.6, 3.9 Hz and dd J = 10.0, 3.2 Hz, 1 H), 3.79–3.57 (m, 3 H), 3.47 (m, 1 H), 3.07 and 2.91 (dd, J = 13.4, 11.3 Hz and dd, J = 13.3, 11.3 Hz, 1 H), 3.00 (br s, 1 H), 2.63 (m, 1 H), 2.06 and 2.04 (two s, 3 H), 1.72 and 1.70 (two s, 3 H), 1.78–1.38 (m, 6 H).

Phenylthio Alcohol 17. A solution of DIBAL (1.6 mmol) in 6.4 mL of THF was treated with 1.5 mmol of n-butyllithium at 0 °C under nitrogen. The resulting clear solution of the "ate" complex was cooled to −78 °C. A solution of phenylthio enone **15** (0.43 g, 1.24 mmol) in 2 mL of THF was added to the "ate" complex via cannula. After 30 min the reaction was quenched by adding 0.1 mL of water and 0.27 g of sodium fluoride. The resulting slurry was stirred for 1 h. Filtration followed by solvent evaporation produced an oil, which was purified by flash chromatography on silica gel with 20% ethyl acetate in hexane to give 390 mg (89% yield) of allylic alcohol **17** (THP diastereomers): ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 4.59 (m, 1 H), 4.11 (m, 1 H), 3.90 and 3.79 (dd, J = 9.4, 3.4 Hz and dd, J = 9.7, 3.4 Hz, 1 H), 3.68 (m, 1 H), 3.48 (m, 1 H), 3.42 and 3.33 (dd, J = 9.6, 3.7 Hz and dd, J = 9.5, 3.2 Hz, 1 H), 3.05 (m, 1 H), 2.91 and 2.87 (dd, J = 9.3, 5.4 Hz and dd, J = 8.6, 5.5 Hz, 1 H), 2.74 (dd, J = 14.5, 10.1 Hz, 1 H), 2.52 (br s, 1 H), 2.08 (m, 1 H), 1.70 (s, 3 H), 1.64 and 1.62 (two s, 3 H), 1.68–1.46 (m, 6 H); IR (neat) 3420, 2932, 2868, 1581, 1479, 1437, 1381, 1350, 1321, 1269, 1200, 1180, 1155, 1132, 1118, 1074, 1030 cm^{-1}; mass spectrum, m/e (relative intensity) 348 (M^+), 330 (M^+ − H_2O), 264 (M^+ − DHP), 263 (M^+ − THP) 246 (M^+ − THPOH), 245, 229, 228, 137, 123, 122, 121, 119, 107, 105, 91, 85 (100), calcd for $C_{20}H_{28}SO_3$ 348.1759, found 348.1739.

Epoxidation of Allylic Alcohol 17. To a solution of allylic alcohol **17** (0.36 g, 1.03 mmol) in 4 mL of dichloromethane was added a solution of 0.74 g (3.41 mmol) of m-chloroperoxybenzoic acid in 7 mL of dichloromethane at 0 °C during 30 min. The reaction mixture was stirred at 0 °C for 1 h. Addition of saturated sodium sulfite was followed by ether extraction. The ether layer was washed with aqueous sodium sulfite, aqueous sodium bicarbonate, and brine and was dried ($MgSO_4$). Filtration and solvent evaporation gave a residue, which was purified by flash chromatography on silica gel to give 0.39 g (95% yield) of epoxy alcohol **24** (THP diastereomers): mp 91–92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2 H), 7.63 (m, 3 H), 4.50 and 4.33 (two m, 1 H), 4.08–3.97 (m, 2 H), 3.82–3.66 (m, 2 H), 3.60–3.35 and 3.28 (m and t, J = 9.1 Hz, 3 H), 3.14 (m, 1 H), 1.89–1.40 (m, 6 H), 1.43 and 1.42 (two s, 3 H), 1.31 and 1.30 (two s, 3 H); IR (neat) 3508, 2930, 2868, 1444, 1381, 1298, 1197, 1144, 1030 cm^{-1}; mass spectrum, m/e (relative intensity) 396 (M^+), 311 (M^+ − THP), 295 (M^+ − OTHP), 293, 263, 170, 154, 153, 152, 151, 143, 139, 125, 123, 122, 109, 85 (100), calcd for $C_{20}H_{28}SO_6$ 396.1606, found 396.1673. Anal. Calcd for $C_{20}H_{28}SO_6$: C, 60.58; S, 8.09. Found: C, 60.43; S, 7.98.

