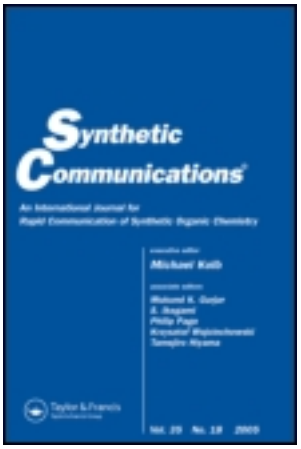

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HYDROXYL SUBSTITUTIONAL EFFECT ON SELECTIVE SYNTHESIS OF *CIS, TRANS* STILBENES AND 3-ARYLCOUMARINS THROUGH PERKIN CONDENSATION

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[1]*Guangzhou Institute of Chemistry, Chinese Academy of Sciences, Guangzhou, China*
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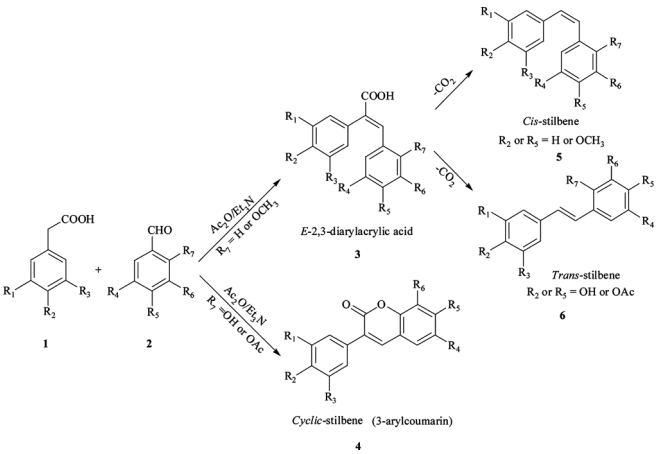
GRAPHICAL ABSTRACT



Abstract *The substitutional effect in the selective synthesis of cis, trans stilbenes and 3-arylcoumarins has been described. The regio- and geometrical selectivity for synthesis of stilbene derivatives under the Perkin strategy strongly depends on the presence or absence of hydroxyl group as well as their positions in the phenyl ring. As a result, practical synthetic strategies were established for preparing various natural stilbenes including combretastatin A-4, pterostilbene, and resveratrol with satisfactory yields (49.2–63.7%).*

Keywords 3-Arylcoumarins; isomerization; Perkin reaction; polyphenolic stilbenes; selectivity

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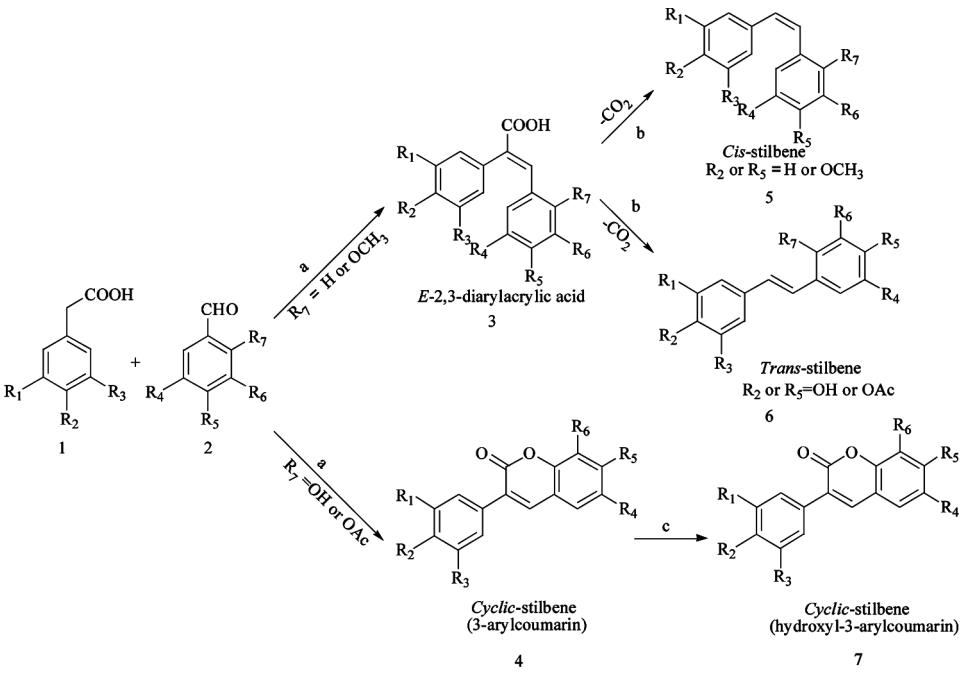
INTRODUCTION

Polyphenolic stilbenes, which often exist as geometrical isomers in *cis* and *trans* forms, have received much attention in recent years because of their great potential of medical applications. Studies have showed that the *cis*-stilbenes exhibited potent antitubulin, antivascular, and anticancer activities in various assays.[1] The typical compound of *cis*-stilbene, combretastatin A-4, is regarded as the lead compound of novel vascular disrupting agents (VDA), and its water-soluble derivative (CA4P) has undergone phase II/III clinical trials in the United States and Europe. *Trans*-stilbenes, such as resveratrol and pterostilbene, are even more renowned for their protecting properties in various disease conditions, such as cancers,[2] heart disease, stroke, Alzheimer disease, inflammations, and infections,[3] and they even show antiaging effects by activating SIRT1 in various organisms.[4] 3-Arylcoumarins, which belong to a minor class of naturally derived isoflavonoids, were scarcely documented previously in terms of bioactivity and structure modifications.[5] These compounds are structurally similar to classical stilbenes except for a heterocyclic ring existing between two phenyl groups and are commonly derived via the phenylpropanoid pathway.[6] Recently, a few studies showed that 3-arylcoumarins, such as glycycoumarin, glycyrin, and asphodelin A, exerted antimicrobial, antidiabetic, anti-HIV, antiaggregatory, and anti-inflammatory activities,[7,8] and demonstrated inhibitory effect on horseradish peroxidase (HRP).[9]

The remarkable medical importance and the scarcity in nature of polyphenolic stilbenes prompted studies for their synthesis. The protocols for establishing ethene bridge between the two phenyl rings are mainly associated with diverse reactions, such as the Wittig reaction,[10] Pd-catalyzed Heck reaction,[11] Lindlar-catalyzed semihydrogenation,[12] Perkin condensation,[13] and Ramberg–Backlund reaction.[14] Among them, the Perkin condensation has proved to be more convenient in terms of procedure, yield, and *cis*-selectivity, and protection or deprotection of hydroxyl group is not needed in most cases. However, when one or more free hydroxyl groups exist in phenolic stilbenes, such as combrestatatin A-4, pterostilbene, resveratrol, and glycyrin, previous synthetic approaches have failed to investigate the substitutional effect of hydroxyl groups and subsequent applicability under the Perkin methodology. This study demonstrates the important role of hydroxyl groups in selective synthesis of *cis, trans*-stilbenes and 3-arylcoumarins. Practical methodologies for the synthesis of various stilbenoids have been established. Representative compounds, including combretastatin A-4, pterostilbene, resveratrol, and some 3-arylcoumarins, have been successfully synthesized with satisfactory yields (49.2–63.7%).

