 

# An Effective System to Synthesize Hypolipidemic Active α-Asarone and Related Methoxylated (*E*)-Arylalkenes[#]

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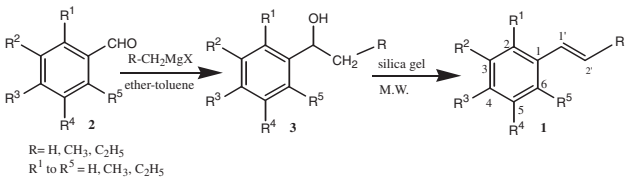
Methoxylated (*E*)-arylalkenes (**1a–1k**) were prepared in two steps by an improved Grignard reaction comprising the reverse addition of alkylmagnesium bromide to benzaldehydes (**2a–2k**) in anhydrous ether and toluene into arylalkanols (**3a–3k**) in high yield, followed by dehydration with silica gel under microwave irradiation for 3–12 min, depending upon the substituents attached to the aromatic ring to afford hypolipidemic active α-asarone (**1a**) and related methoxylated (*E*)-arylalkenes (**1b–1k**).

α-Asarone,[1] (*E*)-1-(2,4,5-trimethoxyphenyl)-1-propene (**1a**), and related methoxylated (*E*)-arylalkenes[2] (**1b–1k**), occurring in a large number of medicinally important plants,[3] including *Acorus calamus*[4] and *Zingiber Cassumunar*,[5] have attracted a lot of interest in recent years due to their sedating, neuroleptic, spasmolytic, antiulcerogenic, antiatherogenic, anti-inflammatory, anti-oxidant properties[6] and, most importantly, anti-platelet and hypolipidemic activities[7] in humans (in vitro). On account of the wide spectrum of their biological activities on one hand and their low availability from natural resources on the other, several synthetic approaches,[3a,5,8,9] including the Wittig–Horner[8b] reaction, the Friedel–Crafts[8h] reaction, Aldol–Grob[8g] reaction and the isomerization of (*Z*)-arylalkene[8i] or γ-arylalkenes[8a,f,j] to (*E*)-arylalkenes,[9] have been undertaken during the past few years. However, the Grignard reaction of benzaldehydes into arylalkanols, followed by their acid catalyzed dehydration into arylalkenes,[7c,10,11] remains the most common approach due to procedural simplicity and economical starting material as well as reagents compared to all other reported routes.[8] However, methoxylated benzaldehydes upon the Grignard reaction mostly end up in poor yield of the product, e.g., 2,4,5-trimethoxybenzaldehyde (**2a**) provides a 30% yield of **1a** along with the formation of an unwanted dimer[11] in 20% yield via intermediate **3a**. Hence, there remains a scope for the development of a practical and efficient protocol for the synthesis of (*E*)-arylalkenes **1a–1k** in good amount. In this light, we herein report on a high-yielding method for the preparation of important bioactive **1a–1k** in 39–74% yields that entails an incremental effect of the reverse addition of alkylmagnasium bromide to benzaldehydes **2a–2k** towards the preparation of arylalkanol derivatives **3a–3k** in high yields, and subsequent dehydration of **3a–3k** with silica gel under microwave irradiation to obtain the title compounds, **1a–1k** (Scheme 1).




Scheme 1.

