Novel biomimetic oxidation of lapachol with H2O2 catalysed by a manganese(III) porphyrin complex

ARTICLE *in* RSC ADVANCES · AUGUST 2011

Impact Factor: 3.84 · DOI: 10.1039/c1ra00578b

RSC Advances

Cite this: *RSC Advances*, 2011, **1**, 1195–1199

www.rsc.org/advances

COMMUNICATION

Novel biomimetic oxidation of lapachol with H_2O_2 catalysed by a manganese(III) porphyrin complex

Sónia M. G. Pires,[a] Rodrigo De Paula,†[a] Mário M. Q. Simões,[a] Artur M. S. Silva,[a] M. Rosário M. Domingues,[a] Isabel C. M. S. Santos,[a] Maria D. Vargas,[b] Vítor F. Ferreira,[b] M. Graça P. M. S. Neves*[a] and José A. S. Cavaleiro*[a]

Received 10th August 2011, Accepted 12th August 2011
DOI: 10.1039/c1ra00578b

The biomimetic oxidation of lapachol (1) using aqueous hydrogen peroxide as oxidant and chloro[5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrinatomanganese(III)] (Mn-Porph) as catalyst is described. A comparison between the obtained results and those described for the oxidation of lapachol using *meta*-chloroperoxybenzoic acid (*m*-CPBA) reveals, besides different reaction products, a completely different selectivity. Unlike the *m*-CPBA approach, where *ortho*-naphthoquinones are obtained, *para*-naphthoquinones are highly favoured when using Mn-Porph and H_2O_2. Moreover, a new lactone is isolated and characterized in the present work.

Introduction

The presence of the quinone structure in several naturally occurring compounds has been associated with their potential biological activity.[1–3] Lapachol (**1**) is the most abundant, naturally occurring naphthoquinone, found in the heartwood of several trees of the *bignoniaceae* family.[4–6] Since it was first isolated by Arnaudon in 1858,[7] lapachol has been studied by several authors and proved to be one of the most versatile biologically active compounds.[8–14] Lapachol and several of its derivatives (Fig. 1), especially *ortho*- and *para*-naphthoquinones (**2**–**5**), are associated with a broad spectrum of biological activities such as anti-tumour, antibiotic, anti-malarial, anti-inflammatory, anti-ulcer, antibacterial, fungicidal and trypanocidal activities. Nowadays these naphthoquinones are considered as privileged structures in medicinal chemistry.[5,15–17]

For such reasons, lapachol (**1**) is undoubtedly an ideal candidate for planned structural modifications in order to understand its structure–activity associations and thus, eventually, develop analogues with improved activities. Moreover it is also important to identify the metabolites resulting from the *in vivo* oxidation of these putative drugs, in order to prevent possible secondary effects.

[a]*Department of Chemistry and QOPNA, University of Aveiro, University Campus, 3810-193, Aveiro, Portugal. E-mail: gneves@ua.pt; jcavaleiro@ua.pt; Fax: +351234370084; Fax: +351234370084; Tel: +351234370710 Tel: +351234370717*
[b]*Chemistry Institute, Fluminense Federal University, Campus do Valonguinho, Niterói, RJ 24020-150, Brazil*
† Present Address: Universidade Federal do Recôncavo da Bahia – Centro de Formação de Professores, 45.300-000 Amargosa/BA – Brazil.

Many drug metabolites are formed by oxidative processes catalysed primarily by cytochrome containing enzymes, mainly by cytochrome P-450 monooxygenase enzymes. Metalloporphyrins have been extensively used as synthetic models mimicking the *in vivo* activity of natural enzymes. Recently, these models have been used as catalysts in the oxidation of known drugs and drug candidates.[18]

Although the oxidation of **1** and some of its analogues, especially β-lapachone **2**, has been studied for several decades, almost all the procedures reported so far have implicated the use of very aggressive oxidizing conditions with little or no environmental concern. The use of powerful and hazardous oxidants such as alkaline $KMnO_4$[19] or *meta*-chloroperoxybenzoic acid (*m*-CPBA)[20] is a common feature to all methodologies.

