Stereoselective Synthesis of 2-Aryltetrahydrofuran-3,4-dicarboxylate Derivatives: Efficient Approach to Tetrahydrofuran Lignans

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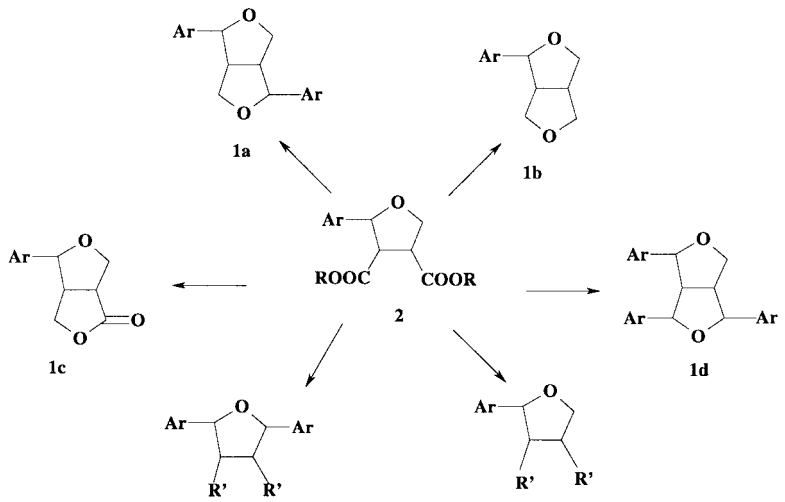
Abstract: A convenient and stereoselective synthetic route to the precursor of natural products, lignans, containing tetrahydrofuran has been developed. A series of asymmetric 2-aryltetrahydrofuran-3,4-carboxylic acid derivatives were synthesized in high yields with this route. The effect of substituents on the Diels−Alder reaction of aryl-substituted oxazoles with alkyne dienophile and on the catalytic hydrogenation of dimethyl 2-arylfuran-3, 4-dicarboxylates has been investigated. The regioselective hydrolyses of the dimethyl ester group was also studied. All products were characterized by elemental analysis, FT-IR, ^{1}H NMR and MS.

Key words: stereoselectivity, Diels−Alder reactions, hydrogenation, hydrolysis, furans

As a major group of natural products, lignans, which widely exist in all parts of various plants, is still receiving considerable interest due to their special biological properties. They present significant activities, such as anti-tumor, antimitotic, antiviral activities and inhibition of specific enzymes.[1] Recently, some derivatives of podophyllotoxin have been used in the clinic. Among the family of lignans, 2-aryl, 2,5-diaryltetrahydrofuran and aryl-substituted 3,7-dioxabicyclo[3.3.0]octane **1** (aryl = 3,4-methenedioxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, etc.) are quite interesting and their synthesis has attracted considerable attention.[2-13]

2-Aryltetrahydrofuran-3,4-dicarboxylates **2** are key starting materials in the synthesis of these natural products containing tetrahydrofuran rings. Compounds **2** could also be the precursors for some natural products, such as lactones, substituted tetrahydrofurans, aryl substituted 3,7-dioxabicyclo[3.3.0]octanes **1**, and so forth (Scheme 1). In this contribution, a stereoselective and straightforward method for the preparation of 2-aryltetrahydrofuran-3,4-dicarboxylate derivatives **2** was developed. The synthetic route to 2-arylfuran-3, 4-dicarboxylate esters through the Diels−Alder reactions of 2-aryl-1,3,4-oxadiazoles, 2-alkyl (or aryl)-4,5-diphenyloxazoles or 2-aryl-4-phenyloxazoles as the dienes with dimethyl acetylenedicarboxylate (DMAD) as the dienophile was studied. The effect of substituted groups on the oxazole ring upon the Diels−Alder reactions was also investigated. In addition, the stereoselective catalytic hydrogenation of the furan ring and regioselective hydrolysis of dimethyl ester groups were demonstrated.

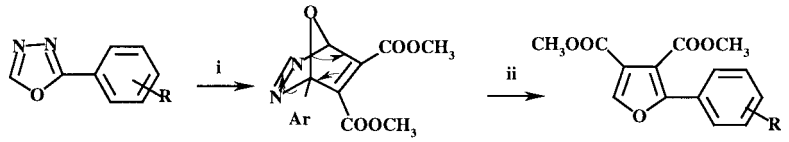
The Diels−Alder reaction is a very useful organic synthetic method. The preparation of heterocyclic compounds utilizing 1,3,4-oxadiazole and oxazole compounds through a tandem Diels−Alder reaction and reverse Diels−Alder reaction has been investigated.[14-20] Furan compounds can be prepared in high yields through the reaction



Scheme 1

of oxadiazoles with alkenes or alkynes that contain angle strain or are electron-rich.[21] Initially, substituted 1,3,4-oxadiazoles were selected as diene because they are easily prepared. Following known reaction conditions, the neat reaction between 2-phenyl-1,3,4-oxadiazole and dimethyl acetylenedicarboxylate at 140−150 °C for 70 hours gave dimethyl 2-phenylfuran-3,4-dicarboxylate in only 10% yield (Scheme 2). However, no desired furan products were obtained under the same conditions using some 1,3,4-oxadiazole derivatives with strong electron-donating or strong electron-withdrawing groups attached onto the phenyl ring. Even after increasing the reaction temperature to over 200 °C, no desired product was found. Instead, dimethyl acetylenedicarboxylate was easily polymerized under the high reaction temperatures to yield an oil or a gum. This is probably due to the fact that the dienophilicity of dimethyl acetylenedicarboxylate towards the 1,3,4-oxadiazoles with aryl-substituted groups is low. All results are outlined in Table 1.

