Reaction of Resorcinol With Acetone

P. Livant,* T. R. Webb, and Weizheng Xu

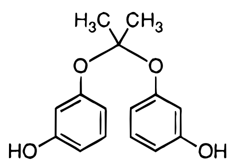
Department of Chemistry, Auburn University, Auburn, Alabama 36849-5312

Received August 26, 1996

Resorcinol is a solid having a reported mp of 109−110 °C.[1] Therefore, it was surprising to obtain by recrystallizing a sample of impure resorcinol from a mixture of chloroform and acetone a solid of mp 182−203 °C.

Since acetone and resorcinol are both venerable organic compounds, rich with history, it is reasonable to suspect that the reaction of resorcinol with acetone had been studied previously. Indeed, to the best of our knowledge, this reaction was reported for the first time in 1892 by Causse.[2] He obtained a solid, mp 212−213 °C, analyzing as $C_{15}H_{16}O_4$ and forming a diacetate and a dibenzoate, for which he proposed structure **1**. This was questioned in 1910 by Schmidlin and Lang who reported following Causse's procedure and obtaining a product (mp 230−240 °C) whose elemental analysis was consistent with the formula $C_{12}H_{14}O_2$, *i.e.* a compound formed by condensation of one resorcinol with two acetones with loss of two waters.[3] No structure was proposed, however.

Sen and co-workers[4] reported in 1930 that the reaction of acetone with resorcinol gave either **2** (mp 153 °C) or **3** (mp 165 °C) depending on the mole ratio of the reactants,



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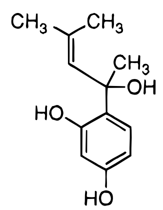

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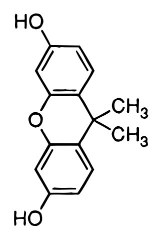

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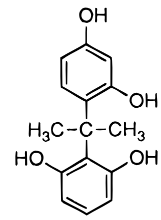
the nature of the acid catalyst, and the temperature and duration of the reaction. The assertion that **3** was orange-red in color was vigorously disputed by Weissberger and Thiele,[5] who, however, did not offer an alternative structure for the product. Malhotra and Banerjee in 1990 studied the kinetics of reaction of acetone with resorcinol and asserted that the product had the structure **4**.[6]

This reaction has appeared more often in the patent literature than in scholarly journals. A 1959 British patent,[7] with admirable candor, properly assigned the product structure ambiguously as either **5** or **6** (mp 225 °C). Since 1959, a plenitude of procedures for synthesizing from acetone and resorcinol a solid with mp *ca.* 225 °C has been patented[8] and all these patent abstracts baldly assert **5** to be the structure of the material



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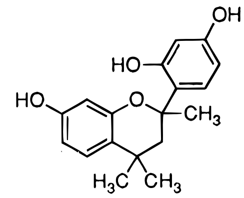

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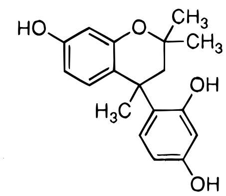

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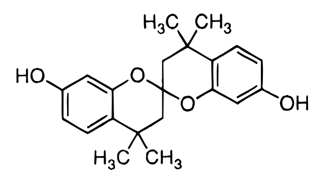

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synthesized but none explain how **6** was excluded from consideration. One lone report[9] contended **6** was obtained in the reaction of resorcinol with mesityl oxide, but it was not clear why **5** was not the product. A few patents[10] reported that spirobichroman **7** was formed in the reaction of acetone with resorcinol. In sum, more than a century after its first report, the structure of the product of the reaction of resorcinol with acetone had not been established.

Results and Discussion

Our curiosity was thus piqued, and we purified the aberrant resorcinol obtained from our "recrystallization". The analytically pure material had mp 231−2 °C. Elemental analysis and HRMS established the formula $C_{18}H_{20}O_4$. The compound formed a trimethyl ether derivative (**8**) and a triacetate derivative (**9**). The ^{13}C-NMR and DEPT-135 spectra showed six quaternary aromatic carbons, four of which were near 158 ppm and therefore bearing oxygen, six methine aromatic carbons, three methyl carbons, one methylene carbon and two quaternary aliphatic carbons. The ^{1}H-NMR and COSY showed two separate aromatic spin systems of three protons each, three methyl singlets, and a methylene AB quartet. These data, taken together, are consistent with *both* **5** *and* **6**, but without further data, distinguishing between the two is impossible.[11]