Protection of Allylic Alcohol 17. Imidazole (0.34 g, 5.04 mmol) and tert-butyldimethylsilyl chloride (0.38 g, 2.52 mmol) were added sequentially to a solution of 0.29 g (0.84 mmol) of allylic alcohol **17** in 3.5 mL of DMF at 25 °C. After 5 h the reaction was quenched by the addition of 20 mL of water and the product was extracted into ether. The ethereal phase was washed with water and brine and was dried ($MgSO_4$). Filtration followed by solvent evaporation produced a yellow oil, which was purified by flash chromatography on silica gel to give 345 mg (88% yield) of **18** (THP diastereomers): ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 5 H), 4.54 and 4.50 (two m, 1 H), 4.27 (br s, 1 H), 3.86 (dd, J = 9.4, 5.2 Hz, 1 H), 3.76 (m, 1 H), 3.63 and 3.24 (dd, J = 9.2, 8.1 Hz and dd, J = 9.1, 8.4 Hz, 1 H), 3.48–3.38 (m, 2 H), 3.06–2.92 (m, 2 H), 2.47 (m, 1 H), 2.09 (m, 1 H), 1.59 (s, 3 H), 1.54 (s, 3 H), 1.66–1.38 (m, 6 H), 0.77 and 0.76 (two s, 9 H), −0.01 and −0.02 (two s, 3 H), −0.05 and −0.07 (two s, 3 H); IR (neat) 2970, 2890, 1600, 1490, 1470, 1450, 1390, 1360, 1330, 1260, 1205, 1190, 1160, 1140, 1125, 1060, 1040 cm^{-1}; mass spectrum, m/e (relative intensity) 462 (M^+), 405 (M^+ − t-Bu), 377 (M^+ − THP), 361 (M^+ − OTHP), 353 (M^+ − SPh), 268, 253, 252, 251, 239, 237, 229, 159, 123, 121, 119, 107, 91, 85 (100), calcd for $C_{26}H_{42}SiSO_3$ 462.2624, found 462.2530.

Epoxidation of 18. A solution of 0.55 g (3.62 mmol) of m-chloroperoxybenzoic acid in 14 mL of dichloromethane was added slowly over a period of 30 min to a solution of 0.33 g (0.72 mmol) of **18** in 3 mL of dichloromethane at −20 °C. The reaction was warmed to −5 °C over 3.5 h, following which a large excess of saturated aqueous sodium sulfite was added to quench the re-

(15) All spectroscopic data for **2** match the values reported by Professor Amos Smith for epi-methylenomycin A; ref 6b.

(16) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

action. The product was extracted into ether. The ethereal layer was washed with saturated aqueous sodium sulfite, saturated aqueous sodium bicarbonate, and brine and was dried ($MgSO_4$). Filtration followed by solvent evaporation gave a mixture of diastereomers, which were separated by flash chromatograhy on silica gel to produce 230 mg (61% yield, TLC R_f = 0.39 in 30% ethyl acetate in hexane) of **19** and 56 mg (15% yield, TLC R_f = 0.36 in 30% ethyl acetate in hexane) of **20**.

