

Article

Anodic Methoxylation of Cinnamate Esters

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Este trabalho descreve a oxidação eletroquímica do 4-metóxi-cinamato de metila e de outros ésteres metílicos do ácido cinâmico di- e tri- metoxilado, em solução metanólica neutra ou alcalina. Nos estudos eletroquímicos foram empregadas voltametria cíclica, bem como eletrólises preparativas a potencial ou corrente controlados, em celas de um ou dois compartimentos. A influência de parâmetros tais como densidade de corrente, tipo de cela, material do eletrodo, solvente, concentração do substrato e base foi investigada para o 4-metóxi-cinamato de metila. Os produtos observados foram resultantes de metoxilações nucleares e/ou na cadeia lateral, entretanto com o aumento do número de metoxilas no anel aromático foram observados principalmente produtos referentes à metoxilação no anel aromático. As estruturas dos produtos também dependem do tipo de procedimento empregado no seu isolamento.

The present work describes the electrochemical oxidation of methyl cinnamate ring methoxylated derivatives in neutral or basic methanolic solution. In the electrochemical studies cyclic voltammetry and preparative electrolyses under controlled potential or current conditions in divided or undivided cells were used. The influence of current density, cell type, electrode material, solvent, substrate and base concentration was investigated for methyl 4-methoxycinnamate. The products result from aromatic ring and side chain methoxylation, however, nuclear methoxylation products were observed in higher yields when the number of methoxy groups in the aromatic ring was increased. The structure of the products is dependent on the work-up procedures.

Keywords: electrochemical oxidation, anodic methoxylation, methyl cinnamate derivatives

Introduction

The oxygenation of aromatic rings by non-electrochemical methods usually involves several steps. Anodic methoxylation of aromatic rings not only furnishes novel addition products of synthetic utility but also serves as a direct method for introducing methoxy groups into aromatic substrates. A great variety of substituted 1,4-dimethoxybenzenes¹, naphthalenes², and benzothio-phenes³ were converted into the corresponding quinone bisketals in high yields under single-cell and constant current conditions. The quinone monoketal, obtained through mild acid hydrolysis of the bisketal, has found extensive use in organic synthesis^{1a,4,5}.

A synthetic application of this method is the anodic methoxylation of methyl eugenol where 1,2- and 1,4-dimethoxy addition products are formed. Reaction of this product mixture with acid affords a convenient synthetic route to γ -asarone: 5-(2-propenyl)-1,2,4-trimethoxy-benzene⁶. A

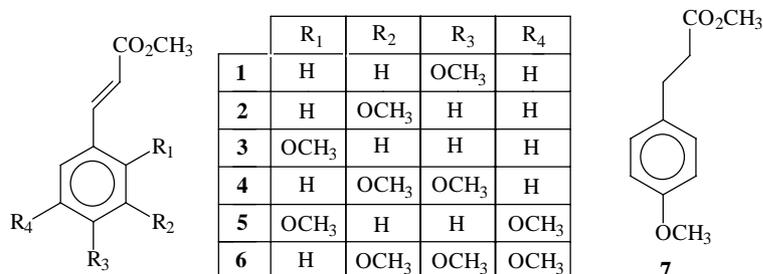
reaction competing with the oxidative addition of methanol to the aromatic ring is the oxidation of benzylic positions, especially those *para* to the methoxy group. The anodic oxidation of methyl eugenol in methanol without added base gave the benzylic substitution product in 60% yield^{6b}.

Here we report the results of the electrochemical oxidation of cinnamates **1** - **6** and the dihydro derivative **7** in methanolic solution.

Results and Discussion

Table-1 shows the oxidation peak potentials (E_{pa}) for **1** - **7**, determined by cyclic voltammetry. The oxidation waves were irreversible and a considerable current decrease was observed during the second cycle. The E_{pa} values were measured in acetonitrile.

Electrochemical oxidation of the aromatic ethers will involve electron transfer from the π -system as normally observed for oxidation of aromatic compounds to radical cations⁷. According to Table 1, the ease of oxidation, related to E_{pa} is in the following order: **6** > **4** > **5** > **1** = **3** > **7** > **2**.

