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Laccase-catalyzed oxidative phenolic coupling of vanillidene derivatives†

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The laccase-catalyzed oxidative phenolic coupling of vanillidene derivatives using aerial oxygen as the oxidant has been developed. Depending on the substitution pattern of the vanillidene double bond of the substrate, either dilactones, dihydrobenzo[*b*]furans or biphenyls are formed.

The phenolic coupling is one of the key reactions in the biosynthesis of many plant secondary metabolites. As an example, a huge number of lignans are formed by oxidative dimerization of *p*-hydroxycinnamic alcohols like *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol.[1] The *p*-hydroxycinnamic alcohols are also decisively involved in the formation of the biopolymer lignin.[1b,2] In addition to the *p*-hydroxycinnamic alcohols, the oxidative dimerization and trimerization of esters of ferulic acid also occupy an important role in the biosynthesis of natural products.[3]

The phenolic natural products depicted in Fig. 1 impressively underline the structural diversity of dimeric, trimeric and tetrameric coupling products of ferulic acid [(*E*)-**1**].[4] Many of them exhibit remarkable biological activities. For example, compounds **3** and **4** show antioxidative properties,[5] and the dihydrobenzo[*b*]furan **6** is an anticancer agent.[6] This is why the selective and efficient oxidative dimerization of ferulic acid and its derivatives is of great importance to the preparation of biologically active phenolic compounds.

In contrast to biosynthesis, the oxidative phenolic coupling still has a minor role in organic synthesis,[7] which is mainly due to the difficulty of controlling both the regio- and stereoselectivity of such couplings. Another important reason is that phenol couplings often require the use of expensive and/or toxic reagents like silver salts. Enzyme-catalyzed phenolic couplings using O_2 as the oxidant provide a valuable alternative as aerial O_2 is one of the cheapest and greenest oxidants available.

In this context, we became interested in laccase-catalyzed oxidations with O_2. Laccases belong to the enzyme class of oxidases.[8] They catalyze one electron oxidations of electron rich substrates with O_2.[9] The resulting radicals can undergo further reactions like dimerizations and polymerizations. The oxidation is accompanied by reduction of O_2 to completely non-toxic H_2O. Laccase-catalyzed transformations have other major benefits as well: they can be performed in aqueous solvent systems and under mild reaction conditions. They do not only meet several of the criteria of green chemistry,[10] but also display a remarkably broad substrate spectrum that can be expanded even more by using mediators. In addition, many of them exhibit a surprisingly high level of selectivity, this being the reason why laccases are highly attractive enzymes for the catalysis of oxidations in organic synthesis.[11]

Among other applications, laccases have been used successfully for the oxidation of several functional groups.[12] The implementation of the laccase-catalyzed oxidation of catechols to *o*-benzoquinones and hydroquinones to *p*-benzoquinones, respectively, in domino processes for the preparation of carbo- and heterocycles is also known.[13] Another field for laccase-catalyzed oxidations is the oxidative coupling of phenolic substrates.[14] As part of our studies related to the development of selective and efficient oxidations with O_2 as the oxidant, we report on laccase-catalyzed oxidative couplings of compounds of types (*E*)-**1**, **14** and **15**, all of which can be regarded as

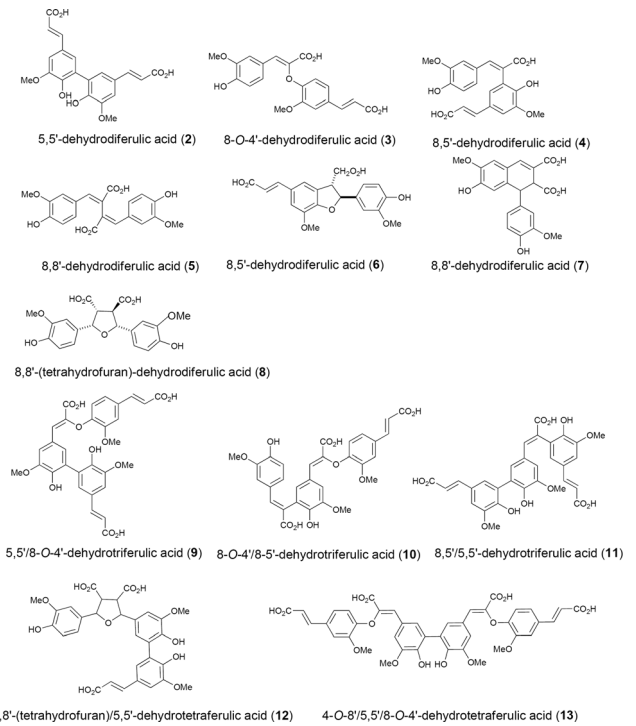

Fig. 1 Ferulic acid oligomers of plant origin.

