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TETRAHEDRON

Total Synthesis of Maesanin and Analogues

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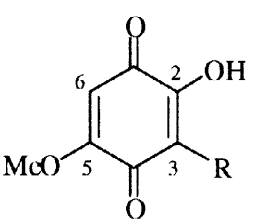
Abstract: An efficient total synthesis of maesanin and related quinones is reported, through direct alkylation of 1,2,4,5-tetramethoxybenzene with alkylbromides, followed by oxidation with ceric ammonium nitrate (CAN) which provokes formation of the quinone and deprotection of the more hindered methyl ether in one step, to furnish the desired 2-hydroxy-5-methoxy-1,4-benzoquinones **1a-h**.

INTRODUCTION

Naturally occuring quinones bearing a saturated or unsaturated side chain are of a great importance owing to their biological activity [1]. Those bearing hydroxyl and methoxyl groups on the quinone nucleus are the most promising. For example, maesanin **1a** [2] originally isolated from the fruit of East African medicinal plant *Maesa lanceolate*, displays antimicrobial activity, host defensive stimulation in mice [3], 5-lipoxygenase inhibitory activity [4, 5], cytotoxicity against several solid tumor cells [6], mitochondrial oxidative phosphorylation [7] and aldol reductase activity [6]. Other related quinones such as pallasone C **1b**, [8] Ardisianone B **1c** (5-lipoxygenase inhibitory activity), [5] hydroxydietrichequinone **1d**, [9] irisoquin **1e** (cytotoxic toward P 388 leukemia cells) [10], 5-O-methyl-rapanone **1f** [9], 5-O-methyl-embelin **1g** (pesticide and antifungal activities) [11], have been isolated from natural sources.



1a: R= $(CH_2)_9CH^{Z}{=}CH(CH_2)_3CH_3$ Maesanin

1b: R= $(CH_2)_9CH^{Z}{=}CH(CH_2)_7CH_3$ Pallasone C

1c R= $(CH_2)_7CH^{Z}{=}CH(CH_2)_3CH_3$ Ardisianone B

1d: R= $(CH_2)_7CH^{Z}{=}CH(CH_2)_7CH_3$ Hydroxydietrichequinone

1e R= $(CH_2)_{17}CH_3$ Irisoquin

1f R= $(CH_2)_{12}CH_3$ 5-O-Methyl-rapanone

1g R= $(CH_2)_{10}CH_3$ 5-O-Methyl-embelin

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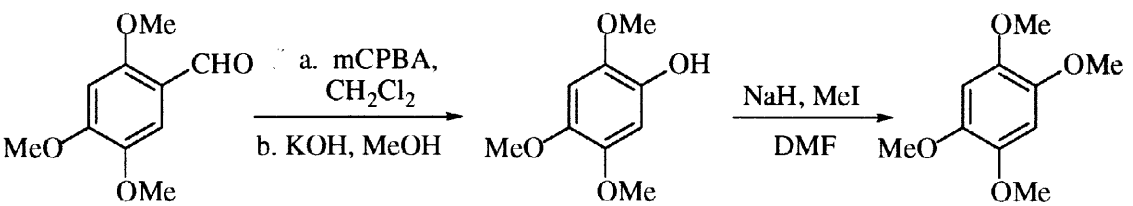
Owing to their interesting biological activities a number of synthetic studies [2, 12, 13, 14] of this important class of compounds were previously published, which, in most cases have been focused on elaboration of the side chain on the aromatic ring. [2, 5, 15] However, direct alkylation of the aromatic ring with an alkyl halide has not been reported, except the palladium-mediated coupling of bromobenzene derivatives with terminal olefin, by which the unsaturated side chain of maesanin was introduced *via* 4 steps reaction. [14]

Herein, we report an efficient and practical synthesis of maesanin **1a** and related alkylated quinones based on the alkylation of 1,2,4,5-tetramethoxybenzene which bears all substituents of the quinone moiety of maesanin, with an appropriate alkylbromide, so the requisite side chain could be introduced in one step. Further oxidation of the resulting tetramethoxybenzyl appendage with ceric ammonium nitrate provided the desired 2-hydroxy-5-methoxy-1,4-benzoquinones.

RESULTS AND DISCUSSION

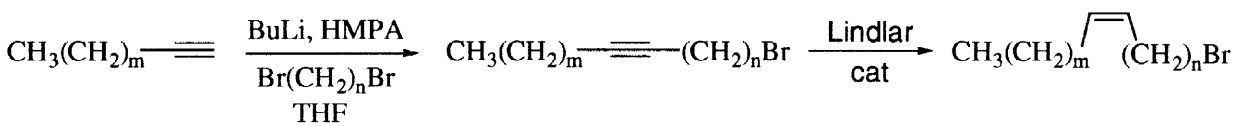
1,2,4,5-Tetramethoxybenzene was prepared by Baeyer-Villiger oxidation of the commercially available trimethoxybenzaldehyde **2** with mCPBA to give the 2-formyloxy-1,4,5-trimethoxybenzene intermediate, which was hydrolyzed with potassium hydroxide providing compound **3**. Protection of the resulting alcohol **3** by methyliodide gave compound **4** [16] in 87% yield over two steps (scheme 1).



2 **3** **4**

Scheme 1

The unsaturated side chains of maesanin and related quinones **1a-1c** were prepared by reaction of 1-alkyne **5a-b** (m=3 or m=7) with n-BuLi in the presence of 4 equiv of dibromoalkanes **6a-b** (n=9 or n=7) giving alkylbromides **7a-c** which were subjected to partial hydrogenation over Lindlar's catalyst providing the bromo olefins **8a-c** [15] in 85%, 80% and 90% yield respectively (scheme 2). Bromo olefin **8d** was previously prepared in one step by radical decarboxylation of readily available oleic acid in the presence of bromotrichloromethane.[17]



