JOC Article

An Efficient Approach to Dihydrofurocoumarins via Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxycoumarins

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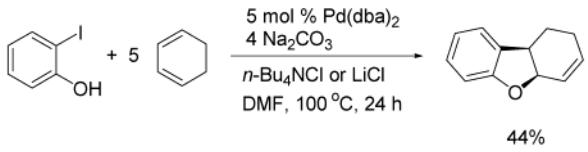
The palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumarins provides an efficient method for the synthesis of biologically interesting dihydrofurocoumarins. The presence of the acetyl group on the phenolic oxygen and the use of silver carbonate as a base are crucial for this process. This reaction is very general and regio- and stereoselective, and a wide variety of terminal, cyclic, and internal 1,3-dienes can be utilized. Derivatization of the annulation products provides an efficient approach to numerous analogues of natural products.

Dihydrofurocoumarins, such as compounds **1**−**7**, are commonly occurring plant metabolites that exhibit pronounced biological properties.[1] Derivatives of columbianetin (**2**) exhibit significant cytotoxicity against KB cells.[2] Derivatives of norpterophyllin (**3**) have high anticoagulant and antifungal activities.[3] Marmesin (**6**) is an effective inhibitor of c-AMP synthetase[4] and acetylcholinesterase,[5] and prandiol (**7**) is an effective antidote against rattlesnake poison.[6]

Numerous attempts to synthesize dihydrofurocoumarins have been reported during the last 30 years. Early methods have involved multiple steps and generally suffer from low (2−20%) overall yields.[7] Modern synthetic approaches involving the Claisen rearrangement of 7-(allyloxy)coumarins,[8] the Sonogashira coupling of *o*-iodohydroxycoumarins with terminal alkynes,[9] Ag(I)- and Ce(IV)-promoted oxidative cycloadditions of 4-hydroxycoumarin to alkenes and dienes,[10] and the Rh(II)-catalyzed annulation of alkenes by 3-diazo-2,4-chromenediones[11] give 30−60% overall yields, but these methods lack broad generality and, therefore, cannot be used for the synthesis of large libraries of biologically active dihydrofurocoumarins.

Palladium-catalyzed annulations developed in our laboratories have provided a versatile route for the construction of complex cyclic systems.[12] Previously we reported an efficient method for the synthesis of *cis*-dihydrobenzofurans by the palladium-catalyzed annulation of 1,3-dienes by *o*-iodophenols (eq 1).[13] Recently we



(1)

communicated a significantly modified procedure for the synthesis of dihydrofurocoumarins.[14] Herein, we report our complete results on the palladium-catalyzed annulation of 1,3-dienes by *o*-iodohydroxycoumarin derivatives that provides a very general and effective route to a wide variety of angular and linear dihydrofurocoumarins.

For our initial optimization work, the annulation of 1,3-cyclohexadiene by iodocoumarin **8** was selected as a

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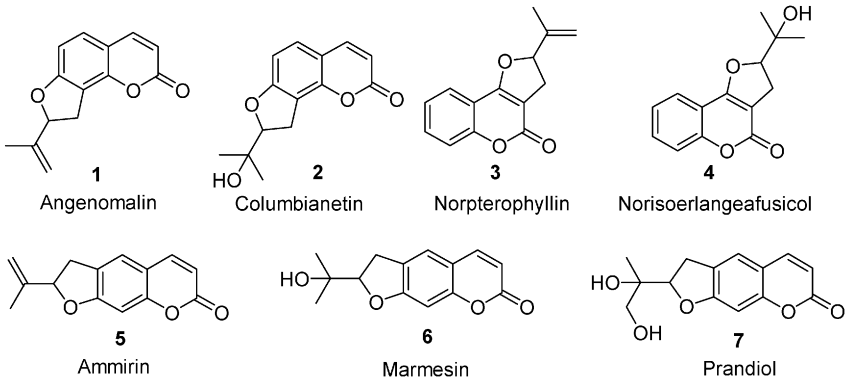
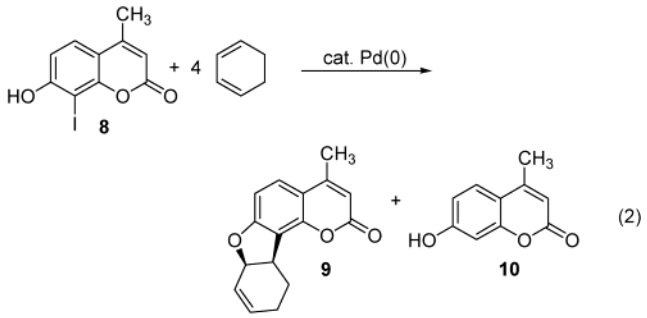


