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Synthesis of coumarins by Pt-catalyzed hydroarylation of propiolic acids with phenols

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Abstract—Synthesis of coumarins from phenols and propiolic acids was examined by using a Pt catalyst such as $PtCl_2$/AgOTf, K_2PtCl_4/AgOTf, and K_2PtCl_4/AgOAc. Propiolic acid reacted even with less reactive phenols in trifluoroacetic acid to give coumarins and dihydrocoumarins. In the case of substituted propiolic acids, phenylpropiolic acid and 2-octynoic acid, the reactions proceeded selectively to afford coumarins in good to high yields.

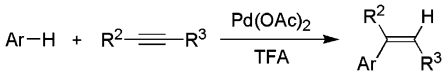
1. Introduction

Coumarin derivatives exist widely in nature, especially in plants, and many of them show a wide range of biological activities.[1,2] To date, many synthetic methods for coumarins have been developed due to their useful properties.[1,3] The representative methods are the Perkin, Pechmann and Knoevenagel reactions. However, there are still limitations such as severe reaction conditions, requirement of a stoichiometric amount of condensing agents, and difficulty of getting the starting materials.

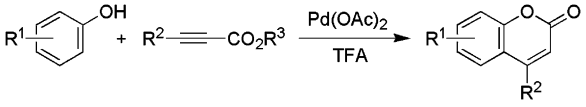
Much effort has been paid to the development of coumarin synthesis through the reaction utilizing a transition metal catalyst.[4–11] However, most of the syntheses require halogenated substrates such as iodophenols and iodoarenes as starting materials for the construction of the coumarin skeleton. These synthetic reactions involve bond cleavage of the C–X bonds by transition metals and produce waste halides. When the atom-economy of the reaction is considered, the use of halogenated substrates is not favorable. If a direct construction of a C–C bond from the C–H bond in simple arenes is possible then this strategy will become a straightforward efficient process.

Trost et al. have developed an atom-economic synthesis of coumarins from the reaction of propiolic acids and phenols in the presence of $Pd_2(dba)_3CHCl_3$ or $Pd(OAc)_2$ catalysts in formic acid.[9] Their reaction did not need any halogenated phenols. Shi and He also reported a direct synthesis of coumarins by the reaction of aryl propiolates with $AuCl_3$/AgOTf catalyst.[10]

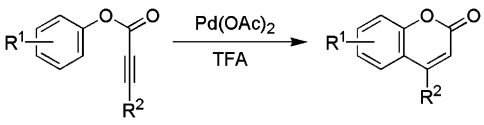
We have reported that the hydroarylation of alkynes proceeded by using $Pd(OAc)_2$ or $PtCl_2$/AgOAc catalyst in trifluoroacetic acid (TFA) to give aryl-substituted alkenes (Eq. 1).[12] This direct functionalization of the C–H bonds in arenes was expanded to the synthesis of coumarins by the intra- or intermolecular hydroarylation of propiolates with phenols (Eqs. 2 and 3).[11] Recently, $PtCl_2$/AgOTf and K_2PtCl_4/AgOTf were found to be effective catalysts for hydroarylation of propiolic acids, affording the corresponding cinnamic acids selectively.[13] Especially, the K_2PtCl_4/AgOTf catalyst was the most effective in application to the hydroarylation of propiolic acid with less reactive benzene. The effectiveness of the Pt catalysts encouraged us to investigate the synthesis of coumarin.



(1)



(2)



(3)

Keywords: Coumarin; Hydroarylation; Propiolic acid; Platinum catalyst; Silver triflate; C–H bond functionalization; Trifluoroacetic acid.
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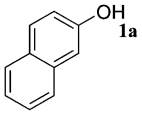
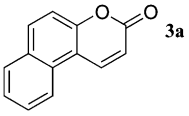
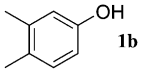
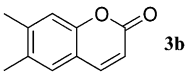
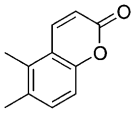
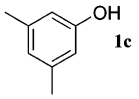
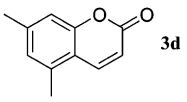
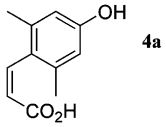
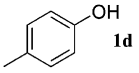
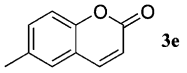
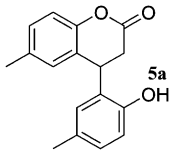
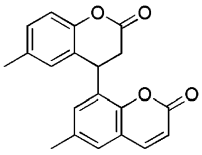
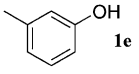
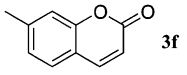
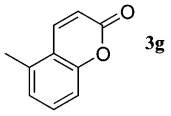
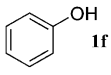
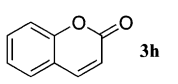
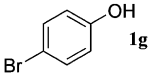
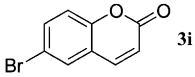
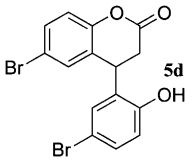
2. Results and discussion

