Reaction of Resorcinol with α,β-Unsaturated Ketones

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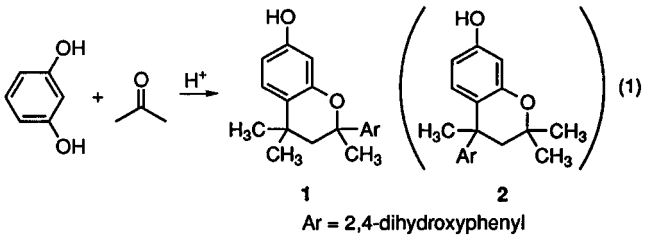
Received August 19, 1997

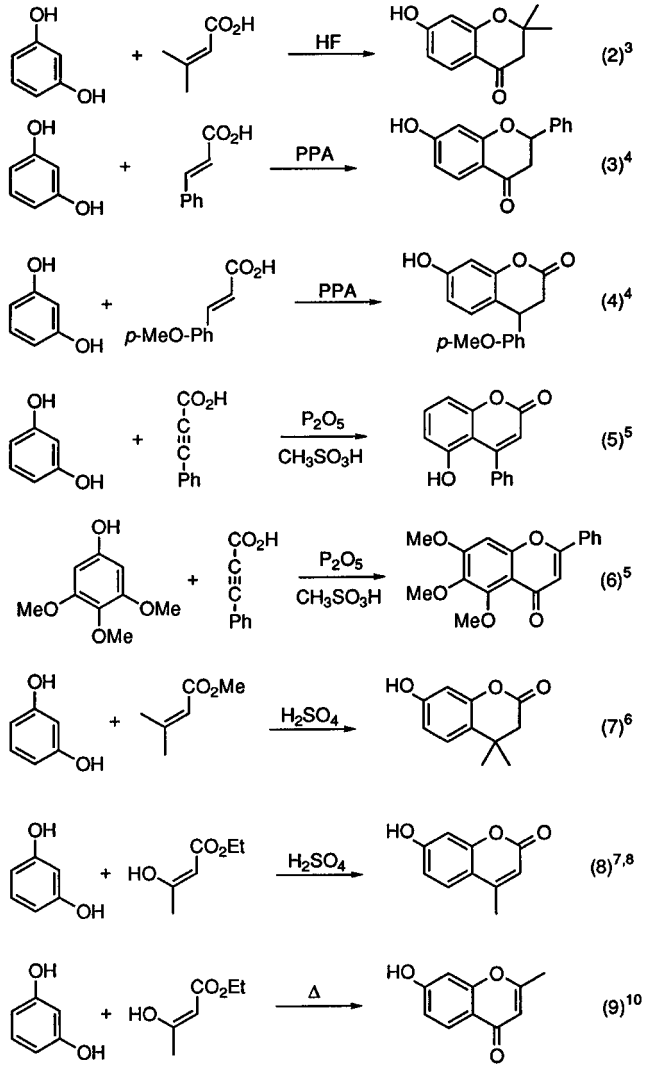
Products of the acid-catalyzed reaction of resorcinol with α,β-unsaturated ketones have been found to fall into two classes. The first type of product is illustrated by 4-(3,4-dihydro-7-hydroxy-2,4,4-trimethyl-2*H*-1-benzopyran-2-yl)-1,3-benzenediol, **1**, formed in 91% yield by the reaction of resorcinol with 4-methyl-3-penten-2-one (mesityl oxide). The second type of product is illustrated by (C_2-symmetric) 2,2′-spirobi(7-hydroxy-4,4-dimethylchroman), **4**, formed in 85% yield by the reaction of resorcinol with 2,6-dimethyl-2,5-heptadien-4-one (phorone). A number of examples of reactions leading, in quite good yields, to products analogous to **1** are presented, as well as some reactions that fail. Flavan **1** is identical to the compound formed by the acid-catalyzed reaction of acetone with excess resorcinol. Compound **1** and a steroidal analogue of **1** have been found to be fluorescent.

Recently, we reported[2] that the acid-catalyzed reaction of acetone with excess resorcinol produced **1**, rather than the chemically reasonable isomeric alternative **2** (eq 1). Because it is impossible to confidently distinguish **1** from **2** by spectroscopic means, an X-ray crystal structure determination was required.



It seemed reasonable to suppose that the dehydrated aldol product from acetone, mesityl oxide (4-methyl-3-penten-2-one), might be an intermediate in the acetone plus resorcinol reaction. As a step toward testing this hypothesis, the reaction of mesityl oxide with resorcinol was examined, and the results are reported herein.

Reactions closely analogous to this are known. To wit, equations 2−9 give examples of reactions of resorcinol with α,β-unsaturated acids, α,β-unsaturated esters, and β-keto esters, the last being the classic von Pechmann reaction. The particular heterocycle obtained is curiously



variable: compare eq 3, which gives a chromanone, and eq 4, which gives a dihyrocoumarin. Also, eq 5 gives a coumarin (note 5-hydroxy rather than 7-hydroxy) while eq 6 gives a chromone. Even the von Pechmann reaction (eq 8), which under conditions of catalysis by H_2SO_4 always gives a coumarin, was once erroneously thought to give a chromone under catalysis with P_2O_5 (the so-

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(2) Livant, P.; Webb, T. R.; Xu, W. *J. Org. Chem.* **1997**, *62*, 737−742.

(3) (a) Offe, H. A.; Barkow, W. *Chem. Ber.* **1947**, *80*, 458−463. (b) Mercier, C. *C. R. Acad. Sci. Ser. C* **1973**, *276*, 1053−1056.

(4) Talapatra, B.; Deb, T.; Talapatra, S. *Indian J. Chem.* **1986**, *25B*, 1122−1125.