19 (THP diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2 H), 7.50 (m, 3 H), 4.57 and 4.49 (t, J = 3.1 Hz and m, 1 H), 3.88 (d, J = 8.9 Hz, 1 H), 3.79 (m, 2 H), 3.63 and 3.25 (dd, J = 9.9, 7.6 Hz and t, J = 9.1 Hz, 1 H), 3.43 (m, 2 H), 3.09 (m, 2 H), 2.34 (m, 1 H), 2.16 (m, 1 H), 1.85–1.40 (m, 6 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 0.76 and 0.75 (two s, 9 H), –0.03 (s, 3 H), –0.08 and –0.09 (two s, 3 H); IR (neat) 2950, 2890, 1475, 1460, 1415, 1395, 1380, 1330, 1315, 1270, 1230, 1205, 1150, 1090, 1040 cm^{-1}; mass spectrum, m/e (relative intensity) 510 (M^+), 495 ($M^+ - CH_3$), 453 (M^+ – t-Bu), 425 (M^+ – THP), 410, 397, 395, 353, 351, 340, 339, 267, 253, 243, 241, 227, 213, 209, 199, 197, 185, 171, 159, 135 (100), 125, 85, calcd for $C_{26}H_{42}SiSO_6$ 510.2471, found 510.2276.

Epoxy Alcohol 21. To a solution of 0.22 g (0.43 mmol) of epoxide **19** in 1 mL of THF was added 0.86 mL of a 1 M solution of tetra-n-butylammonium fluoride in THF. The reaction was stirred for 4 h at 25 °C. Water (3 mL) was added and the product was extracted into ether. The organic phase was washed with water and brine and was dried over $MgSO_4$. Filtration followed by solvent evaporation produced a residue, which was purified by flash chromatograhy on silica gel to give 140 mg (81% yield) of epoxy alcohol **21** (THP diastereomers): mp 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2 H), 7.60 (m, 3 H), 4.60 (m, 1 H), 4.05 and 3.92 (dd, J = 9.9, 2.0 Hz and dd, J = 9.8, 2.3 Hz, 1 H), 3.86–3.67 (m, 2 H), 3.62–3.45 (m, 3 H), 3.34–3.14 (m, 2 H), 2.55 (br s, 1 H), 2.36 and 2.29 (dd, J = 9.7, 4.0 Hz and dd, J = 8.8, 4.0 Hz, 1 H), 1.80–1.47 (m, 6 H), 1.38, 1.36, 1.34 and 1.31 (four s, 6 H); IR (neat) 3520, 2980, 2940, 1460, 1390, 1360, 1320, 1210, 1160, 1095, 1050 cm^{-1}; mass spectrum, m/e (relative intensity) 396 (M^+), 311 (M^+ – THP), 293, 170, 153, 152, 139, 125, 122, 109, 85 (100), calcd for $C_{20}H_{28}SO_6$ 396.1606, found 396.1584. Anal. Calcd for $C_{20}H_{28}SO_6$: C, 60.58; H, 7.12; S, 8.09. Found: C, 60.35; H, 6.90; S, 8.18.

Preparation of Epoxy Enones; General Procedure. To a solution of oxalyl chloride (0.13 g, 1.02 mmol) in 2 mL of dichloromethane was added slowly (10 min) at –78 °C under nitrogen a solution of 0.16 g (2.05 mmol) of dimethyl sulfoxide. After 5 min a solution of 0.5 mmol of epoxy alcohol (**21** or **24**) in 1 mL of dichloromethane was added via cannula. Stirring was continued for an additional 30 min at –78 °C. Triethylamine (0.61 g, 6.03 mmol) was added and the temperature was allowed to rise to 0 °C during 30 min. The addition of 15 mL of ether resulted in the formation of a white precipitate. Filtration followed by solvent evaporation gave a residue, which was dissolved in 2 mL of THF and was treated with 1 mmol of DBU. After 30 min the reaction was quenched by adding water. Following ether extraction the organic phase was washed with water and brine and was dried over $MgSO_4$. The organic extract was filtered and concentrated. The residue after concentration was purified by flash chromatography on silica gel. The yield for the reaction varied between 85% and 95%.

