Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Selective cleavage of the Cα-Cβ linkage in lignin model compounds via Baeyer-Villiger oxidation

Nikhil D. Patil,[a] Soledad G. Yao,[a] Mark S. Meier,*[,a] Justin K. Mobley[a,b] and Mark Crocker[a,b]

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Lignin is an amorphous aromatic polymer derived from plants and is a potential source of fuels and bulk chemicals. Herein, we present a survey of reagents for selective stepwise oxidation of lignin model compounds. Specifically, we have targeted the oxidative cleavage of Cα-Cβ bonds as a means to depolymerize lignin and obtain useful aromatic compounds. In this work, we prepared several lignin model compounds that possess structures, characteristic reactivity, and linkages closely related to the parent lignin polymer. We observed that selective oxidation of benzylic hydroxyl groups, followed by Baeyer-Villiger oxidation of the resulting ketones, successfully cleaves the Cα-Cβ linkage in these model compounds.

Introduction

Lignin is a complex and irregular polymer synthesized from three different monomers (coniferyl, sinapyl, and p-hydroxycinnamyl alcohols) via the phenylpropanoid pathway.[1] A method for breaking apart some of the common linkages would be an extremely important step toward converting lignin from a solid polymer into small molecules that can be processed into fuels or utilized as platform chemicals.[2] Of particular interest to us is an oxidative route because there are a number of sites on the lignin polymer that should be possible to target with oxidizing agents, specifically benzylic C-H and C-OH bonds. Although an oxidative approach to lignin depolymerization comes at the cost of some of lignin's fuel potential, we believe that cutting a small percentage of the linkages can produce new materials that are much more amenable to processing than is raw lignin itself.

Recently, several articles have reported studies of the oxidation of lignin model compounds. Very recently, Toste's group reported the catalytic cleavage of C-O bonds using vanadium-oxo complexes.[3] Hanson, Baker and co-workers studied C-O and C-C bond cleavage using vanadium and copper catalysts.[4,5] Claudia and *et al.* reported the use of a lignin peroxidase biomimetic catalyst in oxidative degradation of lignin model compounds.[6] Bozell and group reported Co-Schiff base-catalyzed oxidative cleavage of monomeric and dimeric lignin models.[7] Of particular note is recent work by Stahl and co-workers, who were the first to report the use of TEMPO and TEMPO derivatives as catalysts for the oxidation of alcohol moieties in lignin models and in the native lignin polymer.[8-10]

In the current work, we aimed to perform selective oxidations of lignin model compounds under mild and practical conditions. The study of the chemistry of lignin model compounds is significantly simpler than is the study of lignin chemistry itself, and model studies enable the careful characterization of products so that issues of selectivity can be addressed. In this study we investigated the hydroxylation of benzylic methylene groups using an iron porphyrin catalyst, and the aerobic catalytic oxidation of benzylic hydroxyl groups using DDQ and TEMPO-based catalytic systems. We also demonstrate Cα-Cβ bond cleavage through Baeyer-Villiger oxidation using H_2O_2/HCO_2H.

Results and Discussion

Synthesis of Lignin Model Compounds. Commonly occurring linkages between monomer units in lignin are β-O-4, 5-5, β-5, 4-O-5, β-1, and β-β, of which the β-O-4 linkage is the most common in most types of lignin[2,11] and can remain important even after Kraft processing[12] or thermal processing in ionic liquids.[13] Six different lignin model compounds were prepared, each with the β-phenethyl phenyl ether structure that is characteristic of the β-O-4 linkage. (For details of the synthesis of the model compounds, see the Supporting Information). Given that different substituent groups are attached to the basic β-phenethyl linkage, each of these molecules has distinct reactivity towards oxidants. Compounds **1**, **2**, **3**, and **5** do not have free phenolic -OH groups, while **4** and **6** are phenols (Figure 1). A short hydrocarbon chain, located distant from other functional groups, provides a useful measure of the selectivity of the various oxidation reactions.[14,15]

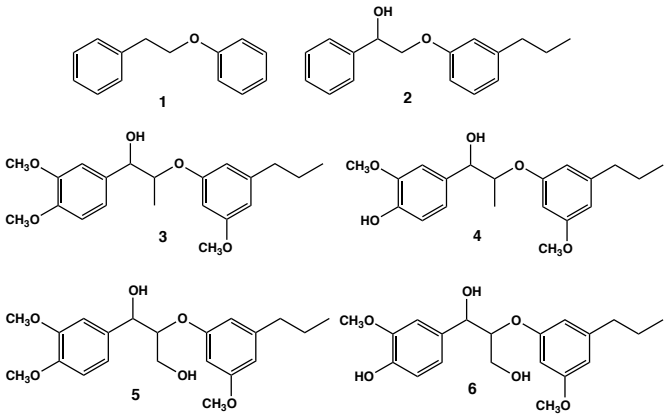
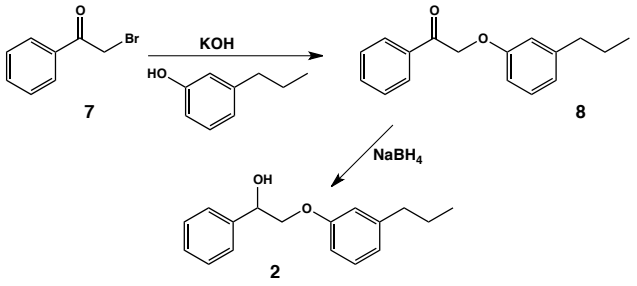


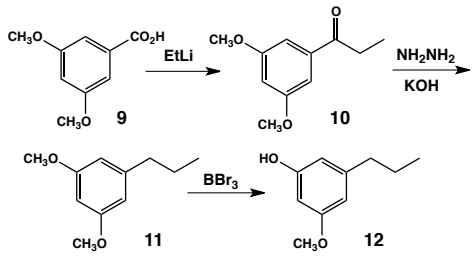
Figure 1. Lignin model compounds used in this work.

Phenethyl phenyl ether (**1**) was prepared by alkylation of phenol with phenethyl bromide.[16] Alcohol **2** was prepared by alkylation of 3-propylphenol with bromoacetophenone (**7**) to produce ketone **8**, followed by reduction with $NaBH_4$ (Scheme 1).



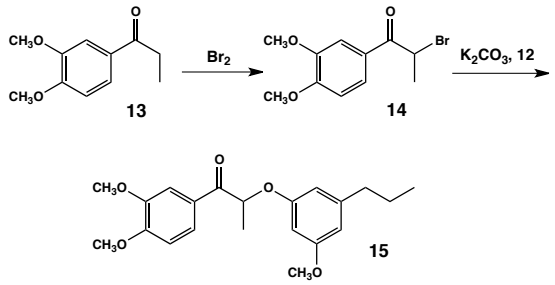
Scheme 1. Preparation of **2**.

Preparation of **3** – **6** required the preparation of 3-methoxy-5-propyl phenol (**12**),[17,18] which was accomplished in three steps from 3,5-dimethoxybenzoic acid (**9**, Scheme 2).



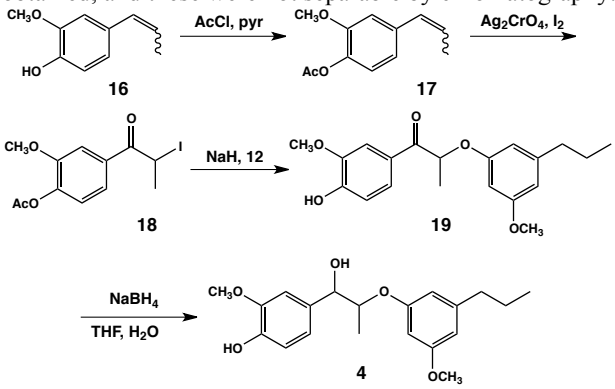
Scheme 2. Preparation of phenol **12**.

Using phenol **12**, the remaining model compounds were prepared from the corresponding phenacyl bromides. For **3**, this process started by bromination of 3,4-dimethoxy-propiophenone (**13**),[19] followed by reaction with phenol **12** to produce ketone **15**, which was reduced with $NaBH_4$ to produce **3** (Scheme 3) as an inseparable pair of diastereomers.



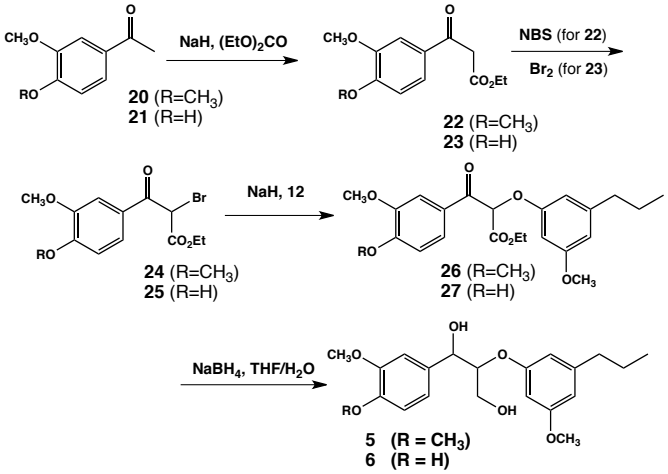
Scheme 3. Preparation of **15**.

Model compound **4** was prepared from commercially-available phenol **16**. After protection of the phenolic hydroxyl,[20] oxidative iodination[21] produced keto iodide **18**, which was converted to **19** and then to **4** under standard conditions (Scheme 4). As expected, a mixture of diastereomers of **4** was obtained, and these were not separable by chromatography.



Scheme 4. Preparation of **19** and **4**.