(5) McGarry, L. W.; Detty, M. R. *J. Org. Chem.* **1990**, *55*, 4349−4356.

(6) Colonge, J.; LeSech, E.; Marey, R. *Bull. Soc. Chim. Fr. Ser. 5* **1957**, 776−779.

(7) Russell, A.; Frye, J. R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 281−285.

(8) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1−58.

(9) (a) Canter, F. W.; Curd, F. H.; Robertson, A. *J. Chem. Soc.* **1931**, 1255−1265. (b) Chakravarti, D. *J. Indian Chem. Soc.* **1931**, *8*, 129−136.

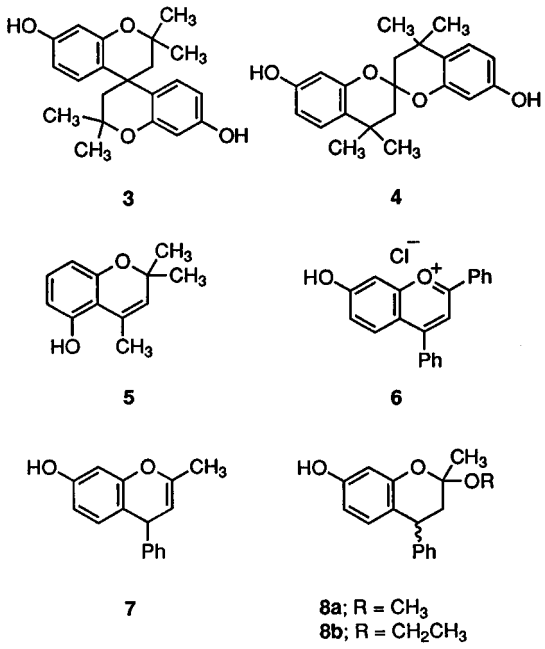
(10) (a) Pillon, D. *Bull. Soc. Chim. Fr.* **1952**, *19*, 324−330. (b) Mentzer, C.; Molho, D.; Vercier, P. *Compt. Rendu* **1951**, *232*, 1488−1490. (c) Mentzer, C.; Molho, D.; Vercier, P. *Bull. Soc. Chim. Fr.* **1952**, *19*, 91−93.

S0022-3263(97)01547-8 CCC: $15.00
Published on Web 01/22/1998

called Simonis reaction).[9] In fact, it does give the Simonis chromone at high temperature in the absence of catalyst (the Mentzer reaction, eq 9).[10]

In contrast to these well-studied reactions, our search of the literature revealed very few reports of the acid-catalyzed reaction of resorcinol with α,β-unsaturated ketones, and of those, most dealt with mesityl oxide. A variety of products has been postulated to arise from the reaction of resorcinol with mesityl oxide. One report claimed that **2** was the product of the reaction of resorcinol with mesityl oxide.[11] Another alleged **3** was the product of reaction of resorcinol with mesityl oxide.[12] A patent claimed that **4** was obtained from the acid-catalyzed reaction of resorcinol, mesityl oxide, and acetone.[13]

A patent gave **5** as the product of *base*-catalyzed reaction of resorcinol and mesityl oxide.[14] Yet another patent claimed **1** resulted from acid-catalyzed reaction of resorcinol and mesityl oxide.[15] Proof of structure was unavailable in this last case, and it is unclear how **2** was ruled out. As for a reaction of resorcinol with an α,β-unsaturated ketone other than mesityl oxide, to the best of our knowledge, there exist only two examples. Namely, benzylidenacetophenone in acid medium and in the presence of an oxidizing agent was reported to give **6**,[16] and benzylideneacetone and resorcinol gave either **7** or **8**, depending on solvent and temperature.[17] In view of this somewhat checkered record, it was decided to expand our investigation to include the acid-catalyzed reactions of resorcinol with α,β-unsaturated ketones in a more general sense.

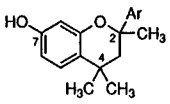
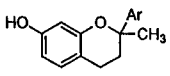
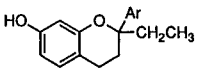
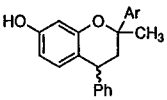
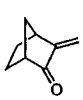
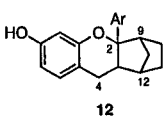
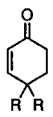
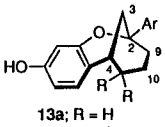
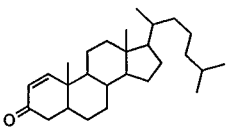
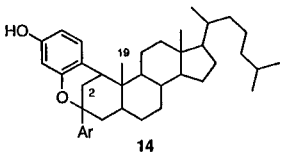
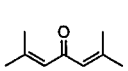
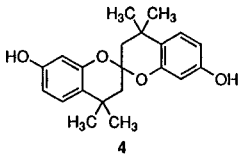
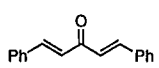
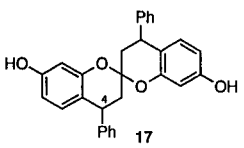


Results and Discussion

Reactions of Resorcinol with α,β-Unsaturated Ketones. The acid-catalyzed reaction of mesityl oxide with excess resorcinol gives **1** in 91% isolated yield (Table 1, entry 1). That the product was indeed **1** rather than the alternatives **2**,[11] **3**,[12] or **4**,[13] suggested previously, was confirmed by the exact match of all spectroscopic data of this product with those of the product of the acetone plus resorcinol reaction, shown previously[2] to be **1** by means of an X-ray structure determination.