5a: m=3
5b: m=7

6a: n=9
6b: n=7

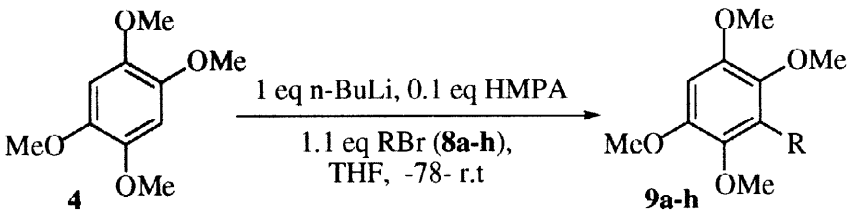
7a: m=3, n=9
7b: m=7, n=9
7c: m=3, n=7

8a: m=3, n=9
8b: m=7, n=9
8c: m=3, n=7

Scheme 2

At this stage, the coupling reaction of tetramethoxybenzene **4** with alkylbromide was performed. Thus, metallation of tetramethoxybenzene **4** with 1 equivalent of n-BuLi in THF, followed by addition of

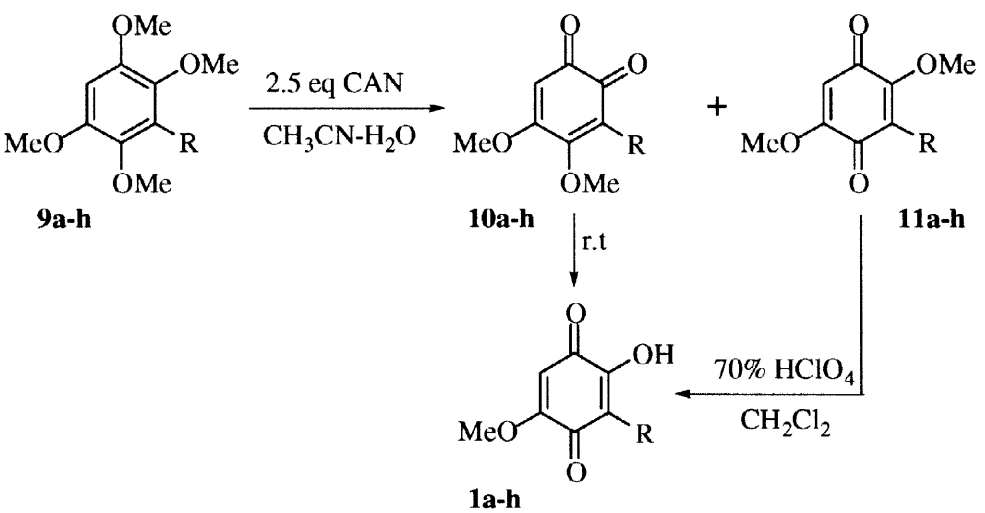
alkenylbromide **8a** afforded alkylated product **9a** in 72% yield. In a similar fashion, alkylation of **4** in the presence of **8b-d** and the readily available alkylbromides **8e-h** gave the desired addition products **9b-h** in good yield. Results are given in scheme 3. Using alkyliodide derivatives of **8** as alkylating agents in order to increase the yield of reaction provided the same results.



8a: R=$(CH_2)_9CH\overset{Z}{=}CH(CH_2)_3CH_3$ **9a** (72%)
8b: R=$(CH_2)_9CH\overset{Z}{=}CH(CH_2)_7CH_3$ **9b** (70%)
8c: R=$(CH_2)_7CH\overset{Z}{=}CH(CH_2)_3CH_3$ **9c** (70%)
8d: R=$(CH_2)_7CH\overset{Z}{=}CH(CH_2)_7CH_3$ **9d** (74%)
8e: R=$(CH_2)_{17}CH_8$ **9e** (71%)
8f: R=$(CH_2)_{12}CH_8$ **9f** (74%)
8g: R=$(CH_2)_{10}CH_3$ **9g** (76%)
8h: R=$(CH_2)_2CH(CH_3)_2$ **9h** (77%)

Scheme 3

Having the alkylated compounds **9a-h** in hand we proceeded to the oxidation with ceric ammonium nitrate (CAN) to accomplish deprotection of methyl ethers and formation of the quinone system. Addition of a solution of ceric ammonium nitrate (2.5 equiv, CH_3CN-H_2O, -5°C) to compound **9a**, resulted in immediate formation of *ortho*-quinone **10a** accompanied by an amount of *para*-quinone **11a** [18] (36%). When the reaction mixture was allowed to stir at room temperature, smooth demethylation of the more hindered methyl group occured, providing maesanin **1a** in 60% yield.



Scheme 4

Treatment of compounds **9b-h** with CAN resulted in formation of the desired compounds **1b-h** along with the *para*-quinones **11b-h** (conditions A). Results are given in table 1. Attempts to reduce either the amount of *ortho*-quinones **10a-h** or *para*-quinones **11a-h** using different solvents or by varying temperature were unsuccessful. However, given that simple acid hydrolysis, using $HClO_4$, extruded the more hindered methoxy group of 2,5-dimethoxy-1,4-benzoquinone substituted with a simple alkyl chain [2b], treatment of the isolated *para*-quinone **11a** with a few drop of $HClO_4$ gave maesanin **1a** in more than 90% yield. Thus, the overall yield of the reaction was improved by treating the crude mixture of CAN oxidation with catalytic amount of $HClO_4$ in CH_2Cl_2 providing compound **1** as the major product (conditions B).

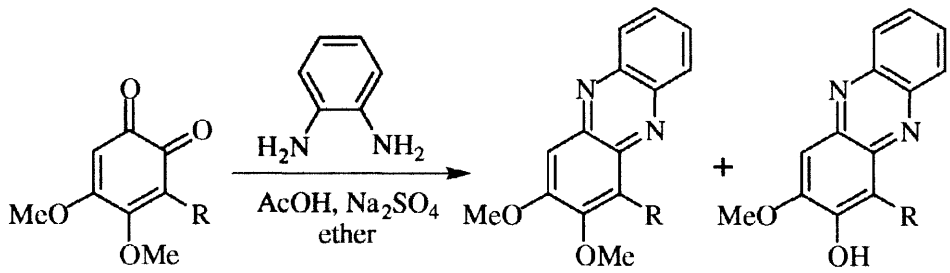
Table 1

entry	substrates	condition	Products yield (%)		
1	**9a**	A	Maesanin	**1a** (60)	**11a** (36)
		B		**1a** (76)	
2	**9b**	A	Pallasone C	**1b** (60)	**11b** (34)
		B		**1b** (74)	
3	**9c**	A	Ardisianone B	**1c** (53)	**11c** (32)
		B		**1c** (76)	
4	**9d**	A	Hydroxydietrichequinone	**1d** (56)	**11d** (31)
		B		**1d** (74)	
5	**9e**	A	Irisoquin	**1e** (61)	**11e** (35)
		B		**1e** (75)	
6	**9f**	A	Methyl-rapanone	**1f** (54)	**11f** (35)
		B		**1f** (78)	
7	**9g**	A	Methyl-embelin	**1g** (56)	**11g** (36)
		B		**1g** (75)	
8	**9h**	A		**1h** (57)	**11h** (36)
		B		**1h** (79)	

