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Metalloporphyrin Catalysed Biomimetic Oxidation of Aryl Benzyl Ethers. Implications for Lignin Peroxidase Catalysis

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Abstract: Metalloporphyrin catalysed oxidation of methoxy- and methylendioxy benzyl ethers was studied. In addition to previously described carbonyl compounds and the corresponding alcohols ring oxygenated products were also isolated. Formation of quinones and quinone acetals was rationalised by the nucleophilic attack of the solvent. This proposal implies that the mechanism of lignin peroxidase catalysis is clearly different from the mechanism of aromatic oxidations catalysed by cytochrome P450. The differening molecular mechanism of oxidations catalysed by the two heme proteins was explained by comparison of active site geometries. Our study also demonstrates that a particular methoxy arene, Verbutin (1), an effective inhibitor of insect cytochrome P450s, is a potential substrate of lignin peroxidase. The high capacity of lignin peroxidase catalysed metabolism of xenobiotics renders the inhibitor an environmentally friendly agrochemical in the fight against metabolic insecticide resistance.

INTRODUCTION

Synthetic metalloporphyrins are widely used to mimic the catalytic action of heme proteins.[1] In addition to cytochrome P450 catalysed oxidation of alkanes and alkenes[2-4] these artificial "enzymes" are known as the biomimetic equivalents of peroxidases[5-8]. Peroxidases and cytochrome P450 utilise similar iron-oxo species (Compound I) as reactive intermediates for oxidative reactions. It is known that cytochrome P450 catalysed oxidations involve oxygen atom transfer whereas peroxidase catalysis is a single electron transfer process. The peroxide shunt, however, part of the catalytic cycle of cytochrome P450s, as well as the formation of Compound I in peroxidase catalysis both require peroxides and therefore these processes can be modelled by H_2O_2 promoted activation of metalloporphyrin catalysts.

Cytochrome P450 catalysed oxidative metabolism is a general mode of detoxification of agrochemicals in insects. Induction and overexpression of these enzymes results in metabolic resistance against formerly active insecticides.[9] Recent strategies in resistance management are focusing on insect selective cytochrome P450

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inhibitors to suppress this metabolic deactivation. Looking for new and selective inhibitors, we developed Verbutin® (**1**), a 2-butinyl ether highly effective for the suppression of metabolic resistance.[10] Although **1** is selective for insect cytochrome P450s we thought that its environmental impact should be studied in a wider context. Fungal and plant peroxidases play an important role in the degradation of xenobiotics.[11] Lignolytic enzymes are characteristic representatives of this class of peroxidases. Since **1** is a benzylic ether dimethoxylated at the aromatic ring, its analogy to the lignin monomer is obvious. Synthetic metalloporphyrins[12] have been used since 1984 to mimic the catalytic action of lignin peroxidase (LiP)[13] and manganese dependent peroxidase (MnP).[14] In this study we investigated the metalloporphyrin catalysed oxidation of the cytochrome P450 inhibitors by H_2O_2 as a simple model for the peroxidase catalyzed enzymatic processes. In addition to the identification of products, plausible mechanisms for the biomimetic transformations were also suggested. We found that oxidation of inhibitors involved not only simple degradation, but also the formation of quinonoid compounds. Such products were also detected very recently by Baciocchi *et al.* but have not been identified.[15] Now characterisation of these quinones permitted us a deeper insight into the mechanism of the enzymatic process.

RESULTS AND DISCUSSION

Site selection in the biomimetic oxidation of **1** was first predicted by quantum chemical calculations. As postulated earlier, formation of the radical intermediate was followed by electron donation to the heme-bound hydroxyl radical.[2] Therefore, comparison of calculated ionisation potentials of all possible intermediates may help to identify the preferred path of oxidation.[16] Since oxidations at the aromatic ring follows a different mechanism, this analysis was only performed for aliphatic sites. Ionisation potentials (IPs) calculated using Koopman's theorem are collected to Table 1.

Table 1. Ionisation potentials calculated for aliphatic radicals formed by oxidation of **1**

Radical formed at	Ionisation potential (eV)
benzylic CH	6.98
butynyl CH_2	7.01
aromatic OCH_3	7.29 / 7.41
terminal CH_3	8.21

The lowest IP obtained for the radical corresponding to the hydrogen abstraction from the benzylic carbon atom indicates that it is is the aliphatic site which is likely to be preferred in biomimetic oxidations.

