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Friedel-Crafts Reaction of Activated Benzene Rings with Captodative and Electron-Deficient Alkenes. A One-Step Synthesis of the Natural Product Methyl 3-(2,4,5-Trimethoxyphenyl)propio

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Friedel–Crafts Reaction of Activated Benzene Rings with Captodative and Electron-Deficient Alkenes. A One-Step Synthesis of the Natural Product Methyl 3-(2,4,5-Trimethoxyphenyl)propionate

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ABSTRACT

Electrophilic aromatic substitution of activated benzenes with the captodative olefin 1-acetylvinyl-1-*p*-nitrobenzoate (**9**), and with the electron-deficient alkenes methyl acrylate (**8a**), methylvinylketone (**8b**), and acrolein (**8c**) were evaluated under Lewis acid catalysis. Olefin **9** proved to be much more reactive than alkenes **8a**–**8c**. We also describe a one-step synthesis of the antifungal and larvicidal natural

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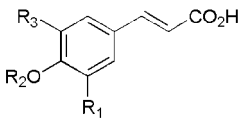
product methyl 3-(2,4,5-trimethoxyphenyl)propionate (**6**), by reaction of 1,2,4-trimethoxybenzene with **8a** under microwave irradiation.

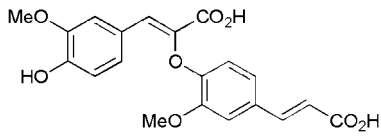
Key Words: Friedel–Crafts; Captodative olefins; Methyl 3-(2,4,5-trimethoxyphenyl)propionate.

INTRODUCTION

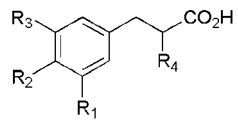
Antioxidant compounds of natural occurrence, containing the basic skeleton of cinnamic acid, have attracted wide interest because of their diverse biological properties. In particular, ferulic acid (**1**),[1] caffeic acid (**2**),[2] and analogs **3a**–**3c**[3] along with some of their dimers **4a**–**4b**,[4] are only a few of a long list of phenolic derivatives exhibiting hypolipidemic, anticancerigenic, antiinflamatory, antimicrobial, and antineoplastic activities.[1b,3,5] These compounds have been isolated from a variety of natural sources (for recent examples, see Ref.[6]). Among the natural derivatives containing a saturated side chain, one can find compounds **5a**–**5b** and the α-hydroxylated **5c**.[7] Recently, methyl 3-(2,4,5-trimethoxyphenyl)propionate (**6**) was isolated from the root bark of *Cordia alliodora*, showing high antifungal and larvicidal activities in biological tests.[8]



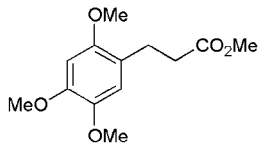
1, $R_1 = R_2 = H$, $R_3 = OMe$
2, $R_1 = R_2 = H$, $R_3 = OH$
3a, $R_1 = R_2 = R_3 = H$ (coumaric acid)
3b, $R_1 = H$, $R_2 = Me$, $R_3 = OH$ (isoferulic acid)
3c, $R_1 = R_3 = OMe$, $R_2 = H$ (sinapic acid)



4a



4b, $R_1 = H$, $R_2 = R_3 = OH$,
$R_4 = O_2CCH{=}CHC_6H_3\text{-}3,4\text{-}(OH)_2$
5a, $R_1 = R_4 = H$, $R_2 = OH$, $R_3 = OMe$
5b, $R_1 = R_3 = OMe$, $R_2 = OH$, $R_4 = H$
5c, $R_1 = R_2 = R_3 = H$, $R_4 = OH$



6

Several strategies have been pursued for the synthesis of this kind of structures. In most cases, they involve the combination of the preformed aryl scaffold with the carboxylic synthon, in order to introduce the propionic

