hancement of the carbon resonances indicated in Table XIII in the single label column were obtained.

The Acetate Double Label Experiment. Repetition of the optimized acetate feeding with sodium [1,2-^{13}C]acetate gave a sample of fonsecin which exhibited well-defined ^{13}C–^{13}C couplings as indicated in Table XIII. The only coupling not observable was that for carbon 1, at δ_C 25.5, which was obscured by solvent peaks. Several spectra were taken of this sample. It should be noted that not every coupling was observable in every spectrum. A sample spectrum has been provided as supplementary material. (See paragraph at end of paper about supplementary material.)

Acknowledgment. This work was partially supported by National Science Foundation Grant No. CHE-76-05757.

Registry No. Fonsecin, 3748-39-8.

Supplementary Material Available: Natural abundance ^{13}C NMR spectrum of fonsecin **3**, as well as gated-decoupled spectrum in the 150–160 ppm region, ^{13}C NMR spectrum of fonsecin derived from $^{13}CH_3{}^{13}CO_2Na$, with expansions of the congested 150–165 ppm and 93–105 ppm regions of the latter (9 pages). Ordering information is given on any current masthead page.

The Synthesis and Chemistry of Functionalized Furochromones. 2.[1] The Synthesis, Sommelet–Hauser Rearrangement, and Conversion of 4,9-Dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one to Ammiol

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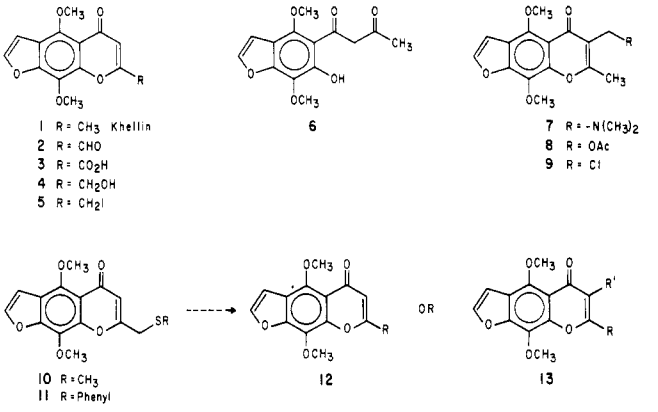
Condensation (NaH/THF) of khellinone **14** with ethyl 2-(methylthio)acetate followed by acid-catalyzed cyclodehydration in methanolic HCl yielded 4,9-dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**10**). Condensation of **14** with ethyl 2-(phenylthio)acetate followed by cyclodehydration yielded the corresponding C-7 (phenylthio)methylene analogue **11**. Sulfide **10** was converted to sulfonium salt **17** which upon treatment with base yielded the rearranged sulfide **18**, 4,9-dimethoxy-6-[(methylthio)methyl]-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one. Desulfurization of **18** yielded the 6,7-dimethylfurochromone **19** while treatment of both **18** and **10** with *N*,*N*-dimethylformamide dimethyl acetal yielded **20** and **21**, respectively. Periodate oxidation of **10** yielded sulfoxide **24** which underwent Pummerer rearrangement to give acetoxy sulfide **25**. Hydrolysis of **25** (to give **2**) and Meerwein–Ponndorf–Verley reduction then yielded ammiol **4**. Treatment of **10** with excess methyl iodide yielded the known allylic iodide **5**. Treatment of **5** with KO_2 or KOAc and then basic hydrolysis of that acetate likewise yielded ammiol. Treatment of **5** with *N*,*N*-dimethylamine afforded the C-7 aminomethylene analogue **27** in 96% yield.

Introduction

As a result of their recently discovered antiatherosclerotic and lipid-altering activity interest in the synthesis and chemistry of furochromones such as khellin (**1**) has increased.[2,3] Crucial to our strategy in exploring the chemistry and structure–activity relationship (SAR) between furochromones and their lipid-altering activity was the identification of certain functionalized furochromones which could accomodate several synthetic objectives. First, these functionalized systems must provide access to "key analogues" necessary in establishing the basis of our analogue program. Secondly, such systems must present the potential for changes in the furochromone system ranging from simple functional group transformations to conversion of the furochromone to other novel heterocyclic compounds.[1] Thus, the key element in our strategy for using functionalized furochromones was to provide a means of combining the synthetic and SAR aspects of as many compounds as possible. For example, each synthesis, in addition to providing a specific target molecule, should, if possible, also present intermediates that might be of general synthetic and/or SAR importance.[4]

Chart I



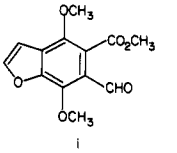
The limited use of *functionalized* furochromones as intermediates in the synthesis of khellin analogues is

(1) For Part 1 of this series see: Gammill, R. B.; Nash, S. A.; Mizsak, S. A. *Tetrahedron Lett.* **1983**, *24*, 3435.

(2) Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672 and references therein.

(3) For a recent total synthesis of khellin see: Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863.

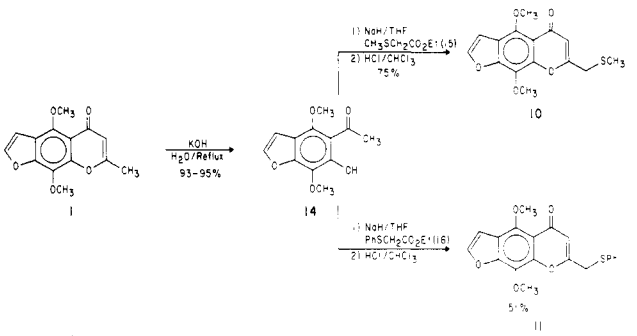
(4) An example of this strategy can be found in our total synthesis of khellin (ref 3). In this synthesis, the subtarget i, which was converted to khellin, is also an interesting intermediate for analogue synthesis.



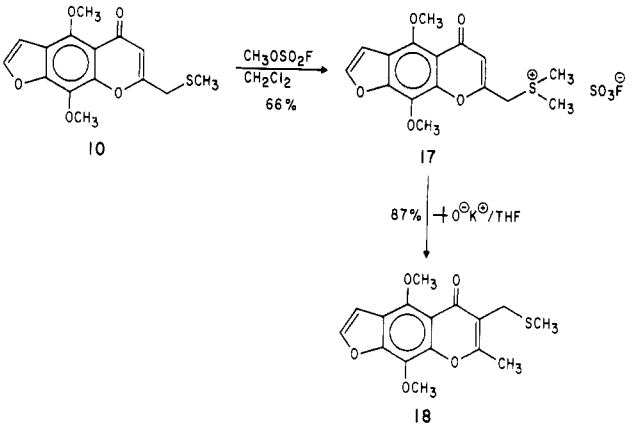
i

0022-3263/84/1949-5035$01.50/0

Scheme I



Scheme II



somewhat surprising in light of the commercial availability of khellin. The C-7 aldehyde **2** and the C-6 (aminomethylene)furochromone **7** are two examples where such systems have been used to advantage in preparing a number of interesting analogues (**3–5**, **8**, and **9**) not easily prepared by other means. Both Mustafa[5] and Renzi[6] have described the conversion of khellin (**1**) to aldehyde **2**. Unfortunately, Mustafa's synthesis was plagued with low yields and Renzi's SeO_2 oxidation of khellin gave, in addition to aldehyde **2**, other oxidation products, all in low yield. Mustafa, however, was able to clearly demonstrate the synthetic utility of aldehyde **2** through its conversion to a number of khellin analogues, including ammiol **4**, which is isolated in only trace amounts along with khellin from *ammi visnaga L.*[7]

The C-6 aminomethylene compound **7** is available in moderate yield from khellin, or more preferably the β-diketone **6**, through a Mannich reaction as described by Reichert, Abu-Shady, and Rehee.[8] Conversion of **7** to the C-6 allylic acetate **8**, and the allylic chloride **9** demonstrate the ease of functional group manipulation in this series.

