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A novel biotransformation of benzofurans and related compounds catalysed by a chloroperoxidase

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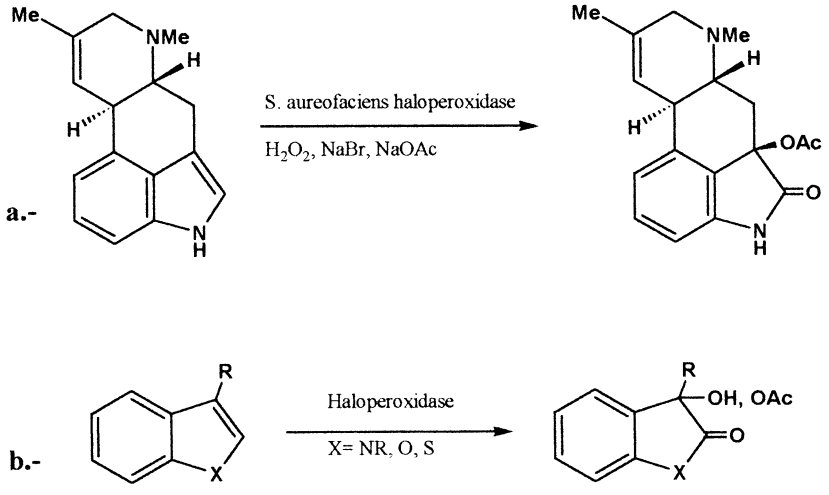
Abstract—The oxidation of 3-alkyl benzofurans, indoles, and a benzothiophene by the chloroperoxidase from *Caldariomyces fumago* has been investigated. Under conditions in which the catalase activity of chloroperoxidase was minimised in the presence of chloride and hydrogen peroxide, 3-methylbenzothiophene was oxidised at sulfur but the indoles (**5**–**9**) and benzofurans (**1**–**4**) gave 2,3-diols as initial products. In the case of *N*-unsubstituted indoles, these tautomerised to give the corresponding lactam. In contrast, the diols (predominantly *trans*) formed from the benzofurans were sufficiently stable for isolation and full characterisation. This novel reaction has the potential to be developed into a useful synthetic biotransformation. © 2001 Elsevier Science Ltd. All rights reserved.

The versatility of chloroperoxidases has attracted significant interest in the field of biotransformations.[1,2] Although many of the earliest examples can be understood by the reaction of hypohalites generated by the enzymes from hydrogen peroxide and halide ion,[3] a significant number of reactions in which non-halogenated, hydroxylated products are formed have been described. In several of these, enantioselectivity has been observed, thereby encouraging the further development of chloroperoxidases in preparative biotransformations.[4] Chloroperoxidases have also been characterised as enzymes in the pathways leading to tetracyclines and other halogenated natural products.[5] Chloroperoxidases belong to several classes; they may be haem-containing,[6] have metals such as vanadium at the active site,[7a] or have esterase characteristics.[7b] Despite the structural and mechanistic differences, the enzymes typically show preferences to react with unhindered, electron rich systems such as aromatic rings and disubstituted alkenes.

During a study of the metabolism of ergot alkaloids, van Pée[2] demonstrated an unusual double oxidation catalysed by a chloroperoxidase (Scheme 1). Ergot alkaloids are



Scheme 1. a. Transformation reported by van Pée.[2] b. Potential generalisation from that reaction.

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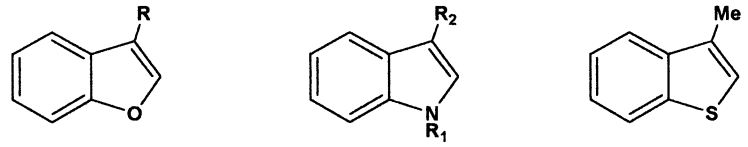


1	R= Me	5	R_1= R_2= Me	10
2	R= Et	6	R_1= H, R_2= Me	
3	R= i-Pr	7	R_1= H, R_2= CH_2CO_2Me	
4	R= CH_2CO_2Me	8	R_1= H, R_2= CH_2CH_2OH	
		9	R_1= H, R_2= CH_2CO_2H	

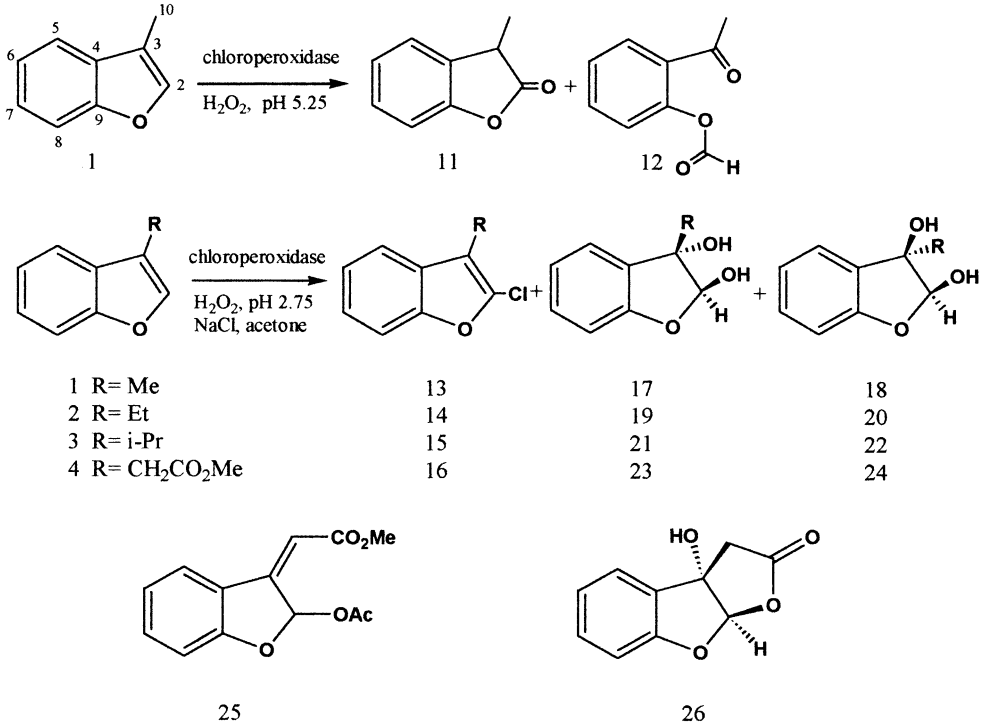
Scheme 2. Compounds tested with the chloroperoxidase from *C. fumago*.

