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ORIGINAL ARTICLE

Convenient synthesis of 3,5-dialkoxy-4-hydroxy cinnamic acids

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Summary
3,5-Dialkoxy-4-hydroxy cinnamic acids **8a-g** have been conveniently synthesized from methyl 4-benzyloxy-3,5-dihydroxybenzoate **4**. In five steps, cinamic acids **8a-g** having various alkoxy groups on C-3 and C-5 positions of the phenyl ring were obtained in 33-70 % overall yields. The antioxidant properties of the newly synthesized amides and the effects on lipid peroxidation in rat brain homogenate will be examined by thiobarbituric acid reactive substances (TBARS) assay and other methods.

Keywords: 3,5-dialkoxy-4-hydroxy cinnamic acids – dialkylation – lipid peroxidation

INTRODUCTION

Reactive oxygen species (ROS) are by-products of the normal metabolic processes in aerobic environments (Chance et al. 1979), and they have been recognized as playing an important role in the initiation and/or progression of various diseases such as ischemia-reperfusion injury, atherosclerosis, and inflammatory injury (Clemens et al. 2000, Keyser et al. 1999, Yamaguchi et al. 1998). Examples of ROS are superoxide, hydrogen peroxide, and hydroxyl radicals (Halliwell et al. 1999). Elimination of ROS is provided by enzymatic and nonenzymatic mechanisms. Natural enzymatic antioxidants include superoxide dismutase, catalase, and glutathione peroxidase which catalytically detoxify ROS, whereas unnatural nonenzymatic antioxidants are primarily reducing agents, such as vitamin C, vitamin E, and glutathione, which can scavenge ROS by hydrogen atom donation in a stochiometric manner. There is growing interest in unnatural antioxidants as a protective strategy against the various neurodegenerative diseases by a block in or removal of oxidative stresses (Harrison et al. 1994).

In the course of the development of new antioxidants as neuroprotective agents, we have been interested in novel 4-hydroxyphenylacetic acid amides and 4-hydroxycinnamamides (Jung et al. 2002). Among the prepared compounds, 3,4-dihydroxycinnamamide **1** exhibited potent inhibition of lipid peroxidation. 3-Alkoxy-4-hydroxyphenylacetic acid amides **2** also provided strong activity and we found that the chain length of the alkoxy group of **2** is important in showing the high lipid peroxidation activity. Based on these

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results, the newly designed 3,5-dialkoxy-4-hydroxycinnamamides **3** as hybrid compounds of antioxidants **1** and **2** were expected to possess strong lipid peroxidation activity. Therefore we needed 3,5-dialkoxy-4-hydroxycinnamic acids **8** as key intermediates for the synthesis of the new antioxidants **3** (Fig. 1).

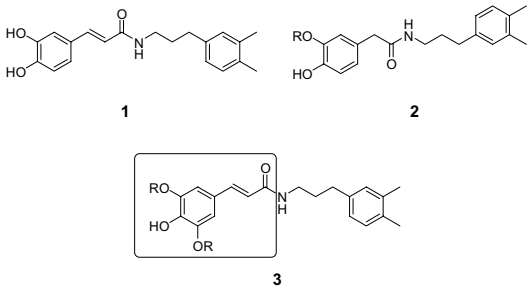


Fig. 1. **Structure of potential antioxidants**

MATERIALS AND METHODS

Synthesis

All reactions were carried out under N_2 atmosphere unless otherwise noted. MeCN was distilled from CaH_2 prior to use. Organic extracts or filtrates were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography was performed with Merck-EM Type 60 (230-400 mesh) silica gel. ^{1}H NMR spectra were measured in $CDCl_3$ by Varian Gemini 200 MHz spectrometers. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Mass spectrometric data determined by use of the electron impact (EIMS) method are reported as m/z (relative intensity). Melting points (m.p.) were uncorrected.