Hydrogen peroxide promoted oxidation of **1** and its methylenedioxyphenyl analogue (Perbutin, **2**) catalysed by 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin iron(III) chloride was studied in organic solvents. All reactions were performed with 30% aq. H_2O_2 in a 1:1 CH_3OH and CH_2Cl_2 mixture. Oxidation of **1** gave acetoveratrole (**3**) and butynol (**4**) as degradation products (34%) identified by the GC analysis of the reaction mixture by direct comparison with authentic standards. These products are derived from the benzylic oxidation of **1**, in accordance with the site selectivity predicted by quantum chemical calculations. Unidentified products were separated by preparative column chromatography and were analysed by ^1H and ^{13}C NMR spectroscopy. Spectral data revealed that oxidation of the aromatic ring led to the corresponding methoxyquinone (**5**) and its acetal (**6**). It is interesting to note that in the magnesium peroxophthalate mediated oxidation of *ortho*-dimethoxyarenes catalysed by metalloporphyrins was first reported by Mansuy *et al.* but only quinones were detected.[17] Similarly to the cleavage of **1**, oxidation of the methylenedioxy analogue (**2**) yielded piperonal (**7**) and butynol (**4**) in yield of 29%. GC analysis of the reaction mixture showed a single ring oxygenated product identified as the quinone acetal **8**.

The formation of degradation products can be rationalised adapting the mechanism suggested by Baciocchi *et al.* (Fig. 1).[15]

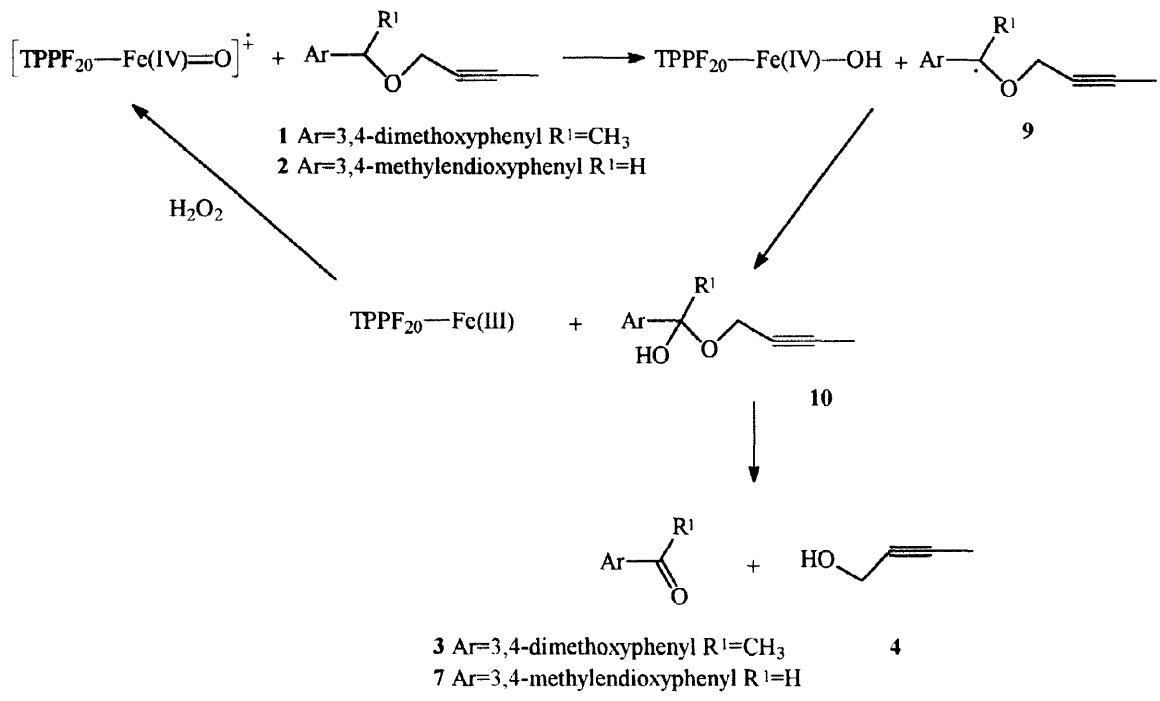


Fig. 1. Proposed mechanism for the formation of degradation products in the biomimetic oxidation of **1** and **2**