Certain α,β-unsaturated ketones other than mesityl oxide react with resorcinol in the same way that mesityl oxide does. Before discussing these examples, it is necessary to address briefly the problem of structure proof, since uncertainties akin to the problem of distin-

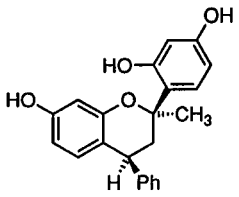
Table 1. Acid-Catalyzed Reactions of α,β-Unsaturated Ketones with Excess Resorcinol

Entry	Ketone	Product[a]	Yield (%)[b]
<1>		 **1**	91
<2>		 **9**	78
<3>		 **10**	85
<4>		 **11**	major 64 minor 12
<5>		 **12**	81
<6>		 **13a**; R = H **13b**; R = CH_3	**13a**; 87 **13b**; 92
<7>		 **14**	91
<8>		 **4**	85
<9>		 **17**	76

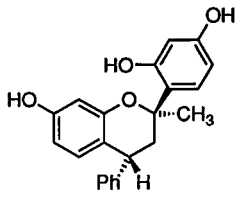
[a] Ar = 2,4-dihydroxyphenyl. [b] Isolated.

guishing **1** and **2** could arise in other cases as well. Fortunately, there is a telltale signal in the ^{13}C NMR of **1** that appears at 79.4 ppm and is due to the aliphatic quaternary carbon bound to oxygen, i.e., C2 according to flavan numbering. Compounds analogous to **2** would not be expected to have a quaternary carbon signal near this chemical shift position, and therefore, we consider the observation of such a signal to be diagnostic of a structure like **1**. In fact, most of the compounds reported below have a signal in the range 79−83 ppm.

Methyl vinyl ketone and ethyl vinyl ketone (Table 1, entries 2 and 3) both work well in this reaction, giving a single product (**9** and **10**, respectively) cleanly and in good yield. (Purification of these, and, to a certain extent, all the products reported in Table 1 was rendered more challenging than usual by their tendency to retain solvent tenaciously. Drying under vacuum at an elevated temperature was usually required to obtain sharp-melting samples that gave correct elemental analysis. To circumvent this problem, acetate derivatives were prepared for almost all the products listed.) A sample of 5-methyl-3-hexen-2-one (sold as a mixture with ca. 20 mol % 5-methyl-4-hexen-2-one) was tried, in the hope that the nonconjugated enone contaminant would not interfere. However, a product that was probably polymeric, judging from the NMR spectra, was obtained. Benzylideneacetone (entry 4) gave **11** in 78% isolated yield as a mixture of two diastereomers in a ratio of about 5:1. Molecular mechanics calculations[18] indicate **11**-*cis* is lower in energy than **11**-*trans* by 1.1 kcal/mol. (Taking, for convenience, this ΔE to be ΔG, and assuming the product distribution results from thermodynamic control, the calculated energy difference of 1.1 kcal/mol at 25 °C corresponds to a predicted ratio of 6.4:1). These calculations suggest, but certainly do not prove, that **11**-*cis* is the major product in this case.

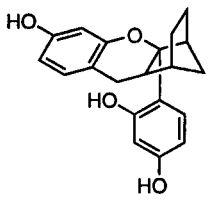


11-*cis*

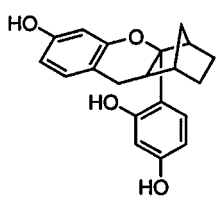


11-*trans*

The cases presented so far involve α,β-unsaturated ketones in which the enone π-system is not part of a ring. The reaction of resorcinol with 3-methylene-2-norbornanone (entry 5) provides a case in which the π-system is exocyclic to a ring. The reaction provides a single product, **12**, cleanly. Curiously, the C2 signal in **12** appeared at 101.0 ppm, rather than the expected 79−83 ppm region. Comparing **10** and **12**, C2 in **10** is bonded to 2,4-dihydroxyphenyl, oxygen, and two secondary carbons, while C2 in **12** is bonded to 2,4-dihydroxyphenyl, oxygen, and two tertiary carbons. The difference is the addition in **12** of two substituents β to C2. Using the venerable Grant and Paul scheme[19] for estimating carbon chemical shifts, the two extra β substituents should cause a downfield shift of 18.8 ppm. The chemical shift of C2 in **10** is 83.2 ppm. Therefore, the predicted value for C2 of **12** is 102.0 ppm, which is tolerably close to the observed value of 101.0 ppm. (The prediction is even better for the corresponding acetate derivatives: 99.7 ppm predicted versus 99.6 ppm actual.) We cannot state with certainty whether **12**-*exo* or **12**-*endo* is formed. (*Exo* and *endo* refer to the pendent 2,4-dihydroxyphenyl substituent.) Molecular mechanics calculations shed no light here since the calculated difference in energy between **12**-*exo* and **12**-*endo* is too small to be relied upon.

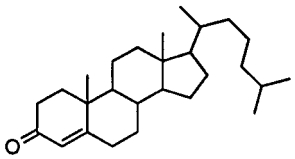


12-*exo*



12-*endo*

Cases in which the enone π-system is endocyclic gave more variable results. 2-Cyclohexenone and 4,4-dimethyl-2-cyclohexenone gave high yields of **13a** and **13b**, respectively (entry 6). Also, a steroidal A-ring α,β-unsaturated ketone, cholest-1-en-3-one, produced the analogous **14** in quite good yield (entry 7). We did not determine whether C2 (steroid numbering) in **14** is syn or anti to C19; however, molecular mechanics calculations predict the syn to be favored by more than 5 kcal/mol. By contrast, the two steroidal α,β-unsaturated ketones **15** and **16** failed to react with resorcinol at all under our standard conditions.