The synthetic route to tetrahydrofuran derivatives is shown in Scheme 3. Aryl-substituted oxazoles were employed in place of 1,3,4-oxadizoles. The reaction of 2,4-diphenyloxazole **3a** with DMAD afforded dimethyl 2-phenylfuran 3,4-dicarboxylate **4a** in a very high yield under the same conditions as used in the reaction of oxadiazoles with DMAD. The results indicate that the reactivity of the oxazoles towards DMAD is higher than that of 1,3,4-oxadiazoles towards DMAD. In order to understand the effect of the substituents of the oxazole ring on the reaction, different substituted oxazoles were prepared as starting materials.[22,23] All the results are shown in Table 2. When two phenyl groups were attached at the C-2 and C-4 positions of the oxazole ring, compound **3a**, the yield of **4a** was 98%. However, when the two phenyl groups were at the C-4 and C-5 positions of the oxazole ring, compound **3e**, the yield of **4e** was decreased to 62%. The noticeable lower reaction yield of **4e** compared with that of compound **4a** may be attributed to the steric hindrance arising from the two close phenyl groups, which is larger

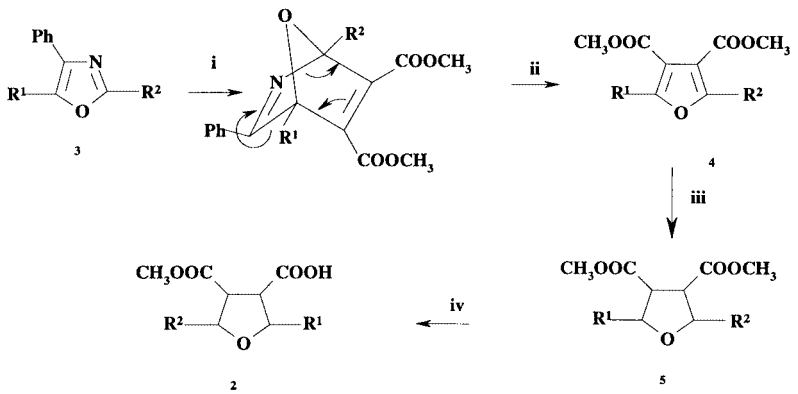


Reagents and conditions: i) DMAD, hydroquinone, Na_2CO_3, 150 °C; ii) $-N_2$

Scheme 2

Table 1 Results of the Diels–Alder Reactions of 2-Aryl-Substituted 1,3,4-Oxadiazoles

R	H	*p*-MeO	*o*-HO	*p*-CH_3	*p*-Br	*p*-Cl	*o*-I	*o*-Cl	*o*-F	*m*-N_2O
Yield %	10	trace	trace	trace	trace	trace	0	0	0	0



Reagents and conditions: i) DMAD, hydroquinone, Na_2CO_3; ii) −PhCN; iii) $-H_2$, Pd/C; iv) KOH, MeOH/H_2O

Scheme 3

Table 2 Yields of Compounds **4a-g** by the Diels−Alder Reactions of Compounds **3a-g** with or without Solvent

Compounds **4**	Yields[a] %	Yields[b] %
4a: R^1 = H, R^2 = Ph	98	98
4b: R^1 = H, R^2 = 3,4-methylenedioxyphenyl	94	98
4c: R^1 = H, R^2 = 3,4-dimethyoxyphenyl	88	98
4d: R^1 = H, R^2 = 3,4,5-trimethoxyphenyl	88	96
4e: R^1 = Ph, R^2 = H	62	65
4f: R^1 = Ph, R^2 = Me	32	37
4g: R^1 = Ph, R^2 = Ph	21	23

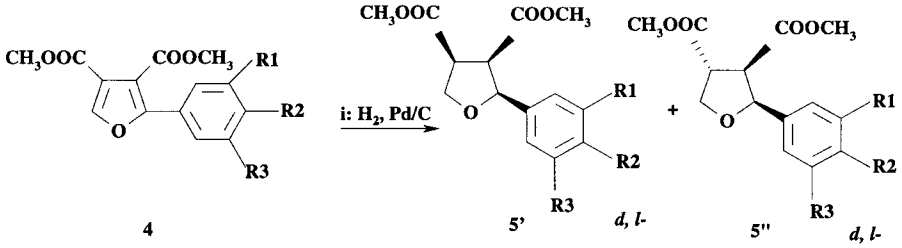
[a] Neat reaction.
[b] Xylene as solvent.

in compound **3e** than that in compound **3a**. In addition, since two phenyl groups on the C-2 and C-4 positions of the oxazole ring can rotate freely, while they cannot freely rotate on the C-4 and C-5 positions, the torsion angle between the phenyl and oxazole rings of 4,5-diphenyloxazole will be larger than that of 2,4-diphenyloxazole. When the third phenyl group was introduced onto the C-2 position of 4,5-diphenyloxazole **3g**, the yield of the furan was further lowered. Thus, 2,4,5-triphenyloxazole **3g** gave the lowest yield of 21%, for compound **4g**.

Most of the Diels-Alder reactions were exothermic, which made the temperature of neat reactions difficult to control. In our reactions, the temperature could reach over 220 °C even though heating was discontinued after the reaction was irradiated. In order to investigate the effect of the solvent on the Diels−Alder reactions and to prevent dimethyl acetylenedicarboxylate from polymerizing, xylene was selected as the solvent because its boiling point is close to the reaction temperature. The results are outlined in Table 2. The comparison of the yields with those obtained in neat reactions suggests that the utilization of this solvent is not important for these Diels−Alder reactions.

