regeneration of the free base gave minovine, mp 119–121 °C (lit.[3] mp 120–122 °C): MS (80 eV), *m/e* (rel intensity) 124 (100), 168 (7), 228 (4), 267 (7), 352 (55) M^+.

(±)-*N*(a)-Methylervinceine (4d). A solution of 35 mg (0.095 mmol) of (±)-ervinceine in 1 mL of dimethylformamide (DMF) was added to 10 mg (0.21 mmol) of 50% sodium hydride oil dispersion and 1 mL of DMF. After the solution was stirred under nitrogen for 0.5 h, 20 μL (~3 equiv) of methyl iodide was added, and stirring was continued for 15 min. The precipitate which formed on pouring the reaction mixture into 5 mL of water was filtered, washed with water, and dissolved in dichloromethane, and the solution was dried over sodium sulfate, filtered, and concentrated to 32 mg (88% yield) of an amorphous product, which showed only one product on TLC (R_f ~ 0.7, ethyl acetate, silica, detection with cerric ammonium nitrate, blue spot with orange center). Preparative TLC of the sample (Merck silica, ethyl acetate) gave 26 mg of recovered product which failed to crystallize: NMR ($CDCl_3$) δ 7.00–7.26 (m, same line shape as in ervinceine, 1 H), 6.30–6.50 (m, 2 H), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.22 (s, 3 H), 3.20–0.80 (m, 15 H), 0.64 (t, 3 H); MS (80 eV), *m/e* (rel intensity) 124 (100), 191 (10), 258 (10), 323 (15), 382 (90) M^+. A picrate had mp 115–118 °C.

Comparative TLC of Vincadifformine (4a), Minovine (4b), Ervinceine (4c), and *N*(a)-Methylervinceine (4d). With Merck silica on aluminum sheets (No. 5755), unactivated, ethyl acetate as solvent, and detection by spray with 10% cerric ammonium nitrate in phosphoric acid, the title compounds gave the following results: **4a**, R_f 0.86, blue with yellow center fades to yellow; **4b**, R_f 0.82, blue with orange center fades to purple with yellow center; **4c**, R_f 0.78, blue with yellow center fades to yellow; **4d**, R_f 0.72, blue with orange center fades to rose.

Acknowledgments. Support for parts of this research project by the National Cancer Institute under National Institutes of Health Research Grant R01 CA 12010 is gratefully acknowledged.

Registry No. (±)-**1d**, 70369-12-9; (±)-**4a**, 18374-17-9; (±)-**4b**, 19621-72-8; (±)-**4b** picrate, 70469-81-7; (±)-**4c**, 69126-63-2; (±)-**4c** picrate, 70369-13-0; (±)-**4d**, 67497-53-4; (±)-**4d** picrate, 70369-14-1; **5a**, 61-54-1; **5a** HCl, 343-94-2; **5b**, 7518-21-0; **5b** HCl, 2826-96-2; **5c**, 3610-36-4; (±)-**6a**, 70369-15-2; (±)-**6b**, 70369-16-3; (±)-**6b** picrate, 70369-17-4; (±)-**6**, 70369-18-5; (±)-**7b**, 70369-19-6; (±)-**7c**, 66859-10-7; tryptamine phthalimide, 15741-71-6; *N*-methyltryptamine phthalimide, 70369-20-9; (±)-4-dimethoxymethylmethanesulfonyloxyhexane, 66859-28-7; dimethyl (±)-3-benzyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate, 70369-21-0; methyl (±)-3-benzyl-8-methoxy-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate, 70369-22-1; methyl pyruvate, 600-22-6.

Michael Additions in Anhydrous Media. Novel Synthesis of Oxygenated Coumarins

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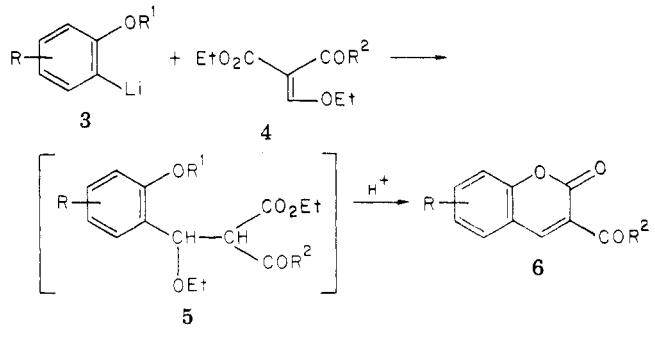
A general procedure is described where an aryllithium, generated by metalation of a protected phenol with *n*-butyllithium, adds in a conjugate manner to diethyl ethoxymethylenemalonate to give after acid hydrolysis an oxygenated 3-carbethoxycoumarin. By this procedure the ethyl vinyl ethers **9**, **11**, **13**, and **15** are converted into the corresponding coumarins **10**, **12**, **14**, and **16** in a single reaction vessel in good yield.