RESULTS AND DISCUSSION

In the course of our studies searching for the synthetic methodologies to produce stilbene derivatives,[15] some meaningful results were obtained with respect to substitutional effect of hydroxyl group under the Perkin methodology (Scheme 1). Conventionally, the Perkin reactions between substituted phenyl acetic acids (**1a–f**) and non-*ortho*-hydroxylated benzaldehydes (**2a–g**) predominantly gave *E*-2,3-diarylacrylic acids (**3a–k**) with *cis* relationship of phenyl rings (Table 1). However, the reaction between **1a–f** and *ortho*-hydroxylated benzaldehydes (**2h–l**) specifically afforded

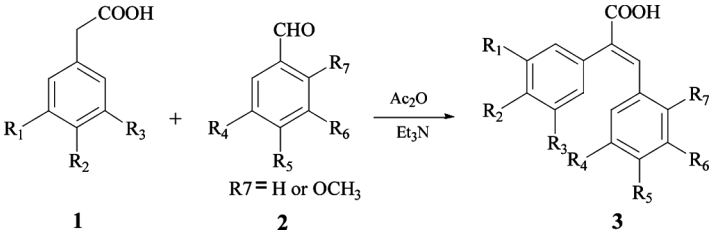


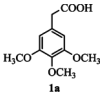
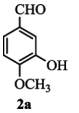
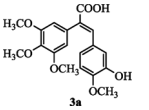
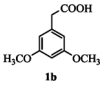
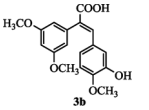
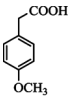
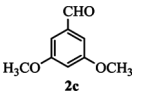
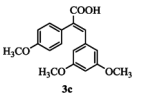
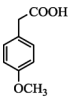
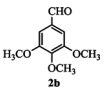
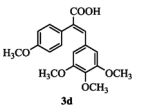
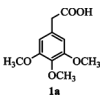
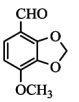
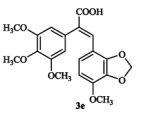
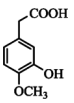
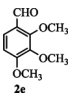
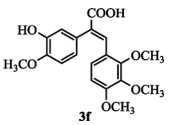
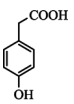
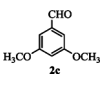
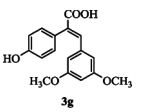
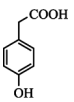
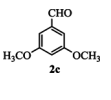
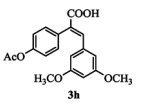
Scheme 1. Substitution effects in the selective synthesis of *cis, trans*-stilbenes and 3-arylcoumarins through Perkin condensation. Reagents and conditions: (a) Ac_2O, Et_3N, reflux; (b) Cu, quinoline, N_2, reflux; (c) 10% $K_2CO_3/H_2O/C_2H_5OH$, rt or 10%$HCl/H_2O/C_2H_5OH$, 80 °C.

a series of cyclic stilbenes (**4a–j**), namely 3-arylcoumarins, and almost no *E*-2,3-diarylacrylic acids were obtained. Hydrolysis of **4a–j** in the presence of HCl/EtOH could afford phenolic products **7a–j** (Table 2). In order to investigate the relationship between the ring-closing selectivity and *ortho*-substitutional pattern for benzaldehydes (**2**), we then transformed 2,3-dihydroxy-4-methoxybenzaldehyde (**2j**) into 2,3-diacetyloxy-4-methoxybenzaldehyde (**2k**) and found that the Perkin condensation between **1a** and **2k** still gave **4a** as the sole product. Further, we replaced **2j** with a more inert substrate such as 2,3,4-trimethoxybenzaldehyde (**2e**) and finally obtained *E*-2,3-diarylacrylic acids (**3f**) as we expected. The 3-arylcoumarins were most probably formed from isomerization of *E*-2,3-diarylacrylic acids and subsequent in situ lactonization between carboxyl group and the adjacent *ortho*-hydroxyl or *ortho*-acetyloxyl group. Owing to the appropriate distance between the carboxyl group and the hydroxyl/acetyloxyl group, an intramolecular cyclization occurred, affording the six-member heterocyclic 3-arylcoumarins, which were more energetically and geometrically favorable.

The configuration of *E*-2,3-diarylacrylic acids (**3**) can be clearly elucidated by ^{1}H NMR spectroscopy. The field effects of carboxylic group in **3a–3k** result in a remarkable downfield shift of the acrylic alkene proton, and similarly, a noticeable field effect of carboxylic group can also be found in the adjacent 2′-H in the B ring. This can be confirmed by chemical shift of the acrylic alkene proton and the 2′-H in the B ring of the corresponding *cis* and *trans* isomers. For example, compound **3g**

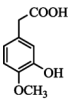
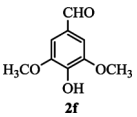
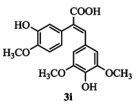
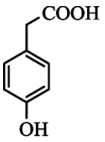
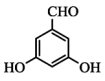
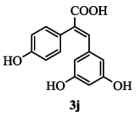
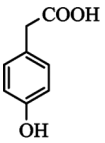
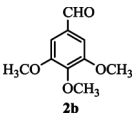
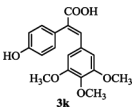
Table 1. Perkin condensations between substituted phenyl acetic acids (**1a–e**) and non-*ortho*-hydroxylated benzaldehydes (**2a–g**) give *E*-2,3-diarylcrylic acids (**3a–k**) as the main products



Substrate				
1	**2**	Product[a]	Yield[b] (%)	Mp (°C)
 **1a**	 **2a**	 **3a**	80	235–237
 **1b**	 **2a**	 **3b**	79	182–184
 **1c**	 **2c**	 **3c**	86.4	140–142
 **1c**	 **2b**	 **3d**	84	208–209
 **1a**	 **2d**	 **3e**	75	218–220
 **1d**	 **2e**	 **3f**	78	187–189
 **1e**	 **2c**	 **3g**	85	225–227
 **1e**	 **2c**	 **3h**	75	182–184

(*Continued*)

Table 1. Continued

Substrate				
1	**2**	Product[a]	Yield[b] (%)	Mp (°C)
 **1d**	 **2f**	 **3i**	70	207–209
 **1e**	 **2g**	 **3j**	81	294–295
 **1e**	 **2b**	 **3k**	82	215–217

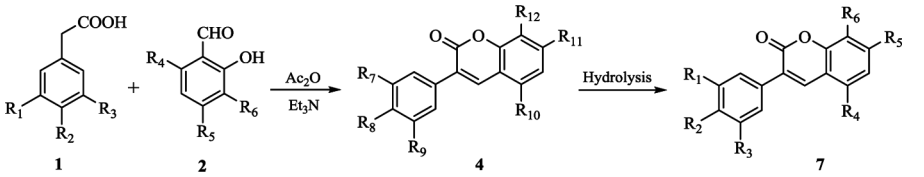
[a]*E*-2,3-diarylcrylic acids were obtained as the sole products after single crystallization. All products were characterized by ^{1}H NMR, IR, and MS spectra.