complex, polycyclic compounds but the reaction site can reasonably be described as a cyclic enamine. Hence it can be asked whether simpler cyclic enamines and other analogous structures such as enol ethers might undergo a similar double oxidation. In view of the ready accessibility of enamines and enol ethers, a double oxidation in one-pot would be a potentially useful reaction, leading potentially to 1,2-dicarbonyl compounds and their derivatives and, if stereochemical control can be obtained, to carbohydrate analogues. We now report the oxidation of electron rich aromatic compounds such as benzofurans and indoles to 1,2-diols and some derivatives, using the fungal chloroperoxidase from *Caldariomyces fumago* in the presence of hydrogen peroxide and chloride ion (Scheme 2).

1. Results and discussion

The primary problems to overcome were to find reaction conditions under which the catalase activity of the chloroperoxidase was not dominant and the enzyme was not deactivated by excess hydrogen peroxide. We found that if the enzyme concentration is too great (>100 units per ml), hydrogen peroxide was rapidly destroyed. If the hydrogen peroxide concentration is too great ($[H_2O_2]$>3 mM), the enzyme was quickly inactivated. The useful operating range was found to be $[H_2O_2]$ 0.06–0.6 mM and [CPO] 60 units per ml.

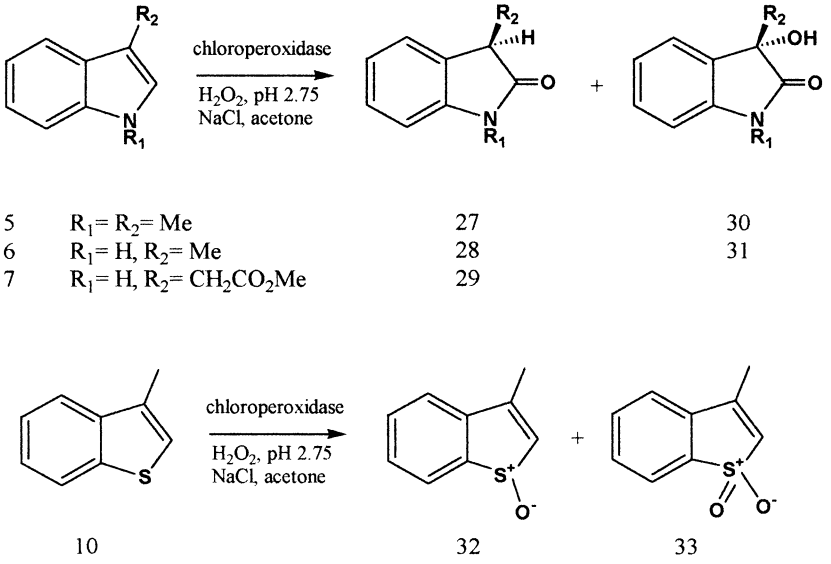
Under conditions where catalase activity was high, the predominant products from benzofurans were heterocyclic ring cleaved compounds such as the ketoformate **12** (Scheme 3). However, at mildly acidic pH, in the presence of acetone and with careful control of both enzyme and hydrogen peroxide concentration, it was possible to isolate significant quantities of 1,2-diol oxidation products of benzofurans (derivatives **1**–**4**) by extraction of the reaction mixture with ethyl acetate (Scheme 3). When dichloromethane was used for extraction, the major product was the lactone **11**, presumably derived by acid-catalysed dehydration of the diol, and the ketoformate **12**. With indole derivatives **5**–**7** as substrates, lactams, and α-hydroxylactams were the main compounds isolated. 3-Methylbenzothiophene (**10**) not surprisingly underwent oxidation



1 R= Me	1	13	17	18
2 R= Et	11	14	19	20
3 R= i-Pr	12	15	21	22
4 R= CH_2CO_2Me		16	23	24

25 26

Scheme 3. Oxidation of benzofurans by chloroperoxidase.



Scheme 4. Oxidation of indoles and thiophene analogues by chloroperoxidase.

Table 1. Percentage of diols and chloride obtained from benzofuran derivatives. Conditions: 0.19 mmol of substrate dissolved in 4 ml phosphate buffer 0.1 M, pH 2.75, 1 ml of acetone, 6 mg sodium chloride, hydrogen peroxide added at 0.12 mmol h^{-1}, CPO 300 units h^{-1}, stirring at room temperature