In 1999 Cunningham *et al.*[21] published a different approach in which they performed the oxidation of some quinone derivatives in much milder reaction conditions using an iron complex of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin as catalyst and hydrogen peroxide as oxidant. In addition to mimicking the *in vivo* activity of natural enzymes, the use of metalloporphyrins allows the oxidation reactions to occur under more environmentally friendly conditions.[22–25]

Those findings, and taking into account the work developed by our group[24–28] in the field of metalloporphyrin catalysed reactions, prompted us to perform the biomimetic lapachol oxidation using

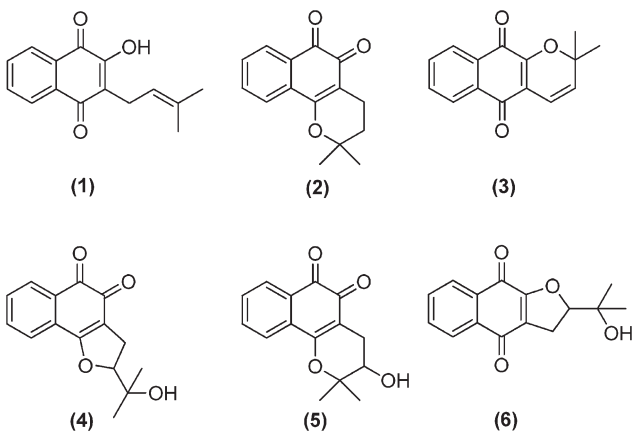

Fig. 1 Lapachol (**1**) and some of its known derivatives (**2**–**6**).

H_2O_2 and for the first time a metalloporphyrin as catalyst. The catalyst, chloro[5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrinato-manganese(III)] (**Mn-Porph**), was chosen due to its robustness towards the planned reaction conditions.[24,25]

Results and discussion

In order to perform the oxidation of lapachol **1**, two distinct approaches were followed: route **A** (using *m*-CPBA) and route **B** (using H_2O_2 and **Mn-Porph**), which is a more environmentally benign procedure. The reactions were followed by TLC and, in both cases, total conversion of **1** was observed. The reactions were completed after 48 h by following route **A**, using 2.5 molar equivalents of *m*-CPBA. For route **B,** the reactions were more efficient and could be performed in 1 h, depending on the substrate/catalyst molar ratio used. After the usual work-up, the reaction products were purified by preparative TLC and characterized by ^{1}H and ^{13}C NMR and by mass spectrometry.

The reaction products obtained by following route **A** (*m*-CPBA) are already known and the structural characterizations are in agreement with literature data.[29–31] However the available spectroscopic information is not complete; so their full NMR characterizations are now being considered. On the other hand, the products obtained by route **B** (**Mn-Porph**/H_2O_2) are completely different. Just by comparison of ^{1}H NMR spectra of **A** and **B** reaction mixtures (Fig. 2), it is possible to observe the differences between the products obtained. With *m*-CPBA, *ortho*-naphthoquinones **4** and **5** are the main products observed. In contrast, for **Mn-Porph** catalysed reactions the selectivity is completely different and *para*-naphthoquinones **3** and **6** are preferentially formed.

In summary, comparing with the classical oxidation methodology, the one now used gives rise to at least three different products. Moreover, in the **Mn-Porph** catalysed reactions, a new lactone (**7**) is observed. The ^{1}H NMR characterization of **7** has put in evidence its non-aromatic character; the two methyl groups have δ 1.39 and δ 1.45 ppm and no protons are detected in the aromatic region of the spectrum. Presumably the formation of such a non-aromatic product can take place by cleavage of the lapachol **1** molecule. This hypothesis is supported by the ^{13}C NMR spectrum of **7**, since only one carbonyl is observed (δ 174.4 ppm) and a few other carbon atoms are registered [δ_C 21.0, 25.8, 38.2, 73.8, 87.2]. The structural confirmation of lactone **7** comes from mass spectrometry; the MS spectrum of **7** shows the ion $[M + H]^+$ at *m*/*z* 131. The MS/MS spectrum of this molecular ion allows the identification of a characteristic fragment ion at *m*/*z* 113 (−18 Da) which corresponds to the loss of H_2O.

The oxidation results from routes **A** and **B** are summarized in Table 1; the yields have been determined by ^{1}H NMR, using the spectra of each reaction mixture. Route **B** was performed using different substrate/catalyst molar ratios, namely 75, 150 and 300. From the results obtained, it is possible to conclude that an increase of the catalyst amount also brings an increase in the yield of lactone **7** and decreases the yields of compounds **3**, **4** and **6**. The presence of **Mn-Porph** not only allows the epoxidation of the side chain double bond of **1**, but also the epoxidation of the double bond present in the quinone ring, which gives access to the molecule cleavage.

