3-Aryl-8-hydroxy-3,4-dihydroisocoumarins: Synthesis of aglycones of macrophylllosides 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 hydroxypbthalides (4a–d) and 3-benzylideneophthalides (5a–e).

Keywords: Benzylphthalides, 3-arylisocoumarins, macrophylllosides, LDA, AlCl3 catalyst.

1. Introduction
3-Aryl-8-hydroxy-3,4-dihydroisocoumarins constitute an important class of naturally occurring oxygen ring compounds, because of their antimicrobial, antifungal and antiallergic activities2–7 and their application as sweetening agents8 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 AlCl3-mediated conversion of 7-methoxy-3-benzylphthalides. The paper also describes the first synthesis of macrophyllols 7a, b, the aglycones of macrophylllosides A, B and C (1a–c), isolated9 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-benzylxoy-3,5-
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 48% yields, respectively. Debenzylation of phenolic ethers under this condition is unprecedented.

The benzylidenephthalides (5a–e) on catalytic hydrogenation using H₂, 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.

Scheme 1. Reagents and conditions: a) i) LDA, THF, –78°C; ii) ArCHO (3); iii) H₂; b) H₃PO₄, HCOOH, heat; c) H₂, Pd-C; d) AlCl₃, CH₂Cl₂, 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 macrophyllloside A (1a) and the aglycone (7b) of macrophylllosides 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. THF was distilled over LiAlH$_4$ before use.

Phthalides (2a, b) were prepared according to the literature procedure.

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

To a stirred solution of syringaldehyde (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 x 20 ml). The combined organic layer was washed with water, dried (Na$_2$SO$_4$) 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. 50°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$_3$): 0.385 (6H, s, 2 x 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 x 20 ml) with chloroform. The combined organic layer was washed with water and dried over anhydrous Na$_2$SO$_4$. The gummy mass, obtained after the evaporation of the solvent, was chromatographed over silica gel using ethyl acetate : 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$_2$O), 3.82 (9H, s, 3 x OCH$_3$), 3.92 (3H, s, -OCH$_3$), 4.28 and 4.71 (1H, 2 x d,
J = 6.0 Hz, CH-CH₂), 5.12 and 5.53 (1H, 2 x d, J = 6 Hz, Ar-CH₂-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; C₁₅H₁₄O₇ requires C, 68.80; H, 5.54%). IR (Nujol): 3410, 1747 cm⁻¹. ¹H NMR (CDCl₃): δ 2.63 (1H, s, –OH, exchangeable with D₂O), 3.74 (6H, s, 2 x OCH₃), 3.92 (3H, s, –OCH₃), 4.09–4.67 (1H, m, CH-CH₂-O-), 5.04 (2H, s, –OCH₂-), 5.14–5.50 (1H, m, Ar-H), 6.45–6.64 (3H, m, Ar-H), 6.88–7.46 (2H, 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; C₁₃H₁₂O₅ requires C, 63.33; H, 5.59%). IR (Nujol): 3370, 1751 cm⁻¹. ¹H NMR (CDCl₃): δ 2.67 (1H, s, –OH, exchangeable with D₂O), 3.71 (3H, s, OCH₃), 3.78 (3H, s, –OCH₃), 3.81 (3H, s, –OCH₃), 4.05 (3H, s, –OCH₃), 5.09 (1H, d, J = 5.0 Hz, CH-CH₂-O-), 5.39 (1H, d, J = 5.0 Hz, Ar-CH₂-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; C₁₉H₁₈O₈ requires C, 61.53; H, 5.68%). IR (Nujol): 3475, 1748 cm⁻¹. ¹H NMR (CDCl₃): δ 2.61 (1H, s, –OH, exchangeable with D₂O), 3.73 (3H, s, OCH₃), 3.83 (3H, s, –OCH₃), 3.85 (6H, s, 2 x –OCH₃), 4.07 (3H, s, –OCH₃), 5.11 (1H, brs, CH-CH₂-O-), 5.42 (1H, brs, Ar-CH₂-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 4e) at 80°C. The reaction mixture was cooled to room temperature, poured into ice-cold water (15 ml) and extracted with chloroform (3 x 10 ml). The combined chloroform extract was washed with water, dried (Na₂SO₄) 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; C₁₉H₁₈O₆ requires C, 66.66; H, 5.30%). IR (Nujol): 1766 cm⁻¹. ¹H NMR (CDCl₃): δ 3.87 (3H, s, OCH₃), 3.91 (6H, s, 2 x OCH₃), 4.0 (3H, s, OCH₃), 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-Benzylxy-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_{32}H_{22}O_{6} requires C, 71.76; H, 5.30%). IR (Nujol): 1762 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 3.73\) (3H, s, OCH\(_3\)), 3.85 (3H, s, \(-\text{OCH}_3\)), 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 requires C, 65.85; H, 4.91%). IR (Nujol): 3430, 1765 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 3.82\) (3H, s, OCH\(_3\)), 3.88 (3H, s, \(-\text{OCH}_3\)), 3.99 (3H, s, OCH\(_3\)), 4.16 (3H, s, OCH\(_3\)), 6.25 (1H, s, exchangeable with D\(_2\)O, \(-\text{OH}\)), 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), 7.5 (1H, s, 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\(_{18}\)H\(_{16}\)O\(_4\) requires C, 66.66; H, 5.30%). IR (Nujol): 1759 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 3.82\) (3H, s, OCH\(_3\)), 3.88 (3H, s, \(-\text{OCH}_3\)), 4.01 (3H, s, \(-\text{OCH}_3\)), 5.70 (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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 3.89\) (3H, s, OCH\(_3\)), 3.91 (3H, s, \(-\text{OCH}_3\)), 3.95 (3H, s, OCH\(_3\)), 4.01 (3H, s, \(-\text{OCH}_3\)), 4.18 (3H, s, \(-\text{OCH}_3\)), 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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 3.11\) (2H, d, \(J=6.3\) Hz, Ar-CH\(_2\)), 3.78 (9H, s, 3 x OCH\(_3\)), 3.94 (3H, s, \(-\text{OCH}_3\)), 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 (CDCl₃): δ 3.11 (2H, d, J = 6.3 Hz, Ar-CH₂), 3.78 (6H, s, 2 × OCH₃), 3.93 (3H, s, OCH₃), 5.41 (1H, s, exchangeable with D₂O, 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-Benzylideneaphthalide (5c) provided 6c in 92% yield. m. p. 158°C; (Found, C, 66.10; H, 6.02; C₁₉H₂₀O₆ requires C, 66.27; H, 5.85%). IR (Nujol): 1738 cm⁻¹. ¹H NMR (CDCl₃): δ 3.07, 3.41 (2H, 2 × dd, J = 15.2 and 6.3 Hz, Ar-CH₂), 3.78 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 4.09 (3H, s, OCH₃), 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-Benzylideneaphthalide (5d) provided 6d in 81% yield as thick liquid; (Found, C, 64.01; H, 5.80; C₂₀H₂₂O₇ requires C, 64.16; H, 5.92%). IR (Neat): 1740 cm⁻¹. ¹H NMR (CDCl₃): δ 3.08, 3.50 (2H, 2 × dd, J = 14.0 and 6.3 Hz, Ar-CH₂), 3.80 (9H, s, 3 × OCH₃), 4.06 (3H, s, OCH₃), 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 AlCl₃ (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 (Na₂SO₄) 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 benzylideneaphthalide (6a) on reaction with AlCl₃ 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; C₁₈H₁₈O₆ requires C, 65.44; H, 5.49%). IR (Nujol): 3410, 1661 cm⁻¹. ¹H NMR (CDCl₃): δ 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 × OCH₃), 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 D₂O). 8a: m. p. 150°C; (Found, C, 65.32; H, 5.38; C₁₈H₁₈O₆ requires C, 65.44; H, 5.49%). IR (Nujol): 3430, 1726 cm⁻¹. ¹H NMR (CDCl₃): δ 3.09–3.16 (2H, m, Ar-CH₂), 3.80 (9H, s, 3 × OCH₃), 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 D₂O).
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 AlCl₃ 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; C₁₇H₁₆O₆ requires C, 64.55; H, 5.10%). IR (Nujol): 3510, 3450, 1661 cm⁻¹. ¹H NMR (CDCl₃): δ 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 x OCH₃), 5.53 (1H, dd, J = 12.6 and 5.35 Hz, H-3), 5.62 (1H, s, OH exchangeable with D₂O), 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, OH exchangeable with D₂O).