This process involves the abstraction of a hydrogen atom from the substrate effected by the activated ferryloxy porphyrin intermediate to form the corresponding radical (**9**) which readily recombines with the hydroxy radical attached to the central iron atom of the catalyst. The unstable hemiacetal (**10**) formed is rapidly hydrolysed to give the corresponding carbonyl compounds (**3** or **7**). This oxidation can be characterised as an oxygen atom transfer which is typical for cytochrome P450 catalysed hydroxylations. In contrast to monooxygenases, lignin peroxidases catalyse the cleavage of C-C bonds as well.[18] According to Baciocchi *et al.*[15] the latter process takes place via hydrogen abstraction from the benzylic OH. Since in our case this function was masked as an aliphatic ether, products corresponding to this route of degradation could not be isolated. This gives further support to Baciocchi's concept. The formation of ring oxygenated products follows a more complicated mechanism (Fig. 2).

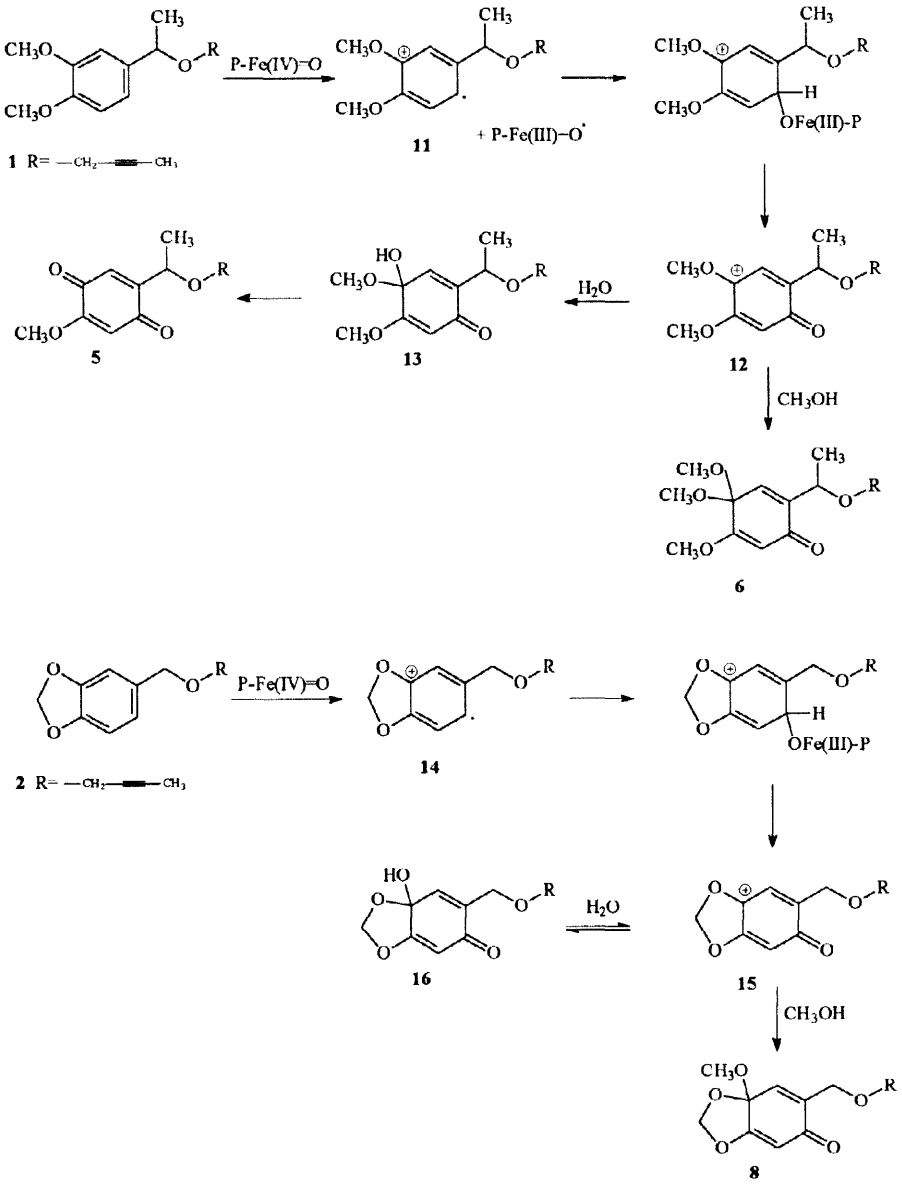


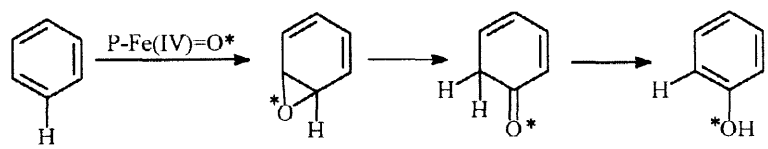
Fig. 2. Proposed mechanism for the formation of quinones in the biomimetic oxidation of **1** and **2**

The reaction is started by the abstraction of the aromatic hydrogen atom at the 6-position to give the corresponding radical cation (**11**) as was detected by EPR spectroscopy.[19] The radical center of **11** can combine with ferryloxy porphyrin to give the cationic intermediate **12**.[20] The electrophilic center of **12** than reacts with nucleophiles available in the reaction mixture. Thus reaction with water yields the hemiacetal **13** which is transformed to quinone **5** by loss of methanol.