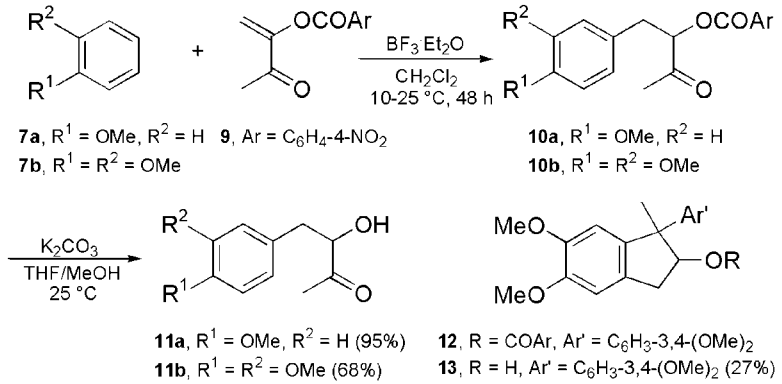
side chain. Common examples of this approach are the condensation between substituted benzaldehydes with malonic acid or malonates,[9] the Heck reaction starting from the aromatic ring and acrylates,[10] or conjugate addition of organocuprates to alkenoic acids and esters.[11]

The introduction of side chains in aromatic rings has been usually carried out by Friedel–Crafts acylation or alkylation with alkyl halides or alkenes.[12] However, conjugate addition of aryl rings to Michael acceptors promoted by Lewis acids, has been mostly limited due to several factors, among them: the difficulty of properly activating the starting substrates, finding optimum reaction conditions, or the formation of mixtures of isomers.[12,13]

As a continuation of our studies on the reactivity of the captodative olefins 1-acetylvinyl-1-arenecarboxylates,[14] and stimulated by the design and synthesis of promising hypolypidemic agents analogous to α-asarone,[15] herein we describe the Friedel–Crafts reactions of activated benzene rings with our captodative oefin **9** and other electron-deficient alkenes (**8a**–**8c**). We also report a straightforward synthesis, based in this methodology, of the natural compound **6**.

RESULTS AND DISCUSSION

Friedel–Crafts propionylation of anisole (**7a**) with either methyl acrylate (**8a**) or methyl vinyl ketone (**8b**), under anhydrous aluminum chloride, was unsuccessful. It is well known that phenols undergo alkylation satisfactorily under these acidic conditions only when the ring is sufficiently activated,[16] or with highly reactive Michael acceptors such as acrylonitrile.[17] In contrast, the captodative olefin 1-acetylvinyl-1-*p*-nitrobenzoate (**9**) reacted with **7a**,



Scheme 1.

Table 1. Friedel–Crafts reactions of substituted benzenes **7a**–**7d** with electrophiles **8a**–**8c** and **9**.[a]

Entry	Aryl[b]	Electrophile	Catalyst[c]	Solvent	T (°C)	t (hr)	Products (ratio)[d]	Yield (%)[e]
1	**7a**	**9**	BF_3Et_2O	CH_2Cl_2	25	48	**10a**	75
2	**7b**	**9**	BF_3Et_2O	CH_2Cl_2	10	48	**10b**	85
3	**7c**	**9**	$AlCl_3$	CH_2Cl_2	25	1	**15**	75
4	**7d**	**8a**	$AlCl_3$	$CHCl_2CHCl_2$	80	168	**6**	37
5	**7d**[f]	**8a**	$AlCl_3$	$CHCl_2CHCl_2$	80	8	**6**	66
6	**7d**	**8b**	$AlCl_3$	CH_2Cl_2	25	30	**17a**	78
7	**7d**	**8c**	$AlCl_3$	CH_2Cl_2	25	24	**17b**	75
8	**7d**	**9**	$AlCl_3$	CH_2Cl_2	25	0.5	**17c**	81

[a]All under N_2 atmosphere.
[b]A 5–10 mol equiv. of aryl compounds **7a** and **7b**, 1.0 mol equiv. of **7c**, and 0.1 mol equiv. of **7d**.
[c]A 2–10 mol equiv. of $BF_3 \cdot Et_2O$, and 1.1 mol equiv. of $AlCl_3$.
[d]Determined by ^1H NMR from the crude mixtures.
[e]Of the major isomer after column chromatography.
[f]Under MW irradiation.

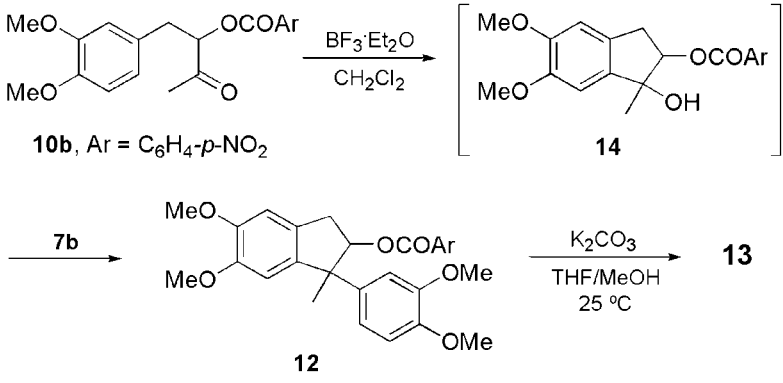
catalyzed by $BF3 \cdot Et_2O$ at room temperature, to give only the para isomer **10a** (Sch. 1) in 75% yield (Table 1). This behavior is different from that of captodative 2-chloroacrylonitrile, which affords a mixture of alkylation products: the para (major product) and ortho isomers and the bis adduct.[18]