The synthetic potential of an (alkylthio)- or (arylthio)methylene group at position seven in khellin, as illustrated by compounds **10** and **11**, was particularly intriguing to us. We viewed the sulfide group as both an entry to other functional groups at C-7 (**10** or **11** to **12**) as well as a means of transferring hetero functionality from C-7 to C-6 (**10** or **11** to **13**).

In this paper we wish to describe the preparation of both **10** and **11** and illustrate the usefulness of **10** in attaining several specific goals in our analogue program, namely, the transfer of functionality to C-6 from C-7, a short and highly efficient synthesis of ammiol and facile routes to other useful furochromone intermediates and analogues.

Data and Results

Furochromones **10** and **11** were both prepared via a combination condensation/acid-catalyzed cyclodehydration between khellinone **14** and ethyl 2-(methylthio)acetate **15** to give **10** and ethyl 2-(phenylthio)acetate **16** to give **11**. Khellin is efficiently converted to khellinone **14** with hot alkali.[9] Addition of a mixture of khellinone and the appropriate ester to a NaH/THF slurry in an ice bath yielded, after a mild acid quench (2 N HCl), an intermediate β-diketone which when treated with acid at reflux yielded the desired furochromones **10** and **11**.[10] Furthermore, this same condensation could be effected with the use of 4 equiv of $NaOCH_3$ in toluene followed by the same acid-catalyzed cyclodehydration. This latter process avoids the use of large quantities of NaH and thus generation of excessive amounts of hydrogen on scale up. It also requires less of the costly ester. Since the formation of **10** proceeded in higher yield and was not complicated by formation of byproducts, subsequent chemistry in this report will be limited to the (methylthio)furochromone **10**.

Sommelet–Hauser Rearrangement of 10. As stated above, one of the areas of interest with respect to furochromone **10** was the transfer of functionality to C-6 from C-7. Although the Sommelet–Hauser rearrangement[11] had not been reported in the chromone literature it seemed well suited for our needs.[12] As illustrated in Scheme II treatment of **10** with methyl fluorosulfonate in CH_2Cl_2 afforded the sulfonium salt **17** as a granular solid in 66% yield. Treatment of **17** with KO-*t*-Bu in aqueous THF proceeded smoothly to afford the desired rearrangement product **18** in 87% isolated yield. The structure of **18** was evident from both the ^1H and ^{13}C NMR (in conjunction with UV, IR, MS). The ^1H NMR of **18** lacked the C-6 vinyl hydrogen present in the starting sulfonium salt. In addition, there were signals at 2.35 δ, corresponding to the C-7 methyl, and 3.68 δ, corresponding to the methylene adjacent to sulfur. In the gated ^{13}C NMR spectrum of **18**,[13] the C-5 carbonyl appeared as a triplet, a result of long range coupling from the methylenes attached to C-6. Thus, a convenient and high yield entry to C-6 functionalized furochromones was available.

Reduction of **18** with Raney nickel cleanly afforded the 6,7-dimethylfurochromone **19** in 79% yield. It is interesting to note that we experienced no over reduction of the furan ring in this reaction.[14]

(5) Mustafa, A.; Starkovsky, N.; Salama, T. I. *J. Org. Chem.* **1961**, *26*, 886.

(6) Renzi, G.; Perini, P. *Farmaco, Ed. Sci.* **1969**, *24*, 1073.

(7) Seitz, G. *Arch. Pharm. (Weinheim, Ger.)* **1954**, *287*, 79.

(8) Reichert, B. *Arch. Pharm. (Weinheim, Ger.)* **1960**, *293*, 111. Abu-Shady, H. *U. A. R., J. Pharm. Sci.* **1970**, *11*, 283. Rehee, U. *Arch. Pharm. (Weinheim, Ger.)* **1974**, *307*, 866.

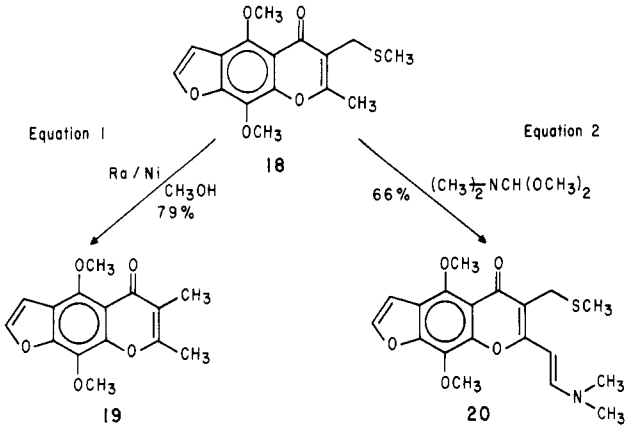
(9) Späth, E.; Gruber, W. *Chem. Ber.* **1938**, *71*, 106.

(10) For examples of this strategy for the preparation of analogues see ref 2 and 3. For a somewhat dated review of furochromone analogue synthesis see: Mustafa, A. In "The Chemistry of Heterocyclic Compounds"; Weissberger, A., Ed.; John Wiley and Sons: New York, 1967; Vol. 23, p 102.

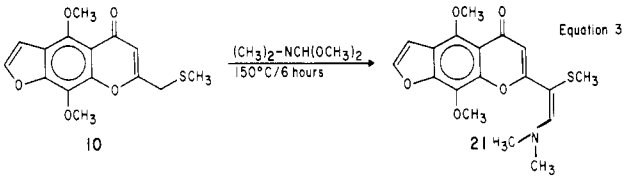
(11) For a recent discussion of this and similar 2,3-sigmatropic rearrangements see: Trost, B. M.; Melvin, L. S., Jr. "Sulfur Ylides. Emerging Synthetic Intermediates"; Academic Press: New York, 1975.

(12) To our knowledge, the 2,3-sigmatropic rearrangement of a sulfonium ylid on an α,β-unsaturated carbonyl system has not been reported. For the rearrangement of a stabilized oxosulfonium ylid on an unsaturated system see: Ide, J.; Kishida, Y. *Tetrahedron Lett.* **1966**, 1787. Tamura, Y.; Miyamoto, T.; Nishimura, T.; Kita, Y. *Tetrahedron Lett.* **1973**, 2351.

(13) In the gated experiment the decoupler is set at 0.



Condensation of **18** with *N,N*-dimethylformamide dimethyl acetal gave the novel 6-[(methylthio)methylene]-7-[2-(*N,N*-dimethylamino)ethylene]furochromone **20** in 66% yield. This reaction illustrates the ease of refunctionalization at C-7. Repeating this latter condensation with **10** afforded **21** in 37% yield. These results clearly indicate that the 2,3-sigmatropic rearrangement can very readily be extended to the pyrone ring system and thus lead to a variety of interestingly substituted and functionalized systems.