Model compounds **5** and **6** were prepared from the appropriate acetophenones (**20** and **21**, respectively). These were converted to the β-ketoesters[22] and then subjected to simple bromination,[23] after which they were alkylated with **12** to give phenyl ethers, and simultaneous reduction of the ketone and ester carbonyls was achieved using $NaBH_4$ in THF/H_2O,[24] producing **5** (R = CH_3) and **6** (R = H). Each was produced as mixtures of diastereomers that did not separate by chromatography (Scheme 5).



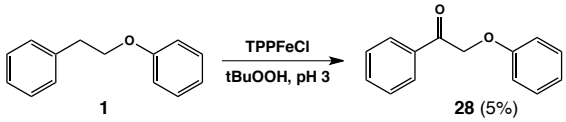
Scheme 5. Preparation of **5** and **6**.

Oxidation of benzylic methylene groups in 1 - 6 by TPPFeCl/tBuOOH. Kirk et al. have performed pioneering

work on the biodegradation of lignin.[25] According to their studies, in the presence of H_2O_2 an extracellular enzyme from white rot fungus, *Phanerochaete chrysosporium*, is accountable for natural biodegradation of lignin.[26] In 1984, oxidases from ligninolytic cultures of *Phanerochaete chrysosporium* were isolated and identified as iron porphyrins and Mn^{+2}-dependent peroxidase.[27,28] The selective catalytic hydroxylation of benzylic methylene groups by lignin-degrading enzymes and by an iron tetraphenylporphyrin (TPP) chloride/tert-butylhydroperoxide (tBuOOH) system has been reported in the literature.[29,30] Accordingly, we investigated the use of the TPPFeCl/tBuOOH system for catalytic hydroxylation of benzylic methylene groups in lignin model compounds. The oxidation of benzylic C-H and C-OH groups in compounds **1** - **6** was carried out by treating 50 mg of each compound with TPPFeCl (0.01 eq) and 70% aq soln of t-BuOOH (1 eq) in the presence of 0.5 ml CH_3CN and 1.5 ml 0.1N pH 3 phosphate buffer at 25 °C for 14 h.[31] As these reactions are heterogeneous, we investigated the effect of different proportions of CH_3CN to pH 3 aqueous phosphate buffer and found that the conversion of **2** was highest in 0.5:1.5 CH_3CN:pH 3 phosphate buffer.

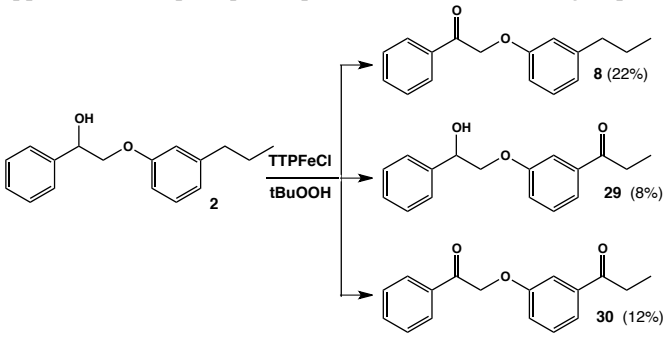
These conditions were used in all of the oxidations in Table 1. We also investigated the effect of several different phase transfer catalysts, but the reaction conversion was unchanged. We also observed that the conversion was significantly reduced when the CH_3CN/phosphate buffer liquid phase was replaced by CH_2Cl_2.

We find that the bulk of the products of these reactions result from either the oxidation of benzylic hydroxyls or the oxidation of benzylic C-H bonds. With the simplest, least functionalized model (**1**), the reaction produced a small amount of benzylic oxidation to produce **28** (5% yield). Most of the starting material **1** (89%) was recovered (Scheme 6).



Scheme 6. Oxidation of **1** with TPPFeCl/tBuOOH.

With more highly functionalized models (**2**, **3**, and **5**), oxidation occurs at several locations. In these compounds, oxidation took place not only at the benzylic C-OH site, but also at the benzylic -CH_2- site (Scheme 7). Key to identification of the benzylic -CH_2- oxidized products (Table 1, line 2) was the change in the ^{1}H NMR spectrum, particularly the disappearance of the downfield triplet of the benzylic -CH_2- groups and the appearance of triplet-quartet patterns due to –CH_2CH_3 groups.

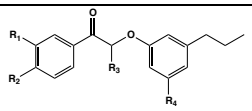
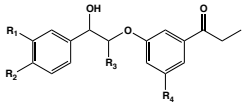
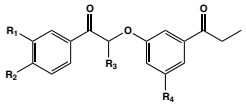


Scheme 7. Oxidation of **2** with TPPFeCl/tBuOOH.

A third oxidation product was obtained and ^{1}H NMR data is consistent with the formation of diketone **30**. In oxidations of **3** and **5**, only small amounts of doubly oxidized material were obtained (observed by GC-MS), and based on the parallel with the oxidation of **2** we believe these compounds are diketones **32** and **35**, respectively.

Compounds **2**, **3**, and **5** are more electron-rich than is **1**, and this feature probably contributes to their increased rate of oxidation relative to **1**. It is also evident that the reaction proceeds at a somewhat higher rate at the benzylic C-OH sites than it does at the benzylic –CH_2- sites, although the differences are not large enough for there to be complete selectivity for the benzylic C-OH. We do not observe oxidative cleavage of the C_α-C_β bond in these model compounds under these conditions.[32]

Table 1: Oxidation of **2**, **3**, and **5** with TPPFeCl/tBuOOH.

	Product[a]	Starting material		
		2[b]	**3**	**5**
1		**8** 24% (49%)	**15** 26% (64%)	**33** 33% (48%)
2		**29** 7%	**31** 2%	**34** 12%
3		**30** 13%	**32** 5%	**35** 3%

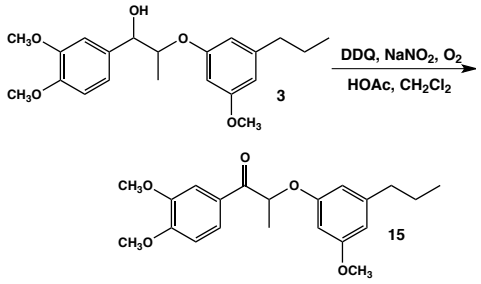
[a] All reactions were carried out for 14 hours.
[b] Yields are for purified, isolated products. Recovered starting material is given in parentheses.
8, **29**, and **30**: $R_{1\text{-}4}$ = H
15, **31**, and **32**: $R_{1,2,4}$ =OCH_3, R_3=CH_3
33-35: $R_{1,2,4}$ =OCH_3, R_3=CH_2OH

Attempts at oxidation of phenols **4** and **6** using this system were not successful. The starting materials were converted to insoluble, chromatographically immobile products, presumably due to polymerization through phenolic oxidative coupling.[33] Oxidation by iron porphyrin complexes and peroxides can proceed via H-atom abstraction,[34] which produces a radical species that can result in oxidative coupling[35] or other processes.[36] These undesired side reactions could be a serious complication when this method is applied to lignin itself, due to the high frequency of unmodified phenolic hydroxyls present in lignin.

Selective oxidation of benzylic hydroxyl groups

Given the undesired reaction at benzylic –CH_2- groups, we turned our attention to oxidation catalysts appropriate to selective oxidation of benzylic hydroxyl groups. Oxidation processes that employ dioxygen are highly desirable because O_2 is inexpensive and no persistent, toxic byproducts are produced from the oxidizing agent itself. Several established oxidation processes promise selective oxidation of benzylic alcohols to ketones but many also have drawbacks, such as the requirement for high-pressure conditions or the use of expensive transition metal catalysts.[37,38] Therefore we screened a set of catalyst systems that should be selective and that operate under mild reaction conditions.

Oxidation by DDQ. In 2012, Wang et al. published a method for the selective oxidation of benzylic hydroxyl groups using $DDQ/NaNO_2/O_2$.[39] This reaction is catalytic in DDQ and $NaNO_2$, and consumes O_2 as the ultimate oxidant. Oxidations of **1** - **6** were carried out by treating 50 mg of each lignin model compound with DDQ (0.01 eq) and $NaNO_2$ (0.1 eq) in 9:1 CH_2Cl_2/acetic acid, under an O_2 atmosphere (1 atm) at 25 °C for 19 h. In the reaction of **3**, oxidation of the benzylic hydroxyl took place, producing **15** (Scheme 8).

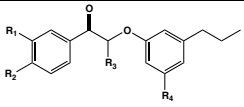
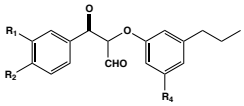


Scheme 8. DDQ oxidation of **3**.

Under these reaction conditions, there was no apparent oxidation of **1** or **2** and only starting material was recovered. In general, when DDQ is added to the substrate, the solution turns blue due to formation of a charge transfer complex between the substrate and DDQ.[40,41] We found that when DDQ was added to solutions of **1** or **2**, the color did not develop, suggesting that these compounds are not sufficiently electron rich to react under these conditions.

The reactions of **3** – **6** with $DDQ/NaNO_2/O_2$ are summarized in Table 2. Unlike the results with $TPPFeCl/H_2O_2$, we do not observe products in which the benzylic $–CH_2-$ is oxidized, although in the GC-MS analysis of the reaction of **6** we found a small amount of doubly oxidized material, and we believe it is most likely aldehyde **37** (Table 2, line 2) resulting from γ-oxidation.

Table 2: Oxidation of **1** – **6** with $DDQ/NaNO_2/O_2$.