General Method for Preparation of Methyl 4-benzyloxy-3,5-dialkoxybenzoate 5

In a typical alkylation of the methyl 4-benzyloxy-3,5-dihydroxy-benzoate **4**, a mixture of **4** (10.0 g, 36 mmol), 1-iodopropane (10.7 ml, 110 mmol), TBAI (404 mg, 1.1 mmol) and K_2CO_3 (10.1 g, 110 mmol) in DMF (30 ml) was heated at 120 ^{o}C for 2 h. The mixture was neutralized with 1N HCl and extracted with EtOAc. The organic layer was washed with 1N HCl, aqueous $NaHSO_4$, and brine. The resulting residue was subjected to fresh column chromatography (EtOAc:Hexane=1:25) to provide methyl 4-benzyloxy-3,5-dipropoxybenzoate **5a** as an oil (10.0 g, 78%).

5a: ^{1}H NMR δ1.05 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.74-1.90 (m, 4H, $2\underline{CH_2}CH_3$), 3.89 (s, 3H, OCH_3), 3.99 (t, J = 6.5 Hz, 4H, $2OCH_2$), 5.09 (s, 2H, OCH_2Ph), 7.27 (s, 2H, ArH), 7.30-7.53 (m, 5H, ArH).

5b: ^{1}H NMR δ0.97 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.45-1.60 (m, 4H, $2\underline{CH_2}CH_3$), 1.73-1.87 (m, 4H, $2\ OCH_2\underline{CH_2}$), 3.89 (s, 3H, $O\underline{CH_3}$), 4.02 (t, J = 6.4 Hz, 4H, $2OCH_2$), 5.08 (s, 2H, $\underline{CH_2}Ph$), 7.03-7.51 (m, 7H, ArH).

5c: ^{1}H NMR δ0.95 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.39-1.53 (m, 8H, $2(\underline{CH_2})_2CH_3$), 1.80-1.87 (m, 4H, $2OCH_2\underline{CH_2}$), 3.89 (s, 3H, OCH_3), 4.03 (t, J = 4.3 Hz, 4H, $2OCH_2$), 5.12 (s, 2H, CH_2Ph), 7.29 (s, 2H, ArH), 7.32-7.55 (m, 5H, ArH).

5d: ^{1}H NMR δ0.93 (t, J = 7.1 Hz, 6H, $2CH_2\underline{CH_3}$), 1.28 (d, J = 5.9 Hz, 6H, $2CH\underline{CH_3}$), 1.34-1.78 (m, 8H, $2(\underline{CH_2})\ _2CH_3$), 3.89 (s, 3H, OCH_3), 4.40-4.48 (m, 2H, 2CH), 5.04 (s, 2H, CH_2Ph), 7.25-7.52 (m, 7H, ArH).

5f: ^{1}H NMR δ0.90 (t, J = 5.7 Hz, 6H, $2CH_3$), 1.28-1.48 (m, 12H, $2(CH_2)_3$), 1.61-1.86 (m, 4H, $2OCH_2\underline{CH_2}$), 3.88 (s, 3H, OCH_3), 4.02-4.09 (m, 4H, $2OCH_2$), 5.13 (s, 2H, CH_2Ph), 7.26-7.49 (m, 7H, ArH).

5g: ^{1}H NMR δ0.86-0.89 (m, 6H, $2CH_3$), 1.30-1.56 (m, 16H, $2(CH_2)_4$), 1.78-1.85 (m, 4H, $2OCH_2\underline{CH_2}$), 3.90 (s, 3H, OCH_3), 4.02 (t, J = 6.5 Hz, 4H, $2OCH_2$), 5.08 (s, 2H, CH_2Ph), 7.25-7.51 (m, 7H, ArH).

5h: ^{1}H NMR δ0.89 (t, J = 5.1 Hz, 6H, $2CH_3$), 1.30-1.57 (m, 24H, $2(\underline{CH_2})_6CH_3$), 1.79-1.86 (m, 4H, $2OCH_2\underline{CH_2}$), 3.90 (s, 3H, OCH_3), 4.02 (t, J = 6.5 Hz, 4H, $2OCH_2$), 5.09 (s, 2H, CH_2Ph), 7.26 (s, 2H, ArH), 7.31-7.51 (m, 5H, ArH).

General Method for Preparation of Methyl 3,5-dialkoxy-4-hydroxybenzoate 6

In a typical reduction of the methyl 4-benzyloxy-3,5-dialkoxybenzoate **5**, a mixture of **5a** (6.60 g, 0.018 mmol) and 10% Pd/C (530 mg) in EtOAc (100 ml) was stirred under an H_2 balloon for 1 h. The mixture was passed over a celite pad and the filtrate was concentrated to provide a solid **6a** (4.28 g, 89%).