(1) Robertson, J. M.; Ubbelohde, A. R. *Proc. R. Soc. A* **1938**, *167*, 122−135.
(2) Causse, M. H. *Bull. Soc. Chim. Paris, Ser. 3* **1892**, *7*, 563−566.
(3) Schmidlin, J.; Lang, R. *Chem. Ber.* **1910**, *43*, 2806−2820.
(4) (a) Sen, R. N.; Quadrat-I-Khuda, M. *J. Indian Chem. Soc.* **1930**, *7*, 167−175. (b) Sen, R. N.; Chattopadhya, N. C.; Sen-Gupta, S. C. *Ibid.* **1930**, *7*, 997−1006.
(5) Weissberger, A.; Thiele, J. *J. Chem. Soc.* **1934**, 148−151.
(6) Malhotra, H. C.; Banerjee, S. *J. Indian Chem. Soc.* **1990**, *67*, 117−119.
(7) N. V. deBataafsche Petroleum Maatschappij Br. Patent 822 659, 1959; *Chem. Abstr.* **1960**, *54*, 7740b.
(8) (a) Bruin, P.; Klootwijk, A. U.S. Patent 2 947 760, 1960; *Chem Abstr.* **1960**, *55*, 13450b. (b) Sumitomo Chem. Co. Ltd. Jpn Patent 80 139 375, 1980; *Chem Abstr.* **1981**, *94*, 103168f. (c) Mitsui Petrochem. Ind. Ltd. Jpn Patent JP 81 05 476, 1981; *Chem Abstr.* **1981**, *95*, 97590q d) Mitsui Petrochem. Ind. Ltd. Jpn Patent JP 82 16 877, 1982; *Chem Abstr.* **1982**, *97*, 6153b. (e) Mitsui Petrochem. Ind. Ltd. Jpn Patent JP 82 114 585, 1982; *Chem Abstr.* **1982**, *97*, 216003d. (f) Mitsui Petrochem. Ind. Ltd. Jpn Patent JP 59 88 479, 1984; *Chem Abstr.* **1984**, *101*, 171099. (g) Mitsui Petrochem. Ind. Ltd. Jpn Patent JP 59 157 113, 1984; *Chem Abstr.* **1985**, *102*, 46742w. (h) Matsunaga, F.; Kondo, M. Jpn Patent JP 61 27 979, 1986; *Chem Abstr.* **1986**, *105*, 42540t. (i) Matsunaga, F.; Kondo, M. Jpn Patent JP 61 27 980, 1986; *Chem Abstr.* **1986**, *105*, 42541u. (j) Matsunaga, F.; Kondo, M. Jpn Patent JP 61 69 770, 1986; *Chem Abstr.* **1986**, *105*, 97315d.
(9) Kondrat'eva, G. G.; Volkotrub, M. N. *Sin. Issled. Eff. Khim-Dobavok., Polim. Mater.* **1969**, No. 2, 373−376.; *Chem. Abstr.***1972**, *76*, 59369z.
(10) (a) Sumitomo Chem. Co. Ltd., Jpn. Patent 80,139,383, 1980; *Chem. Abstr.* **1981**, *94*, 121358x. The abstract contains a misprint: R^1 and R^2 are interchanged. (b) Harada, H.; Usui, M. Jpn. Patent JP 62,-103,085, 1987; *Chem. Abstr.* **1988**, *109*, 92832t. (c) Harada, H.; Usui, M. Jpn. Patent 62,111,988, 1987; *Chem. Abstr.* **1988**, *109*, 149374b.
(11) A referee has proposed that reaction with $(CH_3)_3SiI$ would distinguish **5** and **6**. We thank the referee for this thoughtful suggestion.

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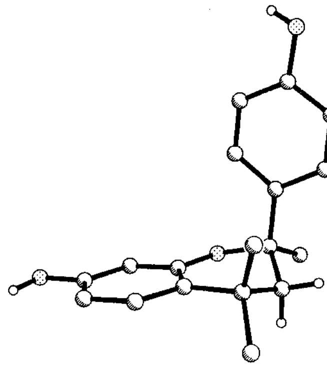


Figure 1. The structure of the product of the reaction of resorcinol with acetone, **5**. The figure was constructed from X-ray crystallographic data. Spheres are of arbitrary radius. Plain spheres represent carbon and the stippled spheres represent oxygen. For clarity, all hydrogens were omitted, save OH hydrogens and two hydrogens on the nonaromatic ring, which are indicated by small spheres. An ether of crystallization (see Figure 2) is not shown.

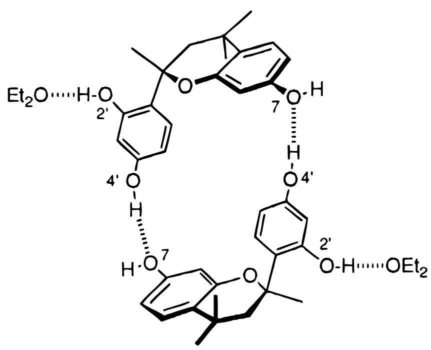


Figure 2. The H-bonded dimer formed by **5** in the solid state. Numbering follows the flavan convention. Average O4′−O7 distance is 2.77 Å, with an average O−H···O angle of 156°. The phenolic OH at 2′ hydrogen-bonds an ether of crystallization.

We were fortunate to be able to grow single crystals of both the "new" material and its triacetate derivative and obtained X-ray structures of the two. On the basis of the X-ray crystal structure of the product (Figure 1) it now may be stated with certainty that the acid-catalyzed reaction of resorcinol with acetone gives **5**. Although the crystal used in the X-ray work came from our serendipitous synthesis, we could also prepare the identical material more conventionally by reaction of acetone with excess resorcinol in ether−CH_2Cl_2 solvent containing 10% aqueous HCl.

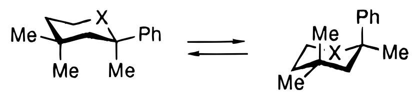
The crystal structure of **5** was not without a small surprise, *viz.* that the 2,4-dihydroxyphenyl substituent was pseudoaxial, as was the corresponding ring of triacetate **9**. On the basis of the *A*-values of phenyl and methyl (2.87 and 1.74 kcal/mol, respectively),[12] one might have crudely predicted a 1.13 kcal/mol advantage for the opposite invertomer. However, in the crystal, **5** is a hydrogen-bonded dimer, as shown in Figure 2, and bears a resemblance to Rebek's "capsule" dimers.[13] However, why does the triacetate derivative, **9**, also sport an axial 2,4-diacetoxyphenyl ring when hydrogen-bond-mediated dimer formation is precluded by the presence of the acetyl groups?

Table 1. Calculations of Conformational Energies

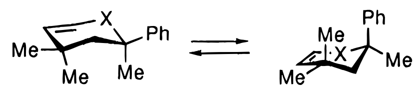
	ΔE (kcal/mol)				
	MM2	MM3	AM1	PM3	3-21G(*)
10e ⇄ **10a**	−2.90	−3.01	−0.14	0.25	−2.04
11e ⇄ **11a**	−3.31	−3.16[a]	−0.76	−0.55	−2.52
12e ⇄ **12a**	−1.70	−1.86	0.35	1.41	−1.12
13e ⇄ **13a**	−2.14[a]	−2.40[a]	−0.36	7.31	−1.34

[a] Missing torsional parameters set to zero.

Modeling the methylated ring of **5** or **9** as **10a** or **10e** (where a and e refer to the phenyl), in **10a** one finds a CH_3/Ph 1,3-diaxial interaction (3.4 kcal/mol)[14] and in **10e** both a CH_3/CH_3 1,3-diaxial interaction (3.7 kcal/mol)[15]



10e; X = CH_2 **10a**; X = CH_2
11e; X = O **11a**; X = O



12e; X = CH_2 **12a**; X = CH_2
13e; X = O **13a**; X = O

and a CH_3/Ph geminal interaction (1.45 kcal/mol).[16] Taking these into account, **10e** ⇄ **10a** is predicted to have $\Delta G = -1.2$ kcal/mol. The experimental ΔG is -1.23 ± 0.01 kcal/mol at 173 K.[14] Better models for **5** (or **9**) include oxygen in the ring (**11**), a double bond in the ring (**12**), or, best, both (**13**). The empirical approach which was successful for **10** cannot be applied to **11**−**13** because not all the required energies of interaction have been measured. We therefore turned to molecular mechanics, semiempirical, and low-level ab initio calculations (Table 1).

