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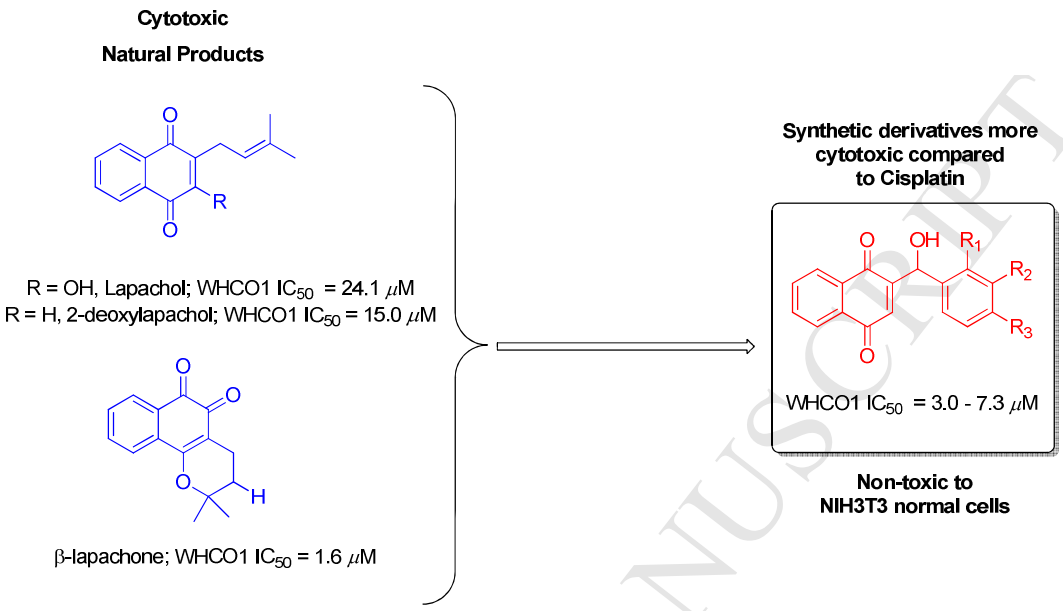
Graphical Abstract



Cytotoxicity of lapachol, β-lapachone and related synthetic 1,4-naphthoquinones against oesophageal cancer cells

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Abstract: Naphthoquinones have been found to have a wide range of biological activities, including cytotoxicity to cancer cells. The secondary metabolites lapachol, α- and β-lapachone and a series of 22 related synthetic 1,4-naphthoquinones were screened against the oesophageal cancer cell line (WHCO1). Most of the compounds exhibited enhanced cytotoxicity (IC_{50} 1.6 to 11.7 μM) compared to the current drug of choice cisplatin (IC_{50} = 16.5 μM). This study also established that the two new synthetic halogenated compounds **12a** and **16a** (IC_{50} = 3.0 and 7.3 μM) and the previously reported compound **11a** (IC_{50} = 1.5 μM), were non-toxic to NIH3T3 normal fibroblast cells. Cell death of oesophageal cancer cells by processes involving PARP cleavage caused by **11a** was shown to be associated with elevated c-Jun levels, suggesting a role for this pathway in the mechanism of action of this cohort of naphthoquinone compounds.

Keywords: *Naphthoquinones, cytotoxicity, SAR, oesophageal cancer cell line WHCO1.*

1. Introduction

Quinones, including 1,4-naphthoquinones, are ubiquitous in nature [1,2] and several well-known anti-cancer drugs used to treat solid tumors (*e.g.* doxorubicin, mitomycin and mitoxantrone) possess a quinonoid structure [3,4]. These compounds have also been identified as privileged structures due to their biological activities and structural properties [5] that have been linked to the stimulation of oxidative stress and alkylation of cellular nucleophiles in cancer cells [6].

Squamous cell oesophageal cancer (SCOC) is the second most common form of cancer reported in poor rural and peri-urban populations in South Africa, with residents of Soweto near Johannesburg having a five-fold increased chance of developing this form of cancer when compared with the global average for the incidence of SCOC [7]. The poor remission rates (20-30%) in early diagnosed cases, albeit current chemotherapeutic interventions using cisplatin and 5-fluorouracil [8], prompted an ongoing programme in South Africa aimed at the discovery of new natural product-derived compounds exhibiting potential anti-oesophageal cancer activity [9,10].

Recently, we have been attracted to the activity of the naturally occurring 1,4-naphthoquinone lapachol (**1**, Figure 1), originally isolated from the wood of several Brazilian tree species of the family Bignoniaceae [11]. Lapachol has a well-documented history of cancer cell cytotoxicity [11], including activity against squamous cell carcinomas [12]. The closely related secondary metabolite β-lapachone (**2**, Figure 1), has recently been shown to exhibit exploitable activity against various cancer molecular targets [13-16] and is currently in phase II clinical trials in the USA for the treatment of advanced solid tumors [17]. Although compound **1** has been licensed in Brazil for general clinical practice as a carcinostatic drug [18], and several studies pertaining to its anticancer properties have been reported [4], there remains some dissension over the effectiveness of **1** as an anticancer drug *per se* due to the reportedly high doses required to achieve therapeutic efficacy, with some side effects observed in treated patients [11]. However, the relative chemical structural simplicity of **1** and **2**, coupled with their well-established cytotoxicity continues

to inspire synthetic attempts to improve the cancer cell cytotoxicity and therapeutic efficacy of these secondary metabolites [4,11,16,19-23], with a recent renewed interest in β-lapachone [16,22,23] as a molecular template. Recently, the potential of **1** and **2** as prototypes to obtain novel anticancer derivatives was explored and several substances were described with potent activity against diverse cancer cell lines with IC_{50} values lower than that of doxorubicin, an important drug used in the therapeutic treatment of cancer [24].

To the best of our knowledge, the secondary metabolites **1** and **2** have not previously been screened for their cytotoxicity against oesophageal cancer cells, and we report here their activities against the WHCO1 oesophageal cancer cell line (a cell line derived from a South African cancer patient) [25], along with a series of 24 related synthetic 1,4-naphthoquinones (Table 1).

Our initial foray into this broad-based structure activity relationship (SAR) study was the synthesis of the marine natural product 2-deoxylapachol (**3**, Figure 1) [26], originally isolated from the New Zealand brown alga *Landsburgia quercifolia* and found to be cytotoxic (IC_{50} = 2.7 μM) against P-388 leukemia cells [27]. Simultaneously, we prepared a number of simple (**8-10** and **11a**, Figure 1), where the effect on cytotoxicity of benzylic hydroxylation compared to hydroxylation at C-2 on the 1,4-naphthoquinone nucleus of **1** and the absence of the hydroxyl functionality in **3** was established by the preparation of **8** [26]. The improved activity of **8** (IC_{50} = 5.2 μM) compared to **1** and **3** (Table 1), encouraged us to further explore the possible role of the oxygenated side chain in defining the cytotoxicity in these compounds. In this preliminary survey [26], the synthetic compound 2-(1-hydroxy-1-phenylmethyl)-1,4-naphthoquinone (**11a**), was found to be the most cytotoxic (IC_{50} = 1.5 μM), *ca.* eleven times more potent than the current drug of choice cisplatin (IC_{50} = 16.5 μM) against the WHCO1 cell line [10]. In this SAR study, we describe an investigation of the effect of different variations on the phenyl moiety in **11a** in an effort to develop chemical entities with enhanced pharmacological activity against the WHCO1 oesophageal cancer cell line.

Figure 1. HEREABOUTS

2. Results and Discussion

2.1. Chemistry

Lapachol was extracted from the heartwood of *Tabebuia* sp. (*Tecoma*) and purified by a series of recrystallizations, generally using hexane as solvent. Initially, β-lapachone (**2**), α-lapachone (**7**) and their derivatives 3-hydroxy-β-lapachone (**4)** and 3-bromo-β-lapachone (**5)** were prepared from **1**, by reaction with sulfuric acid, CH_3COOH/HCl, *m*-CPBA and bromine respectively, as previously reported [28], whilst nor-β-lapachone (**6**) was synthesized in two steps by the Hooker oxidation of lapachol [29].

Our approach to the SAR study around **11a** was three fold. First, the role of the phenyl ring in defining the cytotoxicity of **11a** was explored through (i) the synthesis of five variably halogenated analogues of **11a** (**12a-16a**); (ii) replacing the phenyl ring with naphthyl and furanyl moieties to afford **17a** and **18a** respectively and (iii) extending the length of the side chain containing the phenyl ring to yield **19a** (Scheme 1). Second, the centrality of the benzylic hydroxyl group to the cytotoxicity of **11a** was initially investigated by oxidation of this functionality to afford **11b**, and further oxidation of the benzylic alcohol in **12a**-**19a** to yield **12b**-**19b** respectively, along with the ultimate removal of the hydroxyl functionality to afford **11c** (Scheme 2). Third, the importance of the benzylic carbon to cytotoxicity was investigated by direct coupling of the 1,4-naphthoquinone nucleus to a phenyl ring to give 2-phenyl-1,4-naphthoquinone (**20**, Figure 1).

Adapting the strategy previously used by our research group to prepare **11a** [26], we synthesized compounds **12a**-**16a** from the same aldehyde precursor (**21**) using standard Grignard methodology to yield the dimethoxynaphthalene derivatives **23a**-**27a**, which were then subjected to standard oxidative demethylation using cerium ammonium nitrate (CAN) to obtain the respective naphthoquinones in high yields (80-94%, Scheme 1) . The Grignard approach was also used to prepare **17a** and **19a** in moderate yields (43% and 48% respectively after 2 steps, Scheme 1). Conversely, the furanyl naphthoquinone **18a** was accessed from **21** *via* an *n*-BuLi mediated metal-halogen exchange of 3-bromofuran (Scheme 1) [30].

Scheme 1. HEREABOUTS

The central role of the benzylic alcohol at position C-1` was explored through the oxidation of the hydroxyl functionality in compounds **22a**-**30a** to obtain the dimethoxynaphthalenes **22b**-**30b** in generally quantitative yields (72-100%), followed by CAN deprotection to yield the keto-naphthoquinones **11b** and **12b**-**19b** respectively (Scheme 2). A Ley oxidation [31] was used to oxidize all benzylic alcohols, with the exception of **28a** and **29a** where yields of 91% and 72% for **28b** and **29b** respectively were achieved when using MnO_2 in CH_2Cl_2.

Additionally, to investigate the full effect of oxygenation of the C-1` position on the cytotoxic effect of these naphthoquinone compounds, the C-1` benzylic alcohol functionality was removed by refluxing a solution of the dimethoxynaphthalene precursor **22b**, triethylsilane and boron trifluoride etherate for 2 h at 80-95 °C [32], followed by a CAN oxidative demethylation to yield the desired naphthoquinone **11c** (Scheme 2, 49% yield after 2 steps) [33]. Finally, we completed our array of synthetic compounds available for our SAR studies, by preparing the naphthoquinone **20** (Figure 1) in 80% yield *via* standard palladium acetate mediated coupling of a phenyl ring to 1,4-naphthoquinone [34].

Cognizant of the importance of the biological testing of enantiomerically pure chiral compounds, we generated both enantiomers of **11a**, by initial derivatization of **22a** using (-)-(*S*)-camphanic chloride to yield a mixture of the (*R*,*S*) and (*S*,*S*)-diastereomers **31** and **32** respectively (Scheme 3). Separation of these two diastereomers using normal phase HPLC (99% CH_2Cl_2 and 1% EtOAc) and subsequent crystallization of **31** from aqueous methanol provided an opportunity to establish the *R*-configuration of C-1' in this compound from single crystal analysis (Scheme 3). Finally, saponification of the two diastereomers **31** and **32** using KOH in EtOH**,** followed by standard CAN oxidative demethylation afforded the *R* and *S* enantiomers of naphthoquinone **11a** respectively (Scheme 3).

All the structures of unpublished compounds were confirmed by ^{1}H and ^{13}C NMR, IR and HRESI mass spectra. Compound **31** was obtained in crystalline form and the *R*-

configuration at benzylic chiral center C-1`was assigned using x-ray crystallography, as seen in the ORTEP-3 projection inserted in Scheme 3.

Scheme 2. HEREABOUTS

2.2. Biological Activity

Both natural and synthetic quinones are regularly utilized to explore the cellular mechanisms underpinning cytotoxicity in cancer cells [35]. The redox properties of quinones can often trigger cancer cell apoptosis through oxidative stress induced by the *in situ* production of reactive oxygen species (ROS) [3] while further evidence suggests that some quinones can either interchelate directly with DNA or inhibit proteins regulating DNA replication and nucleotide biogenesis [3,4,35-37]. The MTT assay [38] was utilized to investigate the cytotoxicity and to calculate the IC_{50} values of the naturally occurring naphthoquinones **1**, **2** and **7** together with the semi-synthetic and synthetic compounds **4-6**, **11a-c**, **12a,b**-**19a,b** and **20** (Table 1), using doxorubicin as a positive control (IC_{50} = 0.5 μM). Furthermore, the synthetic compounds **11a** and **12a**-**16a** were tested in a normal cell (NIH3T3 fibroblast cell) cytotoxicity assay [39] in which only the disubstituted phenyl derivative **13a** and the two fluorinated compounds **14a** and **15a** were found to be cytotoxic (IC_{50} = 7.4, 11.7 and 82.0 μM respectively) . More importantly, the synthetic compounds **11a**, **12a** and **16a** were found to be non-toxic in the NIH3T3 normal fibroblast cell assay.

Table 1. HEREABOUTS

In a recent study, Lee *et al.*[14] have shown that β-lapachone-induced apoptosis in the human bladder carcinoma T_{24} cell line is associated with an increase in activity of the intracellular cysteine protease caspase-3, which plays an intrinsic role in the final stages of apoptosis. β-Lapachone **2** has also been shown to induce apoptosis in cancer cells through the activation of the c-Jun signalling pathway [12] whilst the marine triprenylated toluhydroquinone KLM 155 has also been shown by Whibley *et al.* [10] to specifically activate the JNK/c-Jun pathway in WHCO1 cells to subsequently induce apoptosis. c-Jun is both a pro- and anti-apoptotic protein, depending on the cellular environment and other

signals, that enables cells to deal with damage caused by ROS production through the regulation of antioxidant genes [14,40]. The relationship between caspase and JNK is still elusive, although there is strong evidence suggesting that JNK can play an important role in mediating apoptosis [14,41,42]. Increasing emphasis in SCOC chemotherapy has been placed on the identification of critical survival and proliferation pathways by incorporating transcription factors such as the c-Jun (AP1) that could serve as potential chemotherapeutic targets [43].

The secondary metabolites tested in this study showed varying cytotoxicities against the WHCO1 oesophageal cancer cell line (Table 1). β-Lapachone **2** was found to be the most potent **(**IC_{50} = 1.6 μM), 10 times more active than cisplatin (IC_{50} = 16.5 μM) [10]. However, 2-deoxylapachol **3**, lapachol **1** and α-lapachone **7** were shown to be ten, fifteen and eighteen times less cytotoxic (IC_{50} = 15.0, 24.1 and 28.7 μM respectively) than β-lapachone against the WHCO1 cell line (Table 1). 3-Bromo-β-lapachone (**5**, IC_{50} = 1.8 μM) and nor-β-lapachone (**6**, IC_{50} = 2.4 μM) were not significantly more active than β-lapachone, but they still represent important derivatives that are respectively seven and five times more potent than cisplatin.

Twelve synthetic compounds (**4**-**6**, **12a**-**19a**, **20**), excluding compounds reported in our previous study [26], exhibited *ca.* 2-9 fold increase in activity (IC_{50} = 1.8-11.7 μM, Table 1) against the WHCO1 cell line compared to cisplatin, thus representing a significant contribution to our search for pharmacologically more active chemical entities against the WHCO1 oesophageal cancer cell line.