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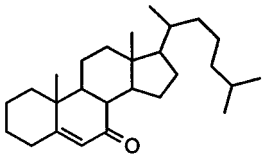


16

2-Cyclopentenone and 2-cycloheptenone reacted with resorcinol but did not give products similar to any discussed thus far. The products were water-soluble, which made separation from excess resorcinol, also water-soluble, a difficult task. In the 2-cycloheptenone case, basifying the aqueous product mixture caused a solid to precipitate. This solid gave a parent peak at *m*/*z* 202 in its mass spectrum, suggesting it is the condensation product of one resorcinol (MW 110) and one 2-cycloheptenone (MW 110) with loss of one water (MW 18). Its ^{13}C NMR spectrum showed no carbonyl carbon. In view of the difficulty in obtaining a pure sample, definitive evidence that would lead to a proof of structure is lacking.

(11) Kondrat'eva, G. G.; Volkotrub, M. N. *Sin. Issled. Eff. Khim-Dobavok., Polim. Mater.* **1969**, No. 2, 373-376; *Chem. Abstr.* **1972**, *76*, 59369z.

(12) Liska, K. J. *J. Med. Chem.* **1972**, *15*, 1177−1179.

(13) Harada, H.; Usui, M. Jpn Patent JP 62,111,988, 1985; *Chem. Abstr.* **1988**, *109*, 149374b.

(14) Kumiai Chemical Industry Co., Ltd., Mitsubishi Petrochemical Co., Ltd. Jpn. Patent 82,109,779, 1982; *Chem. Abstr.* **1982**, *97*, 198111f.

(15) (a) Mitsui Petrochemical Industries, Ltd. Jpn Patent JP 82 16,877, 1982; *Chem. Abstr.* **1982**, *97*, 6153b. (b) Mitsui Petrochemical Industries, Ltd. Jpn Patent JP 82,114,585, 1982; *Chem. Abstr.* **1982**, *97*, 216003d.

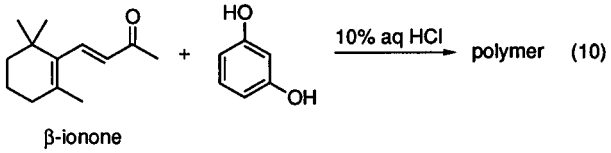
(16) Robinson, R.; Walker, J. *J. Chem. Soc.* **1934**, 1435−40.

(17) Clayton, D. W.; Elstow, W. E.; Ghosh, R.; Platt, B. C. *J. Chem. Soc.* **1953**, 581−586.

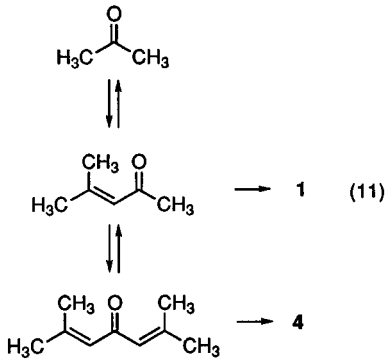
(18) The software used was PCModel (Serena Software), with the "MMX" force field.

(19) Quoted in: Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; p 58.

We also tried more extended π-systems. β-Ionone, an α,β,γ,δ-unsaturated ketone, gave an apparent polymer (eq 10). However, phorone (2,6-dimethyl-2,5-heptadien-

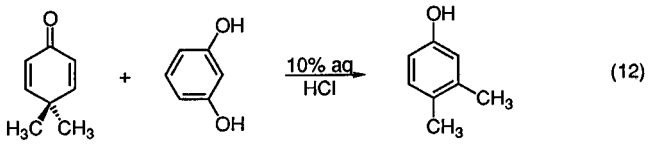


4-one), the "double" aldol condensation product from acetone, did not give **1**, but rather gave an 85% yield of spirochroman **4** (Table 1, entry 8). (This material was previously prepared[12,20] in 26% yield by the reaction of resorcinol with mesityl oxide catalyzed by $FeCl_3$). The fact that, under our conditions, mesityl oxide gave **1** and phorone gave **4** leads one to speculate that in the reactions of acetone with resorcinol in which both **1** and **4** are formed,[2] the amounts of **1** and **4** reflect the amounts of mesityl oxide and phorone, respectively, formed from aldol self-condensations of acetone (eq 11). In support of this suggestion is the observation[2] that acetone and resorcinol tend to give more **4** as the ratio of acetone to resorcinol increases.



Analogously, the reaction of *trans,trans*-dibenzylideneacetone with resorcinol gave spiro compound **17** in 76% yield. ^{1}H NMR of the crude product showed a small amount of what we presume to be another diastereomer of **17**. However, after purification only one diastereomer was obtained, almost certainly the one in which both pendent phenyls are in pseudoequatorial positions. MM2 calculations predict this to be the lowest-energy diastereomer (1.5 kcal/mol lower than di-axial; 2.1 kcal/mol lower than axial−equatorial), and the ^{1}H NMR coupling constants of H4 (chroman numbering), 5.7 and 12.9 Hz, are consistent with the diequatorial diastereomer. It is interesting to note that just as mesityl oxide gave **1** while phorone gave **4**, benzylideneacetone gave a product analogous to **1** (*viz.* **11**) while dibenzylideneactone gave a product analogous to **4** (*viz.* **17**).

A cyclic analogue of phorone is 4,4-dimethyl-2,5-cyclohexadienone. Under our standard reaction conditions, this compound did not react with resorcinol, but rather underwent a dienone−phenol rearrangement (eq 12)[21] to give 3,4-dimethylphenol in 92% yield. The reaction of 4*H*-pyran-4-one with resorcinol gave an intractable product mixture.