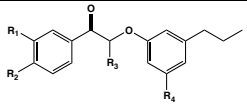
	Product[a]	Starting material			
		3[b]	**4**	**5**	**6**
1		**15** 21% (71%)	**19** 28% (48%)	**33** 28% (62%)	**36** 31% (46%)
2		0%	0%	0%	**37** (trace)

[a] Reactions were carried out for 19 hours using 0.01eq DDQ and 0.1eq $NaNO_2$.
[b] Yields are for purified, isolated products. Recovered starting material is given in parentheses.
3 and **15**: $R_1,R_2,R_4 = OCH_3$, $R_3=CH_3$
4 and **19**: $R_1,R_4=OCH_3$, $R_2=OH$, $R_4=CH_3$
5 and **33**: $R_1,R_2,R_4 = OCH_3$, $R_3=CH_2OH$
6 and **36**: $R_1,R_4=OCH_3$, $R_2=OH$, $R_4=CH_2OH$
37: $R_1, R_4 = OCH_3$, $R_2=OH$

We found that with compounds **3** - **6**, this oxidation process works well but the rate of the reaction was low, with the yields being typically 21% to 33% after 19 h. When the amount of catalyst was increased from 0.01 to 0.1 equivalent, the yield rose to 40-60% after 19 h of reaction time; however, the overall mass balance decreased, consistent with the formation of low molecular weight, water-soluble compounds or chromatographically immobile material. It is important to note that under these conditions, model compounds with unprotected phenolic hydroxyls did not suffer complete polymerization. Oxidation by DDQ is believed to proceed either by hydride transfer or by a rapid series of electron-proton-electron transfer steps where a radical cation intermediate is relatively short-lived,[42] and this may serve to reduce the amount of phenolic oxidative coupling and other side reactions.

Oxidation by TEMPO/$NaNO_2$. TEMPO (2,2,6,6-tetramethyl-piperidin-1-oxy) is a commercially available stable nitroxyl radical which can be used in the conversion of alcohols to the corresponding aldehydes or ketones.[43] We initially focused on the oxidation of **1** - **6** using two different TEMPO-based systems that were developed by Hu and coworkers.[44,45] However, in reactions using $TEMPO/Br_2/NaNO_2$, bromination of the highly electron-rich aromatic ring occurred. The same result occurred using a TEMPO/1,3-dibromo-5,5-dimethyl-hydantoin/$NaNO_2$ system. We also investigated the TEMPO/CAN oxidation system developed by Kim and Jung,[46] however the conversion was quite low. Better results were obtained using an aerobic oxidation system that was published in 2008 by Liang et al.,[47] which uses TEMPO, $NaNO_2$, HCl and NaCl. These reactions (Table 3) were carried by treating 50 mg of **1** - **6** with TEMPO (0.15 eq), $NaNO_2$ (0.25 eq), 36% aq HCl (0.5 eq), NaCl (0.5 eq) and 0.3 mL CH_2Cl_2 under an O_2 atmosphere.[15]

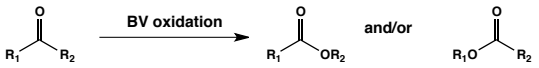
Table 3: Oxidation of **2** – **6** using $TEMPO/NaNO_2/NaCl/O_2$

Product[a]	Starting material				
	2[b]	**3**	**4**	**5**	**6**
	**8** 97% (0%)	**15** 75% (0%)	**19** 0% (0%)	**33** 84% (0%)	**36** 0% (0%)

[a] Reactions were carried out for 19 hours using 0.15eq TEMPO and 0.25eq $NaNO_2$.
[b] Yields are for purified, isolated products. Recovered starting material is given in parentheses.
2 and **8**: $R_{1-4} = H$
3 and **15**: $R_1,R_2,R_4 = OCH_3$, $R_3=CH_3$
4 and **19**: $R_1,R_4=OCH_3$, $R_2=OH$, $R_4=CH_3$
5 and **33**: $R_1,R_2,R_4 = OCH_3$, $R_3=CH_2OH$
6 and **36**: $R_1,R_4=OCH_3$, $R_2=OH$, $R_4=CH_2OH$

This TEMPO-based oxidation system efficiently oxidized benzylic alcohol groups, consistent with the literature.[8] No reaction was observed with **1**, although encouraging results were obtained for compounds **2**, **3** and **5** under these conditions. We found that **4** and **6**, compounds that contain free phenolic hydroxyl groups, were converted into insoluble products (presumably polymeric material). This result suggests the need to protect the phenolic hydroxyl groups in these compounds prior to performing benzylic alcohol oxidations using this oxidation system.

Baeyer-Villiger Oxidation.
Baeyer-Villiger (BV) oxidation (Scheme 9) is a widely-used method for converting ketones into their corresponding esters. In the context of lignin depolymerization, the conversion of benzylic ketones into esters produces a hydrolysable bond that could enable facile cleavage of linkages between lignol monomers. Notably, phenyl groups with electron donating substituents have higher aptitudes for migration to oxygen than do non-substituted phenyl groups or phenyl groups bearing electron accepting substituents.[48]

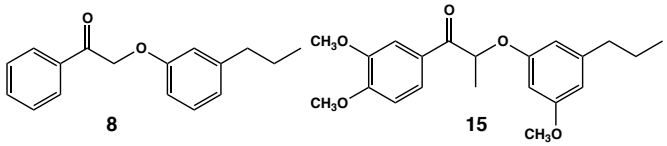


Scheme 9. Baeyer-Villiger Oxidation.

The most commonly used oxidants for BV oxidations are *m*-chloroperbenzoic acid (*m*-CPBA), trifluoroperacetic acid (TFPAA), peroxybenzoic acid and hydrogen peroxide (H_2O_2).[49] While peroxy acids are typically more effective BV oxidants than is H_2O_2 alone, they also generate an equivalent amount of carboxylic acid waste. H_2O_2 on the other hand is an extremely clean oxidant and aqueous H_2O_2 is relatively inexpensive. In addition, after BV oxidation the initial ester can be hydrolyzed to produce the corresponding carboxylic acid and alcohol/phenol, either in situ or as a separate step. However, H_2O_2 is the mildest of the aforementioned oxidants;[49] hence, to increase the oxidant power, the use of a Brønsted or Lewis acid/base catalyst is generally required.[50]

In this study, we used a mixture of formic acid and 30% aqueous H_2O_2 which generates formic peracid in-situ.[51] In order to standardize our reaction conditions, we first studied the oxidation of 4-methyl acetophenone as a simple ketone. We determined that 8 equivalents of both formic acid and H_2O_2 gave the maximum conversion. According to the literature, this reaction proceeds via a concerted non-ionic pathway, which is least energetic in less-polar solvents such as 1,2-dichloroethane.[52] The formic peracid reacts with the ketone to produce the corresponding ester, H_2O_2 functioning as an oxidant, whereas the formic acid acts as a Brønsted catalyst.[51]

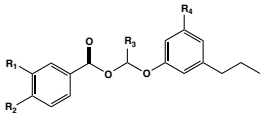
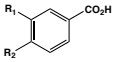
BV oxidations were carried out using **8** and **15** as substrates. Ketones **8** and **15** were prepared in the syntheses of **2** and **3** respectively.



Scheme 10. Ketones derived from lignin models **2**, **3**.

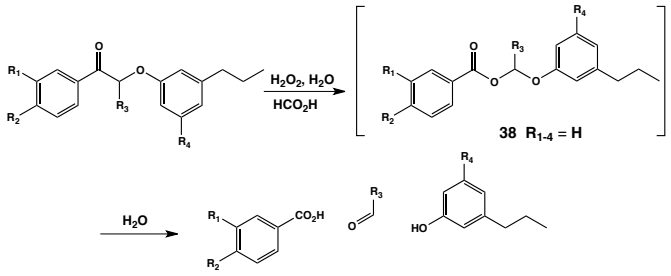
The BV reactions were carried out by treating 50 mg of each substrate with 30% H_2O_2 (8 eq), HCOOH (8 eq) and 1,2-dichloroethane (4 eq) at 50 °C for 24 h. The products obtained are shown in Table 4.

Table 4: Baeyer-Villiger Oxidation of **8**, and **15**

	Product	Starting material	
		8[a]	**15**
1		**38** 10% (90%)	0% (0%)
2		0%	78%

[a] Yields are for purified, isolated products. Recovered starting material is given in parentheses.
8 and **38**: $R_{1\text{-}4}$ = H
15: R_1,R_2,R_4 = OCH_3, R_3=CH_3

From these products, it appears that under these conditions the BV oxidation proceeds via migration of the alkyl group, in the manner shown in Scheme 11, below.



Scheme 11: Baeyer-Villiger Oxidation of **8** and **15**.

In the case of the least electron-rich substrate (**8**), ester **38** was sufficiently stable to be isolated and identified by ^{1}H NMR and MS, with the strongly downfield resonance at 6.0 (s, 2H, -O-CH_2-O-) being key to the structural assignment. In the reaction of **15**, it appears that the ester underwent hydrolysis *in situ* to produce the component benzoic acid, aldehyde, and phenol. In this case, the benzoic acid was isolated but the aldehyde fragment and the phenol fragment were not found, and we suspect that the facile oxidation of these compounds under the reaction conditions probably precludes their isolation – the (volatile) aldehydes likely oxidize to water-soluble carboxylic acids and the phenols likely suffer oxidative polymerization under these conditions.

Conclusions

In this study, we have demonstrated that an iron porphyrin catalyst selectively oxidized benzylic C-H and C-OH groups in non-phenolic lignin model compounds. Phenolic compounds **4** and **6** are lost under these conditions, most likely to insoluble polymeric products. The DDQ/$NaNO_2$ aerobic oxidation system effectively oxidized benzylic hydroxyl groups in these model compounds without affecting unfunctionalized benzylic -CH_2- groups, and compounds with unprotected phenolic hydroxyl groups were not lost to polymerization. The TEMPO/$NaNO_2$ oxidations gave an exceptionally high yield in most cases, although like the TPPFeCl/H_2O_2 approach, this method is not compatible with unprotected phenolic hydroxyls. Finally, we found that Baeyer-Villiger oxidation successfully cleaves the Cα-Cβ linkage in the oxidized lignin model compounds.