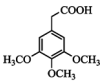
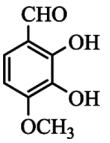
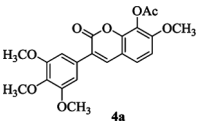
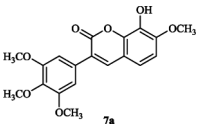
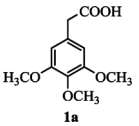
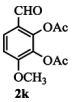
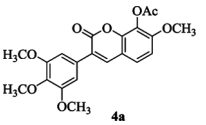
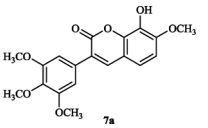
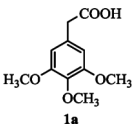
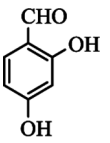
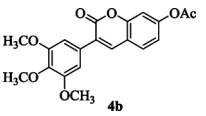
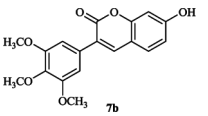
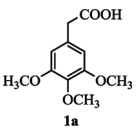
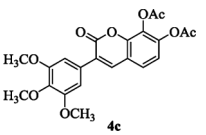
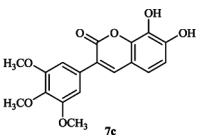
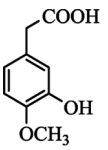
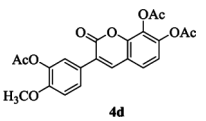
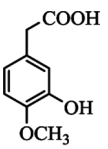
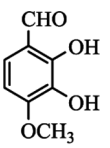
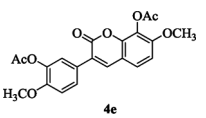
[b]Isolated yields.

showed diagnostic signals at δ_{Ha}7.67 and δ_{Hb}7.02 respectively, and its *trans*-isomer gave corresponding signals at δ_{Ha}6.84 and δ_{Hb}6.87 respectively. Moreover, the 3-arylcoumarins were readily recognized by their characteristic chemical shift of 4-H, for **7f** $\delta_{Ha} = 8.07$ (Fig. 1), indicating the existence of a strong magnetic anisotropic effect of conjugated aryl system.

In addition, geometrical selectivity can be found in the decarboxylation process of *E*-2,3-diarylacrylic acids (**3a–k**). Results showed that the compounds **3a–d** kept the original configuration, giving *cis*-stilbenes (**5a–d**) through decarboxylation. However, **3g–k,** which possesses a *para*-hydroxyl or *para*-acetyloxyl group, readily underwent *cis* to *trans* isomerization in decarboxylation process to afford *trans*-stilbenes (**6a–e**) (Table 3). The formation of a quinoline-induced *para*-quinone intermediate, which is associated with **3g–k**, was the key step for *cis* to *trans* isomerization: The intermediate underwent a rapid rotation around the single bond to give the corresponding *trans*-stilbene (Fig. 2). The *cis* to *trans* isomerization process could also be found in various conditions in recent publications,[16–19] which reinforced the point of view that the *para*-hydroxyl group in phenyl rings or the subsequent *para*-quinone intermediates played a key role on the geometrical selectivity for synthesis of *trans*-stilbenes. The results demonstrate that the presence or absence of *para*-hydroxyl group in the substrates is crucial for geometrical selectivity of decarboxylation reaction. However, it is mainly for this reason that the synthesis of *cis*-stilbenes with a *para*-hydroxyl group could not be accomplished at this stage. The configuration of *cis* and *trans*-stilbene (**5a–d, 6a–e**) are previously established by coupling constant of alkene protons, that is $J_{(CH=CH)} = 12.4$ Hz for *cis*-stilbenes, and $J_{(CH=CH)} = 16$ Hz for *trans*-stilbenes.[13]

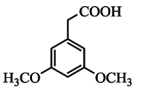
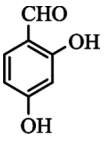
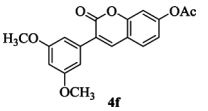
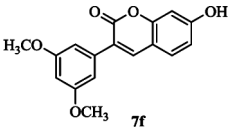
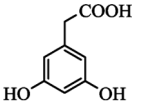
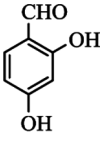
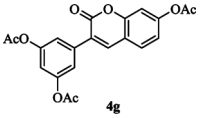
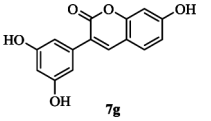
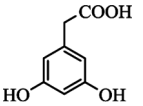
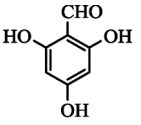
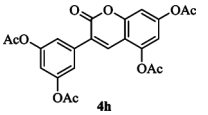
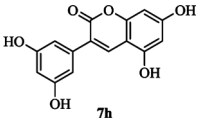
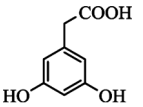
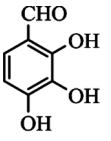
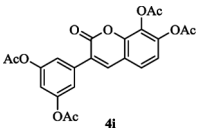
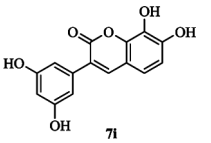
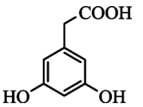
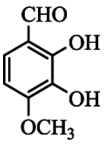
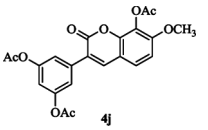
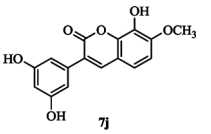
Table 2. Perkin condensations between substituted phenyl acetic acids (**1**) and *ortho*-hydroxylated benzaldehydes (**2h–l**) selectively afford 3-arylcoumarins



Substrate					
1	**2**	Product (**4a–4f**)[a]	Product (**7a–7f**)[a]	Yield[b] (%)	Mp (°C)
 **1a**	 **2j**	 **4a**	 **7a**	85[c] 95[d]	187–188[c] 222–224[d]
 **1a**	 **2k**	 **4a**	 **7a**	88[c]	187–188[c]
 **1a**	 **2i**	 **4b**	 **7b**	88[c] 89[d]	154–155[c] 230–232[d]
 **1a**	 **2h**	 **4c**	 **7c**	90[c] 85[d]	200–201[c] 235–237[d]
 **1d**	 **2h**	 **4d**	ND	80[c]	161–162[c]
 **1d**	 **2j**	 **4e**	ND	82[c]	147–149[c]