## Results and Discussion

In continuation of our ongoing program on the synthesis of bioactive compounds,[12] we were interested to develop a high-yielding and large-scale synthesis of bioactive **1a** and related arylalkenes **1b–1k** through some modifications in the existing Grignard method for the preparation of intermediate arylalkanols **3a–3d** as well as a modification in the crucial dehydration step of arylalkanols **3a–3d**. In initial attempts, we decided to change the solvent[7c,10,11] used for the Grignard reaction from ether or THF to a mixture of toluene with ether or THF, since there are reports in the literature where a mixture of toluene[13] with ether or THF affords increased yields of the addition products compared to those obtained in either ether or THF alone. Moreover, the use of toluene offers additional advantages, like being cheaper, non-hygroscopic and having a higher boiling point compared to ether. Lastly, the replacement of readily flammable ether with a high boiling point toluene is crucial for the industrial scale synthesis of **3a**. Therefore, the Grignard reaction was performed by the addition of **2a** into alkylmagnesium bromide (4 mol. amt.) using a mixture of toluene and ether as solvents, which resulted in an enhancement of the yield of **3a** up to 47% with some unreacted **2a**, and no improvement in the yield of **3a**, even if an excess of Grignard reagent (6 mol. amt.) was added. We then added the Grignard reagent (4 mol. amt.) dropwise to **2a**, instead of a dropwise addition of **2a** to the Grignard reagent, as generally reported.[7c,10] To our surprise, the yield of the arylalkanol **3a** increased up to 78%, which is more than two fold increase than the reported method[11] (30% yield). Similarly, **3b** provided yields of up to 79%, whereas the reported Grignard method provided alkanol[14] **3b** in 67% yield. Although, the inverse addition[15] is well documented in the literature, an incremental effect of the inverse addition in Grignard reaction has been investigated in detail towards the preparation of methoxylated aryl alkanols **3a–3k** for the first time.

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The final step, comprising the dehydration of the alcohols **3a**–**3k** into the desired **1a**–**1k**, remained crucial, as a number of side products[11] formation have been reported in literature using various dehydrating agents,[11,16] such as phosphoryl chloride, *p*-toluenesulfonic acid, thionyl chloride, triphenylphosphine, and oxalic acid. Recently, the dehydration[7c] of some alkanols **3a**–**3d** by prolonged refluxing with anhydrous copper(II) sulfate[17] in toluene into **1a**–**1d** has been reported as being cleaner and better yielding compared to other reagents mentioned above; however, a longer reaction time and no details regarding the yield[7c] prompted us to investigate this methodology in our case. Of late, there has been an increasing penchant to use microwave-assisted[18] techniques in the synthesis of organic compounds due to shorter reaction times, higher yield and operational simplicity achievable in the microwave region compared to conventional methods.[7c,10,11] Hence, keeping all this in mind, compound **3a** was dehydrated with copper(II) sulfate coupled with microwave irradiation, which provided the dehydrated product **1a** in 41% yield within a short reaction time, varying from 2–3 min, along with some unreacted starting material as well as side products, which were too little in amount to cause problems in the product estimation. Attempts to improve the yield of **1a** by either increasing the reaction time or increasing the amount of copper(II) sulfate remained unsuccessful. However, the combination[19] of silica gel and copper(II) sulfate with a gradual increment of silica gel from 1:1 to 4:1 ratio under microwave irradiation increased the yield of **1a** from 47 to 54%, respectively, with very few side products. This experiment indicated that an increase in proportion of silica gel in a mixture of silica gel and copper(II) sulfate would enhance the yield of **1a**. This result prompted us to utilize silica gel[20] alone for the dehydration of **3a** under microwave irradiation, which, in fact, enhanced the yield of product **1a** up to 68% (Table 1). Although the dehydration of **3a** always provided an isomeric mixture of *E* and *Z* of **1a** in 92:8 ratio, upon column purification provided a 74% yield of the product to obtain pure *E*-isomer (68%) after recrystallisation. After a successful synthesis of bioactive **1a** via intermediate **3a**, the method was successfully extended to convert the remaining alcohols **3b**–**3k**, which after column purification provided respective (*E*)-arylalkenes **1b**–**1k** in high yield within 3–12 min, as mentioned in Table 2. It is worth noting that the dehydration of **3j**, **3k** invariably took a longer period (11–12 min), and produced a lower yield (39–48%) for product formation **1j**, **1k** compared to the dehydration of **3a**–**3i** into **1a**–**1i** (59–74%) under microwave irradiation (3 min). The overall silica gel-assisted dehydration is most suitable because it is cost effective, easy to handle and can be removed from the reaction mixture by mere filtration after completion of the reaction. In addition, the mild acidic nature of silica gel avoids the polymerization of arylalkenes, thereby reducing the side products remarkably compared to other reported dehydrating agents.[16,21]