The furan ring of the above products can be readily saturated to yield tetrahydrofuran without ring opening through catalytic hydrogenation in methanol in the presence of 5% Pd-C catalyst under low hydrogen pressure and high reaction temperature.[24] However, under such conditions, the phenyl ring may also be hydrogenated to form cyclohexyl ring. After the investigation for different reaction conditions, as shown in Scheme 4, dimethyl 2-aryltetrahydrofuran-3,4-dicarboxylates **5** were obtained by using 4−5 mol% Pd-C catalyst under 100 MPa of hydrogen atmosphere at 100 °C for 4 hours without hydrogenation of the phenyl ring. Since there are three asymmetric carbons in the hydrogenated products, the resulting stereoselectivity of the products are outlined in Table 3. It can be seen that corresponding to the different substituents on compounds **4**, the 2,3-*cis*-3,4-*cis* compounds are always the main products under our experimental conditions, but the stereoselectivity does depend on the substituents on compounds **4**. When the substituent in C-2 position of the furan ring was the benzene ring, compound **4a**, the product was pure 2,3-*cis*-3,4-*cis* compound **5a′**. If the attached benzene group is substituted, the isomer, 2,3-*cis*-3,4-*trans* compound appeared. The ratios of these isomers, which were separated by flash column chromatography, are shown in Table 3. The ratios of the compounds **5′b−d** and **5″b−d** are approximately 2 to 1.

The relative configurations of the hydrogenation products, **5d′** and **5d″** were determined by X-ray diffraction (Figure). The configurations of other compounds were further confirmed through the comparison of ^{1}H NMR spectra of compounds **5′d** and **5″d**. Comparison of the ^{1}H NMR data of the furan ring of all the hydrogenation products is summarized in Table 4. The chemical shifts of protons on the tetrahydrofuran ring, especially the protons on the C-3 and C-4 positions of the tetrahydrofuran rings in **5b′−d′** are remarkably different from those in **5b″−d″**. The chemical shifts of the protons on the tetrahydrofuran ring of compounds **5a′−c′** were in agreement with those of compound **5d′**, and the chemical shifts of the protons on the tetrahydrofuran ring of compounds **5b″−c″** were also in agreement with those of compound **5d″**. It is evident that the compounds **5a′−c′** were all obtained in the 2,3-*cis*-3,4-*cis* configuration, while compounds **5b″** and **5c″** were also obtained in the form of 2,3-*cis*-3,4-*trans* isomer. The results of the ^{1}H NMR data and the X-ray diffraction data suggest that the catalytic hydrogenation reaction is a 1,2-*cis*-addition mechanism of 2, 3 positions and 4, 5 positions at the furan ring, respectively, and not a 1,4-addition mechanism.

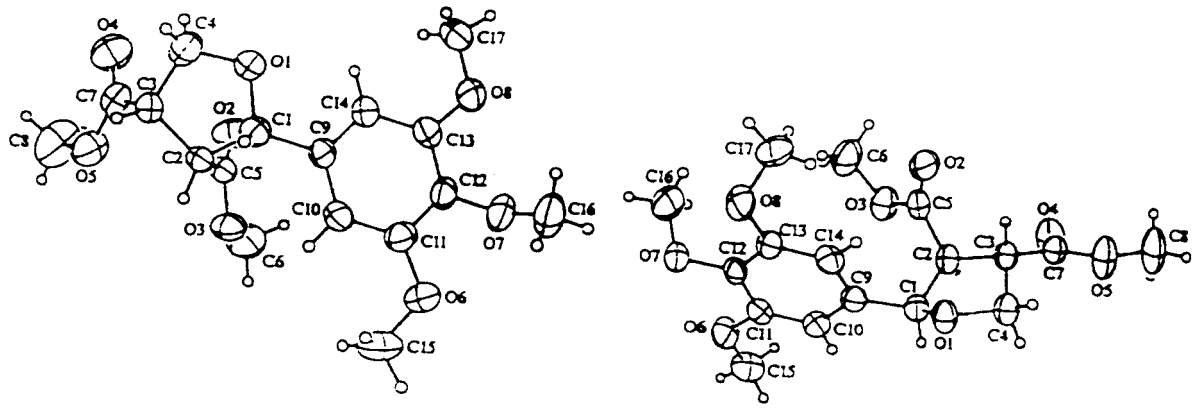


Scheme 4

Table 3 Yields of Coumpounds **5a-d** by Catalytic Hydrogenation of Compounds **4a-d**

Compounds **4**	Yields %	Ratios of Compounds **5′** and **5″**
4a: $R^1 = R^2 = R^3 = H$	91	100/0
4b: $R^1 = H$, R^2, $R^3 = OCH_2O$	76	72/28
4c: $R^1 = H$, $R^2 = R^3 = MeO$	71	67/33
4d: $R^1 = R^2 = R^3 = MeO$	83	67/33

The hydrolysis of compounds **5** was also investigated (Scheme 5). Because of the effect of the aryl group on the tetrahydrofuran ring, the two ester groups have different reactivity. The ^1H NMR chemical shifts of the methyl group of the esters on the C-3 position of the tetrahydrofuran ring are about 3.1−3.3 ppm, while those of the other methyl group on the C-4 position are about 3.70 ppm. Some different bases, such as metal hydroxides and carbonate salts, were employed. When 6 equivalents of KOH solution in methanol and water was employed, compounds **5** were hydrolyzed to 2-aryltetrahydrofuran-3,4-dicarboxylic acid. Other bases did not give ideal results. In order to obtain compounds **2**, different equivalents of KOH solution in methanol and water were used. Monomethyl 2-aryltetrahydrofuran-3-carboxylate-4-carboxylic acid **2** were obtained by selective hydrolysis of compounds **5** with 2 equivalents of KOH-H_2O-MeOH solution for 8 hours at room temperature. The results are shown in Table 5. The configuration of the hydrolysis products of compounds **5b″−d‴″**, compounds **2b″−d″**, was 2,3-*cis*-3,4-*trans*, which was the same as of their starting materials. It indicated that the configuration of compounds **5** remained unchanged during the hydrolysis. However, the hydrolysis products of *dl*-2,3-*cis*-3,4-*cis* compounds **5b′−d′**, compounds **2b′−d′**, were mixtures of 2,3-*cis*-3,4-*trans* and 2,3-*cis*-3,4-*cis* compounds. The configurations of most of the *dl*-2,3-*cis*-3,4-*cis* compounds were converted 2,3-*cis*-3,4-*cis* compounds. The two isomers were easily separated by flash column chromatography. The ratios were determined to be approximately 3 to 1. This proved that 2,3-*cis*-3,4-*trans* compounds are more stable than 2,3-*cis*-3,4-*cis* compounds. A comparison of the ^1H NMR chemical shifts of the remaining methyl ester group of the hydrolysis products with those of compounds **5** are shown in Table 6. The comparison indicated that only the ester group on the 4 position of the tetrahydrofuran ring was hydrolyzed under these conditions. The chemical shifts of the methyl group