The coumarin moiety is widely distributed in nature. Many natural products which contain this subunit exhibit such useful and diverse biological activity as antifungal,[1] anticoagulant,[2] antispasmotic,[3] anticholerostatic,[4] and molluscacide[5] activity. In addition, other coumarins are of much interest as a result of their toxicity,[6] carcinogenicity,[7] and photodynamic effect.[8,9] In this paper a direct, efficient, and operationally convenient approach to the synthesis of oxygenated coumarins based on the Michael addition of aryllithiums to ethoxymethylenemalonates or ethoxymethyleneacetoacetates will be presented.

Scheme I



Results and Discussion

The approach described herein originated from our observation that methyl- and *n*-butyllithium add cleanly in a conjugate manner to ethyl ethoxymethyleneacetoacetate (eq 1). Since many aromatic compounds can be regioselectively metalated, we reasoned that a synthetic approach to the coumarin skeleton via Michael addition of aryllithium reagents followed by lactonization and elimination should be possible. This idea has been realized and is outlined in Scheme I.

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(2) R. B. Arora and C. N. Mathur, *Br. J. Pharmacol.*, **20**, 29 (1963); K. P. Link, *Harv. Lect.*, **39**, 162 (1943).
(3) R. E. Willette and T. O. Soine, *J. Pharm. Sci.*, **51**, 2, 149 (1962).
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(5) A. Schonberg and N. Latif, *J. Am. Chem. Soc.*, **76**, 6208 (1954).
(6) S. Kadis, A. Ciegler, and S. Ajl, *Microb. Toxins*, **7**, Chapter 1 (1972).
(7) G. P. Ellis and G. B. West, *Prog. Med. Chem.*, **10**, 109–115 (1974).
(8) R. Hoffmann, P. Wells, and H. Morrison, *J. Org. Chem.*, **36**, 102 (1971).
(9) P. Wells and H. Morrison, *J. Am. Chem. Soc.*, **97**, 154 (1975).

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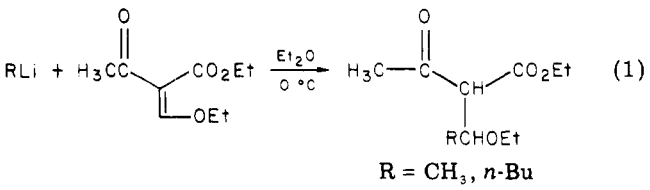
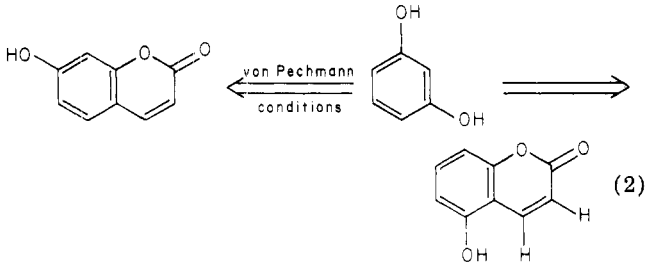


(1)

R = CH_3, *n*-Bu

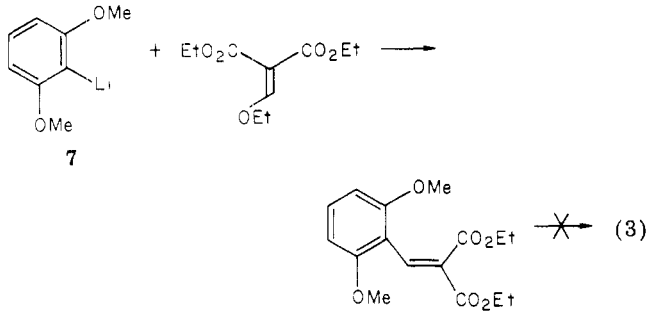
This method represents an important complement to the traditional von Pechmann synthesis[10,11] which affords the isomeric coumarin as illustrated in eq 2. It is also more



(2)

convenient than the Knoevenagel synthesis of coumarins in that the necessity of preparing the requisite salicylaldehyde is eliminated. Since coumarin-3-carboxylic acids can be readily decarboxylated,[12] our method is also applicable to the preparation of coumarins which are unsubstituted in the 3 position.