(*Continued*)

Table 2. Continued

Substrate 1	Substrate 2	Product (**4a–4f**)[a]	Product (**7a–7f**)[a]	Yield[b] (%)	Mp (°C)
 **1b**	 **2i**	 **4f**	 **7f**	91[c] 95[d]	162–164[c] 221–223[d]
 **1f**	 **2i**	 **4g**	 **7g**	74[c] 90[d]	189–191[c] >280[d]
 **1f**	 **2l**	 **4h**	 **7h**	88[c] 94[d]	236–238[c] >280[d]
 **1f**	 **2h**	 **4i**	 **7i**	75[c] 91[d]	168–170[c] >280[d]
 **1f**	 **2j**	 **4j**	 **7j**	76[c] 90.5[d]	204–206[c] 249–251[d]

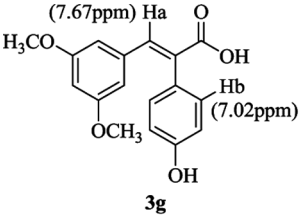
Note. ND, not done.

[a]Free hydroxyl groups in reactants have been acetylated during the reaction to give **4**, followed by hydrolysis to give **7**. All products were characterized by ^{1}H NMR, IR, and MS spectra.

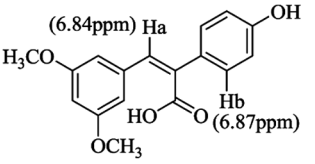
[b]Isolated yields.

[c]Data for compound **4**.

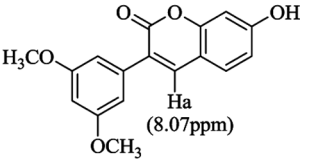
[d]Data for compound **7**.



3g



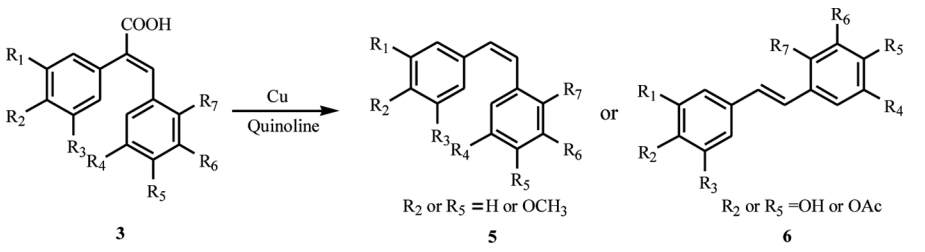
trans-isomer of **3g**



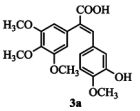
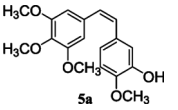
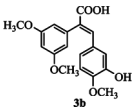
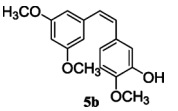
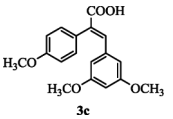
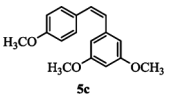
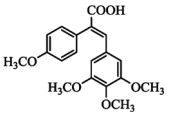
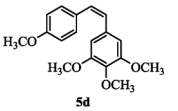
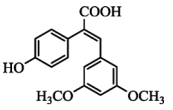
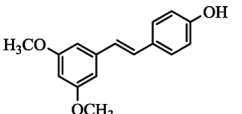
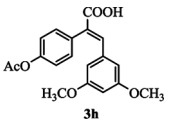
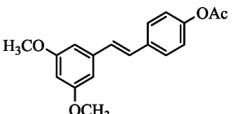
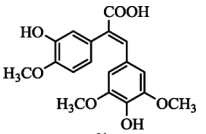
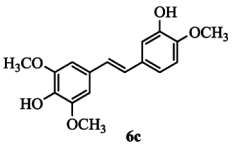
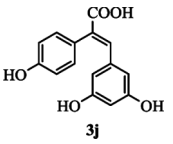
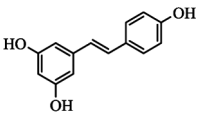
7f

Figure 1. Characteristic proton and chemical shift of corresponding *cis, trans*-stilbene and 3-arylcoumarin.

Table 3. Hydroxyl group induced selectivity in decarboxylation process

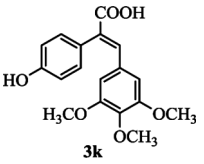
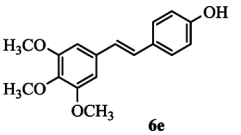


3 5 6

Substrate	Product[a]	Yield[b] (%)	Mp (°C)
 3a	 5a	71[c]	116–117 (lit.[13] 115–116)
 3b	 5b	69[c]	91–93
 3c	 5c	70.6[c]	Pale yellow oil
 3d	 5d	70[c]	Pale yellow oil
 3g	 6a	75[d]	93–94 (lit.[20] 92–94)
 3h	 6b	70[d]	122–123
 3i	 6c	65[d]	148–150 (lit.[21] 150–152)
 3j	 6d	60.8[d]	260–262 (lit.[22] 255–260)

(*Continued*)

Table 3. Continued

Substrate	Product[a]	Yield[b] (%)	Mp (°C)
 **3k**	 **6e**	67[d]	184–185

[a]All products were characterized by ^{1}H NMR, IR, and MS spectroscopy.
[b]Isolated yields.
[c]Z-isomer was obtained as the dominant product (Z-isomers > 95%, determined by ^{1}H NMR) before crystallization.
[d]E-isomer was the only product obtained.

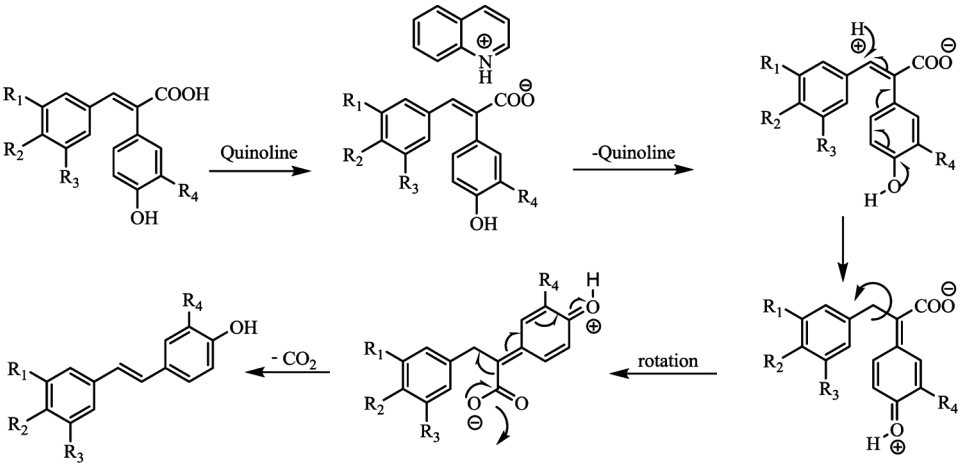


Figure 2. Mechanism of decarboxylation/isomerization of E-2,3-diaryl acrylic acids, which possess a *para*-hydroxyl group.

