A Novel Synthesis of 4-Hydroxy-3-phenylcoumarins by Titanium(III)-Mediated Reductive C–C Bond Formation

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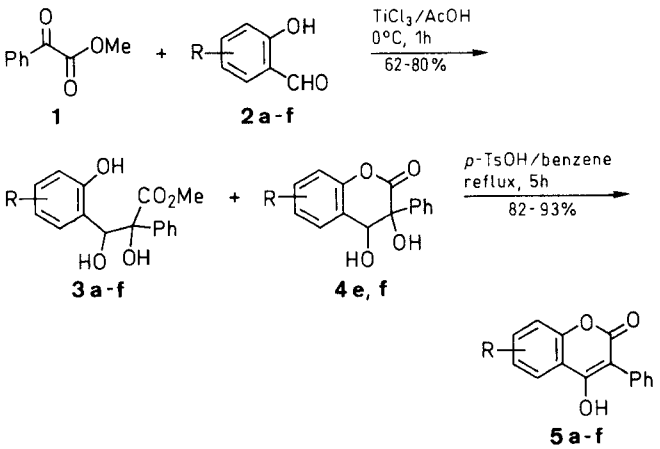
4-Hydroxy-3-phenylcoumarins (4-hydroxy-3-phenyl-2*H*-1-benzopyran-2-ones) were readily synthesized in two steps by the titanium(III)-mediated reaction of methyl benzoylformate and substituted salicylaldehydes followed by lactonization, under acidic conditions, of the resulting methyl 2,3-dihydroxy-3-(2-hydroxyaryl)-2-phenylpropanoates.

We have recently reported that the carbon centered radical hydroxy(methoxycarbonyl)phenylmethyl [Ph–Ċ(OH)–CO_2CH_3], generated by the titanium(III) reduction of methyl benzoylformate, adds to the carbonyl carbon of ketones to give 1,2-diols in moderate to excellent yields.[1] The reaction is sensitive to steric effects and hindered ketones (R^1COR^2; R^1 = Me; R^2 = Ar, *i*-Pr, *c*-C_6H_{11} and *t*-Bu), though in large excess, failed to react. The parent aldehydes (R_1 = H; R_2 = Ph, *c*-C_6H_{11} *and* *t*-Bu) proved to be more reactive and afforded the corresponding 1,2-diols in good yield (75, 52 and 65%, respectively) when an equimolar amount of the reagents was used.[2]

Taking advantage of the greater reactivity of the aldehydic function with respect to the keto function, we have now applied this reaction to the synthesis of 1,2-diols **3**, that could be used as key intermediates for the facile construction of 4-hydroxy-3-phenylcoumarins **5** (Scheme). The biological importance and the therapeutic potential of this class of compounds, and of their further elaborated derivatives,[3] have generated considerable interest in efficient methodologies for their synthesis. Among these, arylation α to the carbonyl group of the 4-hydroxycoumarin skeleton is an obvious synthetic route,[4] whereas an alternative is the formation of the coumarin ring at the final stage.[5]

The synthetic route here reported involves the preparation of fully functionalized 1,2-diols **3a–f** followed by lactonization to the desired 4-hydroxy-3-phenylcoumarins **5a–f** and offers the advantage of simple reaction conditions starting from commercially available reagents, such as **1**, **2a–f**, and titanium(III) chloride.