The reactivity of **9** was assessed with less activated benzenes such as benzene itself, toluene, acetanilide, and iodobenzene, under similar conditions as before, but no condensation products were detected. It is known that only extremely reactive Michael acceptors such as vinylidene cyanide react with aromatic hydrocarbons similar to the above.[19]

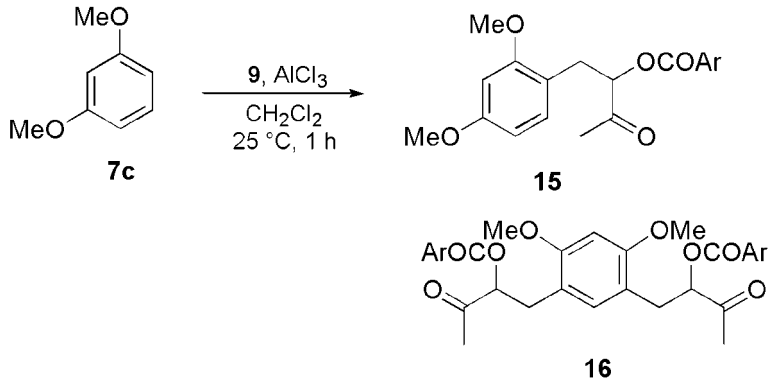
As expected, olefin **9** reacted with veratrol (**7b**) even at a lower reaction temperature (10°C) than that used for **7a**, providing the corresponding adduct **10b** in high yield (Table 1, entry 2). However, olefins **8a** and **8b** did not react with **7b** even in the presence of a large excess of other catalysts ($ZnCl_2$, $TiCl_4$, ZnI_2, and $AlCl_3$), different solvents ($CHCl_2CHCl_2$), temperatures (40°C and 140°C), or energy sources (microwaves), and most of the starting materials were recovered. Under any of these conditions, acrolein (**8c**) polymerizes rapidly.

When compounds **10a** and **10b** were treated with K_2CO_3 in a mixture of THF/MeOH (8 : 1), alcohols **11a** and **11b** were obtained in 95% and 68% yield, respectively (Sch. 1). These alcohols were stable at room temperature and they were purified via standard column chromatography on silica gel.

It is likely that the reactivity of benzenes activated with methoxy groups, in the presence of Lewis acids, was low due to coordination of the catalyst with these substituents.[13a] This hypothesis is supported by the fact that at room temperature, compound **10b** was obtained as a single product in the presence of a large excess of catalyst (10 mol equiv.), while an inseparable mixture of **10b** and a second product (**12**) was observed when only



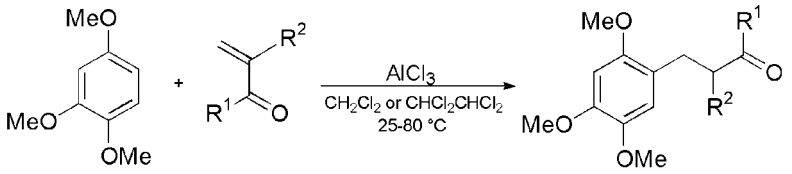
Scheme 2.



Scheme 3.

2 mol equiv. of catalyst were added (Sch. 1). When this mixture was hydrolyzed, compound **13** was isolated by column chromatography. The latter could arise from **10b** through a two-step process: (a) cyclization of **10b** to intermediate **14** due to the activated benzene ring and the electrophilicity of the carbonyl group;[20] (b) alkylation at the position of the tertiary benzylic alcohol of **14** by a second molecule of **7b** promoted by the catalyst (Sch. 2).