First, we examined the reaction of propiolic acid (**2a**) (R^2=H, R^3=H) or ethyl propiolate (**2b**) (R^2=H, R^3=Et) under similar conditions to the previous reports (Eq. 4, Table 1).[13] The reaction with 2-naphthol (**1a**) proceeded at room temperature to give coumarin **3a** selectively in high yield (entries 1 and 2). 3,4-Dimethylphenol (**1b**) gave 6,7-dimethylcoumarin (**3b**) and 5,6-dimethylcoumarin (**3c**) in 46 and 31% yields, respectively (entry 3). In the case of 3,5-dimethylphenol (**1c**), (2*Z*)-cinnamic acid derivative **4a** was obtained as the major product along with coumarin **3d** (entry 4). *p*-Cresol (**1d**) also reacted to give 6-methylcoumarin (**3e**) and dihydrocoumarin **5a** although the reaction was slow at room temperature and required higher temperature (entries 5–7). Furthermore, a small amount of dihydrocoumarin **5b** was formed, which might be derived from the further reaction of **5a** and **2a**. The reaction using an excess

Table 1. The reaction of propiolic acid (**2a**) or its ethyl ester (**2b**) with phenols **1**[a]

Entry	Phenol	R^3	Cat.[b]	Temp (°C)	Time (h)	Products and yields/%[c]			
1	 **1a**	H	A	rt	25	 **3a**	86[d,e]		
2		H	B	rt	25		86[e]		
3	 **1b**	Et	A	rt	45	 **3b**	46[f]	 **3c**	31[f]
4	 **1c**	Et	A	rt	26	 **3d**	37	 **4a**	50
5	 **1d**	Et	A	50	48	 **3e**	35	 **5a**	44
6		H	C	40	48		51		24
7		H	C	rt	90		51		21
8		H	C	40	12		27[g]	 **5b**	15[g]
9	 **1e**	H	C	rt	25	 **3f**	18[f,h]	 **3g**	17[f,h]
10	 **1f**	H	C	40	48	 **3h**	33		
11	 **1g**	H	C	40	90	 **3i**	7	 **5d**	34

[a] Reaction conditions: phenol **1** (4 mmol), **2a** or **2b** (2 mmol), catalyst, and TFA (1 mL).
[b] Catalyst A: $PtCl_2$ (0.05 mmol) and AgOTf (0.10 mmol). B: K_2PtCl_4 (0.05 mmol) and AgOTf (0.10 mmol). C: K_2PtCl_4 (0.02 mmol) and AgOTf (0.08 mmol).
[c] Isolated yields based on **2**.
[d] Compound **1a** (3 mmol) was used.
[e] CH_2Cl_2 (0.75 mL) was added.
[f] The products were obtained as a mixture of the isomeric coumarins. The product ratios were determined by ^1H NMR.
[g] Compound **1d** (2 mmol) and **2a** (3 mmol) were used.
[h] Compound **5c** was also isolated in 27% yield.

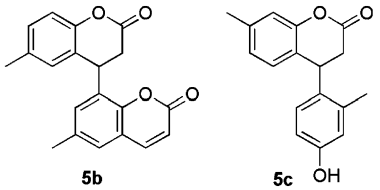
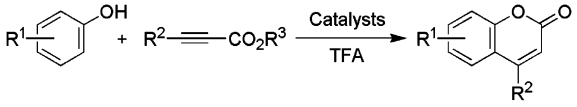


Figure 1.

amount of **2a** was carried out to improve the selectivity of **3e**, resulting in the decrease in the yield of **3e** and the formation of **5b** (entry 8). In contrast to **1d**, the reaction of 3-methylphenol (**1e**) proceeded smoothly at room temperature to give a mixture of 7-methylcoumarin (**3f**) and 5-methylcoumarin (**3g**) along with dihydrocoumarin **5c** (entry 9). The yields were low although most of **2a** was consumed after the reaction. The low yields are attributed to the low selectivity toward the formation of coumarin **3**, similar to the reaction of **1d**. Unsubstituted, simple phenol **1f** reacted to give coumarin (**3h**) in 33% yield (entry 10). Interestingly, 4-bromophenol (**1g**) also participated in this reaction to afford dihydrocoumarin **5d** and 6-bromocoumarin (**3i**) in 34 and 7% yields, respectively (entry 11, Fig. 1).