Table 1. Effect of Catalyst in Dehydration of 2,4,5-Trimethoxyphenyl Propanol (**3a**) into 2,4,5-Trimethoxyphenyl Propene (**1a**)

| Entry | Microwave irradiation | Catalyst | Yield/% |
|---|---|---|---|
| 1 | 3 min | $CuSO_4$ | 41 |
| 2 | 10 min | $CuSO_4$ | 41 |
| 3 | 3 min | $CuSO_4$:Silica gel 1:1 | 47 |
| 4 | 3 min | $CuSO_4$:Silica gel 1:4 | 54 |
| 5 | 3 min | Silica gel | 68 |
| 6 | 10 min | Silica gel | 68 |

## Conclusion

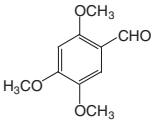
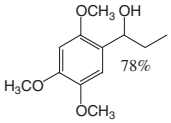
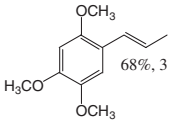
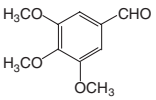
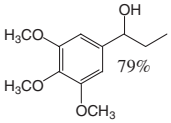
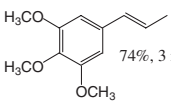
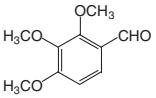
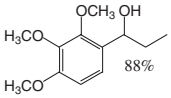
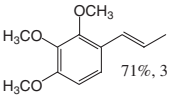
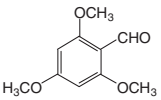
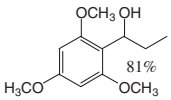
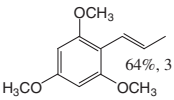
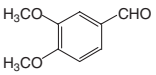
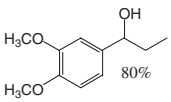
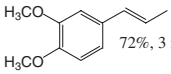
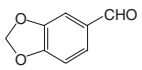
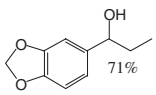
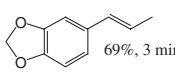
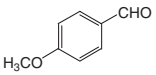
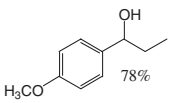
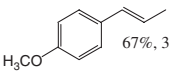
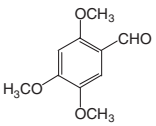
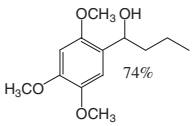
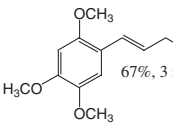
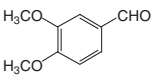
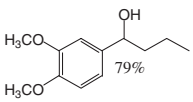
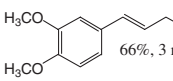
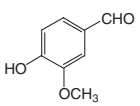
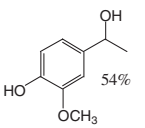
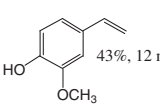
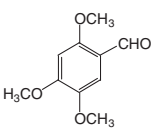
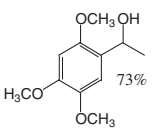
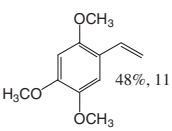
An improved yield of the intermediate arylalkanols **3a**–**3k** by the reverse addition of alkylmagnesium bromide to benzaldehydes (**2a**–**2k**) and a rapid microwave assisted dehydration of **3a**–**3k** with silica gel into arylalkenes **1a**–**1k** within 15 min are the main advantages of this procedure over the existing ones.[7c,8–11].

## Experimental

**General Methods.** All melting points are uncorrected. Silica gel utilized for the dehydration process was 60–120 mesh size (Qualigens grade). Column chromatography was performed on neutral alumina and silica gel (Merck). Commercial reagents and solvents were of analytical grade, or were purified by standard procedures prior to use. All reactions involving air or moisture-sensitive materials were carried out under a nitrogen atmosphere. $^1$H (300 MHz) and $^{13}$C (75.4 MHz) NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer. A Kenstar domestic microwave oven (2450 MHz, 900 Watts) was used for reactions.