Our findings with respect to the substitutional effects on the stereoselective synthesis of stilbenes utilizing the Perkin methodology have been reinforced by successful synthesis of several representative natural stilbenes, including combretastatin A-4 (**5a**), pterostilbene (**6a**), and resveratrol (**6d**) with overall yields of 56.8%, 63.7%, and 49.2%, respectively. Moreover, the selected 3-arylcoumarin hybrids (**7f–j**), which bear close structural resemblance with pterostilbene, resveratrol, oxyresverstrol, piceatannol, and rhapontigenin, have also been synthesized through hydrolysis of **4f–j** (90–95%). Biological studies of these compounds are currently under way in our laboratory.

CONCLUSION

In conclusion, we have revealed the dramatic effect of hydroxyl groups in the selective synthesis of polyphenolic *cis-, trans*-stilbenes and 3-arylcoumarins under

Perkin methodology. Reactions between substituted phenyl acetic acids and non-*ortho*-hydroxylated benzaldehydes give *E*-2,3-diarylcrylic acids, whereas the reactions between substituted phenyl acetic acids and *ortho*-hydroxylated benzaldehydes specifically afford 3-arylcoumarins. Moreover, *para*-hydroxyl or acetyloxy groups in either phenyl ring of *E*-2,3-diarylcrylic acids will lead to an unambiguous *cis* to *trans* isomerization in decarboxylation process, while other substrates still dominantly afford the *cis* products in the same conditions. In accordance with these findings, some scarce natural products with important medical interests, including combretastatin A-4 (*cis*-stilbene), pterostilbene, resveratrol (*trans*-stilbene), and 3-arylcoumarins, were successfully synthesized in a straightforward and practical manner with satisfactory yields. Our finding paves the way for large-scale synthesis of *cis*- and *trans*-stilbenes in the future.

EXPERIMENTAL

All melting points were determined on an X-4 TaiKe melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an Analect RFX-65A IR spectrometer. ^{1}H NMR were obtained from a Brucker DRX 400-MHz spectrometer with tetramethylsilane (TMS) as an internal standard. Electron impact mass spectrometry (EIMS) analyses were performed using a Shimadzu GCMS-QP5050A and Thermo GCMS-MAT95XP mass spectrometer. Elemental analyses were carried out on a Elementar Vario EL element analyzer.

Preparation of E-2,3-Diaryl Acrylic Acid (3)

Triethylamine (11 ml) was added to a solution of substituted phenyl acetic acid (**1a–e**, 40 mmol) and non-*ortho*-hydroxylated benzaldehyde (**2a–g**, 40 mmol) in acetic anhydride (11 ml). The mixture was heated to 110 °C and stirred for 6 h. After cooling, the mixture was acidified with concentrated hydrochloric acid, poured into ice water, stirred, and stored for 4 h. A fuscous yellowish solid was obtained, filtered, dissolved in 10% aqueous NaOH (40 ml), washed, and discolored with ethyl acetate. The organic layers were separated. Hydrochloric acid was added to the aqueous phase until pH 3–4. The precipitated solid was filtered and recrystallized from ethyl acetate to afford *E*-2,3-diaryl acrylic acid (**3**).

Compound 3a, E-2-(3,4,5-trimethoxyphenyl)-3-(3′-hydroxyl-4′-methoxyphenyl) acrylic acid. IR (KBr) (T%): 3342 (48), 2941 (47), 2838 (55), 2628 (62), 1672 (28), 1587 (29), 1508 (21), 1457 (37), 1409 (35), 1342 (58), 1307 (37), 1267 (12), 1238 (21), 1170 (42), 1126 (10), 1058 (68), 1024 (49), 1003 (53), 974 (62), 923 (64); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 3.72 (s, 6H, 3, 5-OCH_3), 3.75 (s, 3H, 4-OCH_3), 3.79 (s, 3H, 4′-OCH_3), 6.51 (s, 2H, 2,6-ArH), 6.63 (d, 1H, $J = 2.0$ Hz, 2′-ArH), 6.71 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 6′-ArH), 6.81 (d, 1H, $J = 8.4$ Hz, 5′-ArH), 7.69 (s, 1H, CH=); EIMS m/z: 360(M^+), 345(M^+-CH_3).

Compound 3b, E-2-(3,5-dimethoxyphenyl)-3-(3′-hydroxyl-4′-methoxyphenyl) acrylic acid. IR (KBr) (T%): 3359 (57), 3012 (65), 2933 (60), 2840 (61), 2638 (66), 1673 (42), 1598 (31), 1508 (43), 1461 (53), 1446 (53), 1423 (49), 1388 (64), 1346 (67), 1297 (46), 1267 (22), 1201 (48), 1149 (35), 1060 (61), 1025 (57),

968 (67), 927 (68); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 6H, 3, 5-OCH_3), 3.84 (s, 3H, 4′-OCH_3), 6.37 (d, 2H, $J = 2.4$ Hz, 2, 6-ArH), 6.46 (t, 1H, $J = 2.4$ Hz, 4-ArH), 6.65 (d, 1H, $J = 8.4$ Hz, 5′-ArH), 6.67 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 6′-ArH), 6.68 (d, 1H, $J = 2.4$ Hz, 2′-ArH), 7.78 (s, 1H, CH=); EIMS m/z: 330 (M^+), 311 (M^+-H_2O), 285 (M^+-CO_2).

Compound 3g, E-2-(4-hydroxyphenyl)-3-(3′, 5′-dimethoxyphenyl) acrylic acid. IR (KBr) (T%): 3397 (52), 3062 (57), 3016 (56), 2952 (52), 2838 (55), 1670 (22), 1590 (29), 1513 (54), 1457 (56), 1427 (37), 1382 (65), 1344 (62), 1286 (35), 1234 (48), 1205 (37), 1155 (38), 1060 (57), 997 (750, 929 (70), 906 (70), 865 (74), 831 (54); ^{1}H NMR (400 Hz, CD_3COCD_3) δ: 3.56 (s, 6H, 3′,5′-OCH_3), 6.32 (m, 3H, 2′,4′,6′-ArH), 6.84 (d, 2H, $J = 8.4$ Hz, 3,5-ArH), 7.02 (d, 2H, $J = 8.4$ Hz, 2,6-ArH), 7.67 (s, 1H, CH=); EIMS m/z: 300 (M^+), 255 (M^+-CO_2).