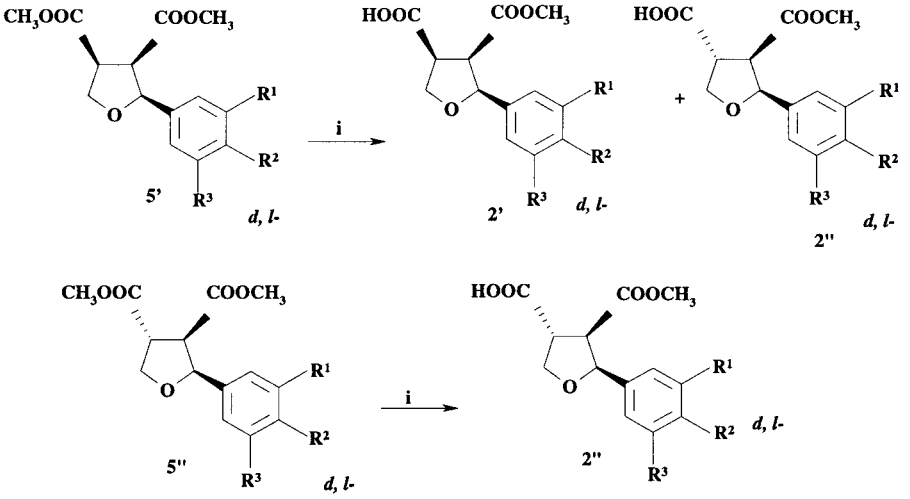


crystal structure of **5d'** crystal structure of **5d''**

Figure

Table 4 ^1H NMR Data (400 MHz, $CDCl_3$) for Protons on the THF Ring of Compounds **5**

Compounds	H-2 (δ, ppm)	H-3 and H-4 (δ, ppm)	H-5 (δ, ppm)	H-5 (δ, ppm)
5a′	5.25 (d, *J* = 1.2 Hz)	3.54−3.60 (m)	4.30−4.35 (m)	4.64−4.68 (m)
5b′	5.14 (d, *J* = 5.42 Hz)	3.53−3.55 (m)	4.28−4.30 (m)	4.60−4.62 (m)
5b″	5.15 (d, *J* = 8.04 Hz)	3.66−3.77 (m)	3.92−3.96 (m)	4.53−4.58 (m)
5c′	5.18 (d, *J* = 5.36 Hz)	3.54−3.61 (m)	4.28−4.33 (m)	4.64−4.68 (m)
5c″	5.16 (d, *J* = 8.40 Hz)	3.67−3.79 (m)	3.93−3.97 (m)	4.56−4.60 (m)
5d′	5.16 (d, *J* = 5.04 Hz)	3.57−3.61 (m)	4.29−4.31 (m)	4.64−4.66 (m)
5d″	5.12 (d, *J* = 7.84 Hz)	3.67−3.76 (m)	3.94−3.98 (m)	4.59−4.60 (m)



Reagents and conditions: i) KOH/MeOH/H_2O

Scheme 5

of the ester on the 3-position of the hydrolysis products are similar to those of compounds **5**.

In summary, a series of optical active 2-arylterahyfuran-3,4-carboxylic acid derivatives have been synthesized in high yields. They are important intermediates in the synthesis of lignans natural products. It was found that the dienophilic activity of DMAD towards oxazole compounds is higher than that towards1,3,4-oxadiazole compounds and the steric-hindrance of oxazole compounds may affect the yield of the Diels–Alder reactions. The hydrogenation of the furan derivatives gave two isomers, which could be separated. Their configurations were confirmed by X-ray diffraction and proton NMR spectroscopy. The substituents on the tetrahydrofuran rings can affect the hydrolyses of the methyl ester groups.

Mps were measured using a Yanaco MP-500 melting point apparatus and are uncorrected. IR measurements were made on KBr pressed pellets or neat on a 75 IR spectrophotometer. ^{1}H NMR spectra were obtained with a ARX-400 NMR instrument and all samples were dissolved in $CDCl_3$. Chemical shifts (δ) were reported in ppm downfield relative to TMS. Mass spectral analyses were carried out on a VG-ZAB-HS mass spectrometer. Reagents and solvents were purified in the usual ways.

Table 5 Yields of Compounds **2** by the Hydrolysis Reaction of Compounds **5**

Reactants	Products	Yield (%)	Ratios of Compounds **2″** and **2′**
5b′	**2b′** and **2b″**	80	74/26
5b″	**2b″**	95	100/0
5c′	**2c′** and **2c″**	85	76/24
5c″	**2c″**	94	100/0
5d′	**2d′** and **2d″**	80	77/23
5d″	**2d″**	97	100/0

Dimethyl 2-Substituted– and 2,5-Disubstituted Furan-3,4-dicarboxylates 4e–f: General Procedure

Method 1

A mixture of 2-substituted-4,5-diphenyloxazole (0.020 mol), dimethyl acetylene dicarboxylate (3.268 g, 0.023 mol), anhyd Na_2CO_3 (0.530 g, 0.005 mol) and *p*-hydroquinone (0.055 g, 0.0005 mol) was degassed three times, and then was stirred and heated at 150–160 °C for 8 h under N_2 atm. After the mixture was cooled, a mixture of Et_2O (50 mL) and H_2O (20 mL) was added. The organic layer was separated and the aqueous layer was extracted thrice with Et_2O. The combined extracts were washed with H_2O, sat. $NaHCO_3$, and brine, and then dried (Na_2SO_4). Evaporation of the solvent gave the crude products, which were purified by column chromatography (CH_2Cl_2) giving the title compounds (yields: 21–62%) as crystals.