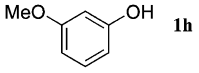
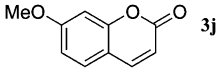
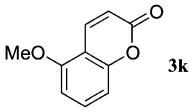
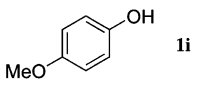
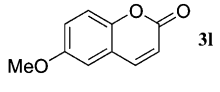
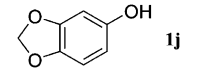
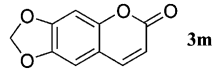
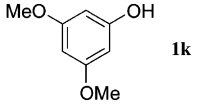
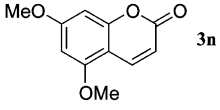


(4)

Next, alkoxyphenols having a strong electron-donating group were examined (Table 2). The reaction of 3-methoxyphenol (**1h**) proceeded at room temperature to give 7-methoxycoumarin (**3j**) and 5-methoxycoumarin (**3k**) in 38 and 10% yields, respectively (entry 1). The yields were not sufficient although most of **2a** used was consumed. ^{1}H NMR analysis of the reaction mixture indicated the formation of dihydrocoumarins. Therefore, further investigation was carried out to improve the selectivity. However, using an excess amount of **2a** or use of AgOAc did not improve the yields (entries 2–5). The reaction of 4-methoxyphenol (**1i**) was slower than that of **1h** (entry 6). The low reactivity of **1i** is in accord with the general concept that a methoxy group activates *ortho* and *para* positions but deactivates the *meta* position for electrophilic aromatic substitution. Sesamol (**1j**) also gave coumarin **3m** (entry 7). Interestingly, the reaction of 3,5-dimethoxyphenol (**1k**) proceeded selectively to afford coumarin **3n** in high yield while **1h**, **1i**, and **1j** gave the corresponding coumarins in low yields (entries 8 and 9).

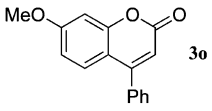
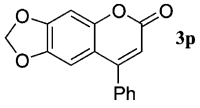
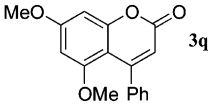
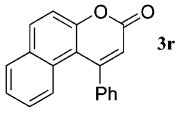
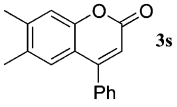
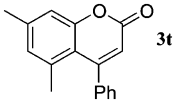
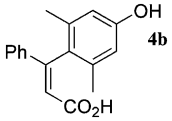
Next, we examined the reaction of the substituted propiolic acids. In contrast to **2a** and **2b**, the reaction of substituted propiolic acids proceeded selectively to give the corresponding coumarins in good to high yields. Table 3 shows the results of the reaction of phenylpropiolic acid (**2c**) (R^2=Ph, R^3=H). In contrast to **2a**, the reaction of **1h** proceeded selectively to give coumarin **3o** in high yield (entries 1–3). Furthermore, higher yield was obtained when the reaction was carried out at room temperature instead of 40 °C. Compound **1j** also gave coumarin **3p** in high yield (entries 4 and 5). 3,5-Dimethoxyphenol (**1k**) gave coumarin **3q** in good yield although the yield was a little bit lower than those of **1h** and **1j** (entry 6). The lower yield of **3q** is possibly attributed to the formation of **7** from the further reaction of coumarin **3q** with **2c**. The formation of **7** analog has been observed in Pd-catalyzed coumarin synthesis.[11b] The reaction of **1a** gave coumarin **3r** in high yield (entries 7 and 8). The reaction of **1b** at 40 °C gave coumarin **3s** in moderate yield because of the lower reactivity of **1b** (entry 9). The reaction of **1c** gave coumarin **3t** and cinnamate **4b**, being similar to the reaction of **2a** (entry 10, Fig. 2).

Table 2. The reaction of propiolic acid (**2a**) with alkoxyphenols[a]

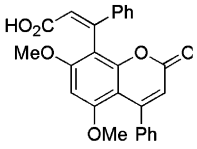
Entry	Phenol	Time (h)	Products and yields %[b]			
1	 **1h**	15	 **3j**	38	 **3k**	10
2		18		28[c]		8[c]
3		11		28[d]		9[d]
4		11		34[d,e]		8[d,e]
5		15		34[f]		11[f]
6	 **1i**	72	 **3l**	22[g]		
7	 **1j**	45	 **3m**	38[g]		
8	 **1k**	15	 **3n**	77[g]		
9		15		81[f,g]		

[a] Reaction conditions: phenol **1** (4 mmol), **2a** (2 mmol), K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), and TFA (1 mL) at rt.
[b] Isolated yields based on **2a**.
[c] Compound **1h** (2 mmol) and **2a** (3 mmol) were used.
[d] Compound **1h** (2 mmol) and **2a** (2.4 mmol) were used.
[e] CH_2Cl_2 (1 mL) was added.
[f] AgOAc (0.08 mmol) was used instead of AgOTf.
[g] CH_2Cl_2 (0.5 mL) was added.