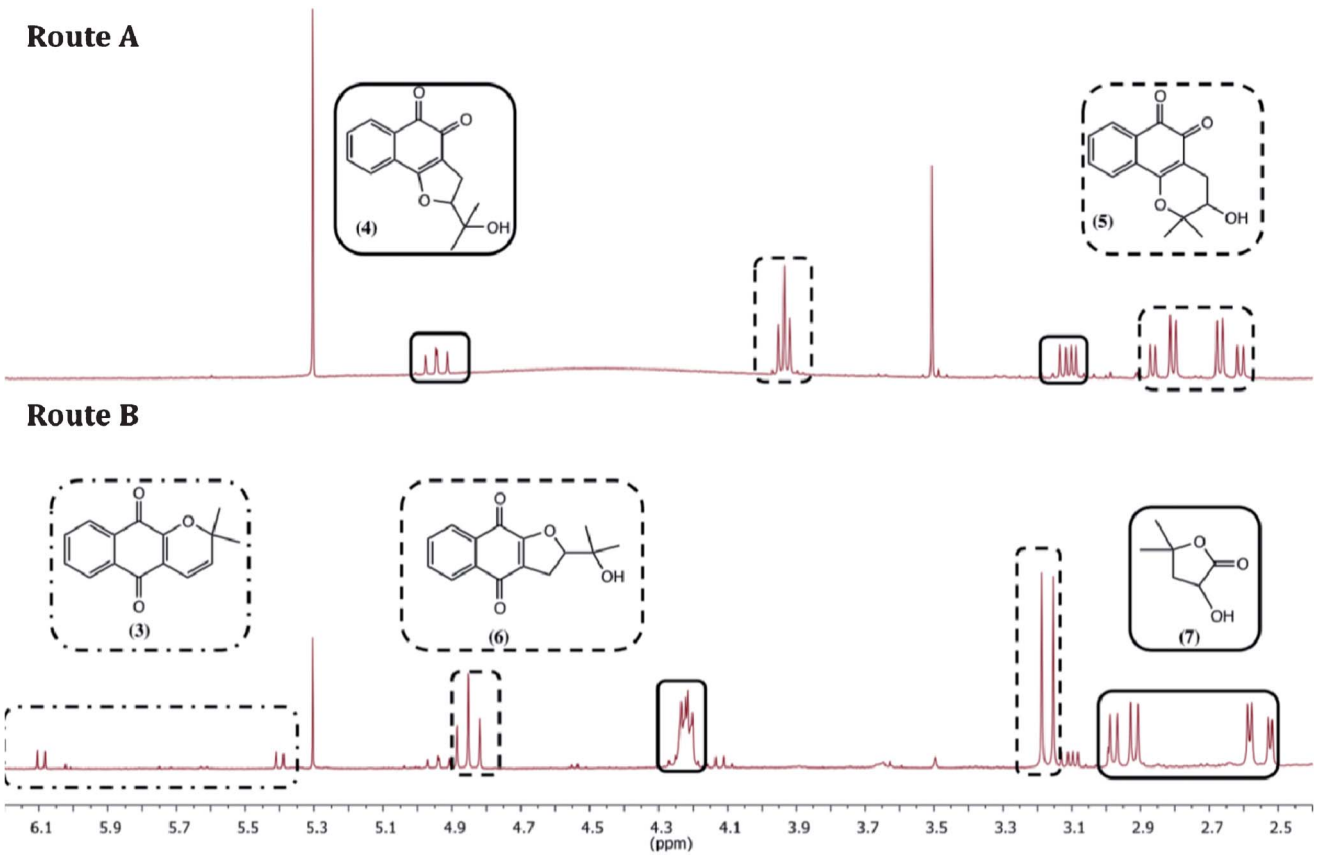

Fig. 2 Aliphatic region of the ^{1}H NMR spectra of the oxidation reaction mixtures (routes **A** and **B**).

Table 1 Oxidation of lapachol **1** using routes **A**[a] and **B**[b]. Products **3**–**7** selectivity (%) was determined by ^{1}H NMR

	Route **A**	Route **B**		
	m-CPBA	Sub/Cat molar ratio 75 : 1 (after 60 min)	Sub/Cat molar ratio 150 : 1 (after 90 min)	Sub/Cat molar ratio 300 : 1 (after 145 min)
3	—	4.0	16.4	18.3
4	26.5	5.9	9.1	12.6
5	73.5	—	—	—
6	—	24.5	42.6	44.7
7	—	65.6	31.9	24.4