This two-step approach may be applicable to the depolymerization of lignin, although these oxidative methods are not fully compatible with unprotected phenolic hydroxyls. Future work will focus on the investigation of catalysts for two-electron oxidation of benzylic hydroxyl groups in hopes of minimizing phenolic oxidative coupling and the resulting cross-linking of phenols.

Experimental Section

Anhydrous solvents were purchased from commercial sources and dispensed with syringe techniques. Column chromatography was performed using silica gel-60 (Supelco) and preparative TLC was carried out with 1mm plates (Merck).

Synthetic procedures for key compounds are given below, and the remaining are available in the Supporting Information.

Preparation of **2**. Sodium borohydride (0.298 g, 7.85 mmol) was added to a solution of **8** (4.0 g, 15.7 mmol) in ethanol (80 mL).[53] The reaction mixture was stirred for 3 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl (30 mL) and concentrated under vacuum. The residue was diluted with water (150 mL) and extracted with CH_2Cl_2 (3 × 70 mL). The organic layer was washed with water and then evaporated to dryness. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:9) to yield **2** 3.75 g, 14.7 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 5H), δ 7.2 (t, J= 8.02 Hz, 1H), δ 6.7 (m, 3H), δ 5.14-5.12 (t, J= 2.74 Hz, 1H), δ 4.12 (dd, J= 3.13 Hz, 1H), δ 4.01 (t, J= 9.38 Hz, 1H), δ2.56 (t, J= 7.43 Hz, 2H), δ 1.64 (tq, J=14.86, 7.43 Hz, 2H), δ 0.94 (t, J= 7.43, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.6, 144.7, 139.9, 129.4, 128.8, 128.4, 126.5, 121.8, 115.1, 111.9, 73.5, 72.8, 38.3, 24.6, 14.0. GC-MS *m/z* (relative intensity): 256 (M^+, 18), 238 (10), 150 (70), 136 (52), 122 (29), 107(100), 91 (57), 79 (71), 65 (13), 51 (15). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1536.

Preparation of **8.** 2-Bromoacetophenone (**7**) (5 g, 25.13 mmol) was added to a solution of 3-propylphenol (4.273 g, 31.42 mmol) and potassium carbonate (4.34 g, 31.36 mmol) in acetone (12 mL).[54] The reaction mixture was heated at reflux for 5 h and was then concentrated under vacuum. The residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with 2N NaOH (63 mL) and with water (63 mL), then evaporated to dryness. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:7) to yield **8** (4.61 g, 18.15 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J=7.82 Hz, 2H), δ 7.61 (t, J=7.43 Hz, 1H), δ 7.49 (t, J=7.63 Hz, 2H), δ 7.20 (t, J=8.12 Hz, 1H), δ 6.83 (d, J=5.87 Hz, 2H), δ 6.77 (d, J=8.38 Hz, 1H), δ 5.24 (s, 2H), δ 2.57 (t, J=7.63 Hz, 2H), δ 1.65 (m, J=14.86 ,7.43 Hz, 2H), δ 0.953 (t, J= 7.43 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) d 194.60, 158.11, 134.66, 133.81, 129.28, 128.82, 128.14, 121.90, 115.33, 111.69, 70.72, 38.04, 24.41, 13.88. GC-MS *m/z* (relative intensity): 254 (M^+, 100), 236 (6), 207 (14), 105 (100), 91 (38), 77 (70), 65 (12), 51(17). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}O_2$ calcd for $C_{17}H_{19}O_2$ 255.1380, found 255.1379.

Preparation of **15.** 3-methoxy-5-propylphenol **12** (1.00 g, 6.05 mmol) and potassium carbonate (0.84 g, 6.05 mmol) were stirred in acetone (18.5 mL). 2-bromo-1-(3,4-dimethoxyphenyl)propan-1-one (1.5 g, 5.5 mmol) was added to the reaction mixture which was then refluxed for 5 h.[55] The reaction mixture was then concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with 2N NaOH and then with water. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:3) to yield **15** quantitatively. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, J=8.4, 1.95, 1H), δ 7.59 (d, J=1.95 Hz, 1H), δ 6.86 (d, J=8.41 Hz, 1H), δ 6.29 (d, J=2.15 Hz, 2H), δ 6.25 (dd, J=2.34, 2.15 Hz, 1H), δ 5.39 (q, J=6.84 Hz, 1H), δ 3.89 (s, 3H), δ 3.85 (s, 3H), δ 3.66 (s, 3H), δ 2.43 (t, J=7.53 Hz, 2H), δ1.67 (d, J=6.84 Hz, 3H), 1.53 (tq, J=7.62, 7.43 Hz, 2H), δ 0.85 (t, J=7.34 Hz, 3H). ^{13}C NMR δ (400 MHz, $CDCl_3$): 197.59, 160.61, 158.47, 153.68, 149.08, 145.25, 127.19, 123.48, 111.11, 110.08, 107.52, 107.24, 98.73, 76.62, 56.05, 55.92, 55.16, 38.23, 24.16, 19.04, 13.75. GC-MS *m/z* (relative intensity): 358 (M^+, 27), 340 (20), 311 (5), 193 (14), 165(100), 151(5.5), 137(5), 121(5.5), 105(2.5), 91 (6), 77(7), 65 (2), 51 (2). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}O_5$ 359.1853, found 359.1855.

Preparation of **3**. Sodium borohydride (0.38 g, 10.06 mmol) was added to a solution of **15** (1.8 g, 5.03 mmol) in THF (13.6 mL) and water (4.5 mL).[24] The reaction mixture was stirred for 4 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and was concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was washed with water and then evaporated to dryness. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:3) to yield **3** (1.66 g, 92%) quantitatively. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 6.95 (m, 2H), δ 6.84 (d, J=8.21 Hz, 1H), δ 6.35 (m, 3H), δ 4.94 (d, 3.52 Hz, 0.25H), δ 4.62 (d, 7.43 Hz, 0.75H), δ 4.5 (qd, J=6.26, 3.91 Hz, 0.25H), 4.34 (qd, J=12. 12, 6.26 Hz, 0.75 H), δ 3.85 (d, 3H), δ 3.84 (d, 3H), δ 3.74 (d, 3H), δ 3.13 (s, 1H), 2.51 (m, 2H), δ 1.625(m, 2H), δ 1.2 (d, 6.25 Hz, 0.75H), δ 1.11 (d, 5.87 Hz, 2.25H), δ 0.94 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 160.82, 160.8, 158.8, 158.6, 149.1, 149.03, 149.0, 148.5, 145.4, 145.3, 133.0, 132.6, 120.0, 118.7, 111.0, 110.2, 109.7, 108.80, 108.77, 107.2, 107.1, 100.0, 99.9, 78.9, 78.0, 77.9, 75.0, 56.0, 55.3, 38.4, 24.5, 24.4, 16.0, 14.0, 13.3. GC-MS *m/z* (relative intensity): Major diastereomer: 360 (M^+, 3), 342 (100), 327 (20), 313(10), 299(20), 284(10), 268(6), 253(6), 239(5), 225(5), 207(13), 194 (68), 178(36), 167(94), 150(36), 139(40), 121(13), 115(17), 107(17), 91 (28), 77(23), 65 (11), 51 (9). Minor diastereomer: 360 (M^+, 1), 342 (63), 327 (14), 313(8), 299(16), 284(8), 268(6), 253(6), 239(5), 225(5), 207(23), 194 (77), 178(32), 167(100), 150(27), 139(40), 121(13), 115(14), 107(17), 91 (32), 77(23), 65 (11), 51 (9). HRMS ESI *m/z* $[M+H-H_2O]^+$ calcd for $C_{21}H_{27}O_4$ 343.1904, found 343.1906.

Preparation of **18**. Iodine (2.85 g, 11.2 mmol), silver chromate (2.74 g, 8.28 mmol), 4 Å molecular sieves (1.3 g) and pyridine (0.3 g, 2.3 mmol) were stirred in dichloromethane (35 mL) at 0 °C for 10 min.[21] 2-methoxy-4-prop-1-enyl)phenyl acetate[20] (1.54g, 7.47 mmol) was dissolved in dichloromethane (10 mL) and was slowly added to above reaction mixture. The reaction mixture was stirred at 0 °C for 20 min and then at room temperature for 1 h. The reaction mixture was then filtered. The filtrate was washed successively with 5% sodium thiosulfate, saturated NaCl, and twice with water. The filtrate was dried over $MgSO_4$ and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (hexane:CH_2Cl_2 1:2) to yield 4-(2-iodopropanoyl)-2-methoxyphenyl acetate (0.814 g, 2.27 mmol, 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J=1.95 Hz, 1H), δ 7.6 (dd, J=8.21, 1.96 Hz, 1H), δ 7.12 (d, 8.21 Hz, 1H), δ 5.46 (q, J= 6.65 Hz, 1H), δ 3.9 (s, 3H), δ 2.34 (s, 3H), δ 2.1 (d, J=6.65 Hz, 3H). (400 MHz, $CDCl_3$): 193.64, 168.38, 151.58, 144.10, 132.29, 122.82, 121.66, 56.07, 22.10, 20.64, 17.66. GC-MS *m/z* (relative intensity): 348 (M^+, 2), 306 (55), 180 (4), 151 (100), 119(7.5), 108(3), 91(9), 79(5), 65(2), 51(5).