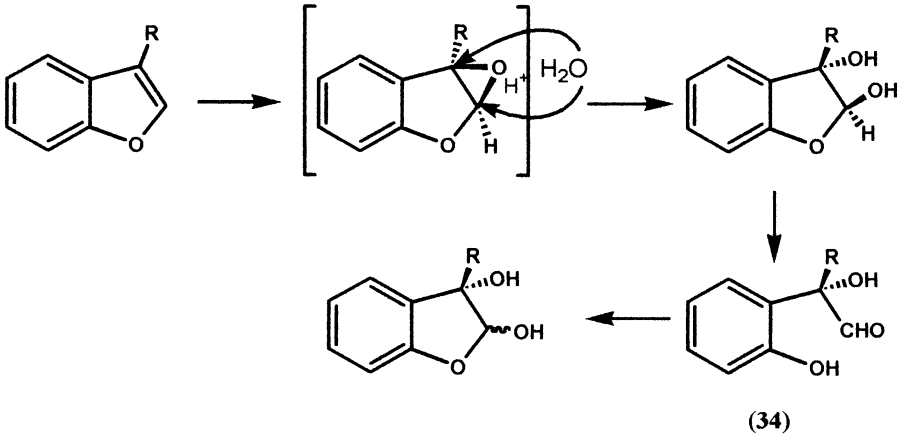
Starting material	2,3-Diols		2-Chloro (%)
	Yield (%)[a]	*trans*/*cis* Ratio[b]	
1	(**17**:**18**) 78	10:1	(**13**) 9
2	(**19**:**20**) 64	20:1	(**14**) 14
3	(**21**:**22**) 46	>50:1[c]	(**15**) 26
4	(**23**:**24**) 50[d]	>50:1[c]	(**16**) 19

[a] Calculated after chromatography purification.
[b] Calculated from ^{1}H NMR spectra.
[c] Compounds **22** and **24** were not detected by ^{1}H NMR.
[d] Combined yield based on derivatives.

at sulfur to form the sulfoxide (**32**) and sulfone (**33**) (Scheme 4).

The general pattern of products obtained from the oxidation of 3-substituted benzofurans was the same for the four examples investigated (Table 1). The products of oxidation were purified by chromatography and unambiguously characterised by MS and NMR spectroscopy. In the case of the benzofurans, evidence for the presence of the diols comes from the resonance for the hemiacetal proton at δ_H 5.5–5.6 and carbon at δ_C 100–105 ppm. The observation of two pairs of resonances in unequal amounts indicates a degree of stereoselectivity in the oxidation. The lower field resonances were more intense than the higher field resonance, suggesting that the *trans*-diol isomer is predominant. Unlike van Pee, who obtained an acetoxy amide as his double oxidation product, the formation of a diol is a new reaction of these systems.

In order to investigate the configuration of the products, attempts were made to derivatise the diols, for example with Mosher's acid. However, no derivatives were preparable from even slightly hindered reagents, including benzoate. Treatment of the diols with acetic anhydride and pyridine did afford a derivative. In the case of the 3-methylbenzofuran (**1**), the diacetate (**17-diAc**) was recrystallised and the configuration determined by X-ray crystallography. Unfortunately, the diacetate of **17** was found to be racemic but was exclusively the *trans* isomer. The initial *trans*/*cis*



Scheme 5. Suggested mechanism for the reaction catalysed by CPO, and possible epimerization of the diols through a hydroxy-aldehyde intermediate.

ratio from the reaction (Table 1), does not correspond to the ratio after acetylation but before recrystallisation, indicating an equilibrium between both isomeric hemiacetals during the treatment with acetic anhydride–pyridine, probably through a hydroxy-aldehyde (**34**) intermediate step (Scheme 5). In the case of the 3-isopropylbenzofuran (**3**), it is noteworthy that only the *trans* isomer could be isolated, as both diol and diacetate, probably because of the larger size of the isopropyl group compared with methyl. In the case of the benzofuran 3-acetic-acid derivative (**4**), two of the isolated products (**25**, **26**) presumably derive from the initial diol (**23**, **24**) that was formed by CPO-catalysed oxidation, followed by dehydration or intramolecular nucleophilic attack.

In the case of indoles **5**–**7**, the products obtained were more similar to those obtained by van Pee.[2] After a short reaction time, the lactams (**27**–**29**) were the main products in our experiments. Longer reaction time gave mainly the α-hydroxylactams (**30**–**31**). In all cases with indoles as substrates, yields were lower than with benzofurans and also the progress of the reaction was more difficult to monitor; reaction conditions had to be checked more often. The alcohol 2-(1-*H*-indol-3-yl)-ethanol (**8**), and the acid 1-*H*-indol-3-yl-acetic (**9**) were also tested as substrates, but no compounds could be isolated from their biotransformation, unchanged starting material being recovered. This indicates that this chloroperoxidase did not accept high polarity functional groups in the side-chain.

Since the products of interest are diols, the role of chloride becomes significant. The oxidation of 3-methylbenzofuran (**1**) was studied in the presence of varying concentrations of chloride (Table 2). If chloride was absent, no diol formation was observed. At high concentrations of chloride, the reactions proceeded easily, hardly affecting the ratio of diols: chloro products. At low concentrations, however, the ratio diols: chloro products increased, but with a considerable decrease of the rate of the reaction. Thus the proportion of diols was not strongly dependent upon chloride concentration, which is consistent with chloride's having a role as a mediator in the reaction. In some cases, for example 3-isopropylbenzofuran, extra chloride had to be added, because the reaction stopped when the chloride was consumed. In control reactions with no enzyme present, no chlorinated compounds were detected in 12 h. In the case of indoles, the role of the chloride was similar, because no reaction took place in the absence of chloride, although no chlorinated derivatives were isolated from these substrates.