6a: ^{1}H NMR δ1.05 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.82-1.92 (m, 4H, $2\underline{CH_2}CH_3$), 3.89 (s, 3H, OCH_3), 4.06 (t, J = 6.5 Hz, 4H, $2OCH_2$), 5.90 (s, 1H, OH), 7.30 (s, 2H, ArH); m.p. 87-89 ^{o}C.

6b: ^{1}H NMR δ0.98 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.45-1.57 (m, 4H, $2\underline{CH_2}CH_3$), 1.79-1.86 (m, 4H, $2OCH_2\underline{CH_2}$), 3.89 (s, 3H, OCH_3), 4.10 (t, J = 6.5 Hz, 4H, $2OCH_2$), 5.88 (s, 1H, OH), 7.30 (s, 2H, ArH).

6c: ^{1}H NMR δ0.93 (t, J = 7.1 Hz, 6H, $2CH_3$), 1.43-1.45 (m, 8H, $2(\underline{CH_2})_2CH_3$), 1.81-1.84 (m, 4H, $2OCH_2\underline{CH_2}$), 3.89 (s, 3H, OCH_3), 4.09 (t, J = 6.7 Hz, 4H, OCH_2), 5.89 (s, 1H, OH), 7.29 (s, 2H, ArH); m.p. 59-61 ^{o}C.

6d: ^{1}H NMR δ0.94 (t, J = 7.3 Hz, 6H, $2CH_3$), 1.32 (d, J = 6.1 Hz, 6H, $2CH\underline{CH_3}$), 1.39-1.90 (m, 8H, $2(\underline{CH_2})\ _2CH_3$), 3.88 (s, 3H, OCH_3), 4.40-4.57 (m, 2H, 2CH), 5.96 (s, 1H, OH), 7.29 (s, 2H, ArH)

6e: ^{1}H NMR δ0.96 (t, J = 7.3 Hz, 12H, $4CH_3$), 1.71 (qui, J = 6.5 Hz, 8H, $4CH_2$), 3.87 (s, 3H, OCH_3), 4.23 (qui, J = 5.8 Hz, 2H, 2CH), 6.01 (s, 1H, OH), 7.26 (s, 2H, ArH).

6g: ^{1}H NMR δ0.89 (t, *J* = 6.9 Hz, 6H, 2CH_3), 1.30-1.45 (m, 16H, 2($\underline{CH_2}$)$_4$$CH_3$), 1.79-1.83 (m, 4H, 2O$CH_2\underline{CH_2}$), 3.88 (s, 3H, OCH_3), 4.05-4.11 (m, 4H, 2OCH_2), 5.87 (s, 1H, OH), 7.29 (s, 2H, ArH).
6h: ^{1}H NMR δ0.88 (t, *J* = 5.5 Hz, 6H, 2CH_3), 1.34-1.60 (m, 16H, 2($\underline{CH_2}$)$_2$$CH_3$), 1.80-1.86 (m, 4H, 2O$CH_2\underline{CH_2}$), 3.90 (s, 3H, OCH_3), 4.02 (t, *J* = 6.4 Hz, 4H, 2OCH_2), 5.10 (s, 2H, CH_2Ph), 7.26 (s, 2H, ArH), 7.31-7.51 (m, 5H, ArH); m.p. 45-47 °C.