The structure of *para*-quinones **11** was proved by methylation of compound **1a** using diazomethane (CH_2N_2), to provide a methylated product which was identical in all respects (TLC, NMR, IR) with compound **11a**. Regarding the structure of *ortho*-quinones **10**, the *ortho*-quinone **10h** was isolated and treated with *ortho*-phenylenediamine [18] to give adducts **12** and **13** in 6% and 52% yields respectively, whose structures were confirmed by NMR and MS. Adduct **13** is the result of conversion of *ortho*-quinone **10** to compound **1**, due to acitity of reaction medium, tautomerisation of this latter to *ortho*-quinone intermediate and subsequent reaction with *ortho*-phenylenediamine. (Scheme 5)

These results show that 1,2-*ortho*-quinones **10** are sensitive to acidic conditions and undergo facile transformation to the more stable 1,4-*para*-quinones. [19] This confirmed that demethylation of **10** was due to the acidity of the reaction medium during CAN oxidation. In fact the pH of the reaction measured at the beginning was 1.3, and dropped to 0.7 was sufficient to cause conversion of *ortho*-quinones **10** to *para*-quinones **1**. In addition, treatment of the isolated *ortho*-quinone **10h** in a CH_3CN-H_2O mixture adjusted to pH 1.3 resulted in

clean transformation of *ortho*-quinone **10h** to *para*-quinone **1h** within 2 hours in nearly quantitative yield, at room temperature.

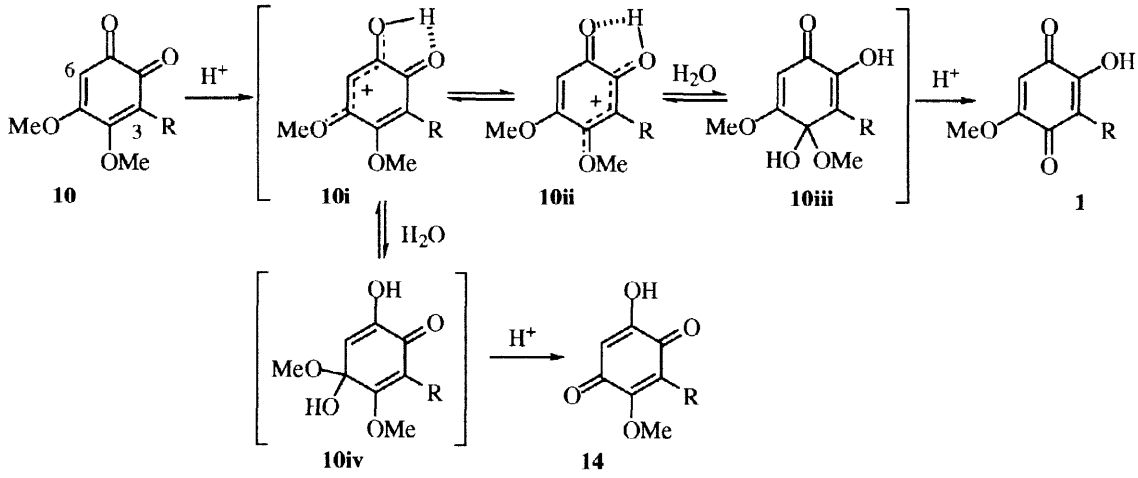


10h **12** **13**

R: $(CH_2)_2CH(CH_3)_2$

Scheme 5

From the above results the selective demethylation could be explained by protonation of *ortho*-quinone **10** giving rise to carbocation intermediates **10i** (site 6) and **10ii** (site 3) The carbocation **10ii** which is stabilized by electron-donor effect due to R substituent led after hydrolysis of the resulting hemiacetal intermediate **10iii** to the desired product **1**. On the other hand, the less stable carbocation **10i** would provide compound **14** which was not observed in our reaction, confirming that the extrusion of the more hindered methyl group occured through the more stable carbocation **10ii** rather than **10i** (scheme 6). However, further studies are needed to determine the influence of R substituents on selective demethylation.



10 **10i** **10ii** **10iii** **1**

10iv **14**

Scheme 6

In summary we have described an efficient and practical synthesis of naturally occuring 2-hydroxy-5-methoxy-1,4-benzoquinones derivatives **1a-h**. For example the total synthesis of maesanin **1a** requires 5+2 steps, and proceeds in 47% overall yield from readily available starting materials. Direct alkylation of tetramethoxybenzene with alkylbromide followed by ceric ammonium nitrate (CAN) oxidation which causes formation of quinone and deprotection of one methyl ether in one pot, offers a rapid access to potentially useful analogues. One example of such analogues is the new quinone **1h**, which showed a remarkable antibiotic activity against *S. aureus* 209 P (CMI 1 μg/ml).

EXPERIMENTAL SECTION

All the reactions were carried out under an argon atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Mass spectra were recorded on a Kratos MS 50 instrument at 70 eV (EI) or Nermag 10-10 (CI, NH_3). I.R. spectra were recorded on a Nicholet (impact 400D) FT IR. All reagents were obtained from commercial suppliers and used without further purification. THF, ether and methylene chloride were freshly distilled from sodium benzophenone and CaH_2 respectively. Flash chromatography was carried out using silicagel 60F254 (Merck) with mixtures of ethyl acetate and hexane as eluent unless specified otherwise. TLC analyses were performed on thin-layer analytical plates 60F254 (Merck). Elementary analyses were carried out in the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette.