**Table 1.** Oxidation peak potentials of **1** - **7** by cyclic voltammetry^a

Compound	Epa ₁ (V)	Epa ₂ (V)	Epa ₃ (V)
1	2.12	2.32	—
2	2.37	—	—
3	2.12	2.40	—
4	1.84	2.16	2.29
5	1.89	1.99	2.23
6	1.80	—	—
7	2.20	—	—

a: V vs Ag/AgI; Pt bead anode, 200 mV s⁻¹; MeCN-NaClO₄ (0.1 mol L⁻¹); substrate: 3 mmol L⁻¹.

In the mono methoxylated compounds series, the *meta* substituted compound **2** shows a more positive oxidation potential than methoxybenzene⁸, but for the *ortho* and *para* substituted substrates **1** and **3** the first oxidation peak potentials are less positive. This difference can be explained considering the presence of the unsaturated side chain which allows a more effective electron delocalization in the intermediate radical cation when *ortho* or *para* in relation to the methoxy substituent whereas in the *meta* position its electron-withdrawing character seems to predominate, destabilizing the intermediate. A similar stabilizing effect is also evident when the oxidation potentials of compounds **1** and **7** are compared.

The presence of two methoxy groups in substrates **4** and **5** causes a negative shift of the first oxidation peak potentials when compared with compounds **1** and **3**. A similar effect is observed in the case of the dimethoxybenzenes in relation to methoxybenzene, but being about 100 mV larger for the 1,4- derivative than for the two other isomers. In our case although the relative position of the methoxy substituents is *para* in compound

5, the negative shift of its oxidation potential is *ca* 50 mV smaller than that observed for **4**. It seems reasonable to suggest that in compound **5** the carbon-carbon double bond destabilizes the radical cation formed, thus the oxidation potential is shifted to a more positive value than that expected for 1,4-dimethoxybenzene. This result could be accounted for by a steric *ortho* effect although for compounds **1** and **3** this effect seems not to be operative. In the case of substrate **4** the negative shift of the first oxidation peak potential shows to be similar to that observed when 1,2-dimethoxybenzene is compared with methoxybenzene⁸. On the other hand a comparison of the second oxidation peak potential of substrates **4** and **5** is noteworthy and shows a reverse situation, the latter being oxidized at a potential *ca* 150 mV less positive than **4**. Compound **6** under cyclic voltammetry conditions (Table 1) presents its oxidation peak potential shifted to a less positive value when compared with substrate **1** and the observed difference is approximately the same as reported for methoxybenzene and 1,2,3-trimethoxybenzene⁸.

The preparative electrolyses were performed in MeOH containing sodium methoxide. The reason for choosing this condition was the observation that in MeOH or MeCN containing solely NaClO₄ the electrolyses afforded untreatable mixtures of products.

Compound **1** was electrolyzed under controlled current conditions in a methanolic solution containing base. After passage of the appropriate amount of electricity, the cell contents were worked-up and the products isolated by column chromatography or by preparative TLC. The results of these electrolyses are shown in Table 2.

Table 2. Electrochemical oxidation of **1**.

Entry	I (mA)	[S] (mol L ⁻¹)	[base] (mol L ⁻¹)	S.M. ^a (%)	Products ^{b,c} (%)					
					7	8	9	10	11	12
1	100	0.16	0.2	30	18	—	—	17	8	—
2	150	0.16	0.2	30	10	4	20	5	8	—
3	100	0.05	0.2	23	—	—	—	27	6	8
4	100	0.05	0.4	26	—	—	—	13	8	18

Conditions: 0.2 mol L⁻¹ NaClO₄ in MeOH solution; undivided cell; Pt foil anode (2.5 x 2.5 cm); W wire cathode and charge = 4 F mol⁻¹.

a- S.M.: Recovered Starting Material; b- the methanolic fraction obtained from chromatographic column (polymeric material) varied from 14 to 28%; c- chromatographic yields using biphenyl ether as internal standard.