model reaction (eq 2). Surprisingly, under the optimal



reaction conditions used in the dihydrobenzofuran project (see eq 1),[13] the annulation gave only a 6% yield of the desired *cis*-dihydrofurocoumarin **9**. Instead, the reduced coumarin **10** was isolated in 88% yield. Possible pathways for formation of product **10** include reduction of the arylpalladium intermediate by formate formed from the DMF solvent and thermal decomposition of the starting aryl iodide or arylpalladium intermediate. Carrying out this reaction without any palladium catalyst resulted in 95% recovery of the starting coumarin **8**. On the other hand, the use of nonreducing solvents, such as *N*,*N*-dimethylacetamide (DMA), acetonitrile, and THF, did not inhibit the undesired reduction. Therefore, formation of the undesired product **10** might reasonably be attributed to thermal decomposition of the arylpalladium intermediate. Variation of the bases, phosphine ligands, and solvents used in this reaction had little effect on the outcome of the reaction. The best result was achieved by using Ag_2CO_3 as a base, dppe as a ligand, and THF as the solvent at 60 °C. This provided a 17% yield of the desired product **9**, a 15% yield of the reduced coumarin **10**, and 63% of the starting material **8**. The positive effect of the Ag_2CO_3 is presumably due to abstraction of a halide from an intermediate arylpalladium halide complex and formation of a cationic arylpalladium intermediate, which is assumed to be more reactive toward addition to the C=C bond.[15]

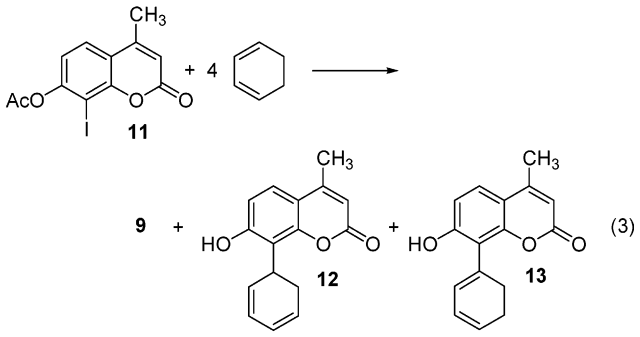
From our preliminary results, it appeared that electron-rich aryl iodides have a great propensity to undergo the undesired reduction.[13] The introduction of an electron-withdrawing acetyl group on the phenolic oxygen would be expected to decrease the electron density of the aromatic ring and might, therefore, be expected to improve the yield of the desired coumarin **9** if there were some way to remove the acetyl group during the annulation process. Acylated phenols are fairly stable in the pH range from 5 to 8 and, therefore, would be expected to tolerate our reaction conditions.[16]

TABLE 1. Optimization of the Annulation (Eq 3)[a]

entry	solvent(s) (ratio)	temp (°C)	% 9	% 11
1	THF	60	5	90
2	THF−H_2O (4:1)	60	21	78
3	1,4-dioxane−H_2O (4:1)	80	44	50
4	1,4-dioxane−H_2O (4:1)	100	64	13
5	1,4-dioxane−H_2O (1:1)	100	40	10

[a] Coumarin **11** (0.25 mmol), $Pd(dba)_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol), 1,3-cyclohexadiene (1.0 mmol), and 5 mL of the solvent were stirred at 100 °C for 24 h.

Using the annulation of 1,3-cyclohexadiene by iodoacetoxycoumarin **11** as a model system, we have examined the effect on the yield of the desired coumarin **9** of various reaction parameters, including the solvent, palladium catalyst, silver salt, phosphine ligand, and reaction temperature (eq 3). Several representative examples



are shown in Table 1. Although the annulation with coumarin **11** under our best previous reaction conditions obtained for coumarin **8** did not show very promising results (entry 1), the addition of water raised the yield of coumarin **9** to 21% (entry 2). In sharp contrast to the annulation of coumarin **8**, the acetoxy derivative **11** did not give any of the reduced coumarin **10** or its acetoxy analogue. Besides that, the recovery of 78% of the starting material **11** indicated that the undesired reduction is completely inhibited under these reaction conditions.