Halogenation of the phenyl moiety in our SAR study did not appear to improve the activity compared to **11a**, but it is however important to note that two of the halogenated derivatives **12a** and **16a** (IC_{50} = 3.0 and 7.3 μM) were more active than cisplatin and were also non-toxic to NIH3T3 normal fibroblast cells. Interestingly, the chlorinated analogues **12a** and **13a** were more cytotoxic (IC_{50} = 3.0 and 3.4 μM respectively) than the fluorinated compounds **14a** and **15a** (IC_{50} = 5.1 and 5.5 μM respectively). The cytotoxicity of the naphthyl, furanyl and phenylethyl derivatives (**17a**-**19a**) were found to be 2.4, 10.9 and 4.8

μM respectively (Table 1), indicating that substitution of the phenyl moiety of compound **11a** with these particular functionalities and/or extending the benzylic side chain did not offer any improvement on the cytotoxicity against the WHCO1 oesophageal cancer cell line.

The IC_{50} values obtained for the oxidized products **11b, 12b-19b** against oesophageal cancer cell lines showed a marked increase (Table 1), indicating a significant decrease in cytotoxicity against the WHCO1 cancer cell line, with **17b** having no activity at all. Therefore, the hydroxyl group at the benzylic position appears to be important in this class of compounds for increased cytotoxicity against the WHCO1 cell line.

Of interest to us was a comparative study of the apoptotic mechanism of action of the racemic mixture of **11a** and the individual enantiomers *R*-**11a** and *S*-**11a** with the previously established mechanism by Whibley *et al.* [10] for the marine natural product KLM 155. The individual enantiomers were initially evaluated against the WHCO1 oesophageal cancer cell line and were found to exhibit similar cytotoxicity (IC_{50} WHCO1, *R*-**11a** = 4.3 μM and *S*-**11a** = 3.8 μM) to the racemate **11a** (Table 1). Although the IC_{50} value (3.9 μM) obtained for **11a** is somewhat higher than the previously reported IC_{50} of 1.5 μM [26], the relative difference between the individual enatiomers *R*-**11a** and *S*-**11a** and the racemate suggests that the absolute configuration at the benzylic position has no effect on the cytotoxicity of **11a**.

Figure 2. HEREABOUTS

A Western blot analysis was performed in order to simultaneously determine whether **11a**, *R*-**11a** and *S*-**11a** caused PARP cleavage (indicative of apoptosis) in oesophageal cancer cells [44] and to investigate the expression levels of c-Jun (Figure 2). The WHCO1 oesophageal cancer cells were treated with varying concentrations of each compound and protein was extracted at the relevant time points. PARP (poly adenosine-diphosphate ribose polymerase) is a known caspase-3 substrate and cleavage of PARP into 116 kDa and 85 kDa fragments is indicative of apoptosis [44], as shown by WHCO1 cells treated with

doxorubicin (dox) as a positive control (Figure 2). PARP cleavage was clearly observed in cells treated with **11a**, *R*-**11a** and *S*-**11a** at a concentration of 20 μM (Figure 2), whilst only slight PARP cleavage was observed with lower concentrations (< 20 μM) at all time points (Figure 2). A concentration-dependent increase in c-Jun levels was observed after all treatment time points (Figure 2), with the highest expression observed after 24h followed by a decline in expression at 48 h (Figures 2B and 2C). These results suggest the activation of the JNK/c-Jun signalling pathway and the associated cleavage of PARP in WHCO1 cells, in a similar manner to the marine natural product KLM 155 [10]. This is the first example of JNK/c-Jun activation in oesophageal cancer cells by naphthoquinone compounds.

3. Conclusion

This SAR study has revealed that the previously established cytotoxicity of **11a** against the WHCO1 oesophageal cancer cells was comparable to that of the well-known cytotoxic natural product β-Lapachone **2** and more than 10-16 fold greater than the related secondary metabolites lapachol **1** and 2-deoxylapachol **3** respectively. Substitution around the phenyl ring in **11a**, replacement of the phenyl ring with either naphthyl or furanyl rings or extending the length of the phenyl substituted side-chain did not appear to significantly enhance the cytotoxicity to oesophageal cancer cells. A considerable reduction in cytotoxicity was observed when the benzylic hydroxyl group in **11a** and related synthetic analogues **12a**-**19a** was oxidized to yield the keto compounds **11b**, **12b**-**19b** or removed completely to provide compounds **11c** and **20**. This indicates the key role that this benzylic hydroxyl functionality plays in enhancing the cytotoxicity observed within this cohort of compounds. Chiral resolution of the racemic mixture of **11a** revealed equipotent cytotoxicity to WHCO1 oesophageal cancer cells for both enantiomers (*R*-**11a** and *S*-**11a**) compared to the racemate. Although variable halogenation of the phenyl ring has not yielded more active compounds than **11a** in our SAR study, we have however produced two compounds **12a** and **16a** that are both significantly more cytotoxic (IC_{50} = 3.0 and 7.3 μM respectively) than the current drug of choice cisplatin and, more importantly, are both non-toxic to NIH3T3 normal fibroblast cells. Additionally, compound **11a** was also found to be non-toxic to NIH3T3 normal fibroblast cells and has also been shown to induce

apoptosis in WHCO1 oesophageal cancer cells by activating the key JNK/c-Jun signalling pathway, in a similar manner to the marine natural product KLM155. The relatively facile synthetic accessibility of the cytotoxic compounds **11a**, **12a** and **16a** renders this SAR study a useful starting point in the search for new and improved pharmacologically improved chemotherapeutic agents against oesophageal cancer.

4. Experimental Section

4.1. Chemistry

Melting points were measured using a Gallenkamp melting point apparatus without correction. NMR spectra were acquired using standard pulse sequences on Bruker Avance 400 MHz and 600 MHz Avance II spectrometers. Chemical shifts are reported in ppm and referenced to residual protonated solvent resonances with TMS as the internal standard. Coupling constants are reported directly from the NMR spectra and corresponding coupling constants have not been matched. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at the sodium-D line (589 nm). Following standard protocol, the concentration of solutions used to determine optical rotations is expressed in g/100 mL. Infrared spectra were recorded on a Perkin-Elmer Spectrum 2000 FT-IR spectrometer and Digilab FTS 3100 Excalibur HE Series with compounds as films (neat) on NaCl discs. Low resolution mass spectra were recorded on a Finnigan GCQ spectrometer at 70 eV. Normal phase semi-preparative HPLC separations were performed on a Whatman Magnum 9 Partisil 10 column and normal phase analytical HPLC separations were performed on a Lux 5u Cellulose-1 0.25 μm column using a Spectra-Physics Spectra-Series P100 isocratic pump and a Waters 410 Differential Refractometer. All reactions requiring anhydrous conditions were conducted in either flame-dried or oven-dried apparatus under an atmosphere of dry argon/nitrogen or using an anhydrous calcium chloride drying tube. Dry solvents were prepared by standard procedures as described by Perrin and Armarego [45] and stored over appropriate drying agent under an atmosphere of dry nitrogen or argon. High-resolution mass spectrometry was performed on a Waters API Q-TOF Ultima instrument using electron-spray ionization in the positive ion mode (ESI+).

4.2. Synthetic Procedure

Compounds **11b** [46], **11c** [33, 47] and **22b** [47] have been reported previously.

The syntheses of the 1,4-dimethoxynaphthalene precursors **23a** and **23b**, using methods A and B respectively, followed by their subsequent CAN oxidative demethylation (Method C) to yield the respective 1,4-naphthoquinone compounds **12a** and **12b** are described below as representatives of the 2-(1`-hydroxy-phenyl-methyl) and 2-benzoyl-1,4-naphtoquinone series of compounds respectively. The syntheses of **18a** and **29a** are also described below.

4.3. Method A

A solution of Grignard reagent (3-5 eq.) was added to a cooled solution (-10 °C) of the aldehyde **21** (1 eq.) in 6 mL anhydrous THF under an Ar atmosphere. The resulting solution was stirred for 1 h at -10 °C and gradually allowed to reach r.t. The mixture was stirred for a further 16 h at r.t. before being quenched with sat. NH_4Cl (10 mL) and extracted with $CHCl_3$ (3 × 3 mL). The combined organic extracts were washed with water (2 × 5 mL) and sat. brine (1 × 5 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting benzylic alcohol product was purified by normal phase semi-preparative HPLC.

4.4. Method B

4.4.1. *N*-morpholine-N-oxide (2-3 eq.), powdered 4Å molecular sieves (60 mg) and tetrapropylammonium perruthenate (TPAP) (0.5 eq) were added to a solution of 1,4-dimethoxynaphthalene benzylic alcohol (1 eq.) in anhydrous CH_2Cl_2 under an atmosphere of argon. After stirring for 2 h the reaction mixture was filtered through a silica/celite plug and concentrated under vacuum to yield the product without the need for further purification.

4.4.2. The 1,4-dimethoxynaphthalene benzylic alcohol (1 eq.) was dissolved in anhydrous CH_2Cl_2 and finely powdered MnO_2 (30 eq.) was added. The solution was stirred at ambient temperature for 48 h and filtered through Celite (coarse 545) to afford the product without any purification.

4.5. Method C

A solution of 2-3 eq. of cerium ammonium nitrate (CAN) in water (0.3 mL) was added dropwise to a solution of the dimethoxynaphthalene precursor (1 eq.) in MeCN (5 mL) until a deep yellow colour persisted. The mixture was diluted with water (5 mL) and extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with water (5 mL) and sat. brine (5 mL), dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The 1,4-naphthoquinone products were purified by normal phase semi-preparative HPLC.

4.6. Synthesis of compounds 11a and 22a.

Compounds **11a** and **22a** were synthesized according to the procedure previously described by us and the ^{1}H, ^{13}C, IR, LRMS and HRMS data obtained for *R*-**11a** and *S*-**11a** were congruent with the data of the racemic mixture of **11a** [26].

***R*-11a :** $[\alpha]_D^{22}$ +29 (*c* 1.29, $CHCl_3$) and ***S*-11a :** $[\alpha]_D^{22}$ -26 (*c* 1.23, $CHCl_3$).

4.7. 2-[1`-Hydroxy-1`-(5`-chlorophenyl)methyl-)-1,4-naphthoquinone (12a).

Standard CAN oxidative demethylation of **23a** (119 mg, 0.36 mmol) using method C, followed by purification using normal phase semi-preparative HPLC (33% EtOAc, 67% hexane) of the crude product afforded **12a** (86 mg, 0.28 mmol) as a yellow amorphous solid. Yield: 80%; IR (film) ν_{max} cm^{-1} 3449, 1654, 1590, 1487, 1297, 1253, 1140, 1051, 944, 776, 743, 715, 600; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05 (1H, m, H-5), 8.01 (1H, m, H-8), 7.71 (2H, m, H-6, H-7), 7.40 (2H, m, H-3`, H-7`), 7.32 (2H, m, H-4`, H-6`), 7.04 (1H, d, J = 1.3 Hz, H-3), 5.93 (1H, d, J = 3.1 Hz, H-1`); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 185.1 ($q_c$, C-4), 185.0 ($q_c$, C-1), 150.5 ($q_c$, C-2), 138.7 ($q_c$, C-2`) 134.3 (q_c, C-5`), 134.2 (CH, C-7), 133.6 (2 × CH, C-3, C-6), 132.0 ($q_c$, C-8a), 131.9 ($q_c$, C-4a), 128.9 (2 × CH, C-4`, C-6`), 128.3 (2 × CH, C-3`, C-7`), 126.6 (CH, C-8), 126.3 (CH, C-5), 70.4 (CH, C-1`); EIMS *m/z* (rel. int.) 298 [M^+] (98), 262 (5), 234 (5) 205 (5), 187 (18), 186 (100), 158 (18), 130 (25), 111 (10), 102 (10), 77 (5); HREIMS *m/z* 298.0388 (calcd for $C_{17}H_{11}O_3Cl$ [M^+] 298.0397).

4.8. 2-[1`-Hydroxy-1`-(5`-chloro-3`-methylphenyl)methyl)-1,4-naphthoquinone (13a).

Standard CAN oxidative demethylation of **24a** (71 mg, 0.21 mmol) using method C, followed by purification using normal phase semi-preparative HPLC (20% EtOAc, 80%

Hexane) of the crude afforded **13a** (56.1 mg, 0.18 mmol) as a yellow amorphous solid. Yield: 87%; IR (film) ν_{max} cm^{-1} 3515, 1657, 1591, 1483, 1303, 1255, 1143, 1045, 938, 877, 770, 747, 714, 698; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.07 (1H, m, H-5), 8.04 (1H, m, H-8), 7.74 (2H, m, H-6, H-7), 7.31 (1H, d, J = 8.2 Hz, H-7') 7.19 (1H, m, H-4'), 7.17 (1H, m, H-6'), 6.85 (1H, d, J = 1.26 Hz, H-3), 6.13 (1H, d, J = 2.9 Hz, H-1'), 2.42 (3H, s, H-8'); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 185.3 (q_c, C-4), 185.1 (q_c, C-1), 150.5 (q_c, C-2), 137.7 (q_c, C-3'), 136.3 (q_c, C-2'), 134.2 (CH, C-7), 134.1 (CH, C-3), 134.0 (q_c, C-5'), 133.9 (CH, C-6), 132.1 (q_c, C-8a), 131.9 (q_c, C-4a), 130.7 (CH, C-4'), 128.1 (CH, C-7'), 126.7 (CH, C-6'), 126.6 (CH, C-8), 126.4 (CH, C-5), 67.0 (CH, C-1'), 19.1 (CH_3, C-8'); EIMS *m/z* (rel. int.) 312[M^+] (75), 299 (8), 297 (20), 295 (8), 260 (8), 231 (5), 202 (7), 187 (18), 186 (100), 158 (18), 153 (7), 130 (22), 125 (9), 105 (3), 102 (9), 89 (6), 77 (4); HREIMS *m/z* 312.0555 (calcd for $C_{18}H_{13}O_3Cl$ [M^+] 312.0548).

4.9. 2-[1`-Hydroxy-1`-(5`-fluorophenyl)methyl]-1,4-naphthoquinone (14a).

Standard CAN oxidative demethylation of **25a** (63 mg, 0.20 mmol) using method C, followed by purification using normal phase semi-preparative HPLC (20% EtOAc, 80% Hexane) of the crude afforded **14a** (50.8 mg, 0.18 mmol) as a yellow amorphous solid. Yield: 90%; IR (film) ν_{max} cm^{-1} 3394, 1651, 1591, 1330, 1300, 1218, 1147, 1057, 1032, 916, 769, 740,719, 697; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06 (1H, m, H-5), 8.02 (1H, m, H-8), 7.72 (2H, m, H-6, H-7), 7.44 (2H, m, H-3`, H-7`), 7.05 (1H, m, H-3), 7.04 (2H, m, H-4`, H-6`), 5.95 (1H, d, J = 3.4 Hz, H-1`); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 185.2 ($q_c$, C-4), 185.0 ($q_c$, C-1), 162.6 ($q_c$, d, $J_{F,C}$ = 247.4 Hz C-5`), 150.7 (q_c, C-2), 136.0 (q_c, d, $J_{F,C}$ = 2.3 Hz, C-2`), 134.0 (CH, C-7), 133.9 (CH, C-6), 133.5 (CH, C-3), 133.1 ($q_c$, C-8a), 131.9 ($q_c$, C-4a), 128.8 (2 × CH, d, $J_{F,C}$ = 7.9 Hz, C-3`, C-7`), 126.6 (CH, C-8), 126.3 (CH, C-5), 115.7 (2 × CH, d, $J_{F,C}$ = 21.3 Hz, C-4`, C-6`), 70.3 (CH, C-1`), EIMS *m/z* (rel. int.) 282 [M^+] (100) 265 (3), 249 (3), 225 (3), 207 (3), 187 (10), 186 (78), 158 (17), 130 (22), 123 (10), 102 (10), 95 (10), 77 (3), 69 (2); HREIMS *m/z* 282.0701 (calcd for $C_{17}H_{11}O_3F$ [M^+] 282.0692).