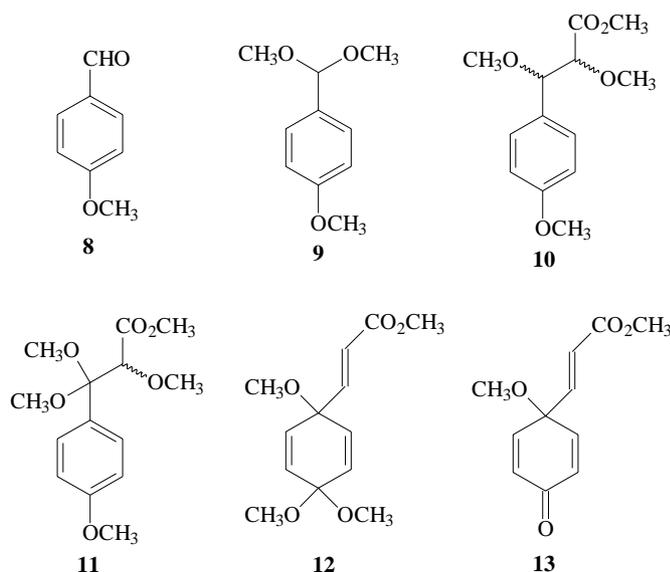
After the passage of 4 F mol^{-1} (current density: 8 mA cm^{-2}) in an undivided cell, **1** (entry 1, Table 2) afforded **7**, formed by reduction of **1** at the cathode, and **10** and **11**, obtained through the olefinic moiety methoxylation, besides recovered starting material. Upon increasing the current density (entry 2, Table 2), product **9** was observed, together with small amounts of *p*-anisaldehyde **8**, formed probably through hydrolysis of **9** during work-up. It is worth mentioning that these results are different from those observed in an experiment conducted in a divided cell. Under these conditions **7** was not formed, being **8** (29%) and **9** (49%), C α -C β bond cleavage products⁹ of **1**, the main products. A disadvantage of this procedure was a decrease of pH of the reaction medium in the anodic compartment during the electrolysis, and it was necessary to add base to the solution at regular intervals. When substrate concentration was decreased three times (entry 3, Table 2), competition between nuclear and side chain methoxylation was detected. The yield of the nuclear methoxylated product, **12**, was increased with larger base/substrate ratio (entry 3 and 4, Table-2), indicating that these conditions favor the aromatic ring methoxylation. Compound **13** was isolated after the crude reaction mixture passed through the column chromatography, indicating an acidic hydrolysis of compound **12**.

The results obtained in the electrochemical oxidation of compound **1** deserve some further comments. It is well known¹⁰ that the anodic oxidation of 4-methylanisole occurs preferentially at the aromatic ring under conditions where formation of methoxyl radicals also takes place (platinum anode, supporting electrolyte NaOMe). This is observed when low current densities and a 1:1 base/substrate ratio or higher current densities

and a 4:1 base/substrate ratio are used, but in the presence of LiBF_4 as supporting electrolyte the side chain methoxylation becomes more competitive. In our case NaClO_4 was used besides variable concentrations of NaOMe. It seems that these conditions favor the formation of side chain substitution and cleavage products (entries 1 and 2, Table 2), the first most probably precursors of the latter as with higher current densities (entry 2) the cleavage products are formed. When higher base/substrate ratios were employed (entries 3 and 4, Table 2) nuclear methoxylation became a competitive pathway in relation to the side chain substitution. It is reasonable to suggest that the electron delocalization in the intermediate radical cation involving the side chain carbon-carbon double bond turns the latter more prone to react with methoxyl radicals therefore competing efficiently with the aromatic nucleus.

If the electrolyses were conducted without base, black polymeric materials were obtained, suggesting that the presence of methoxy radicals formed during the oxidation play an important role in the methoxylation of the intermediate like radical cations as pointed out previously¹⁰. Without base the intermediates seem to react with each other leading to compounds with higher molecular weight.

