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# 3-Aryl-8-hydroxy-3,4-dihydroisocoumarins: Synthesis of aglycones of macrophyllosides A, B and C†

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**Abstract**

A facile, aluminium chloride mediated, one-step conversion of 7-methoxy-3-benzylphthalides (**6a–d**) into 3-aryl-8-hydroxy-3,4-dihydroisocoumarins (**7a–d**) is described. The 7-methoxy-3-benzylphthalides (**6a–d**) are prepared from phthalides (**2a** and **b**) via the intermediacy of hydroxyphthalides (**4a–d**) and 3-benzylidenephthalides (**5a–c**).

**Keywords**: Benzylphthalides, 3-arylisocoumarins, macrophyllosides, LDA, $AlCl_3$ catalyst.

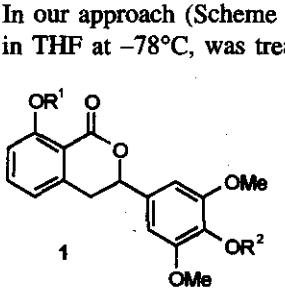
## 1. Introduction

3-Aryl-8-hydroxy-3,4-dihydroisocoumarins constitute an important class of naturally occurring[1] oxygen ring compounds, because of their antimicrobial, antifungal and antiallergic activities[2–7] and their application as sweetening agents[8] and as refrigerants.[9] Hence, a number of methods are reported for their synthesis.[10–22] It is interesting to note that most of these methods involve cyclisation of the stilbene carboxylic acids.

In this paper, we report a new general method (Scheme 1) for the synthesis of the 3-aryl-8-hydroxy-3,4-dihydroisocoumarins via $AlCl_3$-mediated conversion of 7-methoxy-3-benzylphthalides. The paper also describes the first synthesis of macrophyllols **7a, b**, the aglycones of macrophyllosides A, B and C (**1a–c**), isolated[9] from *Hydrangea macrophylla*.

## 2. Results and discussion

In our approach (Scheme 1), the anion generated from 7-methoxyphthalide (**2a**), using LDA in THF at –78°C, was treated with 3,4,5-trimethoxybenzaldehyde (**3a**) and 4-benzyloxy-3,5-

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| 1 | $R^1$ | $R^2$ |
|---|---|---|
| a | glc | Me |
| b | glc | H |
| c | H | glc |

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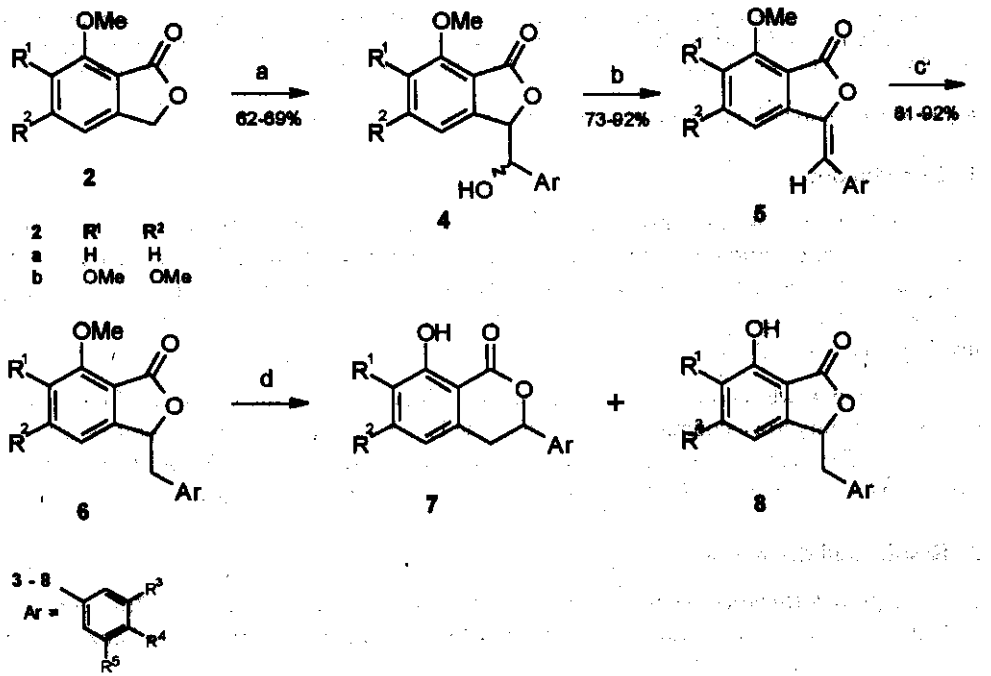
dimethoxybenzaldehyde (**3b**) to obtain the hydroxyphthalides (**4a, b**) in 65% and 67% yields, respectively. The phthalide **2b** on similar reaction with anisaldehyde (**3c**) and veratraldehyde (**3d**) provided the hydroxyphthalides (**4c, d**) in 69% and 62% yields. The hydroxyphthalides (**4a, c** and **d**) on treatment with a mixture of orthophosphoric acid–formic acid afforded the 3-benzylidenephthalides (**5a, c** and **d**) in 73–92% yields. The hydroxyphthalide (**4b**), on similar reaction, provided 3-benzylidenephthalide (**5b** and **e**) in 44% and 46% yields, respectively. Debenzylation of phenolic ethers under this condition is unprecedented.