Epoxy enone 25 (THP diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (m, 1 H), 5.54 (m, 1 H), 4.69 (m, 1 H), 4.12 and 4.00 (dd, J = 9.5, 8.0 Hz and dd, J = 9.5, 5.9 Hz, 1 H), 3.90 (m, 1 H), 3.70 and 3.56 (t, J = 9.3 Hz and m, 2 H), 2.98 (m, 1 H), 1.90–1.53 (m, 6 H), 1.63 and 1.60 (two s, 3 H), 1.46 (s, 3 H); IR (neat) 2970, 2900, 1735, 1645, 1442, 1362, 1347, 1320, 1260, 1199, 1180, 1150, 1130, 1110, 1060, 1017 cm^{-1}; mass spectrum, m/e (relative intensity) 252 (M^+), 168, 151 (M^+ – OTHP), 150 (M^+ – THPOH), 138, 109, 85 (100), calcd for $C_{14}H_{20}O_4$ 252.1361, found 252.1380.

Epoxy enone 22 (THP diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (m, 1 H), 5.43 (m, 1 H), 4.52 and 4.40 (two m, 1 H), 3.90 and 3.82 (dd, J = 9.9, 3.6 Hz and dd, J = 9.4, 3.4 Hz, 1 H), 3.70 and 3.55–3.33 (two m, 3 H), 3.02 (m, 1 H), 1.51 and 1.46 (two s, 3 H), 1.39 and 1.38 (two s, 3 H), 1.68–1.38 (m, 6 H); IR (neat) 2975, 2900, 1740, 1655, 1460, 1450, 1415, 1395, 1360, 1330, 1290, 1265, 1205, 1185, 1160, 1120, 1035 cm^{-1}.

Hydrolysis of the Tetrahydropyranyl Group; General Procedure. A solution of epoxy enone **22** or **25** (0.1 g, 0.4 mmol) in 3 mL of a 1:1 mixture of THF and 3% aqueous HCl was stirred at 25 °C for 10 h. The THF was evaporated from the mixture and the residue was extracted with ether. The organic extract was washed with brine and was dried (Na_2SO_4). Solvent evaporaton produced a residue which was purified by flash chromatography on silica gel to give the corresponding alcohol. The yield varied between 70% and 90%.

Enone alcohol 26: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, J = 2.6 Hz, 1 H), 5.57 (d, J = 2.0 Hz, 1 H), 4.02 (m, 2 H), 2.87 (m, 1 H), 2.38 (br s, 1 H), 1.63 (s, 3 H), 1.47 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 142.3, 121.9, 68.0, 65.3, 62.01, 45.5, 14.7, 8.1; IR (neat) 3500, 2975, 1730, 1650, 1455, 1415, 1390, 1330, 1200, 1115, 1080, 1035 cm^{-1}; mass spectrum, m/e (relative intensity) 168 (M^+), 151, 150 ($M^+ - H_2O$), 149, 139, 138 (100), 137, 125, 110, 109, 97, 95, calcd for $C_9H_{12}O_3$ 168.0786, found 168.0819.

Enone alcohol 23 was obtained as a white crystalline solid, which was recrystallized from ether/hexane: mp 62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, J = 1.6 Hz, 1 H), 5.50 (d, J = 1.1 Hz, 1 H), 3.77 (m, 2 H), 2.97 (m, 1 H), 1.51 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 144.0, 121.3, 67.8, 65.5, 63.6, 47.2, 13.2, 8.2; IR (deposited on NaCl plates as a thin film from a CH_2Cl_2 solution) 3550, 2960, 1735, 1645, 1450, 1395, 1320, 1195, 1100, 1080, 1030 cm^{-1}; mass spectrum, m/e (relative intensity) 168 (M^+), 151, 149, 139, 138 (100), 137, 125, 110, 108, 97, 95, calcd for $C_9H_{12}O_3$ 168.0786, found 168.0773.