[a] The substrate (0.075 mmol) was dissolved in 2.0 mL of CH_2Cl_2 under magnetic stirring at 22 ± 2 °C in the presence of *m*-CPBA (2.5 equiv.). [b] The substrate (0.075 mmol) was dissolved in 2.0 mL of CH_3CN and kept under magnetic stirring at 22 ± 2 °C in the presence of **Mn-Porph** (for sub/cat molar ratio of 75, the catalyst amount was 1.0×10^{-3} mmol; for sub/cat molar ratio of 150, the catalyst amount was 5.0×10^{-4} mmol; for sub/cat molar ratio of 300, the catalyst amount was 2.5×10^{-4} mmol). The co-catalyst used was $NH_4CH_3CO_2$ (0.12 mmol). The oxidant was progressively added at regular intervals of 15 min in small aliquots, each corresponding to a half-substrate amount.

Epoxidation of the quinone ring of **1** seems to be a common process of this type of metalloporphyrin catalysts in naphthoquinones oxidation[21] and it is very similar to what is observed with certain microorganisms.[32]

The identification of **7** proved to be an important feature in order to understand what happens in the oxidation of **1** in route **B**. From the beginning of the work with this catalytic approach, a weight loss in the recovered material was noticed at the end of the reactions. At that point, it proved to be almost impossible, using the already mentioned characterization techniques, to identify other products or even the remaining part of the lapachol molecule, even after identifying compound **7**. Two possible explanations were considered: i) some products formed in the reactions could be lost in the work-up procedure, or ii) the reactions originate volatile compounds that could not be isolated by TLC.

In order to ascertain the volatile products formation, an aliquot from a **Mn-Porph** catalysed reaction was analysed by GC-MS before and after work-up. The GC-MS chromatograms obtained before the work-up procedure clearly reveal the presence of the expected phthalic anhydride **8** and, at least, two additional products, *ortho*-phthalimide **9** (which is explained by the presence of ammonium acetate as co-catalyst) and epoxide **10**, that is actually the precursor of **7**, as proposed in Fig. 3. The C–C cleavage is similar to the first step of Hooker oxidation;[4,19,21,33,34] the epoxidation of the prenyl moiety and the hydroxyl ketone C–C cleavage give rise to **10**. Further oxidation of the aldehyde followed by the ring-opening of the epoxide can justify the formation of lactone **7**. Another reaction having **8** as substrate was performed under similar conditions; the latter gave rise to product **9**.

The chromatogram of the reaction mixture obtained after work-up showed that almost all the previously detected peaks have disappeared; only the peak corresponding to quinone **6** remained unchanged after work-up. This means that the missing volatile reaction products are soluble in water and may be lost during the usual work-up procedure, when the reaction mixture is washed with water.

The products formed *via* both methodologies (Fig. 4) reveal that, besides the lower selectivity achieved with route **B**, different products such as **3** and **6** are obtained, which are interesting compounds due to their important biological activities.[32,35]

Experimental section

Materials and instrumentation

All solvents and reagents were used as received without further purification. Hydrogen peroxide (30% w/w) aqueous solution was purchased from Riedel-de-Haën, ammonium acetate was supplied by Fluka and phthalic anhydride came from Sigma-Aldrich.

The porphyrin free base was prepared according to described procedures.[24,25] The metallation of the free base was performed with $MnCl_2$ according to conventional methods.[24,25] Lapachol can be obtained from the extract of the saw dust of "ipê" (*Tabebuia* sp.)[36] or synthesized from lawsone as described in the literature.[37]

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300.13 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal reference. The GC-MS analyses were performed on a Finnigan Trace GC-MS (Thermo

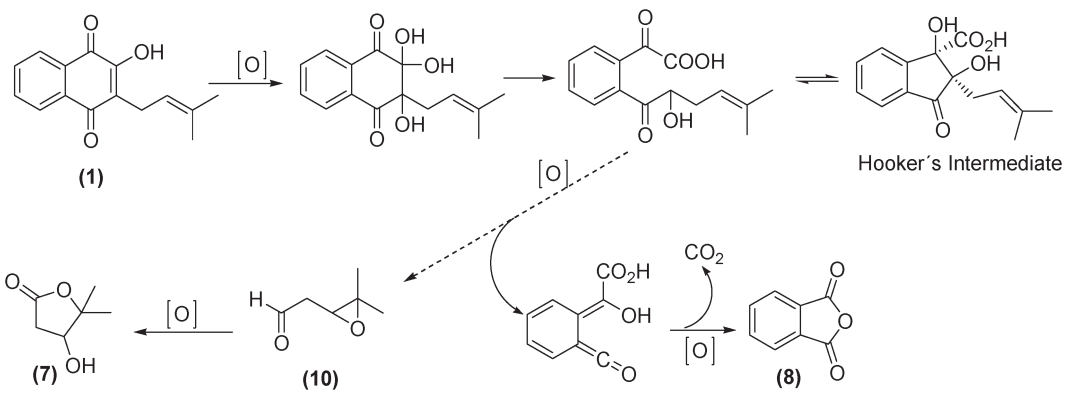

Fig. 3 Mechanistic proposal for the formation of lactone **7**.