Preparation of **19**. 60 % NaH (dispersion in mineral oil) (0.12 g, 3 mmol), freshly prepared **18** (0.416 g, 1.2 mmol) and **12** (0.208 g, 1.25 mmol) were placed in 3 individual one-neck round bottom flasks. The flasks were degassed with N_2 for 15 minutes. THF (7.2 mL) and DMF (2.5 mL) were added to the individual flasks. The solution of NaH in THF/DMF was

cooled to 0 °C, after which the solution of 3-methoxy-5-propylphenol was added. The mixture was stirred at room temperature for 1 h, then cooled to 0 °C again. The solution of **18** was added and the resulting mixture was stirred at room temperature for 3 h. The reaction was poured onto 100 ml ice water. The resulting aqueous layer was extracted with EtOAc (50 mL). The EtOAc extract was washed with water, dried ($MgSO_4$), and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:3) to yield **19** (0.164 g, 0.477 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J_1=8.44, J_2=2.04 Hz, 1H), δ 7.594 (d, J=2.06 Hz, 1H), δ 6.92 (d, J=8.18 Hz, 1H), δ 6.31-6.23 Hz (m, 3H), δ 5.38 (q, J=6.84 Hz, 1H), δ 3.90 (s, 3H), δ 3.69 (s, 3H), δ 2.44 (t, J=7.71 Hz, 2H), δ 1.66 (d, J=6.72 Hz, 3H) δ 1.59-1.49 (m, 2H), δ 0.86 (t, J=7.40 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 197.42, 160.55, 158.41, 150.76, 146.62, 145.16, 126.89, 124.01, 113.88, 110.78, 107.48, 107.21, 98.66, 55.96, 55.09, 38.16, 29.61, 24.08, 19.01, 13.67. GC-MS *m/z* (relative intensity): 344(M^+,34), 326(7), 193(37), 151(100), 138(4), 123(8), 108(4), 91(9), 77(5), 65(3), 52(2). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}O_5$ 345.1697, found 345.1697.

Preparation of **4**. Following a procedure by Baciocchi et al.,[24] **19** (0.5 g, 1.45 mmol) was stirred in THF (6.8 mL) and water (3.4 mL) at room temperature. Sodium borohydride (28 mg, 0.73 mmol) was added over 3 h and the solution was further stirred for 1 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl (3.6 mL) and concentrated under vacuum. The residue was diluted with water (70 mL) and extracted with EtOAc (3 × 35 mL). The residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:3) to yield **4** (0.415 g, 1.2 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 6.98 (dd, 1H), 6.88 (m, 2H), δ 6.36 (m, 3H), δ 5.64 (d, 1H), δ 4.96 (t, 0.25H), δ 4.61 (dd, 0.75H), δ 4.5 (m, 0.25H), δ 4.36 (m, 0.75H), δ 3.91 (d, 3H), δ 3.77 (d, 3H), δ 3.06 (s, 1H), δ 2.53 (m, 2H), δ 1.62 (m, 2H), δ 1.19 (d, 0.75H), δ 1.12 (d, 2.25H), δ 0.95 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 160.91, 160.89, 158.8, 158.6, 146.8, 145.8, 145.5, 145.5, 145.2, 132.3, 131.9, 120.8, 119.5, 114.4, 114.3, 109.6, 109.1, 108.91, 108.86, 107.4, 107.3, 100.07, 100.0, 79.1, 78.2, 78.1, 75.2, 56.2, 55.5, 38.5, 24.54, 24.52, 16.06, 14.05, 13.3. GC-MS *m/z* (relative intensity): major diastereomer: 346 (M^+, 3.5), 328 (100), 313 (15), 229(12), 285(15), 270(8), 253(6), 204(10), 194(60), 180(22), 166(32), 153(100), 138(36), 131(8), 121(16), 115(10), 109(10), 103(10), 91(22), 77(18), 65(12), 51(6). Minor diastereomer: 346 (M^+, 0), 328 (100), 313 (15), 229(10), 285(16), 270(9), 253(5), 207(10), 194(41), 180(29), 166(32), 153(78), 138(43), 131(8), 121(16), 115(10), 107(10), 91(19), 77(17), 65(14), 51(8). HRMS ESI *m/z* $[M+H-H_2O]^+$ calcd for $C_{20}H_{25}O_4$ 329.1747, found 329.1747.

Preparation of **26**. Following the method of Tanaka,[56] 60 % NaH (dispersion in mineral oil) (0.28 g, 7 mmol), **24**[23] (2.3 g, 7 mmol) and **12** (1.16 g, 7 mmol) were placed in 3 individual one-neck round bottom flasks. The flasks were purged with N_2 for 15 min, after which 2 ml THF and 7.6 ml DMF were added to the individual flasks. The solution of NaH in THF/DMF was cooled to 0 °C and the solution of **12** was added. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C again. The solution of **24** was added and the resulting mixture was stirred at room temperature for 8 h. The reaction mixture was then poured onto 100 ml ice water. The resulting aqueous layer was extracted with EtOAc (50 mL). The EtOAc extract was washed with water, dried ($MgSO_4$), and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 3:7) to yield **26** (2.53 g, 0.61 mmol 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J=1.95 Hz, 1H), δ 7.65 (d, J=1.96 Hz, 1H), δ 6.90 (d, J=8.6 Hz, 1H), δ 6.43 (m, 3H), δ 5.83, (s, 1H), δ 4.3 (q, J=7.03 Hz, 2H),), δ 3.91 (s, 3H), δ 3.90 (s, 3H), δ 3.73 (s, 3H), δ 2.51 (t, J=7.04 Hz, 2H), δ 1.60 (tq, J= 7.63 Hz, 2H), δ 1.25 (t, J= 7.24 Hz, 3H), δ 0.92 (t, J= 7.24 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 189.80, 166.85, 160.68, 157.84, 154.19, 149.02, 145.40, 126.91, 124.81, 111.31, 110.14, 108.45, 107.40, 99.01, 81.01, 62.22, 56.03, 55.89, 55.19, 38.16, 24.13, 14.00, 13.69.

Preparation of **27**. 60 % NaH dispersed in mineral oil (0.43 g, 10.8 mmol), ethyl 2-bromo-3-(4-hydroxy-3-methoxyphenyl-3-oxopropanoate (1.37 g, 6.31 mmol) and **12**[18] (1.80 g, 10.8 mmol) were placed in 3 individual one-neck round bottom flasks. The flasks were purged with N_2 for 15 min after which 1.6 ml THF and 5.6 ml DMF were added to each flask. The solution of NaH in THF/DMF was cooled to 0° C and the solution of 3-methoxy-5-propylphenol was added. The mixture was stirred at room temperature for 1 h and then cooled to 0° C again. The ethyl 2-bromo-3-(3,4-dimethoxyphenyl)-3-oxo-propanoate solution was added, and the resulting mixture was stirred at room temperature for 8 h. The mixture was then poured onto 100 ml ice-water. The resulting aqueous layer was extracted with EtOAc (50 mL). The EtOAc extract was washed with water, dried ($MgSO_4$), and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (EtOAc:hexane 3:7) to yield **27** (0.69 g, 27%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (m, 2H), δ 6.95 (m, 1H), δ 6.37 (m, 2H), δ 6.12 (m, 1H), δ 5.7, 5.178 (s, 1H), δ 4.29 (m, 2H), δ 3.94 (d, 3H), δ 3.73 (d, 3H), δ 2.5 (t, 2H), δ 1.58 (m, 2H), δ 0.90 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.81, 166.96, 160.66, 157.84, 151.57, 146.73, 145.42, 126.60, 125.39, 114.21, 114.21, 111.25, 108.50, 107.42, 99.03, 80.88, 62.29, 55.99, 55.21, 38.17, 24.14, 13.99, 13.70.

Preparation of **5**. Following a procedure by Baciocchi et al.,[24] **26** (1.8 g, 4.327 mmol) was stirred in THF (37.5 mL) and H_2O (12.5 mL) at room temperature. Sodium borohydride (1.64 g, 43.27 mmol) was added over 3 h and the solution was further stirred for 24 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl (15 mL) and concentrated under vacuum. The residue was diluted with water (100 mL) and extracted with EtOAc (3 × 50 mL). After removal of solvent under vacuum, the residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:1) to yield **5** (1.11g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$ with one drop of D_2O, mixture of diastereomers): δ 6.94 (m, 2H), δ 6.81 (m, 1H), δ 6.31 (m, 3H), δ 4.97 (m, 1H), δ 4.37-4.15 (m, 1H), δ 3.94-3.92 (m, 2H), δ 3.84 (t, 6H), δ 3.71 (d, 3H), δ 2.47 (m, 2H), δ 1.58 (m, 2H), δ 0.92 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 160.8, 160.7, 159.2, 158.8, 149.2, 149, 148.7, 145.6, 145.4, 133.3, 132.5, 119.4, 118.8, 111.1, 110.1, 109.6, 109.1, 109, 107.8, 107.8, 100.32, 100.26, 82.9, 82, 74.1, 73.7, 61.7, 61.3, 56.01, 55.99, 55.4, 55.3, 38.41, 38.38, 24.44, 24.40, 13.97, 13.96. GC-MS *m/z* (relative intensity): Major diastereomer: 376 (M^+, 0.5), 358(1.5) 328 (10), 192 (100), 167(30), 151(12.5), 139(30), 121(12), 108(8), 91(15), 77(15), 65(7), 51(5.5). Minor diastereomer: 376 (M^+, 0.3), 358(1.1) 328 (7), 210(7), 192 (100), 167(30), 151(11), 139(30), 121(10), 108(8), 91(11), 77(14), 65(7), 51(5.5).