**General Procedure for the Synthesis of Methoxylated Arylalkanols (3a–3k):** A mixture of alkyl bromide (0.048 mol) and Mg (0.048 mol) in 70 mL of ether was stirred for 2 h under a nitrogen atmosphere. Thus formed Grignard reagent was added dropwise in 15–20 min to a cooled mixture of benzaldehydes **2a**–**2k** (0.012 mol) in ether (40 mL) and toluene (70 mL), and stirred for 12–14 h at r.t. until completion of reaction. The cooled mixture was poured into a saturated solution of ammonium chloride and stirred for 20 min. The mixture was extracted with ethyl acetate (2 × 10 mL), and the combined solvent was washed with brine and dried over $Na_2SO_4$. The residue obtained upon evaporation of the filtrate afforded alkanols, which were though sufficiently pure for the next step, were chromatographed on a neutral alumina column using a hexane–ethyl acetate mixture with increasing proportion of ethyl acetate up to 25% to afford alkanol derivatives **3a**–**3k**. Compound **3a**: 78% yield; mp 69–70 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.06 (1H, s, H-6), 6.50 (1H, s, H-3), 4.45 (1H, t, $J$ = 6.6 Hz, H-1′), 3.91, 3.89, and 3.68 (each 3H, s, three –$OCH_3$), 1.81–1.54 (2H, m, H-2′), 0.85 (3H, t, $J$ = 7.4 Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 152.0 (C-2), 148.5 (C-4), 143.7 (C-5), 123.8 (C-1), 110.9 (C-6), 97.9 (C-3), 73.4 (C-1′), 57.0 (4-$OCH_3$), 56.7 (5-$OCH_3$), 56.4 (2-$OCH_3$), 31.9 (C-2′), 11.0 (C-3′). Compound **3b**: 79% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.70 (2H, s, H-2 and H-6), 4.45 (1H, t, $J$ = 7.0 Hz, H-1′), 3.78 (3H, s, 4-$OCH_3$), 3.77 (6H, s, 3-$OCH_3$ and 5-$OCH_3$), 2.47 (1H, br, –OH), 1.79–1.69 (2H, m, H-2′), 0.86 (3H, t, $J$ = 7.0 Hz, H-3′). $^{13}$C NMR $\delta$ 153.4 (C-3 and C-5), 141.1 (C-4), 137.2 (C-1), 103.1 (C-2 and C-6), 75.7 (C-1′), 61.2 (4-$OCH_3$), 56.5 (3-$OCH_3$, 5-$OCH_3$), 32.3 (C-2′), 10.7 (C-3′). Compound **3c**: 88% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 7.01 (1H, d, $J$ = 8.5 Hz, H-5), 6.66 (1H, d, $J$ = 8.5 Hz, H-6), 4.73 (1H, t, $J$ = 6.6 Hz, H-1′), 3.92, 3.87, and 3.85 (each 3H, s, three –$OCH_3$), 2.41 (1H, br, –OH), 1.83–1.71 (2H,

Table 2. Grignard Reaction[a] of Benzaldehydes into Arylalkanols (**3a**–**3k**) and Its Dehydration[b] into Pure (*E*)-Arylalkenes (**1a**–**1k**)

| Run | Benzaldehydes | Arylalkanols (**3**) | (*E*)-Arylalkenes (**1**) |
|---|---|---|---|
| a |  |  78% |  68%, 3 min |
| b |  |  79% |  74%, 3 min |
| c |  |  88% |  71%, 3 min |
| d |  |  81% |  64%, 3 min |
| e |  |  80% |  72%, 3 min |
| f |  |  71% |  69%, 3 min |
| g |  |  78% |  67%, 3 min |
| h |  |  74% |  67%, 3 min |
| i |  |  79% |  66%, 3 min |
| j |  |  54% |  43%, 12 min |
| k |  |  73% |  48%, 11 min |

a) Reaction conditions: alkyl bromide/Mg, toluene. b) Silica gel/dioxane.

