Synthesis of Nectriapyrone

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A totally synthetic route to the antibacterial fungal metabolite nectriapyrone (**1**) has been achieved by condensation of methylmalonyl dichloride with ethyl *trans*-4-methyl-3-oxo-4-hexenoate followed by hydrolysis, decarboxylation, and methylation of the resulting 3-methyl-4-hydroxy-5-carbethoxy-6-(*trans*-1-methyl-1-propenyl)-2-pyrone. Exploration of an alternate scheme involving the dehydrogenation of 6-substituted-4-methoxy-5,6-dihydro-2-pyrones, prepared by Reformatsky reaction of ethyl γ-bromo-β-methoxycrotonate with various aldehydes, was abandoned since it did not appear to have general applicability to the preparation of nectriapyrone and its analogs.

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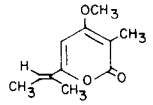
Nectriapyrone (**1**) is an antibacterial pyrone isolated from *Gyrostroma missouriense* Seeler, the imperfect stage of *Thyronectria missouriensis* Seaver (1). It was our desire to develop a feasible synthetic route to this monoterpene in order to prepare analogs with potential antimicrobial activity.



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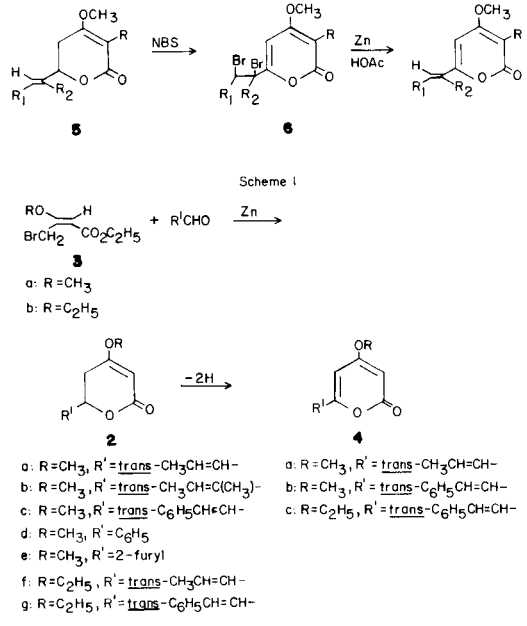
Initial efforts were directed at construction of the 5,6-dihydro-2-pyrone system (**2**) by the Reformatsky reaction of enol ethers of γ-bromo-β-ketoesters (**3**) with appropriate aldehydes (Scheme 1) following the procedure originally developed by Kostermans (2). It was anticipated that the dihydropyrones (**2**) could be dehydrogenated to the desired pyrones (**4**).

Reformatsky reaction of ethyl γ-bromo-β-methoxycrotonate (**3a**) with crotonaldehyde or tiglaldehyde gave the dihydropyrones **2a** or **2b**, respectively. Additional dihydropyrones containing the styryl (**2c**), phenyl (**2d**), and 2-furyl (**2e**) groups at position 6 were prepared along with the ethoxy derivatives **2f** and **2g**.

Treatment of **2a** with chloranil, 2,3-dichloro-5,6-dicyanoquinone (DDQ), selenium dioxide, trityl perchlorate, 5% palladium on charcoal, or *p*-cymene in an attempt to form the pyrone **4a** gave only starting material. The use of sulfur as the dehydrogenation agent led to an intractable tar. Compounds **2b, d, e,** and **f** similarly failed to yield pyrones using a variety of dehydrogenation reagents. These results were surprising in view of the fact that both **2c** and **2g** readily provided the corresponding pyrones **4b** and **4c**, respectively, by refluxing with DDQ in benzene.

During the course of this work we became aware of the synthesis of nectriapyrone and related pyrones by Reffstrup and Boll (3,4) in which dehydrogenation of 5,6-dihydro-2-pyrones containing unsaturated substituents at position 6 is achieved with *N*-bromosuccinimide (NBS). These workers reported the isolation of dibromo derivatives (**6**) from dihydropyrones (**5**) and the dehalogenation of **6** with zinc in acetic acid. In our experience treatment



of similarly substituted dihydropyrones with NBS gave a variety of products. The results of these experiments will be the subject of a future report. It should also be noted that **5** (R = R_1 = R_2 = CH_3), prepared as described by Reffstrup and Boll (3,4), gave only starting material when refluxed with DDQ in benzene.