With regard to **10**, the present MM2 and MM3 results were not too different from $\Delta E = -3.26$ kcal/mol found over two decades ago.[17] The ab initio calculation for **10** appears "best" in the senses that (i) the sign is right, and (ii) if one takes ΔE to be ΔH for the sake of discussion, a ΔS of −4.7 eu would be required to produce the experimental ΔG. This ΔS seems reasonable. By contrast, PM3 gives the wrong sign and would demand $\Delta S = +8.6$ eu, which seems rather large.[18]

It is interesting that all calculations predict the axial phenyl invertomer to be more prevalent in **11**, with ring oxygen, than in **10**. Also, all calculations (save PM3) predict more "a" invertomer in **13**, with ring oxygen, than in **12**. The standard explanation of the 1.45 kcal/mol CH_3/Ph geminal interaction is predicated on the interactions of equatorial H's at the 2 and 6 positions of cyclohexane with the ortho H's of equatorial Ph, as in ***i***,

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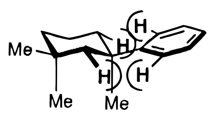
(18) (a) Gundertofte, K.; Palm, J.; Pettersson, I.; Stamvik, A. *J. Comput. Chem.* **1991**, *12*, 200−208 (b) Ferguson, D. M.; Glauser, W. A.; Raber, D. J. *J. Comput. Chem.* **1989**, *10*, 903−910.

Table 2. Product Distributions

	initial conditions		% of mixture[a]			
entry	A:R:HCl[b]	HCl[c]	**5**	**7**	R[b]	others
1	1:6:2	d	93.0	3.9	3.1	–
2	1:6:1	d	99.8	–	0.2	–
3	1:3:1	d	99.0	0.7	0.2	–
4	1:2:1	d	99.4	–	0.6	–
5	1:1:1	d	49.8	29.5	10.8	9.9
6	2:1:1	d	6.9	58.7	26.2	7.3
7	3:1:1	d	17.4	48.6	21.2	12.8
8	6:1:1	d	22.5	13.5	3.8	60.2
9	1:6:1	c	99.6	–	0.4	–
10	1:3:1	c	9.1	72.7	4.5	13.7
11	1:2:1	c	28.3	53.7	–	18.0
12	1:1:1	c	14.8	47.3	21.1	16.8
13	2:1:1	c	20.9	17.8	7.9	53.4
14[d]	3:1:1	c	18	10	3	69
15[d]	6:1:1	c	11	9	1	79
16[d]	2.2:1:1.6	e	23	15	2	60
17[d]	3.8:1:1.1	f	3	17	–	80

[a] From HPLC. [b] A = acetone, R = resorcinol. [c] c = 36% HCl, d = 10% HCl, e = 5% HCl; reaction solvent water, f = 36% HCl; no reaction solvent. [d] A multitude of peaks made integration less trustworthy.

below.[19] One might have thought replacing CH_2 with O,



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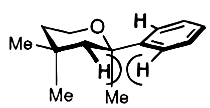

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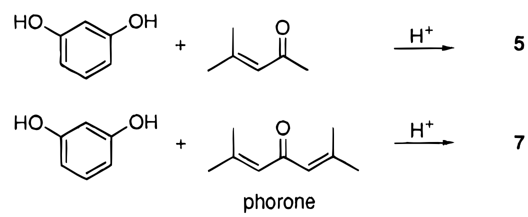
as in ***ii***, would relieve one of the interactions and thus favor the "e" invertomer. However, ***ii*** has two C−O bonds (typically 1.441 Å)[20] where ***i*** had two C−C bonds (typically 1.535 Å).[20] This contraction of the ring dimensions, we believe, magnifies the difference between CH_3/CH_3 1,3-diaxial interaction and CH_3/Ph 1,3-diaxial interaction (with CH_3/CH_3 worse) and accounts for the calculated results. Introduction of the double bond (**10** becoming **12**, or **11** becoming **13**) also contracts the ring dimensions slightly and causes the ring to adopt a half-chair. The proportion of "a" invertomer is always calculated to decrease, which suggests the difference in 1,3-diaxial interactions is diminished, probably as a result of the adoption of the half-chair form.

We have examined the ^{13}C-NMR spectrum of **9** at temperatures down to −118 °C but were unable to "freeze out" the invertomer equilibrium (although differential broadening was observed). Taking **13** as the best approximation to **9**, it is heartening to note that all methods of calculation (except PM3) predict **13a** to be favored, which is consistent with the X-ray result.

The outcome of the reaction of acetone with resorcinol depends on the mole ratio of reactants (see Table 2), and even on whether 10% HCl or 36% HCl is used. Using 10% HCl, **5** is produced exclusively, provided there is an excess of resorcinol (entries 1−4). At equimolar acetone and resorcinol (entry 5) or with acetone in excess (entries 6−8), complex product mixtures are obtained. In certain cases (entries 6 and 7), spirobichroman **7** is clearly the major product, but in other cases (entry 8) at least eleven other peaks aside from **5**, **7**, and resorcinol, roughly comparable in area, could be discerned. An authentic sample of **7** was prepared following a literature method.[21] Using concd HCl instead of 10% HCl gives a clean reaction in only one case (entry 9). As one goes from entry 10 to entry 15, "other" products, which we have not attempted to identify, increase in number and eventually predominate. A particularly striking example of the effect of water concentration in the aqueous HCl used is provided by entries 3 and 10. In the former case, **5** is formed almost quantitatively, while in the latter, **7** is the major product. Entries 16 and 17 reproduced literature reaction conditions reported to lead to **2**[4a] and **1**,[2] respectively. These reactions in fact led to very complex product mixtures. NMR spectra of the latter product mixture strongly suggested oligomer or polymer formation.