Fluorescence Studies. Steroid **14** is fluorescent. At concentrations in ethyl acetate of 0.0061, 0.061, 0.24, and 0.61 mM, **14** exhibited an emission peak at 308 nm. This should be compared to the emission found for resorcinol itself (0.7 mM in EtOAc) at 305 nm. The excitation spectra of **14** (308 nm emission) over this series of concentrations showed a single feature at 280 nm at the two lower concentrations, a broad multipeak band between 274 and 286 nm at 0.24 mM, and two resolved features at 267 and 292 nm at 0.61 mM. At 0.61 mM, the absorption spectrum of **14** shows one band at 280 nm. Emission spectra and excitation spectra were recorded for **1** at concentrations of 0.06 and 0.6 mM in EtOAc, and they were consistent with what was found for **14**: emission at 308 nm, a single excitation band at 283 nm at the lower concentration and two excitations, at 267 and 292 nm, at the higher concentration. In **14** or **1**, the splitting of the excitation band into two bands at higher concentrations is the result of intermolecular association between the resorcinol moieties of **14** or **1**. These spectroscopic results suggest that the reaction of resorcinol with steroidal α,β-unsaturated ketones could be used to append a fluorescent label to a steroid.

Experimental Section

General Procedure for Reaction of Resorcinol with α,β-Unsaturated Ketones. A mixture of 1 equiv of ketone, 6 equiv of resorcinol, and 1 equiv of HCl (as 10% HCl) dissolved in 1:1 (v/v) Et_2O:CH_2Cl_2 was stirred and refluxed for 24 h. Solvents were removed on the rotary evaporator, water was added, and the mixture was extracted repeatedly with CH_2Cl_2. The extracts were washed with warm water and dried over anhydrous Na_2SO_4. After filtration and removal of solvent, the crude product was purified by column chromatography on silica gel with 30:70 (v/v) ethyl acetate:hexanes.

4-(3,4-Dihydro-7-hydroxy-2,4,4-trimethyl-2*H*-1-benzopyran-2-yl)-1,3-benzenediol, 1. Following the general procedure, the reaction of 0.436 g (4.45 mmol) mesityl oxide, 2.940 g (26.70 mmol) of resorcinol, and 1.5 mL of 10% aqueous HCl (4.1 mmol) in 70 mL of 1:1 (v/v) Et_2O:CH_2Cl_2 gave 1.215 g (91%) of a colorless solid, mp 231−232 °C. ^{1}H NMR, ^{13}C, NMR and IR spectra were identical with those obtained for **1** prepared from resorcinol and acetone.[2] In addition, ^{1}H NMR (acetone-d_6, 250 MHz) δ: 0.78 (s, 3H), 1.20 (s, 3H), 1.65 (s, 3H), 1.84 (d, J = 13.9 Hz, 1H), 3.01 (d, J = 13.9 Hz, 1H), 6.18 (dd, J = 8.5, 2.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 8.4, 2.6 Hz, 1H), 6.43 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H).

2,2′-Spirobi(7-hydroxy-4,4-dimethylchroman), 4, was prepared in 85% yield as described previously[2] from 2,6-dimethyl-2,5-heptadien-4-one and resorcinol, mp 199−200 °C (lit.[12,20] mp 199−200 °C).

4-(3,4-Dihydro-7-hydroxy-2-methyl-2*H*-1-benzopyran-2-yl)-1,3-benzenediol, 9. The reaction of 1.03 g (14.7 mmol) of methyl vinyl ketone, 9.71 g (88.2 mmol) of resorcinol, and 5.4 mL of 10% aqueous HCl (15 mmol) produced 3.12 g (78%) of a colorless solid. A 521 mg portion was subjected to silica

(20) Liska assigned structure **3** to his product. However, after we repeated his procedure and obtained a material with identical mp, ^{13}C NMR made it clear that it was indeed **4** that was produced. In particular, the quaternary carbon signal at 99.95 ppm was consistent with the spiro carbon of **4** but inconsistent with any carbon in Liska's proposal.

(21) (a) Waring, A. J. *Adv. Alicycl. Chem.* **1966**, *1*, 129−256. (b) Miller, B. *Mechs. Mol. Migr.* **1968**, *1*, 247−313. (c) Perkins, M. J.; Ward, P. *Mechs. Mol. Migr.* **1971**, *4*, 55−112.

gel chromatography followed by drying at 110 °C under vacuum to give 318 mg of pure **9**, mp 174−176 °C. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 69.98; H, 6.00. HRMS: *m/z* calcd for $C_{16}H_{16}O_4$ 272.1048, found 272.1054. MS (EI): *m/z* (rel intens) 272 (M^+, 17), 257 (11), 150 (45), 137 (28), 123 (100). ^{1}H NMR (methanol-d_4, 250 MHz) δ: 1.63 (s, 3H), 1.81 (m, 1H), 2.28 (m, 1H), 2.43 (m, 1H), 2.87 (m, 1H), 6.12 (dd, J = 8.5, 2.4 Hz, 1H), 6.25 (m, 2H), 6.33 (d, J = 2.3 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H). ^{13}C NMR (methanol-d_4, 62.9 MHz) δ: 158.40 (quat), 157.68 (quat), 156.11 (quat), 156.07 (quat), 130.88 (CH), 129.26 (CH), 122.80 (quat), 115.02 (quat), 108.90 (CH), 107.16 (CH), 104.53 (CH), 104.10 (CH), 80.58 (quat), 32.40 (CH_2), 28.17 (CH_3), 23.38 (CH_2).