Taken together with the stereochemical outcome of the reactions, a tentative suggestion can be made for the mechanism of the reaction catalysed by the chloroperoxidase from *C. fumago* (Scheme 5). Initially, an epoxide is formed either inside the active site of the enzyme or out with the active site by the addition of hypochlorite and elimination of hydrogen chloride. Acid catalysed opening of the epoxide will give the *trans*-diol. In the case of benzofurans, the diols are evidently sufficiently stable for isolation but in the case of indoles, dehydration to give the enol tautomer of the lactams occurs. On the basis of this mechanism it can be suggested that other cyclic enol ethers and enamines might also be substrates. The chief limitation of the reactions discovered so far is the lack of enantiomeric selectivity. This is in contrast with the well-established arene dioxygenase chemistry that also extends to heterocyclic substrates. It could be that other haloperoxidases might have more favourable environments at the active site for enantioselectivity and this is currently being investigated.

Table 2. Product ratio from 3-methylbenzofuran oxidation at different chloride concentrations

Chloride concentration ((M)	Diols:2-chloro ratio	*trans*/*cis* Diol ratio
1.5	8:1	9
0.4	8:1	10
0.1	9:1	10
0.02	15:1	10
0.004	40:1	10

2. Experimental

Compounds **1**–**5**, **7** and **8** were synthesised. Compounds **6**, **9** and **10** are commercially available. **1**–**3** were prepared following Ref. 8, starting from 1-hydroxyacetophenone, 2-hydroxypropiophenone and 1-(2-hydroxyphenyl)-2-methylpropan-1-one, respectively. Compound **4** was prepared following Ref. 9, starting from benzofuran-3-one. Compound **5** was prepared from **6**, by treatment with methyl iodide/potassium carbonate. **7** was obtained from **9**, by treatment with diazomethane. Further reduction with lithium aluminium hydride gave **8**. Chloroperoxidase from *Caldariomyces fumago* was bought from Sigma Co. and was used without further purification.

Low and high resolution mass spectra were obtained on a Jeol JMS-AX505HA mass spectrometer and on a Micromass Autospec spectrometer. NMR spectra were obtained on a Bruker AMX 400 spectrometer operating at 400 MHz for ^{1}H- and 100.6 MHz for ^{13}C NMR. Column chromatography was performed with silica gel Prolabo (200–400 mesh).

2.1. Oxidation by chloroperoxidase—general method

300 units of CPO were added to a phosphoric acid buffer solution (4 ml, 0.1 M, pH 2.75), containing acetone (1 ml), potassium chloride (6 mg, giving 0.02 M solution) and 0.19 mmol of substrate. Hydrogen peroxide solution in distilled water (1.20 M) was added at a rate of 0.12 mmol h^{-1} (100 μl h^{-1}) through a syringe pump, stirring vigorously. Extra portions of CPO (150 units) were added every half hour. The reaction was followed by GC and continued until starting material had disappeared. Hydrogen peroxide concentration was checked regularly, to avoid excess. The reaction was stopped by addition of saturated aqueous sodium sulphite solution (0.1 ml). The aqueous phase was extracted three times with ethyl acetate (3×10 ml). The organic layer was separated, dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with petroleum ether–ethyl acetate mixtures of increasing polarity.

From *3-methylbenzofuran* (**1**) (25 mg, 0.19 mmol) eluting with petroleum ether, 2-chloro-3-methyl-benzofuran (**13**) was obtained (3 mg, 9%). δ_H (400 MHz): 2.21 (3H, s, Me), 7.23–7.30 (2H, m, Ar–H), 7.39–7.45 (2H, m, Ar–H). δ_C (100 MHz): 7.8 (C-10), 110.6 (C-3), 110.7 (C-8), 118.8 (C-6), 122.9 (C-5), 124.1 (C-7), 129.4 (C-4), 138.0 (C-2), 153.2 (C-9). Found $[M]^+$ *m/z* 168.0174. $C_9H_7O^{37}Cl$ requires 168.0156; found $[M]^+$ *m/z* 166.0188. $C_9H_7O^{35}Cl$ requires 166.0185. Elution with pet. ether/EtOAc (7:3) gave 3-methyl-2,3-dihydrobenzofuran-2,3-diol (**17**, **18**) as a mixture (10:1) *trans*/*cis*, (24 mg, 78%, oil) that could not be separated. δ_H (400 MHz): 1.61 (3H, s, Me), 5.46 (1H, s, H-2), 6.82 (1H, d, *J*=7.6 Hz, H-8), 6.95 (1H, dt, *J*=7.6 and 1.0 Hz, H-6), 7.25 (1H, dt, *J*=7.6 and 1.0 Hz, H-7), 7.32 (1H, dd, *J*=7.6 and 1.0 Hz, H-5) (major isomer). δ_C (100 MHz): 23.8 (C-10), 75.9 (C-3), 105.4 (C-2), 110.8 (C-8), 121.5 (C-6), 123.7 (C-5), 130.3 (C-4), 130.8 (C-7), 156.9 (C-9). Found $[M]^+$ *m/z* 166.0634. $C_9H_{10}O_3$ requires 166.0630. LRMS *m/z* (rel. int.) 166 $[M]^+$ (35), 137 (100), 123 (33), 121 (36), 105 (68), 91 (39), 77 (44).