Resorcinol dimethyl ether (**7c**) would be expected to be more reactive in Friedel-Crafts reactions due to the synergistic electron-donor effect of the two methoxy groups. Indeed, when the reaction is carried out with methyl acrylate (**8a**), catalyzed by pyrophosphoric acid or $AlCl_3$, it proceeds in good yield to give mono- or bis-propionate condensation products.[21] We investigated the reaction of **7c** with the captodative alkene **9** in the presence of aluminum



7d

8a, R^1 = OMe, R^2 = H
8b, R^1 = Me, R^2 = H
8c, R^1 = R^2 = H
9, R^1 = Me, R^2 = $OCOC_6H_4$-4-NO_2

6, R^1 = OMe, R^2 = H
17a, R^1 = Me, R^2 = H
17b, R^1 = R^2 = H
17c, R^1 = Me,
R^2 = $OCOC_6H_4$-4-NO_2

Scheme 4.

chloride (Sch. 3), observing a faster condensation with respect to the experiments carried out with **7a** and **7b**, and furnishing the mono-adduct **15** as a single product (Table 1, entry 3); no traces of the bis adduct **16** were detected.

The significant biological activity of α- and β-asarones,[22] and of compound **6**,[8] which possess the 1,2,4-trimethoxyphenyl moiety, prompted us to evaluate the reactivity of 1,2,4-trimethoxybenzene (**7d**) with different Michael acceptors. Table 1 summarizes the results obtained in the condensation of **7d** with **8a**–**8c** and **9** catalyzed by anhydrous $AlCl_3$. Thus, when **8b** and **8c** reacted at room temperature in methylene chloride for more than 24 hr, products **17a** and **17b** were obtained in good yield (Sch. 4). Captodative olefin **9** proved again to be the most reactive electrophile, since it underwent very fast addition (30 min) (Table 1, entry 8) to give **17c** in high yield (Sch. 4). Even though methyl acrylate (**8a**) failed to give the expected product **6** under these conditions, the use of sym-tetrachloroethane[17] as solvent at 80°C for 1 week provided **6** in 37% yield. The reaction time was shortened and the yield improved by microwave irradiation (200 W) of the same mixture in a Teflon screw-capped glass tube at 80°C for 8 hr, giving **6** in 66% yield (Table 1, entry 5). The preparation of **6** represents, at present, the shortest synthesis of this biologically active natural product, since the previously reported syntheses, starting from β-asarone or asaraldehyde, furnished **6** in three steps.[23]

The higher reactivity of olefin **9**, when compared with that of **8a**–**8c**, in electrophilic aromatic substitution, may be explained on the basis of FMO arguments.[24] The energetically more favorable interaction is expected to be that between LUMOalkenes and HOMObenzenes. Calculation (HF/6-31G*) of the FMO energies of compounds **8b**, ethyl acrylate (**8d**), and **9** show that the LUMO energy of **9** is 0.4634 eV and 0.7350 eV lower than the LUMO energies of **8b** and **8d**, respectively.[25]

In summary, we have shown that captodative olefin **9** is a very reactive electrophile in Friedel-Crafts reactions catalyzed by Lewis acids, with activated benzene substrates containing 1–3 methoxy groups. 1,2,4-Trimethoxybenzene (**7d**) undergoes electrophilic aromatic substitution with monosubstituted electron-deficient olefins to give the mono-adduct as the main product. An efficient and total synthesis of the natural fungicide and antilarvarian compound **6** was accomplished in one step.

EXPERIMENTAL

General

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a

Perkin-Elmer 1600 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian Gemini-300 instrument, in $CDCl_3$ as solvent and TMS as internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained, in electron impact (EI) (70 eV) and FAB modes, on a Hewlett-Packard 5971A and on a Jeol JMS-SX 102 spectrometers, respectively. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ), and Centro de Investigaciones Químicas, Universidad Autónoma de Hidalgo (Pachuca, Hgo., Mexico). Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} (0.25 mm) plates, visualizing by long- and short-wavelength UV lamps. Microwave (MW) irradiation was performed on a SEV/MIC-1 MW reactor. All air and moisture sensitive reactions were carried out under nitrogen using oven-dried glassware. Methylene chloride and *sym*-tetrachloroethane were freshly distilled over calcium hydride, prior to use. All other reagents were used without further purification. Olefin **9** was prepared as reported.[14]