Method 2

After a mixture of 2-substituted-4,5-diphenyloxazole (0.020 mol), dimethyl acetylene dicarboxylate (3.126 g, 0.022 mol), anhyd Na_2CO_3 (0.530 g, 0.005 mol) and *p*-hydroquinone (0.033 g, 0.0003 mol) was degassed three times, dry xylene (25 mL) was added through a syringe. The solution was stirred and heated to gentle reflux for 8 h. The mixture was cooled and the work-up procedure was as above. The yields were 23–65%.

Dimethyl 2-Phenylfuran-3,4-dicarboxylate [4e (=4a)]

White needles; mp: 71–73 °C.

IR (KBr): ν = 2980, 1720, 1420, 1280, 1160, 770, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 7.35–7.67 (m, 5H, Ar-H), 7.96 (s, 1H, Fur-H).

EIMS: *m/z* (%) = 260 (M^+), 229 (M^+-OCH_3, 100%), 105 ($PhCO^+$), 77 (Ph^+).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.67; H, 4.61.

Dimethyl 2-Methyl-5-phenylfuran-3,4-dicarboxylate (4f)

White needles; mp: 76–77 °C.

IR (KBr): ν = 2960, 1720, 1460, 830, 765, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3H, $-CH_3$), 3.85 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 7.25–7.75 (m, 5H, Ar-H).

Table 6 Comparison of the ^{1}H NMR shifts (400 MHz, $CDCl_3$; δ, ppm) of the Methyl Ester Groups of Compounds **5** and **2**

	5b′	2b′	5b″	2b″	5c′	2c′	5c″	2c″	5d′	2d′	5d″	2d″
3–OCH_3	3.33	3.33	3.31	3.33	3.28	3.28	3.25	3.27	3.29	3.29	3.27	3.29
4–OCH_3	3.69	–	3.75	–	3.70	–	3.75	–	3.70	–	3.75	–

EIMS: *m/z* (%) = 274 (M^+), 242 [$(M-32)^+$, 100%], 105 ($PhCO^+$), 77 (Ph^+).

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.71; H, 5.10.

Dimethyl 2,5-Diphenylfuran-3,4-dicarboxylate (4g)
White needles; mp = 101−103 °C.

IR (KBr): ν = 2940, 1710, 1460, 820, 760, 795 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 6H, -OCH_3), 7.40−7.88 (m, 10H, Ar-H).

EIMS: *m/z* (%) = 336 (M^+), 305 $(M-OCH_3)^+$, 105 (100), 77.

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.22; H, 4.75.

Dimethyl 2-arylfuran-3,4-dicarboxylates, 4a−d: General Procedure

Method 1
A mixture of 2-aryl-4-phenyloxazole (0.020 mol), dimethyl acetylene dicarboxylate (3.268 g, 0.023 mol), anhyd Na_2CO_3 (0.530 g, 0.005 mol) and *p*-hydroquinone (0.055 g, 0.0005 mol) was degassed three times, then stirred, and gently heated at 140−145 °C for 8 h under N_2 atm. After the mixture was cooled, a mixture of Et_2O (50 mL) and H_2O (20 mL) was added, the organic layer was separated and the aqueous layer was extracted thrice with Et_2O. The combined extracts were washed with H_2O, sat. $NaHCO_3$ and brine, and then dried (Na_2SO_4). Evaporation of the solvent gave the crude products that were purified by recrystallization from 95% EtOH to give needle crystals (yields: 88−98%).

Method 2
After the mixture of 2-aryl-4-phenyloxazole (0.020 mol), dimethyl acetylene dicarboxylate (3.126 g, 0.022 mol), anhyd Na_2CO_3 (0.530 g, 0.005 mol) and *p*-hydroquinone (0.033 g, 0.0003 mol) was degassed for three times, dry xylene (25 mL) was added through a syringe. The solution was stirred and heated to gently reflux for 8 h. The mixture was cooled and the work-up procedure was as above. The crude products were filtered and recrystallized from 95% EtOH to give needle crystals (yields: 96−98%).

Dimethyl 2-Phenylfuran-3,4-dicarboxylate [4a (=4e)]
White needles; mp: 71−73 °C.

IR (KBr): ν = 2980, 1720, 1420, 1280, 1160, 770, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, −OCH_3), 3.90 (s, 3H, -OCH_3), 7.35−7.67 (m, 5H, Ar-H), 7.96 (s, 1H, Fur-H).

EIMS: *m/z* (%) = 260 (M^+), 229 [$(M-OCH_3)^+$, 100], 105 ($PhCO^+$), 77 (Ph^+).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.67; H, 4.61.

Dimethyl 2-(3,4-Methylenedioxyphenyl)furan-3,4-dicarboxylate (4b)
White needles; mp: 101−103 °C.

IR (KBr): ν = 2960, 2880, 1720, 1480, 1440, 1210, 1030, 860, 815, 760, 710 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 6.00 (s, 2H, -OCH_2O-), 6.84−7.27 (m, 3H, Ar-H), 7.91 (s, 1H, Fur-H).