4.10. 2-[1`-Hydroxy-1`-(4`-fluorophenyl)methyl]-1,4-naphthoquinone (15a).

Standard CAN oxidative demethylation of **26a** (53 mg, 0.17 mmol) using method C, followed by purification using normal phase semi-preparative HPLC (20% EtOAc, 80%

Hexane) of the crude afforded **15a** (39.8 mg, 0.14 mmol) as a brown oil. Yield: 83%; IR (film) ν_{max} cm^{-1} 3456, 1658, 1590, 1300, 1250, 1142, 1048, 957, 784, 757, 731, 702; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06 (1H, m, H-5), 8.03 (1H, m, H-8), 7.73 (2H, m, H-6, H-7), 7.32 (1H, m, H-6'), 7.23 (1H, d, J = 7.7 Hz, H-7'), 7.18 (1H, m, H-3'), 7.02 (1H, d, J = 1.2 Hz, H-3), 6.99 (1H, m, H-5'), 5.95 (1H, d, J = 3.8 Hz H-1'); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 185.1 (q_c, C-4), 185.0 (q_c, C-1), 162.9 (q_c, d, $J_{F,C}$ = 246.0 Hz C-4'), 150.3 (q_c, C-2), 142.7 (q_c, d, $J_{F,C}$ = 6.7 Hz, C-2'), 134.2 (CH, C-7), 133.9 (CH, C-6), 133.9 (CH, C-3), 132.0 (q_c, C-8a), 131.9 (q_c, C-4a), 130.3 (CH, d, $J_{F,C}$ = 8.5 Hz, C-6'), 126.6 (CH, C-8), 126.3 (CH, C-5), 122.5 (CH, d, $J_{F,C}$ = 3.0 Hz, C-7'), 115.4 (CH, d, $J_{F,C}$ = 21.3 Hz, C-5'), 113.9 (CH, d, $J_{F,C}$ = 22.5 Hz, C-3'), 70.4 (CH, d, $J_{F,C}$ = 2.2 Hz, C-1'); EIMS *m/z* (rel. int.) 282 [M^+] (100), 263 (8), 218 (19), 187 (15), 186 (42), 158 (12), 130 (12), 123 (8), 102 (7), 95 (7), 77 (4), 69 (5); HREIMS *m/z* 282.0688 (calcd for $C_{17}H_{11}O_3F$ [M^+], 282.0692).

4.11. 2-[1`-Hydroxy-1`-(4`-chlorophenyl)methyl]-1,4-naphthoquinone (16a).

Standard CAN oxidative demethylation of **27a** (51 mg, 0.16 mmol) using method C, followed by purification using normal phase semi-preparative HPLC (20% EtOAc, 80% Hexane) of the crude afforded **16a** (39.1 mg, 0.13 mmol) as a brown oil. Yield: 82%; IR (film) ν_{max} cm^{-1} 3468, 1661, 1592, 1301, 1250, 1143, 1051, 943, 781, 741, 700; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06 (1H, m, H-5), 8.03 (1H, m, H-8), 7.73 (2H, m, H-6, H-7), 7.45 (1H, s, H-3`), 7.35 (1H, m, H-7`), 7.29 (1H, m, H-6`), 7.27 (1H, m, H-5`), 7.04 (1H, d, J = 1.1 Hz, H-3), 5.93 (1H, d, J = 3.5 Hz, C-1`); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 185.1 ($q_c$, C-4), 184.9 ($q_c$, C-1), 150.2 ($q_c$, C-2), 142.2 ($q_c$, C-2`), 134.7 (q_c, C-4`), 134.2 (CH, C-7), 133.9 (CH, C-6), 133.79 (CH, C-3), 131.9 ($q_c$, C-8a), 131.8 (qc, C-4a), 130.0 (CH, C-6`), 128.6 (CH, C-5`), 127.0 (CH, C-3`), 126.6 (CH, C-8), 126.3 (CH, C-5), 125.1 (CH, C-7`), 70.4 (CH, C-1`); EIMS *m/z* (rel. int.) 298 [M^+] (100), 282 (3), 263 (9), 205 (4), 187 (18), 186 (60), 158 (14), 130 (18), 111 (8), 102 (8), 77 (5); HREIMS *m/z* 299.0485 (calcd for $C_{17}H_{12}O_3Cl$ $[M+H]^+$ 299.0475).

4.12. 2-(1`-Hydroxy-1`-naphthylmethyl)-1,4-naphthoquinone (17a).

Standard CAN oxidative demethylation of **28a** (48.2 mg, 0.14 mmol) using method C and subsequent chromatography (25% EtOAc, 75% hexane) afforded **17a** (23.1 mg, 0.07 mmol)

as a yellow oil. Yield: 50%; IR (film) ν_{max} cm^{-1} 3433, 3059, 2919, 1664, 1349, 1297, 1121, 818, 758; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.04 (1H, dd, J = 7.3, 1.2 Hz, H-5), 7.98 (1H, dd, J = 7.3, 1.1 Hz, H-8), 7.93 (1H, br s, H-3`), 7.82 (1H, d, $J$ = 8.0 Hz, H-10`), 7.82 (1H, m, H-5`), 7.80 (1H, m, H-8`), 7.70 (1H, td, J = 7.1, 1.5 Hz, H-7), 7.67 (1H, td, J = 7.4, 1.5 Hz, H-6), 7.53 (1H, dd, J = 8.5, 1.6 Hz, H-11`), 7.47 (1H, td, $J$ = 6.4, 1.6 Hz, H-6`), 7.46 (1H, td, J = 6.4, 1.7 Hz, H-7`), 7.12 (1H, br d, $J$ = 1.2 Hz, H-3), 6.11 (1H, s, H-1`); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 185.3 (q_c, C-4), 185.0 (q_c, C-1), 150.8 (q_c, C-2), 137.5 (q_c, C-2`), 134.0 (CH, C-7), 133.8 (CH, C-6), 133.6 (CH, C-3), 133.2 ($q_c$, C-4`, C9`), 132.1 ($q_c$, C-8a), 131.9 ($q_c$, C-4a), 128.7 (CH, C-10`), 128.1 (CH, C-5`), 127.7 (CH, C-8`), 126.5 (CH, C-8), 126.4 (CH, C-6`, C7`), 126.3 (CH, C-3`), 126.2 (CH, C-5), 124.4 (CH, C-11`), 71.0 (CH, C-1`); EIMS *m/z* (rel. int.) 314 [M^+] (33), 296 (100), 284 (13), 268 (21), 241 (9), 239 (21), 186 (2), 155 (13), 128 (8); HRFABMS *m/z* 314.0935 (calcd for $C_{21}H_{14}O_3$ [M^+], 314.0943).

4.13. 2-(1`-Hydroxy-1`-furanylmethyl)-1,4-naphthoquinone (18a).

Standard CAN oxidative demethylation of **29a** (34 mg, 0.12 mmol) using method C and subsequent chromatography (25% EtOAc, 75% hexane) afforded **18a** (17 mg, 0.066 mmol) as a brown solid. Yield: 55%; IR (film) ν_{max} cm^{-1} 3021, 2401, 1666, 1521, 1302, 1216, 929, 757, 669, 518; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.05 (2H, m, H-8, H-5), 7.74 (1H, td, J = 7.2, 1.9 Hz, H-7), 7.72 (1H, td, J = 7.5, 1.9 Hz, H-6), 7.49 (1H, m, H-5`), 7.37 (1H, t, $J$ = 1.7 Hz, H-4`), 7.04 (1H, br d, J = 1.3 Hz, H-3), 6.41 (1H, br d, J = 1.7 Hz, H-3`), 5.94 (1H, s, H-1`); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 185.3 (q_c, C-4), 185.2 (q_c, C-1), 150.2 (q_c, C-2), 143.6 (CH, H-4`), 140.4 (CH, C-5`), 134.1 (CH, C-7), 133.9 (CH, C-6), 133.5 (CH, C-3), 132.1 (q_c, C-8a), 131.9 (q_c, C-4a), 126.6 (CH, C-5), 126.3 (CH, C-8), 125.4 (q_c, C-2`), 108.8 (CH, C-3`), 64.2 (CH, C-1`); EIMS *m/z* (rel. int.) 254 [M^+] (16), 237 (11), 226 (71), 225 (100), 199 (30), 197 (39), 181 (14), 169 (13), 152 (20), 141 (14), 130 (8), 105 (11), 78 (8), 51 (3); HRFABMS *m/z* 254.0585 (calcd for $C_{15}H_{10}O_4$ [M^+], 254.0579).

4.14. 2-(1`-Hydroxy-3`-phenylpropyl)-1,4-naphthoquinone (19a).

Standard CAN oxidative demethylation of **30a** (38 mg, 0.12 mmol) according to method C and purification of the crude mixture using semi-preparative HPLC (25% EtOAc, 75% hexane) yielded **19a** (45 mg, 0.15 mmol) as a brown oil; Yield: 80%; IR (film) ν_{max} cm^{-1}

3442, 3020, 2401, 1662, 1303, 1216, 1064, 926, 756, 667; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.04 (2H, m, H-8, H-5), 7.72 (2H, m, H-7, H-6), 7.25 (2H, t, J = 7.5 Hz, H-8`, H-6`), 7.20 (2H, d, J = 7.0 Hz, H-9`, H-5`), 7.15 (1H, t, J = 7.3 Hz, H-7`), 6.97 (1H, br s, H-3), 4.83 (1H, dd, $J$ = 8.3, 3.3 Hz, H-1`), 2.89 (1H, m, H-3b`), 2.79 (1H, m, H-3a`), 2.14 (1H, m, H-2b`), 2.00 (1H, m, H-2a`); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 185.4 (q_c, C-4), 185.1 (q_c, C-1), 151.8 (q_c, C-2), 141.0 (q_c, C-4`), 134.0 (CH, C-7), 133.8 (CH, C-6), 133.5 (CH, C-3), 132.2 ($q_c$, C-8a), 131.8 ($q_c$, C-4a), 128.5 (2 × CH, C-8`-, C-6`), 128.5 (2 × CH, C-9`, C-5`), 126.4 (CH, C-5), 126.1 (CH, C-7`), 126.0 (CH, C-8), 68.7 (CH, C-1`), 37.8 ($CH_2$, C-2`), 31.8 (CH_2, C-3`); EIMS *m/z* (rel. int.) 292 [M^+] (12), 274 (43), 257 (9), 228 (3), 202 (5), 188 (100), 160 (41), 133 (6), 105 (9), 79 (4); HRFABMS *m/z* 292.1100 (calcd for $C_{19}H_{16}O_3$ [M^+], 292.1099).

4.15. 2-[1`-Hydroxy-1`-(5`-chlorophenyl)methyl]-1,4-dimethoxynaphthalene (23a).

Compound **23a** was synthesized according to method A using a solution of 4-chlorophenylmagnesium bromide (1 M, 2.76 mmol, 3.0 eq) and aldehyde **21** (198 mg, 0.917 mmol). Normal phase HPLC (20% EtOAc, 80% hexane) of the crude product afforded **23a** (247 mg, 0.75 mmol) as a pink oil. Yield: 82%; IR (film) ν_{max} cm^{-1} 3396, 2936, 1595, 1368, 997, 769, 719; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (1H, d, J = 8.0 Hz, H-5), 8.0 (1H, d J = 8.3 Hz, H-8), 7.54 (1H, td, J = 7.45, 0.95 Hz, H-7), 7.48 (1H, td, J = 7.6, 1.04 Hz, H-6), 7.39 (2H, d, J = 8.4 Hz, H-4`, 6`), 7.29 (2H, d, J = 8.5 Hz, H-3`, 7`), 6.71 (1H, s H-3), 6.32 (1H, s, 1`) 3.92 (3H, s, OMe-4), 3.82 (3H, s, OMe-1); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 152.4 ($q_c$, C-4), 146.6 ($q_c$, C-1), 142.2 ($q_c$, C-2`), 133.1 (q_c, C-5`), 130.9 ($q_c$, C-2), 128.5 (2 × CH, C-3`, 7`), 128.4 ($q_c$, C-8a), 127.8 (2 × CH, C-4`, 6`), 126.8 (CH, C-7), 126.4 ($q_c$, C-4a), 125.7 (CH, C-6), 122.5 (CH, C-5), 121.9 (CH, C-8), 102.1 (CH, C-3), 70.4 (CH, C1`), 62.7 (CH_3, 1-OMe), 55.7 (CH_3, 4-OMe); EIMS *m/z* (rel. Int.) 328 [M^+] (100), 312 (15), 297 (29), 285 (40), 281 (13), 261 (12), 246 (10), 230 (8), 218 (18), 189 (21), 140 (15), 139 (48), 130 (10), 111 (8), 69 (9); HREIMS *m/z* 328.0877 (calcd for $C_{19}H_{17}O_3Cl$ [M + H)]$^+$, 328.0866).

4.16. 2-[1`-Hydroxy-1`-(5`-chloro-3`-methylphenyl)methyl]-1,4-dimethoxynaphthalene (24a).

Compound **24a** was synthesized according to method A using a solution of 4-chloro-2-methyl-phenylmagnesium bromide (0.5 M, 1.38 mmol, 3.0 eq) and aldehyde **21** (100 mg, 0.46 mmol). Normal phase HPLC (20% EtOAc, 80% hexane) of the crude afforded **24a** (150.5 mg, 0.44 mmol) as a yellow amorphous solid. Yield: 96%; IR (film) ν_{max} cm^{-1} 3389, 2937, 1594, 1367, 997, 768, 703; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.21 (1H, d, J = 8.4 Hz, H-5), 8.02 (1H, d, J = 8.3 Hz, H-8), 7.54 (1H, m, H-7), 7.50 (1H, d, J = 8.3 Hz, H-7`), 7.48 (1H, m, H-6), 7.19 (1H, dd, $J$ = 8.3, 2.0 Hz, H-6`), 7.15 (1H, d, J = 1.9 Hz, H-4`), 6.57 (1H, s, H-3), 6.48 (1H, d, $J$ = 3.5 Hz, H-1`), 3.88 (3H, s, OMe-4), 3.85 (3H, s, OMe-1), 2.26 (3H, s, H-8`); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 152.3 ($q_c$, C-4), 146.9 ($q_c$, C-1), 139.7 ($q_c$, C-2`), 137.7 (q_c, C-3`), 133.0 ($q_c$, C-5`), 130.3 (CH, C-4`), 129.9 ($q_c$, C-2), 128.3 ($q_c$, C-8a), 127.9 (CH, C-7`), 126.8 (CH, C-7), 126.4 (q_c, C-4a), 125.9 (CH, C-6`), 125.8 (CH, C-6), 122.5 (CH, C-5), 121.9 (CH, C-8), 102.1 (CH, C-3), 68.7 ($CH_3$, 1-OMe), 67.8 (CH, C-1`), 55.6 (CH_3, 4-OMe), 19.1 (CH_3, C-8`); EIMS *m/z* (rel. int.)342 [M^+] (100), 327 (15), 311 (11), 295 (22), 279 (10), 263 (12), 244 (5), 231 (5), 218 (29), 202 (10), 189 (22), 173 (8), 155 (22), 153 (62), 131 (13), 125 (10), 69 (10); HREIMS *m/z* 342.1018 (calcd for $C_{20}H_{19}O_3Cl$ [M^+], 342.1023).

4.17. 2-[1`-Hydroxy-1`-(5`-fluorophenyl)methyl]-1,4-dimethoxynaphthalene (25a).