While we have not made any rigorous attempt to determine the mechanism of the reaction of acetone with excess resorcinol, we did find that mesityl oxide produces **5** when heated with HCl and excess resorcinol, correcting the earlier report[9] that the product is **6**. Therefore, a mechanism for the acetone plus resorcinol reaction which involves the intermediacy of mesityl oxide is not ruled out. Interestingly, phorone and an excess of resorcinol give **7**, and in much better yield than the literature procedure.[21] It is tempting to speculate that yields of **5** and **7** in Table 2 are a reflection of how much mesityl oxide *vs* phorone is formed by self-condensation of acetone under the particular conditions of the reaction.



As might be expected, ketones other than acetone react with resorcinol to give products analogous to **5**. Two simple examples are cyclopentanone and cyclohexanone,[22] which give **14** and **15**, respectively. The sole aliphatic methine proton in each of these compounds is easy to locate unambiguously using DEPT and C−H correlation techniques, and each is free of overlap with adjacent signals. The coupling constants are 7.9 and 11.2 Hz in the case of the triacetate derivative of **14**, and 4.2 and 12.1 Hz in the case of the triacetate derivative of **15**. This means the proton in question is axial or pseudoaxial, which narrows the choice of the stereochemistry of the

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(21) Liska, K. J. *J. Med. Chem.* **1972**, *15*, 1177−1179. The structure is assigned incorrectly; however, the present spectroscopic evidence leaves little doubt that the material is **7**. Of critical importance is the ^{13}C chemical shift of the spiro carbon, 99.95 ppm, which may be compared with the reported chemical shift of C2 of 2,2-dimethyl-1,3-dioxane, 99.2 ppm (Riddell, F. G. *J. Chem. Soc. B* **1970**, 331−333).

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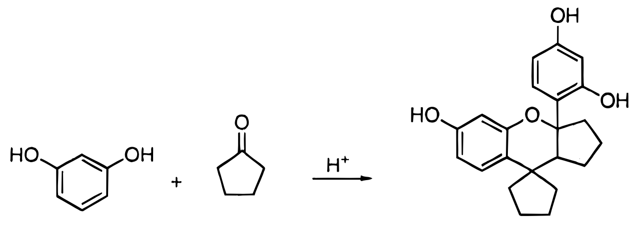

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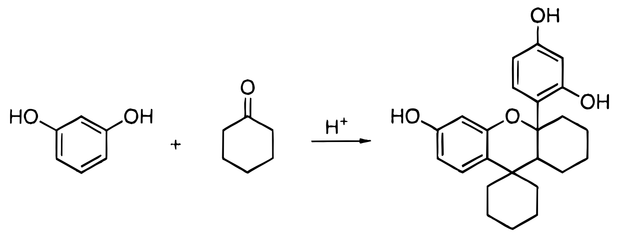

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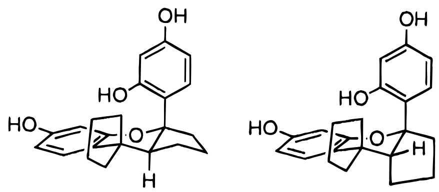
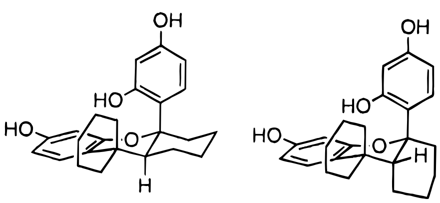
ring junction. As shown, molecular mechanics calculations[23] suggest the *cis* ring junction for both **14** and **15**.



14 trans E_{rel} = +6.9 kcal/mol

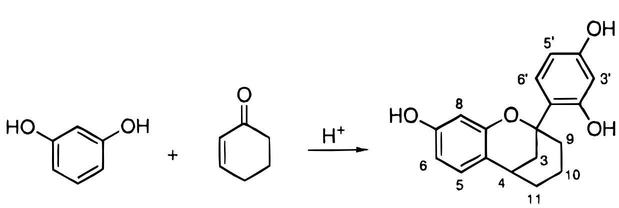
14 cis E_{rel} = 0.0 kcal/mol



15 trans E_{rel} = + 8.1 kcal/mol

15 cis E_{rel} = 0.0 kcal/mol

Finally, we have found that the reaction of resorcinol with mesityl oxide is not an isolated instance: other α,β-unsaturated ketones undergo the analogous reaction with resorcinol. For example, 2-cyclohexenone reacts with resorcinol to give **16**. Investigation of the reaction of resorcinol with other α,β-unsaturated ketones is in progress and will be reported shortly.



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Experimental Section

4-(3,4-Dihydro-7-hydroxy-2,4,4-trimethyl-2*H*-1-benzopyran-2-yl)-1,3-benzenediol, 5. (a) Serendipitous. A mixture of impure resorcinol and acetone was heated to boiling and chloroform added to the cloud point. The mixture was stored in the freezer for 3 days. The precipitated solid, mp 182−203 °C, was recrystallized twice from ether/hexane, mp 231−232 °C. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.04; H, 6.71. HRMS: *m/z* Calcd for $C_{18}H_{20}O_4$: 300.1362. Found: 300.1367. MS (EI): *m/z* (rel intens) 300(M^+,13), 175(21), 163(13), 151(100), 150(34), 137(15), 135(36), 123(27), 107(19), 91(10), 79(12), 77(21), 69(12). ^{1}H-NMR (CD_3OD, 400 MHz): 8.248 (s, 1H), 7.913 (s, 1H), 7.904 (s, 1H), 6.965 (d, J = 8.5, 1H), 6.901 (d, J = 8.4, 1H), 6.297 (d, J = 2.5, 1H), 6.225 (dd, J = 8.4, 2.5, 1H), 6.111 (d, J = 2.4, 1H), 6.032 (dd, J = 8.5, 2.4, 1H), 2.962 (d, J = 13.8, 1H), 1.796 (d, J = 13.8, 1H), 1.612 (s, 3H), 1.174 (s, 3H), 0.748 (s, 3H). ^{13}C-NMR (CD_3CN, 62.9 MHz): 157.94 (quat), 157.05 (quat), 155.74 (quat), 154.24 (quat), 128.79 (CH, 2 C's), 124.31 (quat), 123.90 (quat), 109.64 (CH), 107.48 (CH), 104.38 (CH), 104.25 (CH), 79.37 (quat), 46.51 (CH_2), 33.29 (CH_3), 31.07 (quat), 30.67 (CH_3), 30.04 (CH_3). IR (KBr): 3262(br,s), 2978(m), 2899(m), 1622(s), 1592(m), 1518(m), 1503(s), 1443(s), 1383(m), 1296(s), 1271(m), 1250(m), 1154(s), 1132(s), 1100(s), 1073(m), 997(m), 980(s), 843(s), 804(m) cm^{-1}.