4-(3,4-Dihydro-7-hydroxy-2-ethyl-2*H*-1-benzopyran-2-yl)-1,3-benzenediol, 10. The reaction of 0.52 g (6.2 mmol) of ethyl vinyl ketone, 4.08 g (37.1 mmol) of resorcinol, and 2.3 mL of 10% aqueous HCl (6.3 mmol) generated 1.50 g (85%) of a colorless solid. A 352 mg portion was subjected to silica gel chromatography followed by drying at 110 °C under vacuum to give 275 mg of pure **10**, mp 162−168 °C. HRMS: *m/z* calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1207. MS (EI): *m/z* (rel intens) 286 (M^+, 6), 257 (21), 149 (15), 147 (22), 123 (100). ^{1}H NMR (methanol-d_4, 250 MHz) δ: 0.81 (t, 3H), 1.87 (m, 2H), 2.20 (m, 2H), 2.41 (m, 1H), 2.80 (m, 1H), 6.12 (dd, J = 8.5, 2.5 Hz, 1H), 6.25 (m, 2H), 6.33 (d, J = 2.5 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H). ^{13}C NMR (methanol-d_4, 62.9 MHz) δ: 158.40 (quat), 157.66 (quat), 156.23 (quat), 156.15 (quat), 130.83 (CH), 130.64 (CH), 120.90 (quat), 115.35 (quat), 108.79 (CH), 107.05 (CH), 104.42 (CH), 104.11 (CH), 83.23 (quat), 33.43 (CH_2), 30.96 (CH_2), 23.22 (CH_2), 8.45 (CH_3).

4-(3,4-Dihydro-7-hydroxy-2-methyl-4-phenyl-2*H*-1-benzopyran-2-yl)-1,3-benzenediol, 11. The reaction of 623 mg (4.23 mmol) of *trans*-4-phenyl-3-buten-2-one, 2.81 g (25.5 mmol) of resorcinol, and 2.3 mL of 10% aqueous HCl (6.3 mmol) afforded 1.34 g (90%) of product. Silica gel chromatography (ethyl acetate/hexane) generated 705 mg (64%) of major isomer and 175 mg (12%) of minor isomer. The following data refer to the major isomer. HRMS: *m/z* calcd for $C_{22}H_{20}O_4$ 348.1361, found 348.1350. MS (EI): *m/z* (rel intens) 348 (M^+, 1), 199 (34), 175 (25), 151 (100), 150 (43), 137 (26), 135 (44), 123 (31), 107 (24), 77 (28).

2′,4′,7-Trihydroxy-2,3-norbornanoflavan, 12. The reaction of 938 mg (7.45 mmol) of 3-methylene-2-norbornanone (97% purity), 5.08 g (46.2 mmol) of resorcinol, and 2.8 mL of 10% aqueous HCl (7.6 mmol) gave 1.96 g (81%) of product. A 511 mg portion was recrystallized from $CHCl_3$ to afford 488 mg of pure **12**, mp 190−192 °C. HRMS: *m/z* calcd for $C_{20}H_{20}O_4$ 324.1362, found 324.1362. MS (EI): *m/z* (rel intens) 324 (M^+, 20), 201 (100), 147 (21), 123 (69), 67 (24). ^{1}H NMR (CD_3CN, 400 MHz, assignments from COSY and C−H correlation spectra) δ: 0.78−0.81 (m, 1H), 1.21−1.32 (m, 2H), 1.43−1.49 (m, 2H), 1.75−1.79 (m, 1H), 2.393 (m, 1H; H9), 2.451 (m, 1H; H12), 2.847 and 2.937 (AB quartet, J = 15.0 Hz, 2H; H4a and H4e), 3.267 (d, J = 5.0 Hz, 1H; H3), 6.16−6.24 (m, 4H), 6.742 (dd, J = 8.0, 0.9 Hz, 1H), 6.946 (d, J = 8.2 Hz, 1H). ^{13}C NMR (CD_3CN, 100.6 MHz) δ: 162.52 (quat), 158.44 (quat), 157.73 (quat), 157.18 (quat), 134.32 (CH), 126.47 (CH), 120.92 (quat), 115.88 (quat), 108.21 (CH), 107.91 (CH), 103.78 (CH), 100.99 (quat; C2), 99.58 (CH), 52.65 (CH; C3), 47.22 (CH; C9), 42.32 (CH; C12), 39.41 (CH_2), 39.22 (CH_2), 24.29 (CH_2), 22.72 (CH_2).

2′,4′,7-trihydroxy-2,4-propanoflavan, 13a. The reaction of 0.272 g (2.83 mmol) of 2-cyclohexenone, 1.825 g (16.57 mmol) of resorcinol, and 1.0 mL of 10% aqueous HCl (2.7 mmol) afforded 0.711 g (87%) of a colorless solid, mp 113−130 °C. A portion was subjected to silica gel chromatography (30:70 EtOAc/hexanes) followed by drying at 110 °C under vacuum to give analytically pure **13a**, mp 189−191 °C. Analytical and spectroscopic data were reported previously.[2]