HRMS (ESI) *m/z* $[M+H-H_2O]^+$ calcd for $C_{21}H_{27}O_5$ 359.1853, found 359.1853.

Preparation of **6**. A solution of **27** (1.25 g, 3.11 mmol) in THF (37.5 mL) and H_2O (3.75 mL) was stirred at room temperature. Sodium borohydride (1.18 g, 31.1 mmol) was added over 3 h and the solution was further stirred for 24 h at room temperature. The reaction mixture was treated with a saturated solution of ammonium chloride, after which volatile material was removed under vacuum. The residue was diluted with water (100 mL) and extracted with dichloromethane (3 × 50 mL). After evaporation of the solvent, the residue was subjected to column chromatography on silica gel (EtOAc:hexane 1:1) to produce **6** (0.40 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 6.92 (m, 3H), δ 6.32 (m, 3H), δ 5.79 (s, 1H), δ 4.97 (m, 1H), δ 4.35 (m, 1H), δ 4.11-3.82 (m, 2H), δ 3.85 (d, 3H), δ 3.73 (d, 3H), δ 3.46 (s, 3H), δ 2.48 (m, 2H), δ 1.59 (m, 2H), δ 0.92 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ 160.8, 160.7, 159.2, 158.9, 146.9, 146.8, 145.6, 145.6, 145.4, 145.3, 132.7, 131.9, 119.5, 114.54, 114.5, 109.7, 109.2, 109.1, 109.0, 107.8, 100.34, 100.25, 82.8, 82.0, 74.0, 73.7, 61.6, 61.2, 56.0, 55.4, 55.3, 38.38, 38.35, 24.41, 24.37, 13.94, 13.93. GC-MS *m/z* (relative intensity): Major diastereomer: 362 (M^+, 0.16), 344(1.5) 314 (3.4), 192 (100), 164(32), 153(27.5), 138(18), 121(8), 105(4.5), 93(21), 77(11), 65(15), 51(4). Minor diastereomer: 362 (M^+, 0.2), 344(0.7) 314 (1.4), 192 (100), 164(32), 153(26), 138(18), 121(8), 105(4.5), 93(19), 77(10), 65(13), 51(0.3). HRMS (ESI) *m/z* $[M+H-H_2O]^+$ calcd for $C_{20}H_{25}O_5$ 345.1697, found 345.1696.

TPPFeCl Oxidation of **1**. A mixture of **1** (50 mg, 0.25 mmol), TPPFeCl (1.77 mg, 0.0025 mmol), 70% aq soln of t-BuOOH (0.035 mL, 0.25 mmol), CH_3CN (0.5 mL) and 0.1N pH 3 phosphate buffer (1.5 mL) was stirred at 25ºC for 14 h. The resulting mixture was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative TLC (silica gel, hexane mobile phase) to produce unreacted **1** (44.5 mg, 0.22 mmol, 89%) and **28**[57] (2.7 mg, 0.013 mmol, 5%). **28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.99 (m, 2H), δ 7.64-7.59 (m, 1H), δ 7.53-7.47 (m, 2H), δ 7.32-7.26 (m, 2H), δ 7.01-6.92 (m, 3H), δ 5.271 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 194.55, 158.01, 134.62, 133.85, 129.57, 128.82, 128.15, 121.66, 114.81, 70.82. GC-MS *m/z* (relative intensity): 212 (M^+,29), 194 (3), 165 (2), 105 (100), 91 (7), 77 (40), 65 (6), 51 (11).

TPPFeCl Oxidation of **2.** A mixture of **2** (82.6 mg, 0.0.323 mmol), TPPFeCl (3.05 mg, 0.0033 mmol), 70% aq soln of t-BuOOH (0.044 mL, 0.3227 mmol), CH_3CN (0.8 mL) and 0.1N pH 3 phosphate buffer (2.5 mL) was stirred at 25ºC for 14 h. The resulting mixture was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by silica gel column chromatography (6% EtOAc/hexanes) to produce **2** (40.5 mg, 0.158 mmol, 49%), **8** (19.7 mg, 0.077 mmol, 24%), **29** (6 mg, 0.022 mmol, 7%) and **30** (11 mg, 0.041 mmol, 13%). **29:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.29 (m, 8 H), δ 7.13 (m, 1H), δ 5.19 – 5.09 (m, 1H), δ 4.22 – 4.02 (m, 2H), δ 2.98 (q, J=7.24 Hz, 2H), δ 2.71 (s, 1H), δ 1.21 (t, J=7.23 Hz, 3H). GC-MS m/z (relative intensity): 270 (M^+, 1.6), 241 (4.7), 223 (7), 163 (100), 134 (29.5), 107 (57), 77 (58.5), 57 (22). HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{17}H_{18}O_3$ 270.1256, found 270.1252. **30**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.97 (m, 2H), δ 7.67 – 7.57 (m, 2H), δ 7.55 – 7.48 (m, 3H), δ 7.39 (q, J=7.56 Hz, 1H), δ 7.18 (ddd, J_1=8.23, J_2=2.72, J_3=0.93 Hz, 1H), δ 5.36 (s, 2H), δ 2.98 (q, J=7.23 Hz, 2H), δ 1.21 (t, J=7.21 Hz, 3H). GC-MS *m/z* (relative intensity): 268 (M^+, 12), 239 (8), 165 (3), 133 (3.8), 105 (100), 91 (9), 77 (33), 64 (4), 51 (8). HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{17}H_{16}O_3$ 268.1099, found 268.1096.

TPPFeCl Oxidation of **3**. A mixture of **3** (50 mg, 0.14 mmol), TPPFeCl (0.95 mg, 0.0014 mmol), 70% aq soln of t-BuOOH (0.018 mL, 0.13 mmol), CH_3CN (0.5 mL) and 0.1N pH 3 phosphate buffer (1.5 mL) stirred at 25ºC for 14 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (1:3 EtOAc/hexane) to produce **3** (32 mg, 64%), **15** (12.9 mg, 0.036 mmol, 26%), **31** (0.8 mg, 0.0022 mmol, 2%) and **32** (2.3 mg, 0.0062 mmol, 5%). **31**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.07 (m, 2H), δ 7.00-6.90 (m, 2H), δ 6.84 (dd, J=8.20, 1.31 Hz, 1H), δ 6.70-6.65 (m, 1H), δ 4.64 (d, J=7.44 Hz, 1H), δ 4.50-4.40 (m, 1H), δ 3.89 (s, 3H), δ 3.87 (s, 3H), δ 3.82 (s, 3H), δ 2.94 (q, J=7.03, 1.35 Hz, 2H), δ 1.19 (t, J=7.24 Hz, 3H), δ 1.12 (dd, J_1=6.32 Hz, J_2=1.26 Hz, 3H). GC-MS *m/z* (relative intensity): 374 (M^+, 4), 356 (4), 284 (1), 208 (13), 193 (14), 179 (6), 167 (100), 151 (20), 139 (33), 124 (9), 108 (9), 91 (7.5), 77 (10), 57 (16). **32**: GC-MS *m/z* (relative intensity): 372 (M^+, 6.5), 281 (5), 207 (17), 165 (100), 151 (4), 135 (6.5), 91 (6), 77 (10), 57 (9).

TPPFeCl Oxidation of **4**. A mixture of **4** (42 mg, 0.12 mmol), TPPFeCl (0.85 mg, 0.0012 mmol), 70% aq soln of t-BuOOH (0.017 mL, 0.12 mmol), CH_3CN (0.5 mL) and 0.1N pH 3 phosphate buffer (1.5 mL) was stirred at 25ºC for 14 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Analysis by TLC revealed no chromatographically mobile components, only material that remained at the origin in all solvent systems tried.

TPPFeCl Oxidation of **5**. A mixture of **5** (71.1 mg, 0.189 mmol), TPPFeCl (1.74 mg, 0.00189 mmol), 70% aq soln of t-BuOOH (0.026 mL, 0.189 mmol), CH_3CN (0.7 mL) and 0.1N pH 3 phosphate buffer (2.0 mL) was stirred at 25ºC for 14 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by silica gel column chromatography (7% EtOAc/CH_2Cl_2) to produce **5** (34 mg, 0.09 mmol, 48%), **33** (23 mg, 0.061 mmol, 33%), **34** (9 mg, 0.023 mmol, 12%), and **35** (2 mg, 0.005 mmol, 3%).. **33**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J_1=8.48, J_2=2.11 Hz, 1H), δ 7.54 (d, J=2.05 Hz, 1H), δ 6.87 (d, J=8.52 Hz, 1H), δ 6.34-6.30 Hz (m, 2H), δ 6.27 (t, J=2.44 Hz, 1H), δ 5.47 (dd, J_1=6.25, J_2=4.36 Hz, 1H) δ 4.122 (d, J=4.37 Hz, 1H), δ 4.065 (d, J=6.07 Hz, 1H), δ 3.93 (s, 3H), δ 3.87 (s, 3H), δ 3.70 (s, 3H), δ 2.45 (t, J=7.58 Hz, 2H), δ 1.59-1.49 (m, 2H), δ 0.89 (t, J=7.38 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 195.5, 161, 158.6, 154.4, 149.6, 145.8, 128, 124, 111, 110.5, 108, 108.2, 99.3, 81, 63.8, 56.5, 56.3, 55.6, 38.6, 30, 24.6, 14.1. GC-MS *m/z* (relative intensity): 356 (M-18, 31), 281 (35), 253 (15), 207 (100), 191 (15), 165 (60). HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}O_6$ 375.1802, found 375.1801. **34:** (mixture of two diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.1 (m, 2H), δ 6.98 (m, 2H), δ 6.9 -6.8 (m, 1H), δ 6.7 (m, 1H), δ 5.0 (m, 1H), δ 4.5 – 4.4 (m, 1H), δ 3.9 (m, 1.7H), δ 3.88 (t, 6H), δ 3.81 (d, 3H),), δ 3.7 -3.6 (m, 1H), δ 2.9 (dq, J=10.33, 7.3 Hz, 2H), δ 1.2 (td, J_1=7.22 Hz, J_2=3.95 Hz, 3H. HRMS (ESI) *m/z*

$[M]^+$ calcd for $C_{21}H_{26}O_7$ 390.1679, found 390.1678. **35:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J_1=8.49, J_2=2.15 Hz, 1H), 7.55 (d, J = 2.04 Hz, 1H), 6.90 (d, J=8.55 Hz, 1H), 6.42 (m, 3H), 5.62 (dd, J_1=6.15 Hz, J_2=4.10 Hz, 1 H), 4.06-4.22 (m, 2H), 2.88 (q, J=7.30 Hz, 2H), 1.16 (t, J=7.30 Hz, 3H). **35:** HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{21}H_{24}O_7$ 388.1522, found 388.1525.