(b) From Acetone and Resorcinol. A mixture of 2.063 g (18.74 mmol) of resorcinol, 0.362 g (6.23 mmol) of acetone, 2.0 mL of 10% aqueous HCl, 30 mL of ether, and 30 mL of CH_2Cl_2 was stirred and refluxed 12 h. After removal of solvents, addition of water afforded a precipitate, which was collected and washed repeatedly with water. After oven-drying, 0.826 g of **5** was obtained (88% yield), 97% pure by HPLC, and spectroscopically identical to the material described above.

(c) From Mesityl Oxide and Resorcinol. A mixture of 2.940 g (26.70 mmol) of resorcinol, 0.436 g (4.45 mmol) of mesityl oxide, 1.5 mL of 10% aqueous HCl, 35 mL of ether, and 35 mL of CH_2Cl_2 was stirred and refluxed 12 h. Workup was as in part (b), giving 1.215 g (91%) of **5**, spectroscopically identical to the material described above.

Crystal Structure of 5.[24] A clear plate, 0.60 × 0.55 × 0.25 mm, was mounted on a Siemens R3m/V diffractometer, using Mo Kα radiation (λ = 0.71073 Å). Twenty-four reflections in the range 7.3 < θ < 14.5° were used for determination of lattice parameters. Triclinic, a = 7.9250(10) Å, b = 11.585(2) Å, c = 11.963(2) Å, α = 81.760(10)°, β = 78.940(10)°, γ = 86.410(10)°, V = 1066.1(3) Å^3, Z = 2. Space group $P\bar{1}$. 4073 reflections (3782 independent reflections) were collected in the range 3.5 < 2θ < 50.0; $0 \le h \le 9$, $-13 \le k \le 13$, $-13 \le l \le 14$, of which 2733 were considered ($F > 4.0\sigma(F)$) observed. Two standard reflections were measured every 100 reflections. An empirical absorption correction based on ψ scans was applied; transmission varied between 0.940 and 0.906.

The structure was solved via direct methods using SHELXTL PLUS. Full matrix least squares refinement on F led to R = 4.74%, wR = 7.11% (observed data), R = 6.66%, wR = 7.73% (all data), $w^{-1} = \sigma^2(F) + 0.0017F^2$. Goodness of fit 1.38. A riding, isotropic H model was used. Data-to-parameter ratio 11.2. Largest Δ/σ 0.003; mean Δ/σ 0.001. Largest peak/hole in final difference map: 0.22/−0.28 e Å^{-3}.

2,2′-Spirobi(7-hydroxy-4,4-dimethylchroman), 7. (a) Prepared by the method of Liska[20] with a few minor modifications: the reaction was refluxed 12 h instead of 5 h, the benzene phase was dried over Na_2SO_4 rather than dried azeotropically with ethanol, the black residue was partitioned between water and CH_2Cl_2 twice, the combined CH_2Cl_2 phase was washed twice with water, dried over Na_2SO_4, and filtered, and CH_2Cl_2 was removed to afford additional crude product. Yield after two recrystallizations from $CHCl_3$ 55%, mp 200−201 °C (lit.[20] 199−200 °C). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.96; H, 7.17. HRMS: *m/z* Calcd for $C_{21}H_{24}O_4$: 340.16746. Found: 340.16748. MS (EI): *m/z* (rel intens) 340(M^+, 4), 325(6), 176(9), 175(75), 155(17), 152(10), 151(100), 123(14), 77(12). ^{1}H-NMR (CD_3COCD_3, 250 MHz): 7.169 (d, J = 8.5, 1H), 6.437 (dd, J = 8.5, 2.5, 1H), 6.094 (d, J = 2.5, 1H), 2.078 (d, J = 14.1, 1H), 1.938 (d, J = 14.1, 1H), 1.534 (s, 3H), 1.295 (s, 3H). ^{13}C-NMR (CD_3COCD_3, 63 MHz): 157.20 (quat), 152.18 (quat), 127.98 (CH), 123.47 (quat), 110.19 (CH), 104.55 (CH), 99.95 (quat), 47.38 (CH_2), 32.96 (CH_3), 32.73 (CH_3), 30.93 (quat).

(23) PCMODEL for Windows, Serena Software, 1993. Coupling constants predicted by this software for **14** are J = 7.8, 9.9 Hz and for **15** are J = 3.9, 12.3 Hz.

(24) The author has deposited atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(b) From Phorone and Resorcinol. A mixture of 0.675 g (4.88 mmol) of 2,6-dimethyl-2,5-heptadien-4-one, 3.226 g of resorcinol (29.30 mmol), 1.8 mL of 10% aqueous HCl, 20 mL of ether, and 20 mL of CH_2Cl_2 was stirred and refluxed 24 h. After removal of solvent, the mixture was poured into 100 mL of water, extracted twice with 60 mL CH_2Cl_2, washed with 3 × 60 mL water, and dried over Na_2SO_4. Filtration and removal of solvent gave 1.372 g (85%) of **7**, mp 199−200 °C. Using the method employed for preparing **9** (see below), the diacetate derivative of **7** was prepared, 95% yield, recrystallized from EtOAc/hexanes, mp 194−195 °C. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.65; H, 6.69. HRMS: *m/z* Calcd for $C_{25}H_{28}O_6$: 424.1886. Found: 424.1881. MS (EI): *m/z* (rel intens) 424-(M^+, 6), 409(33), 382(10), 367(17), 217(43), 193(25), 190(12), 175-(45), 151(72), 77(10), 43(100). ^{1}H-NMR (CD_3CN, 250 MHz): 7.404 (d, J = 8.5, 1H), 6.697 (dd, J = 2.2, 8.5, 1H), 6.382 (d, J = 2.2, 1H), 2.155 (s, 3H), 2.150 and 2.055 (AB quartet, J = 14.3), 1.582 (s, 3H), 1.343 (s, 3H). ^{13}C-NMR (CD_3CN, 63 MHz): 170.84 (C═O), 152.05 (quat), 151.07 (quat), 130.76 (quat), 128.90 (CH), 116.67 (CH), 111.87 (CH), 99.92 (quat), 46.92 (CH_2), 33.04 (CH_3), 32.86 (CH_3), 31.68 (quat), 21.55 (CH_3).