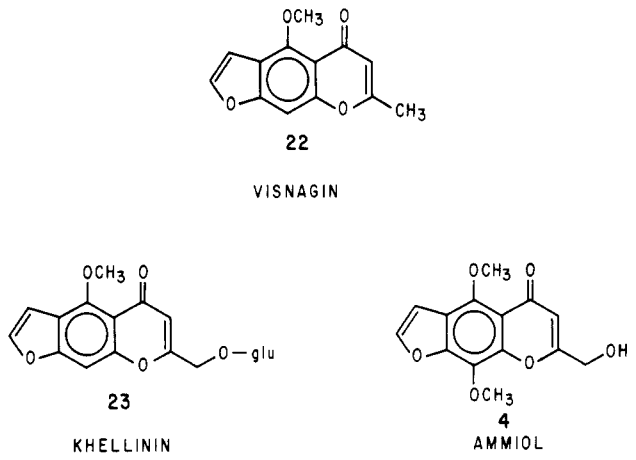
Synthesis of Ammiol. In addition to khellin, there are three additional furochromones which are isolated from *ammi visnaga L.* Of these compounds, visnagin[15] **22** and khellinin[16] **23** also possess lipid-altering activity.[2] The third furochromone, ammiol **4**, which is the least abundant of the four,[7] has not been available in sufficient quantity from *ammi visnaga L.* for assessment in the lipid area and therefore represented an important target. Below we describe two syntheses of ammiol from khellin. In the first synthesis, aldehyde **2**, because of its potential for subsequent transformations, served as our subtarget. In the second synthesis the allylic iodide **5**, for the same reason, was our target.

Oxidation of the (methylthio)furochromone **10** with $NaIO_4$ yielded the sulfoxide **24** in 92% yield. Finding reaction conditions that would cleanly effect a Pummerer rearrangement on the sulfoxide were at first problematic. The use of $(CF_3CO)_2O$,[17] for example, or Ac_2O with[18] and without NaOAc,[19] or extended reaction times at elevated temperatures lead to complex reaction mixtures. We did find, however, that briefly heating **24** in Ac_2O at 40–50 °C for 2–4 min in the presence of TsOH did provide the acetoxy sulfide **25** in 71% yield.[20] Conversion was extremely clean and a purification was not required prior to the hydrolysis to ultimately give the desired aldehyde. Hydrolysis of **25** to afford aldehyde **2** was best conducted by using $CuCl_2/H_2O/CH_3CN$ at reflux for 30 min (96% yield). The use of mercury salts, iodine, or basic reaction conditions gave a complex mixture of products.

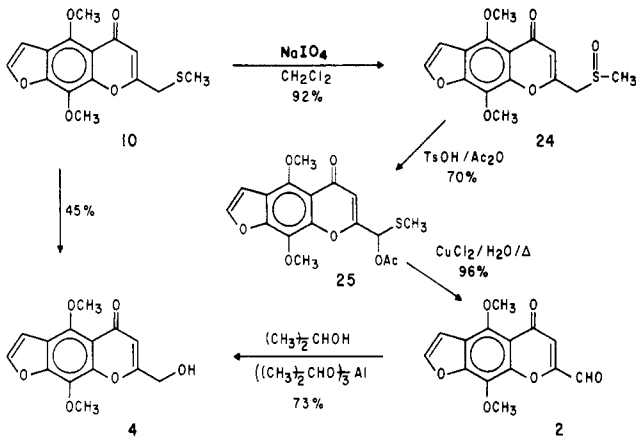
With aldehyde **2** in hand we were able to prepare ammiol by following the procedure of Mustafa.[5] Meerwein–Ponndorf–Verley reduction of **2** cleanly afforded ammiol in 73% yield. The overall yield of this six-step synthesis of ammiol from khellin was 32%. From the functionalized (methylthio)furochromone **10**, the overall yield was 45%.

Still another synthesis of ammiol which proceeded in higher overall yield and in fewer steps is illustrated in Scheme IV. This synthesis makes use of the allylic iodide **5**. Treatment of sulfide **10** with an excess of CH_3I in

Chart II



Scheme III. Synthesis of Ammiol



(14) Raney Active Nickel Catalyst No. 28, purchased from Grace Davison Chemical (W.R. Grace & Co., So. Pittsburgh, TN), was used in this reduction.

(15) Späth, E.; Gruber, W. *Chem. Ber.* **1941**, *71*, 1492.

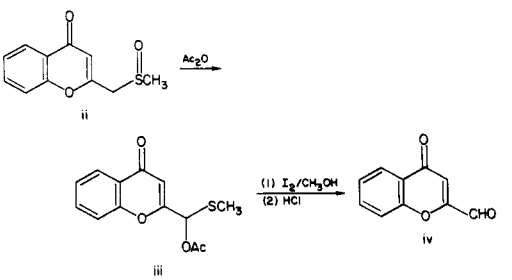
(16) Späth, E.; Gruber, W. *Chem. Ber.* **1941**, *71*, 1549.

(17) Sugihara, H.; Tanikaga, R.; Koji, A. *Synthesis* **1978**, 881.

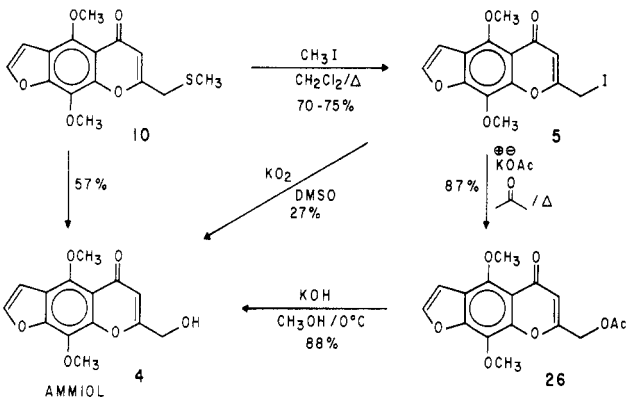
(18) Parham, W. E.; Edwards, L. D. *J. Org. Chem.* **1968**, *33*, 4150. Kise, M.; Oae, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1426.

(19) Irinchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 4280; *Ibid.* **1975**, *97*, 596.

(20) Connor, D. T.; Young, P. A.; Vonstrandtmann, M. *Synthesis* **1978**, 208. These authors have described the Pummerer rearrangement on the chromonesulfoxide ii. In this case, treatment of ii with Ac_2O for 5 h was required to effect rearrangement to give iii. Acetoxy sulfide iii was subsequently converted to aldehyde iv by first treatment with I_2/CH_3OH and then HCl.