Table 3. The reaction of phenylpropiolic acid (**2c**) with phenol **1**[a]

Entry	Phenol	Cat.[b]	Temp (°C)	Time (h)	Products and yields %[c]		
1	**1h**	B	40	40	 **3o**	71[d]	
2	**1h**	B	rt	40		81	
3	**1h**	C	rt	45		82	
4	**1j**	B	rt	40	 **3p**	76	
5	**1j**	C	rt	45		77	
6	**1k**	C	rt	45	 **3q**	69	
7	**1a**	B	rt	40	 **3r**	84[e]	
8	**1a**	C	rt	45		84	
9	**1b**	C	40	45	 **3s**	58[d]	
10	**1c**	C	40	45	 **3t**	50[d]	 **4b** 29[d]

[a] Reaction conditions: phenol **1** (4 mmol), **2c** (2 mmol), catalyst, TFA (1 mL), and CH_2Cl_2 (0.5 mL).
[b] Catalysts B: K_2PtCl_4 (0.05 mmol) and AgOTf (0.10 mmol). C: K_2PtCl_4 (0.02 mmol) and AgOTf (0.08 mmol).
[c] Isolated yields based on **2c**.
[d] $Cl(CH_2)_2Cl$ (0.5 mL) was added instead of CH_2Cl_2.
[e] $Cl(CH_2)_2Cl$ (1 mL) was added instead of CH_2Cl_2.



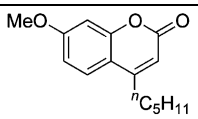
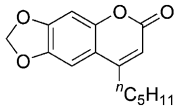
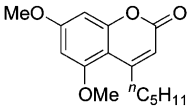
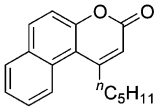
7

Figure 2.

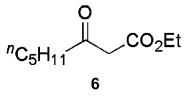
2-Octynoic acid (**2d**) ($R^2={}^nC_5H_{11}$, R^3=H) also reacted with phenols to give the coumarins although the reactivity of **2d** seemed to be lower than that of **2c** (Table 4). The reaction of **1h** gave coumarin **3u** in high yield even at room temperature (entries 1–3). In the case of **1j**, coumarin **3v** was obtained in very low yield when the reaction was carried out at room temperature (entry 4). The elevation of temperature to 40 °C increased the yield but it was not sufficient (entry 5). The ^{1}H NMR analysis of the reaction mixture revealed that the methylenedioxy moiety of **1j** was not present probably because the acetal moiety was hydrolyzed by a strong acid derived from AgOTf. Actually, coumarin **3v** was obtained in high yield when AgOAc was used as co-catalyst instead of AgOTf (entry 6). The reaction of **1k** with ethyl 2-octynoate (**2e**) ($R^2={}^nC_5H_{11}$, R^3=Et) also gave coumarin **3w** in high yield (entry 7). The reaction of **1a** resulted in low yield of coumarin **3x** in contrast to the reaction of **1a** with **2a** or **2c**, indicating that reactivity of **2d** and **2e** was lower than that of **2a**, **2b**, and **2c** (entries 8–13). The reaction also gave ethyl 3-oxooctanoate (**6**) derived from the hydration of **2e** (entry 8). Elongation of the reaction time did not improve the yield (entry 9). The yield of **3x** was somewhat improved when **2d** was used instead of **2e** (entry 10). In this case, the formation of 2-heptanone derived from hydration and decarboxylation of **2d** was observed. The elevation of temperature and the use of AgOAc did not increase the yield (entries 11–13). This result suggests that the coumarin formation competes with the decomposition of **2d** and **2e** (Fig. 3).

The reaction is thought to proceed via the hydroarylation of propiolic acids with phenols, which affords *ortho*-hydroxy substituted cinnamic acids (**A**) followed by the intramolecular esterification of intermediate **A** as depicted in Scheme 1. A similar mechanism has been proposed for Pd(II)-catalyzed reaction of propiolates with phenols giving coumarins.[11b] A very recent report by Tunge and Foresee suggested that the hydroarylation proceeds via aromatic electrophilic substitution, not C–H bond activation.[14] As regards the formation of hydroxyphenyl-substituted dihydrocoumarins **5** in the reaction of **2a**, it was expected that the dihydrocoumarins were formed by the further reaction of coumarins with phenols. However, the reaction of **3e** with **1d** under reaction conditions did not afford dihydrocoumarin **5a**, resulting in the recovery of **3e** and **1d**. This result shows that **3e** formed in the reaction is stable under the reaction conditions. It has been reported that cinnamate derivatives react with phenols in TFA via the formation of carbocation intermediates, affording dihydrocoumarins.[15] A possible route is that dihydrocoumarin **5** is generated by

Table 4. The reaction of 2-octynoic acid (**2d**) or its ethyl ester (**2e**) with phenols **1**[a]