General Method for Preparation of 3,5-Dialkoxy-4-hydroxybenzaldehyde 7

In a typical reduction of the Methyl 3,5-dialkoxy-4-hydroxybenzoate **6**, a mixture of **6a** (4.28 g, 0.016 mol) and $LiAlH_4$ (1.21 mg, 0.032 mmol) was stirred at *r.t.* for 1.5 h. The mixture was acidified with 1N HCl and then extracted with EtOAc. The organic solution was concentrated and the crude was recrystallized from EtOAC and hexane to provide benzyl alcohol (3.58 g, 93%). A mixture of the benzyl alcohol (3.58 g, 0.015 mol) and PCC (6.42 g, 0.030 mol) in CH_2Cl_2 (150 ml) was stirred at *r.t.* for 1 h. The mixture was passed over a celite pad and the filtrate was concentrated to provide a solid **7a** (1.86 g, 52%).
7a: ^{1}H NMR δ1.06 (t, *J* = 7.3 Hz, 6H, 2CH_3), 1.80-1.98 (m, 4H, 2$\underline{CH_2}CH_3$), 4.09 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 6.05 (s, 1H, OH), 7.12 (s, 2H, ArH), 9.79 (s, 1H, CHO); m.p. 52-54 °C.
7b: ^{1}H NMR δ0.99 (t, *J* = 7.3 Hz, 6H, 2CH_3), 1.51 (sex, *J* = 7.5 Hz, 4H, 2CH_2), 1.84 (qui, *J* = 6.8 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.12 (t, *J* = 6.6 Hz, 4H, 2OCH_2), 6.08(s, 1H, OH), 7.12 (s, 2H, ArH), 9.79 (s, 1H, CHO).
7c: ^{1}H NMR δ0.94 (t, *J* = 7.2 Hz, 6H, 2CH_3), 1.35-1.50 (m, 8H, 4CH_2), 1.86 (qui, *J* = 6.9 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.11 (t, *J* = 6.6 Hz, 4H, 2OCH_2), 6.09 (s, 1H, OH), 7.12 (s, 2H, ArH), 9.79 (s, 1H, CHO).
7d: ^{1}H NMR δ0.95 (t, *J* = 7.1 Hz, 6H, 2CH_3), 1.34 (d, *J* = 6.1 Hz, 6H, 2CH$\underline{CH_3}$), 1.39-1.87 (m, 8H, 2(CH_2)$_2$), 4.45-4.54 (m, 2H, 2CH), 6.08 (s, 1H, OH), 7.10 (s, 2H, ArH), 9.77 (s, 1H, CHO).
7e: ^{1}H NMR δ0.99 (t, *J* = 7.4 Hz, 12H, 4CH_3), 1.74 (qui, *J* = 6.9 Hz, 8H, 4CH_2), 4.27 (qui, *J* = 5.9 Hz, 2H, 2CH), 6.13 (s, 1H, OH), 7.09 (s, 2H, ArH), 9.77 (s, 1H, CHO).
7f: ^{1}H NMR δ0.90 (t, *J* = 6.7 Hz, 6H, 2CH_3), 1.28-1.46 (m, 12H, 2($\underline{CH_2}$)$_3$), 1.76-1.90 (m, 4H, 2O$CH_2\underline{CH_2}$), 3.90 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 5.79 (s, 2H, ArH), 9.77 (s, 1H, CHO).
7g: ^{1}H NMR δ0.89 (t, *J* = 6.3 Hz, 6H, 2CH_3), 1.31-1.45 (m, 16H, 2(CH_2)$_4$), 1.85 (qui, *J* = 7.1 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.11 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 6.05 (s, 1H, OH), 7.11 (s, 2H, ArH), 9.79(s, 1H, CHO).
7h: ^{1}H NMR δ0.88 (t, *J* = 6.4 Hz, 6H, 2CH_3), 1.27-1.45 (m, 24H, 2(CH_2)$_6$), 1.85 (qui, *J* = 7.2 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.11 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 6.10 (s, 1H, OH), 7.12 (s, 2H, ArH), 9.78 (s, 1H, CHO).

General Method for Preparation of 3,5-Dialkoxy-4-hydroxycinamic acid 8

In a typical preparation of the 3,5-dialkoxy-4-hydroxycinamic acid **8**, a mixture of **7a** (1.86 g, 7.81 mmol) and malonic acid (3.25 g, 31.2 mmol) in pyridine (10 ml) was stirred at 60-70 °C for 3 h. The mixture was acidified with 1N HCl and extracted with EtOAc. The crude was subjected to fresh column chromatography (EtOAc:Hexane=1:2) and then recrystallized from EtOAc and hexane to provide **8a** as a solid (1.90 g, 87%).