4-(*p*-Anisyl)-3-(*p*-nitrobenzoyloxy)-2-butanone (10a). To a solution of 0.20 g (0.85 mmol) of **9** in dry CH_2Cl_2 (8 mL), at 0°C, 0.24 g (1.70 mmol) of $BF_2 \cdot Et_2O$ and 0.92 g (8.52 mmol) of **7a** were successively added. The mixture was stirred at room temperature under nitrogen for 48 hr. EtOAc (75 mL) was added, and the mixture was washed with water (2 × 10 mL), saturated aqueous solution of $NaHCO_3$ (3 × 15 mL), and water until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc, 9 : 1) to give 0.22 g (75%) of **10a** as a yellow powder: R_f 0.7 (hexane/EtOAc, 7 : 3); mp 81–83°C; IR (CH_2Cl_2) 1726, 1611, 1525, 1345, 1280, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H, CH_3CO), 3.14 (dd, $J = 13.7$, 7.5 Hz, 1H, ArCH_2CH), 3.24 (dd, $J = 13.7$, 4.9 Hz, 1H, ArCH_2CH), 3.78 (s, 3H, OMe), 5.44 (dd, $J = 7.5$, 4.9 Hz, 1H, ArCH_2C*H*), 6.82–6.88 (m, 2H, ArH), 7.16–7.22 (m, 2H, ArH), 8.16–8.21 (m, 2H, ArH), 8.27–8.32 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.1 (*C*H_3CO), 35.9 (ArCH_2CH), 55.2 (MeO), 80.4 (Ar*C*H_2*C*H), 114.1 (ArH), 123.6 (ArH), 127.2 (Ar), 130.3 (ArH), 130.9 (ArH), 134.6 (Ar), 150.8 (Ar), 158.8 (Ar), 164.1 (*C*O_2Me), 204.3 (*C*OCH$_3$); MS (70 eV) m/z 150 ($M^+ - 193$, 100), 134 (5), 120 (9), 104 (36), 92 (19), 76 (27). Anal. calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.07. Found: C, 62.81; H, 4.78; N, 4.14.

4-(3,4-Dimethoxyphenyl)-3-(*p*-nitrobenzoyloxy)-2-butanone (10b). Following the method of preparation of **10a**, with 0.10 g (0.42 mmol) of **9** in dry CH_2Cl_2 (5 mL), 0.58 g (4.10 mmol) of $BF_3 \cdot Et_2O$ and 0.29 g (2.10 mmol) of **7b**, and stirred at 10°C for 48 hr, gave 0.135 g (85%) of **10b** as a pale yellow powder: R_f 0.3 (hexane/EtOAc, 7 : 3); mp 101–103°C; IR (CH_2Cl_2) 1719, 1524, 1352, 1273, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17

(s, 3H, CH_3CO), 3.15 (dd, $J = 14.4$, 7.9 Hz, 1H, $ArCH_2CH$), 3.24 (dd, $J = 14.4$, 5.3 Hz, 1H, $ArCH_2CH$), 3.84 (s, 3H, OMe), 3.85 (s, 3H, OMe), 5.47 (dd, $J = 7.9$, 5.2 Hz, 1H, $ArCH_2CH$), 6.70–6.92 (m, 3H, ArH), 8.16–8.38 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.1 (CH_3CO), 36.4 ($ArCH_2CH$), 55.80 (MeO), 55.85 (Me), 80.2 ($ArCH_2CH$), 111.2 (ArH), 112.3 (ArH), 121.4 (ArH), 123.6 (ArH), 127.6 (Ar), 130.8 (ArH), 134.6 (Ar), 148.2 (Ar), 148.9 (Ar), 150.7 (Ar), 164.0 (CO_2Me), 204.3 ($COCH_3$); MS (70 eV) m/z 175 ($M^+ - 197$, 51), 161 (56), 150 (37), 121 (100), 104 (27), 92 (10), 76 (17). Anal. calcd for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.20; H, 5.20; N, 3.62.