Entry	Phenol	R^3	Cat.[b]	Temp (°C)	Time (h)	Products and yields %[c]	
1	**1h**	H	A	40	45	 **3u**	93
2	**1h**	H	C	40	45		83
3	**1h**	H	C	rt	45		83
4	**1j**	H	C	rt	45	 **3v**	8[d]
5	**1j**	H	C	40	45		41[d]
6	**1j**	H	D	40	45		72[d]
7	**1k**	Et	C	rt	45	 **3w**	87[d]
8	**1a**	Et	C	40	45		13[e]
9	**1a**	Et	C	40	77		16[f]
10	**1a**	H	C	40	45	 **3x**	28[g,h]
11	**1a**	H	D	40	45		28[g]
12	**1a**	H	C	50	45		26[g]
13	**1a**	H	C	60	45		22[g]

[a] Reaction conditions: phenol **1** (4 mmol), **2d** or **2e** (2 mmol), catalyst, and TFA (1 mL) for 45 h.
[b] Catalysts A: $PtCl_2$ (0.05 mmol) and AgOTf (0.10 mmol). C: K_2PtCl_4 (0.02 mmol) and AgOTf (0.08 mmol). D: K_2PtCl_4 (0.02 mmol) and AgOAc (0.08 mmol).
[c] Isolated yields based on **2**.
[d] CH_2Cl_2 (0.5 mL) was added.
[e] CH_2Cl_2 (0.85 mL) was added. Ethyl 3-oxooctanate (**6**) was isolated in 47% yield.
[f] CH_2Cl_2 (1 mL) was added. Compound **6** was isolated in 55% yield.
[g] Compound **1a** (3 mmol) was used. $Cl(CH_2)_2Cl$ (0.5 mL) was added.
[h] 2-Heptanone was formed in 39% GC yield.



6

Figure 3.

the reaction of intermediate **A** with phenols prior to the cyclization of **A**.

In conclusion, we have demonstrated the synthesis of coumarins from phenols and propiolic acids by using Pt catalysts such as $PtCl_2$/AgOTf, K_2PtCl_4/AgOTf, and K_2PtCl_4/AgOAc. The reaction of propiolic acid and its ethyl ester (**2a** and **2b**) proceeded to give coumarin and dihydrocoumarin even in the reaction with less reactive, non-activated phenols. In the cases of substituted propiolic acids **2c**, **2d**, and **2e**, the reactions proceeded selectively to afford coumarins **3** in good to high yields.

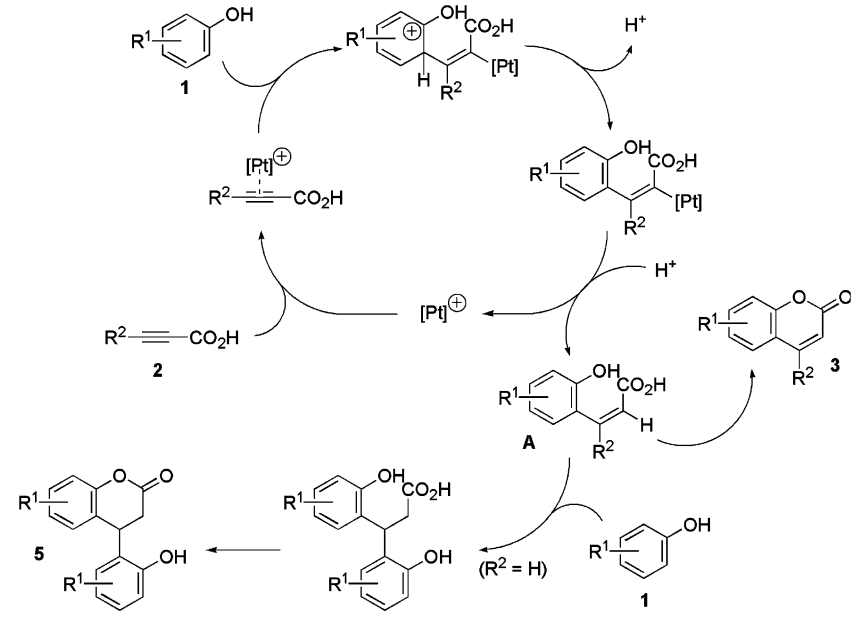
3. Experimental

3.1. General

All solvents and reagents were commercially available and used as received without further purification. All the reactions were conducted in a dry Pyrex tube with a rubber septum. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR using tetramethylsilane (TMS) as internal standard. Melting points were measured with YANACO micro melting apparatus and are uncorrected. Mass spectra were performed on a Shimadzu GC/MS 5020A. Elemental analyses were performed by the Service Centre of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