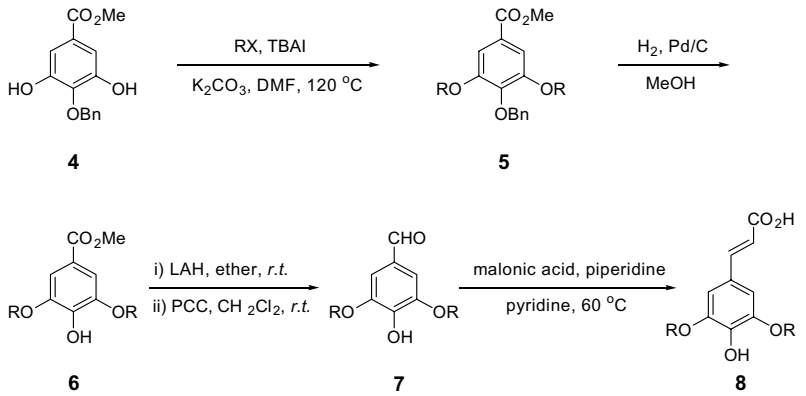
8a: ^{1}H NMR δ1.06 (t, *J* = 7.3 Hz, 6H, 2CH_3), 1.79-1.93 (m, 4H, 2$\underline{CH_2}CH_3$), 4.04 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 6.29 (d, *J* = 15.9 Hz, 1H, CO$\underline{CH}$=CH), 6.79 (s, 2H, ArH), 7.68 (d, *J* = 15.9 Hz, 1H, COCH=$\underline{CH}$); m.p. 152-153 °C.
8b: ^{1}H NMR δ0.99 (t, *J* = 7.3 Hz, 6H, 2CH_3), 1.50 (sex, *J* = 7.5 Hz, 4H, 2CH_2), 1.83 (qui, *J* = 7.2 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.07 (t, *J* = 6.6 Hz, 4H, 2OCH_2), 6.28(d, *J* = 15.8 Hz, 1H, CO$\underline{CH}$=CH), 6.78 (s, 2H, ArH), 7.68 (d, *J* = 15.8 Hz, 1H, COCH=$\underline{CH}$).
8c: ^{1}H NMR δ0.94 (t, *J* = 7.0 Hz, 6H, 2CH_3), 1.34-1.48 (m, 8H, 2(CH_2)$_2$), 1.85 (qui, *J* = 7.0 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.07 (t, *J* = 6.6 Hz, 4H, 2OCH_2), 6.28 (d, *J* = 15.8 Hz, 1H, CO$\underline{CH}$=CH), 6.78 (s, 2H, ArH), 7.68 (d, *J* = 15.8 Hz, 1H, COCH=$\underline{CH}$); m.p 87-88 °C.
8d: ^{1}H NMR δ0.96 (t, *J* = 7.1 Hz, 6H, 2CH_3), 1.33 (d, *J* = 6.1 Hz, 6H, 2CH$\underline{CH_3}$), 1.39-1.86 (m, 8H, 2(CH_2)$_2$), 4.38-4.47 (m, 2H, 2CH), 6.26 (d, *J* = 15.9 Hz, 1H, CO$\underline{CH}$=CH), 6.78 (s, 2H, ArH), 7.67 (d, *J* = 15.9 Hz, 1H, COCH=$\underline{CH}$); m.p. 75-85 °C.
8e: ^{1}H NMR δ0.99 (t, *J* = 7.4 Hz, 12H, 4CH_3), 1.66-1.80 (m, 8H, 4CH_2), 4.19 (qui, *J* = 5.9 Hz, 2H, 2CH), 6.26 (d, *J* = 15.7 Hz, 1H, CO$\underline{CH}$=CH), 6.77 (s, 2H, ArH), 7.67 (d, *J* = 15.7 Hz, 1H, COCH=$\underline{CH}$); m.p. 105-110 °C.
8f: ^{1}H NMR δ0.91-0.94 (m, 6H, 2CH_3), 1.26-1.48 (m, 12H, 2(CH_2)$_3$), 1.77-1.88 (m, 4H, 2O$CH_2\underline{CH_2}$), 4.07 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 6.28 (d, *J* = 15.9 Hz, 1H, CO$\underline{CH}$=CH), 6.78 (s, 2H, ArH), 7.68 (d, *J* = 15.9 Hz, 1H, COCH=$\underline{CH}$); m.p. 102-105 °C.
8g: ^{1}H NMR δ0.90 (t, *J* = 6.4 Hz, 6H, 2CH_3), 1.30-1.45 (m, 16H, 2(CH_2)$_4$), 1.87 (qui, *J* = 7.1 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.06 (t, *J* = 6.6 Hz, 4H, 2OCH_2), 6.28 (d, *J* = 15.8 Hz, 1H, CO$\underline{CH}$=CH), 6.78 (s, 2H, ArH), 7.67 (d, *J* = 15.8 Hz, 1H, COCH=$\underline{CH}$); m.p 84-85 °C.
8h: ^{1}H NMR δ 0.88 (t, *J* = 6.4 Hz, 6H, 2CH_3), 1.28-1.45 (m, 24H, 2(CH_2)$_6$), 1.85 (qui, *J* = 7.2 Hz, 4H, 2O$CH_2\underline{CH_2}$), 4.07 (t, *J* = 6.7 Hz, 4H, 2OCH_2), 6.29 (d, *J* = 15.9 Hz, 1H, CO$\underline{CH}$=CH), 6.78 (s, 2H, ArH), 7.68 (d, *J* = 15.9 Hz, 1H, COCH=$\underline{CH}$); m.p 81-82 °C.