4-(*p*-Anisyl)-3-hydroxy-2-butanone (11a). To a solution of 0.10 g (0.27 mmol) of **10a** in dry THF (8 mL), at 0°C, 0.91 g (6.6 mmol) of K_2CO_3 in dry MeOH (1 mL) were added. The mixture was stirred at room temperature under nitrogen for 15 min. EtOAc (60 mL) was added and the mixture was washed with water until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (3 g, hexane/EtOAc, 8 : 2) to give 0.054 g (95%) of **11a** as a pale yellow oil: R_f 0.62 (hexane/EtOAc, 7 : 3); IR (film) 3465, 1714, 1611, 1513, 1357, 1300, 1247, 1178, 1111, 1086, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3CO), 2.84 (dd, $J = 14.3$, 7.1 Hz, 1H, $ArCH_2CH$), 3.09 (dd, $J = 14.3$, 4.7 Hz, 1H, $ArCH_2CH$), 3.38 (br s, 1H, OH), 3.78 (s, 3H, OMe), 4.36–4.39 (m, 1H, $ArCH_2CH$), 6.81–6.86 (m, 2H, ArH), 7.10–7.26 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.8 (CH_3CO), 39.1 ($ArCH_2CH$), 55.2 (MeO), 77.8 ($ArCH_2CH$), 114.0 (ArH), 128.4 (Ar), 130.2 (ArH), 158.6 (Ar), 209.2 ($COCH_3$); MS (70 eV) m/z 194 (M^+, 10), 176 (1), 121 (100), 107 (4), 91 (15), 77 (13). HRMS (FAB^+) [M^+] (*m*NBA) calcd for $C_{11}H_{14}O_3$: 194.0943. Found: 194.0948.

4-(3,4-Dimethoxyphenyl)-3-hydroxy-2-butanone (11b). Following the method of preparation of **11a**, with 0.11 g (0.29 mmol) of **10b**, and 0.91 g (6.6 mmol) of K_2CO_3, and stirring at room temperature for 24 hr, gave 0.045 g (68%) of **11b** as a yellow oil: R_f 0.18 (hexane/EtOAc, 7 : 3); IR (CH_2Cl_2) 3498, 1708, 1512, 1261, 1136, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H, CH_3CO), 2.84 (dd, $J = 14.3$, 7.1 Hz, 1H, $ArCH_2CH$), 3.10 (dd, $J = 14.3$, 4.7 Hz, 1H, $ArCH_2CH$), 3.41 (br s, 1H, OH), 3.86 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.36–4.43 (m, 1H, $ArCH_2CH$), 6.72–6.82 (m, 3H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.8 (CH_3CO), 39.5 ($ArCH_2CH$), 55.88 (MeO), 55.89 (MeO), 77.7 ($ArCH_2CH$), 111.4 (ArH), 112.7 (ArH), 121.2 (ArH), 129.0 (Ar), 148.2 (Ar), 149.1 (Ar), 209.1 ($COCH_3$); MS (70 eV) m/z 224 (M^+, 5), 151 (100), 137 (5), 121 (4), 107 (8), 91 (4), 77 (5). HRMS (FAB^+) [M^+] (*m*NBA) calcd for $C_{12}H_{16}O_4$: 224.1049. Found: 224.1045.

1-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-1-methyl-2-indanol (13). Following the method of preparation of **10a**, with 0.10 g (0.42 mmol) of **9** in dry CH_2Cl_2 (5 mL), 0.12 g (0.84 mmol) of $BF_3 \cdot Et_2O$, and 0.29 g (2.1 mmol) of **7b**, and stirring the mixture for 24 hr, gave a crude which was purified by column chromatography on silica gel (10 g, hexane/EtOAc, 8 : 2). Hydrolysis of the resultant product following the method of preparation of **11a**, yielded 0.04 g (27%) of **13** as a white powder: R_f 0.22 (hexane/EtOAc, 6 : 4); mp 65–67°C; IR (film) 3502, 1606, 1505, 1463, 1407, 1297, 1252, 1208, 1143, 1080, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H, CH_3), 1.87 (br s, 1H, OH), 2.79 (dd, $J = 15.4$, 6.3 Hz, 1H, H-3), 3.12 (dd, $J = 15.4$, 6.3 Hz, 1H, H-3), 3.77 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.44 (t, $J = 6.3$ Hz, 1H, H-2), 6.53 (s, 1H, ArH), 6.69–6.80 (m, 3H, ArH), 6.82 (s, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 19.8 (CH_3), 38.3 (C-3), 55.4 (C-1), 55.8 (2MeO), 55.9 (MeO), 56.1 (MeO), 83.8 (C-2), 107.7 (ArH), 108.0 (ArH), 110.6 (2Ar), 119.1 (ArH), 131.1 (Ar), 139.6 (Ar), 140.6 (Ar), 147.5 (Ar), 148.5 (Ar), 148.60 (Ar), 148.62 (Ar); MS (70 eV) m/z 344 (M^+, 35), 329 (8), 301 (14), 191 (100), 165 (20), 163 (22), 151 (20), 115 (7), 91 (6), 77 (6). HRMS (FAB^+) [M^+] (*m*NBA) calcd for $C_{20}H_{24}O_5$: 344.1624. Found: 344.1622.