Compound **25a** was synthesized according to method A using a solution of 4-fluorophenylmagnesium bromide (2.0 M, 2.66 mmol, 3.0 eq) and aldehyde **21** (191 mg, 0.89 mmol). Normal phase HPLC (20% EtOAc, 80% hexane) of the crude afforded **25a** (209 mg, 0.67 mmol) as an orange oil. Yield: 75%; IR (film) ν_{max} cm^{-1} 3406, 2937, 1595, 1367, 997, 768, 710; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (1H, d, J = 8.3 Hz, H-5), 8.01 (1H, d, J = 8.4 Hz, H-8), 7.54 (1H, t, J = 7.5 Hz, H-7), 7.48 (1H, t, J =7.5 Hz H-6), 7.42 (2H, m, H-3`, H-7`), 7.01 (2H, t, J = 8.6 H-4`, H-6`), 6.7 (1H, s, H-3) 6.34 (1H, s, H-1`), 3.93 (3H, s, OMe-4), 3.81 (3H, s, OMe-1); $^{13}C$ NMR ($CDCl_3$, 100MHz) $\delta$ 162.1 ($q_c$, d, $J_{F,C}$ = 249.0 Hz, C-5`), 152.4 (q_c, C-4), 146.6 (q_c, C-1), 139.5 (q_c, d, $J_{F,C}$ = 3.0 Hz, C-2`), 131.2 ($q_c$, C-2), 128.4 ($q_c$, C-8a), 128.1 (2 × CH, d, $J_{F,C}$ = 8.1 Hz, C-3`, 7`), 126.8 (CH, C-7), 126.4 (q_c, C-4a), 125.7 (CH, C-6), 122.5 (CH, C-5), 121.9 (CH, C-8), 115.2 (2 × CH, d, $J_{F,C}$

= 21.3 Hz, C-4`,6`), 102.1 (CH, C-3), 70.5 (CH, C-1`), 62.6 (CH_3, 1-OMe), 55.7 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 312 [M^+] (100), 297 (8), 281 (12), 269 (35), 265 (12), 249 (10), 237 (10), 209 (11), 189 (12), 173 (8), 145 (5), 124 (5), 123 (40), 95 (7); HREIMS *m/z* 312.1159 (calcd for $C_{19}H_{17}O_3F$ [M^+], 312.1162).

4.18. 2-[1`-Hydroxy-1`-(4`-fluorophenyl) methyl]-1,4-dimethoxynaphthalene (26a).

Compound **26a** was synthesized according to method A using a solution of 3-fluorophenylmagnesium bromide (1 M, 1.38 mmol, 3.0 eq) and aldehyde **21** (100 mg, 0.46 mmol). Normal phase HPLC (20% EtOAc, 80% hexane) of the crude afforded **26a** (140.7 mg, 0.45 mmol) as an orange oil. Yield: 98%; IR (film) ν_{max} cm^{-1} 3396, 2937, 1590, 1366, 997, 760, 702; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.23 (1H, d, J = 8.3 Hz, H-5), 8.02 (1H, d, J = 8.4 Hz, H-8), 7.54 (1H, t, J = 8.8 Hz, H-7), 7.48 (1H, t, J = 8.8 Hz H-6), 7.27 (1H, m, H-6`), 7.21 (1H, m, H-3`), 7.20 (1H, m, H-7`), 6.93 (1H, m, H-5`), 6.72 (1H, s, H-3), 6.33 (1H, s, H-1`), 3.92 (3H, s, OMe-4), 3.83 (3H, s, OMe-1); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 162.9 ($q_c$, d, $J_{F,C}$ = 246.1 Hz, C-4`), 152.4 (q_c, C-4), 146.7 (q_c, C-1), 146.4 (q_c, d, $J_{F,C}$ = 6.7 Hz, C-2`), 130.9 ($q_c$, C-2), 129.8 (CH, d, $J_{F,C}$ = 8.0 Hz, C-6`), 128.4 (q_c, C-8a), 126.8 (CH, C-7), 126.4 (q_c, C-4a), 125.8 (CH,C-6), 122.5 (CH, C-5), 122.0 (CH, d, $J_{F,C}$ = 4.3 Hz, C-7`), 121.9 (CH, C-8), 114.1 (CH, d, $J_{F,C}$ = 21.4 Hz, C-5`), 113.4 (CH, d, $J_{F,C}$ = 22.2 Hz, C-3`), 102.1 (CH, C-3), 70.5 (CH, C-1`), 62.7 (CH_3, 1-OMe), 55.7 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 312 [M^+] (100), 296 (10), 281 (11), 269 (31), 249 (11), 220 (10), 209 (12), 189 (10), 183 (4), 159 (4), 145 (4), 124 (8), 123 (52), 95 (7); HREIMS *m/z* 312.1160 (calcd for $C_{19}H_{17}O_3F$ [M^+], 312.1162).

4.19. 2-[1`-Hydroxy-1`-(4`-chlorophenyl)methyl]-1,4-dimethoxynaphthalene (27a).

Compound **27a** was synthesized according to method A using a solution of 3-chlorophenylmagnesium bromide (0.5 M, 1.38 mmol, 3.0 eq) and aldehyde **21** (100 mg, 0.46 mmol). Normal phase HPLC (20% EtOAc, 80% hexane) of the crude afforded **27a** (146.4 mg, 0.45 mmol) as an orange oil. Yield: 97%; IR (film) ν_{max} cm^{-1} 3415, 2937, 1594, 1367, 997, 769, 701; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.23 (1H, d, J = 8.3 Hz, H-5), 8.02 (1H, d, J = 8.4 Hz, H-8), 7.55 (1H, m, H-7), 7.49 (2H, m, H-6, 3`), 7.31 (1H, m, H-7`), 7.25 (1H, m, H-6`), 7.22 (1H, m, H-5`), 6.71 (1H, s, H-3), 6.32 (1H, s, H-1`), 3.93 (3H, s, OMe-

4), 3.83 (3H, s, OMe-1); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.44 (q_c, C-4), 146.7 (q_c, C-1), 145.8 (q_c, C-2`), 134.3 ($q_c$, C-4`), 130.8 (q_c, C-2), 129.6 (CH, C-6`), 128.4 ($q_c$, C-8a), 127.5 (CH, C-5`), 126.8 (CH, C-7), 126.5 (CH, C-3`), 126.4 ($q_c$, C-4a), 125.8 (CH, C-6), 124.6 (CH, C-7`), 122.5 (CH, C-5), 122.0 (CH, C-8), 102.1 (CH, C-3), 70.6 (CH,C-1`), 62.8 (CH_3, 1-OMe), 55.8 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 328 [M^+] (100), 312 (10), 297 (15), 285 (33), 281 (10), 265 (8), 246 (8), 218 (12), 202 (8), 189 (18), 159 (5), 141 (15), 139 (55), 111 (7); HREIMS *m/z* 328.0859 (calcd for $C_{19}H_{17}O_3Cl$ [M^+], 328.0866).

4.20. 2-(1`-Hydroxy-1`-naphthylmethyl)-1,4-dimethoxynaphthalene (28a).

A solution of 2-naphthylmagnesium bromide (1.20 g, 5.8 mmol) was prepared *in situ* according to the procedure by Beck *et al*.,[3] and added dropwise *via* cannula to a stirred solution of the **21** (250 mg, 1.16 mmol) in anhydrous THF (5 mL) at -10 °C. The resulting solution was stirred for 1 h at -10 °C and then gradually allowed to reach RT. The resulting mixture was allowed to stir overnight at RT before being quenched with sat. NH_4Cl (10 mL) and extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with water (2 × 5 mL) and sat. brine (1 × 5 mL), dried over Na_2SO_4 and concentrated under vacuum to yield a brown solid (858 mg). Normal phase semi-preparative HPLC of the crude product (25% EtOAc, 75% hexane) afforded **28a** (340 mg, 0.99 mmol) as a pale yellow oil. Yield: 85%; IR (film) ν_{max} cm^{-1} 3407, 3009, 2938, 1508, 1459, 1369, 1092, 999, 756; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.23 (1H, d, *J* = 8.3 Hz, H-5), 8.04 (1H, d, *J* = 8.4 Hz, H-8), 7.95 (1H, s, H-3`), 7.83 (1H, m H-5`), 7.80 (1H, m, H-8`), 7.78 (1H, d, *J* = 8.6 Hz, H-10`), 7.55 (1H, t, *J* = 7.5 Hz, H-7), 7.52 (1H, dd, *J* = 8.6, 1.6 Hz, H-11`), 7.49 (1H, t, *J* = 7.5 Hz, H-6), 7.47 (H, m, H-6`), 7.46 (1H, m, H-7`), 6.81 (1H, s, H-3), 6.53 (1H, s, H-1`), 3.90 (3H, s, OMe-4), 3.83 (3H, s, OMe-1); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.3 (q_c, C-4), 146.7 (q_c, C-1), 141.1 (q_c, C-2`), 133.2 ($q_c$, C-4`), 132.7 (q_c, C-9`), 131.3 ($q_c$, C-2), 128.4 ($q_c$, C-8a), 128.1 (CH, C-10`), 128.1 (CH, C-5`), 127.6 (CH, C-8`), 126.7 (CH, C-7), 126.4 (q_c, C-4a), 126.1 (CH, C-6`), 125.8 (CH, C-7`), 125.6 (CH, C-6), 124.9 (CH, C-11`), 124.8 (CH, C-3`), 122.5 (CH, C-5), 122.0 (CH, C-8), 102.5 (CH, C-3), 71.0 (CH, C-1`), 62.7 (CH_3, 1-OMe), 55.6 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 344 [M^+] (100), 313 (15), 301 (27), 269 (9), 241 (5), 215 (21), 201 (14), 189 (28), 173 (40), 145 (14), 133 (4); HRFABMS *m/z* 344.1425 (calcd for $C_{23}H_{20}O_3$ [M^+], 344.1412).

4.21. 2-(1`-Hydroxy-1`-furanylmethyl)-1,4-dimethoxynaphthalene (29a).

A solution of *n*-butyllithium (1.6 M, 2.9 mL, 4.6 mmol, 10 eq) was added to a solution of 3-bromofuran (680 mg, 4.6 mmol) in THF (5 mL) at -78 °C and the reaction mixture stirred (30 min) before a solution of **21** (210 mg, 0.97 mmol) in dry THF (5 mL) was added dropwise *via* cannula. The reaction was stirred at -78 °C (30 min) and gradually allowed to reach RT. The reaction mixture was quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with sat. brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (339 mg). Normal phase HPLC (25% EtOAc, 75% hexane) of the crude mixture afforded **29a** (200 mg, 0.70 mmol) as a yellow oil. Yield: 73%; IR (film) ν_{max} cm^{-1} 3420, 3014, 2842, 1596, 1461, 1371, 1217, 1092,1000, 875, 758; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.23 (1H, d, J = 8.3 Hz, H-5), 8.02 (1H, d, J = 8.3 Hz, H-8), 7.54 (1H, td, J = 6.8, 1.1 Hz, H-7), 7.48 (1H, td, J = 6.8, 1.1 Hz, H-6), 7.37 (1H, t, J = 1.6 Hz, H-4`), 7.32 (1H, br s, H-5`), 6.83 (1H, s, H-3), 6.39 (1H, br d, J = 1.1 Hz, H-3`), 6.30 (1H, s, H-1`), 3.94 (3H, s, OMe-4), 3.84 (3H, s, OMe-1); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.3 (q_c, C-4), 146.3 (q_c, C-1), 143.3 (CH, C-4`), 139.8 (CH, C-5`), 130.6 (q_c, C-2), 128.9 (q_c, C-2`), 128.3 ($q_c$, C-8a), 126.7 (CH, C-7), 126.4 ($q_c$, C-4a), 125.7 (CH, C-6), 122.4 (CH, C-5), 122.0 (CH, C-8), 109.5 (CH, C-3), 102.0 (CH, C-3`), 64.6 (CH, C-1`), 62.8 (CH_3, 1-OMe), 55.7 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 284 [M^+] (54), 252 (100), 239 (24), 236 (10), 209 (29), 196 (15), 181 (25), 165 (15), 152 (42); HRFABMS *m/z* 284.1058 (calcd for $C_{17}H_{16}O_4$ [M^+], 284.1049).

4.22. 2-(1`-Hydroxy-3`-phenylpropyl)-1,4-dimethoxynaphthalene (30a).

Compound **30a** was synthesized according to method A using a solution of phenylethylmagnesium bromide (1 M, 3.5 mL, 3.5 mmol) and aldehyde **21** (250 mg, 1.16 mmol). Trituration of the crude product with 1:1 hexane/EtOAc afforded **30a** (222 mg, 0.70 mmol) as fine white needles. Yield: 60 %; mp 109-110 °C; IR (film) ν_{max} cm^{-1} 3438, 3020, 1597, 1460, 1217, 1000, 770; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.25 (1H, d, J = 8.2 Hz, H-5), 8.03 (1H, d, J = 8.2 Hz, H-8), 7.53 (1H, td, J = 7.6, 1.1 Hz, H-7), 7.47 (1H, td, J = 7.6, 1.1 Hz, H-6), 7.28 (2H, t, J = 7.5 Hz, H-6`, H-8`), 7.23 (2H, d, J = 7.0 Hz, H-5`, H-9`), 7.18 (1H, t, J = 7.3 Hz, H-7`), 6.89 (1H, s, H-3), 5.29 (1H, dd, $J$ = 8.3, 4.7 Hz, H-1`), 3.99 (3H, s, OMe-4), 3.82 (3H, s, OMe-1), 2.90 (1H, ddd, J = 14.3, 10.0, 5.2 Hz, H-2b`), 2.74 (1H,

ddd, *J* = 13.9, 9.6, 6.8 Hz, H-2a`), 2.23 (1H, dddd, *J* = 13.8, 9.4, 8.8, 5.2 Hz, H-3b`), 2.07 (1H, m, H-3a`); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 152.4 ($q_c$, C-4), 146.0 ($q_c$, C-1), 141.8 ($q_c$, C-4`), 132.0 (q_c, C-2), 128.5 (2 × CH, C-5`, C-7`), 128.4 (2 × CH, C-6`, C-8`), 128.4 (q_c, C-8a), 126.6 (CH, C-7), 126.2 (q_c, C-4a), 125.8 (CH, C-7`), 125.4 (CH, C-6), 122.4 (CH, C-5), 121.9 (CH, C-8), 101.6 (CH, C-3), 68.2 (CH, C-1`), 62.6 (CH_3, 1-OMe), 55.7 (CH_3, 4-OMe), 39.9 (CH_2, C-2`), 32.4 ($CH_2$, C-3`); EIMS *m/z* (rel. int.) 322 [M^+] (73), 304 (12), 217 (100), 202 (17), 189 (29), 174 (12), 159 (9), 105 (5), 93 (3); HRFABMS *m/z* 322.1569 (calcd for $C_{21}H_{22}O_3$ [M^+], 322.1569).

4.23. 2-(5`-Chlorobenzoyl)-1,4-naphthoquinone (12b).

Standard CAN oxidative demethylation of **23b** (16 mg, 0.05 mmol) according to method C and subsequent normal phase semi-preparative HPLC (20% EtOAc, 80% hexane) of the crude product afforded **12b** (12 mg, mmol) as a yellow amorphous solid. Yield: 81%; IR (film) ν_{max} cm^{-1} 2162, 1665, 1587, 1487, 1401, 1347, 1296, 1251, 1175, 1092, 983, 780,; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.14 (1H, m, H-5), 8.10 (1H, m, H-8), 7.82 (4H, m, H-6, H-7, H-3`, H-7`), 7.67 (2H, m, C-4`, C-6`) ^{13}C NMR ($CDCl_3$, 150 MHz) δ 190.8 (q_c, C-1`), 184.3 ($q_c$, C-4), 183.1 ($q_c$, C-1), 146.7 ($q_c$, C-2), 141.2 ($q_c$, C-2`), 135.9 (q_c, C-3), 134.6 (CH, C-6), 134.5 (CH, C-7), 133.8 (q_c, C-5`), 131.8 ($q_c$, C-8a), 131.4 ($q_c$, C-4a), 130.91 (2 × CH, C-3`, C-7`), 129.91 (2 × CH, C-4`, C-6`), 126.9 (CH, C-8), 126.5 (CH, C-5); EIMS m/z (rel. int.) 296 [M^+] (20), 281 (4), 268 (6), 261 (55), 233 (9), 219 (28), 207 (8), 186 (5), 176 (7), 154 (9), 141 (35), 139 (100), 131 (23), 129 (9), 113 (18), 111 (51), 101 (21), 75 (41), 69 (46), 53 (9), 50 (13); HREIMS *m/z* 297.0312 (calcd for $C_{17}H_{10}O_3Cl$ [M+H]$^+$ 297.0313).