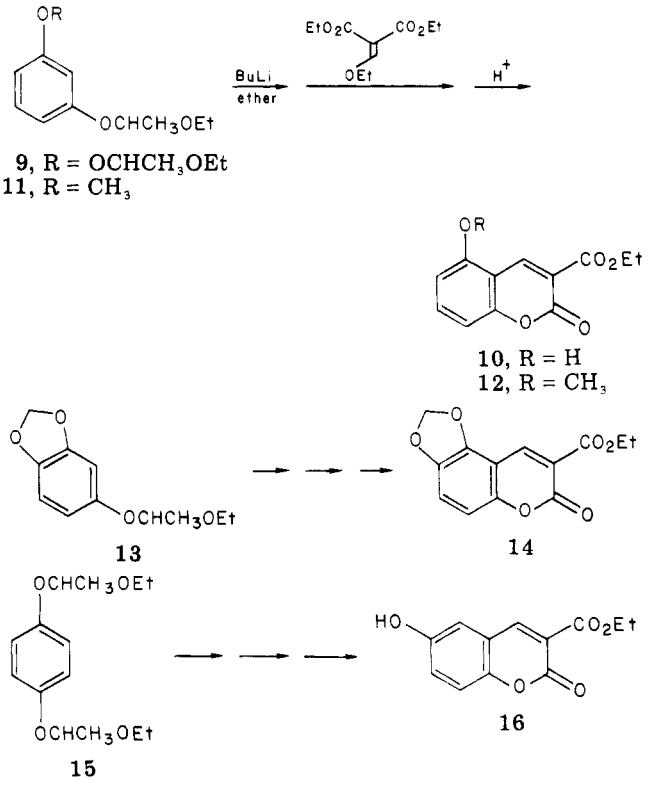
Unexpectedly the selection of the phenol protecting group proved to be difficult. For example, the aryllithium **7**[13] on reaction with diethyl ethoxymethylenemalonate gives cleanly the diether **8** which could not be demethylated to obtain the desired coumarin (eq 3). All at-



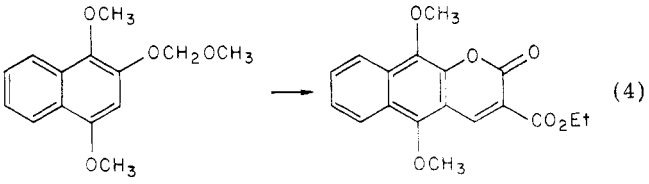
(3)

tempted reaction conditions (BBr_3/CH_2Cl_2, Py·HCl, HBr/HOAc, HI, LiSMe/HMPA) led to the decomposition of **8**. After much experimentation the ethyl vinyl ether and the methoxymethyl protecting groups were found to be suitable. Both can be removed under mild hydrolytic conditions. This also affords added experimental convenience, since the transformation of **3** into **6** can be accomplished in a single reaction vessel! The reaction is simple to perform. The aryl ether is metalated with *n*-butyllithium at 0 °C in ether. To the aryllithium reagent is added an ethereal solution of diethyl ethoxymethylenemalonate. The reaction is very exothermic. After a few minutes the reaction is quenched with concentrated hydrochloric acid, followed by vigorous stirring at room temperature for a couple of hours. Examples of coumarin synthesis utilizing our procedure are illustrated in Scheme II.