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† Electronic supplementary information (ESI) available: Experimental data and copies of the ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c2gc35848d

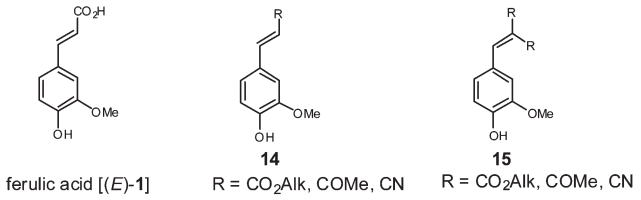
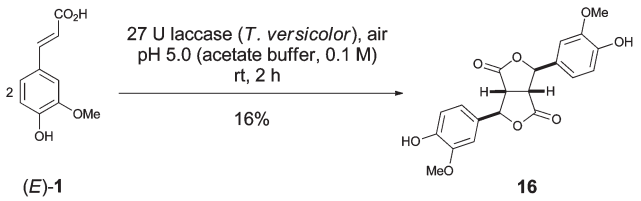


Fig. 2 Structures of vanillidene derivatives.



Scheme 1 Laccase-catalyzed oxidation of ferulic acid [(*E*)-**1**].

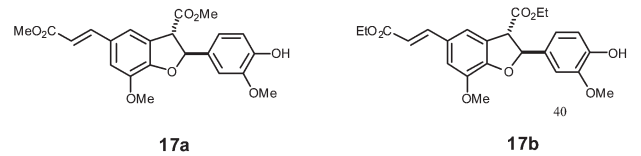


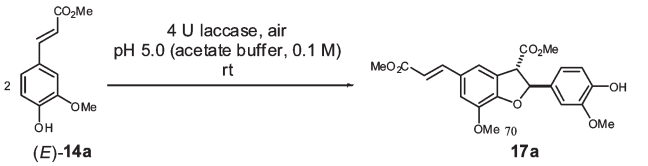
Fig. 3 Dihydrobenzo[*b*]furans **17a,b** as products of the oxidative dimerization of ferulic acid esters (*E*)-**14a,b**.

vanillidene derivatives. Apart from the reactions of ferulic acid [(*E*)-**1**] and other disubstituted vanillidenes **14**, we focused on the transformations of trisubstituted vanillidenes of type **15**, which have remained largely unexplored. This is also the first report on the influence of the substitution pattern at the vanillidene double bond on the outcome of the oxidative coupling (Fig. 2).

The oxidation of ferulic acid [(*E*)-**1**] has already been studied with a number of reagents including $FeCl_3/O_2$ [15] and peroxidase/H_2O_2.[16] In most cases the dilactone **16** was formed. When, for example, (*E*)-**1** was reacted with 2 equiv. of $FeCl_3$ in the presence of aerial O_2, **16** was isolated in 56% yield.[15b] The laccase-catalyzed oxidative coupling of (*E*)-**1** with aerial O_2 as the oxidant has also been studied.[17] But instead of the dilactone compounds **3** and **6** were formed. When we reacted 2.6 mmol (*E*)-**1** with 27 U laccase (*T. versicolor*)‡ and aerial O_2 in acetate buffer (pH 5.0) at rt for 2 h, the dilactone **16** could be isolated in 16% yield (Scheme 1). In addition to **16** we observed the formation of further products whose structures were not elucidated.