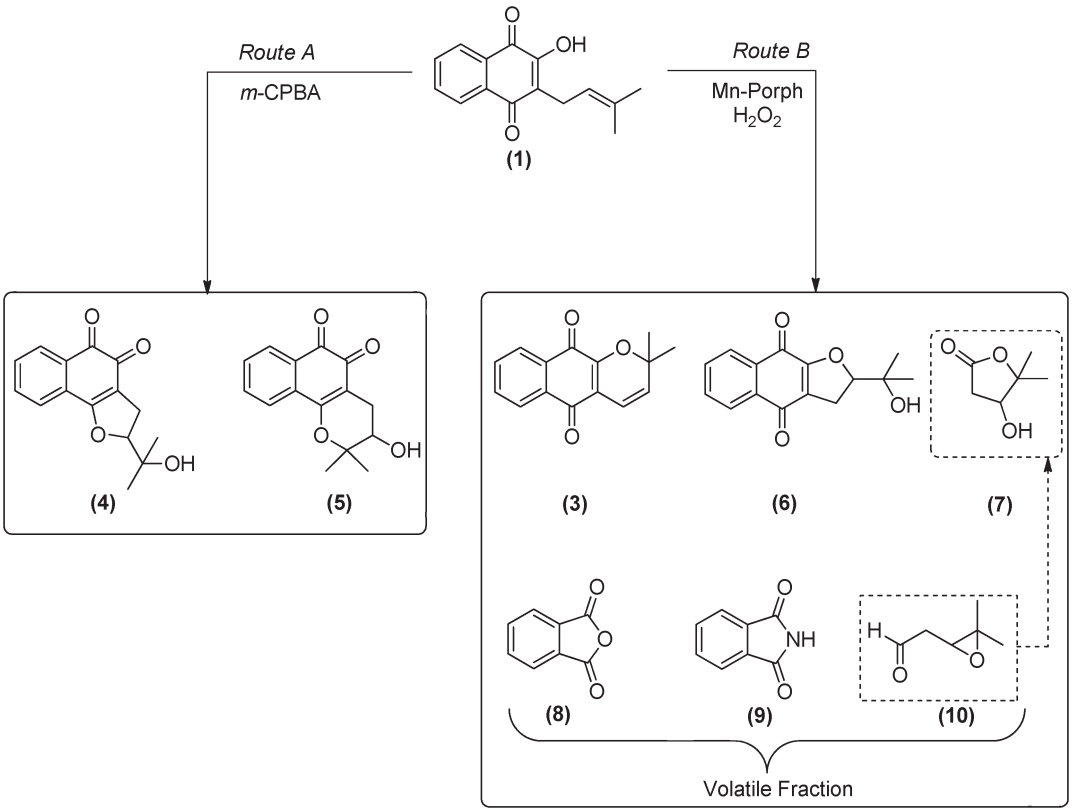

Fig. 4 Identified products obtained for routes **A** and **B.**

Quest CE instruments) using helium as the carrier gas (35 cm s^{-1}). The column used was a silica capillary DB-5 type column (30 m × 0.25 mm i.d., 0.25 μm film thickness). Positive ESI-MS analysis was performed on a Q-TOF2 mass spectrometer (Micromass, Manchester, UK) using a flow rate of 10 μL min^{-1}, cone voltage of 35 V, capillary voltage of 3 kV. The source temperature was 80 °C and the desolvation temperature was 150 °C.

Dehydro-α-lapachone 3 ($C_{15}H_{14}O_3$)

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.45 (s, 6H, 2 CH_3), 5.40 (d, 1H, *J* = 6.6 Hz, –CH=CH–), 6.10 (d, 1H, *J* = 6.6 Hz, –CH=CH–), 7.70–7.90 (m, 4H, ArH). ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 18.0, 23.9, 83.7, 86.0, 98.5, 123.6, 126.5, 126.6, 131.6, 133.0, 133.3, 134.8, 161.8, 177.6, 181.0. ESI-MS *m*/*z* 265.1 $[M + Na]^+$.