2,4,5-trimethoxy-phenol (3):

To a solution of benzaldehyde (3.92 g, 20 mmol) in dry CH_2Cl_2 (40 mL), 70% mCPBA (5 g, 30mmol) was added at 0°C. The mixture was stirred for 2h at room temperature and the resulting precipitates were filtered. The filtrate was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried and concentrated to yield the formate intermediate which was hydrolyzed with 10% KOH in EtOH at 50°C for 2h. The mixture was extracted with ether and the aqueous layer was acidified with dil HCl and again extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to a flash chromatography using hexane-ethylacetate (8-2) as eluent to give compound **3** (3.42 g, 93% yield) as a light pink solid , mp : 59 °C; ^1H NMR ($CDCl_3$) 6.60 (1H, s), 6.57 (1H, s), 5.54 (1H, s), 3.82 (6H, s), 3.79 (3H, s); ^{13}C NMR ($CDCl_3$) 143.7, 141.9, 139.5, 100.8, 99.5, 57.0, 56.8, 56.3; I.R.(KBr) 3415, 3080, 3005, 2940, 2840, 1625, 1525, 1200, 855 cm^{-1}; $[M+H]^+(CH_4)$: *m/z* 185; HRMS (CI, CH_4) calcd. for $C_9H_{13}O_4$: 185.0814, found: 185.0806.

1,2,4,5-tetramethoxybenzene (4):

To a solution of NaH (60% oil dispersion; 0.895 g, 22.4 mmol, washed with several portions of hexane) in dry DMF was added a solution of alcohol **3**(3.42 g, 18.6 mmol) in dry DMF (30 mL) and the mixture was stirred at 0 °C for 30 min. MeI was added (1.74 mL, 27.9 mmol) in one portion and the mixture was stirred at room temperature for 1 h. MeOH was added and DMF evaporated under reduced pressure. The residue was extracted with ether, washed successively with water, brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue purified over a silica gel column using hexane:ethylacetate (8:2) as eluent to give compound **4** (3.46 g, 94%), white needles, mp : 101-102 °C (lit.[15] , 103°C) ; ^1H NMR ($CDCl_3$) 6.60 (2H, s), 3.84 (12H, s); ^{13}C NMR ($CDCl_3$), 143.1, 100.6, 57.0; I.R.(KBr) 3010, 2975, 2855, 1550, 1480, 1455, 1235, 1205; M^+(EI): *m/z* 198; calcd. for $C_{10}H_{14}O_4$: C 60.58, H 7.12; found: C 60.52, H 7.09.

(Z)-1-bromo-10-pentadecene (8a):

To a solution of 1-hexyne **5a** (5 mmol, 563 µl), HMPA (0.5 mmol, 87 µl), and 2mg of triphenylmethane in dry THF (50 mL) under argon at -40 °C was added n-BuLi (5 mmol) dropwise. The mixture was stirred at

this temperature until the solution turned pink-red colour, then 1,9-dibromononane **6a** (20 mmol, 4.04 mL) was added at -40 °C and the mixture heated under reflux for 48 h. THF was removed under reduced pressure, the residue dissolved in hexane, washed with water, and brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The excess of dibromide was removed in high vaccum. The remaining residual liquid was subjected to silica gel column chromatography using heptane as eluent, providing the bromoalkyne **7a** as a colourless oil which was dissolved in dry benzene. To this solution was added 254 mg (20% w/w) of Lindlar catalyst ($Pd/CaCO_3/Pb$) and the mixture was stirred at room temperature under 1 atm hydrogen (balloon) for 12 h. The reaction was filtered through Celite, and the filtrate concentrated in vacuo. Flash chromatography using hexane as eluent afforded the *cis*-alkene **8a** (1.23 g, 85%) as a colourless oil.

^1H NMR ($CDCl_3$) 5.32 (2H, dd AB syst J = 6Hz), 3.38 (2H, t), 2.03 (4H, m), 1.84 (2H, m), 1.43-1.37 (2H, m), 1.28-1.26 (14H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 129.9, 129.8, 33.8, 32.8, 32.6, 31.9, 29.7, 29.5, 29.3, 29.3, 29.1, 28.8, 28.2, 27.2, 22.8, 14.2; I.R.(neat) 1660, 1470, 730; M^+(EI): 288-290. Spectral data were in agreement with values given in literature [11].

(Z)-1-bromo-10-nonadecene (8b):

This compound was prepared according to the procedure described for **8a**, from 1-decyne (5 mmol, 0.900 mL) and 1,9-dibromononane (20 mmol, 4.04 mL). (1.38 g, 80%), colourless oil; ^1H NMR ($CDCl_3$) 5.34 (2H, dd AB syst J = 6Hz), 3.39 (2H, t), 2.01 (4H, m), 1.86 (2H, m), 1.44-1.39 (2H, m), 1.29-1.27 (22H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$), 129.9, 129.8, 33.9, 32.8, 32.6, 31.9, 29.8, 29.5, 29.4, 29.3, 29.2, 28.8, 28.2, 27.2, 22.7, 14.1; I.R.(neat) 1660, 1470, 732; M^+(EI): *m/z* 344-346; Spectral data were in agreement with literature values [11].

(Z)-1-bromo-8-tridecene (8c):

This compound was prepared according to the procedure described for **8a**, from 1-hexyne (5 mmol, 0.563 mL) and 1,7-dibromoheptane (20 mmol, 3.42 mL). (1.17 g, 90%), colourless oil, ^1H NMR ($CDCl_3$) 5.34 (2H, dd AB syst J = 6Hz), 3.39 (2H, t), 2.02 (4H, m), 1.85 (2H, m), 1.44-1.40 (2H, m), 1.33-1.30 (10H, m), 0.89 (3H, t); ^{13}C NMR ($CDCl_3$) 129.9, 129.6, 33.8, 32.8, 31.9, 29.6, 29.0, 28.6, 28.1, 27.1, 26.9, 22.3, 14.0; I.R.(neat) 1660, 1474, 732; M^+(EI): *m/z* 260-262; calcd. for $C_{13}H_{25}Br$: C 59.77, H 9.65; found: C 59.57, H 9.63.

Addition of 1,2,4,5-tetramethoxybenzene to bromoalkyl: general procedure.