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Great improvements were subsequently achieved by using a 4:1 1,4-dioxane/water mixture as the solvent at higher temperatures. Increasing the reaction temperature to 80 and 100 °C improved the yield of the desired product **2** to 44% (entry 3) and 64% (entry 4), respectively. Besides the desired product, significant amounts of Heck-type products **12** and **13** were detected among the inseparable mixture of side products. A further increase in the water concentration resulted in a decrease in the yield of **9**, perhaps due to partial hydrolysis of the starting material **11** (entry 5). The use of polar solvents, such as DMF, DMA, and acetonitrile, apparently resulted in rapid hydrolysis of the starting material **11**. Further optimizations, which utilized $Pd(OAc)_2$ as the catalyst; dppp, dppb, BINAP, and PPh_3 as the phosphine ligand; and AgOAc, Ag_3PO_4 and Ag_2O as the silver salt, only resulted in a lower yield of the annulated product **9**. We have thus used the following "optimal" procedure for all subsequent annulations: the iodoacetoxycoumarin (0.25 mmol), $Pd(dba)_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol), 1,3-diene (1.0 mmol), and 5 mL of a 4:1 1,4-dioxane/water mixture were stirred at 100 °C for 24 h.

Next, the scope and limitations of this annulation have been studied by using various 1,3-dienes and representative examples are shown in Table 2. An increase in the ring size of the cyclic 1,3-diene leads to a significantly lower yield of annulation product (entries 1−3). Cyclopentadiene failed to give any annulation products, presumably due to rapid dimerization or some other side reaction. Most terminal 1,3-dienes have given the expected annulation products **16**−**23** in 61 to 83% yields with excellent regioselectivity (entries 4−11). Running the reaction of 2,3-dimethyl-1,3-butadiene on a 2.0-mmol scale with only 10 mL of the 4:1 1,4-dioxane/water mixture resulted in an even higher 91% yield (entry 11), indicating the utility of this procedure for practical applications. The higher yield in the larger scale reaction is presumably due to an increase in the concentration of the reagents by a factor of 4 that facilitates coordination of the 1,3-diene to the arylpalladium intermediate. The regioselectivity in these experiments can be explained by the greater affinity of the arylpalladium intermediate for the less hindered terminal double bond over an internal double bond. The annulation of isoprene gave a 3:2 mixture of regioisomers **24a** and **24b** in a 73% yield (entry 12). The annulation of isoprene by *o*-iodophenol is mostly governed by steric factors, favoring addition to the less hindered double bond and affording a 7:1 ratio of the corresponding annulation products.[13] The poor regioselectivity in entry 12 presumably results from the higher reactivity of the presumed cationic arylpalladium intermediate toward the more electron-rich disubstituted double bond leading to a competition between steric and electronic factors, which produces the two different products.

2,4-Hexadiene (a 3:2 mixture of trans,trans and cis,-trans stereoisomers),[17] which has generally been unreactive and afforded dismal yields in most of our previous palladium annulation chemistry, gave a 3:2 ratio of trans- and cis-stereoisomers **25a** and **25b** in a 60% overall yield (entry 13). Surprisingly, the use of 95% pure *trans,trans*-2,4-hexadiene gave a 20:1 ratio of isomers **25a** and **25b** in a 70% yield (entry 13). This result will be discussed further in our later discussion of the reaction mechanism. Remarkably, in all of our previous palladium annulation chemistry, relatively hindered 1,3-dienes, like those employed in entries 2, 3, 9−11, and 13, were completely unreactive and only 1,3-dienes bearing monosubstituted terminal double bonds have given satisfactory results. The exclusive generation of *E*-stereochemistry in the newly formed double bond in products **17**, **18**, **20**, and **21** is consistent with the intermediacy of a *syn*-π-allylpalladium intermediate in these reactions.[18] The annulation of methyl *trans,trans*-2,4-hexadienoate failed, presumably because of the low affinity of the cationic arylpalladium intermediate for the electron-deficient double bond. Relatively sterically hindered 2,3-diphenyl-1,3-butadiene gave only a 10% yield of the desired product **26** (entry 14), while the even more hindered dienes 1,4-diphenyl-1,3-butadiene and 2,5-dimethyl-2,4-hexadiene were completely unreactive. The attempted annulations of 2,3-dimethoxy-1,3-butadiene, 1-methoxy-1,3-cyclohexadiene, 1,4-pentadiene, cycloheptatriene, and cyclohexene did not afford any recognizable products.