TPPFeCl Oxidation of **6**. A mixture of **6** (50 mg, 0.14 mmol), TPPFeCl (0.95 mg, 0.0014 mmol), 70% aq soln of t-BuOOH (0.018 mL, 0.13 mmol), CH_3CN (0.5 mL) and 0.1N pH 3 phosphate buffer (1.5 mL) was stirred at 25ºC for 14 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were chromatographically immobile.

DDQ Oxidation of **1**. A mixture of **1** (50 mg, 0.25 mmol), DDQ (0.57 mg, 0.0025 mmol), $NaNO_2$ (1.74 mg, 0.025 mmol), CH_2Cl_2 (1.8 mL) and acetic acid (0.2 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 19 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The sole observed product was isolated by preparative silica gel TLC (hexane) to produce of **1** (100%).

DDQ Oxidation of **2**. A mixture of **2** (50 mg, 0.2 mmol), DDQ (0.44 mg, 0.002 mmol), $NaNO_2$ (1.35 mg, 0.02 mmol), CH_2Cl_2 (1.8 mL) and acetic acid (0.2 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 19 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:1) to produce **2** (100%).

DDQ Oxidation of **3**. A mixture of **3** (50 mg, 0.14 mmol), DDQ (0.32 mg, 0.0014 mmol), $NaNO_2$ (0.96 mg, 0.014 mmol), CH_2Cl_2 (1.8 mL) and acetic acid (0.2 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 19 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:3) to produce **3** (35.7 mg, 0.099 mmol, 71%) and **15** (10.7 mg, 0.03 mmol, 21%).

DDQ Oxidation of **4**. A mixture of **4** (41 mg, 0.12 mmol), DDQ (0.27 mg, 0.0012 mmol), $NaNO_2$ (0.82 mg, 0.012 mmol), CH_2Cl_2 (1.47 mL) and acetic acid (0.16 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 19 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:3) to produce **4** (19.7 mg, 0.057 mmol, 48%) and **19** (11.3 mg, 0.03 mmol, 28%).

DDQ Oxidation of **5**. A mixture of **5** (43.3 mg, 0.12 mmol), DDQ (0.28 mg, 0.0012 mmol), $NaNO_2$ (0.8 mg, 0.012 mmol), CH_2Cl_2 (1.6 mL) and acetic acid (0.17 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 19 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:1) to produce **5** (26.7 mg, 0.07 mmol, 62%) and **33** (12 mg, 0.032 mmol, 28%).

DDQ Oxidation of **6**. A mixture of **6** (59.6 mg, 0.165 mmol), DDQ (0.38 mg, 0.0016 mmol), $NaNO_2$ (1.14 mg, 0.016 mmol), CH_2Cl_2 (2.1 mL) and acetic acid (0.24 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 19 h. The product was extracted with ethyl acetate and washed with saturated aq NaCl soln. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:1) to produce **6** (28.0 mg, 0.077 mmol, 46%) and **36** (18.4 mg, 0.05 mmol, 31%) and **37** (trace). **36:** ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.67 (m, 1H), δ 7.57 (d, 1H), δ 6.95 (dd, 1H), δ 6.38 – 6.31 (m, 2H), δ 6.29 (t, J =2.31 Hz, 1H), δ 6.19 (s, 1H), δ 5.49 (dd, J=6.15 Hz, 4.21 Hz, 1 H), δ 4.18 – 4.02 (m, 2H), δ 3.90 (s, 3H), δ 3.72 (s, 3H), δ 2.54 – 2.41 (m, 2 H), δ 2.36 (s, 1 H), δ 1.59 – 1.47 (m, 2 H), δ 0.91 – 0.83 (m, 3 H). ^{13}CNMR (400 MHz, $CDCl_3$): δ 194.93, 160.68, 158.28, 151.24, 146.80, 145.44, 127.59, 124.08, 114.09, 110.65, 107.76, 107.63, 98.98, 80.66, 63.47, 56.03, 55.21, 38.21, 24.16, 13.74. GC-MS m/z (relative intensity): 330 (M^+- 30 (loss of CH_2O, McLafferty rearrangement), 22), 287 (1.6), 151 (100), 137 (6), 123 (5), 108 (3), 91 (2.6), 77 (2.6), 65 (2), 52 (1). HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}O_6$ 361.1646, found 361.1646.

TEMPO/$NaNO_2$ Oxidation of **1**. A mixture of **1** (50 mg, 0.25 mmol), TEMPO (5.91 mg, 0.038 mmol), $NaNO_2$ (4.36 mg, 0.063 mmol), 36% aq HCl (10.38 µL, 0.125 mmol), NaCl (7.37 mg, 0.125 mmol) and CH_2Cl_2 (0.3 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 14 h. The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, $NaHCO_3$ and then with the water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC to yield of **1** (100%).

TEMPO/$NaNO_2$ Oxidation of **2**. A mixture of **2** (50 mg, 0.2 mmol), TEMPO (4.57 mg, 0.03 mmol), $NaNO_2$ (3.37 mg, 0.05 mmol), 36% aq HCl (8.25 µL, 0.1 mmol), NaCl (5.7 mg, 0.1 mmol) and CH_2Cl_2 (0.3 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 14 h The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, $NaHCO_3$ and then with the water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:9) to yield **8** (48.5 mg, 0.19 mg, 97%).

TEMPO/$NaNO_2$ Oxidation of **3**. A mixture of **3** (30 mg, 0.083 mmol), TEMPO (2.0 mg, 0.012 mmol), $NaNO_2$ (1.44 mg, 0.021 mmol), 36% aq HCl (1.3 µL, 0.042 mmol), NaCl (2.44 mg, 0.042 mmol) and CH_2Cl_2 (0.18 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 14 h. The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, $NaHCO_3$ and then with the water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:3) to yield **15** (22.4 mg, 0.62 mmol, 81%).

TEMPO/$NaNO_2$ Oxidation of **4**. A mixture of **4** (25 mg, 0.072 mmol), TEMPO (1.69 mg, 0.011 mmol), $NaNO_2$ (1.25 mg,

0.018 mmol), 36% aq HCl (3.24 μL, 0.036 mmol), NaCl (2.1 mg, 0.036 mmol) and CH_2Cl_2 (0.15 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 14 h. The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, $NaHCO_3$ and then with the water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were chromatographically immobile.

TEMPO/$NaNO_2$ Oxidation of **5**. A mixture of **5** (60 mg, 0.16 mmol), TEMPO (3.73 mg, 0.024 mmol), $NaNO_2$ (2.75 mg, 0.033 mmol), 36% aq HCl (6.6 μL, 0.078 mmol), NaCl (4.70 mg, 0.08 mmol) and CH_2Cl_2 (0.36 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 14 h. The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, $NaHCO_3$ and then with the water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:1) to yield **33** (50.4 mg, 0.135 mmol, 84%).

TEMPO/$NaNO_2$ Oxidation of **6**. A mixture of **6** (30 mg, 0.083 mmol), TEMPO (1.94 mg, 0.012 mmol), $NaNO_2$ (1.43 mg, 0.021 mmol), 36% aq HCl (3.4 μL, 0.042 mmol), NaCl (2.42 mg, 0.041 mmol) and CH_2Cl_2 (0.18 mL) stirred under an O_2 atmosphere (1 atm) at 25 °C for 14 h. The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$, $NaHCO_3$ and then with the water. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The products were chromatographically immobile.

Baeyer-Villiger Oxidation of **8**. A mixture of **8** (67.7 mg, 26.6 mmol), 30% aq H_2O_2 (0.21 mL, 2.13 mmol), HCO_2H (0.08 mL, 2.13 mmol), and 1, 2–dichloroethane (0.085 mL, 1.064 mmol) was heated at 50 °C for 24 h. The product was extracted with ethyl acetate, the organic layer was dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by silica gel column chromatography (5% EtOAc/hexanes) to yield **8** (56. 9 mg, 0.22 mmol, 84%) and **38** (7.9 mg, 0.03 mmol, 11%). **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2H), δ 7.57 (tt, J=7.40, 1.33 Hz, 1H), δ 7.43 (t, J=7.8 Hz, 2H), δ 7.21 (t, J=7.84 Hz, 1H), δ 6.94-6.86 (m, 3H), δ 6.00 (s, 2H), δ 2.56 (t, J=7.64 Hz, 2H), δ 1.67-1.55 (m, 2H), δ 0.92 (t, J = 7.27 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.49, 156.92, 144.63, 133.44, 129.87, 129.46, 129.32, 128.45, 123.04, 116.5, 113.05, 86.37, 37.94, 24.34, 13.74. GC-MS *m/z* (relative intensity): 270 (M^+,39), 252 (47), 241 (7), 223 (32), 207 (5), 195 (5), 178 (10), 165 (23), 151 (12), 135 (6), 120 (43), 105 (100), 91 (23), 77 (46), 65 (10), 51 (12). HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{17}H_{18}O_3$ 270.1256, found 270.1255.