2-(1-Hydroxy-1-methylethyl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione 4 ($C_{15}H_{14}O_4$)

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.39 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.10–3.13 (m, 2H, –CH_2–), 4.94 (*t*, 1H, *J* = 9.3 Hz, –O–CH–), 7.57–7.66 (m, 2H, ArH), 8.07–8.13 (m, 2H, Ar–H). ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 24.3, 25.8, 27.5, 71.9, 93.5, 116.0, 124,4, 127.3, 129.6, 130.7, 132.1, 134.5, 169.7, 175.4, 181.0. ESI-MS *m*/*z* 281.1 $[M + Na]^+$.

2-Hydroxy-β-lapachone 5 ($C_{15}H_{14}O_4$)

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.46 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.63 (dd, 1H, *J* = 5.1 Hz and *J* = 17.7 Hz, –CH–), 2.83 (dd, 1H, *J* = 5.1 Hz and *J* = 17.7 Hz, –CH–), 3.93 (t, 1H, *J* = 5.1 Hz, –O–CH–), 7.53 (td, 1H, *J* = 1.4 Hz and *J* = 7.6 Hz, ArH), 7.67 (td, 1H, *J* = 1.1 Hz and *J* = 7.6 Hz, Ar–H), 7.85 (dd, 1H, *J* = 1.1 Hz and *J* = 7.6 Hz, ArH), 8.07 (dd, 1H, *J* = 1.4 Hz and *J* = 7.6 Hz). ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 22.1, 25.1, 25.4, 68.3, 81.4, 110.4, 124.4, 128.8, 130.0, 130.9, 132.0, 134.9, 161.5, 178.7, 179.5. ESI-MS *m*/*z* 281.1 $[M + Na]^+$.

2-(1-Hydroxy-1-methylethyl)-2,3-dihydronaphtho[2,3-*b*]furan-4,9-dione 6 ($C_{15}H_{14}O_4$)

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.26 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.17 (d, 2H, *J* = 10.0 Hz, –CH_2–) 4.86 (t, 1H, *J* = 10.0 Hz, –O–CH–) 7.66–7.76 (m, 2H, ArH), 8.06–8.10 (m, 2H, Ar–H). ^{13}C ($CDCl_3$, 75 MHz) δ (ppm): 24.0, 25.8, 28.4, 71.7, 92.1, 125.0, 126.1, 126.3, 131.5, 132.9, 133.0, 134.2, 159.9, 177.7, 182.2. ESI-MS *m*/*z* 281.1 $[M + Na]^+$

4-Hydroxy-5,5-dimethyldihydrofuran-2(3*H*)-one 7 ($C_6H_{10}O_3$)

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.55 (dd, 1H, *J* = 1.9 Hz and *J* = 10.8 Hz, –CH_2–), 2.95 (dd, 1H, *J* = 3.8 Hz and *J* = 10.8 Hz, –CH_2–), 4.21–4.23 (m, 1H, –CH–OH). ^{13}C ($CDCl_3$, 75 MHz) δ (ppm) : 21.0 (–CH_3), 25.8 (–CH_3), 38.2 (–CH_2–), 73.8 (C–OH), 87.2 (–$C(CH_3)_2$), 174.3 (–C=O). ESI-MS *m*/*z* 131.0 $[M + H]^+$.

Phthalic anhydride 8 ($C_8H_4O_3$)

MS (EI) *m*/*z* (rel. int., %): 149 (3), 148 ($M^{\bullet+}$, 38), 104 (100), 76 (63), 50 (25).

ortho-Phthalimide 9 ($C_8H_5O_2N$)

MS (EI) *m*/*z* (rel. int., %): 148 (9), 147 ($M^{\bullet+}$, 100), 104 (44), 76 (38), 50 (13).

3,4-Epoxy-4-methylpentanal 10 ($C_6H_{10}O_2$)

MS (EI) *m/z* (rel. int., %): 115 (4), 85 (41), 59 (100), 58 (39), 43 (46), 42 (34), 41 (39) 39 (16).