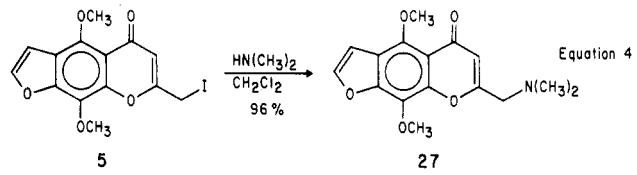


Scheme IV. Synthesis of Ammiol



CH_2Cl_2 at reflux for three days cleanly afforded the highly reactive allylic iodide **5** in 75% yield. Ammiol was obtained directly from **5** by addition of the allylic iodide to a Me_2SO solution of KO_2, or, addition of KO_2 to a THF solution of **5** containing an equivalent of 18-crown-6. The yield in both cases was a disappointing 27%. A more suitable synthesis of **4** was realized, however, through treatment of **5** with KOAc in refluxing acetone which afforded the allylic acetate **26** in 88% yield. Careful hydrolysis of **26** with aqueous sodium hydroxide then afforded ammiol in 87% yield. The overall yield of ammiol from khellin in this latter synthesis was 42%. The yield from (methylthio)furochromone **10** was 57%.

Further utility of the allylic iodide **5** is shown by its conversion to the C-7 aminomethylene compound **27** in 96% yield. Such compounds are only available in poor yield from the classical condensation/cyclization route used in the synthesis of sulfide **10**.[21]



Equation 4

Conclusion

We have demonstrated that functionalized furochromones[22] such as **10** can serve several purposes in analogue exploration. In this paper, we demonstrated that functional group manipulations can lead to specific key analogues (i.e., ammiol) necessary for SAR analysis. In addition, the ease of conversion of **10** to the aldehyde **2** and the allylic iodide **5** provide intermediates that can themselves serve as valuable sources of SAR information as well as being useful in the preparation of other important analogues, for example, the high yield preparation of the C-7 aminomethylene compound **27**. We were also able to use the functionalized furochromone **10** for the regiospecific transfer of functionality from C-7 to C-6.

Experimental Section

General Methods. Mass spectra, infrared spectra, ultraviolet spectra, and combustion analysis were obtained by the physical and analytical chemistry department of The Upjohn Company. ^1H NMR spectra were obtained at 60 MHz in deuteriochloroform solutions containing Me_4Si as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 197 spectrophotometer. Combustion analyses were also obtained from Micro-Analysis, Inc., Wilmington, DE. Thin-layer chromatography (TLC) was conducted with Merck glass plates precoated with silica gel 60 F-254. The TLC plates were visualized by UV light or iodine. Column chromatography was conducted at medium pressure utilizing silica gel 60 (E. Merck, 230–400 mesh). All solvents for chromatography were reagent grade distilled in glass (Burdick and Jackson).

6-Hydroxy-4,7-dimethoxy-5-benzofuranyl Methyl Ketone (14). To a stirred solution of 193.2 g (3.45 mol) of KOH in 1500 mL of H_2O heated to approximately 75 °C was added 300 g (1.15 mol) of khellin in six 50-g portions over approximately 30 min. After complete addition of khellin, the reaction was heated at reflux for 2 h. At the end of the reflux period, the reaction was allowed to cool to room temperature and 300 mL of concentrated HCl was added. The resulting precipitate was collected via filtration and dried at room temperature in a vacuum oven overnight. The crude yellow solid was recrystallized from 1 L of CH_3OH affording 251 g (93%) of **14**: mp 99–100 °C; silica gel TLC R_f 0.60 in (1:1) hexane/EtOAc; IR ($CHCl_3$) 3160, 3140, 2700, 1695, 1680, 1620, 1590, 1550, 1300, 1265, 1150, 1075, 1060 cm^{-1}; NMR ($CDCl_3$, δ) 7.52 (d, 1 H, J = 2.1 Hz), 6.91 (d, 1 H, J = 2.1 Hz), 4.15 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 2.72 (s, 3 H, CH_3), 13.06 (s, 1 H, phenolic OH, exchanges with D_2O); mass spectrum, ions at m/e (relative intensity) 236 (100), 221 (66), 206 (29), 203 (25), 191 (19), 175 (21), 163 (14), 119 (11). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.08. Found: C, 60.65; H, 5.15.

4,9-Dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*]-[1]benzopyran-5-one (10). To a sodium hydride (40.0 g, 50% oil dispersion, 0.833 mol)/THF (30 mL, freshly distilled from $LiAlH_4$) slurry, under a blanket of N_2, was added dropwise a mixture of 6-hydroxy-4,7-dimethoxy-5-benzofuranyl methyl ketone (**14**, 50.0 g, 0.211 mol), ethyl 2-(methylthio)acetate (**15**, 56.5 g, 0.422 mol), and THF (50 mL). Addition of this mixture was over approximately 45 min. Occasional cooling via an ice bath was necessary. After complete addition, the reaction was heated on a steam bath for 15 min. Examination of the reaction via TLC (1:1 hexane/EtOAc, aliquot quenched by addition to a 1:1 mixture of THF/5% HCl) indicated the absence of all starting material and the presence of a new product (R_f 0.54 in 1:1 hexane/EtOAc). The reaction was cooled to room temperature and excess NaH carefully neutralized with H_2O (150 mL). The reaction was then extracted with Et_2O (2 × 250 mL) and the Et_2O layer discarded. The aqueous basic layer was then diluted with CH_3OH (150 mL) and made strongly acidic with concentrated HCl (approximately 125 mL). That mixture was then refluxed for 25 min at which time TLC (100% EtOAc) indicated the absence of starting material and the presence of a new product (R_f 0.63 in EtOAc). The reaction was allowed to cool to room temperature and extracted with CH_2Cl_2 (2 × 300 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and solvent removed in vacuo to give 47.0 g (73%) of **10** as a tan solid (mp 148–150 °C). An analytical sample was prepared by recrystallization from methanol: mp 149–150 °C; silica gel TLC R_f 0.63 in 100% EtOAc; IR ($CHCl_3$) 1650, 1625, 1545, 1480, 1380, 1125, 1070, 1060, 845, 760 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.10 (d, 1 H, J = 2.1 Hz), 7.05 (d, 1 H, J = 2.1 Hz), 6.18 (s, 1 H, vinyl hydrogen), 4.2 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 3.60 (s, 2 H, CH_2SCH_3), 2.25 (s, 3 H, CH_2SCH_3); mass spectrum, ions at m/e 306, 291, 277, 259, 244, 231, 216, 201. Anal. Calcd for $C_{15}H_{14}O_5S$: C, 58.82; H, 4.57; S, 10.45. Found: C, 58.87; H, 4.76; S, 10.62.

Large Scale Preparation of 4,9-Dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (10) Using Sodium Methoxide. Under an atmosphere of nitrogen, sodium methoxide (91.36 g, 1.69 mol) was added to a flame dried 2-L, 3-neck round-bottom flask equipped with a mechanical stirrer, reflux condenser, and addition funnel (500 mL). Toluene (500 mL) was added to the flask. Khellinone (**14**, 100 g, 0.423 mol) and ethyl 2-(methylthio)acetate (**15**, 79.4 g, 0.592 mol), in toluene (500 mL), were added to the sodium methoxide slurry in a steady stream over approximately 15 min. The temperature of the reaction rose to 65 °C. The reaction was then heated at reflux for 15 h. The reaction was cooled (ice bath) and 2 N HCl (500

(21) In ref 2 we report the preparation of **27** from khellinone and ethyl α-(*N,N*-dimethylamino)acetate in 3% yield. Experimental details of that reaction can be found in U.S. Patent 4 304 722.