The benzylidenephthalides (**5a–e**) on catalytic hydrogenation using $H_2$, Pd/C in ethyl acetate solution provided the 3-benzylphthalides (**6a–d**) in 81–92% yields. Subsequent treatment of 3-benzylphthalides (**6a, b, d**) with aluminium chloride in methylene chloride at room temperature, provided 3-aryl-8-hydroxy-3, 4-dihydroisocoumarins (**7a, b** and **d**) in 60–63% yield along with 7-hydroxy-3-benzylphthalides (**8a, b** and **d**) in 19–31% yield. However, under similar condition, the phthalide (**6c**) provided exclusively the 8-hydroxyisocoumarin (**7c**) in 73% yield.




| 4-5 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | 6-8 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a | H | H | OMe | OMe | OMe | a | H | H | OMe | OMe | OMe |
| b | H | H | OMe | OBn | OMe | b | H | H | OMe | OH | OMe |
| c | OMe | OMe | H | OMe | H | c | OMe | OMe | H | OMe | H |
| d | OMe | OMe | OMe | OMe | H | d | OMe | OMe | OMe | OMe | H |
| e | H | H | OMe | OH | OMe | | | | | | |

Scheme 1. Reagents and conditions: a) i) LDA, THF, – 78°C; ii) ArCHO (3); iii) $H^+$; b) $H_3PO_4$, HCOOH, heat; c) $H_2$, Pd-C; d) $AlCl_3$, $CH_2Cl_2$, r.t.

In conclusion, we have developed a simple aluminium chloride-catalyzed one-pot conversion of 3-benzyl-7-methoxyphthalides (**6**) into 3-aryl-8-hydroxy-3,4-dihydroisocoumarins (**7**). The synthesis of the aglycone (**7a**) of macrophylloside A (**1a**) and the aglycone (**7b**) of macrophyllosides B and C (**1b, c**) is reported here for the first time.