4.24. 2-(5`-Chloro-3`-methylbenzoyl)-1,4-naphthoquinone (13b).

Standard CAN oxidative demethylation of **24b** using method C (19 mg, 0.06 mmol) and subsequent normal phase semi-preparative HPLC (20% EtOAc, 80% Hexane) of the crude afforded **13b** (16.4 mg, 0.05 mmol) as a yellow oil. Yield: 88%; IR (film) ν_{max} cm^{-1} 2163, 1664, 1592, 1557, 1447, 1345, 1296, 1247, 1103, 1029, 976, 880, 774, 722; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.13 (1H, m, H-5), 8.08 (1H, m, H-8), 7.81 (2H, m, H-6, H-7), 7.45 (1H, d, *J* = 8.3 Hz, H-7`), 7.34 (1H, d, *J* = 1.6 Hz, H-4`), 7.21 (1H, dd, *J* = 8.3, 1.8 Hz, H-

6`), 6.99 (1H, s, H-3), 2.63 (1H, s, H-8`), ^{13}C NMR ($CDCl_3$, 150 MHz) δ 193.0 (q_c, C-1`), 184.6 ($q_c$, C-4), 183.3 ($q_c$, C-1), 147.5 ($q_c$, C-2), 142. 2 ($q_c$, C-2`), 139.2 (q_c, C-3`), 135.8 (CH, C-3), 134.5 (2 × CH, C-6, C-7), 133.5 ($q_c$, C-5`), 132.8 (CH, C-7`), 132.4 (CH, C-4`), 131.9 (q_c, C-8a), 131.5 (q_c, C-4a), 126.9 (CH, C-8), 126.5 (CH, C-5), 126.0 (CH, C-6`), 21.4 ($CH_3$, C-8`); EIMS *m/z* (rel. int.) 310 [M^+] (62), 275 (58), 276 (12), 275 (56), 265 (10), 254 (17), 247 (12), 219 (12), 202 (8), 189 (17), 186 (45), 155 (31), 153 (100), 130 (17), 127 (25), 125 (77), 105 (13), 101 (29), 89 (63), 75 (32), 63 (23); HREIMS *m/z* 310.0410 (calcd for $C_{18}H_{11}O_3Cl$ [M^+] 310.0397).

4.25. 2-(5`-Fluorobenzoyl)-1,4-naphthoquinone (14b).

Standard CAN oxidative demethylation of **25b** using method C (17 mg, 0.05 mmol) and subsequent normal phase semi-preparative HPLC (20% EtOAc, 80% Hexane) of the crude afforded **14b** (7.6 mg, 0.027 mmol) as a yellow oil. Yield: 54%; IR (film) ν_{max} cm^{-1} 2161, 1665, 1594, 1506, 1411, 1346, 1296, 1250, 1156, 160, 774, 719; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.14 (1H, m, H-5), 8.11 (1H, m, H-8), 7.92 (1H, m, H-3`, H-7`), 7.82 (1H, m, H-6, H-7), 7.17 (1H, m, H-4`, H-6`), 6.99 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 600 MHz) δ 190.3 (q_c, C-1`), 184.3 ($q_c$, C-4), 183.2 ($q_c$, C-1), 166.6 ($q_c$, d, $J_{F,C}$ = 257.7 Hz, C-5`), 146.9 (q_c, C-2), 135.7 (CH, C-3), 134.6 (2 × CH, C-6, C-7), 132.4 (2 × CH, d, $J_{F,C}$ = 9.8 Hz, C-3`, C-7`), 131.9 (q_c, d, $J_{F,C}$ = 3.1 Hz, C-2`), 131.8 ($q_c$, C-8a), 131.5 ($q_c$, C-4a), 126.9 (CH, C-8), 126.5 (CH, C-5), 116.2 (2 × CH, d, $J_{F,C}$ = 22.4 Hz, C-4`, C-6`); EIMS *m*/z (rel. int.) 280 [M^+] (42), 252 (7), 224 (4), 219 (13), 207 (5), 186 (5), 157 (5), 130 (12), 123 (100), 104 (8), 101 (13), 95 (51), 75(31), 69 (20), 50 (8); HREIMS *m/z* 280.0525 (calcd for $C_{17}H_9O_3F$ [M^+] 280.0536).

4.26. 2-(4`-Fluorobenzoyl)-1,4-naphthoquinone (15b).

Standard CAN oxidative demethylation of **26b** using method C (21 mg, 0.07 mmol) and subsequent normal phase semi-preparative HPLC (20% EtOAc, 80% Hexane) of the crude afforded **15b** (16.9 mg, 0.06 mmol) as a yellow oil. Yield: 86%; IR (film) ν_{max} cm^{-1} 3071, 2161, 1664, 1588, 1482, 1445, 1347, 1251, 1124, 897, 769, 675; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.15 (1H, m, H-5), 8.11 (1H, m, H-8), 7.83 (2H, m, H-6, H-7), 7.63 (1H, m, H7`), 7.60 (1H, m, H-3`), 7.47 (1H, m, H-6`), 7.35 (1H, m, H-5`), 7.01 (1H, s, H-3); ^{13}C NMR

($CDCl_3$, 600 MHz) δ 190.8 (q_c, d, $J_{F,C}$ = 2.4 Hz, C-1`), 184.2 ($q_c$, C-4), 183.1 ($q_c$, C-1), 162.8 ($q_c$, d, $J_{F,C}$ = 249.8 Hz, C-4`), 146.6 (q_c, C-2), 137.5 (q_c, d, $J_{F,C}$ = 6.7 Hz, C-2`), 135.9 (CH, C-3), 134.6 (CH, C-7), 134.5 (CH, C-6), 131.8 ($q_c$, C-8a), 131.4 ($q_c$, C-4a), 130.6 (CH, d, $J_{F,C}$ = 7.7 Hz C-6`), 126.9 (CH, C-8), 126.6 (CH, C-5), 125.6 (CH, d, $J_{F,C}$ = 2.7 Hz, C-7`), 121.6 (CH, d, $J_{F,C}$ = 21.4 Hz, C-5`), 115.9 (CH, d, $J_{F,C}$ = 22.5 Hz, C-3`); EIMS *m/z* (rel. int.) 280 [M^+] (58), 264 (4), 252 (10), 224 (9), 196 (8), 186 (4), 157 (8), 129 (9), 123 (100), 104 (12), 101 (24), 95 (61), 75 (41), 69 (15); HREIMS *m/z* 280.0532 (calcd for $C_{17}H_9O_3F$ [M^+] 280.0536).

4.27. 2-(4`-Chlorbenzoyl)-1,4-naphthoquinone (16b).

Standard CAN oxidative demethylation of **27b** using method C (32 mg, 0.1 mmol) and subsequent normal phase semi-preparative HPLC (20% EtOAc, 80% Hexane) of the crude afforded **16b** (23.6 mg, 0.08 mmol) as a yellow oil. Yield: 80%; IR (film) ν_{max} cm^{-1} 3319, 3066, 2159, 1659, 1589, 1426, 1345, 1295, 1238, 917, 781, 734, 591; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.14 (1H, m, H-5), 8.11 (1H, m, H-8), 7.86 (1H, m, H-3`), 7.82 (2H, m, H-6, H-7), 7.74 (1H, d, *J* = 7.8 Hz, H-5`), 7.60 (1H, d, *J* = 7.9 Hz, H-7`), 7.43 (1H, d, *J* = 7.9 Hz, H-6`), 7.00 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 190.8 (q_c, C-1`), 184.2 ($q_c$, C-4), 183.1 ($q_c$, C-1), 146.5 ($q_c$, C-2), 137.0 ($q_c$, C-2`), 135.9 (CH, C-3), 135.3 (q_c, C-4`), 134.6 (CH, C-7), 134.5 (CH, C-6), 134.4 (CH, C-3`), 131.8 (q_c, C-8a), 131.4 (q_c, C-4a), 130.2 (CH, C-6`), 129.3 (CH, C-5`), 127.7 (CH, C-7`), 126.9 (CH, C-8), 126.6 (CH, C-5); EIMS *m/z* (rel. int.) 296 [M^+] (45), 270 (7), 261 (38), 233 (20), 205 (8), 176 (9), 157 (8), 141 (32), 139 (100), 129 (12), 113 (22), 111 (66), 101 (38), 85 (4), 75 (62), 63 (4); HREIMS *m/z* 296.0252 (calcd for $C_{17}H_9O_3Cl$ [M^+] 296.0240).

4.28. 2-Naphthoyl-1,4-naphthoquinone (17b).

Standard CAN oxidative demethylation of **28b** (34 mg, 0.10 mmol) using method C and subsequent purification of the crude using normal phase semi-preparative HPLC (25% EtOAc, 75% hexane) yielded **17b** (18.7 mg, 0.06 mmol) as a yellow solid. Yield: 60%; IR (film) ν_{max} cm^{-1} 3020, 2401, 1662, 1589, 1469, 1216, 1076, 916, 757, 669; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.31 (1H, s, H-3`), 8.17 (1H, d, *J* = 7.1 Hz, H-5), 8.13(1H, d, *J* = 7.1 Hz, H-8), 8.02 (1H, d, *J* = 8.6 Hz, H-11`), 7.94 (1H, d, *J* = 8.6 Hz, H-10`), 7.91 (1H, d, *J* =

8.4 Hz, H-5`), 7.89 (1H, d, *J* = 8.4 Hz, H-8`), 7.84 (1H, td, *J* = 7.8, 1.5 Hz, H-6), 7.82 (1H, td, *J* = 7.8, 1.5 Hz, H-7), 7.63 (1H, t, *J* = 7.5 Hz, H-6`), 7.55 (1H, t, *J* = 7.5 Hz, H-7`), 7.06 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 191.8 (q_c, C-1`), 184.5 ($q_c$, C-4), 183.3 ($q_c$, C-1), 147.2 ($q_c$, C-2), 136.2 ($q_c$, C-4`), 135.6 (CH, C-3), 134.5 (2 × CH, C-7, C-6), 132.9 (q_c, C-2`), 132.7 (CH, C-3`), 132.3 (q_c, C-9`), 131.9 ($q_c$, C-4a), 131.6 ($q_c$, C-8a), 129.8 (CH, C-5`), 129.4 (CH, C-6`), 129.0 (CH, C-10`), 127.9 (CH, C-8`), 127.2 (CH, C-7`), 126.9 (CH, C-8), 126.5 (CH, C-5), 123.9 (CH, C-11`); EIMS *m/z* (rel. int.) 312 [M^+] (100), 284 (41), 255 (12), 239 (3), 228 (5), 155 (37), 145 (13), 128 (10), 101 (2), 77 (5); HRFABMS *m/z* 312.0788 (calcd for $C_{21}H_{12}O_3$ [M^+], 312.0786).

4.29. 2-Furanoyl-1,4-naphthoquinone (18b).

Standard CAN oxidative demethylation of **29b** (22 mg, 0.08 mmol) using method C and subsequent purification of the crude using normal phase semi-preparative HPLC (25% EtOAc, 75% hexane) yielded **18b** (11 mg, 0.044 mmol) as fine yellow needles from hexane/CH_2Cl_2. Yield: 56%; mp 138-141 °C; IR (film) ν_{max} cm^{-1} 3021, 2401, 1669, 1513, 1301, 1216, 1167, 928, 873, 769, 669; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.13 (1H, m, H-8), 8.12 (1H, m, H-5), 7.93 (1H, s, H-5`), 7.81 (2H, m, H-7, H-6), 7.51 (1H, t, *J* = 1.6Hz, H-4`), 7.02 (1H, s, H-3), 6.87 (1H, br d, *J* = 1.5 Hz, H-3`); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 184.7 ($q_c$, C-4), 184.7 ($q_c$, C-1`), 182.7 (q_c, C-1), 150.0 (CH, C-5`), 146.3 ($q_c$, C-2), 144.9 (CH, C-4`), 135.2 (CH, C-3), 134.5 (CH, C-7), 134.5 (CH, C-6), 131.7 (q_c, C-4a), 131.5 (q_c, C-8a), 127.1 (q_c, C-2`), 126.9 (CH, C-8), 126.4 (CH, C-5), 108.8 (CH, C-3`); EIMS *m/z* (rel. int.) 252 [M^+] (54), 242 (4), 224 (100), 203 (3), 196 (25), 185 (3), 168 (17), 157 (6), 140 (8), 129 (5), 95 (47), 91 (2), 75 (10); HRFABMS *m/z* 252.0431 (calcd for $C_{15}H_8O_4$ [M^+], 252.0423).

4.30. 2-(1`-Oxo-3`-phenylpropyl)-1,4-naphthoquinone (19b).

Standard CAN oxidative demethylation of **30b** (32.5 mg, 0.10 mmol) according to method C, followed by normal phase semi-preparative HPLC (17% EtOAc, 83% hexane) yielded **19b** (28.8 mg, 0.10 mmol) as a brown solid. Yield: 98%; IR (film) ν_{max} cm^{-1} 3020, 2410, 1670, 1579, 1463, 1218, 1104, 967, 933, 754, 669; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.10 (1H, dd, *J* = 7.1, 1.6 Hz, H-8), 8.07 (1H, dd, *J* = 7.0, 1.7 Hz, H-5), 7.80 (1H, td, *J* = 7.4, 1.6 Hz,

H-7), 7.78 (1H, td, *J* = 7.3, 1.6 Hz, H-6), 7.27 (2H, t, *J* = 7.5 Hz, H-7`, H-6`), 7.22 (2H, d, *J* = 7.4 Hz, H-9`, H-5`), 7.18 (1H, t, *J* = 7.3 Hz, H-5`), 7.04 (1H, s, H-3); 3.30 (2H, t, *J* = 7.5 Hz, $H_2$-2`), 3.03 (2H, t, *J* = 7.5 Hz, H_2-3`); $^{13}$C NMR ($CDCl_3$, 150 MHz) *δ* 199.7 ($q_c$, C-1`), 184.9 (q_c, C-4), 183.3 (q_c, C-1), 145.5 (q_c, C-2), 140.4 (q_c, C-4`), 137.0 (CH, C-3), 134.5 (CH, C-7), 134.4 (CH, C-6), 131.7 ($q_c$, C-8a), 131.7 ($q_c$, C-4a), 128.6 (2 × CH, C-8`, C-6`), 128.4 (2 × CH, C-9`, C-5`), 126.8 (CH, C-8`), 126.3 (CH, C-5`), 45.0 ($CH_2$, C-2`), 29.6 (CH_2, C-3`); EIMS *m/z* (rel. int.) 290 [M^+] (100), 274 (12), 237 (25), 202 (33), 187 (44), 105 (22), 91 (39)69 (24); HRFABMS *m/z* 290.0947 (calcd for $C_{19}H_{14}O_3$ [M^+], 290.0943).

4.31. 2-(5`-Chlorobenzoyl)-1,4-dimethoxynaphthalene (23b).