Scheme II

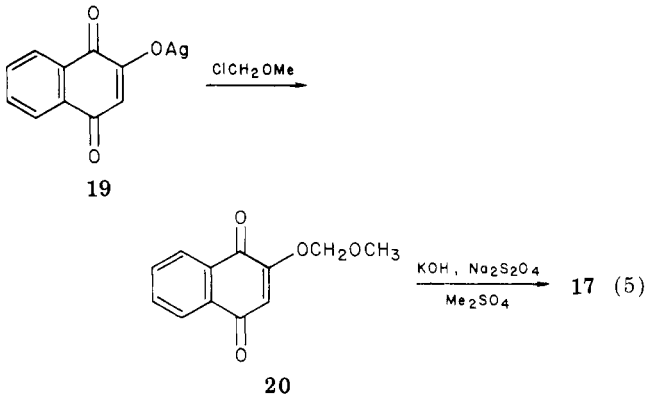


This process also works well for polycyclic aromatic ethers as exemplified by the transformation of **17** into coumarin **18** (eq 4). Compound **17** is prepared by al-



(4)

kylation of the silver salt of lawsone (**19**) with chloromethyl methyl ether to give the 1,4-naphthoquinone **20**. Reductive methylation of **20** with alkaline sodium dithionite and dimethyl sulfate provides **17** (eq 5).



(5)

This coumarin synthesis provides an efficient and convergent synthetic route to a variety of oxygenated coumarins. The reaction proceeds under mild conditions with readily available starting materials.

Experimental Section

General Procedures. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. NMR spectra were determined on a Varian A-60 or Varian EM-360 spectrometer; chemical shifts are

(10) For a review of coumarin synthesis, see S. Wawzonek, *Heterocycl. Compd.*, **2**, Chapter 2 (1950).
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(12) T. Boehm and E. Profft, *Arch. Pharm.*, **269**, 25 (1931).
(13) H. Gilman, H. B. Willis, T. H. Cook, F. J. Webband, and R. N. Meals, *J. Am. Chem. Soc.*, **62**, 667 (1940).

reported in δ with tetramethylsilane as an internal standard. Infrared spectra were obtained on a Beckman IR 4250 or Beckman Acculab 2 spectrophotometer as a neat film or Nujol mull. Only significant peaks are reported. Exact mass determinations were obtained with an AEI MS-902 high-resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

For the metalation reactions, all experiments were run under an atmosphere of dry nitrogen in a flame-dried flask. The ether was distilled from lithium aluminum hydride under nitrogen just prior to utilization. General drying of organic solutions during workup was performed over anhydrous sodium sulfate. Column chromatography employed silica gel obtained from J. T. Baker Chemical Co., 60–200 mesh.

General Preparation of Ethyl Vinyl Ethers (EVE). The protection of sesamol is typical.

EVE of Sesamol (13). To a solution of 4.14 g (30 mmol) of sesamol in 30 mL of methylene chloride is added 4.3 mL (45 mmol) of ethyl vinyl ether. The solution is cooled in an ice slush bath, and a few drops of concentrated hydrochloric acid are added. The reaction is stirred for approximately 12 h (overnight is convenient) at room temperature. Ether is added and the solution washed with 10% sodium carbonate and brine and then dried. Concentration in vacuo affords a slightly colored oil which is placed on a vacuum pump for 2 h. The yield of **13** is 5.25 g (83%): IR (film) 1200–1050 (multiple bands), 940 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 3 H), 1.45 (d, J = 5 Hz, 3 H), 3.7 (m, 2 H), 5.25 (q, J = 5 Hz, 1 H), 5.9 (s, 2 H), 6.3–6.8 (m, 3 H); mass spectrum $C_{11}H_{14}O_4$ requires m/e 210.0892, measured m/e 210.0887. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.69; H, 6.64. Elemental analysis obtained on material purified by bulb-to-bulb distillation; oven temperature 120 °C (1 mm).

EVE of Hydroquinone (15): bp 114 °C (1.5 mm); yield 98%; IR (film) 1510, 1230–1050 (multiple bands), 850 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 6 H), 1.47 (d, J = 5 Hz, 6 H), 3.7 (m, 4 H), 5.3 (q, J = 5 Hz, 2 H), 7.0 (s, 4 H); mass spectrum $C_{14}H_{22}O_4$ requires m/e 254.1518, measured m/e 254.1523. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.98; H, 8.90.