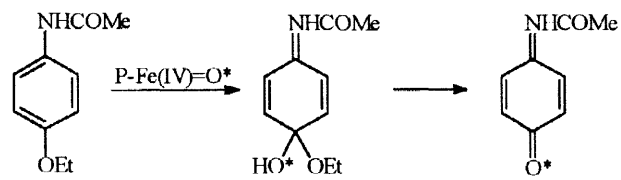
Methanol also attacks the same center to give the corresponding quinone acetal **6**. Since this is the only way to rationalise the formation of both ring hydroxylated products we conclude that the second oxygen of the quinone structure was incorporated from the solvent. This was further supported by the oxidation of **2**. The formation of the corresponding radical cation **14** is followed by its oxidation effected by the ferryloxy porphyrin to give cation **15** which reacts with water or methanol. Nucleophilic addition of water yields the hemiacetal **16**. A quinone derived from **16** could not be detected probably because demethoxylation was inhibited by the methylenedioxy unit. Methanol, however, attacks the cationic center to give **8** as the only product. Since there is no way to form the corresponding quinone from **2** this provides further evidence that quinone acetals are formed via the nucleophilic attack of the solvent rather than acetalisation of the preformed quinones. The crucial role of the solvent can therefore be expected in enzymatic reactions as well.

Incorporation of the solvent found in the biomimetic oxidation of **1** and **2**, however, suggest a different mechanism from that described for cytochrome P450 catalysed oxidations (Fig. 3).