The oxidation of **23a** (29 mg, 0.08 mmol) using method B4.4.1 yield **23b** as a yellow amorphous solid (22.9 mg, 0.07 mmol). Yield: 88%; IR (film) ν_{max} cm^{-1} 2932, 2849, 1967, 1652, 1586, 1459, 1368, 1245, 1092, 1003, 958, 822, 770, 754, 667; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.23 (1H, m, H-5), 8.13 (1H, m, H-8), 7.86 (2H, d, *J* = 8.5 Hz, H-3`, H-7`), 7.59 (2H, m, H-6, H-7), 7.46 (2H, d, *J* = 8.5 Hz, H-4`, H-6`), 6.76 (1H, s, H-3), 3.98 (3H, s, OMe-4), 3.71 (3H, s, OMe-1); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.8 (q_c, C-1`), 151.9 ($q_c$, C-4), 148.8 ($q_c$, C-1), 139.6 ($q_c$, C-2'), 136.0 ($q_c$, C-5'), 131.4 (2 × CH, C-3`, C-7`) 128.7 (2 × CH, C-4`, C-6`), 128.5 (q_c, C-8a), 128.1 (q_c, C-4a), 127.3 (CH, C-7), 127.2 (CH, C-6), 126.7 (q_c, C-2), 122.7 (CH, C-8), 122.5 (CH, C-5), 102.8 (CH, C-3), 63.7 (CH_3, 1-OMe), 55.0 (CH_3, 4-OMe); EIMS *m/z* (rel. int) 326 [M^+] (100), 311 (60), 309 (26), 296 (25), 276 (26), 261 (11), 248 (40), 233 (32), 205 (12), 201 (18), 189 (9), 157 (4), 141 (8), 139 (22), 129 (12), 110 (30), 101 (12), 75 (12); HREIMS *m/z* 326.0713 (calcd for $C_{19}H_{15}O_3Cl$ [M^+], 326.0710).

4.32. 2-(5`-Chloro-3`-methylbenzoyl)-1,4-dimethoxynaphthalene (24b).

The oxidation of **24a** (44 mg, 0.13 mmol) using method B4.4.1 yield **24b** as a yellow amorphous solid (43.8 mg, 0.13 mmol). Yield: 99%; IR (film) ν_{max} cm^{-1} 2933, 2849, 2160, 1652, 1593, 1459, 1369, 1235, 1114, 1098, 1003, 957, 881, 770, 712; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.28 (1H, m, H-5), 8.09 (1H, m, H-8), 7.58 (2H, m, H-6, H-7), 7.38 (1H, d, *J* = 8.3 Hz, H-7'), 7.29 (1H, d, *J* = 1.6 Hz, H-4'), 7.18 (1H, dd, *J* = 8.3, 1.9 Hz, H-6') 6.91 (1H, s, H-3), 4.00 (3H, s, OMe-4), 3.63 (3H, s, OMe-1), 2.51 (3H, s, H-8'); ^{13}C NMR ($CDCl_3$, 150 MHz) *δ* 197.5 (q_c, C-1'), 151.9 (q_c, C-4), 150.3 (q_c, C-1), 139.9 (q_c, C-2'),

137.6 (q_c, C-5'), 136.9 (q_c, C-3'), 131.7 (CH, C-7'), 131.2 (CH, C-4'), 128.7 (q_c, C-8a), 128.6 (q_c, C-4a), 127.7 (CH, C-2), 127.6 (CH, C-7), 127.2 (q_c, C-6), 125.6 (CH, C-6'), 123.0 (CH, C-8), 122.6 (CH, C-5), 102.8 (CH, C-3), 63.8 (CH_3, 1-OMe), 55.1 (CH_3, 4-OMe), 20.6 (CH_3, C-8'); EIMS *m/z* (rel. int.) 340 [M^+] (100), 325 (60), 310 (30), 290 (19), 275 (14), 262 (14), 247 (21), 215 (11), 201 (32), 189 (4), 155 (5), 153 (26), 129 (19), 125 (31), 114 (13), 101 (18), 89 (20), 63 (8); HREIMS *m/z* 340.0866. (calcd for $C_{20}H_{17}O_3Cl$ [M^+], 340.0866).

4.33. 2-(5`-Fluorobenzoyl)-1,4-dimethoxynaphthalene (25b).

The oxidation of **25a** (40 mg, 0.13 mmol) using method B4.4.1 yielded **25b** as a yellow amorphous solid (38.7 mg, 0.12 mmol). Yield: 93%; IR (film) ν_{max} cm^{-1} 2935, 2847, 1664, 1594, 1505, 1460, 14098, 1369, 1235, 1152, 1094, 1004, 959, 854, 769, 713; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.29 (1H, m, H-5), 8.13 (1H, m, H-8), 7.93 (2H, m, H-3`, H-7`), 7.59 (2H, m, H-6, H-7), 7.13 (2H, m, H-6`), 6.76 (1H, s, H-3), 3.98 (3H, s, OMe-4), 3.72 (3H, s, OMe-1); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 195.4 ($q_c$, C-1`), 165.9 (q_c, d, $J_{F,C}$ = 255.5 Hz, C-5`), 151.9 ($q_c$, C-4), 148.5 ($q_c$, C-1), 133.9 ($q_c$, C-2`), 132.7 (2 × CH, d, $J_{F,C}$ = 9.2 Hz, C-3`, C-7`), 128.5 (q_c, C-8a), 127.9 (q_c, C-4a), 127.3 (CH, C-7), 127.2 (CH, C-6), 126.9 (q_c, C-2), 122.7 (CH, C-8), 122.5 (CH, C-5), 115.5 (2 × CH, d, $J_{F,C}$ = 21.9 Hz, C-4`, C-6`), 102.8 (CH, C-3), 63.6 (CH_3, 1-OMe), 55.1 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 310 [M^+] (100), 295 (61), 293 (22), 280 (34), 267 (21), 252 (31), 236 (20), 223 (11), 207 (21), 201 (16), 195 (4), 183 (3) 157 (4), 129 (11), 123 (31), 114 (9), 101 (13), 95 (38), 75 (14), 69 (10); HREIMS *m/z* 310.0996 (calcd for $C_{19}H_{15}O_3F$ [M^+], 310.1005).

4.34. 2-(4`-Fluorobenzoyl)-1,4-dimethoxynaphthalene (26b).

The oxidation of **26a** (46 mg, 0.15 mmol) using method B4.4.1 yielded **26b** as a yellow amorphous solid (45.1 mg, 0.145 mmol). Yield: 97%; IR (film) ν_{max} cm^{-1} 2935, 2847, 1667, 1588, 1459, 1369, 1255, 1110, 1092, 966, 802, 764, 675; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.29 (1H, m, H-5), 8.13 (1H, m, H-8), 7.74 (1H, d, *J* = 7.7 Hz, H-7`), 7.61 (1H, m, H-3`), 7.59 (2H, m, H-6, H-7), 7.42 (1H, m, H-6`), 7.28 (1H, m, H-5`), 6.76 (1H, s, H-3), 3.99 (3H, s, OMe-4), 3.73 (3H, s, OMe-1); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.8 (q_c, C-1`), 162.7 ($q_c$, d, $J_{F,C}$ = 247.8 Hz, C-4`), 151.9 (q_c, C-4), 148.9 (q_c, C-1), 139.9 (q_c, d, $J_{F,C}$ = 6.6 Hz, C-2`), 129.9 (CH, d, $J_{F,C}$ = 7.3 Hz, C-6`), 128.5 (q_c, C-8a), 128.1 (q_c, C-2), 127.3 (CH,

C-7), 127.2 (CH, C-6), 126.6 (q_c, C-4a), 125.9 (CH, d, $J_{F,C}$ = 2.9 Hz, C-7`), 122.8 (CH, C-8), 122.5 (CH, C-5), 120.1 (CH, d, $J_{F,C}$ =21.8 Hz, C-5`), 116.3 (CH, d, $J_{F,C}$ = 22.3 Hz, C-3`), 102.7 (CH, C-3), 63.8 (CH_3, 1-OMe), 55.8 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 310 [M^+] (100), 295 (70), 280 (36), 267 (13), 252 (29), 236 (17), 223 (10), 207 (29), 196 (12), 157 (4), 129 (12), 123 (18), 101 (12), 95 (29), 75 (6); HREIMS *m/z* 310.1003 (calcd for $C_{19}H_{15}O_3F$ [M^+] 310.1005).

4.35. 2-(4`-Chlorobenzoyl)-1,4-dimethoxynaphthalene (27b).

The oxidation of **27a** (71.6 mg, 0.22 mmol) using method B4.4.1 yielded **27b** as a yellow amorphous solid (69.5 mg, 0.21 mmol). Yield: 97%; IR (film) ν_{max} cm^{-1} 2934, 2844, 2159, 1663, 1592, 1459, 1369, 1234, 1119, 1096, 1009, 961, 818, 771, 750, 673; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.29 (1H, m, H-5), 8.14 (1H, m, H-8), 7.88 (1H, t, *J* = 1.7 Hz, H-3`), 7.74 (1H, m, H-7`), 7.60 (2H, m, H-6, H-7), 7.55 (1H, m, H-5`), 7.39 (1H, t, *J* = 7.9, H-6`), 6.76 (1H, s, H-3), 3.99 (3H, s, OMe-4), 3.72 (3H, s, OMe-1); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.7 (q_c, C-1`), 151.9 ($q_c$, C-4), 149.0 ($q_c$, C-1), 139.4 ($q_c$, C-2`), 134.6 (q_c, C-4`), 133.0 (CH, C-5`), 129.6 (CH, C-3`), 128.5 ($q_c$, C-2), 128.2 (CH, C-7`), 128.1 (q_c, C-8a), 127.4 (q_c, C-4a), 127.3 (CH, C-6`), 126.5 (2 × CH, C-6, C-7), 122.8 (CH, C-8), 122.6 (CH, C-5), 102.7 (CH, C-3), 63.8 (CH_3, 1-OMe), 55.8 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 326 [M^+] (100), 311 (61), 309 (22), 296 (22), 276 (37), 261 (12), 248 (33), 233 (30), 215 (8), 205 (12), 189 (8), 140 (6), 139 (18), 129 (16), 110 (23), 101 (13), 75 (9), HREIMS *m/z* 326.0708 (calcd for $C_{19}H_{15}O_3Cl$ [M^+] 326.0710).

4.36. 2-Naphthoyl-1,4-dimethoxynaphthalene (28b).

Oxidation of **28a** (100 mg, 0.29 mmol) using method B4.4.2 yielded **28b** (90.5 mg, 0.26 mmol) as light yellow crystals from hexane. Yield: 91%; mp 106-109 °C; IR (film) ν_{max} cm^{-1} 3019, 2938, 2400, 1656, 1461, 1372, 1216, 1111, 1032, 968, 770, 668; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.35 (1H, s, H-3`), 8.34 (1H, m, H-5), 8.18 (1H, m, H-5), 8.07 (1H, dd, *J* = 8.7, 1.5 Hz, H-11`), 7.93 (1H, d, *J* = 8.4 Hz, H-10`), 7.88 (2H, m, H-6`, H-5`), 7.62 (2H, m, H-7, H-6), 7.59 (1H, t, *J* = 7.3 Hz, H-7`), 7.51 (1H, d, *J* = 7.2 Hz, H-8`), 6.84 (1H, s, H-3), 3.99 (3H, s, OMe-4), 3.76 (3H, s, OMe-1); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 197.0 ($q_c$, C-1`), 151.7 (q_c, C-4), 148.7 (q_c, C-1), 135.7 (q_c, C-4`), 135.0 ($q_c$, C-2`), 132.5 (CH, C-3`), 132.5 ($q_c$, C-9`), 129.7 (CH, C-5`), 128.6 ($q_c$, C-8a), 128.5 (CH, C-8`), 128.2 (CH, C-10`), 127.9

(q_c, C-2), 127.8 (CH, C-6`), 127.3 ($q_c$, C-4a), 127.2 (CH, C-7), 127.1 (CH, C-6), 126.6 (CH, C-7`), 125.1 (CH, C-11`), 122.8 (CH, C-8), 122.5 (CH, C-5), 103.1 (CH, C-3), 63.6 (CH_3, 1-OMe), 55.8 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 342 [M^+] (100), 327 (40), 312 (33), 294 (6), 256 (11), 200 (30), 173 (2), 155 (9), 127 (6), 77 (1); HRFABMS *m/z* 342.1252 (calcd for $C_{23}H_{18}O_3$ [M^+], 342.1256).

4.37. 2-Furanoyl-1,4-dimethoxynaphthalene (29b).

Oxidation of **29a** (30.0 mg, 0.11 mmol) according to method B4.4.2 afforded **29b** (22.3 mg, 0.08 mmol) as a brown oil. Yield: 72%; IR (film) ν_{max} cm^{-1} 3024, 2963, 2407, 1651, 1574, 1219, 1096, 926, 756; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.27 (1H, dd, *J* = 7.5, 1.6 Hz, H-5), 8.17 (1H, dd, *J* = 7.2, 1.8 Hz, H-8), 7.90 (1H, s, H-5`), 7.60 (1H, td, *J* = 6.9, 1.5 Hz, H-6), 7.57 (1H, td, *J* = 6.8, 1.5 Hz, H-7), 7.47 (1H, t, 1.6 Hz, H-4`), 6.92 (1H, br d, *J* = 1.5 Hz, H-3`), 6.79 (1H, s, H-3), 3.98 (3H, s, OMe-4), 3.83 (3H, s, OMe-1); $^{13}C$ NMR ($CDCl_3$, 150 MHz) $\delta$ 189.9 ($q_c$, C-1`), 151.7 (q_c, C-4), 150.3 (CH, C-5`), 148.2 ($q_c$, C-1), 143.9 (CH, C-4`), 128.7 (q_c, C-8a), 128.0 (q_c, C-4a), 127.8 (2 × q_c, C-2, C-2`), 127.2 (CH, C-6), 127.1 (CH, C-7), 122.8 (CH, C-8), 122.4 (CH, C-5), 109.4 (CH, C-3`), 102.7 (CH, C-3), 63.8 (CH_3, 1-OMe), 55.8 (CH_3, 4-OMe); EIMS *m/z* (rel. int.) 282 [M^+] (100), 267 (13), 265 (21), 253 (13), 239 (68), 211 (31), 201 (26), 196 (24), 173 (11), 139 (11), 129 (16); HRFABMS *m/z* 282.0897 (calcd for $C_{17}H_{14}O_4$ [$M]^+$, 282.0892).

4.38. 2-(1`-Oxo-3`-phenylpropyl)-1,4-dimethoxynaphthalene (30b).

Oxidation of **30a** (50 mg, 0.16 mmol) according to method B4.4.1 afforded **30b** (49.7 mg, 0.16 mmol) as yellow crystals from hexane/CH_2Cl_2. Yield: 100%; mp 80-82 °C; IR (film) ν_{max} cm^{-1} 3020, 2938, 2401, 1668, 1596, 1459, 1372, 1216, 1101, 966, 929, 758, 670; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.25 (1H, m, H-5), 8.14 (1H, m, H-8), 7.60 (1H, m, H-6), 7.56 (1H, m, H-7), 7.29 (2H, t, *J* = 6.7 Hz, H-8`, H-6`), 7.28 (2H, d, *J* = 6.5 Hz, H-9`, H-5`), 7.19 (1H, tt, *J* = 6.5, 2.1 Hz, H-7`), 6.99 (1H, s, H-3), 3.99 (3H, s, OMe-4), 3.87 (3H, s, OMe-1), 3.50 (2H, t, *J* = 7.5 Hz, $H_2$-2`), 3.10 (2H, t, *J* = 7.5 Hz, H_2-3`); $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 202.1 ($q_c$, C-1`), 151.9 (q_c, C-4), 151.0 (q_c, C-1), 141.5 (q_c, C-4`), 128.8 ($q_c$, C-4a), 128.7 ($q_c$, C-8a), 128.5 (2 × CH, C-5`, C-9`), 128.4 (2 × CH, C-6`, C-8`), 127.6 (CH, C-7), 127.4 ($q_c$, C-2), 127.1 (CH, C-6), 126.0 (CH, C-7`), 123.1 (CH, C-8), 122.5 (CH, C-5), 102.2 (CH, C-3), 63.9 (CH_3, 1-OMe), 55.7 (CH_3, 4-OMe), 44.7 (CH_2, C-2`), 30.6 (CH_2, C-

3`); LREIMS *m/z* (rel. int.) 320 [M^+] (100), 289 (15), 215 (80), 201 (13), 149 (6), 69 (11); HREIMS *m/z* 321.1496 (calcd for $C_{21}H_{21}O_3$ [(M + H)]$^+$, 321.1485).