m, H-2′), 0.96 (3H, t, $J = 7.4$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 153.3 (C-3), 151.5 (C-2), 142.3 (C-4), 130.4 (C-1), 122.4 (C-5), 107.5 (C-6), 71.9 (C-1′), 61.5 (3-$OCH_3$), 61.0 (2-$OCH_3$), 56.3 (4-$OCH_3$), 31.4 (C-2′), 10.9 (C-3′). Compound **3d**: 81% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.1 (2H, s, H-3, H-5), 4.91 (1H, t, $J = 6.6$ Hz, H-1′), 3.73 (6H, s, 2-$OCH_3$ and 6-$OCH_3$), 3.72 (3H, s, 4-$OCH_3$), 2.93 (1H, br, –OH), 1.89–1.63 (2H, m, H-2′), 0.83 (3H, t, $J = 7.4$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.1 (C-4), 158.3 (C-2 and C-6), 112.5 (C-1), 90.9 (C-3 and C-5), 71.7 (C-1′), 55.1 (2-$OCH_3$ and 6-$OCH_3$), 53.4 (4-$OCH_3$), 30.5 (C-2′), 10.7 (C-3′). Compound **3e**: 80% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.86–6.81 (3H, m, H-6, H-5, and H-2), 4.49 (1H, t, $J = 6.6$ Hz, H-1′), 3.86 and 3.83 (each 3H, s, two –$OCH_3$), 2.25 (1H, br, OH), 1.79–1.68 (2H, m, H-2′), 0.89 (3H, t, $J = 6.4$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 149.1 (C-3), 148.5 (C-4), 137.3 (C-1), 118.8 (C-6), 113.1 (C-5), 108.7 (C-2), 76.1 (C-1′), 56.4 (4-$OCH_3$), 56.1 (3-$OCH_3$), 31.8 (C-2′), 10.6 (C-3′). Compound **3f**: 71% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.85 (1H, s, H-2), 6.79 (2H, m, H-5 and H-6), 5.93 (2H, s, –$OCH_2O$–), 4.50 (1H, t, $J = 6.5$ Hz, H-1′), 1.89 (1H, br, OH), 1.79–1.68 (2H, m, H-2′), 0.87 (3H, t, $J = 7.4$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 148.2 (C-3), 147.3 (C-4), 139.2 (C-1), 119.7 (C-6), 108.7 (C-5), 106.3 (C-2), 101.5 (–$OCH_2O$–), 76.4 (C-1′), 32.2 (C-2′), 10.4 (C-3′). Compound **3g**: 78% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.96–6.79 (4H, m,