Allowing an equimolar amount of **1** and **2** to react in glacial acetic acid for 1 hour at 0 °C with a 15% aqueous acidic titanium(III) chloride solution, led to the formation of **3a–f** (*threo* and *erythro* mixture) and **4e,f** (one isomer) (Scheme). After workup, flash chromatography of the residue on a silica gel column afforded the products **3,4** in the yields shown in the Table. Partial lactonization of one isomer of **3e,f** to **4e,f** occurred, either in the reaction medium or during workup. When it was possible, the isomers of **3a–f** and **4e,f** have been carefully purified but, in practice, their mixture could be directly cyclized and dehydrated to 4-hydroxy-3-phenylcoumarins **5a–f** under acidic conditions[6] (reflux in benzene with *p*-toluenesulfonic acid for 5 hours. This last step occurred quite readily and the desired **5a–f** crystallized out directly from the benzene solution on cooling in the yields listed in the Table. It should be pointed out that, at 50–80 °C, salicylaldehydes are reduced by titanium(III) to the corresponding dimeric 2-(benzofuran-2-yl)phenols[7]. By performing the reaction at 0 °C, the selective reduction of **1** occurred and only traces (< 5%) of reduction products, derived from **2a–f**, were formed. The presence of an electron-withdrawing substituent in the salicylaldehyde (R = Cl, Br) increases the yield of **3**, whereas, among the three isomeric methoxysalicylaldehydes examined (R = 3-OMe, 4-OMe, 5-OMe), only the two bearing the methoxy group in a meta position to the aldehydic function (**2d** and **2e**) afforded **3**. Dihydroxybenzaldehydes behave similarly and of the two isomers investigated (i.e. 2,5- and 2,4-dihydroxy) the first gave solely **3**. This synthetic limitation has to be correlated with the decrease of electrophilicity at the aldehydic carbonyl C-atom when the conjugation with an electron-donating group occurs.



2,3	R	4,5	R
a	H	**a**	H
b	5-Cl	**b**	6-Cl
c	5-Br	**c**	6-Br
d	3-OMe	**d**	8-OMe
e	5-OMe	**e**	6-OMe
f	**5-OH**	**f**	6-OH

Scheme

Table. Synthesis of Coumarins **5** via the Intermediates **3** and **4**

Intermediates	Yield (%)[a]	Product	Yield (%)[b]
3a	70	**5a**	82
3b	75	**5b**	90
3c	80	**5c**	90
3d	69	**5d**	88
3e + **4e**	32 + 30	**5e**	93
3f + **4f**	35 + 33	**5f**	92

[a] Yields of products isolated are based on the starting **1**.
[b] Yields of products isolated are based on the intermediate **3**.

In conclusion, the use of appropriately substituted salicylaldehydes allowed the facile preparation of 1,2-diols **3**, which proved to be valuable intermediates for the synthesis of 4-hydroxy-3-phenylcoumarins **5**.

All starting reagents were commercially available research grade chemicals and were used as received. The solution of $TiCl_3$ (15% w/v, C. Erba) was standardized by titration against 0.1 N Ce(IV), prior to use. ^1H NMR spectra of $CDCl_3$ solutions (if not otherwise stated) were recorded with a 250 MHz Bruker Model AC-250 instrument. TMS served as an internal standard. IR spectra of mineral oil mulls (if not otherwise stated) were recorded with a Hitachi-Perkin-Elmer Model E-177 instrument. Mass spectra were recorded with a Hitachi-Perkin-Elmer Model RMU-6D spectrometer operated at 70 eV.[8] The solvents used were distilled prior to use. Melting points (uncorrected) were measured with a Kofler apparatus. All reactions were monitored by thin layer and column chromatography by using silica gel precoated plates 60 F_{254} and silica gel (0.04–0.063 mm), respectively, purchased from Merck. Microanalyses were performed by the Analytical Section of REDOX Laboratories, Cologno Monzese (Milano).

Methyl 2,3-Dihydroxy-3-(2-hydroxyaryl)-2-phenylpropanoates 3a–f; General Procedure:

To a well stirred solution of **1** (2.46 g, 15 mmol) in glacial AcOH (40 mL) at 0 °C was added 15% aq $TiCl_3$ (40 mL, 35 mmol) in one portion. The mixture was stirred for 1 h, kept at 0 °C, and then it was extracted with EtOAc (3 × 150 mL). The combined extracts were washed with distilled H_2O (2 × 50 mL), dried (Na_2SO_4) and concentrated in vacuo. A thick reddish-brown residue was obtained. Flash chromatography of the residue, on a silica gel column with the appropriate eluant, gave, as a rule, unreacted **1** and **2**, reduction products of **2** (< 5%), methyl mandelate and traces of dimers, **3** and **4**, in that order. Both **3** and **4** were colorless crystalline solids.

Methyl 2,3-Dihydroxy-3-(2-hydroxyphenyl)-2-phenylpropanoate (**3a**):

The residue was purified on a silica gel column with hexane/$CHCl_3$/Et_2O (5:4:1).