3.2. The procedure for the synthesis of coumarins by the Pt-catalyzed hydroarylation of propiolic acids with phenols. Typical example: the reaction of 3-methoxyphenol (1h) and phenylpropiolic acid (2c) by using K_2PtCl_2/AgOTf catalyst (Table 3, entry 3)

After a mixture of K_2PtCl_2 (0.02 mmol), AgOTf (0.08 mmol), and trifluoroacetic acid (TFA) (1 mL) was stirred at room temperature for 1 h, **1h** (4 mmol) and **2c** (2 mmol) was added



Scheme 1. The plausible mechanism of the reaction.

to the mixture. The mixture was continuously stirred at a room temperature (27–32 °C) for 45 h. After the reaction, the mixture was poured into water (20 mL), neutralized by $NaHCO_3$, and extracted with diethyl ether (20 mL×4). The ethereal layer was washed with 2 N NaOH aqueous solution (10 mL×3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent to give 4-phenyl-7-methoxycoumarin (**3o**) in 82%.

In some reactions, cinnamic acid **4** and dihydrocoumarin **5** were obtained from the water layer. The procedure is as follows: the combined water layer was acidified by concd HCl aqueous solution (ca. 36%) on ice/water bath and extracted with CH_2Cl_2 (20 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

3.2.1. 3*H*-Naphtho[2,1-*b*]pyran-3-one (3a).[9b,11d,16] Pink crystals. Mp 117–118 °C (AcOEt/hexane).

3.2.2. 6,7-Dimethylcoumarin (3b).[17,18] This compound was partially isolated from the mixture of **3b** and **3c**. Colorless crystals. Mp 146–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 6.33 (d, J=9.6 Hz, 1H, vinyl), 7.11 (s, 1H, aryl), 7.21 (s, 1H, aryl), 7.62 (d, J=9.6 Hz, 1H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.04, 20.21, 115.32, 116.54, 117.28, 127.83, 133.07, 141.81, 143.23, 152.39, 161.22.

3.2.3. 5,6-Dimethylcoumarin (3c).[17] This compound was obtained as a mixture of **3b** and **3c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.40 (d, J=9.9 Hz, 1H, vinyl), 7.09 (d, J=8.4 Hz, 1H, aryl), 7.31 (d, J=8.4 Hz, 1H, aryl), 7.99 (d, J=9.9 Hz, 1H, vinyl).

3.2.4. 5,7-Dimethylcoumarin (3d).[11d,18,19] Colorless crystals. Mp 133–135 °C (CH_2Cl_2/hexane).

3.2.5. 6-Methylcoumarin (3e).[16] Colorless crystals. Mp 73.5–74 °C (CH_2Cl_2/hexane).

3.2.6. 7-Methycoumarin (3f).[16,17] ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, CH_3), 6.35 (d, J=9.6 Hz, 1H, vinyl), 7.10 (d, J=7.8 Hz, 1H, aryl), 7.14 (s, 1H, aryl), 7.36 (d, J=7.8 Hz, 1H, aryl), 7.67 (d, J=9.6 Hz, 1H, vinyl). 7-Methylcoumarin (**3f**) and 5-methylcoumarin (**3g**) were obtained as an inseparable mixture.

3.2.7. 5-Methycoumarin (3g).[17] ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 6.43 (d, J=9.6 Hz, 1H, vinyl), 7.10 (d, J=8.1 Hz, 1H, aryl), 7.18 (d, J=8.1 Hz, 1H, aryl), 7.40 (app t, J=8.1 Hz, 1H, aryl), 7.92 (d, J=9.6 Hz, 1H, vinyl). 7-Methylcoumarin (**3f**) and 5-methylcoumarin (**3g**) were obtained as an inseparable mixture.

3.2.8. Coumarin (3h).[16,20] Colorless crystals. Mp 67–68 °C (hexane).

3.2.9. 6-Bromocoumarin (3i).[21] Colorless crystals. Mp 160–163 °C (CH_2Cl_2/hexane).

3.2.10. 7-Methoxycoumarin (3j).[9b,11c,d] Colorless crystals. Mp 117–118 °C (CH_2Cl_2/hexane).

3.2.11. 5-Methoxycoumarin (3k).[9b,11d] Colorless crystals. Mp 82–83 °C (CH_2Cl_2/hexane).

3.2.12. 6-Methoxycoumarin (3l).[11c,d] Yellow crystals. Mp 101–103 °C (CH_2Cl_2/hexane).

3.2.13. 6,7-Methylenedioxycoumarin (3m).[9b,11d] Dark crystals. Mp 225–227 °C (CH_2Cl_2/hexane).

3.2.14. 5,7-Dimethoxycoumarin (3n).[11c,d] Colorless crystals. Mp 147.5–149 °C (CH_2Cl_2/hexane).