H-6, H-5, H-3, and H-2), 4.59 (1H, t, $J = 6.4$ Hz, H-1′), 3.82 (3H, s, 4-$OCH_3$), 1.72–1.65 (2H, m, H-2′), 0.91 (3H, t, $J = 7.5$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.1 (C-4), 146.2 (C-1), 129.1 (C-6), 118.1 (C-5), 112.8 (C-2), 111.7 (C-3), 76.1 (C-1′) 55.2 (4-$OCH_3$), 31.7 (C-2′), 10.2 (C-3′). Compound **3h**: 74% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.62 (1H, s, H-6), 6.34 (1H, s, H-3), 4.29 (1H, t, $J = 6.4$ Hz, H-1′), 3.82 (6H, s, 4-$OCH_3$ and 5-$OCH_3$), 3.61 (3H, s, 2-$OCH_3$), 1.76–1.41 (2H, m, H-2′), 1.26–1.21 (2H, m, H-3′), 0.86 (3H, t, $J = 7.0$ Hz, H-4′); $^{13}$C NMR ($CDCl_3$) $\delta$ 151.2 (C-4), 147.2 (C-5), 142.4 (C-2), 118.8 (C-1), 109.9 (C-6), 97.9 (C-3), 73.8 (C-1′), 56.3 (4-$OCH_3$), 56.8 (5-$OCH_3$), 55.8 (2-$OCH_3$), 28.1 (C-2′), 23.2 (C-3′), 14.4 (C-4′). Compound **3i**: 79% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.78–6.72 (3H, m, H-6, H-5, and H-2), 4.29 (1H, t, $J = 6.6$ Hz, H-1′), 3.84 and 3.81 (each 3H, s, two –$OCH_3$), 1.72–1.42 (2H, m, H-2′), 1.28–1.21 (2H, m, H-3′), 0.88 (3H, t, $J = 7.0$ Hz, H-4′); $^{13}$C NMR ($CDCl_3$) $\delta$ 148.4 (C-3), 147.5 (C-4), 137.1 (C-1), 118.4 (C-6), 113.5 (C-5), 108.2 (C-2), 73.2 (C-1′), 56.2 (4-$OCH_3$), 56.0 (3-$OCH_3$), 27.7 (C-2′), 23.1 (C-3′), 13.9 (C-4′). Compound **3j**: 54% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.86–6.74 (3H, m, H-6, H-2, and H-5), 5.58 (1H, s, 4-OH), 4.77 (1H, q, $J = 7.0$ Hz, H-1′), 3.83 (3-$OCH_3$), 2.09 (1H, s, OH), 1.42 (3H, d, $J = 7.0$ Hz, H-2′); $^{13}$C NMR ($CDCl_3$) $\delta$ 146.6 (C-4), 145.0 (C-3), 137.9 (C-1), 118.3 (C-5), 114.1 (C-6), 108.0 (C-2), 70.3 (C-1′), 55.9 (3-$OCH_3$), 25.1 (C-2′). Compound **3k**: 73% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.85 (1H, s, H-6), 6.43 (1H, s, H-3), 4.98 (1H, q, $J = 7.1$ Hz, H-1′), 3.79 (6H, s, 4-$OCH_3$ and 5-$OCH_3$), 3.74 (3H, s, 2-$OCH_3$), 2.52 (1H, br, OH), 1.38 (3H, d, $J = 7.1$ Hz, H-2′); $^{13}$C NMR ($CDCl_3$) $\delta$ 150.9 (C-4), 149.0 (C-5), 143.5 (C-2), 125.7 (C-1), 110.8 (C-6), 97.9 (C-3), 66.1 (C-1′), 56.6 (4-$OCH_3$), 56.2 (5-$OCH_3$), 55.1 (2-$OCH_3$), 23.6 (C-2′).