4.39. Synthesis of compounds 31 and 32.

The benzylic alcohol **22a** (300 mg, 1.02 mmol), (-)-(*S*)-camphanic chloride (508 mg, 2.34 mmol, 2.3 eq), Et_3N (853 μL, 6.12 mmol, 6.0 eq) and DMAP (63 mg, 0.51 mmol, 0.5 eq) were dissolved in anhydrous CH_2Cl_2 (30 mL) under Ar atmosphere and stirred at ambient temperature for 5 h. The reaction mixture was concentrated to dryness, taken up in Et_2O (20 mL) and washed with 1M HCl (10 mL) followed by H_2O (10 mL). The organic portion was dried over $MgSO_4$ and concentrated to give a pale yellow oil (659 mg). All our attempts at fractional crystallization of the mixture using a variety of solvents (*e. g.* hexane, EtOAc, MeOH, EtOH, H_2O, Et_2O, 2-methoxyethanol, petroleum ether) and mixtures of these solvents failed to afford any separation. Normal phase HPLC (99% CH_2Cl_2, 1% EtOAc) of the crude mixture (190 mg, 0.4 mmol) afforded *R*-camphanate ester (91 mg, 0.19 mmol, 50%) and *S*-camphanate ester (88 mg, 0.19 mmol, 50%) in 70% overall yield. Fine white needles (suitable for X-ray crystallography) of one of the diastereomers were obtained from the initial dissolution of the compound in hot methanol, followed by the slow diffusion of water into the solution over a few days. Single crystal analysis (Scheme 2) established the *R*-configuration of C-1` for compound **31**.

Fine white needles (from MeOH/H_2O); mp 162-166 °C; $[\alpha]_D^{22}$ +39 (*c* 0.23, $CHCl_3$); IR (film) ν_{max} cm^{-1} 3686, 3021, 2401, 1785, 1667, 1522, 1423, 1215, 1019, 929, 757, 669, 511; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.21 (1H, d, *J* = 8.4 Hz, H-5), 8.06 (1H, d, *J* = 8.4 Hz, H-8), 7.60 (1H, s, H-1`), 7.55 (1H, t, *J* = 7.6 Hz, H-7), 7.49 (1H, t, *J* = 7.6 Hz, H-6), 7.44 (2H, d, *J* = 7.8 Hz, H-7`, H-3`), 7.32 (2H, t, *J* = 7.6 Hz, H-6`, H-4`), 7.26 (1H, t, *J* = 7.4 Hz, H-5`), 6.78 (1H, s, H-3), 3.98 (3H, s, 1-OMe), 3.90 (3H, s, 4-OMe), 2.49 (1H, ddd, *J* = 13.8, 10.9, 4.2 Hz, H-3``b), 2.11 (1H, ddd, *J* = 13.8, 9.4, 4.6 Hz, H-3``a), 1.93 (1H, ddd, *J* = 13.2, 10.9, 4.5 Hz, H-4``b), 1.71 (1H, ddd, *J* = 13.5, 9.5, 4.3 Hz, H-4``a), 1.10 (3H, s, H_3-8``), 1.02 (3H, s, $H_3$-10``), 0.90 (3H, s, H_3-9``); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 178.3 ($q_c$, C-6``), 166.7 (q_c, C-1``), 152.3 (q_c, C-4), 146.7 (q_c, C-1), 139.4 (q_c, C-2`), 128.5 (2 × CH, C-6`, C-4`), 128.3 ($q_c$, C-8a), 128.0 (CH, C-5`), 127.3 (q_c, C-2), 126.8 (CH, C-7), 126.7 (2 × CH, C-7`, C-3`), 126.6 (q_c, C-4a), 126.0 (CH, C-6), 122.5 (CH, C-5), 122.3 (CH, C-8), 101.4 (CH,

C-3), 91.1 (q_c, C-2``), 72.9 (CH, C-1`), 62.4 ($CH_3$, OMe-1), 55.6 ($CH_3$, OMe-4), 54.9 ($q_c$, C-7``), 54.5 (q_c, C-5``), 30.8 ($CH_2$, C-3``), 28.9 (CH_2, C-4``), 16.9 ($CH_3$, C-9``), 16.7 (CH_3, C-10``), 9.7 ($CH_3$, C-8``); EIMS *m/z* (rel. int.) 474 [M^+] (100), 277 (35), 261 (19), 236 (6), 167 (13), 149 (27), 91 (22), 69 (15), 57 (8); HRFABMS *m/z* 474.2031 (calcd for $C_{29}H_{30}O_6$ [M^+], 474.2042).

Crystal data for **31** : $C_{29}H_{30}O_6$, M = 474.53, 0.16 × 0.08 × 0.03 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.1443 (3) Å , b = 12.0135 (5) Å, c = 33.3284 (10) Å, V = 2460.08 (17) $Å^3$, Z = 4, D_c = 1.2812 g/cm^3, F_{000} = 1008, μ(MoKα) = 0.089 mm^{-1}, T = 100 K, $2\theta_{max}$ = 25984 reflections collected, 3077 unique (R_{int} = 1.023). R_1 = 1.023, wR_2 = 0.08, R indices based on 3077 reflections with I > 2σ(I) (refinement of F^2), 321 parameters, 0 restraint.

4.40. *S*-Camphanate ester 32: White plates (from MeOH); mp 153-155 °C; $[\alpha]_D^{22}$ -13 (*c* 0.08, $CHCl_3$); IR (film) ν_{max} cm^{-1} 3684, 3020, 2401, 1523, 1423, 1372, 1216, 1101, 929, 759, 670, 512; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.21 (1H, d, *J* = 8.4 Hz, H-5), 8.06 (1H, d, *J* = 8.4 Hz, H-8), 7.60 (1H, s, H-1`), 7.55 (1H, t, *J* = 7.6 Hz, H-7), 7.49 (1H, t, *J* = 7.6 Hz, H-6), 7.41 (2H, d, *J* = 7.6 Hz, H-7`, H-3`), 7.31 (2H, t, *J* = 7.7 Hz, H-6`, H-4`), 7.26 (1H, t, *J* = 7.3 Hz, H-5`), 6.78 (1H, s, H-3), 3.98 (3H, s, 1-OMe), 3.93 (3H, s, 4-OMe), 2.46 (1H, ddd, *J* = 13.9, 10.8, 4.3 Hz, H-3``b), 2.05 (1H, ddd, *J* = 13.8, 9.4, 4.6 Hz, H-3``a), 1.92 (1H, ddd, *J* = 15.0, 10.7, 4.5 Hz, H-4``b), 1.70 (1H, ddd, *J* = 13.5, 9.4, 4.4 Hz, H-4``a), 1.11 (3H, s, H_3-8``), 1.07 (3H, s, $H_3$-10``), 0.90 (3H, s, H_3-9``); $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 178.3 ($q_c$, C-6``), 166.7 (q_c, C-1``), 152.4 (q_c, C-4), 146.8 (q_c, C-1), 139.4 (q_c, C-2`), 128.5 (2 × CH, C-6`, C-4`), 128.3 ($q_c$, C-8a), 128.0 (CH, C-5`), 127.3 (q_c, C-2), 126.9 (CH, C-7), 126.6 (2 × CH, C-7`, C-3`), 126.6 (q_c, C-4a), 126.0 (CH, C-6), 122.5 (CH, C-5), 122.3 (CH, C-8), 101.5 (CH, C-3), 91.1 (q_c, C-2``), 72.9 (CH, C-1`), 62.4 ($CH_3$, OMe-1), 55.7 ($CH_3$, OMe-4), 54.9 ($q_c$, C-7``), 54.3 (q_c, C-5``), 30.8 ($CH_2$, C-3``), 28.9 (CH_2, C-4``), 16.8 (2 × $CH_3$, C-10``, 9``), 9.7 ($CH_3$, C-8``); EIMS *m/z* (rel. int.) 474 [M^+] (100), 294 (7), 277 (38), 261 (30), 202 (8), 167 (32), 149 (78), 91 (24), 57 (19); HRFABMS *m/z* 474.2040 (calcd for $C_{29}H_{30}O_6$ [M^+],474.2042).

5. Biology

5.1. Cytotoxicity against oesophageal cancer line

To determine IC_{50} values, 1500 cells per well were seeded in 90 μL Dulbecco/Vogt Modified Eagle's Minimal Essential Medium (DMEM) in Cellstar 96-well plates. After incubation (24 h), test samples were plated at a range of concentrations in 10 μL medium, with a final concentration of 0.2% DMSO and again incubated for 48 h. Observations were made and processed in the manner described for the MTT assay. MTT reagent (10 μL, Roche cat # 1465007) was added and the cells incubated (4 h, 37 °C). Solubilization reagent (100 μL) was added to each well and incubation continued (16 h, 37 °C). Upon completion of the incubation time, plates were read (595 nm) on an Anthos microplate reader 2001. A dose-response curve was analyzed by non-linear regression analysis [non-linear regression (sigmoidal dose response with variable slope)] using the GraphPad Prism 4.00 package of GraphPad software, San Diego, USA to determine the specific IC50 value for the compound tested against the WHCO1 cell line. The formula used was Y = bottom + [(top-bottom)/(1 + 10(logIC50 – X) × hillslope)], where Y is the absorbance at 595 nm, X is the concentration of the test compound, bottom is the minimum absorbance (also the absorbance of the medium blank) and the hillslope is the slope of the curve. The IC_{50} value for each compound was obtained by plotting its log concentration [μM] against the corrected optical density reading at 595 nm, using doxorubicin as a positive control (IC_{50} = 0.5 μM).

5.2. Cytotoxicity against normal fibroblast cell line

NIH3T3 fibroblasts were maintained in DMEM containing 10 % (v/v) heat-inactivated FCS, 100 U/ml penicillin, 100 μg/ml streptomycin and 12.5 μg/ml amphotericin (PSA) at 37 ºC in a humidified 9% CO_2 incubator. Determination of the IC_{50} concentration was performed as previously described. Eight NIH3T3 fibroblasts (1000 cells/well) were seeded into 96 well plates overnight, after which they were treated with a range of concentrations (0, 10, 100, 1 000 and 10 000 *n*M) of the compounds or vehicle control (0.02% v/v). The plates were incubated for 96 hours prior to addition of 10 μL of a 5 mg/mL MTT solution. Plates were incubated for 4 hours, solubilization reagent added and absorbance at 595 nm

recorded using a Powerwave spectrophotometer (BioTek). IC_{50} values were calculated from the dose response curve (log concentration versus correct absorbance at 595 nm) using non-linear regression with GraphPad as previously described. All treatments were conducted 5 times with reproducible results.

6. X-ray Crystallographic Analysis

Crystallographic data for **31** have been deposited at the Cambridge Crystallographic Data Centre (CCDC No. 881689).

Acknowledgements

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References

[1] S.N. Sunassee, M.T. Davies-Coleman, Nat. Prod. Rep. 29 (2012) 513-535.

[2] C. Asche, Mini-Rev. Med. Chem. 5 (2005) 449-467.

[3] P. Kovacic, R. Somanathan, Anti-Cancer Agents Med. Chem. 11 (2011) 658-668.

[4] E. Salustiano, C. Netto, R. Fernandes, A. da Silva, T. Bacelar, C. Castro, C. Buarque, R. Maia, V. Rumjanek, P. Costa, Invest. New Drugs 28 (2009) 139-144.

[5] L. Constantino, D. Barlocco, Curr. Med. Chem. 13 (2006) 65–85.

[6] B.C. Cavalcanti, F.W.A. Barros, I.O. Cabral, J.R.O. Ferreira, H.I.F. Magalhães, H.V.N. Júnior, E.N. da Silva Júnior, F.C. de Abreu, C.O. Costa, M.O.F. Goulart, M.O. Moraes, C. Pessoa, Chem. Res. Toxicol. 24 (2011) 1560–1574.

[7] N. Mqoqi, P. Keller, J. Madhoo, F. Sitas, National Cancer Registry of South Africa, South African Institute for Medical Research: Johannesburg, (2003).

[8] W. Scheithauer, Ann. Oncol. 15 (2004) 97-100.

[9] C.E. Whibley, R.A. Keyzers, A.G. Soper, M.T. Davies-Coleman, T. Samaai, D.T. Hendricks, Ann. NY Acad. Sci. 1056 (2005) 405-412.

[10] C.E. Whibley, K.L. McPhail, R.A. Keyzers, M.F. Maritz, V.D. Leaner, M.J. Birrer, M.T. Davies-Coleman, D.T. Hendricks, Mol. Cancer Ther. 6 (2007) 2535-2543.

[11] H. Hussain, K. Krohn, V.U. Ahmad, G.A. Miana, I.V. Green, Arkivoc (2007) 145-171.

[12] E.R. de Almeida, Open Nat. Prod. J. 2 (2009) 42-47.

[13] C.J. Li, Y.Z. Li, A.V. Pinto, A.B. Pardee, P. Nat. Acad. Sci. USA. 96 (1999) 13369-13374.

[14] J.I. Lee, D.Y. Choi, H.S. Chung, H.G. Seo, H.J. Woo, B.T. Choi, Y.H. Choi, Exp. Oncol. 28 (2006) 30-35.

[15] Y.Z. Li, X.G. Sun, J.T. Lamont, A.B. Pardee, C.J. Li, P. Nat. Acad. Sci. USA. 100 (2003) 2674-2678.

[16] E.N. da Silva Júnior, C.F. de Deus, B.C. Cavalcanti, C. Pessoa, L.V. Costa-Lotufo, R.C. Montenegro, M.O. de Moraes, M.C.F.R. Pinto, C.A. de Simone, V.F. Ferreira, M.O.F. Goulart, C.K.Z. de Andrade, A.V. Pinto, J. Med. Chem. 53 (2010) 504-508.

[17] G.M. Cragg, P.G. Grothaus, D.J. Newman, Chem. Rev. 109 (2009) 3012-3043.

[18] E.N. da Silva Júnior, M.C.F.R. Pinto, K.C.G. de Moura, C.A. de Simone, C.J. Nascimento, C.K.Z. de Andrade, A.V. Pinto, Tetrahedron Lett. 50 (2009) 1575-1577.

[19] E.N. da Silva Júnior, M.C.B.V. de Souza, A.V. Pinto, M.C.F.R. Pinto, M.O.F. Goulart, F.W.A. Barros, C. Pessoa, L.V. Costa-Lotufo, R.C. Montenegro, M.O. de Moraes, V.F. Ferreira, Bioorg. Med. Chem. 15 (2007) 7035-7041.

[20] K.O. Eyong, P.S. Kumar, V. Kuete, G.N. Folefoc, E.A. Nkengfack, S. Baskaran, Bioorg. Med. Chem. 18 (2008) 5387-5390.

[21] P. Singh, V. Krishna, P. Khandelwal, K.K. Sharma, M.C. Sharma, J. Indian Chem. Soc. 87, (2010) 85-95.

[22] M.N. da Silva, V.F. Ferreira, M.C.B.V. de Souza, Quim. Nova 26 (2003) 407-416.

[23] D.R. da Rocha, A.C.G. de Souza, J.A.L.C. Resende, W.C. Santos, E.A. dos Santos, C. Pessoa, M.O. de Moraes, L.V. Costa-Lotufo, R.C. Montenegro, V.F. Ferreira, Org. Biomol. Chem. 9 (2011) 4315-4322.