Then, the oxidative coupling of the ferulic acid esters (*E*)-**14a–d** was studied. The reactions of (*E*)-**14a,b** have already been performed with a number of oxidants including Ag_2O,[3b,18] Co(salen)/O_2,[19] AIBN[20] and peroxidase/H_2O_2.[21] In most cases the main products were dihydrobenzo[*b*]furans **17a,b** (Fig. 3). As many compounds with a dihydrobenzo[*b*]furan core exhibit interesting biological properties, they receive much attention in medicinal chemistry.[16c,18b] So far, the best results have been obtained with Ag_2O as the oxidant. This, however, requires the use of at least one equivalent of the expensive and toxic oxidant.[18] The laccase-catalyzed oxidation of (*E*)-**14a** is also known, but the structures of the products formed have not been elucidated.[22]

Table 1 Optimization of the laccase-catalyzed oxidative dimerization of (*E*)-**14a**[a]



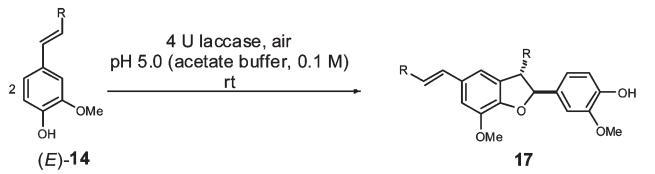
Entry	Laccase	Cosolvent (vol%)	*t* (h)	Yield **17a** (%)[b]
1	*Tv*[c]	DMSO (2)	0.25	11
2	*Tv*[c]	DMSO (2)	1	38
3	*Tv*[c]	DMSO (2)	16	40
4	*Tv*[c]	DMSO (1)	1	37
5	*Tv*[c]	DMSO (10)	1	27
6	*Tv*[c]	Acetone (2)	1	21
7	*Tv*[c]	Acetone (10)	1	31
8	*Tv*[c]	EtOH (2)	1	21
9	*Tv*[c]	—	1	8
10	*Tv*[c]	—	2	26
11	*Ab*[d]	DMSO (2)	1	15
12	*Ab*[d]	DMSO (2)	16	22
13	—	DMSO (2)	1	—

[a] 0.4 mmol (*E*)-**14a** were reacted. [b] Yields refer to yields after flash chromatography. [c] Commercially available laccase from *Trametes versicolor*. [d] Commercially available laccase from *Agaricus bisporus*.

Our own experiments concerning the laccase-catalyzed reaction of ferulic acid esters (*E*)-**14a–d** clearly revealed the formation of dihydrobenzo[*b*]furans **17a–d** as main products in diastereoselectively pure form. The required esters (*E*)-**14a–d** were obtained in high yields by simple esterification of (*E*)-**1** with the corresponding alcohols according to the procedure of Ralph *et al.*[21a] To start with, the laccase-catalyzed oxidation of methyl ferulate (*E*)-**14a** was performed using different laccases under different reaction conditions (Table 1). The best yield of **17a** was achieved when the coupling of (*E*)-**14a** was run with 4 U laccase from *T. versicolor* as the catalyst in a 98 : 2-mixture of acetate buffer (0.1 M, pH 5.0) and DMSO (Table 1, entry 3) for 16 h. These conditions allowed the isolation of the diastereoisomerically pure 8,5′-coupling product **17a** with 40% yield. HPLC separation of the enantiomers of **17a** using a chiral phase demonstrated that the product of the laccase-catalyzed oxidation of (*E*)-**14a** was racemic. Coupling experiments with *Agaricus bisporus* as the catalyst resulted in lower yields (Table 1, entries 11 and 12) as did the use of other co-solvents (Table 1, entries 6–8) and other concentrations of DMSO (Table 1, entries 4 and 5). In a control experiment the oxidative dimerization of (*E*)-**14a** did not occur in the absence of laccase (Table 1, entry 13).

It was also established that **17a** is not stable under reaction conditions but slowly decomposes to yield products of unknown structure. The laccase-catalyzed dimerization could be extended to the ethylester (*E*)-**14b**, the *n*-propylester (*E*)-**14c** and the *n*-butylester (*E*)-**14d** (Table 2, entries 1–7). Again, the corresponding dihydrobenzofurans were isolated as the only products in diastereoisomerically pure form. However, the yields of **17b–d** were lower than that of **17a** (Table 2, entries 3, 6, and 7).

Table 2 Laccase-catalyzed oxidative dimerizations of (*E*)-**14b–f**



Entry	(*E*)-**14**	R	Laccase	U (laccase)	*t* (h)	Yield **17** (%)[c]
1	**b**[a]	CO_2Et	*Tv*[d]	4	1	23
2	**b**[a]	CO_2Et	*Tv*[d]	4	5	25
3	**b**[a]	CO_2Et	*Tv*[d]	4	16	29
4	**b**[a]	CO_2Et	*Tv*[d]	4	36	23
5	**b**[a]	CO_2Et	*Ab*[e]	4	16	22
6	**c**[a]	CO_2n-Pr	*Tv*[d]	4	16	23
7	**d**[b]	CO_2n-Bu	*Tv*[d]	80	3	22
8	**e**[a]	COMe	*Tv*[d]	4	9	25
9	**f**[a]	CN	*Tv*[d]	4	10	—

[a] 0.4 mmol substrate were reacted. [b] 2.1 mmol **14d** were reacted. [c] Yields refer to yields after flash chromatography. [d] Commercially available laccase from *Trametes versicolor*. [e] Commercially available laccase from *Agaricus bisporus*.