First eluted isomer **3a**; yield: 1.5 g (35%), mp 130–131 °C (hexane/Et_2O, 1:1).

$C_{16}H_{16}O_5$ (288.3) calc. C 66.66 H 5.59 found 66.61 5.55

IR (Nujol): ν = 3600–3300, 1720, 1230, 1120 cm^{-1}.

MS: m/z = 288 (M^+), 270, 253, 228, 211, 183, 166 (100), 123, 107, 105, 77, 65, 51.

^1H NMR ($CDCl_3$): δ = 2.90 (s, 1 H, OH, D_2O-exch), 3.73 (s, 3 H, CH_3), 4.22 (s, 1 H, OH, D_2O exch), 5.48 (s, 1 H, CH), 6.75–7.00 (m, 3 H, Ar H), 7.2 (m, 1 H, Ar H), 7.40 (m, 3 H, Ph H), 7.75 (m, 2 H, Ph H), 8.05 (s, 1 H, OH, D_2O exch).

Second eluted isomer **3a**; yield: 1.5 g (35%), 127–128 °C (hexane/Et_2O, 1:1).

$C_{16}H_{16}O_5$ (288.3) calc. C 66.66 H 5.59 found 66.62 5.53

IR (Nujol): ν = 3500–3100, 1720, 1250 cm^{-1}.

^1H NMR ($CDCl_3$) δ = 3.50 (d, J = 5 Hz, 1 H, OH, D_2O exch), 3.90 (s, 3 H, CH_3), 4.80 (s, 1 H, OH, D_2O exch), 5.45 (d, J = 5 Hz, 1 H, CH, s after D_2O exch), 6.50 (m, 2 H, Ph H), 6.8 (m, 1 H, Ar H), 7.05 (m, 1 H, Ar H), 7.24 (m, 3 H, Ph H), 7.52 (m, 2 H, Ph H), 8.35 (s, 1 H, OH, D_2O exch).

Methyl 3-(5-Chloro-2-hydroxyphenyl)-2,3-dihydroxy-2-phenylpropanoate (**3b**):

The residue was chromatographed on a silica gel column with hexane/$CHCl_3$/Et_2O (5:4:1).The first isomer **3b** was eluted together with methyl mandelate. By dissolving this fraction in hexane/Et_2O (1:1), **3b** crystallized.

First eluted isomer **3b**; yield: 1.7 g (35%), mp 98–100 °C (aq MeOH).

$C_{16}H_{15}ClO_5$ (322.7) calc. C 59.54 H 4.68 found 59.49 4.59

IR (Nujol): ν = 3500–3350, 1700, 1275, 1170, 1130, 745 cm^{-1}.

MS: m/z = 324–322 (M^+), 292–290 (M–MeOH), 264–262, 247–245, 219–217, 182, 166 (100), 159–157, 107, 105, 79, 77.

^1H NMR ($CDCl_3$): δ = 2.85 (s, 1 H, OH, D_2O exch), 3.80 (s, 3 H, CH_3), 4.15 (s, 1 H, OH, D_2O exch), 5.40 (s, 1 H, CH), 6.82 (d, J = 8.5 Hz, 1 H, Ar H), 6.95 (d, J = 3 Hz, 1 H, Ar H), 7.15 (dd, J = 3, 8.5 Hz, 1 H, Ar H), 7.42 (m, 3 H, Ph H), 7.72 (m, 2 H, Ph H), 8.00 (s, 1 H, OH, D_2O exch).

Second eluted isomer **3b**; yield: 1.95 g (40%), mp 134–136 °C (aq MeOH).

$C_{16}H_{15}ClO_5$ (322.7) calc. C 59.54 H 4.68 found 59.49 4.61

IR (Nujol): ν = 3580, 3420, 1725, 1220, 825 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.80 (br s, 1 H, OH, D_2O exch), 3.88 (s, 3 H, CH_3), 4.90 (s, 1 H, OH, D_2O exch), 5.42 (s, 1 H, CH), 6.47 (d, J = 2.5 Hz, 1 H, Ar H), 6.68 (d, J = 8.5 Hz, 1 H, Ar H), 6.95 (dd, J = 2.5, 8.5 Hz, 1 H, Ar H), 7.25 (m, 3 H, Ph H), 7.50 (m, 2 H, Ph H), 8.50 (s, 1 H, OH, D_2O exch).