## 3. Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer FTIR-1615 spectrophotometer and $^1$H NMR spectra in $CDCl_3$ solutions on a Jeol FX 90Q (90 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from TMS. *n*-Butyllithium (prepared) was used as 1.25 M solution in *n*-hexane.[23] THF was distilled over $LiAlH_4$ before use. Phthalides (**2a, b**) were prepared according to the literature procedure.[24, 25]

### 3.1. *4-Benzyloxy-3,5-dimethoxybenzaldehyde (3b)*

To a stirred solution of syringaldehyde[26] (0.91 g, 0.5 mmole) in dry DMF (10 ml), anhydrous potassium carbonate (0.82 g, 0.6 mmole) and benzyl bromide (0.71 ml, 0.6 mmole) were added and the reaction mixture was stirred at room temperature for 6 h. Ice-cold water (10 ml) was added to it and extracted with methylene chloride (3 × 20 ml). The combined organic layer was washed with water, dried ($Na_2SO_4$) and evaporated to give a thick liquid product which was chromatographed over silica gel using hexane as an eluant to give a solid which on recrystallization from hexane afforded **3b** (1.28 g, 94%), m. p. 60°C. (Found: C, 70.46; H, 6.19, $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%); IR (Nujol): 1682 cm$^{-1}$ (–CHO);$^1$H NMR ($CDCl_3$) : $\delta$ 3.85 (6H, s, 2 × $OCH_3$), 5.10 (2H, s, –$OCH_2$), 7.08 (2H, s, Ar-H), 7.22–7.53 (5H, brs, Ar-H), 10.06 (1H, s, –CHO).

### 3.2. *Preparation of 3-(1-hydroxybenzyl)phthalides (4a–d): General procedure*

A solution of the appropriate phthalide (**2**) (1.2 mmole) in THF (10 ml) was added to a stirred solution of LDA (1.3 mmole) in THF (5 ml) at –78°C under nitrogen atmosphere. After 20 min, a solution of the corresponding arylaldehyde (**3**) (1.3 mmole) in THF (5 ml) was added and the stirring continued at –78°C for 30 min. Then the reaction was quenched by the addition of ice-cold water (10 ml). THF was removed under reduced pressure, the aqueous solution acidified and extracted (3 × 20 ml) with chloroform. The combined organic layer was washed with water and dried over anhydrous $Na_2SO_4$. The gummy mass, obtained after the evaporation of the solvent, was chromatographed over silica gel using ethyl acetate : hexane (3:7) as an eluant to give a solid which on recrystallization from methylene chloride–hexane provided the hydroxyphthalides (**4a–d**).

### 3.3. *3-(α-Hydroxy-3,4,5-trimethoxybenzyl)-7-methoxyphthalide (4a)*

Anion of phthalide (**2a**) on reaction with 3,4,5-trimethoxybenzaldehyde (**3a**) gave hydroxyphthalide (**4a**) in 62% yield, m. p. 50°C (Found, C, 63.48; H, 5.75; $C_{19}H_{20}O_7$ requires C, 63.33; H, 5.59%). IR (Nujol): 3470, 1759 cm$^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ 2.64 (1H, s, -OH, exchangeable with $D_2O$), 3.82 (9H, s, 3 × $OCH_3$), 3.92 (3H, s, –$OCH_3$), 4.28 and 4.71 (1H, 2 × d,

$J$ = 6.0 Hz, CH-OH), 5.12 and 5.53 (1H, 2 × d, $J$ = 6 Hz, Ar-CH-O-), 6.45–6.64 (3H, m, Ar-H), 6.88–7.46 (2H, m, Ar-H).

3.4. *3-(α-Hydroxy-4-benzyloxy-3,5-dimethoxybenzyl)-7-methoxyphthalide (4b)*

Anion of phthalide (**2a**) on reaction with 4-benzyloxy-3,5-dimethoxybenzaldehyde (**3b**) gave hydroxyphthalide (**4b**) in 67% yield. m.p. 45°C; (Found, C, 68.68; H, 5.36; $C_{25}H_{24}O_7$ requires C, 68.80; H, 5.54%). IR (Nujol): 3410, 1747 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.63 (1H, s, –OH, exchangeable with $D_2O$), 3.74 (6H, s, 2 × $OCH_3$), 3.92 (3H, s, –$OCH_3$), 4.09–4.67 (1H, m, CH-OH), 5.04 (2H, s, –$OCH_2$–), 5.14–5.50 (1H, m, Ar-CH-O), 6.35–6.61 (3H, m, Ar-H), 6.84 (1H, d, $J$ = 8.8 Hz, Ar-H), 7.15–7.57 (6H, m, Ar-H).