RESULTS AND DISCUSSION

In the course of our research aimed at the development of new 3,5-dialkoxy-4-hydroxy cinnamic acid amides **3** as antioxidants, we needed 3,5-dialkoxy-4-hydroxy cinnamic acids **8**, which contain various alkoxy groups on C-3 and C-5 positions of the phenyl ring. In the literature, 3,5-dialkoxy-4-hydroxy cinnamic acids **8** had not been described. Thus, a general synthetic method of 3,5-dialkoxy-4-hydroxy cinnamic acids **8** from methyl 4-benzyloxy-3,5-dihydroxy-benzoate **4** through four consequent steps was developed; (1) dialkylation of methyl 4-benzyloxy-3,5-dihydroxy-benzoate with benzyl bromide, (2) debenzylation, (3) reduction and oxidation of methyl benzoate, and (4) coupling of benzaldehyde with malonic acid (Scheme 1).

Table 1. **Yields of compounds 5, 6, 7, and 8**

entry	R	Yield(%)			
		5	6	7	8
a	$CH_2CH_2CH_3$	78	89	93	87
b	$CH_2(CH_2)_2CH_3$	97	100	93	67
c	$CH_2(CH_2)_3CH_3$	82	100	98	87
d	$CH(CH_3)(CH_2)_2CH_3$	68	100	99	58
e	$CH(CH_2CH_3)_2$	68	100	99	57
f	$CH_2(CH_2)_4CH_3$	86	100	98	60
g	$CH_2(CH_2)_5CH_3$	78	100	84	72
h	$CH_2(CH_2)_7CH_3$	69	100	70	69



Scheme 1. **Synthesis of 3,5-dialkoxy-4-hydroxy cinnamic acids**

Methyl 4-benzyloxy-3,5-dihydroxy-benzoate **4** was easily obtained from the benzylation of methyl gallate (Yu et al. 1993, Mannekens et al. 2000). Dialkylation of **4** with the corresponding alkyl bromides or alkyl iodides was attempted in refluxing methyl isobutyl ketone or in DMF at 120 °C in the presence of tetrabutylammonium iodide (TBAI) (Hersmis et al. 2001). Methyl 3,5-dialkoxy-4-hydroxybenzoates **6** were obtained as a quantitative yield from the crude mixture **5** stirring

with palladium carbon in methanol under hydrogen atmosphere. Attempts to reduce 3,5-dialkoxy-4-hydroxybenzoates **6** with LAH in THF followed by oxidation with PCC resulted in the aldehydes **7** in 64–100% yields. Coupling of the aldehydes **7** with malonic acid and piperidine in pyridine provided the cinnamic acids **8** in moderate yields (57–87%) (Kingsbury and Max 1978). The yields of each compound are shown in Table 1.

The antioxidant properties of the newly synthesized amides and the effects on lipid peroxidation in rat brain homogenate will be examined by thiobarbituric acid reactive substances (TBARS) assay and other methods, and the detailed results will be discussed in due course.

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