Methyl 3-(5-Bromo-2-hydroxyphenyl)-2,3-dihydroxy-2-phenylpropanoate (**3c**):

The residue was chromatographed on a silica gel column with hexane/EtOAc (7:3).

First eluted isomer **3c**; yield: 2.4 g (43%), mp 108–110 °C (aq MeOH).

$C_{16}H_{15}BrO_5$ (367.2) calc. C 52.34 H 4.12 found 52.23 4.06

IR (Nujol): ν = 3510, 3480, 3290, 1715, 1250, 1170, 1120 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.25 (s, 1 H, OH, D_2O exch), 3.72 (s, 3 H, CH_3), 4.22 (s, 1 H, OH, D_2O exch), 5.40 (s, 1 H, CH), 6.72 (d, J = 8.5 Hz, 1 H, Ar H), 7.05 (d, J = 2 Hz, 1 H, Ar H), 7.27 (dd, J = 2, 8.5 Hz, 1 H, Ar H), 7.35 (m, 3 H, Ph H), 7.65 (m, 2 H, Ph H), 8.1 (s, 1 H, OH, D_2O exch).

Second eluted isomer **3c**; yield: 2.1 g (37%), mp 138 °C (hexane/Et_2O).

$C_{16}H_{15}BrO_5$ (367.2) calc. C 52.34 H 4.12 found 52.19 4.05

IR (Nujol): ν = 3580, 3480, 3430, 1725, 1220, 1110 cm^{-1}.

MS: m/z = 368–366 (M^+), 333–331, 291–289, 263–261, 203, 202, 201, 200, 166 (100), 107, 105, 94, 79, 77.

^1H NMR ($CDCl_3$): δ = 3.50 (s, 1 H, OH, D_2O exch), 3.92 (s, 3 H, CH_3), 4.78 (s, 1 H, OH, D_2O exch), 5.38 (s, 1 H, CH), 6.62 (d, J = 2.5 Hz, 1 H, Ar H), 6.67 (d, 8.5 Hz, 1 H, Ar H), 7.12 (dd, J = 2.5, 8.5 Hz, 1 H, Ar H), 7.28 (m, 3 H, Ph H), 7.51 (m, 2 H, Ph H), 8.4 (s, 1 H, OH, D_2O exch).

Methyl 2,3-Dihydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-phenylpropanoate (**3d**):

The crude residue was dissolved in $CHCl_3$/Et_2O (8:2). From the solution, on standing at r. t. for 24 h, the higher melting point isomer **3d** crystallized.

Higher melting isomer **3d**; yield: 1.9 g (40%), mp 155–156 °C.

$C_{17}H_{18}O_6$ (318.3) calc. C 64.14 H 5.70 found 64.10 5.60

IR (Nujol): ν = 3550, 3450, 1725, 1275, 1250 cm^{-1}.

MS: m/z = 318 (M^+), 283, 241, 213, 166, 153 (100), 107, 105, 93, 77, 65, 51.

^1H NMR ($CDCl_3$): δ = 3.14 (d, J = 4.5 Hz, 1 H, OH, D_2O exch), 3.65 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 4.06 (s, 1 H, OH, D_2O exch), 5.68 (d, J = 4.5 Hz, 1 H, CH, s after D_2O exch), 6.70 (s, 1 H, OH, D_2O exch), 6.82 (s, 3 H, Ar H), 7.40 (m, 3 H, Ph H), 7.78 (m, 2 H, Ph H).

The mother liquor of the above crystallization, stripped of solvents in vacuo, was chromatographed on a silica gel column with $CHCl_3$/Et_2O/hexane (4:4:2). The last eluted fraction corresponded to the lower melting isomer **3d**.

Lower melting isomer **3d**; yield: 1.4 g (29%), mp 136°C ($CHCl_3$).