In view of these results we decided to examine an alternate synthetic route in which the appropriately substituted 2-pyrone is formed directly from acyclic precursors. An especially attractive method for the synthesis of 3,6-disubstituted-4-hydroxy-2-pyrones has been described by Boltze and Heidenbluth (5). According to this procedure condensation of a monosubstituted malonyl dichloride with ethyl

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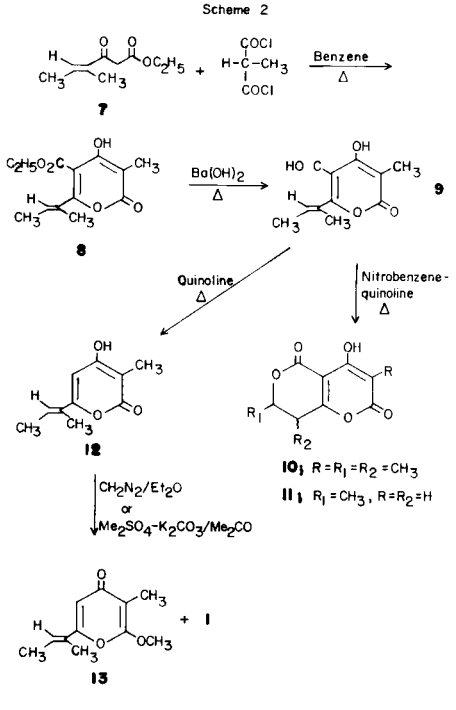
acetoacetate yields 3-substituted-5-ethoxycarbonyl-4-hydroxy-6-methyl-2-pyrones. Hydrolysis affords the corresponding 5-carboxy-2-pyrones which are then decarboxylated to give 3-substituted-4-hydroxy-6-methyl-2-pyrones. Application of this route to nectriapyrone required the synthesis of ethyl *trans*-4-methyl-3-oxo-4-hexenoate (**7**) which was prepared by the condensation of trimethylsilyl ethoxycarbonylacetate with tiglyl chloride according to the method of Pichat and Beaucort (6). Refluxing **7** with methylmalonyl dichloride in benzene gave an 18% yield, after chromatographic separation, of the desired pyrone ester (**8**) which was saponified to the acid (**9**) (Scheme 2). Attempted decarboxylation of **9** by refluxing in nitrobenzene containing a few drops of quinoline (5) gave a product whose nmr spectrum indicated an apparent mixture of *cis*- and *trans*-dimethyl-δ-lactones (**10**). Kato *et al.* (7) have reported that attempted decarboxylation of 4-hydroxy-6-(*trans*-1-propenyl)-2-oxo-pyran-5-carboxylic acid under identical conditions gave the δ-lactone **11**. The desired **12** was obtained in 75% yield when **9** was heated in quinoline at 210-220°. Stirring **12** in ethereal diazomethane gave nectriapyrone (**1**), which was identical in all respects with the natural product, along with the corresponding γ-pyrone (**13**). The formation of **13** could be minimized by using dimethyl sulfate-potassium carbonate in acetone as the methylating agent.

Scheme 2



In a subsequent publication we will describe the general utility of this preparative scheme for the synthesis of analogs of **1** possessing antimicrobial activity.

EXPERIMENTAL

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-33 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian EM-360 spectrometer with tetramethylsilane as internal standard. Ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

4-Methoxy-6-(*trans*-1-propenyl)-5,6-dihydro-2-pyrone (**2a**).