To a solution of 1,2,4,5-tetramethoxybenzene **4** (1 mmol, 198 mg) and HMPA (0.1 mmol, 0.017 mL) in dry THF (5 mL), was added n-BuLi (1.6 M in hexane, 0.625 mL, 1 mmol), dropwise, at -40 °C over 30 min. The reaction was warmed to -10 °C over 1h and stirred at this temperature for an additional 1 h. To this was added a solution of alkylbromide **8a-h** (1.1 mmol) and the reaction was stirred overnight. The reaction mixture was quenched with saturated NH_4Cl, and extracted with ether. The organic layer was washed with water, and brine, dried over $MgSO_4$ and concentrated. The residue was purified over silica gel using hexane-ethylacetate as eluent, affording alkylated compounds **9a-h.**

(Z)-1-[2,3,5,6-tetramethoxyphenyl]-10-pentadecene (9a):

Colourless oil; ^1H NMR ($CDCl_3$) 6.41 (1H, s), 5.36 (2H, AB syst J = 5 Hz), 3.84 (6H, s), 3.77 (6H, s), 2.61 (2H, t), 2.00 (4H, m), 1.51 (2H, m), 1.39-1.28 (16H, m), 0.89 (3H, t); ^{13}C NMR ($CDCl_3$) 148.7, 141.0,

131.1, 129.9, 129.8, 96.6, 60.9, 56.2, 32.6, 31.9, 30.7, 29.9, 29.7, 29.6, 29.5, 29.3, 29.1, 27.1, 24.6, 22.6, 13.9; I.R.(neat) 2930, 2845, 1600, 1492, 1470, 1090, 851, 810, 732; M^+(EI) *m/z* 406; calcd. for $C_{25}H_{42}O_4$: C 73.85, H 10.41; found: C 73.71, H 10.23.

(Z)-1-[2,3,5,6-tetramethoxyphenyl]-10-nonadecene (9b):

Colourless oil; ^1H NMR ($CDCl_3$) 6.41 (1H, s), 5.34 (2H, t AB syst J = 5 Hz), 3.84 (6H, s), 3.77 (6H, s), 2.61 (2H, t), 2.00 (4H, m), 1.53 (2H, m), 1.32-1.27 (24H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 148.7, 141.0, 131.1, 129.9, 129.8, 96.7, 60.8, 56.2, 32.5, 31.9, 30.7, 29.9, 29.7, 29.6, 29.5, 29.3, 29.1, 27.1, 24.6, 22.6, 14.0; I.R.(neat) 2930, 2845, 1600, 1492, 1470, 1090, 851, 810, 730; M^+(EI): *m/z* 450; calcd. for $C_{29}H_{50}O_4$: C 75.28, H 10.89; found: C 75.12, H 10.77.

(Z)-1-[2,3,5,6-tetramethoxyphenyl]-8-tridecene (9c):

Colourless oil; ^1H NMR ($CDCl_3$) 6.41 (1H, s), 5.34 (2H, AB syst J = 5 Hz), 3.84(6H, s), 3.77 (6H, s), 2.61 (2H, t), 2.01 (4H, m), 1.53(2H, m), 1.37-1.27 (12H, m), 0.89 (3H, t); ^{13}C NMR ($CDCl_3$), 148.7, 141.0, 131.0, 129.9, 129.7, 96.6, 60.8, 56.1, 32.6, 31.9, 30.7, 29.9, 29.7, 29.3, 29.2, 27.1, 26.8, 24.6, 22.3, 13.9; I.R.(neat) 2930, 2845, 1655, 1600, 1492, 1470, 1090, 851, 810, 734; M^+(EI):*m/z* 378; calcd. for $C_{23}H_{38}O_4$: C 73.31, H 10.19; found: C 72.98, H 10.12.

(Z)-1-[2,3,5,6-tetramethoxyphenyl]-8-heptadecene (9d):

Colourless oil; ^1H NMR ($CDCl_3$) 6.40 (1H, s), 5.33 (2H, AB syst J = 5 Hz), 3.82 (6H, s), 3.76 (6H, s), 2.62 (2H, t), 2.00 (4H, m), 1.52 (2H, m), 1.33-1.27 (20H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 148.6, 141.0, 130.8, 129.7, 129.6, 96.6, 60.6, 56.0, 31.8, 30.6, 29.8, 29.7, 29.6, 29.4, 29.2, 29.1, 27.1, 24.5, 22.5, 13.9; I.R.(neat) 2930, 2850, 1652, 1600, 1492, 1470, 1095, 851, 810, 732; M^+(EI): *m/z* 434; calcd. for $C_{27}H_{46}O_4$: C 74.60, H 10.67; found: C 74.38, H 10.58.

1-[2,3,5,6-tetramethoxyphenyl]-octadecane (9e):

White cryst., mp : 45 °C; ^1H NMR ($CDCl_3$) 6.41 (1H, s), 3.84 (6H, s), 3.77 (6H, s), 2.61 (2H, t), 1.53 (2H, m), 1.38-1.26 (30H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 148.8, 141.0, 131.1, 96.7, 60.9, 56.2, 31.9, 30.8, 30.0, 29.7, 29.6, 29.5, 29.4, 29.0, 24.7, 22.7, 14.1; I.R.(KBr) 2922, 2845, 1600, 1498, 1470, 1095, 807; M^+(EI): *m/z* 450; calcd. for $C_{28}H_{50}O_4$: C 74.62, H 11.18; found: C 74.69, H 11.04.

1-[2,3,5,6-tetramethoxyphenyl]-tridecane (9f):

White cryst., mp : 31-32 °C; ^1H NMR ($CDCl_3$) 6.41 (1H, s), 3.84 (6H, s), 3.77 (6H, s), 2.61 (2H, t), 1.53 (2H, m), 1.48-1.26 (20H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 148.8, 141.0, 131.1, 96.6, 60.9, 56.2, 31.9, 30.7, 30.0, 29.7, 29.5, 29.4, 29.3, 24.6, 22.6, 14.1; I.R.(KBr) 2920, 2850, 1600, 1490, 1465, 1095; M^+(EI): *m/z* 380; calcd. for $C_{23}H_{40}O_4$: C 72.59, H 10.59; found: C 72.62, H 10.53.

1-[2,3,5,6-tetramethoxyphenyl]-undecane (9g):

Colourless oil, ^1H NMR ($CDCl_3$), δ (ppm) 6.41 (1H, s), 3.83 (6H, s), 3.77 (6H, s), 2.61 (2H, t), 1.53 (2H, m), 1.48-1.26 (16H, m), 0.87 (3H, t); ^{13}C NMR ($CDCl_3$) 148.7, 141.0, 131.0, 96.6, 60.8, 56.1, 31.8, 30.7, 29.9,

29.6, 29.55, 29.5, 29.4, 29.3, 24.6, 22.6, 14.0; I.R.(neat) 2925, 2855, 1600, 1492, 1095, 852, 807; $[M+H]^+(CH_4)$: *m/z* 353; HRMS (CI, NH_3), calcd. for $C_{21}H_{36}O_4$: 352.2613, found: 352.2625.