$C_{17}H_{18}O_6$ (318.3) calc. C 64.14 H 5.70 found 64.20 5.59

IR (Nujol): ν = 3480, 3450, 3310, 2560 (OH intramolecular H-bonded), 1730, 1250 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.6 (d, J = 8.5 Hz, 1 H, OH, D_2O exch), 3.78 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 4.43 (s, 1 H, OH, D_2O exch), 5.72 (d, J = 8.5 Hz, 1 H, CH, s after D_2O exch), 6.54 (m, 2 H, Ar H), 6.60 (s, 1 H, OH, D_2O exch), 6.65 (m, 1 H, Ar H), 7.22 (m, 3 H, Ph H), 7.55 (m, 2 H, Ph H).

Methyl 2,3-Dihydroxy-3-(2-hydroxy-5-methoxyphenyl)-2-phenylpropanoate (**3e**) *and 3,4-Dihydroxy-6-methoxy-2-phenylchroman-2-one* (**4e**):

The crude residue was chromatographed on a silica gel column with hexane/EtOAc (7:3). The last eluted fraction (2.8 g) was a mixture of **3e** (both isomers in a 1:2 ratio by ^1H NMR analysis) and **4e** (one isomer). By dissolving this fraction in hexane/Et_2O (1:1), **4e** crystallized.

4e; yield: 1.26 g (30%), mp 147–149°C (EtOAc/hexane).

$C_{16}H_{14}O_5$ (286.3) calc. C 67.13 H 4.93 found 66.98 4.80

IR (Nujol): ν = 3400–3200, 1780, 1740 (C=O intermolecular H-bonded), 1200, 1090, 1030 cm^{-1}; ($CHCl_3$): ν = 3530, 1765, 1200, 1090, 1030 cm^{-1}.

MS: m/z = 286 (M^+), 268 ($M-H_2O$), 258 (M–CO, m* = 232.7), 242 ($M-CO_2$), 153 (100), 152, 137, 125, 105, 77.

^1H NMR ($CDCl_3$): δ = 3.60 (s, 1 H, OH, D_2O exch), 3.72 (s, 3 H, CH_3), 4.34 (s, 1 H, OH, D_2O exch), 4.86 (s, 1 H, CH), 6.74 (d, J = 3 Hz, 1 H, Ar H), 6.82 (dd, J = 3, 8.5 Hz, 1 H, Ar H), 7.03 (d, J = 8.5 Hz, 1 H, Ar H), 7.25 (m, 5 H, Ph H).

The mother liquor of the above crystallization, stripped of solvents in vacuo, gave **3e**; yield: 1.5 g (32%). Separation of the two isomers **3e** was not achieved: the less abundant one (higher R_f value) partially lactonized to **4e** during purification or simply on standing; the more abundant one was slightly contaminated with both the other isomer and **4e**.

Less abundant isomer **3e**; thick liquid.

^1H NMR ($CDCl_3$): δ = 3.20 (s, 1 H, OH, D_2O exch), 3.66 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 4.30 (s, 1 H, OH, D_2O exch), 5.44 (s, 1 H, CH), 6.53 (d, J = 3 Hz, 1 H, Ar H), 6.73 (dd, J = 3, 9 Hz, 1 H, Ar H), 6.78 (d, J = 9 Hz, 1 H, Ar H), 7.40 (m, 3 H, CH_3), 7.70 (m, 2 H, Ph H), 7.80 (br s, 1 H, OH, D_2O exch).

More abundant isomer **3e**; thick liquid.

IR (film): ν = 3420, 1730, 1500, 1250, 1040 cm^{-1}.

MS: m/z = 318 (M^+), 286, 258, 166, 153, 152, 137, 105 (100), 77.

^1H NMR ($CDCl_3$): δ = 3.40 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 4.30 (s, 1 H, OH, D_2O exch), 4.80 (s, 1 H, OH, D_2O exch), 5.38 (s, 1 H, CH), 6.01 (d, J = 3 Hz, 1 H, Ar H), 6.56 (dd, J = 3, 9 Hz, 1 H, Ar H), 6.72 (d, J = 9 Hz, 1 H, Ar H), 7.25 (m, 3 H, Ph H), 7.52 (m, 2 H, Ph H), 8.00 (s, 1 H, OH, D_2O exch).