(22) During the preparation of this manuscript, Eiden and Schuenemann reported the preparation of several 6-acyl-7-(methylthio)furochromones. These functionalized furochromones react with hydrazine, amidines, and guanidine to yield pyrazolo- and pyrimidinonorkhellin analogues: Eiden, F.; Schuenemann, J. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 203.

mL) added. The toluene layer was separated and the aqueous layer extracted with toluene (3 × 100 mL). The toluene extracts were dried (Na_2SO_4) and the volume of the solution reduced to approximately 0.5 L. Anhydrous HCl gas was then bubbled through the solution for 1 min. The solution turned dark red and the flask was filled with a solid. After standing over night the toluene was evaporated and the resulting brown solid washed with ether/Skelly-B (1/10) and collected on a filter to afford 110 g of the product as a light tan solid. The filtrate will be discussed below. Chromatography over Florosil (1100 g, $CHCl_3$/EtOAc 1/1) followed by an ether/Skelly-B wash afforded 93.79 g of **10**. The filtrate from the initial ether wash was evaporated to yield 10 g of a dark oil which was chromatographed over Florosil (600 g, $CHCl_3$/EtOAc 1/1) to yield an additional 4.24 g of **10**. Total yield of **10**, 98.0 g (75.7%).

4,9-Dimethoxy-7-[(phenylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (11). To a NaH (30.48 g, 50% oil dispersion, 0.635 mol)/THF (50 mL, freshly distilled from $LiAlH_4$) slurry, under a blanket of nitrogen, was added dropwise a mixture of **14** (30.0 g, 0.127 mol), methyl 2-(phenylthio)acetate (**16**, 46.2 g, 0.254 mol), and THF (50 mL). Addition of this mixture was at such a rate to maintain a gentle reflux. Addition took approximately 1 h. After complete addition, the reaction was heated on a steam bath for 15 min. The reaction was allowed to cool to room temperature and excess NaH was carefully quenched with ice. The reaction was then diluted with H_2O (100 mL) and extracted with Et_2O (4 × 50 mL). The organic extracts were discarded. The aqueous basic layer was diluted with CH_3OH (600 mL) and concentrated HCl (180 mL). The mixture was then refluxed for 3 h. The reaction was allowed to cool to room temperature, was extracted with CH_2Cl_2 (4 × 500 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo to give approximately 60 g of a dark brown oil. The crude reaction was chromatographed over 2.1 kg of silica gel packed in 25% hexane/EtOAc. The oil was placed on the column in 100 mL of 25% hexane/EtOAc. Fractions of 250 mL were collected. The appropriate fractions were combined and evaporated in vacuo to give 24.31 g of a white solid which was recrystallized from methanol to give 20.22 g of **11**: mp 133–134 °C; silica gel TLC R_f 0.46 in 25% hexane/EtOAc; IR ($CHCl_3$) 3140, 3120, 1690, 1620, 1590, 1545, 1485, 1385, 1365, 1345, 1210, 1125, 1070, 1055, 735 cm^{-1}; NMR ($CDCl_3$, δ) 7.18 (d, 1 H, J = 2.1 Hz), 7.20–7.55 (m, 5 H, aromatic protons), 7.0 (d, 1 H, J = 2.1 Hz), 6.08 (s, 1 H, vinyl hydrogen), 4.15 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 3.98 (s, 2 H, CH_2SPh); mass spectrum, ions at m/e 368, 260, 259, 258, 231, 216. Anal. C, 65.21; H, 4.34; S, 8.69. Found: C, 64.98; H, 4.24; S, 8.56.

[(4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*][1]-benzopyran-7-yl)methyl]dimethylsulfonium Fluorosulfate (17). To a solution of 4,9-dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**10**) (3.06 g, 10 mmol) in CH_2Cl_2 (50 mL) was added dropwise CH_3OSO_2F (1.14 g, 10 mmol) in CH_2Cl_2 (15 mL) over approximately 30 min at room temperature. The reaction was allowed to stir an additional 30 min, during which time a solid separated. The reaction was filtered giving 2.78 g (66%) of a tan solid [mp 193–195 °C dec]. An analytical sample was obtained via recrystallization from methanol: mp 193–195 °C dec; IR ($CHCl_3$) 3120, 3080, 1665, 1635, 1605, 1555, 1480, 1350, 1295, 1205, 1135, 1085, 1070 cm^{-1}; NMR (Me_2SO-d_6, δ) 7.82 (d, 1 H, J = 2.1 Hz), 7.10 (d, 1 H, J = 2.1 Hz), 6.40 (s, 1 H, vinyl hydrogen), 4.85 (s, 2 H, CH_2S), 4.20 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 3.15 (s, 6 H, $S^+(CH_3)_2$). Anal. Calcd for $C_{16}H_{17}O_8S_2F$: C, 45.71; H, 4.04; S, 15.23. Found: C, 46.01; H, 4.37; S, 15.28.

4,9-Dimethoxy-6-[(methylthio)methyl]-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (18). To a THF solution (150 mL) of KO-*t*-Bu (1.26 g, 12.2 mmol) was added [(4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*][1]benzopyran-7-yl)methyl]dimethylsulfonium fluorosulfate (**17**, 5.14 g, 12.2 mmol). Water (10.0 mL) was then added to this heterogeneous solution. The reaction first turned pink, then red, and after stirring overnight, was yellow. The reaction was poured into CH_2Cl_2 (250 mL) and the resulting solution washed with 5% HCl (3 × 100 mL). The CH_2Cl_2 solution was dried ($MgSO_4$) and solvent removed in vacuo to give 3.59 g of a light tan solid. That tan solid was chromatographed over 200 g of gravity grade silica gel packed in 10% EtOAc/$CHCl_3$. Appropriate fractions were combined to give 3.39 g (87%) of **18**: mp 151–152 °C; silica gel TLC R_f 0.6 in 10% EtOAc/$CHCl_3$; IR ($CHCl_3$) (CH) 3120, 3100, (C=O/C=C) 1630, 1615, (C=C) 1600, 1545, 1485, (CO/other) 1270, 1135, 1065, 780 cm^{-1}; NMR ($CDCl_3$, δ) 7.65 (d, 1 H, J = 2 Hz), 7.03 (d, 1 H, J = 2 Hz), 4.18 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 3.68 (s, 2 H, CH_2S), 2.5 (s, 3 H, CH_3), 2.2 (s, 3 H, SCH_3); mass spectrum, ions at m/e (relative intensity) 320 (100), 305 (77), 290 (27), 275 (36), 273 (76), 274 (98), 259 (37), 205 (26), 177 (23), 43 (22); UV (EtOH) λ_{max} (ϵ) 214 (14 950), 249 (45 300), 281 (4750), 284 (4850), 298 (sh) (3550), 328 (5150). Anal. Calcd for $C_{16}H_{16}O_5S$: C, 60.00; H, 5.00; S, 10.00. Found: C, 60.00; H, 4.92; S, 9.89.