**General Procedure for Dehydration of Arylalkanols 3a–3k into (*E*)-Arylalkenes 1a–1k under Microwave-Irradiation:** Arylalkanols (**3a**–**3k**) (0.01 mol), anhydrous silica gel (4.0 g) in dioxane (6–8 mL) were suspended in a 100 mL Erlenmeyer flask, and the mixture was irradiated under microwave radiation for 3–12 min in parts until the disappearance of the starting material based upon a TLC analysis. Upon cooling, the mixture was washed with ethyl acetate (3 × 10 mL) and filtered. The combined organic layer was washed with water and dried over anhydrous $Na_2SO_4$. The solvent was evaporated, and the obtained liquid was chromatographed on a silica-gel column using a hexane–ethyl acetate mixture with increasing proportion of ethyl acetate up to 20% followed by recrystallisation to afford (*E*)-arylalkenes (**1a**–**1k**). Compound **1a**: 68% yield; white solid; mp 44–45 °C (lit.[7c] mp 44–45 °C); $^1$H NMR ($CDCl_3$) $\delta$ 6.91 (1H, s, H-6), 6.64 (1H, dd, $J = 1.5$, 16.0 Hz, H-1′), 6.45 (1H, s, H-3), 6.02 (1H, dq, $J = 6.2$, 16.0 Hz, H-2′), 3.84, 3.81, and 3.77 (each 3H, s, three $OCH_3$), 1.87 (3H, dd, $J = 6.2$, 1.5 Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 149.9 (C-2), 148.0 (C-4), 142.6 (C-5), 124.4 (C-1′), 123.4 (C-2′), 118.3 (C-1), 109.2 (C-6), 97.3 (C-3), 56.1 (4-$OCH_3$), 55.7 (5-$OCH_3$), 55.1 (2-$OCH_3$), 18.7 (C-3′). Compound **1b**: 74% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.50 (2H, s, H-2 and H-6), 6.31 (1H, dq, $J = 1.4$, 15.7 Hz, H-1′), 6.12 (1H, dq, $J = 6.3$, 15.7 Hz, H-2′), 3.81 (3H, s, 4-$OCH_3$), 3.78 (6H, s, 3-$OCH_3$ and 5-$OCH_3$), 1.82 (3H, d, $J = 6.3$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 153.3 (C-4), 137.5 (C-3 and C-5), 134.1 (C-1′), 131.3 (C-1), 125.6 (C-2′), 103.1 (C-2 and C-6), 61.1 (4-$OCH_3$), 56.4 (3-$OCH_3$ and 5-$OCH_3$), 18.6 (C-3′). Compound **1c**: 71% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 7.10 (1H, d, $J = 8.7$ Hz, H-5), 6.64 (1H, s, H-6), 6.58 (1H, dq, $J = 1.7$, 15.9 Hz, H-1′), 6.12 (1H, dq, $J = 6.6$, 15.9 Hz, H-2′), 3.89 (3H, s, 2-$OCH_3$), 3.86 (3H, s, 4-$OCH_3$), 3.84 (3H, s, 3-$OCH_3$), 1.88 (3H, d, $J = 1.7$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 152.9 (C-3), 151.3 (C-2), 142.7 (C-4), 125.5 (C-1), 125.4 (C-1′), 124.7 (C-2′), 120.8 (C-5), 108.1 (C-6), 61.4 (3-$OCH_3$), 61.2 (2-$OCH_3$), 56.4 (4-$OCH_3$), 19.2 (C-3′). Compound **1d**: 64% yield; mp 71–72 °C (lit.[7c] mp 72–73 °C); $^1$H NMR ($CDCl_3$) $\delta$ 6.57 (1H, d, $J = 16.1$ Hz, H-1′), 6.50 (1H, dq, $J = 5.5$, 16.1 Hz, H-2′), 6.14 (2H, s, H-3 and H-5), 3.81 (6H, s, 2-$OCH_3$ and 6-$OCH_3$), 3.70 (3H, s, 4-$OCH_3$), 1.89 (3H, d, $J = 5.5$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.1 (C-4), 158.3 (C-2 and C-6), 128.7 (C-1′), 121.5 (C-2′), 112.5 (C-1), 90.9 (C-3 and C-5), 55.1 (2-$OCH_3$ and 6-$OCH_3$), 53.4 (4-$OCH_3$), 19.8 (C-3′). Compound **1e**: 72% yield; liquid; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.90–6.78 (3H, m, H-6, H-5, and H-2), 6.35 (1H, d, $J = 16.2$ Hz, H-1′), 6.11 (1H, m, H-2′), 3.87, 3.83 (each 3H, s, two $OCH_3$), 1.87 (3H, d, $J = 6.2$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 149.3 (C-4), 148.5 (C-3), 131.5 (C-1′), 131.0 (C-2′), 124.0 (C-1), 119.0 (C-5), 111.4 (C-6), 108.7 (C-2), 56.0 (3-$OCH_3$), 56.0 (4-$OCH_3$), 18.8 (C-3′). Compound **1f**: 69% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.92 (1H, s, H-2), 6.77 (2H, d, H-5 and H-6), 6.35 (1H, d, $J = 16.2$ Hz, H-1′), 6.11 (1H, m, H-2′), 5.95 (2H, s, –$OCH_2O$–), 1.95 (3H, d, $J = 6.2$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 147.9 (C-4), 146.5 (C-3), 132.5 (C-1′), 130.6 (C-2′), 123.8 (C-1), 120.0 (C-5), 108.1 (C-6), 105.3 (C-2), 100.6 (–$OCH_2O$–), 18.3 (C-3′). Compound **1g**: 67% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.96 (2H, d, H-2 and H-6), 6.88 (1H, d, $J = 16.2$ Hz, H-1′), 6.45 (2H, d, H-3 and H-5), 6.31 (1H, m, H-2′), 3.83 (3H, s, $OCH_3$), 1.87 (3H, d, $J = 6.2$ Hz, H-3′); $^{13}$C NMR ($CDCl_3$) $\delta$ 155.3 (C-4), 131.5 (C-1′), 128.5 (C-3), 127.8 (C-5), 127.6 (C-2′), 126.0 (C-1), 110.4 (C-6), 108.7 (C-2), 56.0 (4-$OCH_3$), 18.8 (C-3′). Compound **1h**: 67% yield; mp 40–41 °C (reported as a liquid in literature[5]); $^1$H NMR ($CDCl_3$) $\delta$ 6.82 (1H, s, H-6), 6.54 (1H, d, $J = 16.2$ Hz, H-1′), 6.29 (1H, s, H-3), 5.96 (1H, m, H-2′), 3.66 (6H, s, 4-$OCH_3$ and 5-$OCH_3$), 3.60 (3H, s, 2-$OCH_3$), 2.08 (2H, m, H-3′), 0.93 (3H, t, $J = 7.1$ Hz, H-4′); $^{13}$C NMR ($CDCl_3$) $\delta$ 151.5 (C-4), 148.8 (C-5), 143.3 (C-2), 130.6 (C-1′), 123.2 (C-2′), 118.8 (C-1), 109.9 (C-6), 97.9 (C-3), 56.3 (4-$OCH_3$), 56.8 (5-$OCH_3$), 55.8 (2-$OCH_3$), 26.3 (C-3′), 14.3 (C-4′). Compound **1i**: 66% yield; liquid; $^1$H NMR ($CDCl_3$) 6.90–6.79 (3H, m, H-6, H-5, and H-2), 6.51 (1H, d, $J = 16.1$ Hz, H-1′), 5.42 (1H, m, H-2′), 3.84, 3.81 (each 3H, s, two $OCH_3$), 2.21 (2H, m, H-3′), 1.02 (3H, t, $J = 7.0$ Hz, H-4′); $^{13}$C NMR ($CDCl_3$) $\delta$ 149.4 (C-4), 148.3 (C-3), 130.2 (C-1′), 128.2 (C-2′), 123.8 (C-1), 118.7 (C-5), 108.5 (C-6), 97.9 (C-2), 56.2 (3-$OCH_3$) 55.9 (4-$OCH_3$), 25.7 (C-3′), 14.9 (C-4′). Compound **1j**: 43% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 6.96 (3H, m, H-6, H-2, and H-5), 6.70 (1H, d, $J = 16.2$ Hz, H-1′), 5.93 (1H, s, OH), 5.66 (1H, d, $J = 17.6$ Hz, H-2′a), 5.19 (1H, d, $J = 10.9$ Hz, H-2′b), 3.90 (3H, s, 3-OMe); $^{13}$C NMR ($CDCl_3$) $\delta$ 147.1 (C-4), 146.07 (C-3), 137.1 (C-1′), 130.3 (C-1), 120.1 (C-5), 114.5 (C-6), 111.4 (C-2′), 108.2 (C-2), 56.8 (3-$OCH_3$). Compound **1k**: 48% yield; liquid; $^1$H NMR ($CDCl_3$) $\delta$ 7.03 (1H, s, H-6), 6.94 (1H, d, $J = 16.5$ Hz, H-1′), 6.49 (1H, s, H-3), 5.62 (1H, d, $J = 17.6$ Hz, H-2′a), 5.18 (1H, d, $J = 10.8$ Hz, H-2′b), 3.88, 3.86, and 3.81 (each 3H, s, three $OCH_3$); $^{13}$C NMR ($CDCl_3$) $\delta$ 151.4 (C-4), 149.7 (C-5), 143.4 (C-2), 130.9 (C-1′), 118.6 (C-1), 112.0 (C-2′), 109.9 (C-6), 97.8 (C-3), 56.7 (4-$OCH_3$), 56.5 (5-$OCH_3$), 56.0 (2-$OCH_3$).

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