Methyl 2,3-Dihydroxy-3-(2,5-dihydroxyphenyl)-2-phenylpropanoate (**3f**) *and 3,4,6-Trihydroxy-3-phenylchroman-2-one* (**4f**):

The crude residue was chromatographed on a silica gel column with hexane/EtOAc (1:1). The last eluted fraction (3 g) was a mixture of **3f** (both isomers in a 1:2 ratio by ^1H NMR analysis) and **4f** (one isomer). By dissolving this fraction in hexane/EtOAc (1:1), **4f** crystallized.

4f; yield: 1.35 g (33%), mp 213–214°C (hexane/EtOAc).

$C_{15}H_{12}O_5$ (272.3) calc. C 66.17 H 4.44 found 65.97 4.32

IR (Nujol): ν = 3440, 3350, 3180, 1775, 1205, 1170 cm^{-1}.

MS: m/z = 272 (M^+), 244 (M–CO, m* = 218.9), 139 (100), 111, 105, 77.

^1H NMR (DMSO-d_6): δ = 4.78 (d, J = 2.5 Hz, 1 H, CH, s after D_2O exch), 5.30 (d, J = 2.5 Hz, 1 H, OH, D_2 exch), 5.78 (s, 1 H, OH, D_2O exch), 6.66 (d, J = 2.7 Hz, 1 H, Ar H), 6.71 (dd, J = 2.7, 8.5 Hz, 1 H, Ar H), 6.86 (d, J = 8.5 Hz, 1 H, Ar H), 7.22 (m, 3 H, Ph H), 7.32 (m, 2 H, Ph H), 8.95 (s, 1 H, OH, D_2O exch).

The mother liquor of the above crystallization, stripped of solvents in vacuo, gave **3f**; yield: 1.6 g (35%). Separation of the two isomers **3f** was not achieved: the less abundant one (higher R_f value) partially lactonized to **4f**, the more abundant one was slightly contaminated with both the other isomer and **4f**.

Less abundant isomer **3f**; thick liquid.

^1H NMR (DMSO-d_6): δ = 3.50 (s, 3 H, CH_3), 4.90 (d, J = 6 Hz, 1 H, OH, D_2O exch), 5.48 (d, J = 6 Hz, 1 H, CH, s after D_2O exch), 5.98 (s, 1 H, OH, D_2O exch), 6.70 (m, 3 H, Ar H), 7.35 (m, 3 H, Ph H), 7.62 (m, 2 H, Ph H), 8.55 (s, 1 H, OH, D_2O exch), 8.70 (s, 1 H, OH, D_2O exch).

More abundant isomer **3f**; thick liquid.

^1H NMr (DMSO-d_6): δ = 3.70 (s, 3 H, CH_3), 5.55 (d, J = 6 Hz, 1 H, OH, D_2O exch), 5.75 (d, J = 6 Hz, 1 H, CH, s after D_2O exch), 5.94 (s, 1 H, OH, D_2O exch), 6.36 (m, 2 H, Ar H), 6.83 (m, 1 H, Ar H), 7.15 (m, 3 H, Ph H), 7.52 (m, 2 H, Ph H), 8.4 (s, 1 H, OH, D_2O exch), 8.50 (s, 1 H, OH, D_2O exch).

4-Hydroxy-3-phenylcoumarins 5; General Procedure:

A solution of **3** (5 mmol) and *p*-TsOH · H_2O (0.15 g, 0.79 mmol) in anhydr. benzene (30–40 mL) was stirred for 5 h under reflux. Coumarins **5b–f** crystallized directly as white needles from the benzene solution, cooled overnight at 0°C. As for **5a**, the following procedure was used: the benzene solution was washed with distilled H_2O (2 × 5 mL), dried (Na_2SO_4) and concentrated in vacuo. A white residue was left. Purification of the residue on a silica gel column with Et_2O/hexane (3:1) afforded **5a** as white needles.

4-Hydroxy-3-phenylcoumarin (**5a**); yield: 0.98 g (82%), mp 235–237°C (MeOH/benzene) (Lit.[9] 236–237°C).

IR ($CHCl_3$): ν = 3460, 1700, 1310, 1185 cm^{-1}.

MS: m/z = 238 (M^+, 100), 237 (50), 181, 152, 123, 77, 65, 51.

6-Chloro-4-hydroxy-3-phenylcoumarin (**5b**); yield: 1.23 g (90%), mp 232°C (benzene), 240°C ($CHCl_3$) (Lit.[10] 250°C).