4,9-Dimethoxy-6,7-dimethyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (19). To a CH_3OH solution (60 mL) of 4,9-dimethoxy-6-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**18**, 1.0 g, 3.1 mmol) was added approximately 5 g of Ra/Ni.[9] That mixture was refluxed for 1 h, the reaction cooled, and the Ra/Ni catalyst removed by filtration. The CH_3OH was removed in vacuo to give a solid which was recrystallized from CH_3OH to give 670 mg (79%) of **19**: mp 105–107 °C; silica gel TLC R_f 0.71 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) (CH) 3120, (C=O/C=C) 1645, 1620, (C=C) 1600, 1540, 1480, (CO/other) 1355, 1335 cm^{-1}; NMR ($CDCl_3$, δ) 7.65 (d, 1 H, J = 2 Hz), 7.01 (d, 1 H, J = 2 Hz), 4.20(s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 2.45 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3); mass spectrum, ions at m/e (relative intensity) 274 (92), 260 (15), 259 (100), 245 (44), 231 (46), 230 (69), 203 (26), 177 (15), 137 (8); UV (EtOH) λ_{max} (ϵ) 220 (15 150), 247 (44 150), 282 (4700), 332 (5450). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.10. Found: C, 65.49; H, 5.21.

(*E*)-4,9-Dimethoxy-6-[(methylthio)methyl]-7-[1-(*N*,*N*-dimethylamino)ethen-2-yl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (20). 4,9-Dimethoxy-6-[(methylthio)methyl]-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**18**, 6.0 g, 18.6 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (8 mL) were heated neat at 150 °C for 3 h. The reaction was cooled to room temperature and CH_3OH and excess acetal removed in vacuo to give a brown solid. That solid was washed with ether to give 4.58 g (66%) of completely homogeneous **20**: mp 160–162 °C; silica gel TLC R_f 0.57 in 1% CH_3OH/EtOAC; IR ($CHCl_3$) (CH) 3140, 3120, (C=O/C=C) 1630, 1620, 1600, (C=C) 1575, 1545, (CO/other) 1380, 1345, 1270, 1135, 1095, 1065, 955, 780 cm^{-1}; NMR ($CDCl_3$, δ) 7.55 (d, 1 H, J = 2 Hz), 7.51 (d, 1 H, J = 13 Hz), 6.95 (d, 1 H, J = 2 Hz), 5.08 (d, 1 H, J = 13 Hz), 4.15 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 3.78 (s, 2 H, CH_2S), 3.00 (s, 6 H, $N(CH_3)_2$), 2.15 (s, 3 H, SCH_3); mass spectrum, ions at m/e (relative intensity) 375 (8), 374 (14), 329 (19), 328 (72), 327 (100), 298 (30), 297 (57), 256 (11), 108 (20), 107 (20); UV (EtOH) λ_{max} (ϵ) 216 (25 000), 228 (22 850), 241 (25 400), 256 (24 850), 284 (sh) (12 850), 390 (44 900). Anal. Calcd for $C_{19}H_{21}NO_5S$: C, 60.80; H, 5.60; N, 3.73; S, 8.53. Found: C, 60.80; H, 5.80; N, 3.52; S, 8.50.

(*E*)-7-[2-(Methylthio)-1-(*N*,*N*-dimethylamino)ethen-2-yl]-4,9-dimethoxy-5*H*-furo[3,2-*g*][1]benzopyran-5-one (21). 4,9-Dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**10**, 7.8 g, 25.4 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (20 mL) were heated at 150 °C for 6 h. During that time, the reaction turned dark purple. The reaction was cooled to room temperature and the excess CH_3OH and acetal were removed in vacuo to give a dark oil. That oil was dissolved in 10% CH_3OH/$CHCl_3$ stirred with 15 g of silica gel for 15 min, and then filtered to give, after removal of solvent, a brown oil. That oil was chromatographed over 300 g of silica gel (10% CH_3OH/$CHCl_3$) to give 3.52 g (37%) of **21**: mp 133–138 °C; TLC SiO_2 R_f 0.36 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) (C=O/C=C) 1600, 1565, (CO/other) 1360, 1325, 1190, 1065 cm^{-1}; NMR ($CDCl_3$, δ) 7.71 (s, 1 H, vinyl), 7.60 (d, 1 H, J = 2 Hz), 6.96 (d, 1 H, J = 2 Hz), 6.69 (s, 1 H, vinyl), 4.17 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 3.33 (s, 6 H, $N(CH_3)_2$), 2.12 (s, 3 H, SCH_3); mass spectrum, ions at m/e (relative intensity) 361 (70), 356 (100), 284 (9), 205 (9), 177 (11), 126 (17); UV (EtOH) λ_{max} (ϵ) 214 (26 150), 239 (24 150), 254 (28 350), 381 (36 000). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 59.83; H, 5.26; N, 3.87; S, 8.86. Found: C, 59.52; H, 5.25; N, 3.83; S, 8.85.

4,9-Dimethoxy-7-[(methylsulfinyl)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (24). 4,9-Dimethoxy-7-[(methylthio)-methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**10**, 22.55 g, 73.7 mmol) was added to sodium metaperiodate (15.80 g, 73.8 mmol) in a 1-L flask. Those solids were suspended in a solvent mixture consisting of H_2O (200 mL), CH_3OH (375 mL), and THF (125

mL). That mixture was stirred under N_2 for three days at room temperature and then filtered. The filter cake was washed with 1:1 MeOH/$CHCl_3$ (200 mL) and EtOAc (2 × 150 mL). The resulting clear filtrate was then taken to dryness in vacuo. The dry residue was chromatographed on 8.5 × 120 cm of gravity grade silica gel, eluting with 5% $CH_3OH/CHCl_3$. Appropriate fractions were combined and the solvent removed in vacuo to give 22 g (92%) of **24**: mp 170–174 °C; silica gel TLC R_f 0.34 in 10% MeOH/$CHCl_3$; IR ($CHCl_3$) (C=CH) 3140, 3120, (C=O/C=C) 1650, 1620, 1550, 1480, (CO/other) 1380, 1365, (CO/SO) 1060 cm^{-1}; NMR ($CDCl_3$, δ) 7.75 (d, 1 H, J = 2 Hz), 7.05 (d, 1 H, J = 2 Hz), 6.32 (s, 1 H, vinyl proton), 4.20 (s, 3 H, OCH_3), 4.10 (s, 2 H), 4.05 (s, 3 H, OCH_3), 2.88 (s, 3 H, SCH_3); mass spectrum, ions at m/e (relative intensity) 322 (19), 259 (26), 232 (14), 231 (100), 217 (5), 216 (36), 205 (6), 201 (22), 177 (12), 63 (6); UV (EtOH) λ_{max} (ϵ) 211 (22950), 254 (37300), 286 (sh) (4700), 337 (4300). Anal. Calcd for $C_{15}H_{14}SO_6$: C, 55.90; H, 4.34; S, 9.93. Found: C, 55.93; H, 4.53; S, 9.98.