1,3-Dimethoxy-4-(3,4-dihydro-7-methoxy-2,4,4-trimethyl-2*H*-1-benzopyran-2-yl)benzene, 8. A mixture of 0.510 g (1.70 mmol) of **5**, 0.790 g (5.57 mmol) of methyl iodide, 2.0 g (14 mmol) of K_2CO_3, and 20 mL of acetone was stirred and refluxed 12 h. Acetone and excess methyl iodide were removed on the rotary evaporator, 70 mL of water was added, and the mixture was extracted with 3 × 40 mL of ether. The ether extracts were dried over Na_2SO_4 and filtered, and the solvent was removed. The solid residue was recrystallized from ether/hexane to afford 0.540 g of **8** (93%), mp 102−103 °C. Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.56; H, 7.68. HRMS: *m/z* Calcd for $C_{21}H_{26}O_4$: 342.1831. Found: 342.1835. MS (EI): *m/z* (rel intens) 342(M^+,18), 189(18), 178(49), 165(52), 164(15), 163(100), 149(24), 135(35), 121(15), 91(18), 77(20), 59(20), 57(25), 56(20), 43(52), 41(32), 29(19), 27(17), 15(34). ^{1}H-NMR (CD_3CN, 250 MHz): 7.13 (d, J = 8.6, 1H), 7.07 (d, J = 8.5, 1H), 6.51 (d, J = 2.6, 1H), 6.49 (d, J = 2.5, 1H), 6.45 (dd, J = 8.5, 2.6, 1H), 6.32 (dd, J = 8.6, 2.5, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 2.95 (d, J = 14.0, 1H), 1.87 (d, J = 14.0, 1H), 1.61 (s, 3H), 1.19 (s, 3H), 0.63 (s, 3H). ^{13}C-NMR (CD_3CN, 63 MHz): 161.18 (quat), 160.10 (quat), 158.68 (quat), 154.72 (quat), 128.64 (CH), 128.31 (CH), 126.63 (quat), 124.85 (quat), 108.32 (CH), 104.94 (CH), 102.77 (CH), 100.25 (CH), 78.79 (quat), 55.96 (CH_3, 3 C's), 46.61 (CH_2), 33.31 (CH_3), 31.12 (quat), 30.42 (CH_3), 30.06 (CH_3). IR: 1617(s), 1582(s), 1505(s), 1466(m), 1443(m), 1414(m), 1256(s), 1204(s), 1165(s), 1132(m), 1113(m), 1065(m), 1032(m), 988(m), 837(m) cm^{-1}.

1,3-Diacetoxy-4-(3,4-dihydro-7-acetoxy-2,4,4-trimethyl-2*H*-1-benzopyran-2-yl)benzene, 9. A 0.603 g (2.01 mmol) amount of **5** and 10 mL of dry pyridine were placed in a 25 mL three-necked round-bottom flask fitted with a thermometer, condenser, addition funnel, and magnetic stir bar. Acetic anhydride (3.246 g, 31.8 mmol) was added dropwise to the stirred solution, and the reaction mixture was stirred at 40−50 °C for 1.5 h. After allowing to cool to room temperature, the mixture was poured onto 60 mL ice−water whereupon a precipitate formed. This was collected by filtration, recrystallized from ethyl acetate/hexane, and dried *in vacuo*, giving 0.710 g of **9**, mp 127−130 °C (83%). One further recrystallization provided an analytically pure sample, mp 129−130 °C. Anal. Calcd for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C, 67.59; H, 6.12. HRMS: *m/z* Calcd for $C_{24}H_{26}O_7$: 426.1679. Found: 426.1686. MS (EI): *m/z* (rel intens) 426(M^+,5), 384(4), 193(12), 192(11), 175(13), 163(26), 151-(49), 150(88) 137(21), 135(22), 123(12), 107(12), 77(11), 43(100), 15(33). ^{1}H-NMR (CD_3CN, 250 MHz): 0.76 (s, 3H), 1.30 (s, 3H), 1.61 (s, 3H), 2.10 (d, J = 14.4), 2.20 (s, 3H), 2.24 (s, 3H), 2.34 (s, 3H), 2.67 (d, J = 14.4), 6.65 (dd, J = 8.5, 2.4, 1H), 6.72 (d, J = 2.4, 1H), 6.86 (dd, J = 8.6, 2.4, 1H), 6.92 (d, J = 2.3, 1H), 7.25 (d, J = 8.5, 1H), 7.41 (d, J = 8.6, 1H). ^{13}C-NMR (CD_3CN, 63 MHz): 170.55 (quat), 170.22 (quat), 169.94 (quat), 153.69 (quat), 151.07 (quat, 2 Cs), 148.76 (quat), 135.43 (quat), 129.97 (quat), 128.57 (CH, 2 Cs), 120.13 (CH), 118.76 (CH), 115.71 (CH), 111.53 (CH), 78.51 (quat), 46.89 (CH_2), 32.70 (CH_3), 31.47 (quat), 30.91 (CH_3), 31.30 (CH_3), 21.85 (CH_3), 21.34 (CH_3), 21.27 (CH_3). IR: 1763(vs), 1611(s), 1590(s), 1497(s), 1422(s), 1372(s), 1312(m), 1215(br, s), 1148(s), 1129(s), 1103(s), 1059(s), 1017(s), 974(m), 903(s), 856(w), 814(w) cm^{-1}.