3.5. *3-(α-Hydroxy-4-methoxybenzyl)-5,6,7-trimethoxyphthalide (4c)*

Anion of phthalide (**2b**) on reaction with 4-methoxybenzaldehyde (**3c**) gave hydroxyphthalide (**4c**) in 69% yield. m. p. 122°C; (Found, C, 63.27; H, 5.35; $C_{19}H_{20}O_7$ requires C, 63.33; H, 5.59%). IR (Nujol): 3370, 1751 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.67 (1H, s, –OH, exchangeable with $D_2O$), 3.71 (3H, s, $OCH_3$), 3.78 (3H, s, –$OCH_3$), 3.81 (3H, s, –$OCH_3$), 4.05 (3H, s, –$OCH_3$), 5.09 (1H, d, $J$ = 5.0 Hz, CH-OH), 5.39 (1H, d, $J$ = 5.0 Hz, Ar-CH-O-), 6.32 (1H, s, Ar-H), 6.88 (2H, d, $J$ = 9.0 Hz, Ar-H), 7.30 (2H, d, $J$ = 9.0 Hz, Ar-H).

3.6. *3-(α-Hydroxy-3,4-dimethoxybenzyl)-5,6,7-trimethoxyphthalide (4d)*

Anion of phthalide **2b** on reaction with 3,4-dimethoxybenzaldehyde (**3d**) gave hydroxyphthalide (**4d**) in 62% yield. m. p. 129–30°C; (Found, C, 61.41; H, 5.77; $C_{20}H_{22}O_8$ requires C, 61.53; H, 5.68%). IR (Nujol): 3475, 1748 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.61 (1H, s, –OH, exchangeable with $D_2O$), 3.73 (3H, s, $OCH_3$), 3.83 (3H, s, –$OCH_3$), 3.85 (6H, s, 2 × –$OCH_3$), 4.07 (3H, s, –$OCH_3$), 5.11 (1H, brs, CH-OH), 5.42 (1H, brs, Ar-CH-O-), 6.35 (1H, s, Ar-H), 6.91 (3H, m, Ar-H).

3.7. *Preparation of (Z)-3-benzylidenephthalides (5a–e): General procedure*

Orthophosphoric acid (2 ml) was added to the mixture of appropriate hydroxyphthalide (**4a–d**) (0.55 mmol) in formic acid (2 ml), and heated for 4 h (2 h in the case of **4c**) at 80°C. The reaction mixture was cooled to room temperature, poured into ice-cold water (15 ml) and extracted with chloroform (3 × 10 ml). The combined chloroform extract was washed with water, dried ($Na_2SO_4$) and evaporated to give a solid, which on chromatography over silica gel using ethyl acetate : hexane (1 : 9) as an eluant gave a solid. On recrystallization from methylene chloride–hexane it provided benzylidenephthalides (**5a–e**).

3.8. *(Z)-3-(3,4,5-Trimethoxybenzylidene)-7-methoxyphthalide (5a)*

Hydroxyphthalide (**4a**) on reaction with formic acid and orthophosphoric acid provided the phthalide (**5a**) in 76% yield. m. p. 193°C; (Found, C, 66.50; H, 5.49; $C_{19}H_{18}O_6$ requires C, 66.66; H, 5.30%). IR (Nujol): 1766 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.87 (3H, s, $OCH_3$), 3.91 (6H, s, 2 × $OCH_3$), 4.0 (3H, s, $OCH_3$), 6.28 (1H, s, Ar-CH=), 6.90 (1H, d, $J$ = 8.8 Hz, Ar-H), 7.07 (2H, s, Ar-H), 7.26 (1H, d, $J$ = 8.8 Hz, Ar-H), 7.57 (1H, t, $J$ = 8.8 Hz, Ar-H).