4,9-Dimethoxy-7-[(methylthio)acetoxymethyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (25). 4,9-Dimethoxy-7-[(methylsulfinyl)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**24**, 5.0 g, 15.5 mmol) was added to Ac_2O (50 mL). That solution was warmed to get all of the sulfoxide into solution. Once a homogeneous solution was obtained, TsOH (20 mg) was added and the reaction temperature raised to 40 °C for five min. Acetic anhydride was removed in vacuo to give a brown solid. That solid was washed with CH_3OH and filtered to give pure **25**, 4.20 g (71%). An analytical sample was prepared by recrystallization from EtOAc/hexane: mp 125–127 °C; silica gel TLC R_f 0.75 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) (CH) 3120, 3080, (C=O/C=O/C=C) 1750, 1660, 1635, 1610, (C=C) 1555, 1480, (CO/other) 1355, 1210, 1135, 1090, 1070, 1020, 940, 845, 740 cm^{-1}; NMR ($CDCl_3$, δ) 7.75 (d, 1 H, J = 2 Hz), 7.10 (d, 1 H, J = 2 Hz), 6.78 (s, 1 H, methine), 6.40 (s, 1 H, vinyl), 4.22 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 2.29 (s, 6 H, $COCH_3$, SCH_3); mass spectrum, ions at m/e (relative intensity) 364 (100), 317 (57), 289 (15), 275 (57), 260 (22), 259 (15); UV (EtOH) λ_{max} (ϵ) 213 (22650), 251 (32900), 285 (5000), 337 (4100). Anal. Calcd for $C_{17}H_{16}O_7S$: C, 56.04; H, 4.39; S, 8.79. Found: C, 56.09; H, 4.61;, S, 8.84.

4,9-Dimethoxy-7-formyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (2). The acetoxy sulfide **25** (13.47 g, 35.4 mmol) and $CuCl_2 \cdot 2H_2O$ (13.47 g) were added to 300 mL of a 1:1 mixture of CH_3CN/H_2O. That mixture was refluxed for 30 min during which time the color of the reaction changed from blue to yellow. The reaction was cooled to room temperature and extracted with EtOAc (3 × 200 mL) then $CHCl_3$ (2 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to give 9.34 g (96%) of **2**. That material was completely homogeneous via TLC and used for subsequent reactions. An analytical sample was prepared by recrystallization from $CHCl_3$: mp 182–184 °C; silica gel TLC R_f 0.58 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) 3160, 3130, 3080, 2740, 1710, 1655, 1625, 1610, 1560, 1480, 1475, 1345, 1130; 1090, 1070, 765 cm^{-1}; NMR ($CDCl_3$, δ) 9.77 (s, 1 H, aldehyde), 7.68 (d, 1 H, J = 2 Hz), 7.03 (d, 1 H, J = 2 Hz), 6.75 (s, 1 H, vinyl), 4.05 (s, 3 H, OCH_3), 4.07 (s, 3 H, OCH_3); mass spectrum, ions at m/e (relative intensity) 274 (100), 260 (16), 259 (98), 246 (12), 245 (76), 231 (51), 230 (62), 203 (32), 147 (12); UV (EtOH) λ_{max} (ϵ) 213 (sh) (19150), 216 (19400), 246 (33100), 262 (sh) (22350), 281 (sh) (4400), 334 (4400). Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.31; H, 3.64. Found: C, 61.34; H, 3.95.

4,9-Dimethoxy-7-(hydroxymethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one, Ammiol (4). To isopropyl alcohol (250 mL) was added aldehyde **2** (8.12 g, 29.6 mmol) and $Al(O\text{-}i\text{-}Pr)_3$ (18.13 g). That mixture was then heated at reflux for 30 min. The reaction was cooled to room temperature, poured into 2 N HCl (500 mL), and vigorously stirred for 15–20 min. That mixture was then extracted with EtOAc (3 × 200 mL) and $CHCl_3$ (2 × 500 mL). The organic layers were combined and dried ($MgSO_4$), and solvent removed in vacuo to give 8.0 g of crude ammiol. That material was heated in CH_3OH, cooled, and filtered to give 6.0 g (73%) of pure ammiol. An analytical sample was prepared as follows. Ammiol (4.90 g) was added to Ac_2O/pyridine (1:1, 80 mL) and stirred at room temperature overnight. The Ac_2O/pyridine was removed in vacuo and the resulting acetate chromatographed (silica gel, 20% EtOAc/$CHCl_3$) to give 5.0 g of ammiol acetate, **26**, mp 102–104 °C. The acetate (1 g) in 10 mL of CH_3OH was treated with 10 mL of a 2 N NaOH solution. The resulting solid was filtered and air dried to give 750 mg of ammiol: mp 210–212 °C; silica gel TLC R_f 0.44 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) 3200, 3100, 2950, 2850, 1650, 1615, 1540, 1480, 1440, 1380, 1350, 1320, 1120, 1075 cm^{-1}; ^1H NMR ($Me_2SO\text{-}d_6$, δ) 8.12 (d, 1 H, J = 2 Hz), 7.22 (d, 1 H, J = 2 Hz), 6.20 (s, 1 H, vinyl), 4.42 (s, 2 H, CH_2OH), 4.09 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3); mass spectrum, ions at m/e (relative intensity) 276 (95), 261 (100), 247 (37), 233 (27), 232 (40), 205 (24), 203 (17), 179 (41), 138 (58); UV (EtOH) λ_{max} (ϵ) 216 (19700), 247 (37500), 279 (4750), 332 (4700). Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.86; H, 4.34. Found: C, 60.64; H, 4.48.

4,9-Dimethoxy-7-(iodomethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one (5). 4,9-Dimethoxy-7-[(methylthio)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**10**, 15.0 g, 49.0 mmol), CH_3I (300 g), and CH_2Cl_2 (30 mL) were refluxed for three days. During that time a white solid separated from solution. The reaction was cooled to room temperature and filtered. The CH_3I and CH_2Cl_2 were removed in vacuo yielding a yellow solid. That material was suspended in CH_2Cl_2 and the solid removed by filtration. The CH_2Cl_2 was removed in vacuo and the resulting brown solid washed with Et_2O to give 15.0 g (79%) of **5**: mp 157–159 °C (lit.[4] mp 158–159 °C); silica gel TLC R_f 0.76 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) 3000, 2940, 2850, 1650, 1620, 1540, 1475, 1440, 1380, 1340, 1150, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.70 (d, 1 H, J = 2 Hz), 7.05 (d, 1 H, J = 2 Hz), 6.34 (s, 1 H, vinyl), 4.30 (s, 2 H, CH_2I), 4.23 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3); mass spectrum, ions at m/e (relative intensity) 386, 260 (53), 259 (66), 254 (84), 246 (20), 245 (46), 231 (100), 217 (21), 216 (45), 142 (68), 127 (39). Anal. Calcd for $C_{14}H_{11}IO_5$: C, 43.54; H, 2.87; I, 32,86. Found: C, 43.48; H, 2.88; I, 33.09. UV (EtOH) λ_{max} (ϵ) 216 (30250), 253 (35550), 340 (4250).