3.2.15. 7-Methoxy-4-phenylcoumarin (3o).[11c,d] White powder. Mp 111–111.5 °C (CH_2Cl_2/hexane).

3.2.16. 6,7-Methylenedioxy-4-phenylcoumarin (3p).[11c,d] Slightly green crystals. Mp 142–144 °C (CH_2Cl_2/hexane).

3.2.17. 5,7-Dimethoxy-4-phenylcoumarin (3q).[9b,11c,d] Colorless crystals. Mp 169–171 °C (CH_2Cl_2/hexane).

3.2.18. 1-Phenyl-3*H*-naphtho[2,1-*b*]pyran-3-one (3r).[11c,d] Light yellow crystals. Mp 160–161 °C (CH_2Cl_2/hexane).

3.2.19. 6,7-Dimethy-4-phenylcoumarin (3s).[11c,d] Colorless crystals. Mp 144–146 °C (CH_2Cl_2/hexane).

3.2.20. 5,7-Dimethy-4-phenylcoumarin (3t).[11a,c] White powder. Mp 94–95 °C (hexane).

3.2.21. 7-Methoxy-4-*n*-pentylcoumarin (3u).[11d,22] Colorless crystals. Mp 68–69.5 °C (CH_2Cl_2/hexane).

3.2.22. 6,7-Methylenedioxy-4-*n*-pentylcoumarin (3v).[11d] Slightly yellow crystals. Mp 106–107.5 °C (CH_2Cl_2/hexane).

3.2.23. 5,7-Dimethoxy-4-*n*-pentylcoumarin (3w).[11c,d] Colorless crystals. Mp 102–103 °C (CH_2Cl_2/hexane).

3.2.24. 1-*n*-Pentyl-3*H*-naphtho[2,1-*b*]pyran-3-one (3x). Colorless crystals. Mp 98.5–99.5 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, J=7.2 Hz, 3H, CH_3), 1.37–1.56 (m, 4H, CH_2), 1.77–1.87 (m, 2H, CH_2), 3.23 (t, J=7.7 Hz, 2H, CH_2), 6.41 (s, 1H, vinyl), 7.47 (d, J=9.0 Hz, 1H, aryl), 7.55 (dd, J=6.9, 8.1 Hz, 1H, aryl), 7.65 (ddd, J=1.5, 6.9, 8.7 Hz, 1H, aryl), 7.92 (dd, J=1.5, 8.1 Hz, 1H, aryl), 7.97 (d, J=9.0 Hz, 2H, aryl), 8.47 (d, J=8.7 Hz, 1H, aryl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.90, 22.33, 28.33, 31.51, 37.47, 113.91, 115.19, 117.90, 124.89, 125.26, 127.76, 129.64, 129.66, 131.30, 133.49, 154.78, 158.17, 160.51. MS (EI, *m*/*z*): 266 (M^+). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.97; H, 6.85.

3.2.25. (2*Z*)-3-(4-Hydroxy-2,6-dimethylphenyl)propenoic acid (4a). Slightly orange crystals. Mp 170–172 °C (AcOEt/hexane). ^{1}H NMR (300 MHz, CD_3OD): δ 2.12 (s, 6H, CH_3), 6.08 (d, J=12.0 Hz, 1H, vinyl), 6.45 (s, 2H, aryl), 7.01 (d, J=12.0 Hz, 1H, vinyl). ^{13}C NMR (75.5 MHz, CD_3OD): δ 20.53, 114.90, 123.88, 128.39, 137.40, 145.21,

157.27, 169.38. MS (EI, *m*/*z*): 192 (M^+). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.58; H, 6.31.

3.2.26. (2*Z*)-3-(4-Hydroxy-2,6-dimethylphenyl)cinnamic acid (4b). Light yellow crystals. Mp 219–221 °C (AcOEt/hexane). ^{1}H NMR (300 MHz, CD_3OD): δ 1.97 (s, 6H, CH_3), 6.53 (s, 2H, aryl), 6.64 (s, 1H, vinyl), 7.32 (app s, 5H, phenyl). ^{13}C NMR (75.5 MHz, CD_3OD): δ 20.20, 115.08, 119.26, 128.00, 129.73, 130.56, 130.86, 137.36, 140.26, 156.35, 157.37, 169.35. MS (EI, *m*/*z*): 268 (M^+). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.96; H, 6.00. The stereochemistry of **4b** was determined by NOE experiments.