11,11-Dimethyl-2′,4′,7-trihydroxy-2,4-propanoflavan, 13b. Following the general procedure, 1.72 g (13.8 mmol) of 4,4-dimethyl-2-cyclohexenone, 8.86 g (80.5 mmol) of resorcinol, and 4.8 mL of 10% aqueous HCl gave 4.01 g (92%) of product. A 501 mg portion was recrystallized from $CHCl_3$ to afford 408 mg of pure **13b**, mp 187−188 °C. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 72.84; H, 6.74. HRMS: *m/z* calcd for $C_{20}H_{22}O_4$ 326.1518, found 326.1515. MS (EI): *m/z* (rel intens) 326 (M, 27), 270 (52), 269 (21), 255 (100), 161 (29). ^{1}H NMR ($CDCl_3$, 400 MHz; assignments from COSY and C−H correlation spectra) δ: 0.870 (s, 3H), 1.185 (s, 3H), 1.21 (m, 1H; H10a or H10e), 1.367 (dt, J = 13.6, 4.6 Hz, 1H, H10e or H10a), 1.916 (dt, J = 14.0, 5.0 Hz, 1H; H9a), 2.009 (dt, J = 13.3, 3.0 Hz, 1H; H3e), 2.280 (m, 1H; H9e), 2.505 (approximately quintet, J = 3.0 Hz, 1H; H4), 2.664 (dd, J = 13.5, 3.1 Hz, 1H; H3a), 4.493 (s, 1H; OH), 4.817 (s, 1H; OH), 6.35−6.38 (m, 3H), 6.424 (d, J = 2.5 Hz, 1H), 6.864 (d, J = 8.7 Hz, 1H), 7.005 (d, J = 8.4 Hz, 1H), 8.207 (s, 1H; OH). A long-range coupling, H3e/H9e, was evident in the COSY spectrum. ^{1}H NMR (CD_3CN, 400 MHz; assignments from COSY and C−H correlation spectra) δ: 0.845 (s, 3H), 1.119 (m, 1H; H10a or H10e), 1.224 (s, 3H), 1.367 (dt, J = 13.3, 4.8 Hz, 1H; H10e or H10a), 1.584 (dt, J = 13.5, 2.9, 1H; H3e), 1.733 (m, 1H; H9e), 2.404 (approx quintet, J = 2.7 Hz, 1H; H4), 2.630 (dt, J = 13.9, 5.2 Hz, 1H; H9a), 2.129 (dd, J = 13.6, 3.0 Hz, 1H; H3a), 6.24−6.30 (m, 3H), 6.343 (d, J = 2.5 Hz, 1H), 6.781 (d, J = 8.2 Hz, 1H), 7.326 (d, J = 9.2 Hz, 1H). H3e/H9e coupling was evident in the COSY spectrum. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 156.61 (quat), 156.24 (quat), 155.39 (quat), 154.66 (quat), 131.46 (CH), 126.10 (CH), 122.39 (quat), 117.61 (quat), 107.36 (CH), 106.93 (CH), 104.94 (CH), 102.24 (CH), 82.02 (quat.; C2), 42.71 (CH; C4), 35.81 (CH_2; C9), 33.86 (quat; C11), 31.49 (CH_2; C10), 30.77 (CH_2; C3), 29.55 (CH_3), 25.05 (CH_3).

2′,4′,7-Trihydroxy-2,4-(1,3-cholestano)flavan, 14. The reaction of 0.173 g (0.451 mmol) of cholest-1-en-3-one, 0.496 g (4.50 mmol) of resorcinol, and 0.2 mL of 10% aqueous HCl according to the general procedure gave 0.239 g (91%) of crude product. Recrystallization from EtOAc/hexanes and drying under vacuum at 110 °C afforded 0.218 g (83%) of analytically pure **14**, mp 265−266 °C. Anal. Calcd for $C_{39}H_{54}O_4$: C, 79.82; H, 9.28. Found: C, 79.72; H, 9.24. HRMS: *m/z* calcd for $C_{39}H_{54}O_4$ 586.4022, found 586.4020. MS (EI): *m/z* (rel intens) 586 (M, 7), 271 (21), 270 (100), 255 (97), 161 (36), 123 (79). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.300 (s, 1H, OH), 7.002 (d, J = 8.6 Hz, 1H), 6.914 (d, J = 8.2 Hz, 1H), 6.55−6.35 (m, 4H), 4.963 (s, 1H, OH), 4.919 (s, 1H, OH), 2.956 (approx quintet, J = 2.5 Hz, 1H), 2.616 (dd, J = 13.6, 2.9 Hz, 1H), 2.03−0.70 (m), 1.634 (s, 3H), 1.033 (s, 3H) 0.941 (d, J = 6.5 Hz, 3H), 0.874 (d, J = 6.6 Hz, 3H), 0.871 (d, J = 6.6 Hz, 3H), 0.704 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ: 156.49 (quat), 156.21 (quat), 155.34 (quat), 155.22 (quat), 130.29 (CH), 126.15 (CH), 122.31 (quat), 116.82 (quat), 107.65 (CH), 106.96 (CH), 104.92 (CH), 102.32 (CH), 82.77 (quat, C3), 56.41 (CH, C14 or C17), 56.24 (CH, C17 or C14), 48.17 (CH, C9), 42.86 (quat, C13), 42.50 (CH, C1?), 39.74 (CH_2, C4 or C12), 39.69 (CH_2, C12 or C4), 39.55 (CH_2, C24), 39.42 (CH, C5?), 37.01 (quat, C10), 36.19 (CH, C20), 35.93 (CH_2, C22), 35.80 (CH, C8), 31.13 (CH_2, C7 or C2), 30.64 (CH_2, C2 or C7), 28.19 (CH_2, C16), 28.02 (CH, C25), 27.64 (CH_2, C6?), 24.02 (CH_2, C15), 23.82 (CH_2, C23), 22.78 (CH_3, C26 or C27), 22.55 (CH_3, C27 or C26), 21.92 (CH_2, C11), 18.71 (CH_3, C21), 14.15 (CH_3, C19), 12.42 (CH_3, C18).