In an effort to broaden the scope of this reaction, similar reactions have been performed on coumarins **27**, **35**, and **37**. All 1,3-dienes investigated have reacted with coumarin **27** to give the expected annulation products **28**−**34** in high yields (entries 15−21). Coumarin **35** gave the expected product **36** in a good yield, even when using relatively hindered 2,3-dimethyl-1,3-butadiene (entry 22). Annulation of the coumarin **37** under our "optimal" reaction conditions resulted in hydrolysis of the acetyl group. The facile hydrolysis is consistent with the higher acidity of 4-hydroxycoumarin than 7-hydroxycoumarin.[19] The same reaction without the addition of water gave a 48% yield of dihydrofurocoumarin **38** (entry 23). In this experiment, the acetyl group is quite possibly still being hydrolyzed by trace amounts of water present in commercial 1,4-dioxane.

Chemical modification of the prepared dihydrofurocoumarins enhances the utility of our approach for the synthesis of various potentially biologically interesting products. For example, the hydroxymercuration/demercuration[20] and dihydroxylation[21] of coumarin **23** gave the corresponding alcohol **39** and diol **40**, close analogues of columbianetin (**2**) and prandiol (**7**), respectively, in high yields (Scheme 1). The dehydrogenation[22] of coumarin **9** afforded benzofurocoumarin **41** in a 90% yield. According to previous reports benzofurocoumarins, have a high potential for the treatment of psoriasis and related diseases.[22,23]

A proposed mechanism for this annulation process is shown in Scheme 2. Initial oxidative addition of the

(17) The ratio of trans,trans to cis,trans isomers was determined by gas chromatography.

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TABLE 2. Synthesis of Dihydrofurocoumarins by the Annulation of 1,3-Dienes[a]

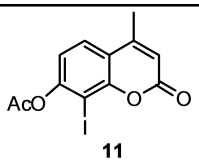
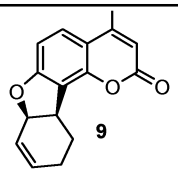
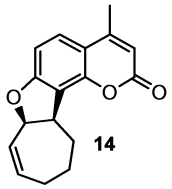
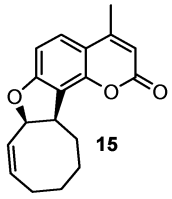
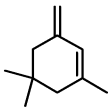
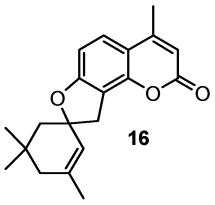
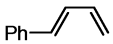
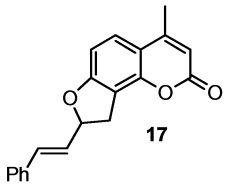
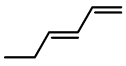
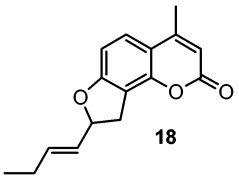
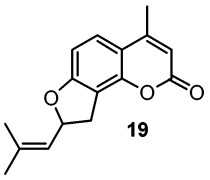
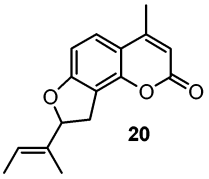
entry	coumarin	1,3-diene	product(s)	% yield[b] (ratio of isomers)
1	 **11**		 **9**	64
2			 **14**	25
3			 **15**	28
4			 **16**	61
5			 **17**	79
6			 **18**	80
7			 **19**	78
8			 **20**	83

Table 2 (Continued)