EVE of Resorcinol (9): bp 105–107 °C (1.5 mm); yield 70%; IR (film) 1600, 1180–1050 (multiple bands), 855, 775, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (t, J = 7 Hz, 6 H), 1.5 (d, J = 5 Hz, 6 H), 3.65 (m, 4 H), 5.35 (q, J = 5 Hz, 2 H), 6.63 (d, J = 7 Hz, 2 H), 6.71 (s, 1 H), 7.13 (t, J = 7 Hz, 1 H); mass spectrum $C_{14}H_{22}O_4$ requires m/e 254.1518, measured m/e 254.1518.

EVE of *m*-Methoxyphenol (11): bp 95 °C (1.5 mm); yield 92%; IR (film) 1600, 1200–1045 (multiple bands), 955, 765, 685 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3 H), 1.42 (d, J = 5 Hz, 3 H), 3.6 (m, 2 H), 3.72 (s, 3 H), 5.3 (q, J = 5 Hz, 1 H), 6.55 (m, 3 H), 7.1 (m, 1 H); mass spectrum $C_{11}H_{16}O_3$ requires m/e 196.1099, measured m/e 196.1093. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.51; H, 8.37.

2-Methoxymethoxy-1,4-naphthoquinone (20). To a suspension of 5.6 g (20 mmol) of the silver salt of 2-hydroxy-1,4-naphthoquinone (lawsone)[14] in 30 mL of benzene, cooled in ice slush bath, is added 1.5 mL of chloromethyl methyl ether. The red silver salt is replaced by a light brown suspension. As soon as the red color disappears, the reaction mixture is diluted with ether and filtered (but not through Celite). After thorough washing with ether, the combined filtrates are washed twice with 6 N NH_4OH, once with 1 N NaOH, and finally with brine. After drying and concentration in vacuo a light yellow solid is obtained and is sufficiently pure for next step: yield of **20** 2.3 g (53%); mp 116–118 °C (aqueous acetone); IR (mull) 1690, 1655, 1620, 1000 cm^{-1}; NMR ($CDCl_3$) δ 3.5 (s, 3 H), 5.2 (s, 2 H), 6.5 (s, 1 H), 7.6–8.2 (m, 4 H); mass spectrum $C_{12}H_{10}O_4$ requires m/e 218.0579, measured m/e 218.0586. Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.21; H, 4.71.

1,4-Dimethoxy-2-methoxymethoxynaphthalene (17). To a solution of 4.6 g (21 mmol) of **20** in 80 mL of acetone is added a solution of 15 g of sodium dithionite in 80 mL of water. The mixture is stirred at room temperature for 13 h, eventually becoming a clear solution. The major portion of the acetone is removed under reduced pressure. A solution of 15 g of KOH in 35 mL of water is added in one portion. A light green solution is obtained. After the solution was cooled in an ice slush bath, 30 mL of dimethyl sulfate was added. The green coloration disappears within a few minutes. After a few minutes the ice bath is removed and stirring is continued at room temperature for an additional 7 h. The reaction mixture is extracted twice with ether, and the combined extracts are washed with brine, dried, and concentrated in vacuo. The crude product is chromatographed on silica gel (100 g) with hexane–ether, 3/1. The pure product is obtained as a colorless oil which crystallizes to a waxy solid (mp 33–34 °C) on storage in the refrigerator: yield of **17** 4.3 g (82%); IR (film) 1680, 1600, 1465, 1375, 1100, 770 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (s, 3 H), 3.9 (s, 6 H), 5.28 (s, 2 H), 6.75 (s, 1 H), 7.45 (m, 2 H), 8.2 (m, 2 H); mass spectrum $C_{14}H_{16}O_4$ requires m/e 248.1049, measured m/e 248.1042. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.71; H, 6.73.

Preparation of Coumarins from Protected Phenols. The procedure for the preparation of **18** from **17** is typical.

Preparation of 18 from 17. To a solution of 3.7 g (15 mmol) of **17** in 15 mL of ether, cooled in an ice slush bath, is added 20 mmol of butyllithium (as a solution in hexane). Stirring is continued at 0 °C for 4 h. A precipitate forms. At −20 °C a solution of 5 mL (25 mmol) of diethyl ethoxymethylenemalonate in 5 mL of ether is added and the precipitate dissolves immediately. The reaction is stirred an additional 15 min, 30 mL of tetrahydrofuran is added and the reaction is quenched with 5 mL of concentrated hydrochloric acid followed by stirring at room temperature for 4 h. The workup involves dilution with methylene chloride, washing twice with brine, and drying and concentrating in vacuo. The crude product is chromatographed on silica gel (100 g) with hexane–ether, 2/1: mp 170 °C (95% EtOH); yield of **18** 2.4 g (49%); IR (mull) 1750, 1730, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (t, J = 7 Hz, 3 H), 4.18 (s, 3 H), 4.2 (s, 3 H), 4.45 (q, J = 7 Hz, 2 H), 7.6 (m, 2 H), 8.2 (m, 2 H), 8.9 (s, 1 H); mass spectrum $C_{18}H_{16}O_6$ requires m/e 328.0947, measured m/e 328.0953. Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 66.00; H, 4.98.