3.9. *(Z)-3-(4-Benzyloxy-3,5-dimethoxybenzylidene)-7-methoxyphthalide (**5b**) and (Z)-3-(4-hydroxy-3,5-dimethoxybenzylidene)-7-methoxyphthalide (**5e**)*

Hydroxyphthalide (**4b**) on reaction with formic acid and orthophosphoric acid provided the mixture of phthalides (**5b, e**) in 44% and 46% yields, respectively. **5b**: m. p. 155°C; (Found, C, 71.87; H, 5.18; $C_{25}H_{22}O_6$ requires C, 71.76; H, 5.30%). IR (Nujol): 1762 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.73 (3H, s, $OCH_3$), 3.85 (3H, s, $-OCH_3$), 3.95 (3H, s, $OCH_3$), 5.02 (2H, s, $OCH_2$), 6.25 (1H, s, Ar-CH=), 6.74–7.68 (10H, m, Ar-H); **5e**: m. p. 185°C; (Found, C, 65.70; H, 4.94; $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.91%). IR (Nujol): 3430, 1765 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.97 (6H, s, $2 \times OCH_3$), 3.99 (3H, s, $-OCH_3$), 5.70 (1H, s, exchangeable with $D_2O$, –OH), 6.27 (1H, s, Ar-CH=), 6.89 (1H, d, $J = 7.6$ Hz, Ar-H), 7.08 (2H, s, Ar-H), 7.26 (1H, d, $J = 7.6$ Hz, Ar-H), 7.57 (1H, t, $J = 8.0$ Hz, Ar-H).

3.10. *(Z)-3-(4-Methoxybenzylidene)-5,6,7-trimethoxyphthalide (**5c**)*

Hydroxyphthalide (**4c**) on reaction with formic acid and orthophosphoric acid provided the phthalide (**5c**) in 88% yield. m. p. 144°C; (Found, C, 66.86; H, 5.47; $C_{19}H_{18}O_6$ requires C, 66.66; H, 5.30%). IR (Nujol): 1759 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.82 (3H, s, $OCH_3$), 3.88 (3H, s, $-OCH_3$), 3.99 (3H, s, $OCH_3$), 4.16 (3H, s, $OCH_3$), 6.25 (1H, s, Ar-CH=), 6.92 (3H, m, Ar-H), 7.78 (2H, d, $J = 8.8$ Hz, Ar-H).

3.11. *(Z)-3-(3,4-Dimethoxybenzylidene)-5,6,7-trimethoxyphthalide (**5d**)*

Hydroxyphthalide (**4d**) on reaction with formic acid and orthophosphoric acid provided the phthalide (**5d**) in 73% yield. m. p. 150°C; (Found, C, 64.62; H, 5.41; $C_{20}H_{20}O_7$ requires C, 64.51; H, 5.41%). IR (Nujol): 1763 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.89 (3H, s, $OCH_3$), 3.91 (3H, s, $-OCH_3$), 3.95 (3H, s, $OCH_3$), 4.01 (3H, s, $-OCH_3$), 4.18 (3H, s, $-OCH_3$), 6.21 (1H, s, Ar-CH=), 6.87 (2H, m, Ar-H), 7.34 (2H, m, Ar-H).

3.12. *Preparation of (±)-3-benzylphthalides (**6a–d**): General procedure*

To a solution of appropriate 3-benzylidenephthalide (**5a–d**) (0.4 mmol) in ethyl acetate (20 ml) was added 10% palladium on carbon (15 mg) and hydrogenated at about 80 psi pressure of hydrogen. The reaction was complete in 4 h (6 h in the case of **5b**). The catalyst was filtered and the filtrate evaporated to give a semisolid. It was passed through a column of silica gel using chloroform as an eluant to give a solid, which on recrystallization from methylene chloride–hexane furnished phthalides (**6a–d**).