Treatment of the crude mixture (**17**, **18**) (10 mg) with acetic anhydride–pyridine overnight, at room temperature gave, eluting with petroleum ether/EtOAc (9:1), *trans*-diacetate of 3-methyl-2,3-dihydro-benzofuran-2,3-diol (**17-diAc**), (10 mg, 67%): mp (pet. ether/EtOAc) 127–128°. δ_H (400 MHz): 1.90, 2.00, 2.14 (3H each, s, Me), 6.80 (1H, s, H-2), 6.94 (1H, d, *J*=7.5 Hz, H-8) 7.03 (1H, dt, *J*=7.5 and 1.0 Hz, H-6), 7.32 (1H, dt, *J*=7.5 and 1.0 Hz, H-7), 7.53 (1H, dd, *J*=7.5 and 1.0 Hz, H-5). δ_C (100 MHz): 17.7 (C-10), 20.9 and 21.9 (AcO–), 87.4 (C-3), 101.7 (C-2), 110.8 (C-8), 121.9 (C-6), 126.1 (C-5), 126.8 (C-4), 131.3 (C-7), 158.9 (C-9), 169.2 and 169.9 (AcO–). Found $[M]^+$ *m/z* 250.0837. $C_{13}H_{14}O_5$ requires 250.0841. LRMS *m/z* (rel. int.) 250 $[M]^+$ (64), 207 (24), 190 (28), 180 (58), 165 (38), 148 (73), 137 (100), 120 (31). Further elution gave the *cis*-derivative (**18-diAc**) which did not readily crystallise, (3.5 mg, 23%). δ_H (400 MHz): 1.79, 2.04, 2.13 (3H each, s, Me), 6.73 (1H, s, H-2), 6.92 (1H, d, *J*=7.5 Hz, H-8), 7.06 (1H, dt, *J*=7.5 and 1.0 Hz, H-6), 7.29 (1H, dt, *J*=7.5 and 1.0 Hz, H-7), 7.38 (1H, dd, *J*=7.5 and 1.0 Hz, H-5). δ_C (100 MHz): 20.8 and 21.1 (AcO–), 23.9 (C-10), 84.0 (C-3), 99.9 (C-2), 111.1 (C-8), 122.5, 123.5 (C-5 and C-6), 128.9 (C-4), 130.4 (C-7), 155.8 (C-9), 168.9, 169.9 (AcO–). Found $[M]^+$ *m/z* 250.0848. $C_{13}H_{14}O_5$ requires 250.0841. LRMS *m/z* (rel. int.) 250 $[M]^+$ (49), 207 (11), 179 (34), 165 (68), 148 (82), 137 (100), 120 (63), 91 (27).

From *3-ethylbenzofuran* (**2**) (28 mg, 0.19 mmol) eluting with petroleum ether, 2-chloro-3-ethyl-benzofuran (**14**), was obtained (5 mg, 14%). δ_H (400 MHz): 1.28 (3H, t, *J*=7.6 Hz, H-11), 2.69 (2H, q, *J*=7.6 Hz, H-10), 7.23–7.29 (2H, m, Ar–H), 7.41 (1H, m, Ar–H), 7.49 (1H, m, Ar–H). Elution with pet. ether/EtOAc (7:3) gave 3-ethyl-2,3-dihydrobenzofuran-2,3-diol (**19**, **20**), as a mixture (20:1) *trans*/*cis* (22 mg, 64%, oil) that could not be separated. δ_H (400 MHz): 1.03 (3H, t, *J*=7.5 Hz, H-11), 1.93 and 2.05 (1H each, dq, *J*=7.5 and 15.0 Hz, H-10), 2.64 (1H, br s, –OH), 4.15 (1H, d, *J*=8.0 Hz, –OH), 5.57 (1H, d, *J*=8.0 Hz, H-2), 6.87 (1H, d, *J*=7.5 Hz, H-8), 6.99 (1H, dt, *J*=7.5 and 1.0 Hz, H-6), 7.29 (1H, dt, *J*=7.5 and 1.0 Hz, H-7), 7.33 (1H, dd, *J*=7.5 and 1.0 Hz, H-5). δ_C (100 MHz): 7.6 (C-11), 30.5 (C-10), 78.9 (C-3), 101.5 (C-2), 110.7 (C-8), 121.4 (C-6), 124.1 (C-5), 129.2 (C-4), 130.7 (C-7), 157.3 (C-9). Found $[M]^+$ *m/z* 180.0786. $C_{10}H_{12}O_3$ requires 180.0786. LRMS *m/z* (rel. int.) 180 $[M]^+$ (18), 157 (27), 151 (44), 133 (33), 123 (95), 131 (100), 105 (30), 95 (30).

Treatment of the diol (**19**, **20**) (22 mg) with acetic anhydride–pyridine overnight, at room temperature gave, eluting with petroleum ether/EtOAc (9:1) *trans*-diacetate of 3-ethyl-2,3-dihydrobenzofuran-2,3-diol (**19-diAc**) (15 mg, 46%, oil). δ_H (400 MHz): 0.99 (3H, t, *J*=7.4 Hz, H-11), 2.00, 2.14 (3H each, s, Me), 2.09 and 2.87 (1H each, dq, *J*=7.4 and 14.8 Hz, H-10), 6.72 (1H, s, H-2), 6.93 (1H, d, *J*=7.5 Hz, H-8), 7.01 (1H, dt, *J*=7.5 and 1.0 Hz, H-6), 7.30 (1H, dt, *J*=7.5 and 1.0 Hz, H-7), 7.59 (1H, dd, *J*=7.5 and 1.0 Hz, H-5). δ_C (100 MHz): 8.6 (C-11), 23.4 (C-10), 20.9 and 21.7 (AcO–), 90.4 (C-3), 101.6 (C-2), 110.8 (C-8), 121.6 (C-6), 127.3 (C-5), 126.1 (C-4), 131.2 (C-7), 159.3 (C-9), 169.2 and 169.5 (AcO–). Found $[M]^+$ *m/z* 264.0990. $C_{14}H_{16}O_5$ requires 264.0998. LRMS *m/z* (rel. int.) 264 $[M]^+$ (5), 204 (10), 179 (16), 162 (100), 151 (31), 147 (65), 145 (12), 144 (39), 115 (33). Further elution gave the *cis*-derivative (**20-diAc**) (13 mg, 40%, oil). δ_H (400 MHz): 0.87 (3H, t, *J*=7.5 Hz, H-11), 2.04, 2.14 (3H each, s, Me), 2.03 and 2.41 (1H each, dq, *J*=7.5 and 15.0 Hz, H-10), 6.74 (1H, s, H-2), 6.92 (1H, d, *J*=7.5 Hz, H-8), 7.05 (1H, dt, *J*=7.5 and 1.0 Hz, H-6), 7.30 (1H, dt, *J*=7.5 and 1.0 Hz, H-7), 7.36 (1H, dd, *J*=7.5 and 1.0 Hz, H-5). δ_C (100 MHz): 6.9 (C-11), 20.8 and 21.0 (AcO–), 28.6 (C-10), 87.0 (C-3), 99.8 (C-2), 111.1 (C-8), 122.1 (C-6), 124.6 (C-5), 126.8 (C-4), 130.4 (C-7), 156.4 (C-9), 168.9 and 169.8 (AcO–). Found $[M]^+$ *m/z* 264.0995. $C_{14}H_{16}O_5$ requires 264.0998. LRMS *m/z* (rel. int.) 264 $[M]^+$ (22), 204 (11), 193 (10), 179 (37), 162 (100), 151 (99), 147 (70), 144 (36), 134 (29), 115 (36), 91 (24).