EIMS: *m/z* (%) = 304 (M^+, 100), 289 $(M-CH_3)^+$, 273 $(M-OCH_3)^+$.

Anal. calcd for $C_{15}H_{12}O_7$: C, 59.21; H, 3.98. Found: C, 59.17; H, 4.03.

Dimethyl 2-(3,4-Dimethoxyphenyl)furan-3,4-dicarboxylate (4c)
White needles; mp: 102−103 °C.

IR (KBr): ν = 2960, 1740, 1710, 1600, 1510, 1450, 1260, 1130, 840, 805, 760, 705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3), 6.90−7.34 (m, 3H, Ar-H), 7.93 (s, 1H, Fur-H).

EIMS: *m/z* (%) = 320 (M^+, 100), 305 $(M-CH_3)^+$, 289 $(M-OCH_3)^+$.

Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.98; H, 5.07.

Dimethyl 2-(3,4,5-Trimethoxyphenyl)furan-3,4-dicarboxylate (4d)
White plate crystals; mp: 150.5−152 °C.

IR (KBr): ν = 1730, 1715, 1580, 1505, 1350, 1290, 1250, 1210,1130, 1070, 1005, 860, 815, 770, 710 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87−3.91 (m, 15H, -OCH_3), 7.03 (s, 2H, Ar-H), 7.95 (s, 1H, Fur-H).

EIMS: *m/z* (%) = 350 (M^+, 100), 335 $(M-CH_3)^+$, 319 $(M-OCH_3)^+$, 307 $(M-CH_3CO)^+$.

Anal. Calcd for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.24, H, 5.29.

Dimethyl 2-Aryltetrahydrofuran-3,4-dicarboxylate 5: General Procedure
Dimethyl 2-arylfuran-3,4-dicarboxylate (0.01 mol), 10% Pd-C catalyst (0.5 g) and anhyd MeOH (60 mL) were added in an autoclave. The autoclave was degassed three times, then filled with H_2 to 100 MPa pressure. The mixture was stirred and heated to 100 °C for 4 h. After cooling and releasing the pressure, the catalyst was filtered, and the solvent was removed in vacuo. The products were purified by recrystallization from MeOH or separated by flash column chromatography [(EtOAc/petroleum ether (60−90 °C), 1:2.5].

Dimethyl 2-Phenyltetrahydrofuran-3,4-dicarboxylate (5a)
White needles; yield: 91.2%; mp: 91−93 °C.

IR (KBr): ν = 2920, 1730, 1430, 1320, 1250, 1010, 750, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17 (s, 3H, -OCH_3), 3.54−3.60 (m, 2H, -C^3H-, -C^4H-), 3.69 (s, 3H, -OCH_3), 4.30−4.35 (m, 1H, -OC^5H-), 4.64−4.68 (m, 1H, -OC^5H-), 5.25−5.26 (d, 1H, *J* = 1.2 Hz, -OC^2H-), 7.26−7.32 (m, 5H, Ph-H).

EIMS: *m/z* (%) = 264 (M^+), 232 $(M-CH_3OH)^+$, 204, 145, 127, 99 (100).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.66; H, 6.05.

Dimethyl 2-(3,4-Methylenedioxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5b)
White solid; yield: 76%.

EIMS: *m/z* (%) = 308 (M^+), 278 ($M-CH_2O)^+$, 189, 149, 127, 99 (100).

***dl*-2,3-*cis*-3,4-*cis*-Dimethyl 2-(3,4-Methylenedioxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5b′)**
White needles; content: 72% of 76%; mp: 96−97 °C.

IR (KBr): ν = 2960, 1730, 1500, 1440, 1240, 1030, 930, 870, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.33 (s, 3H, -OCH_3), 3.53−3.55 (m, 2H, -C^3H-, -C^4H-), 3.69 (s, 3H, -OCH_3), 4.28−4.30 (m, 1H, -OC^5H-), 4.60−4.62 (m, 1H, -OC^5H-), 5.14−5.16 (d, 1H, *J* = 5.42 Hz, −C^2H-), 5.94 (s, 2H, -OCH_2O-), 6.77−6.80 (m, 3H, Ar-H).

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.42; H, 5.18.

***dl*-2,3-*cis*-3,4-*trans*-Dimethyl 2-(3,4-Methylenedioxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5b″)**
White rhombohedron crystals; content: 28% of 76%; mp: 55−56 °C.

IR (KBr): ν = 2960, 2880, 1720, 1500, 1440, 1250, 1170, 1030, 930, 865, 820 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.31 (s, 3H, -OCH_3), 3.66−3.77 (m, 2H, -C^3H-, -C^4H-), 3.75 (s, 3H, -OCH_3), 3.92−3.96 (m, 1H, -C^5H-), 4.53−4.58 (m, 1H, -OC^5H-), 5.15−5.17 (d, 1H, *J* = 8.04 Hz, -C^2H-), 5.94 (s, 2H, -OCH_2O-), 6.75−6.77 (m, 3H, Ar-H).

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.40; H, 5.20.

Dimethyl 2-(3,4-Dimethoxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5c)
White needles; yield: 71%.

EIMS: *m/z* (%) = 324 (M^+, 100), 309 ($M-CH_3)^+$, 293 ($M-OCH_3)^+$, 261, 205, 165, 127, 97.

***dl*-2,3-*cis*-3,4-*cis*-Dimethyl 2-(3,4-Dimethoxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5c′)**
White needles; content: 67% of 71%; mp: 103−104 °C.

IR (KBr): ν = 2980, 1730, 1600, 1520, 1440, 1240, 1030, 865, 820, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.28 (s, 3H, -OCH_3), 3.54−3.61 (m, 2H, -C^3H-, -C^4H-), 3.70 (s, 3H, -OCH_3), 3.87 (s, 6H, -OCH_3), 4.28−4.33 (m, 1H, -OC^5H-), 4.64−4.68 (1H, m, -OC^5H-), 5.18−5.19 (d, 1H, *J* = 5.36 Hz, −C^2H-), 6.80−6.88 (m, 3H, Ar-H).

Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.23; H, 6.20.

***dl*-2,3-*cis*-3,4-*trans*-Dimethyl 2-(3,4-Dimethoxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5c″)**
White granular solid; content: 33% of 71%; mp: 38−40 °C.

IR (KBr): ν = 2980, 1730, 1600, 1520, 1440, 1240, 1030, 865, 820, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.25 (s, 3H, -OCH_3), 3.67−3.79 (m, 2H, -C^3H-, -C^4H-), 3.75 (s, 3H, -OCH_3), 3.87 (s, 6H, -OCH_3), 3.93−3.97 (m, 1H, -OC^5H-), 4.56−4.60 (m, 1H, -OC^5H-), 5.16−5.18 (d, 1H, *J* = 8.40 Hz, −C^2H-), 6.80−6.83 (m, 3H, Ar-H).

Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.20, H, 6.28.

Dimethyl 2-(3,4,5-Trimethoxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5d)
White solid; yield: 83%.

EIMS: *m/z* (%) = 354 (M^+, 100), 339 ($M-CH_3)^+$, 323 ($M-OCH_3)^+$, 236.

***dl*-2,3-*cis*-3,4-*cis*-Dimethyl 2-(3,4,5-Trimethoxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5d′)**
White needles; content: 67% of 83%; mp: 96−97 °C.

IR (KBr): ν = 2980, 1720, 1580, 1500, 1470, 1435, 1370, 1220, 1120, 1000 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.29 (s, 3H, -OCH_3), 3.57−3.61 (m, 2H, -C^3H-, -C^4H-), 3.70 (s, 3H, -OCH_3), 3.85 (s, 9H, Ar-OCH_3), 4.29−4.31 (m, 1H, -OC^5H-), 4.64−4.66 (m, 1H, -OC^5H-), 5.16−5.17 (d, 1H, *J* = 5.04 Hz, −C^2H-), 6.55 (s, 2H, Ar-H).

Anal. Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.47; H, 5.79.

***dl*-2,3-*cis*-3,4-*trans*-Dimethyl 2-(3,4,5-Trimethoxyphenyl)tetrahydrofuran-3,4-dicarboxylate (5d″)**
White plate crystals; content: 33% of 83%; mp: 83−85 °C.

IR (KBr): ν = 2980, 1720, 1590, 1500, 1435, 1370, 1220, 1120, 1000 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.27 (s, 3H, -OCH_3), 3.67−3.76 (m, 2H, -C^3H-, -C^4H-), 3.75 (s, 3H, C^4-CO_2CH_3), 3.82−3.85 (s, 9H, 3 (Ar-OCH_3), 3.94−3.98 (m, 1H, -OC^5H-), 4.59−4.60 (m, 1H, -OC^5H-), 5.13−5.15 (d, 1H, *J* = 7.84 Hz, -C^2H-), 6.52 (s, 2H, Ar-H).

Anal. Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.47; H, 5.79.

Monomethyl 2-Aryltetrahydrofuran-3-carboxylate-4-carboxylic acid 2: General Procedure

(1) Hydrolysis of *dl*-2,3-*cis*-3,4-*trans*-Dimethyl 2-Aryltetrahydrofuran-3,4-dicarboxylate 5″
After KOH (1.122 g, 0.02 mol) was dissolved in a mixture of MeOH (20 mL) and deionized H_2O (10 mL), 2,3-*cis*-3, 4-*trans*-dimethyl 2-aryltetrahydrofuran-3,4-dicarboxylate (0.01 mol) was added to this solution. The mixture was stirred at r.t. for 6−8 h, then acidified with concd HCl. The organic layer was extracted with Et_2O and the combined extract was washed with H_2O, sat. $NaHCO_3$, and brine. After drying ($MgSO_4$), the solvent was removed in vacuo. The residue was purified by recrystallization from 60% MeOH to give white crystals.

***dl*-2,3-*cis*-3,4-*trans*-Monomethyl 2-(3,4-methylenedioxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2b″)**
White needles; yield: 95%; mp: 119−121 °C.

IR (KBr): ν = 3600 (b), 1720, 1695, 1500, 1440, 1330, 1240, 1190, 1170, 1030, 930, 875, 800, 650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.33 (s, 3H, -OCH_3), 3.67−3.82 (m, 2H, -C^3H-, -C^4H-), 3.98−4.02 (m, 1H, -OC^5H-), 4.57−4.61 (m, 1H, -OC^5H-), 5.17−5.19 (d, 1H, *J* = 8.00 Hz, −C^2H-), 5.94 (s, 2H, -OCH_2O-), 6.73−6.77 (m, 3H, Ar-H), 11.00−11.25 (br, 1H, -COOH).

EIMS: *m/z* (%) = 294 (M^+), 261, 233, 190, 149, 99 (100).

Anal. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 57.21; H, 5.11.

***dl*-2,3-*cis*-3,4-*trans*-Monomethyl 2-(3,4-Dimethoxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2c″)**
White needles; yield: 94%; mp: 125−126.5 °C.

IR (KBr): ν = 3200, 1740, 1695, 1505, 1460, 1420, 1320, 1245, 1200, 1130, 1070, 1010, 930, 795 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.27 (s, 3H, C^3-CO_2CH_3), 3.67−3.86 (m, 2H, -C^3H-, -C^4H-), 3.87−3.88 (s, 6H, Ar-OCH_3), 4.00−4.04 (m, 1H, -OC^5H-), 4.60−4.64 (m, 1H, -OC^5H-), 5.18−5.20 (d, 1H, *J* = 8.00 Hz,-C^2H-), 6.81−6.85 (m, 3H, Ar-H), 7.40−9.80 (br, 1H, -COOH).