3.2.27. 4-(2-Hydroxy-5-methylphenyl)-6-methyl-3,4-dihydrocoumarin (5a). Colorless crystals. Mp 166–168 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.26 (s, 6H, CH_3), 2.95 (dd, *J*=6.6, 16.1 Hz, 1H, $COCH_2$), 3.19 (dd, *J*=5.7, 16.1 Hz, 1H, $COCH_2$), 4.59 (dd, *J*=5.7, 6.6 Hz, 1H, CH), 6.05 (br s, 1H, OH), 6.54 (d, *J*=2.1 Hz, 1H, aryl), 6.61 (d, *J*=8.1 Hz, 1H, aryl), 6.85 (dd, *J*=2.1, 8.1 Hz, 1H, aryl), 6.86 (d, *J*=2.1 Hz, 1H, aryl), 7.01 (d, *J*=8.1 Hz, 1H, aryl), 7.09 (dd, *J*=2.1, 8.1 Hz, 1H, aryl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.52, 20.71, 35.17, 35.26, 115.51, 116.66, 124.55, 126.48, 128.76, 129.02, 129.13, 129.97, 134.44, 149.84, 151.03, 169.83, 169.86. MS (EI, *m*/*z*): 268 (M^+). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.87; H, 5.97. The structure of **5a** was determined by NOE experiments.

3.2.28. 6,6′-Dimethyl-3,4-dihydro-[4,8′]bichromenyl-2,2′-dione (5b). Colorless crystals. Mp 244–246 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.08 (dd, *J*=6.0, 15.9 Hz, 1H, $COCH_2$), 3.14 (dd, *J*=4.5, 15.9 Hz, 1H, $COCH_2$), 4.98 (dd, *J*=4.5, 6.0 Hz, 1H, CH), 6.45 (d, *J*=9.6 Hz, 1H, vinyl), 6.77 (d, *J*=1.8 Hz, 1H, aryl), 6.92 (d, *J*=1.8 Hz, 1H, aryl), 7.08 (d, *J*=8.1 Hz, 1H, aryl), 7.16 (dd, *J*=1.8, 8.1 Hz, 1H, aryl), 7.19 (d, *J*=1.8 Hz, 1H, aryl), 7.68 (d, *J*=9.6 Hz, 1H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.74, 20.84, 33.69, 35.80, 116.66, 117.05, 118.93, 123.44, 127.34, 128.49, 128.84, 129.81, 131.26, 134.51, 134.72, 143.75, 149.23, 150.19, 160.36, 167.53. MS (EI, *m*/*z*): 320 (M^+). Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.74; H, 5.05.

3.2.29. 4-(4-Hydroxy-2-methylphenyl)-7-methyl-3,4-dihydrocoumarin (5c). Colorless crystals. Mp 183–185 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.88 (dd, *J*=7.2, 15.9 Hz, 1H, $COCH_2$), 2.99 (dd, *J*=5.7, 15.9 Hz, 1H, $COCH_2$), 4.51 (dd, *J*=5.7, 7.2 Hz, 1H, CH), 6.48 (dd, *J*=2.1, 8.4 Hz, 1H, aryl), 6.54 (d, *J*=8.4 Hz, 1H, aryl), 6.63 (d, *J*=2.1 Hz, 1H, aryl), 6.78 (d, *J*=7.8 Hz, 1H, aryl), 6.91 (d, *J*=7.8 Hz, 1H, aryl), 7.00 (s, 1H, aryl), 9.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 19.15, 20.55, 34.78, 35.82, 113.16, 116.74, 117.39, 123.58, 125.16, 127.46, 127.86, 129.29, 137.02, 138.12, 151.58, 156.08, 167.94. MS (EI, *m*/*z*): 268 (M^+). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.98; H, 6.01. The structure of **5c** was determined by NOE experiments.

3.2.30. 4-(5-Bromo-2-hydroxyphenyl)-6-bromo-3,4-dihydrocoumarin (5d). Colorless crystals. Mp 237.5–238.5 °C (AcOEt). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.04 (dd, *J*=5.7, 16.2 Hz, 1H, $COCH_2$), 3.14 (dd, *J*=6.9, 16.2 Hz, 1H, $COCH_2$), 4.62 (dd, *J*=5.7, 6.9 Hz, 1H, CH), 6.81 (d, *J*=8.4 Hz, 1H, aryl), 6.96 (d, *J*=2.4 Hz, 1H, aryl), 7.12 (d, *J*=8.7 Hz, 1H, aryl), 7.25 (d, *J*=2.1 Hz, 1H, aryl), 7.28 (dd, *J*=2.4, 8.4 Hz, 1H, aryl), 7.50 (dd, *J*=2.1, 8.7 Hz, 1H, aryl). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 33.45, 34.79, 110.23, 116.07, 117.65, 118.88, 127.08, 129.45, 130.51, 130.83, 131.26, 131.36, 150.82, 154.41, 167.03. MS (EI, *m*/*z*): 396, 398, 400 (M^+). Anal. Calcd for $C_{15}H_{10}Br_2O_3$: C, 45.26; H, 2.53. Found: C, 45.36; H, 2.46.

3.2.31. Ethyl 3-oxooctanoate (6).[23] Yellow liquid.

References and notes

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