a). NIH shift



b). Oxidation of arenes substituted by electron donor substituents



c). Ipso substitution

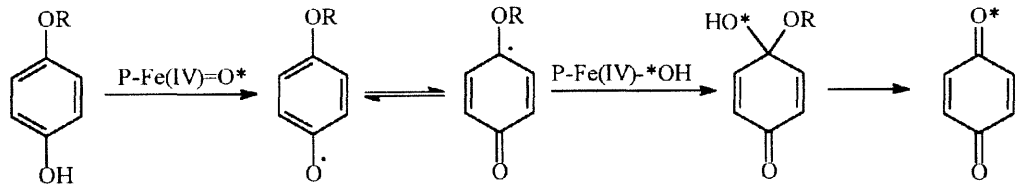


Fig. 3 Aromatic oxidations catalysed by cytochrome P450

Cytochrome P450 catalyses several reactions including *O*-demethylation and aromatic oxidations. Aromatic compounds are usually oxidised via the formation of an epoxide intermediate (NIH shift mechanism)[21] incorporating the ferryl oxygen atom into the aromatic system (Fig. 3a). In contrast, cytochrome P450 catalysed oxidation of arenes containing strong electron donor substituents are likely to involve by pathways avoiding epoxide intermediates.[22] Radiolabelling studies, however, demonstrated that it is still the ferryl oxygen which is incorporated (Fig. 3b).[23] The recently discovered *ipso* substitution represents an alternative way for the transformation of aromatic substrates (Fig. 3c).[24] *Ipso* substitution involves the cleavage of the aromatic carbon-oxygen bond via a radical intermediate formed by hydrogen abstraction from the phenolic hydroxy group. Recombination of this radical with the hydroxy radical attached to the central iron atom gives the corresponding quinone with an oxygen atom derived from the catalytically active ferryloxy unit. It is interesting that the structure of the radical intermediate resembles the cation **12** except for its ionic and nonradical character. A cationic intermediate similar to **12** was, however, detected in the cytochrome P450 catalysed oxidation of 9-methylanthracene.[25] Since the product distribution of the latter reaction could be reproduced using horseradish peroxidase, a peroxidase limited to electron transfer reactions, it was concluded that cationic intermediates (e.g. **12**) can be formed via electron transfer and/or hydrogen atom abstraction. Considering the possible formation of the cationic intermediate in cytochrome P450 catalysed oxidations, it is interesting whether the solvent participates in the catalytic cycle. Considering the possible ways of aromatic oxidations one can conclude that it is the nature of oxygen atom transfer which excludes solvent incorporation in cytochrome P450 catalysed oxidations. In addition to the difference between the underlying molecular mechanisms, differences between the three dimensional structure of cytochrome P450 and LiP are also characteristic.

a). b)

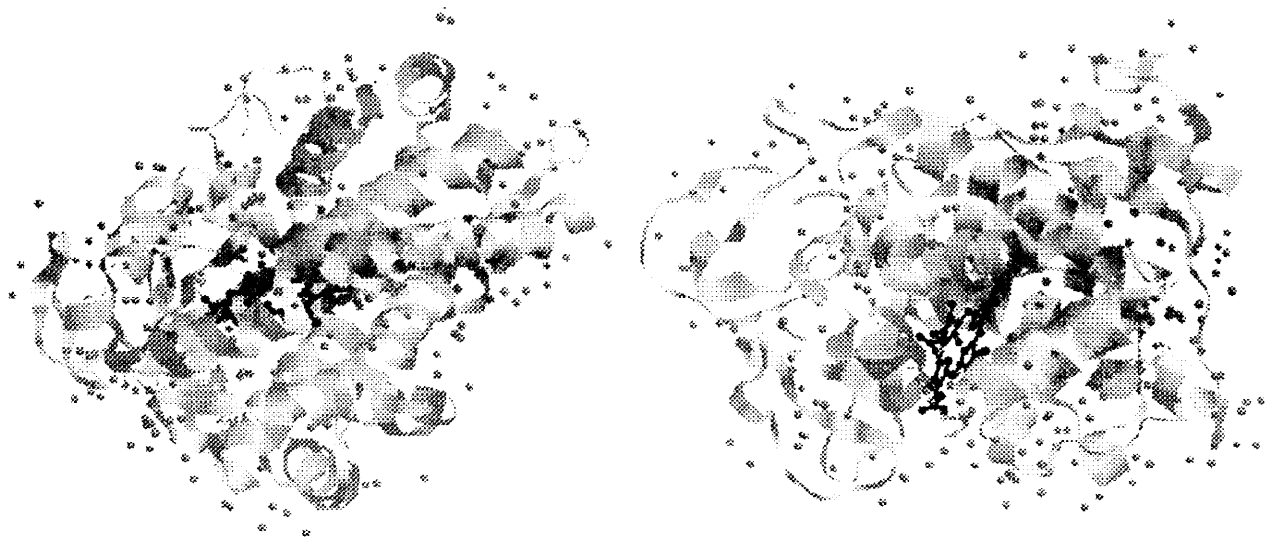


Fig. 4. High resolution X-ray structure of cytochrome P450cam (a) and LiP (b). Proteins are shown in ribbon representation, protoporphyrin IX units are shown in ball-and-stick form, crystallographic water molecules are indicated by gray spots.