EIMS: *m/z* (%) = 310 (M^+, 100), 295, 279, 247, 206, 165, 99.

Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.82; H, 5.86.

***dl*-2,3-*cis*-3,4-*trans*-Monomethyl 2-(3,4,5-Trimethoxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2d″)**
White needles; yield: 97%; mp: 115.5−117 °C.

IR (KBr): ν = 3200, 1730, 1600, 1470, 1430, 1235, 1180, 1130, 990, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.29 (s, 3H, -OCH_3), 3.69−3.80 (m, 2H, -C^3H-, -C^4H-), 3.78 (s, 3H, Ar-OCH_3), 3.85 (s, 6H, Ar-OCH_3), 4.01−4.05 (m, 1H, -OC^5H-), 4.61−4.66 (m, 1H, -OC^5H-), 5.15−5.17 (d, 1H, *J* = 7.90 Hz, -C^2H-), 6.55 (s, 2H, Ar-H), 6.90−8.00 (br, 1H, -COOH).

EIMS: *m/z* (%) = 340 (M^+, 100), 309, 281, 236, 181, 99.

Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92. Found: C, 56.18; H, 5.86.

(2) Hydrolysis of *dl*-2,3-*cis*-3,4-*cis*-Dimethyl 2-Aryltetrahydrofuran-3,4-dicarboxylate 5′
After KOH (1.122 g, 0.02 mol) was dissolved in a mixture of MeOH (20 mL) and deionized H_2O (10 mL), 2,3-*cis*-3,4-*trans*-dimethyl 2-aryltetrahydrofuran-3,4-dicarboxylate (0.01 mol) was added to this solution. The mixture was stirred at r.t. for 6−8 h, then acidified with concd HCl. The organic layer was extracted with Et_2O and the combined extract was washed with H_2O, sat. $NaHCO_3$, and brine. After drying ($MgSO_4$), the solvent was removed under vacuum. The residue of *dl*-2, 3-*cis*-3, 4-*trans* products and *dl*-2,3-*cis*-3, 4-*cis* products were separated by flash column chromatography [EtOAc/petroleum ether (60−90 °C, 1:2.5] to give two sets of white crystals.

***dl*-2,3-*cis*-3,4-*trans*-Monomethyl 2-(3,4-Methylenedioxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2b″)**
Content: 59% of 80% (yield).

***dl*-2,3-*cis*-3,4-*cis*-Monomethyl 2-(3,4-Methylenedioxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2b′)**
White needles; content: 21% of 80% (yield); mp: 161−162 °C.

IR (KBr): ν = 3600, 1700, 1680, 1475, 1420, 1305, 1220, 1070, 1010, 930 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.33 (s, 3H, -OCH_3), 3.52−3.67 (m, 2H, -C^3H-, -C^4H-), 4.26−4.31(m, 1H, OC^5H-), 4.59−4.64 (m, 1H, -OC^5H-), 5.15−5.16 (d, 1H, *J* = 5.60 Hz, −C^2H-), 5.94 (s, 2H, -OCH_2O-), 6.74−6.83 (m, 3H, Ar-H), 7.30−9.60 (br, 1H, -COOH).

EIMS: *m/z* (%) = 294 (M^+), 261, 233, 189, 149, 99 (100).

Anal. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 56.85; H, 4.94.

***dl*-2,3-*cis*-3,4-*trans*-Monomethyl 2-(3,4-Dimethoxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2c″)**
Content: 65% of 85% (yield).

***dl*-2,3-*cis*-3,4-*cis*-Monomethyl 2-(3,4-Dimethoxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2c′)**
White needles; content: 20% of 85% (yield); mp: 156−158 °C.

IR (KBr): ν = 3310, 1730, 1700, 1500, 1380, 1280, 1250, 1120, 1115, 960, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.28 (s, 3H, -OCH_3), 3.54−3.67 (m, 2H, -C^3H-, -C^4H-), 3.87 (s, 6H, Ar-OCH_3), 4.27−4.32 (m, 1H, -OC^5H-), 4.64−4.68 (m, 1H, -OC^5H-), 5.19−5.20 (d, 1H, *J* = 5.60 Hz, −C^2H-), 5.40−6.70 (b, 1H, -COOH), 6.80−6.87 (m, 3H, Ar-H).

EIMS: *m/z* (%) = 310 (M^+, 100), 295, 278, 206, 165, 99.

Anal. Calcd for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85. Found: C, 57.89; H, 5.84.

***dl*-2,3-*cis*-3,4-*trans*-Monomethyl 2-(3,4,5-Trimethoxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2d″)**
Content: 62% of 80% (yield).

***dl*-2,3-*cis*-3,4-*cis*-Monomethyl 2-(3,4,5-Trimethoxyphenyl)tetrahydrofuran-3-carboxylate-4-carboxylic Acid (2d′)**
White needles; content: 18% of 80% (yield); mp: 156−158 °C.

IR (KBr): ν = 3210, 1720, 1670, 1575, 1500, 1440, 1370, 1225, 1180, 1105, 1070, 970, 750, 670 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.29 (s, 3H, OCH_3), 3.56−3.68 (m, 2H, -C^3H-, -C^4H-), 3.82 (s, 3H, Ar-OCH_3), 3.85 (s, 6H, Ar-OCH_3), 4.28−4.32 (m, 1H, -OC^5H-), 4.64−4.68 (m, 1H, -OC^5H-), 5.17−5.18 (d, 1H, *J* = 5.60 Hz, −C^2H-), 6.52 (s, 2H, Ar-H), 9.16 (br, 1H, -COOH).

EIMS: *m/z* (%) = 340 (M^+, 100), 308, 281, 236, 195, 181, 99.

Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.46; H, 5.92. Found: C, 56.18; H, 5.86.

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