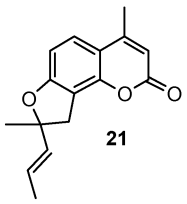
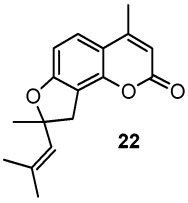
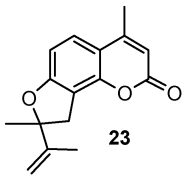
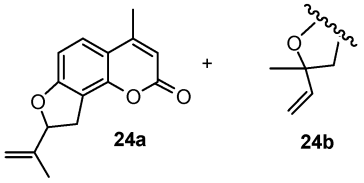
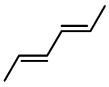
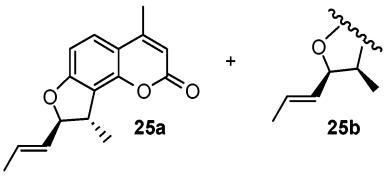
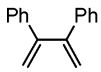
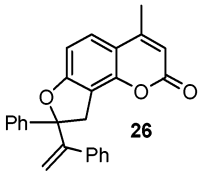
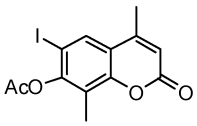
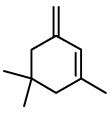
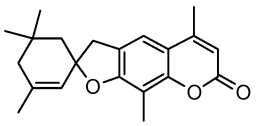
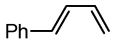
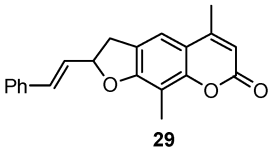
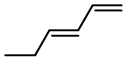
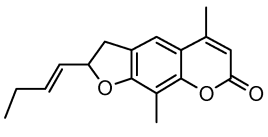
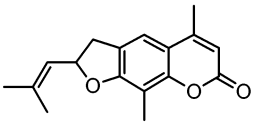
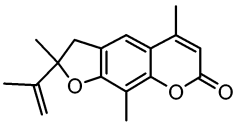
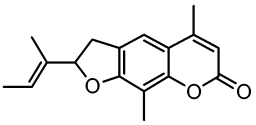
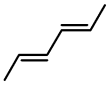
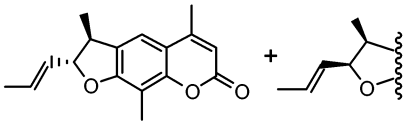
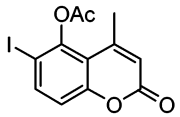
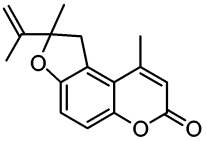
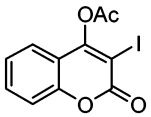
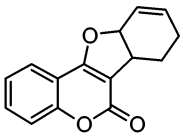
entry	coumarin	1,3-diene	product(s)	% yield[b] (ratio of isomers)
9			 **21**	78
10			 **22**	75
11			 **23**	75, 91[c]
12			 **24a** **24b**	73 (3:2)
13			 **25a** **25b**	60 (3:2)[d] 70 (20:1)[e]
14			 **26**	10
15	 **27**		 **28**	72
16			 **29**	73
17			 **30**	75

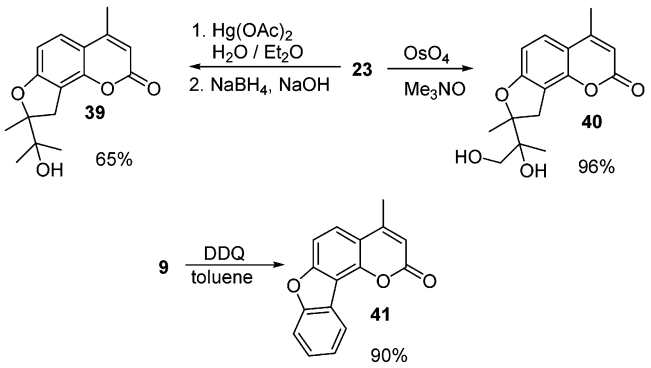
Table 2 (Continued)

entry	coumarin	1,3-diene	product(s)	% yield[b] (ratio of isomers)
18			 **31**	79
19			 **32**	70
20			 **33**	75
21			 **34a** **34b**	60 (3:2)[d] 67 (20:1)[e]
22	 **35**		 **36**	58
23[f]	 **37**		 **38**	48