Fig. 4 shows the high resolution X-ray structures of cytochrome P450cam[26] and LiP.[27] The most important difference between the two is the location of the active sites. In cytochrome P450 the active site is located inside the protein while in LiP it is closer to the surface. Since solvation of proteins is more complete at the surface than inside, involvement of solvent molecules in LiP catalysis is not unexpected. Furthermore it has been demonstrated that 3,4-dimethoxybenzyl alcohol binds closer to the protein surface in LiP[28] that in cytochrome P450 where oxygen atom transfer requires closer contact between the substrate and the catalytically active ferryloxy porphyrin. In contrast, the long range electron transfer applied in peroxidase catalysis allows the substrate to bind at or near the heme edge.[29] Since both cytochrome P450 and LiP contain protoporhyrin IX it was also suggested that it is the axial ligand which may play a critical role in determining the mechanism of oxidation.[11] Methylendioxyphenyl inhibitors (e.g. **2**) act via binding to the iron atom of the heme center interfering thereby with the iron-axial ligand interaction.[30] Drifting of the axial thiolate is a characteristic response to inhibitor binding in cytochrome P450 preventing further metabolism. Due to the different behaviour of the imidazolate axial ligand in LiP, lignin peroxidase catalysed metabolism is not inhibited. In conclusion, differences between (i) active site locations and (ii) tha nature of axial ligands connected to the prosthetic heme unit might be responsible on one hand for the selective inhibition of cytochrome P450 and on the other selective metabolism by LiP.

Results obtained by the biomimetic oxidation of **1** and **2** suggest that these compounds are potential substrates for lignin peroxidases. This proposal is in accordance with a number of *in vitro* studies demonstrating the oxidation by peroxidases of dimethoxylated arenes to corresponding quinones. Lignin peroxidase from *Phanerochaete chrysosporium* oxidises veratryl alcohol to 2-hydroxymethyl-5-methoxy-1,4-benzoquinone which is a structural analogue of **5**.[31] Quinones were also isolated from oxidations catalysed by LiP,[32] MnP[33] and several *Agrobacterium* species.[34] Proposed oxidation of **1** and **2** by peroxidases demonstrates that our cytochrome P450 inhibitors are easily metabolised under field conditions which suggests that these compounds are environmentally safe agrochemicals.

EXPERIMENTAL

General. All NMR spectra were recorded in $CDCl_3$ on a BRUKER DRX-400 spectrometer with a 5 mm dual probehead. ^1H (400 MHz) and proton-decoupled ^{13}C NMR (100 MHz) and DEPT-135 measurements were made in $CDCl_3$. Assignments were based on HMQC and HMBC measurements. The applied ^1H and ^{13}C 90° pulse length were 18.7 μs (PL=0db) and 11.6 μs (PL=0db), respectively; the proton-decoupling pulse length was 95 μs (PL=15db). The proton spectra were recorded with 32K, the carbon spectra with 64K complex data points. Chemical shifts are reported relative to tetramethylsilane (TMS). 2D spectra (HMQC and HMBC) were also recorded in $CDCl_3$ using the standard BRUKER pulse sequences. For HMQC spectra, 256 increments of 1024 complex data points in the t_2 dimension were collected in TPPI mode and for HMBC in QF mode. After zero-filling to 512 points in the second t_1 dimension, the time domains were treated by sine square shifted by 90°

in both dimensions for HMQC, sine square in t_2 and sine shifted by 90° in t_1 for HMBC and Fourier transform. IR spectra were recorded on a Perkin Elmer 398 spectrometer in $CHCl_3$. Mass spectrometry measurement was performed by a VG QUATTRO triplequad spectrometer (Micromass, Manchester UK) with electrospray ionization.

Reaction mixtures were monitored by capillary GC using a CHROMPACK CP 9000 chromatograph equipped with WCOT fused silica column with stationary phase of CP-SIL-8CB (60m x 0.53 mm, df 1.5 μm).

General Procedure for Biomimetic Oxidations. The alkyl arylether (1.1 mmol) and 0.01 molar eq. of *meso*-tetrakis(pentafluorophenyl)porphyrin Fe(III) Cl were dissolved in 30 mL of the solvent (methanol/dichloroethane 1:1) and 0.4 molar eq. of H_2O_2 was added. Reaction mixtures were stirred for 30 min at room temperature and the solvents were evaporated. Residues were directly analyzed by GC. Products were identified using the internal standards of **3**, **4** and **7**. Unidentified products were isolated using preparative column chromatography (eluent: hexane-ethyl acetate 7:3) and analysed by ^1H and ^{13}C NMR spectroscopy.