3.13. *(±)-3-(3,4,5-Trimethoxybenzyl)-7-methoxyphthalide (**6a**)*

3-Benzylidenephthalide (**5a**) provided **6a** in 92% yield. m. p. 88°C; (Found, C, 66.37; H, 5.89; $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85%). IR (Nujol): 1758 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.11 (2H, d, $J = 6.3$ Hz, $ArCH_2$), 3.78 (9H, s, $3 \times OCH_3$), 3.94 (3H, s, $-OCH_3$), 5.57 (1H, t, $J = 6.3$ Hz, Ar-CH-O), 6.37 (2H, s, Ar-H), 6.75 (1H, d, $J = 7.6$ Hz, Ar-H), 6.84 (2H, d, $J = 7.6$ Hz, Ar-H), 7.54 (1H, t, $J = 7.6$ Hz, Ar-H).

3.14. *(±)-3-(4-Hydroxy-3,5-dimethoxybenzyl)-7-methoxyphthalide (**6b**)*

3-Benzylidenephthalides (**5b, e**) provided **6b** in 88% and 92% yield, respectively. m. p. 50°C; (Found, C, 65.25; H, 5.46; $C_{18}H_{18}O_6$ requires C, 65.44; H, 5.49%). IR (Nujol): 3450,

1758 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.11 (2H, d, $J$ = 6.3 Hz, Ar-$CH_2$), 3.78 (6H, s, 2 × $OCH_3$), 3.93 (3H, s, $OCH_3$), 5.41 (1H, s, exchangeable with $D_2O$, OH), 5.57 (1H, t, $J$ = 6.3 Hz, Ar-CH-O), 6.36 (2H, s, Ar-H), 6.82 (2H, m, Ar-H), 7.54 (1H, t, $J$ = 7.6 Hz, Ar-H).

3.15. *(±)-3-(4-Methoxybenzyl)-5,6,7-trimethoxyphthalide (**6c**)*

3-Benzylidenephthalide (**5c**) provided **6c** in 92% yield. m. p. 158°C; (Found, C, 66.10; H, 6.02; $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85%). IR (Nujol): 1738 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.07, 3.41(2H, 2 × dd, $J$ = 15.2 and 6.3 Hz, Ar-$CH_2$), 3.78 (3H, s, $OCH_3$), 3.83 (3H, s, $OCH_3$), 3.85 (3H, s, –$OCH_3$), 4.09 (3H, s, –$OCH_3$), 5.44 (1H, t, $J$ = 6.3 Hz, Ar-CH-O), 6.29 (1H, s, Ar-H), 6.82 (2H, d, $J$ = 8.8 Hz, Ar-H), 7.54 (2H, d, $J$ = 8.8 Hz, Ar-H).

3.16 *(±)-3-(3,4-Dimethoxybenzyl)-5,6,7-trimethoxyphthalide (**6d**)*

3-Benzylidenephthalide (**5d**) provided **6d** in 81% yield as thick liquid; (Found, C, 64.01; H, 5.80; $C_{20}H_{22}O_7$ requires C, 64.16; H, 5.92%). IR (Neat): 1740 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.08, 3.50 (2H, 2 × dd, $J$ = 14.0 and 6.3 Hz, Ar-$CH_2$), 3.80 (12H, s, 4 × $OCH_3$), 4.06 (3H, s, –$OCH_3$), 5.45 (1H, t, $J$ = 6.3 Hz, Ar-CH-O), 6.27 (1H, s, Ar-H), 6.72 (3H, bs, Ar-H).