1-[2,3,5,6-tetramethoxyphenyl]-isopentane (9h):

White cryst., mp : 31-32 °C; ^1H NMR ($CDCl_3$) 6.41 (1H, s), 3.84 (6H, s), 3.77 (6H, s), 2.61 (2H, m), 1.61 (1H, m), 1.46-1.38 (2H, m), 0.95 (6H, d); ^{13}C NMR ($CDCl_3$) 148.8, 141.0, 131.3, 96.6, 60.8, 56.2, 40.0, 28.4, 22.5, 22.4; I.R.(KBr) 2920, 2850, 1598, 1465, 1095; $[M+H]^+(CH_4)$: 269; HRMS (CI, CH_4), calcd. for $C_{15}H_{25}O_4$: 269.1753, found: 269.1754.

General procedure of oxidation by CAN:

Condition A :To a solution of compound **9a-h** (1 mmol) in CH_3CN (10 mL), was added a solution of ammonium cerium(IV) nitrate (2.5 mmol) in CH_3CN-H_2O (10 mL, 7:3) dropwise at -7 °C (salt-ice bath) over 1 h. The reaction was allowed to stir at rt for 2 h, and diluted with ether (50 mL). The organic layer was washed with distilled water (20 mL), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel using hexane:EtOAc (9:1 to 6:4) as eluent to give compounds **11a-h** and **1a-h.**

Condition B: The crude mixture of **11a-h** and **1a-h,** without purification, was dissolved in dry CH_2Cl_2 (10 mL) and treated with few drops of $HClO_4$. The mixture was stirred at room temperature for 4 h, the mixture diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel as described in condition A to afford compounds **1a-h.**

2-Hydroxy-5-methoxy-3-(10-pentadecenyl)-1,4-benzoquinone (Maesanin) (1a):

Orange cryst., mp : 68-69 °C (lit [2] 69 °C); R_f: 0.33 (7:3 hexane:AcoEt); ^1H NMR ($CDCl_3$) 7.23 (1H, br), 5.84 (1H, s), 5.34 (2H, t, AB syst J = 5 Hz), 3.86 (3H, s), 2.44 (2H, t), 2.01 (4H, m), 1.44 (2H, m), 1.26 (16H, m), 0.89 (3H, t); ^{13}C NMR ($CDCl_3$) 182.8, 181.7, 161.1, 151.5, 129.8, 119.2, 102.1, 56.6, 32.5, 31.8, 29.7, 29.5, 29.3, 29.2, 28.8, 28.6, 27.9, 27.1, 24.6, 22.6, 22.5, 14.0; I.R.(KBr) 3350, 2920, 2840, 1665, 1640, 1598, 1465, 1205, 730; M^+(EI): *m/z* 362. Calcd. for $C_{22}H_{34}O_4$: C 72.89, H 9.45; found: C 72.61, H 9.61. Spectral data were in agreement with literature values. [2]

2-5-dimethoxy-3-(10-pentadecenyl)-1,4-benzoquinone (11a):

Yellow oil; R_f : 0.49 (7:3 hexane:AcoEt); ^1H NMR ($CDCl_3$) 5.73 (1H, s), 5.34 (2H, t AB syst J = 4.5 Hz), 4.04 (3H, s), 3.81 (3H, s), 2.43 (2H, t), 2.01 (4H, m), 1.38 (2H, m), 1.27 (16H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 183.4, 182.3, 158.6, 155.7, 130.5, 129.7, 105.2, 61.2, 56.2, 32.5, 31.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.6, 28.3, 27.1, 23.0, 22.6, 13.9; I.R.(neat) 2935, 2850, 1670, 1605, 1460, 1340, 1215, 1045, 842, 725; M^+(EI): *m/z* 376; calcd. for $C_{23}H_{36}O_4$: C 73.37, H 9.64; found: C 73.21, H 9.85.

2-Hydroxy-5-methoxy-3-(10-nonadecenyl)-1,4-benzoquinone (Pallasone C) (1b):

Orange cryst., mp : 72-73 °C; R_f: 0.39 (7:3 hexane:AcOEt); ^1H NMR ($CDCl_3$) 7.24 (1H, br), 5.84 (1H, s), 5.34 (2H, t AB syst J = 5 Hz), 3.86 (3H, s), 2.44 (2H, t), 2.00 (4H, m), 1.44 (2H, m), 1.26 (24H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$), 182.8, 181.6, 161.0, 151.5, 129.8, 119.2, 102.1, 56.6, 32.5, 31.8, 29.7, 29.5, 29.3, 29.2, 28.8, 28.6, 27.9, 27.1, 24.6, 22.6, 22.5, 14.0; I.R.(KBr) 3350, 2920, 2840, 1665, 1640, 1598, 1465, 1210, 1204, 733; M^+(EI): *m/z* 418. Spectral data were in agreement with literature values . [8]

2-5-dimethoxy-3-(10-nonadecenyl)-1,4-benzoquinone (11b):

Yellow oil; R_f: 0.52 (7:3 hexane:AcOEt); ^1H NMR ($CDCl_3$) 5.73 (1H, s), 5.34 (2H, AB syst J = 4.5 Hz), 4.05 (3H, s), 3.80 (3H, s), 2.43 (2H, t), 2.00 (4H, m), 1.38 (2H, m), 1.27 (24H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 183.5, 182.3, 158.7, 155.8, 130.6, 129.8, 105.3, 61.2, 56.3, 32.5, 31.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.6, 28.3, 27.1, 23.0, 22.6, 14.0; I.R.(neat) 2930, 2854, 1670, 1600, 1460, 1330, 1216, 1045, 845, 720; M^+(EI): *m/z* 432; calcd. for $C_{27}H_{44}O_4$: C 74.96, H 10.25; found: C 74.72, H 10.11.