From *3-isopropylbenzofuran* (**3**), (30 mg, 0.19 mmol) eluting with petroleum ether, 2-chloro-3-isopropylbenzofuran (**15**), was obtained (9 mg, 26%, oil). δ_H (400 MHz): 1.41 (6H, t, *J*=7.1 Hz, Me), 3.17 (1H, m, H-10), 7.20–7.30 (2H, m, Ar–H), 7.41 (1H, m, Ar–H), 7.59 (1H, m, Ar–H). Elution with pet. ether/EtOAc (6:4) gave 3-isopropyl-2,3-dihydro-benzofuran-2,3-diol (**21**), (17 mg, 46%, oil). δ_H (400 MHz): 0.94 and 1.04 (3H each, d, *J*=6.9 Hz, Me), 2.26 (1H, m, H-10), 2.50 (1H, br s, –OH), 4.59 (1H, br s, –OH), 5.62 (1H, s, H-2), 6.83 (1H, d, *J*=7.5 Hz, H-8), 6.95 (1H, dt, *J*=7.5 and 1.0 Hz, H-6), 7.25 (1H, dt, *J*=7.5 and 1.0 Hz, H-7), 7.28 (1H, dd, *J*=7.5 and 1.0 Hz, H-5). δ_C (100 MHz): 16.1 (C-12), 17.4 (C-11), 34.7 (C-10), 81.7 (C-3), 101.5 (C-2), 110.6 (C-8), 121.3 (C-6), 124.4 (C-5), 128.4 (C-4), 130.7 (C-7), 157.8 (C-9). Found $[M]^+$ *m/z* 194.0948. $C_{11}H_{14}O_3$ requires 194.0943. LRMS *m/z* (rel. int.) 194 $[M]^+$ (13), 165 (22), 151 (34), 133 (73), 121 (23), 105 (24), 86 (100).

Treatment of the diol (**21**) (10 mg) with acetic anhydride–pyridine overnight, at room temperature gave, after removing solvent under vacuum, *trans*-diacetate of 3-isopropyl-2,3-dihydro-benzofuran-2,3-diol (**21-diAc**), (12 mg, 84%, colourless crystals): mp 93–95° (pet. ether/EtOAc). δ_H (400 MHz): 0.69 and 0.99 (3H each, d, *J*=6.8 Hz, Me), 2.04 and 2.14 (3H each, s, AcO–), 3.03 (1H, m, H-10), 6.79 (1H, s, H-2), 6.91 (1H, d, *J*=7.5 Hz, H-8), 7.04 (1H, dt,

J=7.5 and 1.0 Hz, H-6), 7.31 (1H, dt, J=7.5 and 1.0 Hz, H-7), 7.34 (1H, dd, J=7.5 and 1.0 Hz, H-5).δ_C (100 MHz): 15.6 (C-12), 16.4 (C-11), 20.8 and 21.1 (AcO–), 31.8 (C-10), 89.9 (C-3), 99.3 (C-2), 110.8 (C-8), 121.9 (C-6), 125.3 (C-5), 123.9 (C-4), 130.6 (C-7), 157.3 (C-9), 168.9 and 169.7 (AcO–). Found $[M]^+$ m/z 278.1151. $C_{15}H_{18}O_5$ requires 278.1154. LRMS m/z (rel. int.) 278 $[M]^+$ (19), 235 (9), 218 (9), 193 (59), 176 (86), 165 (27), 161 (100), 158 (42), 133 (45), 131 (15).