Baeyer-Villiger Oxidation of **15**. A mixture of ketone **15** (24 mg, 0.067 mmol), 30% aq H_2O_2 (0.067 mL, 0.54 mmol), HCO_2H (0.02 mL, 0.54 mmol) and 1, 2–dichloroethane (0.021 mL, 0.268 mmol) was refluxed at 50 °C for 24 h. The product was extracted with ethyl acetate, the organic layer was dried over $MgSO_4$ and concentrated under vacuum. The products were isolated by preparative silica gel TLC (EtOAc:hexane 1:3) to yield 3,4-dimethoxybenzoic acid (9.5 mg, 0.05 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J_1 = 8.36, J_2 = 1.8 Hz, 1H), δ 7.574 (d, J=2.04 Hz, 1H), δ 6.90 (d, J = 8.69 Hz, 1H), δ 3.936 (s, 3H), 3.924 (s, 3H). MS *m/z* (relative intensity): 182 (M^+, 100), 167(24), 149(1), 139(5), 121(12), 111(19), 95(9), 83(2), 77(8), 65(5), 51(9).

Acknowledgements

This work was financially supported by the National Science Foundation (NSF-EFRI-0937657 and NSF-IIA-1355438).

Notes and references

[a] *Department of Chemistry, University of Kentucky, Lexington, KY 40506, USA*

[b] *Center for Applied Energy Research, Lexington, KY 40511, USA*

† Electronic Supplementary Information (ESI) available: [NMR spectra of **2** – **6**. **8**, **15**, **18**, **19**, **26** - **31**, **33** – **36**, and **38**]. See DOI: 10.1039/b000000x/

1 Chakar, F. S.; Ragauskas, A. J. *Ind. Crop. Prod.* **2004**, *20*, 131.
2 Zakzeski, J.; Bruijnincx, P. C. A.; Jongerius, A. L.; Weckhuysen, B. M. *Chemical Rev.* **2010**, *110*, 3552.
3 Son, S.; Toste, F. D. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 3791.
4 Hanson, S. K.; Baker, R. T.; Gordon, J. C.; Scott, B. L.; Thorn, D. L. *Inorg. Chem.* **2010**, *49*, 5611.
5 Hanson, S. K.; Wu, R. L.; Silks, L. A. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 3410.
6 Crestini, C.; Pastorini, A.; Tagliatesta, P. *Eur. J. Inorg. Chem.* **2004**, 4477.
7 Biannic, B.; Bozell, J. J. *Organic Lett.* **2013**, *15*, 2730.
8 Rahimi, A.; Azarpira, A.; Kim, H.; Ralph, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 6415.
9 Rahimi, A.; Ulbrich, A.; Coon, J. J.; Stahl, S. S. *Nature* **2014**, *515*, 249.
10 Lancefield, C. S.; Ojo, O. S.; Tran, F.; Westwood, N. J. *Angewandte Chemie International Edition* **2015**, *54*, 258.
11 Reale, S.; Di Tullio, A.; Spreti, N.; De Angelis, F. *Mass Spectrom. Rev.* **2004**, *23*, 87.
12 Tran, F.; Lancefield, C. S.; Kamer, P. C. J.; Lebl, T.; Westwood, N. J. *Green Chem.* **2014**, 244.
13 Wen, J.-L.; Yuan, T.-Q.; Sun, S.-L.; Xu, F.; Sun, R.-C. *Green Chem.* **2014**, *16*, 181.
14 Amen-Chen, C.; Pakdel, H.; Roy, C. *Bioresource Technol.* **2001**, *79*, 277.
15 Cui, F. T.; Wijesekera, T.; Dolphin, D.; Farrell, R.; Skerker, P. *J. Biotechnol.* **1993**, *30*, 15.
16 Klein, M. T.; Virk, P. S. *Ind. Eng. Chem. Fund.* **1983**, *22*, 35.
17 Cordoba, R.; Tormo, N. S.; Medarde, A. F.; Plumet, J. *Bioorgan. Med. Chem.* **2007**, *15*, 5300.
18 Elix, J. A.; Wardlaw, J. H. *Aust. J. Chem.* **1997**, *50*, 1145.
19 Li, X.; Jiang, J.-H.; Chen, Q.; Xiao, S.-X.; Li, C.-H.; Gu, H.-W.; Zhang, H.; Hu, J.-L.; Yao, F.-H.; Li, Q.-G. *Eur. J. Med. Chem.* **2013**, *62*, 605.
20 Carrasco, H.; Raimondi, M.; Svetaz, L.; Di Liberto, M.; Rodriguez, M. V.; Espinoza, L.; Madrid, A.; Zacchino, S. *Molecules* **2012**, *17*, 1002.
21 Cardillo, G.; Shimizu, M. *J. Org. Chem.* **1977**, *42*, 4268.
22 Pericas, A.; Shafir, A.; Vallribera, A. *Tetrahedron* **2008**, *64*, 9258.
23 Pearl, I. A.; Gratzl, J. *J. Org. Chem.* **1962**, *27*, 2111.
24 Baciocchi, E.; Fabbri, C.; Lanzalunga, O. *J. Org. Chem.* **2003**, *68*, 9061.
25 Kirk, T. K.; Connors, W. J.; Bleam, R. D.; Hackett, W. F.; Zeikus, J. G. *Proc. Natl. Acad. Sci. USA* **1975**, *72*, 2515.
26 Tien, M.; Kirk, T. K. *Science* **1983**, *221*, 661.
27 Gold, M. H.; Kuwahara, M.; Chiu, A. A.; Glenn, J. K. *Arch. Biochem. Biophys.* **1984**, *234*, 353.
28 Kuwahara, M.; Glenn, J. K.; Morgan, M. A.; Gold, M. H. *Febs Lett* **1984**, *169*, 247.
29 Tien, M.; Kirk, T. K. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 2280.

30 Edwards, S. L.; Raag, R.; Wariishi, H.; Gold, M. H.; Poulos, T. L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 750.
31 Labat, G.; Meunier, B. *J. Org. Chem.* **1989**, *54*, 5008.
32 Cui, F.; Dolphin, D. *Bioog. Med. Chem.* **1994**, *2*, 735.
33 Heap, L.; Green, A.; Brown, D.; Dongen, B.; Turner, N. *Catal. Sci. Technol.* **2014**, *4*, 2251.
34 Lindsay Smith, J. R.; Mortimer, D. N. *J. Chem. Soc. Perkin II* **1986**, *19*, 1743.
35 Scott, A. I. *Q. Rev. Chem. Soc.* **1965**, *19*, 1.
36 Brovo, A.; Fontana, F.; Minisci, F. *Chemistry Lett.* **1996**, 401.
37 Zhou, L. P.; Chen, Y.; Yang, X. M.; Su, Y. L.; Zhang, W.; Xu, J. *Catalysis Lett.* **2008**, *125*, 154.
38 Sharma, G. V. M.; Lavanya, B.; Mahalingam, A. K.; Krishna, P. R. *Tetrahedron Lett.* **2000**, *41*, 10323.
39 Wang, L. Y.; Li, J.; Yang, H.; Lv, Y.; Gao, S. *J. Org. Chem.* **2012**, *77*, 790.
40 Kumar, T. V.; Veeraiah, T.; Venkateshwarlu, G. *Proc. Ind. Acad. Sci. Chem. Sci.* **2000**, *112*, 119.
41 Zhang, W.; Ma, H.; Zhou, L. P.; Miao, H.; Xu, J. *Chinese J. Catal.* **2009**, *30*, 86.
42 Miller, L. L.; Valentine, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 3982.
43 Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860.
44 Liu, R. H.; Liang, X. M.; Dong, C. Y.; Hu, X. Q. *J. Am. Chem. Soc.* **2004**, *126*, 4112.
45 Liu, R. H.; Dong, C. Y.; Liang, X. M.; Wang, X. J.; Hu, X. Q. *J. Org. Chem.* **2005**, *70*, 729.
46 Kim, S. S.; Jung, H. C. *Synthesis* **2003**, 2135.
47 Wang, X. L.; Liu, R. H.; Jin, Y.; Liang, X. M. *Chem. Eur. J.* **2008**, *14*, 2679.
48 Doering, W. V.; Speers, L. *J. Am. Chem. Soc.* **1950**, *72*, 5515.
49 ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chemical Rev.* **2004**, *104*, 4105.
50 Liou, Y.; Huang, C. *Int. J. Appl. Sci. Eng* **2006**, *4*, 235.
51 Liu, B.; Meng, X. G.; Li, W. Y.; Zhou, L. C.; Hu, C. W. *J. Phys. Chem. A* **2012**, *116*, 2920.
52 Mora-Diez, N.; Keller, S.; Alvarez-Idaboy, J. R. *Org. Biomol. Chem.* **2009**, *7*, 3682.
53 Kandanarachchi, P. H.; Autrey, T.; Franz, J. A. *J. Org. Chem.* **2002**, *67*, 7937.
54 Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12554.
55 Head, F. S. H.; Lund, G. *J. Chem. Soc. C.* **1969**, 37.
56 Tanaka, H.; Kato, I.; Ito, K. *Chem. Pharm. Bull.* **1986**, *34*, 628.
57 Lee, J. H.; Kim, M.; Kim, I. *J. Org. Chem.* **2014**, *79*, 6153.