In a dry 250 ml. three-neck round bottom flask fitted with a condenser (calcium chloride tube), mechanical stirrer, dropping funnel, and nitrogen inlet tube was placed zinc metal (3.27 g., 0.05 mole) in 50 ml. of dry benzene. In the dropping funnel was placed a mixture of ethyl γ-bromo-β-methoxy-*cis*-crotonate (**3a**) (2) and freshly distilled crotonaldehyde (4.0 g., 0.051 mole) in 50 ml. of benzene. The benzene in the reaction flask was heated to reflux and a small aliquot of the dropping funnel mixture added dropwise to initiate the reaction. The reaction mixture turned light green initially and, as it progressed, became orange. The addition required 30 minutes and the reaction mixture was refluxed with stirring for an additional 3 hours. An orange-brown precipitate had formed. The reaction mixture was cooled and poured over ice. The product was extracted with ether and the ethereal extract washed with water and dried (magnesium sulfate). Evaporation of the solvent gave an orange oil which, on standing, afforded crystals (2.14 g.). Recrystallization from diethyl ether gave the desired dihydropyrone (1.94 g., 23% yield), m.p. 80-81°, lit. (4) m.p. 79-80°; ir (chloroform): 1700 and 1630 cm^{-1}; nmr (deuteriochloroform): δ 1.77 (d, 3H, J = 5 Hz), 2.47 (s, 1H), 2.57 (d, 1H, J = 2 Hz), 3.80 (s, 3H), 4.88 (m, 1H), 5.20 (s, 1H), and 5.78 (m, 2H); uv (95% ethanol): 234 nm (ε = 17,240).

4-Methoxy-6-(1-Methyl-*trans*-1-propenyl)-5,6-dihydro-2-pyrone (**2b**).

This compound was obtained in 30% yield from tiglaldehyde and **3a** as a clear oil, b.p. 138-140° (0.08 mm), by the same procedure used to prepare **2a**; ir (chloroform): 1700 and 1625 cm^{-1}; nmr (deuteriochloroform): δ 1.70 (m, 6H), 2.34 (d, 1H, J = 4 Hz), 2.52 (d, 1H, J = 11 Hz), 3.77 (s, 3H), 4.50-4.85 (m, 1H), 5.10 (s, 1H), and 5.63 (m, 1H); uv (95% ethanol): 234 nm (ε = 12,400).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.95; H, 7.78.

4-Methoxy-6-(*trans*-2-phenylethenyl)-5,6-dihydro-2-pyrone or *R,S*-Kawain (**2c**).

This compound was obtained in 36% yield from cinnamaldehyde and **3a** by the same procedure used to prepare **2a**, m.p. 146-147°, lit. m.p. 145° (2), 142-144° (8), and 145-146° (9); ir (chloroform): 1710 and 1630 cm^{-1}; nmr (deuteriochloroform): δ 2.53 (s, 1H), 2.63 (d, 1H, J = 2 Hz), 3.77 (s, 3H), 5.10 (m, 1H), 5.22 (s, 1H), 6.25 (d, 1H, J = 16 Hz), 6.80 (d, 1H, J = 16 Hz), and 7.40 (s, 5H); uv (95% ethanol): 244 nm (ε = 36,290).

4-Methoxy-6-phenyl-5,6-dihydro-2-pyrone (**2d**).

This compound was obtained in 45% yield from benzaldehyde and **3a** by a procedure essentially identical to the preparation of **2a** except that dioxane was used as the solvent for the reaction in place of benzene, m.p. 143-144°, lit. (10) m.p. 143-144°; ir (chloroform): 1710 and 1630 cm^{-1}; nmr (deuteriochloroform): δ 2.70 (m, 2H), 3.80 (s, 3H), 5.30 (s, 1H), 5.57 (d, 1H, J = 6 Hz), and 7.45 (s, 5H); uv (95% ethanol): 235 nm (ε = 16,230).

4-Methoxy-6-(2-furyl)-5,6-dihydro-2-pyrone (**2e**).

This product was prepared in 39% yield from **3a** and furan-2-carboxyaldehyde by the same method used to obtain **2a** except that dioxane was used as the reaction solvent in place of benzene, m.p. 125-126°; ir (chloroform): 1710 and 1630 cm^{-1}; nmr (deuteriochloroform): δ 2.77 (m, 2H), 3.82 (s, 3H), 5.28 (s, 1H), 5.43, 5.62 (dd, 1H, J = 5 Hz), 6.47 (m, 2H), and 7.50 (m, 1H); uv (95% ethanol): 223 nm (ε = 26,900).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.99; H, 5.07.