1-[1-(2-Butynyloxy)ethyl]-4-methoxy-1,4-cyclohexadiene-3,6-dione (5) from 1: 10 mg, 4.3%, yellow oil. ^1H-NMR: δ 1.37 (d, *J*=6.5 Hz, 3H, CH_3-C), 1.86 (t, *J*=2.3 Hz, 3H, CH_3-C≡C), 3.84 (s, 3H, OCH_3), 4.04 (dq, *J*=15.3 and 2.3 Hz, 2H, -OCH_{2a}), 4.13 (dq, *J*=15.3 and 2.3 Hz, 2H, -OCH_{2b}), 4.73 (dq, *J*=6.5 and 1.3 Hz, 1H, -OCH), 5.92 (s, 1H, 5-H), 6.77 (d, *J*=1.3 Hz, 1H, 2-H). ^{13}C-NMR: δ 3.6 ($\underline{C}H_3$-C≡), 21.7 ($\underline{C}H_3$-CH), 56.3 (OCH_3), 57.1 (OCH_2), 70.0 (CH_3-$\underline{C}H$), 74.6 (CH_3-$\underline{C}$≡), 83.1 (CH_2-$\underline{C}$≡), 107.1 (C-5), 129.0 (C-2), 150.6 (C-1), 158.7 (C-4), 182.3 (C-3), 187.1 (C-6). ν_{max} ($CHCl_3$) 2926, 2846, 2335, 2281, 1689, 1657, 1607, 1460. Calc. for C 66.66 H 6.02, Found C 65.43 H 5.84. MS: (M+1) 235.

4-[1-(2-Butynyloxy)ethyl]-4-methoxy-1,6,6-trimethoxy-1,4-cyclohexadiene-3-one (6) from 1: 14 mg, 5.0%, pale yellow oil. ^1H-NMR δ 1.25 (d, *J*=6.4 Hz, 3H, CH_3-C≡C), 1.76 (t, *J*=2.0 Hz, 3H, CH_3-C), 3.24 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.96 (dq, *J*=15.1 and 2.0 Hz, 2H, -OCH_{2a}), 4.03 (dq, *J*=15.1 and 2.0 Hz, 2H, -OCH_{2b}), 4.58 (qd, *J*=6.4 and 1.2 Hz, 1H, -OCH), 5.54 (s, 1H, 2-H), 6.59 (d, J=1.2 Hz, 1H, 5-H). ^{13}C-NMR: δ 3.4 ($\underline{C}H_3$-C≡), 22.0 ($\underline{C}H_3$-CH), 51.2, 55.9, 55.9 (OCH_3), 56.7 (OCH_2), 70.3 (CH_3-$\underline{C}H$), 74.7 (CH_3-$\underline{C}$≡), 82.2 (CH_2-$\underline{C}$≡), 94.3 (C-6), 103.8 (C-2), 133.9 (C-5), 142.6 (C-4), 169.0 (C-1), 185.3 (C-3). ν_{max} ($CHCl_3$) 2924, 2704, 2665, 2323, 2273, 1655, 1606, 1479. Calc. for C 64.27 H 7.19, Found C 64.02 H 7.08.

5-(2-Butynyloxy)methyl-3a-methoxy-3a,6-dihydrobenzo[d][1,3]dioxole-6-one (8) from 2: 16 mg, 6.4%, yellow oil. ^1H-NMR δ 1.78 (t, *J*=2.3 Hz, 3H, CH_3-C), 3.34 (s, 3H, OCH_3), 4.21 (m, 2H, -OCH_2-C≡), 4.29 (dq, *J*=15.8 and 2.2 Hz, 1H, OCH_{2a}), 4.43 (dq, *J*=15.8 and 2.2 Hz, 1H, -OCH_{2b}), 5.59 (s, 2H, O-CH_2-O), 5.65 (s, 1H, 7-H), 6.94 (t, *J*=2.2 Hz, 1H, 4-H). ^{13}C-NMR: δ 3.6 ($\underline{C}H_3$-C≡), 51.4 (OCH_3), 58.9 (O$\underline{C}H_2$-C≡), 66.0 (OCH_2), 74.6 (CH_3-$\underline{C}$≡), 83.1 (CH_2-$\underline{C}$≡), 97.6 (C-3a), 98.7 (O-CH_2-O), 98.8 (C-7), 127.0 (C-4), 140.2 (C-5), 168.6 (C-7a), 186.3 (C-6). ν_{max} ($CHCl_3$) 2920, 2846, 2335, 2281, 1654, 1607, 1464. Calc. for C 62.40 H 5.64, Found C 62.05 H 5.38.

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