To verify the effect of the electrode material on the course of the reaction, platinum was substituted for graphite but under these conditions a dark solution containing a complex mixture of products was obtained. Probably the substrate is preferentially adsorbed at the electrode surface producing intermediates with reactive sites at the aromatic ring and the side chain, which react with each other producing a complex mixture¹⁰.



The oxidation of **2** and **3** was conducted under similar conditions used for **1**, and in all cases complex mixtures containing a tar like material together with starting material were obtained. Even when the charge was increased from 4 to 8 F mol⁻¹, the starting material was recovered with **2** (32%) and **3** (20%). A different behavior was observed with the dimethoxylated **4** and **5** when compared to *ortho* **3** and *meta* **2** derivatives. Table 3 shows the oxidation products of **4** and **5** obtained under different experimental conditions.

Compound **4** afforded the trimethoxyderivative **14** after acidic work-up conditions (entries 1 and 2, Table 3). When the work-up was conducted under neutral conditions compounds **15** and **16**, the 1,2- and 1,4-addition products, were isolated (entry 3, Table 3). This difference of products observed when different work-up procedures were employed became clear when it was shown that **15** and **16** were transformed into **14** when treated with MeOH/H₂SO₄ solution. Similar results were previously reported for the anodic methoxylation of methyl eugenol⁶ where 1,2- and 1,4- addition products were also isolated under basic work-up conditions^{6b} and a trimethoxybenzene derivative under acidic work-up^{6a}. Wang and Swenton^{6b} showed that the 1,2- and 1,4-addition products are transformed into the trimethoxybenzene derivative when treated with acid.

Compound **5** is a 1,4-dimethoxybenzene derivative and the electrolysis conducts to the corresponding quinone bisketal like **17**. Product **17** was previously obtained in 46% yield by Swenton *et al.*² electrolyzing **5** at controlled potential in CH₃OH/KOH solution and undivided cell. According to Table 3 (entries 4, 5 and 6) the electrolysis product was mainly **17** and after its isolation, the product was stirred in an acid solution affording **18**, an aromatic compound.

When **6** was electrolyzed at constant current, a very complex mixture was obtained together with polymeric material. This compound is the easiest oxidizable compound (1.80 V) of the series studied and presumably a further oxidation is occurring, leading to a complex mixture.

To evaluate the conjugated double bond effect of the side chain, **7** was electrolyzed at constant current, undivided cell and basic conditions to afford the methoxylated product at the C α position, **19** (30%) and the 1,4- nuclear addition product **20** (41%).

Conclusions

The results presented here indicate that depending on the electrolysis conditions, the anodic oxidation of **1** led to both aromatic ring and side chain methoxylated compounds. The best yields of nuclear methoxylated product **12** were obtained when larger base/substrate ratios were used. The presence of base showed to be important otherwise black polymeric materials were obtained. These findings agree with the EECrCp mechanism suggested by Dolson and Swenton¹¹ in which the involvement of methoxy radicals plays an important role. For **7**, although less reactive than **1**, methoxylation at the aromatic ring and/or side chain was also observed. Compound **2** has been shown to be less reactive than other mono-methoxylated compounds and **6** was more reactive but afforded a complex mixture of products. Dimethoxylated compounds **4** and **5** yielded mainly aromatic ring methoxylated products whose structures depend upon the work-up procedures. Under basic or neutral conditions cyclohexadiene derivatives (**15**, **16** or **17**) are isolated whereas in acidic medium trimethoxybenzene derivatives (**14** or **18**) are obtained. It is noteworthy that products **15** and **16** can be converted into **14**, and also compound **18** can be easily obtained from product **17**, in good yields stirring them in MeOH/H₂SO₄ solution at room temperature.