[24] E.N. da Silva Júnior, B.C. Cavalcanti, T.T. Guimarães, M.C.F.R. Pinto, I.O. Cabral, C. Pessoa, L.V. Costa-Lotufo, M.O. de Moraes, C.K.Z. de Andrade, M.R. dos Santos, C.A. de Simone, M.O.F. Goulart, A.V. Pinto, Eur. J. Med. Chem. 46 (2011) 399-410.

[25] R.B. Veale, S. Thornley, S. Afr. J. Sci. 85 (1989) 375-379.

[26] S.N. Sunassee, A.W.W. Van Wyk, O. Osoniyi, D.T. Hendricks, M.T. Davies-Coleman, J. Chem. Res. -S (2007) 677-679.

[27] N.B. Perry, J.W. Blunt, M.H.G. Munro, J. Nat. Prod. 54 (1991) 978-985.

[28] (a) C.E.M. Carvalho, V.F. Ferreira, A.V. Pinto, M.C.F.R. Pinto, W. Harrison, Dyes Pigm. 52 (2002) 209-214. (b) S.G. Renou, S.E. Asis, M.I. Abasolo, D.G. Bekerman, A.M. Bruno, Pharmazie 58 (2003), 690-695. (c) J.S. Sun, A.H. Geiser, B. Frydman, Tetrahedron Lett. 39 (1998) 8221-8224. (d) M.C.F.R. Pinto, A.V. Pinto, C.G.T. Oliveira, An. Acad. Bras. Cien. 52 (1980) 481-482.

[29] (a) L.F. Fieser, M. Fieser, J. Am. Chem. Soc. 70 (1948) 3215-3222. (b) A.C. Franscisco, G.O. Silveira, J.A.L.C. Resende, T.L. Balliano, V.R.S. Malta, A.V. Pinto, Acta Cryst. E66 (2010) o341.

[30] I.S. Marcos, M.A. Escola, R.F. Moro, P. Basabe, D. Diez, F. Sanz, F. Mollinedo, J. Iglesia-Vicente, B.G. Sierra, J.G. Urones, Bioorg. Med. Chem. 15 (2007) 5719-5737.

[31] S.V. Ley, J. Norman, W.P. Griffith, S.P. Marsden, Synthesis (1994) 639-666.

[32] O.D. Dailey. J. Org. Chem. 52 (1987) 1984-1989.

[33] W. Williams, X. Sun, D. Jebaratnam. J. Org. Chem. 62 (1997) 4364-4369.

[34] T. Itahara, J. Org. Chem. 50 (1985) 5546-5550.

[35] T.J. Monks, D.C. Jones, Curr. Drug Metab. 3 (2002) 425-438.

[36] P. Krishnan, K.F. Bastow, Biochem. Pharmacol. 60 (2000) 1367-1379.

[37] Y.P. Chau, S.G. Shiah, M.J. Don, M.L. Kuo, Free Radical Biol. Med. 24 (1998) 660-670.

[38] J. Carmichael, W.G. DeGraff, A.F. Gazdar, J.D. Minna, J.B. Mitchell, Cancer Res. 47, (1987) 936-944.

[39] A. Boumendjel, J. Boccard, P.A. Carrupt, E. Nicolle, M. Blanc, A. Geze, L. Choisnard, D. Wouessidjewe, E.L. Matera, C. Dumonet, J. Med. Chem. 51 (2008) 2307-2310.

[40] S. Mandlekar, R. Yu, T.H. Tan, A.N.T. Kong, Cancer Res. 60 (2000) 5995-6000.

[41] A. Matsuzawa, H. Ichijo, Biochim. Biophys. Acta 1780 (2008) 1325-1336.

[42] M.A. Bogoyevitch, K.R.W. Ngoei, T.T. Zhao, Y.Y.C. Yeap, D.C.H. Ng, Biochim. Biophys. Acta 1804 (2010) 463-475.

[43] G.D. Stoner, L.S. Wang, T. Chen, Toxicol. Appl. Pharm. 224 (2007) 337-349.

[44] (a) M. Tewari, L.T. Quan, K. O'Rourke, S. Desnoyers, Z. Zheng, D.R. Beidler, G.G. Poirier, G.S. Salvesen, V.M. Dixit. Cell 81 (1995) 801-809. (b) M. Germain, E.B. Affar, D. D'amours, V.M. Dixit, G.S. Salvesen, G.G. Poirier. J. Biol. Chem. 274 (1999) 28379-28384.

[45] D.D. Perrin, W.L.F. Armarego. Purification of Laboratory Chemicals, third ed., Pergamon press, Oxford, 1988.

[46] M.G. Ettlinger. J. Am. Chem. Soc. 72 (1950) 3666-3672.

[47] B.S. Joshi, Q. Jiang, T. Rho, S.W. Pelletier. J. Org. Chem. 59 (1994) 8220-8232.

Research highlights

1. 1,4-naphthoquinones derivatives were obtained with antitumor activity.

2. New quinonoid prototypes were developed with moderate activity against the oesophageal cancer cell line WHCO1.

3. Some of the substances described were more active than lapachol and the current drug of choice cisplatin.

4. Three cytotoxic compounds were found to be non-toxic against NIH3T3 normal fibroblast cells.

Table

Table 1. Summary of the IC_{50} values of compounds tested against the $WHCO_1$ esophageal cancer cell line.

Compounds	IC_{50} (μM)	95% C.I.[a]
lapachol **(1)**	24.1	13.4-43.4
β-lapachone **(2)**	1.6	1.3-1.9
3	15.0	13.2-16.8
4	6.5	6.0-6.9
5	1.8	1.3-2.3
6	2.4	2.2-2.6
7	28.7	20.1-39.8
8	5.2	4.9-5.4
9	6.4	6.0-6.8
10	4.3	3.1-5.5
11a	3.9*	3.7-4.1*
***R*-11a**	4.3	4.1-4.5
***S*-11a**	3.8	3.4-4.3
11b	63.4	54.6-73.6
11c	21.6	19.6-23.6
12a	3.0	2.8-3.3
12b	72.9	59.7-89.0
13a	3.4	3.2-3.6
13b	50.4	43.4-58.4
14a	5.1	4.8-5.4
14b	74.9	69.3-80.9
15a	5.5	5.0-6.0
15b	94.8	86.3-104.4
16a	7.3	6.8-7.8
16b	94.8	75.9-118.6
17a	2.4	1.3-3.4
17b	NA†	-
18a	10.9	9.8-12.0
18b	96.9	92.3-101.7
19a	4.8	2.4-7.2
19b	83.7	78.2-89.4
20	11.7	10.6-12.8

[a]Confidence Interval, †Not Active, *previously reported [26] as IC_{50} = 1.5 μM (95% C.I. of 1.1-1.9)

Legends to Scheme and Figures

Figure 1. *Ortho* and *para*-naphthoquinones evaluated against esophageal cancer cell line.

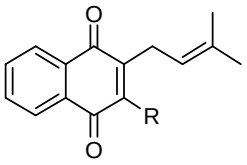
Scheme 1. General procedure for the preparation of compounds **11a-19a** *via* their dimethoxy precursors **22a-30a**.

Scheme 2. (a) NMO (3.0 eq), TPAP, CH_2Cl_2, 2h (except for **28a** and **29a**: MnO_2 (30 eq), CH_2Cl_2, 48h.

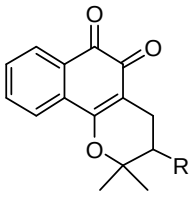
Scheme 3. Chiral resolution of (±)-**11a** *via* **31** and **32** (Insert showing ORTEP-3 projection for compound **31**). Reagents and conditions : (a) (-)-(*S*)-camphanic chloride, Et_3N, DMAP, CH_2Cl_2, RT; (b) KOH, EtOH; (c) CAN, H_2O, MeCN.

Figure 2. Western Blot analysis of WHCO1 esophageal cancer cells treated with varying concentrations of racemic **11a**, ***S*-11a** and ***R*-11a** at A) 6 hours B) 24 hours and C) 48 hours. Cells treated with doxorubicin (0.5 μM) were included as a positive control for PARP cleavage.

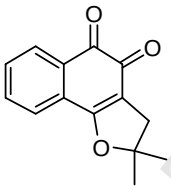
Figure 1.



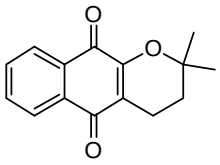
1 R = OH, lapachol
3 R = H, 2-deoxylapachol



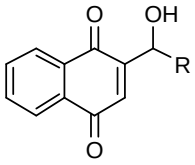
2 R = H, β–lapachone
4 R = OH
5 R = Br



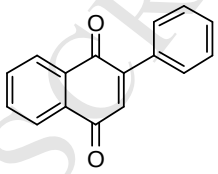
6, nor-β–lapachone



7, α-lapachone

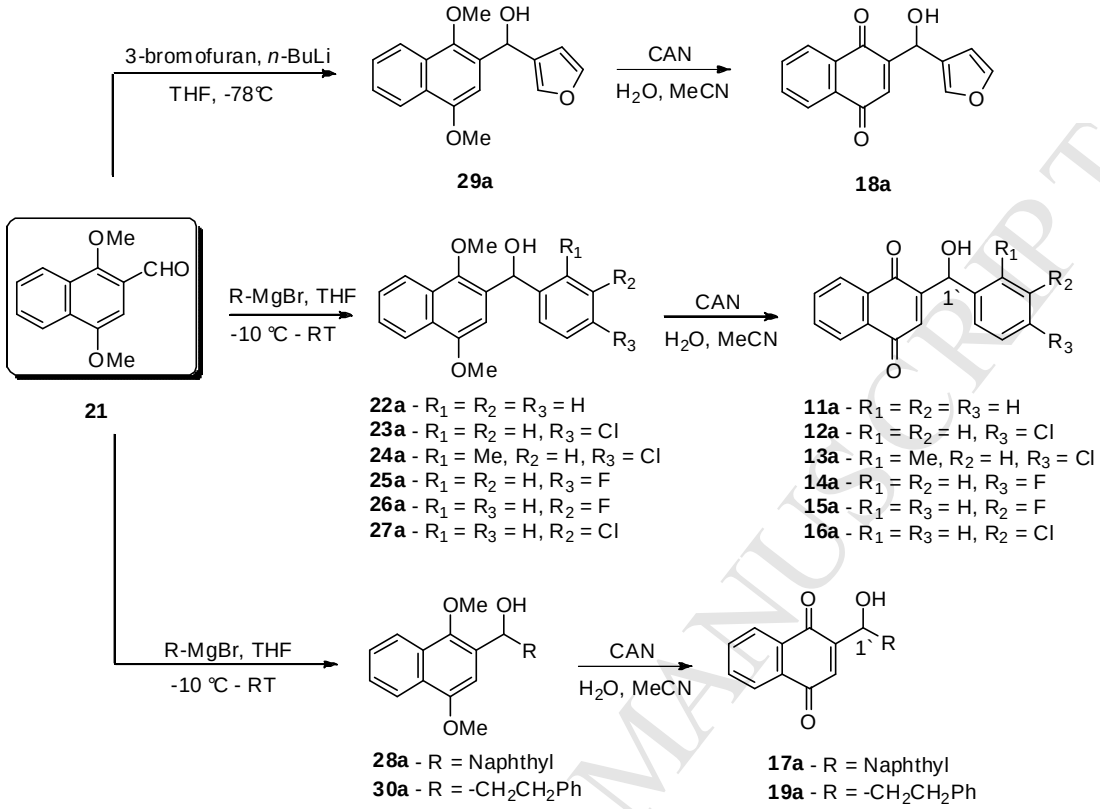


8 R = $CH=C(Me)_2$
9 R = Me
10 R = $CH=CH_2$
11a R = Ph

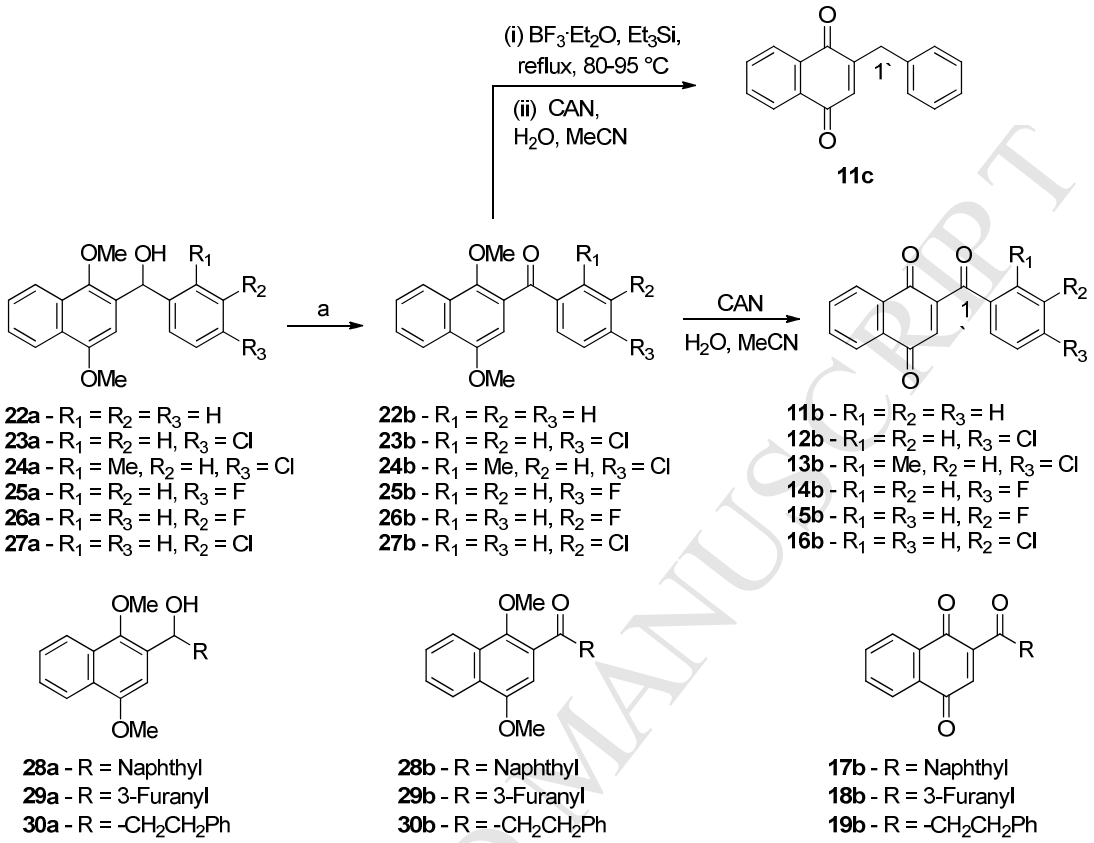


20

Scheme 1.



Scheme 2.



Scheme 3.

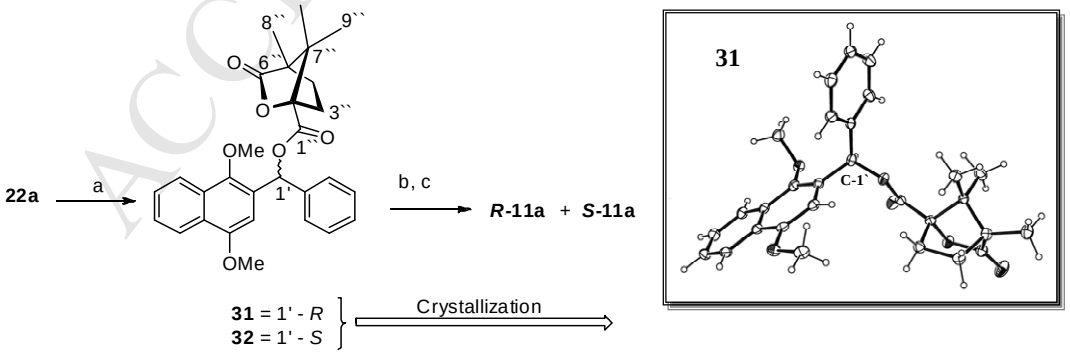


Figure 2.