From *methyl benzofuran-3-yl-acetate* (**4**) (36.5 mg, 0.19 mmol), adding under rigorous control, hydrogen peroxide and CPO for 10 h, and treating the crude extract with acetic anhydride–pyridine overnight at room temperature, eluting with pet. ether/EtOAc (19:1), the 2-chloro derivative (**16**) was obtained (8 mg, 19%, oil). δ_H (400 MHz): 3.69 (2H, s, H-10), 3.73 (3H, s, –OMe), 7.25–7.32 (2H, m, Ar–H), 7.43 (1H, m, Ar–H), 7.49 (1H, m, Ar–H). δ_C (100 MHz): 29.5 (C-10), 52.3 (–OMe), 108.4 (C-3), 111.0 (C-8), 119.2 (C-5), 123.4 and 124.6 (C-5, C-7), 128.2 (C-4), 139.6 (C-2), 153.4 (C-9), 170.1 (–COOMe). Found $[M]^+m/z$ 226.0212. $C_{11}H_9O_3{}^{37}Cl$ requires 226.0211. LRMS m/z (rel. int.) 226 $[M]^+$ (14), 224 (44), 167 (33), 165 (100), 139 (5), 137 (15), 102 (40), 101 (69), 83 (18), 75 (40). Further elution gave starting material (**4**) (5 mg). Elution with pet. ether/EtOAc (4:1) gave methyl 2-acetoxy-benzofuran-3-ylideneacetate (**25**), (8 mg, 17%, oil). δ_H (400 MHz): 2.14 (3H, s, AcO–), 3.78 (3H, s, –OMe), 6.38 (1H, d, J=1.9 Hz, H-2), 6.99 (1H, dd, J=7.7 Hz, H-8), 7.04 (1H, dt, J=7.7 and 0.9 Hz, H-6), 7.40 (1H, dt, J=7.7 and 0.9 Hz, H-7), 7.51 (1H, dd, J=7.7 and 0.9 Hz, H-5), 7.62 (1H, d, J=1.9 Hz, H-10). Elution with pet. ether/EtOAc (6:4) gave methyl 2,3-diacetoxy, 2-3-dihydrobenzofuran-3-yl-acetate (**23-diAc**), (16 mg, 27%, oil). δ_H (400 MHz): 1.98 and 2.08 (3H each, s, AcO–), 3.12 and 4.10 (1H each, d, J=16.5 Hz, H-10), 3.72 (3H, s, –OMe), 6.87 (1H, s, H-2), 6.96 (1H, d, J=7.6 Hz, H-8), 7.03 (1H, dt, J=7.6 and 1.0 Hz, H-6), 7.34 (1H, dt, J=7.6 and 1.0 Hz, H-7), 7.62 (1H, dd, J=7.6 and 1.0 Hz, H-5). δ_C (100 MHz): 20.7 and 21.7 (AcO–), 35.8 (C-10), 52.0 (–OMe), 86.6 (C-3), 101.4 (C-2), 111.2 (C-8), 121.8 (C-6), 124.8 (C-4), 127.5 (C-5), 131.8 (C-7), 159.3 (C-9), 168.5, 169.5 and 169.8 (–CO–). Found $[M]^+$ m/z 308.0852. $C_{15}H_{16}O_7$ requires 308.0896. LRMS m/z (rel. int.) 308 $[M]^+$ (30), 248 (6), 237 (16), 223 (42), 206 (93), 195 (82), 163 (39), 146 (100), 121 (82). Elution with pet. ether/EtOAc (1:1), gave methyl 2-acetoxy-3-hydroxy-2-3-dihydrobenzofuran-3-yl-acetate acid (**23-Ac**), (3 mg, 6%, oil). δ_H (400 MHz): 2.08 (3H, s, AcO–), 3.00 and 3.14 (1H each, d, J=17.0 Hz, H-10), 3.80 (3H, s, –OMe), 6.64 (1H, s, H-2), 6.96 (1H, dd, J=7.5 and 0.9 Hz, Ar–H), 7.04 (1H, dt, J=7.5 and 0.9 Hz, Ar–H), 7.31–7.35 (2H, m, Ar-H). δ_C (100 MHz): 20.7 (AcO–), 38.5 (C-10), 52.3 (–OMe), 80.0 (C-3), 103.7 (C-2), 111.2 (C-8), 122.3 and 123.7 (C-5, C-6), 127.9 (C-4), 131.3 (C-7), 158.4 (C-9), 168.8 and 172.9 (–CO–). Found $[M]^+m/z$ 266.0808. $C_{13}H_{14}O_6$ requires 266.0790. LRMS m/z (rel. int.) 266 $[M]^+$ (10), 248 (4), 223 (20), 206 (29), 195 (37), 163 (37), 146 (53), 121 (100).

When the crude mixture was not treated with acetic anhydride–pyridine, but purified by column chromatography, 3a-hydroxy-3a,8a-dihydro-3H-1,8-dioxacyclopenta[a]inden-2-one (**26**) could also be isolated, (7 mg, 20%, oil), a compound that was not present in the crude reaction mixture. δ_H (400 MHz): 2.53 (1H, br s, –OH), 3.18 and 3.24 (1H each, d, J=18.1 Hz, H-10), 6.22 (1H, s, H-2), 7.00 (1H, d, J=7.5 Hz, H-8), 7.12 (1H, dt, J=7.5 and 0.8 Hz, H-6), 7.40 (1H, dt, J=7.5 and 0.8 Hz, H-7), 7.42 (1H, dd, J=7.5 and 0.8 Hz, H-5). δ_C (100 MHz): 41.0 (C-10), 83.2 (C-3), 111.7 (C-2), 112.0 (C-8), 123.6 (C-6), 124.2 (C-5), 127.5 (C-4), 132.4 (C-7), 158.0 (C-9), 171.4 (C-11). Found $[M]^+m/z$ 192.0403 $C_{10}H_8O_4$ requires 192.0423. LRMS m/z (rel. int.) 192 $[M]^+$ (11), 248 (6), 164 (10), 163 (100), 121 (45), 91 (11).