Experimental

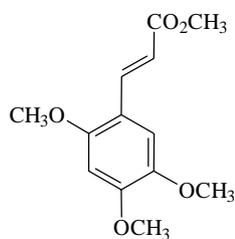
NMR spectra (¹H and ¹³C) were recorded on Brukers AC-200, DPX-300 and DRX-500 CDCl₃ solutions. Chemical shifts are reported as δ values relative to

Table 3. Electrochemical oxidation of **4**, **5** and **7**.

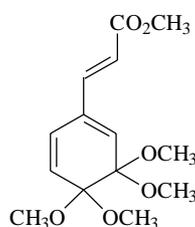
entry	compound	I or E	Substrate (mol L ⁻¹)	Base (mol L ⁻¹)	S.M. ^e	Products (% yield) ^f
1 ^a	4	1.0 V	0.16	0.2	26	14 (35)
2 ^a	4	100 mA	0.16	0.2	17	14 (49)
3 ^b	4	1.3 V	0.16	0.2	5	15 (33), 16 (40)
4 ^c	5	1.0 V	0.05	0.2	13	17 ^g (73), mixture (14)
5 ^d	5	1.3 V	0.07	0.2	12	17 (46), mixture (42)
6 ^c	5	125 mA	0.07	0.05	10	17 (64), mixture (26)
7 ^c	7	200 mA	0.16	0.2	15	19 (30), 20 (41)

Conditions: 0.2 mol L⁻¹ NaClO₄ in MeOH solution; Pt foil anode (2.5 x 2.5 cm); W wire cathode and charge = 4 F mol⁻¹, reference Ag/Ag⁺ (silver wire in MeOH 0.1 mol L⁻¹ NaClO₄ / 0.01 mol L⁻¹ AgNO₃).

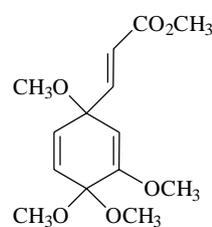
a- divided cell, acid work-up; b- divided cell, neutral work-up; c- undivided cell, basic work-up; d- divided cell, basic work-up; e- S.M. = recovered starting material; f- chromatographic yields using biphenyl ether as internal standard; g- **17** was stirred in 0.1 mol L⁻¹ H₂SO₄/MeOH solution affording **18** (70-80% yield).



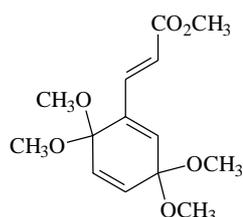
14



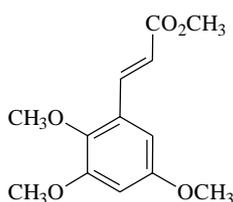
15



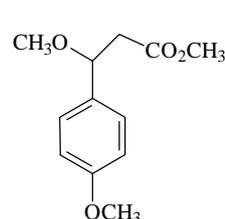
16



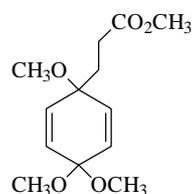
17



18



19



20

tetramethylsilane (TMS) as internal reference. GLC analyses were performed on a HP5890 instrument, (fused silica capillary column SE-30, 12m x 0.2mm) and mass spectra were recorded on a Hewlett Packard HP 5988A GLC/MS instrument at 70 eV (EI). Some of the products have been identified by comparison to authentic samples.

Electrochemical Experiments

Cyclic voltammetry experiments were run in a three compartment cell using a Princeton Applied Research (PAR) 173 potentiostat/galvanostat. The reference electrode was Ag/AgI (a silver wire immersed in an acetonitrile solution 0.1mol L⁻¹ in NaClO₄ and 0.04mol L⁻¹ in tetrabutylammonium iodide), platinum bead as working electrode and platinum foil as counter electrode. Solvent supporting electrolyte was 0.1 mol L⁻¹ NaClO₄ in acetonitrile, the substrate concentration was 3 mmol L⁻¹, and the sweep rate was 200 mV s⁻¹.