3.17. *(± )-3-Aryl-8-hydroxy-3,4-dihydroisocoumarins (**7a–d**) and (±)-3-benzyl-7-hydroxyphthalides (**8a–c**): General procedure*

A suspension of anhydrous $AlCl_3$ (0.116 g, 0.9 mmol) in dry methylene chloride (15 ml) was stirred at room temperature for 20 min and a solution of appropriate (±) 3-benzylphthalide (**6a–d**) (0.3 mmole) in methylene chloride (10 ml) was added to it (5 min). It was stirred for 6 h and poured slowly into ice-cold solution of HCl (1;1, 15 ml). The methylene chloride layer was separated and the aqueous layer extracted with methylene chloride (2 × 15 ml). The combined organic extract was washed with water, dried ($Na_2SO_4$) and evaporated to give a solid, which was chromatographed over silica gel using ethyl acetate: hexane (1 : 9) as an eluant. The initial fractions gave a solid, which was recrystallized from methylene chloride–hexane to provide 3-aryl-8-hydroxyisocoumarins (**7a–d**) and the latter fractions gave 7-hydroxy-3-benzylphthalides (**8a, b, d**).

3.18. *(±)-3-(3,4,5-Trimethoxyphenyl)-8-hydroxy-3,4-dihydroisocoumarin (**7a**) and (±)-3-(3,4,5-Trimethoxybenzyl)-7-hydroxyphthalide (**8a**)*

The benzylphthalide (**6a**) on reaction with $AlCl_3$ provided **7a** and **8a** in 60% and 25% yields, respectively; **7a:** m. p. 152°C (lit.[9] m. p. 151–54°C); (Found, C, 65.25; H, 5.46; $C_{18}H_{18}O_6$ requires C, 65.44; H, 5.49%). IR (Nujol): 3410, 1661 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.09 (1H, dd, $J$ = 16.1 and 5.3 Hz, H-4), 3.32 (1H, dd, $J$ = 16.1 and 12.6 Hz, H-4), 3.9 (9H, s, 3 × $OCH_3$), 5.51 (1H, dd, $J$ = 12.6 and 5.3 Hz, H-3), 6.67 (2H, s, Ar-H), 6.74 (1H, d, $J$ = 8.5 Hz, H-7), 6.92 (1H, d, $J$ = 8.5 Hz, H-5), 7.44 (1H, t, $J$ = 8.5 Hz, H-6), 10.95 (1H, s, OH exchangeable with $D_2O$). **8a:** m. p. 150°C; (Found, C, 65.32; H, 5.38; $C_{18}H_{18}O_6$ requires C, 65.44; H, 5.49%). IR (Nujol): 3430, 1726 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.09–3.16 (2H, m, Ar-$CH_2$), 3.80 (9H, s, 3 × $OCH_3$), 5.67 (1H, t, $J$ = 6.3 Hz, Ar-CH-O), 6.36 (2H, s, Ar-H), 6.68 (1H, d, $J$ = 8.8 Hz, Ar-H), 6.87 (1H, d, $J$ = 8.8 Hz, Ar-H), 7.47 (1H, t, $J$ = 8.8 Hz, Ar-H), 7.68 (1H, s, OH exchangeable with $D_2O$).

3.19. *(±)-3-(3,5-Dimethoxy-4-hydroxyphenyl)-8-hydroxy-3,4-dihydroisocoumarin (7b) and (±)-3-(3,5-Dimethoxy-4-hydroxybenzyl)-7-hydroxyphthalide (8b)*