Oxidation of lapachol 1 using *m*-CPBA – Route A

Lapachol (**1**) (18.0 mg; 0.075 mmol) was dissolved in 2.0 ml of CH_2Cl_2 and *m*-CPBA was added (2.5 equiv). The mixture was kept under magnetic stirring and protected from light at 22 ± 2 °C for 48 h. After that time, the substrate was completely consumed (confirmed by TLC). The mixture was dissolved in CH_2Cl_2 and washed with basic water (K_2CO_3). The organic layer was recovered and dried through anhydrous sodium sulfate and evaporated under reduced pressure.

Oxidation of lapachol 1 using Mn-Porph – Route B

In a typical experiment based on our earlier work, lapachol **1** (18.0 mg; 0.075 mmol), catalyst (depending on catalyst/substrate molar ratio) and co-catalyst (ammonium acetate, 0.12 mmol) were dissolved in CH_3CN (2.0 ml). The mixture was kept under magnetic stirring at room temperature (22 ± 2 °C) and protected from light. The oxidant, 30% H_2O_2 (w/w) diluted in CH_3CN (1 : 10) was added at regular intervals of 15 min in aliquots each one corresponding to a half substrate amount (3.7×10^{-2} mmol). The reaction was followed by TLC and was stopped when the substrate had been consumed or when no more reaction evolution was observed after two successive analyses. The reaction mixture was then diluted in CH_2Cl_2 and washed with water. The organic layer was recovered and dried through anhydrous sodium sulfate and evaporated. After that, the obtained material was submitted to silica gel preparative TLC using a mixture of ethyl acetate/hexane (2 : 1) as eluent.

Conclusions

The procedure involving the use of the manganese porphyrin complex not only allows the study of some metabolites formed during lapachol **1** oxidation, but also provides a totally different selectivity towards cyclised quinones formed in the reaction. Using **Mn-Porph** as catalyst, the *para*-quinones are highly favoured, in contrast to what happens in classical oxidation with *m*-CPBA. It should be noted that the **Mn-Porph** catalysed reactions are more selective for furanaphthoquinones (51.7%) than those with *m*-CPBA reaction (26.5%). Also, under **Mn-Porph** catalysed reactions, it is possible to use a benign, environmentally clean oxidant (H_2O_2), instead of *m*-CPBA which generates *meta*-chlorobenzoic acid as by-product. We are currently extending this oxidative methodology to other metalloporphyrin derivatives in order to understand the catalyst structure–activity relationship with the products formed.

Acknowledgements

Thanks are due to Fundação para a Ciência e a Tecnologia (FCT/FEDER) for funding the Organic Chemistry Research Unit (QOPNA). S.M.G. Pires also thanks FCT for her PhD Grant (SFRH/BD/64354/2009). V. F. Ferreira and M. D. Vargas thank PRONEX-FAPERJ for their financial support. Authors acknowledge the Portuguese National NMR Network, supported with funds from FCT.