2,2′-Spirobi(7-hydroxy-4-phenylchroman), 17. A mixture of 0.474 g (2.02 mmol) of *trans*,*trans*-dibenzylideneacetone, 1.339 g (12.2 mmol) of resorcinol, 0.2 mL of 36% HCl, 25 mL of ether, and 25 mL of CH_2Cl_2 was stirred and refluxed 24 h. After removal of solvents, addition of water afforded a precipitate, which was collected and washed repeatedly with water. After vacuum-drying, the product was subjected to silica gel column chromatography (30:70 (v/v) EtOAc:hexanes) to yield 0.671 g (76%) of **17** as a 3:1 mixture of diastereomers, mp 270−283 °C. After recrystallization from CH_2Cl_2/CH_3CN, the major diastereomer was obtained, mp 299−302 °C. HRMS: *m/z* calcd for $C_{29}H_{24}O_4$ 436.1675, found 436.1676. MS (EI): *m/z* (rel intens) 436 (M, 4), 237 (10), 270 (100), 199 (100), 197 (18). ^{1}H NMR (CD_3COCD_3, 250 MHz) δ: 7.38−7.28 (m, 5H), 6.511 (d, J = 8.5 Hz, 1H), 6.36−6.32 (m, 2H), 4.499 (dd, J = 5.7, 12.9 Hz, 1H), 2.406 (dd, J = 5.7, 13.4 Hz, 1H), 2.196 (app t, J = 13.2 Hz, 1H). ^{13}C NMR (CD_3,$COCD_3$, 62.9 MHz) δ: 157.97 (quat), 153.86 (quat), 145.56 (quat), 130.64 (CH), 129.77 (CH), 129.59 (CH), 127.65 (CH), 118.26 (quat), 109.80 (CH), 104.29 (CH), 97.75 (quat), 41.72 (CH_2), 38.17 (CH).

Preparation of Acetate Derivatives. The following general procedure was used: To a solution of 2 mmol of hydroxy compound in 10 mL of dry pyridine was added 32 mmol of acetic anhydride dropwise with stirring. The reaction mixture was stirred for 1.5 h at 40−50 °C, allowed to cool to room temperature, and poured onto 60 mL of ice−water. The precipitate that formed was collected by filtration, recrystallized from EtOAc/hexanes, and dried at 110 °C in vacuo. Usually, one further recrystallization provided an analytically pure acetate. Complete spectroscopic data are given in the Supporting Information.

(a) Triacetate from **1**: 83% yield, mp 129−130 °C. Analytical and spectroscopic data as well as X-ray crystal structure were reported previously.[2]

(b) Diacetate from **4**: 95% yield, mp 194−5 °C. Analytical and spectroscopic data were reported previously.[2]

(c) Triacetate from **10**: 92% yield, mp 135−136 °C. Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.89; H, 5.90. HRMS: *m*/*z* calcd for $C_{23}H_{24}O_7$ 412.1522, found 412.1526.

(d) Triacetate from **11** (major isomer): mp 190−192 °C. HRMS: *m*/*z* calcd for $C_{28}H_{26}O_7$ 474.1678, found 474.1681.

(e) Triacetate from **12**: 92% yield. HRMS: *m*/*z* calcd for $C_{26}H_{26}O_7$ 450.1678, found 450.1675.

(f) Triacetate from **13a**: 91% yield, mp 145−146 °C. Analytical and spectroscopic data were reported previously.[2]

(g) Triacetate from **13b**: 94% yield, mp 88−92 °C. HRMS: *m*/*z* calcd for $C_{26}H_{28}O_7$ 452.1835, found 452.1831.

(h) Diacetate from **17**: 95% yield. mp 220−221 °C. HRMS: *m*/*z* calcd for $C_{33}H_{28}O_6$ 520.1886, found 520.1879.

3,4-Dimethylphenol. The reaction of 1.37 g (11.2 mmol) of 4,4-dimethyl-2,5-cyclohexadienone (prepared according to the published procedure[22]), 7.42 g (67.4 mmol) of resorcinol, and 4.0 mL of 10% aqueous HCl (11 mmol) gave a solid product. This was subjected to silica gel chromatography (EtOAc: hexane 1:3) and vacuum distillation, which afforded 1.268 g (92%) of 3,4-dimethylphenol, mp 66−68 °C (lit.[23] mp 65.11 ± 0.01 °C). MS (EI): *m*/*z* (rel intens) 122 (M^+, 68), 121 (41), 107 (100), 91 (24), 77 (38). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.005 (d, J = 8.0 Hz, 1H), 6.666 (d, J = 2.5 Hz, 1H), 6.000 (dd, J = 8.0, 2.8 Hz, 1H), 2.232 (s, 3H), 2.204 (s, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz): 153.42, 137.95, 130.47, 128.64, 116.58, 112.34, 19.82, 18.72.

Acknowledgment. We thank Prof. Vincenzo Cammarata for assistance with the fluorescence studies and Dr. K. P. Sarathy of the Auburn University NMR Center for a generous allocation of instrument time. Also, we are indebted to Mr. Steven Kizito for providing the steroids.

Supporting Information Available: Copies of NMR spectra for **10**−**12**, **17**, and the acetate derivatives of **11**, **12**, **13b** and **17**, listings of mass spectral data for **9**−**12** and **13b**−**17**, ^{13}C NMR data for **13b**, and listings of mass spectral, ^{1}H NMR, and ^{13}C NMR data for the acetate derivatives (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9715478

(22) (a) Zimmerman, H. E.; Binkley, R. W.; McCullough, J. J.; Zimmerman, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 6589. (b) Zimmerman, H. E.; Hackett, P.; Juers, D. F.; McCall, J. M.; Schroder, B. *J. Am. Chem. Soc.* **1971**, *93*, 3653.

(23) Andon, R. J. L.; Biddiscombe, D. P.; Cox, J. D.; Handley, R.; Harrop, D.; Herington, E. F. G.; Martin, J. F. *J. Chem. Soc.* **1960**, 5246−5254.