4-(2,4-Dimethoxyphenyl)-3-(*p*-nitrobenzoyloxy)-2-butanone (15). Following the method of preparation of **10a**, with 0.102 g (0.43 mmol) of **9** in dry CH_2Cl_2 (5 mL), 0.058 g (0.43 mmol) of $AlCl_3$ and 0.06 g (0.43 mmol) of **7c**, gave 0.12 g (75%) of **15** as a pale yellow powder: R_f 0.76 (hexane/EtOAc, 7 : 3); mp 67–69°C; IR (CH_2Cl_2) 1719, 1610, 1587, 1526, 1464, 1345, 1208, 1115, 1102, 1034, 837, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H, CH_3CO), 3.04 (dd, $J = 14.1$, 8.1 Hz, 1H, ArCH_2CH), 3.30 (dd, $J = 14.1$, 5.2 Hz, 1H, ArCH_2CH), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 5.48 (dd, $J = 8.1$, 5.2 Hz, 1H, ArCH_2CH), 6.40–6.43 (m, 3H, ArH), 7.10 (d, $J = 8.1$ Hz, 1H, ArH), 8.14–8.28 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.8 (CH_3CO), 31.0 (ArCH_2CH), 55.2 (MeO), 55.3 (MeO), 79.2 (ArCH_2CH), 98.4 (ArH), 104.0 (ArH), 115.9 (Ar), 123.5 (ArH), 130.8 (ArH), 131.5 (ArH), 134.9 (Ar), 150.5 (Ar), 158.2 (Ar), 160.3 (Ar), 164.0 (CO_2Me), 204.1 ($COCH_3$); MS (70 eV) m/z 373 (M^+, 3), 206 (30), 191 (23), 175 (43), 151 (100), 121 (24), 104 (16), 76 (10). HRMS (FAB^+) [M^+] (mNBA) calcd for $C_{19}H_{19}NO_7$: 373.1162. Found: 373.1162.

4-(2,4,5-Trimethoxyphenyl)-2-butanone (17a).[26] To a solution of 0.25 g (1.49 mmol) of **7d** in dry CH_2Cl_2 (5 mL), at 0°C under nitrogen, 0.20 g (1.49 mmol) of $AlCl_3$ and 1.043 g (14.9 mmol) of **8b** were successively added. The mixture was stirred at room temperature for 30 hr. EtOAc (75 mL) was added, and the mixture was washed with water (2 × 10 mL), saturated aqueous solution of $NaHCO_3$ (3 × 15 mL), and water until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under

vacuum. The residue was purified by column chromatography on silica gel (10 g, hexane/EtOAc, 9 : 1) to give 0.276 g (78%) of **17a** as a yellow powder: R_f 0.74 (hexane/EtOAc, 7 : 3); mp 52–54°C; IR (CH_2Cl_2) 1708, 1609, 1512, 1459, 1399, 1359, 1315, 1273, 1201, 1120, 1031, 853, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3CO), 2.66–2.74 (m, 2H, $ArCH_2CH_2CO$), 2.77–2.85 (m, 2H, $ArCH_2CH_2CO$), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.51 (s, 1H, ArH), 6.71 (s, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.5 ($ArCH_2CH_2CO$), 29.9 (CH_3CO), 44.1 ($ArCH_2CH_2CO$), 56.11 (MeO), 56.15 (MeO), 56.5 (MeO), 97.5 (ArH), 114.2 (ArH), 120.6 (Ar), 142.6 (Ar), 147.8 (Ar), 151.4 (Ar), 208.8 ($COCH_3$); MS (70 eV) m/z 238 (M^+, 59), 223 (6), 196 (7), 181 (100), 151 (28), 136 (6), 121 (4), 91 (4), 77 (5). Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.55; H, 7.41.