From *3-methylindole* (**6**) (25 mg, 0.19 mmol), and stopping the reaction after 4 h, eluting with petroleum ether/EtOAc (7:3), 3-methyl-1,3-dihydroindol-2-one (**28**)[9] was obtained (13 mg, 47%), as a colourless solid: mp 100–102 °C (pet. ether/EtOAc) (Lit.[11] 120°C). δ_H(400 MHz): 1.51 (3H, d, J=7.7 Hz, H-10), 3.47 (1H, q, J=7.7 Hz, H-3), 6.91 (1H, d, J=7.5 Hz, H-8), 7.04 (1H, dt, J=7.5 and 0.9 Hz, H-6), 7.18–7.24 (2H, m, H-5 and H-7), 8.55 (1H, br s, N–H). δ_C (100 MHz): 15.2 (C-10), 41.0 (C-3), 109.6 (C-8), 122.4 and 123.8 (C-5, C-6), 127.8 (C-7), 131.2 (C-4), 141.1 (C-9), 181.2 (C-2). Found $[M]^+m/z$ 147.0683. C_9H_9NO requires 147.0684. LRMS m/z (rel. int.) 147 $[M]^+$ (100), 132 (20), 119 (61), 118 (30), 91 (10), 77 (7).

When the reaction was continued for a longer time (10 h), the main isolated compound was 3-hydroxy, 3-methyl-1,3-dihydroindol-2-one (**31**),[10] (7 mg, 23%), as a white powder: mp 147–149°C,[11] (pet. ether/EtOAc) (Lit.[12] 161–162°C). δ_H (400 MHz): 1.63 (3H, s, H-9), 2.88 (1H, br s, –OH), 6.89 (1H, d, J=7.6 Hz, H-8), 7.10 (1H, dt J=7.6 and 0.9 Hz, H-6), 7.28 (1H, dt, J=7.5 and 0.9 Hz, H-7), 7.41 (1H, dd, J=7.5 and 0.9 Hz, H-5), 7.85 (1H, br s, –NH). δ_C (100 MHz): 24.8 (C-10), 73.9 (C-3), 110.3 (C-8), 123.3 and 123.9 (C-5, C-6), 129.7 (C-7), 131.7 (C-4), 139.7 (C-9), 180.2 (–CO–). Found $[M]^+$ m/z 163.0641. $C_9H_9NO_2$ requires 163.0633. LRMS m/z (rel. int.) 163 $[M]^+$ (8), 145 (100), 135 (10), 120 (20), 117 (72), 90 (56).

From *1,3-dimethylindole* (**5**) (28 mg, 0.19 mmol), and stopping the reaction after 4 h, eluting with petroleum ether/EtOAc (7:3), 1,3-dimethyl-1,3-dihydroindol-2-one (**27**),[13] was obtained (16 mg, 52%). δ_H (400 MHz): 1.49 (3H, d, J=7.6 Hz, H-10), 3.22 (3H, s, –NMe), 3.44 (1H, q, J=7.6 Hz, H-3), 6.83 (1H, d, J=7.5 Hz, H-8), 7.06 (1H, dt, J=7.5 and 0.9 Hz, H-6), 7.24 (1H, d, J=7.5 Hz, H-5), 7.28 (1H, t, J=7.5 Hz, H-7). δ_C (100 MHz): 15.3 (C-10), 26.1 (C-3), 40.5 (–NMe), 107.9 (C-8), 122.4 and 123.4 (C-5, C-6), 127.8 (C-7), 130.7 (C-4), 144.0 (C-9), 178.7 (C-2). Found $[M]^+$ m/z 161.0855. $C_{10}H_{11}NO$ requires 161.0841. LRMS m/z (rel. int.) 161 $[M]^+$ (100), 146 (54), 132 (23), 118 (79), 91 (19), 77 (16). Elution with pet. ether/EtOAc (1:1) gave 3-hydroxy-1,3-dimethyl-1,3-dihydroindol-2-one (**30**),[14] (3 mg, 9%) as a white powder: mp 140–142°C (pet. ether/EtOAc) (Lit.[14] 148–149°C). δ_H (400 MHz): 1.61 (3H, s, H-10), 2.67 (1H, br s, –OH), 3.21 (3H, s, –NMe), 6.86 (1H, d, J=7.5 Hz, H-8), 7.12 (1H, dt, J=7.5 and 0.9 Hz, H-6), 7.34 (1H, dt, J=7.5 and 0.9 Hz, H-5), 7.42 (1H, dd, J=7.5 and 0.9 Hz, H-7). δ_C (100 MHz): 24.8 (C-10), 26.2 (–NMe), 73.6 (C-3), 108.5 (C-8), 123.2 and 123.4 (C-5, C-6), 129.7 (C-7), 131.3 (C-4), 142.9 (C-9), 178.4 (C-2). Found $[M]^+$ m/z 178.0770.

$C_{10}H_{11}NO_2$ requires 177.0900. LRMS *m/z* (rel. int.) 177 $[M]^+$ (100), 162 (55), 160 (22), 149 (28), 134 (84), 132 (27), 116 (10), 106 (13), 91 (9).

From *methyl 1-H-indol-3-yl-acetate* (**7**) (36 mg, 0.19 mmol), eluting with pet. ether/EtOAc (6:4), methyl ester of 2-oxo-2,3-dihydro-1H-indol-3-yl-acetic acid (**29**)[15] was obtained (23 mg, 59%). δ_H (400 MHz): 2.82 (1H, dd, *J*=17.0 and 8.1 Hz, H-10), 3.07 (1H, dd, *J*=17.0 and 4.5 Hz, H-10), 3.68 (3H, s, –OMe), 3.80 (1H, dd, *J*=8.1 and 4.5 Hz, H-3), 6.86 (1H, d, *J*=7.5 Hz, H-8), 7.00 (1H, t, *J*=7.5 Hz, H-6), 7.19–7.24 (2H, m, H-5 and H-7), 7.86 (1H, br s, –NH). Found $[M]^+$ at *m/z* 205.0719. $C_{11}H_{11}NO_3$ requires 205.0739. LRMS *m/z* (rel. int.) 205 $[M]^+$ (45), 174 (8), 173 (11), 146 (41), 145 (100), 132 (12), 128 (13), 117 (37), 90 (8).

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