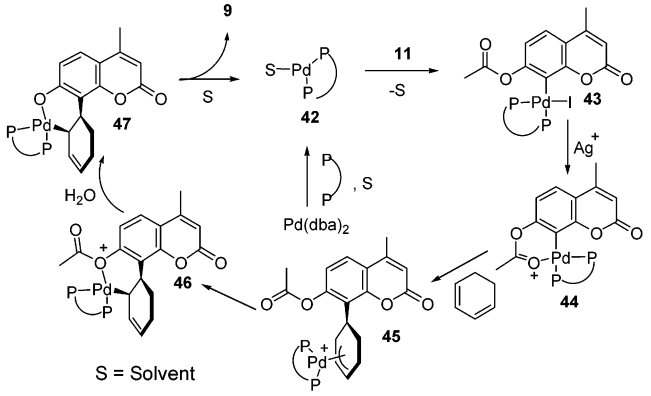
[a] See the text for the experimental procedure. [b] All yields are isolated and based on a single run. [c] This experiment was performed on a 2.0-mmol scale. [d] A 3:2 mixture of trans,trans and cis,trans isomers was used. [e] The diene used was 95% trans,trans. [f] No water has been employed in the solvent.

iodocoumarin **11** to palladium(0) intermediate **42** generated in situ forms arylpalladium intermediate **43**. Abstraction of the iodide by Ag_2CO_3 leads to a cationic intermediate **44**, presumably stabilized by coordination to the neighboring acetyl group. According to our results, the presence of the acetyl group completely inhibits formation of the undesired reduction product **10** and dramatically improves the yield of the desired product **9**. This may be due to the lower propensity of complex **44**, compared to its phenol analogue**,** to undergo thermal decomposition. Next, complex **44** adds to the 1,3-diene in a cis-fashion to give π-allylpalladium intermediate **45**. Coordination of the acetoxy oxygen to the palladium atom leading to the formation of intermediate **46** restricts rotation of the C−C bonds in the allyl moiety, and is, presumably, responsible for the high stereoselectivity when *trans,trans*-2,4-hexadiene is utilized (Table 2, entries 13 and 21). Since no hydrolysis of the starting material **11** has been observed under our reaction conditions, the deacylation of intermediate **46** is presumably accelerated by coordination of the acetyl oxygen atom to the cationic palladium center. Finally, complex **47** undergoes reductive elimination to give the final product **9** and regenerates the palladium catalyst **42**.

SCHEME 1



SCHEME 2



Conclusions

In summary, we have developed an efficient palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumarins, which affords good yields of dihydrofurocoumarins. The process is quite general and regio- and stereoselective, and a variety of *o*-iodoacetoxycoumarins, as well as symmetrical and unsymmetrical 1,3-dienes, can be utilized. Derivatization of the annulation products provides an efficient approach to numerous analogues of a very important class of biologically active natural products.

Experimental Section

General Procedure for the Pd-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxycoumarins. *o*-Iodoacetoxycoumarin (0.25 mmol), $Pd(dba)_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol), and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, and filtered, and the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography with use of silica gel as a solid phase and 4:1 hexanes−ethyl acetate as the eluent to afford after solvent removal the final product. Solid products were then recrystallized from 1:1 ethanol−water.

7a,10,11,11a-Tetrahydro-4-methylbenzo[*b*]-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (9). 9 was obtained in 64% yield: white solid, mp 164−165 °C; ^{1}H NMR ($CDCl_3$) δ 1.43−2.32 (m, 4H), 2.40 (d, J = 1.2 Hz, 3H), 3.67 (m, 1H), 5.07 (m, 1H), 6.04 (m, 1H), 6.11 (d, J = 1.2 Hz, 1H), 6.21 (m, 1H), 6.76 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 23.3, 24.2, 38.4, 80.6, 107.2, 111.4, 114.3, 118.6, 123.3, 125.6, 134.8, 151.3, 153.4, 161.4, 163.1; IR (neat) 1733, 1615 cm^{-1}; HRMS m/z 254.0946 (calcd for $C_{16}H_{14}O_3$, 254.0943).

The product characterization data for all other dihydrofurocoumarins and derivatives prepared appears in the Supporting Information.

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Supporting Information Available: General experimental procedures and spectral data for the compounds listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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