Compound 3i, E-2-(3-hydroxy-4-methoxyphenyl)-3-(3′,5′-dimethoxy-4′-hydroxyphenyl) acrylic acid. IR (KBr) (T%): 3428 (37), 2940 (49), 1675 (36), 1610 (44), 1590 (44), 1511 (27), 1457 (43), 1427 (44), 1263 (23), 1236 (27), 1110 (31), 1018 (59), 985 (66), 925 (63); ^{1}H NMR(400 Hz, $CDCl_3$) δ: 3.62 (s, 6H, 3′,5′-OCH_3), 3.89 (s, 3H, 4-OCH_3), 5.52 (s, 1H, OH), 6.39(s, 2H, 2′,6′-ArH), 6.75 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz, 6-ArH), 6.86 (d, 1H, $J = 2.0$ Hz, 2-ArH), 6.89 (d, 1H, $J = 8.0$ Hz, 5-ArH), 7.77 (s, 1H, =CH); EIMS m/z: 346 (M^+), 302 (M^+-CO_2).

Compound 3j, E-2-(4-hydroxyphenyl)-3-(3′,5′-dihydroxyphenyl) acrylic acid. IR (KBr) (T%): 3419 (49), 3056 (64), 1668 (33), 1617 (52), 1593 (45), 1516 (56), 1429 (88), 1280 (38), 1253 (48), 1203 (54), 1176 (60), 1153 (46), 1006 (69); ^{1}H NMR (400 Hz, CD_3COCD_3,) δ: 6.19 (d, 2H, $J = 2.0$ Hz, 2, 6-ArH), 6.26 (t, 1H, $J = 2.0$ Hz, 4-ArH), 6.82 (d, 2H, $J = 8.4$ Hz, 2′,6′-ArH), 7.04 (d, 2H, $J = 8.4$ Hz, 3′,5′-ArH), 7.63 (s, 1H, =CH), 8.27 (s, 2H, $2 \times$ OH), 8.43 (s, 1H, OH), 10.8 (s, 1H, COOH); ESIMS m/z: 272 (M^+).

Decarboxylation

A mixture of *E*-2,3-diacrylic acid (**3**) (10 mmol) and copper powder (80 mmol) in 20 ml quinoline was stirred at 200 °C for 3 h under N_2 atmosphere. After cooling, ethyl acetate was added, and the copper powder was filtered off. The filtrate was washed with 2 M hydrochloric acid, and the water layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried ($MgSO_4$), and evaporated in vacuum to afford a brown viscous solid, which was re-extracted with hot petroleum ether (60–90 °C) and recrystallized from ethyl acetate/petroleum ether (60–90 °C) to give the product (**5** or **6**) as a colorless crystal.

Compound 5a, Z-3′-hydroxyl-3,4,4′,5-tetramethoxystilbene (Combretastatin A-4). IR (KBr) (T%): 3424 (6), 3002 (w, 10), 2938 (9), 2836 (11), 1579 (11), 1508 (6), 1459 (15), 1419 (15), 1328 (23), 1274 (14), 1238 (11), 1182 (36), 1126 (4) 1025 (37), 1004 (35), 944 (56), 881 (48), 854 (47); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.68 (s, 6H, 3, 5-OCH_3), 3.84 (s, 3H, 4-OCH_3), 3.89 (s, 3H, 4′-OCH_3), 5.49 (s, 1H, OH), 6.42 (d, 1H, $J = 12.4$ Hz, CH=), 6.45 (d, 1H, $J = 12.4$ Hz, CH=), 6.51 (s, 2H, 2, 6-ArH), 6.71 (d, 1H, $J = 8.0$ Hz, 5′-ArH), 6.79 (dd, 1H, $J_1 = 8.0$ Hz,

$J_2 = 2.0$ Hz, 6′-ArH), 6.91 (d, 1H, $J = 2.0$ Hz, 2′-ArH); EIMS m/z: 316 (M^+), 301 (M^+-CH_3). Anal. calc. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.33%. Found: C, 68.26; H, 6.27%.

Compound 5b, Z-3′-hydroxyl-3,4′,5-trimethoxylstilbene. IR (KBr) (T%): 3436 (10), 3073 (31), 2996 (24), 2965 (24), 2938 (24), 2839 (26), 2040 (49), 1662 (68), 1587 (6), 1514 (8), 1461 (10), 1444 (14), 1402 (28), 1344 (22), 1268 (3), 1203 (9), 1155 (4), 1126 (15), 1052 (13), 1024 (17), 964 (32), 924 (21), 887 (22); ^{1}H NMR(400 Hz, $CDCl_3$) δ: 3.56 (s, 6H, 3, 5-OCH_3), 3.84 (s, 3H, 4′-OCH_3); 5.50 (s, 1H, OH), 6.30 (t, 1H, $J = 2.0$ Hz, 4-ArH), 6.43 (d, 1H, $J = 12.4$ Hz, =CH), 6.44 (d, 2H, $J = 2.0$ Hz, 3,5-ArH), 6.48 (d, 1H, $J = 12.4$ Hz, =CH), 6.69 (d, 1H, $J = 8.0$ Hz, 5′-ArH), 6.77 (d, 1H, $J = 8.0$ Hz, 6′-ArH), 6.87 (d, 1H, $J = 2.0$ Hz, 2′-ArH); EIMS m/z: 286 (M^+), 271 (M^+-CH_3); HREIMS m/z: 286.1197, calculated for $C_{17}H_{18}O_4$: 286.1200.

Compound 6a, E-4′-hydroxy-3,5-dimethoxylstilbene (pterostilbene). IR (KBr) (T%): 3224 (24), 2933 (32), 2830 (32), 2364 (39), 1589 (14), 1511 (30), 1454 (32), 1421 (34), 1359 (36), 1295 (34), 1238 (25), 1203 (25), 1182 (38), 1151 (18), 1062 (30), 964 (36); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 6H, 3, 5-OCH_3), 6.36 (t, 1H, $J = 2.0$ Hz, 4-ArH), 6.63 (d, 2H, $J = 2.0$ Hz, 2, 6-ArH), 6.81 (dd, 2H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 2′,6′-ArH), 6.87 (d, 1H, $J = 16$ Hz, CH=), 7.01 (d, 1H, $J = 16$ Hz, CH=), 7.38 (dd, 2H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 3′,5′-ArH); EIMS m/z: 256 (M^+); HREIMS m/z: 256.1092 calculated for $C_{16}H_{16}O_3$: 256.1094.