Starting material preparation

The 2-methoxy-, 3-methoxy- and 2,5-dimethoxy-cinnamic acids were purchased from Aldrich Chemical Co. The 4-methoxy-, 3,4-dimethoxy- and 3,4,5-trimethoxy-

cinnamic acids were prepared by Knoevenagel synthesis¹². The 3-(4-methoxyphenyl)propanoic acid was prepared from malonic ester¹³. The methyl esters were obtained by esterification with methanol in acidic medium¹⁴.

General procedure for the electrolyses

The compounds **1** - **7** (3.5 – 5.5 mmol) were electrolyzed in two different cells: undivided and divided cell made of glass (35 or 70 mL) and equipped with a platinum foil (2.5 x 2.5 cm) or a graphite plate (3.5 x 4.5 cm) as working electrode and a tungsten wire as counter electrode. The electrolyses were conducted at constant current or controlled potential (see Tables 2 and 3). The solvent was dry methanol containing NaClO₄ as supporting electrolyte or sodium methoxide in methanol (see details in Tables 2 and 3). After the passage of the appropriate amount of electricity the cell contents were worked up using 3 different procedures: *i*) The solvent was evaporated until dryness under reduced pressure and a solution of 0.1mol L⁻¹ H₂SO₄ in methanol was added until pH 7.0. The mixture was extracted with dichloromethane or ethyl ether (3x50 mL), washed with water (3x10mL) and dried over magnesium sulfate (neutral procedure). *ii*) The solvent was

evaporated and the residue was extracted directly, washed and dried (basic procedure). *iii*) After the evaporation of the solvent, the mixture was acidulated (pH=2) with diluted HClO₄, and then extracted, washed and dried.

In all cases the solvent was stripped in vacuum and the mixture was passed through to a chromatographic column (SiO₂ Merck 60G or alumina) using hexane/ethyl acetate in varying proportions as eluent. Yields were calculated from gas chromatography using biphenyl ether as the internal standard.

Electrolysis products identification

The products **8** and **9** were characterized by comparison of their MS spectra with those of the authentic samples.

8, MS (*m/z*): 136(67), 135(100), 107(20), 92(18), 77(40), 63(24), 50(19).

9, MS (*m/z*): 182(2), 151(100), 135(10), 108(6), 75(10), 51(4).

10, ¹H-NMR 200MHz, δ (CDCl₃) 3.22 (3H, s), 3.36 (3H, s), 3.61(3H, s), 3.77 (3H, s), 3.83 (1H, d, *J* 5.3Hz), 4.42 (1H, d, *J* 5.3Hz), 6.85 (2H, d, *J* 8.7Hz), 7.25 (2H, d, *J* 8.7Hz). ¹³C NMR 40MHz δ (CDCl₃) 51.8, 55.1, 57.2, 59.1, 83.2, 85.2, 113.7, 128.9, 130.8, 159.7, 170.8.

11, ¹H NMR 300MHz, δ(CDCl₃) 3.26 (3H, s), 3.28 (3H, s), 3.42 (3H, s), 3.68 (3H, s), 3.80 (3H, s), 4.48 (1H, s), 6.87 (2H, d, *J* 8.7Hz), 7.28 (2H, d, *J* 8.7Hz). ¹³C NMR 75MHz δ(CDCl₃) 51.5, 51.7, 52.2, 55.1, 57.2, 84.6, 103.0, 113.5, 127.8, 129.5, 159.7, 170.8. MS (*m/z*): M⁺ – OCH₃, 253(1), 225(3), 179(3), 151(100), 135(12), 77(6).

12, MS (*m/z*): 254(10), 239(11), 223(100), 191(53), 161(79), 123(28), 89(55), 75(50).

13, ¹H NMR 200MHz, δ (CDCl₃) 3.32 (3H, s), 3.75 (3H, s), 6.23 (1H, d, *J* 15.6Hz), 6.43 (2H, d, *J* 10.0Hz), 6.63 (1H, d, *J* 15.6Hz), 6.69 (2H, d, *J* 10.0 Hz). ¹³C NMR 40MHz δ (CDCl₃) 51.8, 52.9, 74.8, 122.4, 131.6, 144.3, 147.6, 166.1, 184.4. MS (*m/z*): 209(10), 176(100), 161(27), 148(93), 14(47), 121(81), 105(28), 91(54), 63(70).