2-Hydroxy-5-methoxy-3-(8-tridecenyl)-1,4-benzoquinone (Ardisianone B) (1c):

Orange cryst., mp : 63 °C (lit [6] 62-64 °C); R_f: 0.32 (7:3 hexane:AcoEt); ^1H NMR ($CDCl_3$) 7.26 (1H, br), 5.85 (1H, s), 5.34 (2H, t AB syst J = 5 Hz), 3.86 (3H, s), 2.44 (2H, t), 2.00 (4H, m), 1.44 (2H, m), 1.30 (12H, m), 0.89 (3H, t); ^{13}C NMR ($CDCl_3$) 182.8, 181.6, 161.0, 151.6, 129.7, 119.2, 102.1, 56.6, 32.4, 31.8, 29.6, 29.5, 29.4, 29.2, 29.1, 28.9, 28.6, 27.9, 27.0, 26.8, 22.5, 22.2, 13.9; I.R.(KBr) 3340, 2925, 2850, 1662, 1637, 1598, 1464, 1380, 1205, 700; $[M+H]^+(CH_4)$: *m/z* 335; HRMS (CI, CH_4) calcd. for $C_{20}H_{31}O_4$: 335.2233, found: 335.2222. Spectral data were in agreement with literature values. [5]

2-5-dimethoxy-3-(8-tridecenyl)-1,4-benzoquinone (11c):

Yellow oil; R_f: 0.47 (7:3 hexane:AcOEt); ^1H NMR ($CDCl_3$) 5.73 (1H, s), 5.34 (2H, t AB syst J = 5 Hz), 4.05 (3H, s), 3.81 (3H, s), 2.42 (2H, t), 2.00 (4H, m), 1.34 (2H, m), 1.29 (12H, m), 0.89 (3H, t); ^{13}C NMR ($CDCl_3$) 183.4, 182.3, 158.6, 155.8, 130.5, 129.7, 105.3, 61.2, 56.2, 32.4, 31.8, 29.6, 29.5, 29.4, 29.2, 29.0, 28.5, 27.1, 22.9, 22.6, 13.9; I.R.(neat) 2930, 2850, 1660, 1600, 1460, 1320, 1215, 1045, 840, 736; M^+(EI): *m/z* 348; calcd. for $C_{21}H_{32}O_4$: C 72.38, H 9.26; found: C 72.13, H 9.22.

2-Hydroxy-5-methoxy-3-(8-heptadecenyl)-1,4-benzoquinone (Hydroxydietrichequinone) (1d):

Orange cryst., mp : 66-67 °C; R_f 0.37 (7:3 hexane:AcOEt); ^1H NMR ($CDCl_3$) 7.25 (1H, br), 5.84 (1H, s), 5.34 (2H, t AB syst J = 5 Hz), 3.86(3H, s), 2.44 (2H, t), 2.00 (4H, m), 1.44 (2H, m), 1.26 (20H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 182.8, 181.7, 161.1, 151.5, 129.8, 129.7, 119.2, 102.1, 56.7, 32.5, 31.9, 29.7, 29.5, 29.3, 29.2, 28.8, 28.6, 27.9, 27.1, 24.6, 22.6, 22.5, 14.1; I.R.(KBr) 3350, 2920, 2840, 1660, 1645, 1598, 1465, 1210, 1200, 732; $[M+H]^+(CH_4)$: *m/z* 391; HRMS (CI, CH_4) calcd. for $C_{24}H_{39}O_4$: 391.2848, found: 391.2837. Spectral data were in agreement with literature values . [9]

2-5-dimethoxy-3-(8-heptadecenyl)-1,4-benzoquinone (11d):

Yellow oil; R_f: 0.48 (7:3 hexane::AcOEt); ^1H NMR ($CDCl_3$) 5.73 (1H, s), 5.33 (2H, t AB syst J = 5 Hz), 4.05 (3H, s), 3.81 (3H, s), 2.42 (2H, t), 2.00 (4H, m), 1.38 (2H, m), 1.27 (20H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 183.4, 182.3, 158.6, 155.7, 130.5, 129.8, 129.7, 105.2, 61.2, 56.2, 32.4, 31.8, 29.6, 29.5, 29.4, 29.2, 29.0, 28.5, 27.1, 22.9, 22.6, 14.0; I.R.(neat) 2935, 2850, 1670, 1605, 1460, 1340, 1215, 1045, 842, 730; $[M+H]^+(CH_4)$: *m/z* 405; HRMS (CI, CH_4) calcd. for $C_{25}H_{41}O_4$: 405.3005, found: 405.3027.

2-Hydroxy-5-methoxy-3-octadecyl-1,4-benzoquinone (Irisoquin) (1e):

Orange cryst., mp : 98-99 °C (lit [7] 98-100 °C); R_f: 0.35 (7:3 hexane:AcOEt); ^1H NMR ($CDCl_3$) 7.27 (1H, br), 5.84 (1H, s), 3.86 (3H, s), 2.44 (2H, t), 1.42 (2H, m), 1.25 (30H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 182.8, 181.6, 161.1, 151.5, 119.2, 102.1, 56.7, 31.9, 29.6, 29.5, 29.4, 28.0, 22.6, 14.1; I.R.(KBr) 3350, 2920, 2820, 1670, 1638, 1597, 1460, 1220, 1202; M^+(EI): *m/z* 406. Spectral data were in agreement with literature values. [10]

2-5-dimethoxy-3-octadecyl-1,4-benzoquinone (11e):

Yellow cryst., mp : 75-76 °C; R*f* : 0.53 (7:3 hexane:AcOEt); ^{1}H NMR ($CDCl_3$) 5.73 (1H, s), 4.05 (3H, s), 3.81 (3H, s), 2.42 (2H, t), 1.38 (2H, m), 1.25 (30H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 183.5, 182.3, 158.7, 155.8, 130.6, 105.3, 61.2, 56.3, 31.9, 29.6, 29.5, 29.3, 28.6, 23.0, 22.6, 14.0; I.R.(KBr) 2910, 2845, 1670, 1597, 1460, 1220, 1047, 871; M^+(EI): *m/z* 420; calcd. for $C_{26}H_{44}O_4$: C 74.24, H 10.54; found: C 74.48, H 10.44.