Jones Oxidation of Enone Alcohols; General Procedure. A solution of enone alcohol **23** or **26** (40 mg, 0.24 mmol) in 2 mL of acetone was treated at 0 °C with freshly prepared Jones reagent until a persistent orange color was observed. The progress of the reaction was also monitored by thin layer chromatography. After nearly 2 h, 2-propanol was added to destroy the excess oxidant. Water (2 mL) was added and the product was extracted into dichloromethane. The organic extract was washed with brine and was dried over Na_2SO_4. Filtration followed by evaporation produced a product that was nearly pure. The only impurity that was detected by ^{1}H NMR was hydrocarbon grease. For removal of this impurity the product acid was dissolved in ether and was extracted into aqueous sodium bicarbonate. The aqueous bicarbonate layer was first washed with ether and was then cautiously acidified with 3% aqueous HCl. The product was extracted into dichloromethane. The organic extract was washed with brine and dried over Na_2SO_4. Solvent evaporation produced the pure product. The yield varied between 70% and 90%.

***d,l-epi*-Methylenomycin A (2)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1 H), 6.42 (d, J = 2.7 Hz, 1 H), 5.84 (d, J = 2.1 Hz, 1 H), 3.68 (unresolved dd, 1 H), 1.70 (s, 3 H), 1.49 (s, 3 H); IR (deposited on NaCl plates as a thin film from a CH_2Cl_2 solution) 3300, 2930, 1740, 1710, 1645, 1445, 1380, 1320, 1210, 1160, 1110, 1070, 1035 cm^{-1}; mass spectrum, m/e (relative intensity) 182 (M^+), 164, 140 ($M^+ - CO_2$), 139 (M^+ – COOH), 138, 137, 123, 122, 121, 120, 112, 111, 110, 109 (100), calcd for $C_9H_{10}O_4$ 182.0579, found 182.0554.

***d,l*-Methylenomycin A (1)** was obtained as a low melting (mp 105–108 °C) white crystalline solid after bicarbonate workup: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.6 (br s, 1 H), 6.24 (unresolved d, 1 H), 5.64 (unresolved d, 1 H), 3.81 (m, 1 H), 1.58 (s, 3 H), 1.48 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.22, 174.68, 140.00, 123.21, 66.14, 65.00, 51.21, 13.64, 8.04; IR (deposited on NaCl plates as a thin film from a CH_2Cl_2 solution) 3200, 2990, 2940, 1740, 1645, 1390, 1310, 1210, 1165, 1103, 1070, 1030 cm^{-1}; mass spectrum, m/e (relative intensity) 182 (M^+), 140 ($M^+ - CO_2$), 139 (M^+ – COOH), 138, 137 (100), 110, 109, 108, 95, calcd for $C_9H_{10}O_4$ 182.0579, found 182.0534.

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Registry No. *dl*-**1**, 64911-60-0; *dl*-**2**, 74807-63-9; *dl*-**5**, 102368-42-3; *dl*-**6**, 117653-48-2; *dl*-**8**, 117653-49-3; *dl*-**9**, 117653-50-6; *dl*-**10**, 117653-51-7; *dl*-**11**, 108560-13-0; *dl*-**12**, 117653-53-9; **13**, 102368-38-7; *dl*-**14** (isomer 1), 102368-45-6; *dl*-**14** (isomer 2), 102368-44-5; *dl*-**15** (isomer 1), 117653-55-1; *dl*-**15** (isomer 2),

117708-31-3; *dl*-**16** (isomer 1), 117708-27-7; *dl*-**16** (isomer 2), 117708-32-4; *dl*-**17** (isomer 1), 117653-56-2; *dl*-**17** (isomer 2), 117708-33-5; *dl*-**18** (isomer 1), 117653-57-3; *dl*-**18** (isomer 2), 117708-34-6; *dl*-**19** (isomer 1), 117653-58-4; *dl*-**19** (isomer 2), 117708-35-7; *dl*-**20** (isomer 1), 117708-28-8; *dl*-**20** (isomer 2), 117708-36-8; *dl*-**21** (isomer 1), 117708-29-9; *dl*-**21** (isomer 2), 117708-37-9; *dl*-**22** (isomer 1), 117653-60-8; *dl*-**22** (isomer 2), 117708-39-1; *dl*-**23**, 117708-40-4; *dl*-**24** (isomer 1), 117653-59-5; *dl*-**24** (isomer 2), 117709-10-1; *dl*-**25** (isomer 1), 117708-30-2; *dl*-**25** (isomer 2), 117708-38-0; *dl*-**26**, 117653-61-9; *dl*-$THPOCH_2CH{=}CH_2$, 4203-49-0; *dl*-$(EtO)_2POCH(CH_3)COCH_3$, 117653-52-8; $CH_3OCH_2OC(Li){=}C{=}CH_2$, 117653-54-0.