14, ¹H NMR 200MHz, δ (CDCl₃) 3.79 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.92 (3H, s), 6.34 (1H, d, *J* 16.1Hz), 6.50 (1H, s), 7.12 (1H, s), 7.97 (1H, d, *J* 16.1Hz). ¹³C NMR 75MHz, δ (CDCl₃) 51.8, 56.1, 56.5, 97.1, 111.1, 115.5, 143.4, 148.8, 153.9, 166.8, 168.1.

15, ¹H NMR 300MHz, δ(CDCl₃) 3.40 (6H, s), 3.41 (6H, s), 3.92 (3H, s), 6.03 (1H, d, *J* 10.7Hz), 6.15 (1H, s), 6.31 (1H, d, *J* 10.7 Hz), 6.37 (1H, d, *J* 16.0 Hz), 7.64 (1H, d, *J* 16.0 Hz).

16, ¹H NMR 300MHz, δ (CDCl₃) 3.40 (6H, s), 3.80 (3H, s), 3.90 (3H, s), 6.08 (1H, d, *J* 16.0Hz), 6.87 (1H, d, *J* 8.3Hz), 7.05 (1H, d, *J* 1.9Hz), 7.11 (1H, dd, *J* 1.9 and 8.3Hz), 7.29 (1H, d, *J* 16.0Hz).

17², ¹H NMR 200MHz, δ (CDCl₃) 2.97 (6H, s), 3.33 (6H, s), 3.77 (3H, s), 5.93 (1H, d, *J* 10.6Hz), 6.31 (1H, dd, *J* 2.6 and 10.6Hz), 6.48 (1H, d, *J* 2.6Hz), 6.70 (1H, d, *J* 10.0 Hz), 7.13 (1H, d, *J* 10.0 Hz). MS (*m/z*): 284(2), 253(40), 221(23), 211(28), 181(54), 117(23), 105(32), 75(100).

18, ¹H NMR 200MHz, δ (CDCl₃) 3.80 (6H, s), 3.81 (3H, s), 3.86 (3H, s), 6.46 (1H, d, *J* 16.2Hz), 6.53 (1H, d, *J* 2.8Hz), 6.59 (1H, d, *J* 2.8Hz), 7.98 (1H, d, *J* 16.2Hz). ¹³C NMR 75MHz, δ (CDCl₃): 51.8, 55.5, 55.8, 61.5, 102.5, 104.8, 119.1, 128.1, 139.5, 142.9, 153.7, 156.0, 167.4. MS (*m/z*): 254(1), 222(70), 191(100), 176(21), 161(14), 148(30), 133(24), 105(25), 91(11), 77(20).

19, ¹H NMR 200MHz, δ (CDCl₃) 2.56 (1H, dd, *J* 4.8 and 15.2Hz), 2.82 (1H, dd, *J* 9.0 and 15.2Hz), 3.20 (3H, s), 3.68 (3H, s), 3.79 (3H, s), 4.59 (1H, dd, *J* 4.8 and 9.0 Hz), 6.89 (2H, d, *J* 8.7Hz), 7.27 (2H, d, *J* 8.7Hz). ¹³C NMR 75MHz, δ (CDCl₃) 43.3, 51.7, 55.3, 56.5, 79.5, 113.9, 127.8, 144.5, 159.0, 169.0. MS (*m/z*): 224(4), 164(12), 151(100), 121(18), 107(5), 91(81), 77(10).

20, ¹H NMR 200MHz, δ (CDCl₃) 2.10 (4H, m), 3.26 (3H, s), 3.31 (6H, s), 3.78 (3H, s), 5.81 (2H, d, *J* 10.2 Hz), 6.16 (2H, d, *J* 10.2 Hz). MS (*m/z*): 256(2), 224(100), 177(23), 164(32), 151(67), 121(45), 91(19), 77(20).

Acknowledgements

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