2-Hydroxy-5-methoxy-3-tridecyl-1,4-benzoquinone (5-O-methyl-rapanone) (1f):

Orange cryst., mp : 87-88 °C (lit [10] 90-91 °C); R*f* : 0.32 (7:3 hexane:AcOEt); ^{1}H NMR ($CDCl_3$) 7.26 (1H, br), 5.86 (1H, s), 3.86 (3H, s), 2.44 (2H, t), 1.44 (2H, m), 1.25 (20H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$), 182.8, 181.6, 161.0, 151.6, 119.2, 102.1, 56.6, 31.8, 29.5, 29.4, 29.3, 29.2, 29.1, 27.9, 22.6, 14.0; I.R.(KBr) 3350, 2920, 2830, 1670, 1640, 1595, 1460, 1210, 1205; $M^{+\bullet}$(EI): *m/z* 336. Spectral data were in agreement with literature values. [9]

2-5-dimethoxy-3-tridecyl-1,4-benzoquinone (11f):

Yellow cryst., mp : 54-55 °C; R*f* : 0.49 (7/3 hexane/AcOEt); ^{1}H NMR ($CDCl_3$) 5.73 (1H, s), 4.05 (3H, s), 3.81 (3H, s), 2.42 (2H, t), 1.37 (2H, m), 1.25 (20H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 183.4, 182.2, 158.6, 155.7, 130.5, 105.2, 61.1, 56.2, 31.8, 29.5, 29.4, 29.2, 28.5, 22.9, 22.5, 14.0; I.R.(neat) 2915, 2850, 1675, 1600, 1463, 1200, 1050; M^+(EI): *m/z* 350; calcd. for $C_{21}H_{34}O_4$: C 71.96, H 9.78; found: C 71.95, H 9.68.

2-Hydroxy-5-methoxy-3-undecyl-1,4-benzoquinone (5-O-methyl-embelin) (1g):

Orange cryst., mp : 85-86 °C (lit [8] 90 °C); R*f* : 0.32 (7:3 hexane:AcOEt); ^{1}H NMR ($CDCl_3$) 7.26 (1H, br), 5.85 (1H, s), 3.86 (3H, s), 2.44 (2H, t), 1.45 (2H, m), 1.25 (16H, m), 0.88 (3H, t); ^{13}C NMR ($CDCl_3$) 182.8, 181.6, 161.0, 151.6, 119.2, 102.1, 56.6, 31.8, 29.5, 29.4, 29.3, 29.2, 29.1, 27.9, 22.6, 14.0; I.R.(KBr) 3355, 2920, 2840, 1670, 1642, 1598, 1460, 1210, 1204; M^+(EI): *m/z* 308. Spectral data were in agreement with literature values. [11]

2-5-dimethoxy-3-undecyl-1,4-benzoquinone (11g):

Yellow cryst., mp : 52-53 °C; R*f* : 0.48 (7:3 hexane:AcOEt); ^{1}H NMR ($CDCl_3$) 5.73 (1H, s), 4.05 (3H, s), 3.81 (3H, s), 2.43 (2H, dd), 1.37 (2H, m), 1.25 (16H, m), 0.88(3H, t); ^{13}C NMR ($CDCl_3$), 183.5, 182.3, 158.7, 155.8, 130.6, 105.3, 61.2, 56.3, 31.8, 29.6, 29.5, 29.3, 28.6, 23.0, 22.6, 14.0; I.R.(neat) 2920, 2850, 1660, 1600, 1462, 1210, 1045; M^+(EI): *m/z* 322; calcd. for $C_{19}H_{30}O_4$: C 70.77, H 9.38; found: C 70.51, H 9.32.

2-Hydroxy-5-methoxy-3-isopentyl-1,4-benzoquinone (1h):

Orange cryst., mp : 98-99 °C; R*f* : 0.28 (7:3 hexane:AcoEt); ^{1}H NMR ($CDCl_3$), 7.5 (1H, br), 5.85 (1H, s), 3.86 (3H, s), 2.44 (2H, dd), 1.54 (1H, m), 1.33 (2H, m), 0.92 (6H, d); ^{13}C NMR ($CDCl_3$) 182.8, 181.6, 161.0, 151.5, 119.4, 102.1, 56.6, 36.8, 27.9, 22.3, 20.5; I.R.(KBr) 3340, 2925, 2850, 1600, 1464, 1205; M^+(EI): *m/z* 224; calcd. for $C_{12}H_{16}O_4$: C 64.27, H 7.19; found: C 64.22, H 7.29.

2-5-dimethoxy-3-isopentyl-1,4-benzoquinone (11h):

Yellow oil; Rf : 0.41 (7:3 hexane:AcOEt); ^{1}H NMR ($CDCl_3$) 5.73 (1H, s), 4.05 (3H, s), 3.82 (3H, s), 2.42 (2H, dd), 1.55 (1H, m), 1.27 (2H, m), 0.92 (6H, d); ^{13}C NMR ($CDCl_3$) 183.3, 182.2, 158.6, 155.6, 130.7, 105.2, 61.1, 56.2, 37.6, 27.9, 22.2, 20.9; I.R.(neat) 2930, 2850, 1600, 1460, 1320, 1215, 1045; $M^+(CH_4)$: *m/z* 238, $[M+3H]^+(CH_4)$: *m/z* 241; m/z calcd. for $C_{21}H_{32}O_4$: C 65.53, H 7.61; found: C 65.23, H 7.67.

4-5-dimethoxy-3-isopentyl-1,2-benzoquinone (10h):

Bright orange cryst., mp : 74-75°C; R_f : 0.28 (5:5 hexane:AcOEt); ^1H NMR ($CDCl_3$), 5.57 (1H, s), 3.82 (6H, s), 2.29 (2H, dd), 1.44 (1H, m), 1.17 (2H, m), 0.80 (6H, d); ^{13}C NMR ($CDCl_3$) 180.3, 178.3, 166.1, 158.7, 130.1, 100.8, 61.6, 56.5, 37.6, 27.7, 22.0, 21.0; I.R.(neat) 3062, 2954, 2851, 1671, 1650, 1580, 1375, 1233, 1045; $[M+2H]^+(CH_4)$: *m/z* 240, $[M+3H]^+(CH_4)$: *m/z* 241; HRMS (CI, CH_4) calcd. for $C_{13}H_{20}O_4$: 240.1362, found: 240.1370, calcd. for $C_{13}H_{21}O_4$: 241.1440, found: 241.1421.

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19 For transformation of *ortho*-quinone derivatives to *para*-quinones and details of the mechanism of reaction, see ref. 12