4-Ethoxy-6-(*trans*-1-propenyl)-5,6-dihydro-2-pyrone (**2f**).

This compound was prepared in 27% yield from crotonaldehyde and **3b** (9) by the same procedure used to obtain **2a**, m.p. 58-59°; ir (chloroform): 1710 and 1635 cm^{-1}; nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7 Hz), 1.73 (d, 3H, J = 5 Hz), 2.37 (s, 1H), 2.50 (d, 1H, J = 2 Hz), 4.00 (q, 2H, J = 7 Hz), 4.78 (m, 1H), 5.08 (s, 1H), and 5.85-6.10 (m, 2H); uv (95% ethanol): 235 nm (ε = 20,600).

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.95; H, 7.72.

4-Ethoxy-6-(*trans*-2-phenethenyl)-5,6-dihydro-2-pyrone (**2g**).

This compound was prepared in 15% yield from cinnamaldehyde and **3b** by the same procedure used to obtain **2a**, m.p. 100-101°, lit. (9) m.p. 99-100°; ir: 1710 and 1635 cm^{-1}; nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7 Hz), 2.52 (s, 1H), 2.63 (s, 1H), 3.95 (q, 2H, J = 7 Hz), 5.03 (m, 1H), 5.17 (s, 1H), 6.23 (d, 1H, J = 16 Hz), 6.78 (d, 1H, J = 16 Hz), and 7.37 (s, 5H); uv (95% ethanol): 243 nm (ε = 18,950).

4-Methoxy-6-(*trans*-2-phenethenyl)-2-pyrone (**4b**).

In a 50 ml. pear-shaped flask fitted with a condenser (calcium chloride tube) was placed a mixture of **2c** (230 mg., 1.0 mmole) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) (227 mg., 1.0 mmole) in 15 ml. of dry benzene. The wine red solution was refluxed for four hours during which the reaction turned yellow with the formation of a tan precipitate. The reaction mixture was cooled, filtered, and the precipitate (DDQH) was washed with cold benzene. The benzene solution was concentrated to dryness and the crystalline residue recrystallized from methanol to afford the desired pyrone, 208 mg. (91% yield), m.p. 138-140°, lit. m.p. 138-140° (11), 138.5-139.5° (12), and 134-136° (13); ir (chloroform): 1735, 1720, 1709, 1625, and 1560 cm^{-1}; nmr (deuteriochloroform): δ 3.78 (s, 3H), 5.48 (d, 1H, J = 2 Hz), 5.95 (d, 1H, J = 2 Hz), 6.55 (d, 1H, J = 16 Hz), 7.42 (m, 5H), and 7.50 (d, 1H, J = 16 Hz); uv (95% ethanol): 344 (ε = 26,300), 255 (ε = 14,000), and 231.5 nm (ε = 16,600).

4-Ethoxy-6-(*trans*-2-phenylethenyl)-2-pyrone (**4c**).

This compound was obtained in 86% yield by dehydrogenation of **2g** with DDQ in benzene essentially as described for the preparation of **4b**, m.p. 146-147°; ir (chloroform): 1735, 1710, 1650, 1625, and 1560 cm^{-1}; nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7 Hz), 4.03 (q, 2H, J = 7 Hz), 5.45 (d, 1H, J = 2 Hz), 5.98 (d, 1H, J = 2 Hz), 6.57 (d, 1H, J = 16 Hz), 7.42 (m, 5H), and 7.52 (d, 1H, J = 16 Hz); uv (95% ethanol): 343 (ε = 24,300), 254 (ε = 20,250), and 231.5 nm (ε = 20,870).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.30; H, 5.77.

Ethyl *trans*-4-Methyl-3-oxo-4-hexenoate (**7**).