The benzylphthalide (**6b**) on reaction with $AlCl_3$ provided **7b** and **8b** in 63% and 31% yields, respectively. **7b:** m. p. 153°C (lit.[9] m. p. 154–155.5°C); (Found, C, 64.31; H, 5.13; $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.10%). IR (Nujol): 3510, 3450, 1661 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.10 (1H, dd, $J$ = 16.0 and 5.3 Hz, H-4), 3.30 (1H, dd, $J$ = 16.0 and 12.6 Hz, H-4), 3.91 (6H, s, 2 × $OCH_3$), 5.53 (1H, dd, $J$ = 12.6 and 5.35 Hz, H-3), 5.62 (1H, s, OH exchangeable with $D_2O$), 6.67 (2H, s, Ar-H), 6.75 (1H, d, $J$ = 8.5 Hz, H-7), 6.96 (1H, d, $J$ = 8.5 Hz, H-5), 7.46 (1H, t, $J$ = 8.5 Hz, H-6), 10.98 (1H, s, 8-OH exchangeable with $D_2O$). **8b:** m. p. 145°C; (Found, C, 64.46; H, 5.21; $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.10%). IR (Nujol): 3430, 1730 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.08–3.16 (2H, m, $ArCH_2$), 3.81 (6H, s, 2 × $OCH_3$), 5.42 (1H, s, OH exchangeable with $D_2O$), 5.65 (1H, t, $J$ = 6.3 Hz, Ar-CH-O), 6.37 (2H, s, Ar-H), 6.67 (1H, d, $J$ = 7.6 Hz, Ar-H), 6.87 (1H, d, $J$ = 7.6 Hz, Ar-H), 7.46 (1H, t, $J$ = 7.6 Hz, Ar-H), 7.70 (1H, s, OH exchangeable with $D_2O$).

3.20. *(±)-3-(4-Methoxyphenyl)-6,7-dimethoxy-8-hydroxy-3,4-dihydroisocoumarin (7c)*

The benzylphthalide (**6c**) on reaction with $AlCl_3$ provided **7c** in 73% yield. m. p. 175°C; (Found, C, 65.54; H, 5.60; $C_{18}H_{18}O_6$ requires C, 65.44; H, 5.49%). IR (Nujol): 3350, 1660 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.04 (1H, dd, $J$ = 15.2 and 3.8 Hz, H-4), 3.32 (1H, dd, $J$ = 15.2 and 11.4 Hz, H-4), 3.80 (1H, s, $OCH_3$), 3.87 (1H, s, $OCH_3$), 3.90 (1H, s, $OCH_3$), 5.47 (1H, dd, $J$ = 11.4 and 3.8 Hz, H-3), 6.29 (1H, s, Ar-H), 6.91 (2H, d, $J$ = 8.8 Hz, Ar-H), 7.36 (2H, d, $J$ = 8.8 Hz, Ar-H), 11.07 (1H, s, OH exchangeable with $D_2O$).

3.21. *(±)-3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-8-hydroxy-3,4-dihydroisocoumarin (7d) and (±)-3-(3,4-dimethoxybenzyl)-5,6-dimethoxy-7-hydroxyphthalide (8d)*

The benzylphthalide (**6d**) provided **7d** and **8d** in 63% and 19% yields respectively. **7d**: m.p. 148°C; (Found, C, 63.11; H, 5.79; $C_{19}H_{20}O_7$ requires C, 63.33; H, 5.59%). IR (Nujol): 3409, 1661 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.07 (1H, dd, $J$ = 15.2 and 3.8 Hz, H-4), 3.35 (1H, dd, $J$ = 15.2 and 11.4 Hz, H-4), 3.87 (12H, s, 4 × $OCH_3$), 5.47 (1H, dd, $J$ = 11.4 and 3.8 Hz, H-3), 6.32 (1H, s, Ar-H), 6.95 (3H, bs, Ar-H), 11.08 (1H, s, OH exchangeable with $D_2O$). **8d:** Thick liquid; (Found, C, 63.22; H, 5.65; $C_{19}H_{20}O_7$ requires C, 63.33; H, 5.59%). IR (Neat): 3340, 1740 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.07–3.18 (2H, m, Ar-$CH_2$), 3.80 (12H, s, 4 × $OCH_3$), 5.50 (1H, t, $J$ = 6.3 Hz, Ar-CH-O), 6.29 (1H, s, Ar-H), 6.34 (1H, s, OH exchangeable with $D_2O$), 6.72 (3H, bs, Ar-H).

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