References

1 P. J. O'Brien, *Chem.-Biol. Interact.*, 1991, **80**, 1–41.
2 A. V. Pinto and S. L. de Castro, *Molecules*, 2009, **14**, 4570–4590.
3 E. N. da Silva Junior, M. A. B. F. de Moura, A. V. Pinto, M. C. F. R. Pinto, M. C. B. V. de Souza, A. J. Araújo, C. Pessoa, L. V. Costa-Lotufo, R. C. Montenegro, M. O. de Moraes, V. F. Ferreira and M. O. F. Goulart, *J. Braz. Chem. Soc.*, 2009, **20**, 635–643.
4 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. Andrade and A. V. Pinto, *Tetrahedron Lett.*, 2009, **50**, 1575–1577.
5 C. F. Santana, O. G. Lima, I. L. D'Albuquerque, A. L. Lacerda and D. G. Martins, *Rev. Inst. Antibiot.*, 1968, **8**, 89–94.
6 J. R. G. Castellanos, J. M. Prieto and M. Heinrich, *J. Ethnopharmacol.*, 2009, **121**, 1–13.
7 M. Arnaudon, *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, 1858, **46**, 1152–1156.
8 S. C. Hooker, *J. Chem. Soc.*, 1892, **61**, 611–650.
9 S. C. Hooker, *J. Am. Chem. Soc.*, 1936, **58**, 1181–1190.
10 E. Paternó, *Gazz. Chim. Ital.*, 1882, **12**, 337–392.
11 L. F. Fieser, F. C. Chang, W. G. Dauben, C. Heidelberger, H. Heymann and A. M. Selingman, *J. Pharmacol. Exp. Ther.*, 1948, **94**, 85–96.
12 N. McHardy, A. T. Hudson, D. W. T. Morgan, D. G. Rae and T. T. Dolan, *Res. Vet. Sci.*, 1983, **35**, 347–352.
13 P. Boehm, K. Cooper, A. T. Hudson, J. P. Elphick and N. McHardy, *J. Med. Chem.*, 1981, **24**, 295–299.
14 F. G. G. Miranda, J. C. Vilar, I. A. N. Alves, S. C. H. Cavalcanti and A. R. Antoniolli, *BMC Pharmacol.*, 2001, **1**, 6–10.
15 A. S. Cunha, E. L. S. Lima, A. C. Pinto, A. Esteves-Souza, A. Echevarria, C. A. Camara, M. D. Vargas and J. C. Torres, *J. Braz. Chem. Soc.*, 2006, **17**, 439–442.
16 C. A. Camara, A. C. Pinto, M. A. Rosa and M. D. Vargas, *Tetrahedron*, 2001, **57**, 9569–9574.
17 M. D. F. Santos, J. T. Litivack-Junior, R. V. Antunes, T. M. S. Silva and C. A. Camara, *J. Braz. Chem. Soc.*, 2011, **22**, 796–800.
18 F. P. Guengerich, *Chem. Res. Toxicol.*, 2001, **14**, 611–650.
19 S. C. Hooker, *J. Am. Chem. Soc.*, 1936, **58**, 1168–1173.
20 M. Cortes, J. Katalinic and J. Valderrama, *An. Quim.*, 1983, **79C**, 202–205.
21 I. D. Cunningham, T. N. Danks, K. T. A. O'Connell and P. W. Scott, *J. Org. Chem.*, 1999, **64**, 7330–7337.
22 R. A. Sheldon, *Metalloporphyrins in Catalytic Oxidations*, Marcel Dekker: New York, 1994.
23 J. T. Groves in *Cytochrome P-450: Structure, Mechanism and Biochemistry*, Ed.: P. R. Ortiz de Montellano, Kluwer Academic/Plenum Publishers, New York, 2005, 3rd ed. 1–43.
24 S. L. H. Rebelo, M. M. Q. Simões, M. G. P. M. S. Neves, A. M. S. Silva and J. A. S. Cavaleiro, *Chem. Commun.*, 2004, 608–609.
25 S. L. H. Rebelo, M. M. Pereira, M. M. Q. Simões, M. G. P. M. S. Neves and J. A. S. Cavaleiro, *J. Catal.*, 2005, **234**, 76–87.
26 R. De Paula, M. M. Q. Simões, M. G. P. M. S. Neves and J. A. S. Cavaleiro, *Catal. Commun.*, 2008, **10**, 57–60.
27 S. M. G. Pires, R. De Paula, M. M. Q. Simões, M. G. P. M. S. Neves, I. C. M. S. Santos, A. C. Tomé and J. A. S. Cavaleiro, *Catal. Commun.*, 2009, **11**, 24–28.
28 M. M. Q. Simões, R. De Paula, M. G. P. M. S. Neves and J. A. S. Cavaleiro, *J. Porphyrins Phthalocyanines*, 2009, **13**, 589–596.
29 J. Mock, S. T. Murphy, E. Richie and W. C. Taylor, *Aust. J. Chem.*, 1973, **26**, 1121–1130.
30 M. Onitsuka, M. Fujiu, N. Shinma and H. B. Maruyama, *Chem. Pharm. Bull.*, 1983, **31**, 1670–1675.
31 M. Girard, J. C. Ethier, D. Kindack, B. A. Dawson and D. V. C. Awang, *J. Nat. Prod.*, 1987, **50**, 1149–1151.
32 S. Otten and J. P. Rosazza, *Appl. Environ. Microbiol.*, 1978, **35**, 554–557.
33 K. Lee, P. Turbull and H. W. Moore, *J. Org. Chem.*, 1995, **60**, 461–464.
34 A. I. Franscisco, G. Q. Silveira, J. A. L. C. Resende, T. L. Balliano, V. R. S. Malta and A. V. Pinto, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2010, **E66**, 341.
35 E. P. Sacau, A. Estévez-Braun, A. G. Ravelo, E. A. Ferro, H. Tokuda, T. Mukainaka and H. Nishino, *Bioorg. Med. Chem.*, 2003, **11**, 483–488.
36 V. F. Ferreira, *Química Nova na Escola*, 1996, **4**, 35–36.
37 S. B. Ferreira, D. R. da Rocha, J. W. M. Carneiro, W. C. Santos and V. F. Ferreira, *Synlett*, 2011, 1551–1554.