Anodic Oxidation Studies of *p*-Methoxyanilides. A General Method for Preparation of Acylated Quinone Imine Ketals

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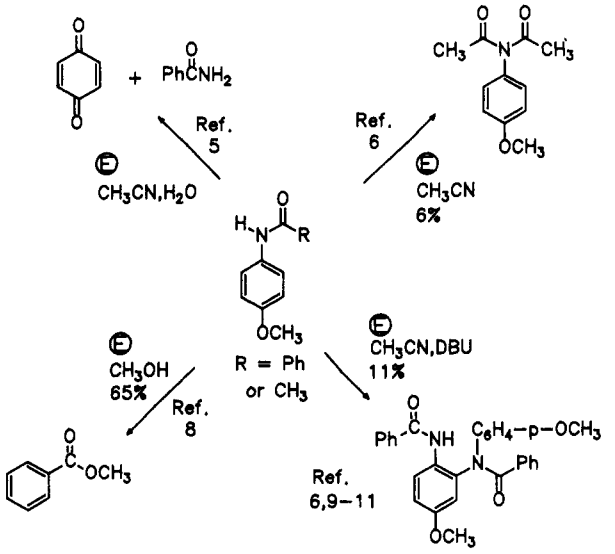
Anodic oxidation of a methanolic solution of 4-methoxybenzanilide **1a** or 4-methoxyacetanilide **1b** in a single-cell apparatus at constant current using lithium perchlorate as the supporting electrolyte afforded high yields of *N*-benzoyl- and *N*-acetyl-1,4,4-trimethoxy-1-amino-2,5-cyclohexadiene, respectively. This is the first time anodic 1,4-addition products have been characterized from anodic oxidation of anilides. When these anodic oxidations were performed in the presence of either sodium bicarbonate or 2,6-lutidine, acylated quinone imine ketals were obtained in excellent yield. The yield of acylated quinone imine ketals from these anodic oxidations is dependent upon the anode material, current density, water content of the methanol, and workup procedures. Experimental conditions have been established for conducting these reactions for a number of derivatives of **1a** and **1b** in high yield and acylated quinone imine ketals are now readily available via the anodic oxidation of *p*-methoxyanilides.

Although the anodic oxidation of anilines has been extensively studied[1-3] and preparative scale experiments were performed as long ago as 1875,[4] the electrochemical oxidation of the corresponding amides has received less attention.[5-11] Scheme I summarizes some of the results previously reported from anodic oxidations of *p*-methoxyanilide derivatives, the main theme of the present study.

Many of the products isolated from the anodic oxidation of anilides in both acetonitrile and methanol could be rationalized as arising from hydrolysis of a quinone imine formed in the reaction. For anodic oxidations in acetonitrile it was suggested that adventitious water hydrolyzed the primary oxidation product,[8] resulting in the isolation of benzoquinone and benzamide (Scheme I). However, in no case was a quinone imine intermediate isolated from these reactions. Somewhat more surprising, the product isolated from anodic oxidation in methanol (Scheme I) involved reaction of some intermediate with the solvent.

Scheme I. Selected Examples of Anodic Oxidation of *p*-Methoxyanilides



Our early experiences in conducting anodic oxidations of anilides paralleled some of the literature results: complex reaction mixtures and poor accounting of material. For example, anodic oxidation of **1a** in methanolic potassium hydroxide, conditions used for the conversion of 1,4-dimethoxybenzene to benzoquinone diketal,[12] afforded

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