IR (Nujol): ν = 3340, 1695, 1180 cm^{-1}.

MS: m/z = 274–272 (M^+, 100), 273–271 (50), 237 (M–Cl, (20), m* = 206), 216–214 (50), 152, 76, 63.

^1H NMR ($CDCl_3$/DMSO-d_6): δ = 7.16 (dd, J = 1.2, 1.5 Hz, 1 H, Ar H), 7.30 (2 d, J = 1.2, 1.5 Hz, 2 H, Ar H), 7.40 (m, 2 H, Ph H), 7.50 (m, 3 H, Ph H), 9.50 (br s, 1 H, OH, D_2O exch).

6-Bromo-4-hydroxy-3-phenylcoumarin (**5c**); yield: 1.43 g (90%), mp 242°C (benzene/MeOH).

$C_{15}H_9BrO_3$ (317.1) calc. C 56.81 H 2.86 found 56.67 2.75

IR (Nujol): ν = 3350, 1700, 1250, 1185 cm^{-1}.

MS: m/z = 318–316 (M^+, 100), 317–315 (50), 260–258 (50), 237 (M–Br, (25), m* = 176.6), 152, 76, 63, 51.

^1H NMR ($CDCl_3$/DMSO-d_6): δ = 7.24 (d, J = 9 Hz, 1 H, Ar H), 7.29 (d, J = 2 Hz, 1 H, Ar H), 7.40 (dd, J = 2, 9 Hz, 1 H, Ar H), 7.42–7.55 (m, 5 H, Ph H), 9.75 (s, 1 H, OH, D_2O exch).

4-Hydroxy-8-methoxy-3-phenylcoumarin (**5d**); yield: 1.18 g (88%), mp 224°C (benzene/MeOH) (Lit.[11] 192°C).

$C_{16}H_{12}O_4$ (268.3) calc. C 71.64 H 4.51 found 71.50 4.48

IR (Nujol): ν = 3340, 1695, 1210 cm^{-1}.

MS: m/z = 268 (M^+, 100), 267 (20), 253 (10), 211 (32), 78 (30).

^{1}H NMR ($CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 6.36 (s, 1 H, OH, D_2O exch), 6.85 (dd, J = 1.5, 8 Hz, 1 H, Ar H), 6.99 (dd, J = 1.5, 8.3 Hz, 1 H, Ar H), 7.15 (dd, J = 8, 8.3 Hz, 1 H, Ar H), 7.50 (m, 5 H, Ph H).

4-Hydroxy-6-methoxy-3-phenylcoumarin (**5e**); yield: 1.25 g (93%), mp 220–221 °C (either benzene or MeOH) (Lit.[12] 205, 215, 223 °C).

MS: m/z = 268 (M^+, 100), 267 (10), 211 (50).

^{1}H NMR ($CDCl_3$): δ = 3.70 (s, 3 H, CH_3), 6.40 (s, 1 H, OH, D_2O exch), 6.73 (d, J = 3 Hz, 1 H, Ar H), 6.98 (dd, J = 3, 9.5 Hz, 1 H, Ar H), 7.33 (d, J = 9.5 Hz, 1 H, Ar H), 7.5 (m, 5 H, Ph H).

4,6-Dihydroxy-3-phenylcoumarin (**5f**); yield: 1.17 g (92%), mp 269–270 °C (aq MeOH, darkening at 220 °C).

$C_{15}H_{10}O_4$	calc.	C 70.86	H 3.96
(254.2)	found	70.72	3.85

IR (KBr): ν = 3460, 3250, 1660, 1450, 1240, 1200 cm^{-1}.

MS: m/z = 254 (M^+, 100), 253 (22), 197 (100).

^{1}H NMR (DMSO-d_6): δ = 6.50 (d, J = 2.8 Hz, 1 H, Ar H), 6.93 (dd, J = 2.8, 8.8 Hz, 1 H, Ar H), 7.33 (d, J = 8.8 Hz, 1 H, Ar H), 7.40 (m, 2 H, Ph H), 7.55 (m, 3 H, Ph H), 9.50 (s, 1 H, OH, D_2O exch), 9.85 (s, 1 H, OH, D_2O exch).

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