Compound 6c, E-3′,4-dihydroxyl-3,4′,5-trimethoxystilbene. IR (KBr) (T%): 3502 (50), 3467 (46), 3001 (65), 2937 (62), 2840 (63), 1604 (59), 1513 (35), 1462 (55), 1425 (61), 1328 (50), 1294 (57), 1271 (51), 1249 (54), 1217 (46), 1112 (43), 1026 (61), 964 (66); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.89 (s, 3H, 4′-OCH_3), 3.92 (s, 6H, 3, 5-OCH_3), 5.52 (s, 1H, OH), 5.58 (s, 1H, OH), 6.69 (d, 1H, $J = 16$ Hz CH=), 6.73 (d, 1H, $J = 16$ Hz CH=), 6.81 (d, 1H, $J = 8.4$ Hz, 5′-ArH), 6.85 (s, 2H, 2, 6-ArH), 6.94 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 6′-ArH), 7.10 (d, 1H, $J = 2.0$ Hz, 2′-ArH); EIMS m/z: 302 (M^+), 287 (M^+-CH_3); HREIMS m/z: 302.1147, calculated for $C_{17}H_{18}O_5$: 302.1149.

Compound 6d, E-3,4′,5-trihydroxylstilbene (Resveratrol). IR (KBr) (T%): 3292 (15), 3020 (37), 1606 (29), 1587 (18), 1512 (29), 1461 (42), 1444 (38), 1384 (34), 1326 (36), 1301 (50), 1265 (45), 1247 (43), 1214 (50), 1174 (49), 1151 (23), 1107 (60), 1010 (46), 987 (41), 966 (38); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 6.26 (t, 1H, $J = 2.0$ Hz, 4-ArH), 6.54 (d, 2H, $J = 2.0$ Hz, 3, 5-ArH), 6.86 (d, 1H, $J = 16$ Hz, CH=), 6.87 (dd, 2H, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 2′,6′-ArH), 7.02 (d, 1H, $J = 16$ Hz, CH=), 7.41 (dd, 2H, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 3′,5′-ArH), 8.21 (s, 2H, 3,5-OH, D_2O exchangeable), 8.43 (s, 1H, 4′-OH, D_2O exchangeable); EIMS m/z: 288 (M^+), 211, 181, 152, 115.

Preparation of 3-Arylcoumarin (4)

Triethylamine (4 ml) was added to a solution of *ortho*-hydroxylated benzaldehyde (**2h–l**, 10 mmol) and substituted phenyl acetic acid (**1**, 10 mmol) in acetic anhydride (6 ml). The mixture was heated to 120 °C and stirred for 8 h. After cooling, it was poured into ice water, stirred, and stored for 4 h. The precipitated yellowish solid was filtered, washed with water, dried, and recrystallized from ethyl acetate to give the title compound.

Compound 4f, 7-acetyloxy-3-(3′,5′-dimethoxyphenyl) coumarin. IR (KBr) (T%): 3064 (64), 2994 (63), 2969 (61), 2940 (60), 2840 (63), 1758 (25), 1712 (13), 1594 (23), 1461 (47), 1427 (33), 1351 (49), 1209 (12), 1153 (24), 1122 (46), 1058 (41), 1012 (44), 916 (52), 881 (65), 848 (45); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H, 7-OAc), 6.49 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 6.80 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 7.05 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 6-H), 7.12 (d, 1H, $J = 2.0$ Hz, 8-H), 7.51 (d, 1H, $J = 8.4$ Hz, 5-H), 7.77 (s, 1H, 4-H); EIMS m/z: 340 (M^+), 298 (M^+-Ac).

Compound 4g, 7-acetoxy-3-(3′,5′-diacetoxyphenyl) coumarin. IR (KBr) (T%): 3079 (50), 2362 (56), 1764 (25), 1724 (28), 1614 (37), 1500 (58), 1434 (49), 1369 (44), 1307 (55), 1201 (19), 1151 (43), 1122 (33), 1022 (42), 950 (60), 921 (51); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 6H, 3′,5′-OAc), 2.33 (s, 3H, 7-OAc), 6.97 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 7.06 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 6-H), 7.13 (d, 1H, $J = 2.0$ Hz, 8-H), 7.36 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 7.52 (d, 1H, $J = 8.4$ Hz, 5-H), 7.83 (s, 1H, 4-H); EIMS m/z: 396 (M^+), 354 (M^+-Ac), 312 (M^+-2Ac), 270 (M^+-3Ac).

Compound 4h, 5,7-diacetoxy-3-(3′,5′-diacetoxyphenyl) coumarin. IR (KBr) (T%): 3120 (64), 3087 (64), 2938 (68), 1762 (21), 1733 (25), 1614 (35), 1488 (65), 1434 (51), 1373 (43), 1297 (55), 1209 (19), 1182 (16), 1130 (28), 1101 (49), 1076 (46), 1024 (43), 904 (50), 858 (68); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 6H, 3′,5′-OAc), 2.31 (s, 3H, 7-OAc), 2.40 (s, 3H, 5-OAc), 6.99 (d, 2H, $J = 1.6$ Hz, 2′,6′-ArH), 7.05 (t, 1H, $J = 1.6$ Hz, 4′-ArH), 7.30 (d, 2H, $J = 2.0$ Hz, 6, 8-H), 7.78 (s, 1H, 4-H); EIMS m/z: 454 (M^+), 412 (M^+-Ac), 370 (M^+-2Ac), 328 (M^+-3Ac), 286 (M^+-4Ac).

Compound 4i, 7,8-diacetoxy-3-(3′,5′-diacetoxyphenyl) coumarin. IR (KBr) (T%): 3085 (56), 2940 (61), 2362 (65), 1783 (21), 1735 (18), 1612 (38), 1492 (55), 1436 (42), 1373 (30), 1322 (49), 1253 (38), 1201 (8), 1157(28), 1130 (26), 1108 (34), 1078 (42), 1052 (28), 1025 (30), 917 (43), 879 (43); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 6H, 3′,5′-OAc), 2.31 (s, 3H, 8-OAc), 2.40 (s, 3H, 7-OAc), 6.98 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 7.12 (d, 1H, $J = 8.4$ Hz, 6-H), 7.32 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 7.39 (d, 1H, $J = 8.4$ Hz, 5-H), 7.80 (s, 1H, 4-H); EIMS m/z: 454 (M^+), 412 (M^+-Ac), 370 (M^+-2Ac), 328 (M^+-3Ac), 286 (M^+-4Ac).

Compound 4j, 7-methoxy-8-acetoxy-3-(3′,5′-diacetoxyphenyl) coumarin. IR (KBr) (T%): 3093 (59), 2938 (60), 2844 (63), 2362 (66), 1772 (14), 1741 (21), 1616 (29), 1581 (48), 1506 (46), 1463 (48), 1438 (44), 1369 (38), 1324 (50), 1297 (31), 1193 (9), 1120 (24), 1068 (40), 1024 (37), 914 (50); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 2.27 (s, 6H, 3′,5′-OAc), 2.40 (s, 3H, 8-OAc), 3.94 (s, 3H, OCH_3), 7.00 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 7.19 (d, 1H, $J = 8.8$ Hz, 6-H), 7.43 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 7.66 (d, 1H, $J = 8.8$ Hz, 5-H), 8.199 (s, 1H, 4-H); EIMS m/z: 426 (M^+), 384 (M^+-Ac), 342 (M^+-2Ac), 300 (M^+-3Ac) (100%), 285 (M^+-3Ac-CH_3).