A solution of 18.27 g. (0.09 mole) of trimethylsilyl ethoxycarbonylacetate (6) in 100 ml. of dry ether was cooled with stirring under dry nitrogen to -78°. To this cold solution was added dropwise with stirring 32.5 ml. of 1.38*M* *n*-butyllithium in hexane over a period of thirty minutes. After the addition was complete, the reaction mixture was stirred at -78° for twenty minutes and then treated dropwise with a solution of 2.13 g. (0.018 mole) of tiglyl chloride (14) in 10 ml. of dry 1,2-dimethoxyethane. After the addition was complete, the reaction mixture was stirred at -78° for one hour and then warmed to 0° over twenty minutes. Water (20 ml.) was then added dropwise to the reaction mixture while stirring at 0°. After stirring for an additional ten minutes at 0°, the reaction mixture was concentrated. The residue was partitioned between water and ether. The ether layer was washed with saturated aqueous sodium bicarbonate solution followed by saturated aqueous sodium chloride solution, dried (anhydrous magnesium sulfate), and concentrated to an oil. Distillation (bath temperature below 140°) over hydroquinone afforded 2.37 g. (68% yield) of pure **7**, b.p. 67-70° (0.10 mm), lit. (15), b.p. 110° (15 mm); ir (chloroform): 3040, 3005, 2990, 2940, 1740, and 1670 cm^{-1}; nmr (deuteriochloroform): δ 1.22 (t, 3H, J = 7 Hz), 1.77 (m, 3H), 1.93 (m, 3H, J = 1 Hz), 3.69 (s, 2H), 4.13 (q, 2H, J = 7 Hz), 5.13 (s, 1H), 6.74 (m, 1H, J = 7 Hz and 1.5 Hz), and 12.25 (s, 1H); uv (95% ethanol): 231 (ε = 21,000) and 276 nm (ε = 1,690), changing to 231 (ε = 19,500) and 288 nm (ε = 4,450) upon addition of base.

Ethyl 3-Methyl-4-hydroxy-6-(1-methyl-*trans*-1-propenyl)-2-pyrone-5-carboxylate (**8**).

A solution of 2.37 g. (13.9 mmoles) of **7** in 12 ml. of dry benzene was heated to reflux and treated dropwise with a solution of 2.43 g. (15.6 mmoles) of methylmalonyl dichloride (16) in 12 ml. of dry benzene under nitrogen. The reaction mixture was refluxed under nitrogen for twenty hours, cooled, and extracted with 10% aqueous sodium carbonate solution (3 x 30 ml.). The aqueous extract was washed with ether and acidified with concentrated hydrochloric acid while stirring at 5°. The precipitate was extracted into ether. The ether layer was washed with saturated aqueous sodium chloride solution, dried (anhydrous sodium sulfate), and concentrated to give 1.08 g. of semi-solid material. Column chromatography on silica gel (5% ether in benzene as eluant) afforded 633 mg. (18% yield) of crystalline **8**, m.p. 82-82.5°. Recrystallization from petroleum ether (b.p. 30-75°) raised the m.p. to 85-86°; ir (chloroform): 3650-3100, 3020, 2940, 2880, 1740-1690, 1640, and 1570 cm^{-1}; nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7 Hz), 1.77 (d, 3H, J = 7 Hz and J = 1 Hz), 1.91 (s, 3H), 1.93 (d, 3H, J = 1.5 Hz), 1.97 (s, 3H), 4.30 (q, 2H, J = 7 Hz), 5.72 (m, 1H, J = 7 Hz and J = 1.5 Hz), and 11.03 (s, 1H); uv (95% ethanol): 305 (ε = 8400) and 227 nm (ε = 26,000), changing to 299 (ε = 16,300) and 230 nm (shoulder, ε = 12,400) upon the addition of base.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.92; H, 6.44.

3-Methyl-4-hydroxy-6-(1-methyl-*trans*-1-propenyl)-2-pyrone-5-carboxylic Acid (**9**).

A mixture of 618 mg. (2.45 mmoles) of **8** and 1.82 g. of barium hydroxide octahydrate in 10 ml. of water was heated with stirring at 110-120° for fifteen minutes. The reaction mixture was cooled and acidified with 10% hydrochloric acid. The precipitated solid was removed by filtration and washed several times with water to give 498 mg. (90% yield) of colorless solid, m.p. 147-153°. Recrystallization from benzene-methanol gave the analytical sample, m.p. 158-159°; ir (Nujol): 3600-3020, 1695, 1680-1660, 1580, 1535, and 840 cm^{-1}; nmr (hexadeuterioacetone): δ 1.80 (m, 3H, J = 7 Hz and J = 1 Hz), 1.87 (s, 3H), 2.00 (m, 3H, J = 1.5 Hz and J = 1 Hz), 5.90 (m, 1H, J = 7 Hz and J = 1.5 Hz), and 8.56 (s, 2H); uv (95% ethanol): 304 (ε = 7500) and 207 nm (shoulder, ε = 30,600), changing to 300 (ε = 14,000) and 225 nm (shoulder, ε = 64,000) upon addition of base.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.91; H, 5.45.