4,9-Dimethoxy-7-(hydroxymethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one, Ammiol (4). To a flame-dried 10-mL round-bottom flask was added KO_2 (36.7 mg, 51.8 × 10^{-5} M). That was immediately covered with Me_2SO (2 mL) under an atmosphere of N_2 and then stirred for 30 min at room temperature to allow the KO_2 to dissolve. 4,9-Dimethoxy-7-(iodomethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**5**, 200 mg, 51.8 × 10^{-5} M) was then added to the above solution portionwise over 15–20 min. After complete addition, the reaction was stirred for an additional 15 min and then quenched by addition of brine (approximately 10 mL). That was extracted with $CHCl_3$ (3 × 20 mL) and dried ($MgSO_4$) and the solvent removed in vacuo to give 90 mg of a brown solid which was washed with a small amount of $CHCl_3$ and then recrystallized from aqueous CH_3OH (2 mL) to give 38 mg (27%) of product: mp 210–212 °C (lit.[4] mp 211 °C); silica gel TLC R_f 0.44 in 1% CH_3OH/EtOAc; IR ($CHCl_3$) 3200, 3100, 2950, 2850, 1655, 1616, 1540, 1480, 1440, 1380, 1350, 1320, 1120, 1075 cm^{-1}; ^1H NMR ($Me_2SO\text{-}d_6$) 8.12 (d, 1 H, J = 2 Hz), 7.22 (d, 1 H, J = 2 Hz), 6.20 (s, 1 H, vinyl), 4.42 (broad, 2 H, CH_2OH), 4.09 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3); mass spectrum, ions at m/e (relative intensity) 276 (95), 261 (100), 247 (37), 233 (27), 232 (40), 205 (24), 203 (17), 179 (41), 138 (58). Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.84; H, 4.34. Found: C, 60.60; H, 4.34. UV (EtOH) 216 (19700), 247 (37500), 179 (4750), 332 (4700).

4,9-Dimethoxy-7-(acetoxymethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one (26) and Ammiol 4. 4,9-Dimethoxy-7-(iodomethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one (1.10 g, 2.85 mmol) was combined with KOAc (1.10 g, 11.2 mmol) in acetone (30 mL). That suspension was heated to reflux for 16 h, then allowed to cool to room temperature. The solid precipitate was removed via filtration and the filtrate was taken to dryness in vacuo. The dry residue was suspended in 20% EtOAc/$CHCl_3$ (100 mL) and filtered. This filtrate was again evaporated to afford ca 900 mg of nearly pure product. Chromatography (HPLC, Merck B Column) with 10% EtOAc/$CHCl_3$ afforded 810 mg (87%) of pure ammiol acetate: mp 102–104 °C (lit.[4] mp 102–103 °C); silica gel TLC R_f 0.46 in 100% EtOAc; IR ($CHCl_3$) 3140, 3000, 2950, 2850, 1750, 1655, 1620, 1540, 1480, 1440, 1380, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.65 (d, 1 H, J = 2 Hz), 7.03 (d, 1 H, J = 2 Hz), 6.23 (s, 1 H, vinyl hydrogen), 5.03 (s, 2 H, CH_2OAc), 4.20 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 2.20 (s, 3 H, $COCH_3$); mass spectrum, ions at m/e (relative intensity) 318 (100), 303 (85), 289 (37), 261 (41), 243 (16), 232 (17), 231 (18), 201 (16). Anal. Calcd for $C_{16}H_{14}O_7$: C, 60.40; H, 4.40. Found: C, 60.26; H, 4.61. UV (EtOH) λ_{max} (ϵ)

214 (20 850), 247 (34 350), 282 (4550), 334 (4350).

A methanolic solution (10 mL) of **26** (1.0 g, 3.1 mmol) was treated with 2 N NaOH (10 mL) at 0 °C. The resulting solid was collected by filtration and dried to give 750 mg (87%) of analytically pure ammiol: mp 210–212 °C. Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.84; H, 4.34. Found: C, 60.64; H, 4.48.

4,9-Dimethoxy-7-[(dimethylamino)methyl]-5*H*-furo[3,2-*g*][1]benzopyran-5-one (27). A methylene chloride solution (50 mL) of 4,9-dimethoxy-7-(iodomethyl)-5*H*-furo[3,2-*g*][1]benzopyran-5-one (1.19 g, 3.08 mmol) was treated with anhydrous dimethylamine for 5 min. After stirring for 3 h at room temperature, the solution was washed with H_2O (2 × 20 mL) and dried over Na_2SO_4. Evaporation gave an oil which was chromatographed over a Merck B Column in 10% MeOH/$CHCl_3$. Appropriate fractions were combined and the solvent removed in vacuo to give 0.90 g (97%) of a yellow oil which slowly crystallized: mp 107–109 °C; silica gel TLC R_f 0.35 in 10% $CH_3OH/CHCl_3$; IR ($CHCl_3$) 3120, 3080, 3060, 2790, 1650, 1630, 1620, 1595, 1545, 1485, 1385, 1075, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) 7.65 (d, 1 H, J = 2 Hz), 7.03 (d, 1 H, J = 2 Hz), 6.28 (s, 1 H, vinyl), 4.19 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.34 (s, 2 H, $CH_2N(CH_3)_2$) 2.38 (s, 6 H, $N(CH_3)_2$); mass spectrum, ions at m/e (relative intensity) 304 (11), 303 (60), 288 (25), 274 (9), 243 (10), 231 (8), 84 (10), 71 (12), 58 (100); UV (EtOH) λ_{max} (ϵ) 213 (20 300), 248 (35 150), 280 sh (4650), 333 (4450). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.61; N, 4.62. Found: C, 63.63; H, 5.66; N, 4.66.

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(*S*)-Tetrahydro-5-oxo-2-furancarboxylic Acid: A Chiral Derivatizing Reagent for Asymmetric Alcohols

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The use of (*S*)-tetrahydro-5-oxo-2-furancarboxylic (TOF) acid as a potential derivatizing reagent for the determination of the enantiomeric composition of chiral alcohols was investigated. A series of chiral alcohols of widely varying structural type were derivatized with this acid and compared with two widely used acids (*S*)-α-acetoxypropanoic and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic. The resolution of the diastereomeric esters was measured on five different capillary gas chromatographic (CGC) columns and one high-performance liquid chromatographic (HPLC) column. The ^{13}C NMR spectra of these derivatives were recorded and examined for possible correlations between configuration and carbon chemical shift values. The chromatographic data provide a starting point for the selection of a derivatizing agent and column combination applicable to the CGC analysis of chiral alcohol enantiomeric purity, and the HPLC data allow selection of a derivatizing agent and solvent system for the HPLC analytical or preparative resolution of a chiral alcohol. The ^{13}C NMR data provide information applicable to the assignment of the configuration to the resolved diastereomers.

Chiral alcohols and their derivatives are ubiquitous with numerous examples being found in the terpenoid family, the steroids, and particularly the field of insect pheromones.[1,2] Asymmetric alcohols occur as natural products and frequently as intermediates in the synthesis of chiral molecules.[2-12] The determination of the degree of chirality or enantiomeric excess (% ee) is critical both to the successful completion of an asymmetric synthesis and to the understanding of the results obtained from the biological evaluation of a chiral natural product. Many methods have been developed for the determination of the degree of enantiomeric purity of chiral alcohols, and although some preliminary success has been achieved in the direct gas chromatographic (GC) resolution of enantiomeric alcohols with chiral liquid phases,[13,14] the majority of gas chromatographic chiral alcohol resolutions utilize the formation of diastereomers with an enantiomerically pure chiral acid such as α-(alkanyloxy)propanoic,[15,16] α-hydroxy- and α-acetoxyalkanoic,[17] halogen-substituted α-(alkanoyloxy)-alkanoic,[18,19] (*S*)-α-acetoxypropanoic ((*S*)-lactic),[16,20-25] or

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