Preparation of Phenolic 3-Arylcoumarin (7)

Compound **4** (1.25 mmol) was added to a 10% solution of HCl (15 ml) and ethanol (5 ml). The mixture was heated to 80 °C and stirred for 5–12 h. After cooling, it was poured into ice water, and the precipitated solid was filtered, washed with water, dried, and recrystallized from ethanol/water to give the title compound.

Compound 7f, 7-hydroxy-3-(3′,5′-dimethoxyphenyl) coumarin. IR (KBr) (T%): 3284 (36), 2958 (58), 2836 (61), 1697 (27), 1598 (26), 1571 (35), 1508 (46), 1457 (49), 1425 (56), 1346 (45), 1303 (31), 1259 (57), 1234 (56), 1199 (38), 1157 (28), 1128 (46), 1064 (58), 1010 (52), 952 (72), 925 (68); ^{1}H NMR (400 MHz,CD_3COCD_3) δ: 3.80 (s, 6H, 3′,5′-OCH_3), 6.49 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 6.77 (d, 1H, $J = 2.4$ Hz, 8-H), 6.85 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 6-H), 6.90 (d, 2H, $J = 2.4$ Hz, 2′,6′-ArH), 7.56 (d, 1H, $J = 8.4$ Hz, 5-H), 8.07 (s, 1H, 4-H); ^{13}C NMR (400 MHz, CD_3COCD_3) δ: 55.7, 100.8, 102.8, 107.5, 113.5, 114.0, 124.1, 130.7, 138.2, 141.5, 156.3, 160.6, 161.6, 161.9; EIMS m/z: 298 (M^+), 269.

Compound 7g, 7-hydroxy-3-(3′,5′-dihydroxyphenyl) coumarin. IR (KBr) (T%): 3168 (W, 18), 2362 (35), 1683 (16), 1616 (12), 1571 (16), 1509 (24), 1469 (26), 1380 (34), 1326 (20), 1301 (18), 1241 (29), 1201 (27), 1160 (15), 1133 (22), 1031 (40), 1002 (33), 931 (42), 887 (40), 840 (28); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 6.36 (t, 1H, $J = 2.4$ Hz, 4′-ArH), 6.70 (d, 2H, $J = 2.4$ Hz, 2′,6′-ArH), 6.75 (d, 1H, $J = 2.0$ Hz, 8-H), 6.85 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 6-H), 7.55 (d, 1H, $J = 8.4$ Hz, 5-H), 7.93 (s, 1H, 4-H); ^{13}CNMR (400 MHz, CD_3COCD_3) δ: 102.7, 103.3, 107.9, 113.4, 114.0, 124.3, 130.6, 138.1, 1411.0, 156.1, 159.1, 160.7, 161.8; ESIMS m/z: 270.3 (M^+), 269.2 (M^+-H).

Compound 7h, 5,7-dihydroxy-3-(3′,5′-dihydroxyphenyl) coumarin. IR (KBr) (T%): 3259 (w, 26), 1691 (24), 1612 (20), 1519 (39), 1482 (35), 1413 (33), 1344 (29), 1294 (31), 1253 (37), 1209 (35), 1157 (23), 1083 (37), 1039 (46), 1004 (38), 943 (51), 892 (49); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 6.30(d, 1H, $J = 2.0$ Hz, 4′-ArH), 6.35(d, 1H, $J = 2.4$ Hz, 6-H), 6.37(d, 1H, $J = 2.4$ Hz, 8-H), 6.74 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 8.09 (s, 1H, 4-H), 8.30(s, 2H, 3′,5′-OH), 9.32 (s, 1H, 5-OH), 9.63 (s, 1H, 7-OH); ^{13}CNMR (400 MHz, CD_3COCD_3) δ: 95.0, 99.1, 99.2, 103.7, 107.8, 108.2, 113.7, 117.2, 120.4, 122.0, 135.3, 135.8, 138.5, 156.7, 157.1, 159.1, 160.8, 162.6; ESIMS m/z: 286.2 (M^+), 285.2 (M^+-H), 269.2.

Compound 7i, 7,8-dihydroxy-3-(3′,5′-dihydroxyphenyl) coumarin. IR (KBr) (T%): 3208 (W, 29), 1695 (26), 1612 (25), 1517 (48), 1467 (36), 1402 (49), 1351 (33), 1295 (41), 1263 (41), 1207 (42), 1157 (35), 1120 (43), 1083 (55), 1054 (49), 1004 (51), 943 (65), 836 (53); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 6.36 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 6.69 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 6.87 (d, 1H, $J = 8.4$ Hz, 5-H), 7.10 (d, 1H, $J = 8.4$ Hz, 6-H), 7.91 (s, 1H, 4-H); ^{13}C NMR (400 MHz, CD_3COCD_3) δ: 103.3, 107.9, 113.4, 114.1, 120.2, 124.2, 132.4, 138.2, 141.6, 143.9, 149.8, 159.1, 160.3; ESIMS m/z: 286.2 (M^+), 285.2 (M^+-H).

Compound 7j, 7-methoxy-8-hydroxy-3-(3′,5′-dihydroxyphenyl) coumarin. IR (KBr) (T%): 3558 (35), 3486 (33), 3261 (W, 24), 2842 (39), 1679 (22), 1604 (18), 1508 (33), 1446 (26), 1394 (40), 1342 (28), 1284 (24), 1203 (34), 1155 (28), 1126 (27), 1103 (36), 1074 (31), 1004 (37), 946 (50), 852 (41); ^{1}H NMR (400 MHz, CD_3COCD_3) δ: 3.95 (s, 3H, 7-OCH_3), 6.38 (t, 1H, $J = 2.0$ Hz, 4′-ArH), 6.73 (d, 2H, $J = 2.0$ Hz, 2′,6′-ArH), 7.03 (d, 1H, $J = 8.8$ Hz, 6-H), 7.20 (d, 1H, $J = 8.8$ Hz, 5-H), 7.94 (s, 1H, 4-H), 8.33 (s, 2H, 3′,5′-OH), 8.34 (s, 1H, 8-OH); ^{13}CNMR (400 MHz, CD_3COCD_3) δ: 55.8, 103.4, 108.0, 109.2, 115.2, 119.5, 125.2, 134.2, 138.1, 141.2, 142.9, 151.1, 159.1, 160.3; ESIMS m/z: 300.1 (M^+), 299.0 (M^+-H), 284.1 (M^+-H-CH_3).

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