3-(2,4,5-Trimethoxyphenyl)propionaldehyde (17b).[27] Following the method of preparation of **17a**, with 0.834 g (14.9 mmol) of **8c**, and stirring for 24 hr, gave 0.25 g (75%) of **17b** as a pale yellow oil: R_f 0.72 (hexane/EtOAc, 7 : 3); IR (CH_2Cl_2) 1717, 1608, 1511, 1459, 1397, 1316, 1202, 1119, 1030, 859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (br t, $J = 7.3$ Hz, 2H, $ArCH_2CH_2CO$), 2.88 (t, $J = 7.3$ Hz, 2H, $ArCH_2CH_2CO$), 3.80 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.51 (s, 1H, ArH), 6.71 (s, 1H, ArH), 9.80 (s, 1H, CHO); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 23.0 ($ArCH_2CH_2CO$), 44.2 ($ArCH_2CH_2CO$), 56.0 (MeO), 56.1 (MeO), 56.6 (MeO), 97.4 (ArH), 114.1 (ArH), 119.8 (Ar), 142.6 (Ar), 148.0 (Ar), 151.3 (Ar), 202.6 (CHO); MS (70 eV) m/z 224 (M^+, 59), 209 (4), 181 (100), 168 (35), 151 (34), 136 (11), 121 (9), 91 (9), 77 (14). Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.18; H, 6.95.

3-(*p*-Nitrobenzoyloxy)-4-(2,4,5-trimethoxyphenyl)-2-butanone (17c). Following the method of preparation of **17a**, with 0.348 g (1.49 mmol) of **9**, and stirring for 30 min, gave 0.486 g (81%) of **17c** as a yellow powder: R_f 0.71 (hexane/EtOAc, 7 : 3); mp 77–79°C; IR (CH_2Cl_2) 1719, 1608, 1522, 1464, 1439, 1401, 1344, 1279, 1214, 1224, 1118, 1102, 1014, 853, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H, CH_3CO), 3.06 (dd, $J = 14.1$, 8.1 Hz, 1H, $ArCH_2CH$), 3.31 (dd, $J = 14.1$, 5.1 Hz, 1H, $ArCH_2CH$), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.49 (dd, $J = 8.1$, 5.1 Hz, 1H, $ArCH_2CH$), 6.51 (s, 1H, ArH), 6.74 (s, 1H, ArH), 8.15–8.19 (m, 2H, ArH), 8.26–8.30 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 26.9 (CH_3CO), 31.1 ($ArCH_2CH$), 55.9 (MeO), 56.1 (Me), 56.6 (MeO), 79.3 ($ArCH_2CH$), 96.9 (ArH), 114.6 (ArH), 115.2 (Ar), 123.5 (ArH), 130.8 (ArH), 134.9 (Ar), 142.6 (Ar), 149.0 (Ar), 150.6 (Ar), 151.7 (Ar), 164.0 (CO_2Me), 204.1 ($COCH_3$); MS (70 eV) m/z 403 (M^+, 9), 236 (8), 205 (54), 181 (100), 151 (21), 150 (20), 136 (7), 104 (12), 76 (6). HRMS (FAB^+) [M^+] (*m*NBA) calcd for $C_{20}H_{21}NO_8$: 403.1267. Found: 403.1270.

Methyl 3-(2,4,5-trimethoxyphenyl)propionate (6).[8] Method A: Following the method of preparation of **17a**, with 1.28 g (14.9 mmol) of **8a** (adding in 1 mol equiv. each portion every 3 hr) in *sym*-tetrachloroethane as solvent (7 mL), and stirring for 1 week, gave 0.14 g (37%) of **6** as a white gum. Method B: Following method A, stirring under MW irradiation (200 W) to 80°C for 8 hr in a Teflon screw-capped ACE pressure tube, gave 0.249 g (66%) of **6** as a white gum. R_f 0.69 (hexane/EtOAc, 7 : 3); mp 50–52°C; IR (CH_2Cl_2) 1733, 1609, 1513, 1444, 1399, 1312, 1290, 1204, 1123, 1034, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (t, $J = 7.8$ Hz, 2H, $ArCH_2CH_2CO$), 2.85 (t, $J = 7.8$ Hz, 2H, $ArCH_2CH_2CO$), 3.64 (s, 3H, CO_2Me), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.48 (s, 1H, ArH), 6.69 (s, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 25.6 ($ArCH_2CH_2CO$), 34.4 ($ArCH_2CH_2CO$), 51.4 (CO_2CH_3), 56.05 (MeO), 56.10 (MeO), 56.5 (MeO), 97.4 (ArH), 114.1 (ArH), 120.1 (Ar), 142.6 (Ar), 147.9 (Ar), 151.4 (Ar), 173.7 (CO_2CH_3); MS (70 eV) m/z 254 (M^+, 41), 239 (10), 211 (6), 181 (100), 151 (29), 121 (4), 91 (3), 77 (5). HRMS (FAB^+) [M^+] (*m*NBA) calcd for $C_{13}H_{18}O_5$: 254.1154. Found: 254.1161.

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