3-Methyl-4-hydroxy-6-(1-methyl-*trans*-1-propenyl)-2-pyrone (**12**).

A solution of 429 mg. (1.92 mmoles) of **9** in 4 ml. of freshly distilled quinoline was heated at 210-220° with stirring for fifteen minutes under dry nitrogen. The reaction mixture was cooled and dissolved in ether. The ethereal solution was washed with 10% hydrochloric acid and then with saturated sodium chloride solution, dried (anhydrous sodium sulfate), and concentrated to yield 280 mg. (75% yield) of a brown powder, m.p. 200-205°. An analytical sample was obtained upon recrystallization from benzene-methanol, m.p. 207-208°; ir (Nujol): 3300-3040, 1740, 1700, 1620, 1560, and 835 cm^{-1}; nmr (DMSO-d_6): δ 1.78 (s, 9H), 6.16 (s, 1H), 6.45 (m, 1H, J = 7 Hz and J = 1.5 Hz), and 11.00 (s, 1H); uv (95% ethanol): 302 (ε = 11,400), 278 (shoulder, ε = 5700), 270 (ε = 6200), and 232 nm (ε = 57,000), changing to 319 (ε = 10,800), 278 (shoulder, ε = 8250), 268 (ε = 9300), and 231 nm (ε = 77,000) upon addition of base.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.77; H, 6.68.

When the above reaction was conducted using nitrobenzene as the solvent with a drop of quinoline (5), the only product which could be isolated was a mixture of the *cis*- and *trans*-δ lactones **10**. This formulation was based on the appearance in the nmr spectrum (deuteriochloroform) of a series of four doublets (each with J = 7 Hz), integrating for a total of six protons, at δ 1.33, 1.41, 1.49, and 1.58.

3-Methyl-4-methoxy-6-(1-methyl-*trans*-1-propenyl)-2-pyrone (**1**) or Nectriapyrone.

A solution of 191 mg. (1.06 mmoles) of **12** in a large excess of ethereal diazomethane was stirred at room temperature for 24 hours. The ether

was evaporated and the residue separated on preparative thin layer chromatography (Silica gel 254 + 366; 5% methanol in chloroform). The higher Rf material was removed from the adsorbent and recrystallized from hexane-ether to provide 106 mg., m.p. 101-102°, lit. (1) m.p. 100-102°; ir (chloroform): 1685, 1645, 1622, 1551, 1165, 910, and 850 cm^{-1}; nmr (deuteriochloroform): δ 1.87 (s, 3H), 1.90 (m, 3H), 1.93 (s, 3H), 3.95 (s, 3H), 6.13 (s, 1H), and 6.71 (m, 1H, J = 7 Hz and J = 1.5 Hz); uv (95% ethanol): 327 (ε = 15,000) and 227 nm (ε = 37,600).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.04; H, 7.22.

The lower Rf material was characterized as the 2-methoxy-4-pyrone derivative **13** based on its thin layer chromatographic mobility and spectral data: ir (chloroform): 1710, 1660, 1620, 1530, 910, and 850 cm^{-1}; nmr (deuteriochloroform): δ 1.86 (s, 6H), 1.90 (s, 3H), 4.05 (s, 3H), 6.22 (s, 1H), and 7.30 (s, 1H).

The methylation of **12** could also be conducted by stirring with dimethyl sulfate and anhydrous potassium carbonate in acetone at room temperature for five hours. Only traces of **13** could be detected by thin layer chromatography of the crude product. The separation of the desired isomer **1** from **13** could be effected by recrystallization of the crude reaction product in hexane.

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