8b: m. p. 145°C; (Found, C, 64.46; H, 5.21; C₁₇H₁₆O₆ requires C, 64.55; H, 5.10%). IR (Nujol): 3430, 1730 cm⁻¹. ¹H NMR (CDCl₃): 0.30-3.16 (2H, m, Ar-CH₂), 3.81 (6H, s, 2 x OCH₃), 5.42 (1H, s, OH exchangeable with D₂O), 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 D₂O).

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

The benzylphthalide (6c) on reaction with AlCl₃ provided 7c in 73% yield. m. p. 175°C; (Found, C, 65.54; H, 5.60; C₁₈H₁₈O₆ requires C, 65.44; H, 5.49%). IR (Nujol): 3350, 1660 cm⁻¹. ¹H NMR (CDCl₃): δ 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), 3.87 (1H, s, OCH₃), 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 D₂O).

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; C₁₉H₂₀O₇ requires C, 63.33; H, 5.59%). IR (Nujol): 3409, 1661 cm⁻¹. ¹H NMR (CDCl₃): δ 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 x OCH₃), 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 D₂O). 8d: Thick liquid; (Found, C, 63.22; H, 5.65; C₁₉H₂₀O₇ requires C, 63.33; H, 5.59%). IR (Neat): 3340, 1740 cm⁻¹. ¹H NMR (CDCl₃): δ 3.07-3.18 (2H, m, Ar-CH₂), 3.80 (12H, s, 4 x OCH₃), 5.50 (1H, t, J = 6.3 Hz, Ar-CH-O), 6.29 (1H, s, Ar-H), 6.34 (1H, s, OH exchangeable with D₂O), 6.72 (3H, bs, Ar-H).

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