Crystal Structure of 9.[24] A clear truncated plate 0.26 × 0.40 × 0.55 mm was selected. Twenty-four reflections in the range 7.0 < θ < 15.0° gave a monoclinic cell, a = 9.563(5) Å, b = 15.014(8) Å, c = 16.458(7) Å, β = 105.84(4)°, V = 2273(2) Å^3, $P2_1/n$, Z = 4 using a Siemens R3m/V diffractometer and Mo Kα radiation (λ = 0.71073 Å). An amount of 4465 reflections (4029 independent reflections) were collected, 3.5 ≤ 2θ ≤ 50.0°, 0 ≤ h ≤ 11, 0 ≤ k ≤ 17, −19 ≤ l ≤ 18, of which 2176 were considered observed ($F > 4.0\sigma(F)$). Two standard reflections were measured every 100 reflections. An empirical absorption correction based on ψ scans was applied; transmission varied between 0.936 and 0.890. Structure solution and refinement were carried out as for **5**; however $w^{-1} = \sigma^2(F) + 0.0008F^2$, and data-to-parameter ratio was 7.8. Final R = 5.14%, wR = 6.23% (observed data), R = 10.24%, wR = 7.29% (all data), goodness of fit 1.42. Largest Δ/σ 0.002; mean Δ/σ 0.000. Largest peak/hole in final difference map: 0.21/−0.17 e Å^{-3}.

2′,4′,7-Trihydroxy-2,3-propanoflavan-4-spirocyclopentane, 14. A mixture of 1.011 g (12.02 mmol) of cyclopentanone, 3.965 g (36.01 mmol) of resorcinol, 4.4 mL of 10% aqueous HCl, 35 mL of ether, and 35 mL of CH_2Cl_2 was stirred and refluxed 24 h. Solvents were removed, and the mixture was poured into 100 mL of water and taken up into 3 × 50 mL of CH_2Cl_2. The organic phase was washed with water 3 × 50 mL, dried over Na_2SO_4, and filtered and solvent removed to afford 1.423 g of crude **14**. HRMS: *m/z* Calcd for $C_{22}H_{24}O_4$: 352.1675. Found: 352.1681. MS (EI): *m/z* (rel intens) 352(M^+,8), 190(11), 177-(100), 176(71), 175(27), 161(24), 159(11), 149(21), 147(32), 123-(51), 115(10), 107(10), 91(17), 84(15), 77(17), 69(15), 67(10), 65(10), 56(13), 55(44), 43(15). Since **14** was difficult to purify satisfactorily, its triacetate derivative was prepared using the procedure to make **9**, mp 162−163.5 °C, after recrystallization from EtOAc/hexanes and drying under vacuum, 92% yield. HRMS: *m/z* Calcd for $C_{28}H_{30}O_7$: 478.19915. Found: 478.19919. MS (EI): *m/z* (rel intens) 478(M^+,5), 436(11), 219(37), 218(49), 201(15), 178(10), 177(82), 176(100), 175(21), 161(15), 149(11), 147(21), 123(36), 43(79) ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.547 (d, J = 8.7, 1H), 7.051 (d, J = 8.5, 1H), 6.940 (d, J = 2.3, 1H), 6.882 (dd, J = 2.3, 8.7, 1H), 6.730 (d, J = 2.3, 1H), 6.623 (dd, J = 2.4, 8.5, 1H), 2.765 (dd, J = 7.9, 11.2, 1H), 2.346 (s, 3H), 2.298 (s, 3H), 2.254 (s, 3H), 2.309 (m, 1H), 2.125 (m, 1H), 2.00−1.46 (m, 10H), 1.15−0.98 (m, 2H) ^{13}C-NMR ($CDCl_3$, 63 MHz, proton correlations from C−H correlation spectrum): 169.41 (C═O), 168.81 (C═O), 168.28 (C═O), 152.74 (quat), 149.62 (quat), 149.54 (quat), 146.79 (quat), 132.96 (quat), 128.56 (CH, 7.55), 127.69 (CH, 7.05), 127.14 (quat), 118.66 (CH, 6.88), 116.88 (CH, 6.94), 113.66 (CH, 6.62), 109.44 (CH, 6.73), 87.17 (quat), 51.04 (CH, 2.77), 44.74 (quat), 41.53 (two CH_2s, 0.98, 1.11, 2.12, 2.31), 38.84 (CH_2, 1.56, 1.94), 28.81 (CH_2, 1.50, 1.93), 24.48 (CH_2, 1.54), 24.34 (CH_2, 1.73), 21.75 (CH_2, 1.72, 1.85), 21.36 (CH_3), 21.16 (CH_3), 21.09 (CH_3).

2,3-Butano-2′,4′,7-trihydroxyflavan-4-spirocyclohexane, 15. The procedure used to prepare **14** was used. A 0.620 g (6.32 mmol) amount of cyclohexanone, 2.085 g (18.94 mmol) of resorcinol, 2.3 mL of 10% aqueous HCl, 20 mL each of ether and CH_2Cl_2, reflux 24 h. A 1.182 g amount of crude product, mp 219−221 °C, after vacuum drying. HRMS: *m/z* Calcd for $C_{24}H_{28}O_4$: 380.1988. Found: 380.1987. MS (EI): *m/z* (rel intens) 380(M^+,10), 309(10), 191(65), 190(81), 175(20), 162(26), 161(51), 147(44), 123(100), 115(12), 91(15), 81(11), 69(14), 55-(14). Since **15** was difficult to purify satisfactorily, its triacetate derivative was prepared using the procedure to make **9**, mp 200−201 °C, after recrystallization from EtOAc/hexanes, 91% yield. Anal. Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.77. Found: C, 71.03; H, 6.81. HRMS: *m/z* Calcd for $C_{30}H_{34}O_7$: 506.230. Found: 506.229. MS (EI): *m/z* (rel intens) 507(12), 506(M^+,12), 464-(11), 274(11), 233(69), 232(67), 191(100), 189(79), 187(11), 175-(20), 173(13), 165(10), 162(21), 161(45), 149(10), 147(31), 123(65), 91(10), 44(22), 43(75) ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.294 (d, J = 8.8, 1H), 7.159 (d, J = 8.6, 1H), 6.949 (d, J = 2.3, 1H), 6.789 (dd, J = 2.3, 8.8, 1H), 6.770 (d, J = 2.5, 1H), 6.631 (dd, J = 2.5, 8.6, 1H), 3.134 (dd, J = 4.2, 12.1, 1H), 2.413 (s, 3H), 2.298 (s, 3H), 2.224 (s, 3H), 1.90−1.52 (m, 11H), 1.48−1.15 (m, 5H), 0.99−0.75 (m, 2H). ^{13}C-NMR ($CDCl_3$, 63 MHz, proton correlations from C−H correlation spectrum): 169.36 (C═O), 168.63 (C═O), 168.03 (C═O), 152.83 (quat), 149.45 (quat), 149.28 (quat), 146.85 (quat), 135.86 (quat), 128.00 (quat), 127.74 (CH, 7.16), 127.44 (CH, 7.29), 118.92 (CH, 6.78), 116.90 (CH, 6.95), 113.95 (CH, 6.63), 109.44 (CH, 6.77), 79.42 (quat), 39.56 (CH_2, 0.84), 39.38 (CH_2, 1.84), 38.24 (quat), 35.65 (CH_2, 1.75), 35.42 (CH, 3.13), 26.27 (CH_2, 1.30, 1.86), 26.13 (CH_2, 1.21, 1.69), 24.76 (CH_2, 1.17, 1.80), 22.25 (CH_2, 1.40, 1.62), 21.81 (CH_2, 1.20, 1.58), 21.74 (CH_3, 2.40), 21.42 (CH_2, 1.60), 21.18 (CH_3, 2.30), 21.07 (CH_3, 2.20).