Preparation of 14 from 13: yield 42%; mp 190 °C (95% EtOH); IR (mull) 1760, 1710, 1645, 1575 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3 H), 4.5 (q, J = 7 Hz, 2 H), 6.3 (s, 2 H), 6.9 (d, J = 9 Hz, 1 H), 7.2 (d, J = 9 Hz, 1 H), 8.7 (s, 1 H); mass spectrum $C_{13}H_{10}O_6$ requires m/e 262.0477, measured m/e 262.0475. Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.72; H, 3.83.

Preparation of 12 from 11: yield 41%; mp 133–134 °C (95% EtOH); IR (mull) 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, J = 7 Hz, 3 H), 3.8 (s, 3 H), 4.2 (q, J = 7 Hz, 2 H), 6.7 (t, J = 8 Hz, 2 H), 7.2 (q, J = 8 Hz, 1 H), 8.7 (s, 1 H); mass spectrum $C_{13}H_{12}O_5$ requires m/e 248.0685, measured m/e 248.0682. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.97; H, 5.09.

Preparation of 10 from 9: yield 41%; mp 235–237 °C (hexane–ethyl acetate); IR (mull) 3350, 1740 (broad) cm^{-1}; NMR (acetone-d_6) δ 1.35 (t, J = 7 Hz, 3 H), 4.3 (q, J = 7 Hz, 2 H), 6.75 (m, 2 H), 7.5 (t, J = 8 Hz, 1 H), 8.8 (s, 1 H); mass spectrum $C_{12}H_{10}O_5$ requires m/e 234.0528, measured m/e 234.0539. Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.40; H, 4.26.

Preparation of 16 from 15: yield 37%; mp 182–184 °C (ethyl acetate–acetone); IR (mull) 3300, 1740 (br), 1580 cm^{-1}; NMR (acetone-d_6) δ 1.30 (t, J = 7 Hz, 3 H), 4.3 (q, J = 7 H, 2 H), 6.9 (m, 3 H), 8.5 (s, 1 H); mass spectrum $C_{12}H_{10}O_5$ requires m/e 234.0528, measured m/e 234.0529. Thin-layer chromatography (E. Merck silica gel 60 F-254 precoated plates) indicates a single spot: R_f 0.25 in ether, R_f 0.55 in ethyl acetate.

Preparation of 8. *m*-Dimethoxybenzene was lithiated according to Gilman[13] and reacted as in the preparation of **18**. The product is obtained as a viscous oil in 66% yield: IR (film) 1740, 1600, 1480, 780, 735 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (m, 6 H), 3.8 (s, 6 H), 4.2 (m, 4 H), 6.55 (d, J = 9 Hz, 2 H), 7.2 (t, J = 9 Hz, 1 H), 8.0 (s, 1 H); TLC R_f 0.6 in ether.

Registry No. **8**, 70160-45-1; **9**, 70160-46-2; **10**, 70160-47-3; **11**, 70160-48-4; **12**, 70160-49-5; **13**, 28583-33-7; **14**, 70160-50-8; **15**, 1706-74-7; **16**, 70160-51-9; **17**, 70160-52-0; **18**, 70160-53-1; **19**, 36417-25-1; **20**, 70160-54-2; sesamol, 533-31-3; ethyl vinyl ether, 109-92-2; chloromethyl methyl ether, 107-30-2; diethyl ethoxymethylenemalonate, 87-13-8; *m*-dimethoxybenzene, 151-10-0; 1,4-dimethoxy-3-methoxymethoxynaphthalen-2-yllithium, 70160-44-0.

(14) L. F. Fieser, *J. Am. Chem. Soc.*, **48**, 3201 (1926).