2′,4′,7-Trihydroxy-2,4-propanoflavan, 16. A mixture of 0.272 g (2.83 mmol) of 2-cyclohexenone, 1.825 g (16.57 mmol) of resorcinol, 1 mL of 10% aq HCl, 15 mL of ether, and 15 mL of CH_2Cl_2 was stirred and refluxed 12 h. After removing solvent at the rotary evaporator, the residue was taken up in 80 mL of water and extracted with 3 × 30 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with 2 × 40 mL water, dried over Na_2SO_4, and filtered, and the solvent was removed to afford 0.711 g (87%) of a colorless solid. This was subjected to silica gel chromatography (ethyl acetate:hexanes 30:70) followed by drying at 110 °C under vacuum to give 608 mg (72%) analytically pure **16**, mp 190−191 °C. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.40; H, 6.13. HRMS: *m/z* Calcd for $C_{18}H_{18}O_4$: 298.1205. Found: 298.1202. MS (EI): *m/z* (rel intens) 298(M^+,45), 255(66), 188(36), 176(41), 175(35), 162(30), 161(58), 160(25), 149(43), 148(23), 147(63), 136(99), 123(100), 115(22), 107(26), 91(29), 77(47), 69(34), 65(23). ^{1}H-NMR (CD_3-OD, 400 MHz; assignments from COSY and C−H correlation spectra): 1.510 (m, 2H; H10a and H10e), 1.658 (m, 1H; H11e), 1.792 (m, 1H; H11a), 1.858 (m, 1H; H3e), 2.008 (m, 1H; H9e), 2.251 (m, 1H; H9a), 2.692 (dd J = 13.0, 2.9, 1H; H3a), 3.011 (approximately quintet J = 3.2, 1H; H4), 6.27−6.34 (m, 4H), 6.820 (d J = 8.1, 1H; H5 or H6′), 7.245 (d J = 9.2, 1H; H6′ or H5). The COSY revealed several long-range couplings: H3e/H9e, H3e/H11e, H9e/H11e. ^{13}C-NMR (CD_3CN, 63 MHz): 158.42 (quat), 157.45 (quat), 157.00 (quat), 156.65 (quat), 129.91 (CH), 127.54 (CH), 123.62 (quat), 119.25 (quat), 108.84 (CH), 107.76 (CH), 105.05 (CH), 102.64 (CH), 81.84 (quat; C2), 39.44 (CH_2; C9), 34.81 (CH_2; C3), 33.29 (CH_2; C11), 32.81 (CH; C4), 19.30 (CH_2; C10). The triacetate derivative of **16** was prepared as before, mp 145−146 °C, 91% yield. Anal. Calcd for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70. Found: C, 67.89; H, 5.71. HRMS: *m/z* Calcd for $C_{24}H_{24}O_7$: 424.1522. Found: 424.1524. MS (EI): *m/z* (rel intens) 424(M^+,8), 382(11), 381(14), 365(15), 340(12), 339(15), 323(12),297(15), 255(16), 188(16), 187(11), 176(13), 175(14), 162-(14), 161(20), 149(20), 147(22), 136(44), 123(51), 43(100). ^{1}H-NMR (CD_3CN, 250 MHz): 7.589 (d, J = 8.6, 1H), 7.099 (d, J = 8.1, 1H), 7.023 (dd, J = 2.4, 8.6, 1H), 6.881 (d, J = 2.4, 1H), 6.579 (dd, J = 2.3, 8.1, 1H), 6.463 (d, J = 2.3, 1H), 3.19 (m, 1H), 2.4−1.4 (m), 2.244 (s, 3H), 2.215 (s, 3H), 2.026 (s, 3H). ^{13}C-NMR (CD_3CN, 63 MHz): 170.61 (C=O), 170.36 (C=O), 170.17 (C=O), 157.45 (quat), 151.53 (quat), 151.38 (quat), 150.32 (quat), 135.72 (quat), 129.72 (CH), 128.34 (CH), 125.27 (quat), 120.12 (CH), 119.53 (CH), 114.16 (CH), 109.50 (CH), 78.80 (quat), 38.25 (CH_2), 34.44 (CH_2), 33.42 (CH), 21.56 (CH_3), 21.34 (CH_3), 21.31 (CH_3), 19.25 (CH_2)

Table 2. Resorcinol, acetone, and HCl (10% or 36%) were stirred and refluxed in a mixture of 2 mL of ether and 2 mL of CH_2Cl_2 for 12 h. The reaction mixture was poured into 50 mL of H_2O, and the precipitate thus formed was collected by filtration, washed thoroughly with water, and dried at 80 °C overnight. The product mixtures were analyzed by HPLC on a C18 column using acetonitrile:water 65:35, with UV detection at 280 nm. Integration of the chromatogram of a weighed mixture of **5** and **7** gave areas within 1% of the actual mole fractions.

JO961647Y