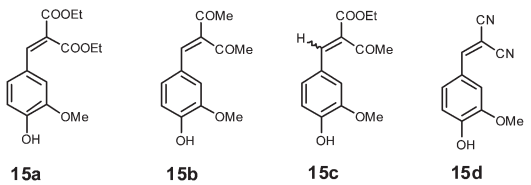


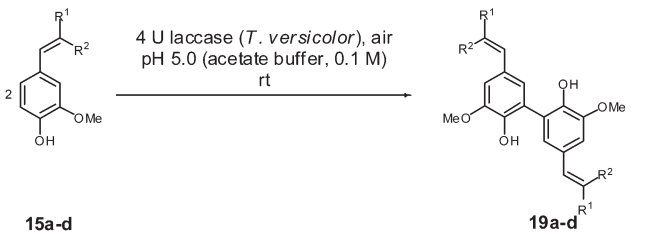
Fig. 4 Structures of vanillidene β-dicarbonyls **15a–d**.

It is remarkable that the dihydrobenzo[*b*]furan formation was not restricted to the unsaturated esters (*E*)-**14a–d** but could also be achieved with the corresponding unsaturated ketone (*E*)-**14e**. Reaction of (*E*)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one [(*E*)-**14e**][23] under standard conditions delivered the dihydrobenzo[*b*]furan **17e** in diastereoisomerically pure form with 25% yield (Table 2, entry 8). Experiments with (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylonitrile [(*E*)-**14f**][24] as the substrate were rather disappointing as an inseparable product mixture was obtained (Table 2, entry 9). It should be emphasized that the laccase-catalyzed oxidative dimerization of disubstituted vanillidene derivatives (*E*)-**14a–e** occurs with diastereoselective formation of the dihydrobenzo[*b*]furan skeleton.

Next, the influence of a further substituent at the vanillidene double bond on the outcome of the oxidation experiments was studied. The required trisubstituted vanillidene β-dicarbonyls **15** could easily be prepared by Knoevenagel condensation between vanillin (**18**) and the corresponding β-dicarbonyls with yields ranging from 67 to 96% (Fig. 4).[25] With the vanillidene β-dicarbonyls **15a–d** at hand, the laccase-catalyzed oxidations were run under the conditions that had been optimized for the dimerizations of **14** (Table 3).

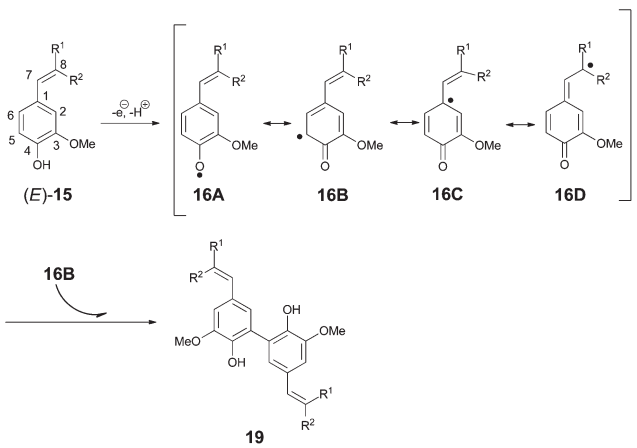
Again, the exclusive formation of phenolic coupling products was observed. Using **15a–d** as the substrates, not a trace of the expected 8,5′-coupling products **17** was formed. Instead, the exclusive formation of biphenyls **19a–d**, which can be regarded as products of a 5,5′-coupling, was observed with yields between 80 and 100%§ (Table 3, entries 1–4). As demonstrated in control experiments the dimerization of **15a–d** did not proceed in the absence of laccase.

Table 3 Laccase-catalyzed oxidative dimerizations of **15a–d**[a]



Entry	**15**	R^1, R^2	DMSO (mL)	Buffer (mL)	*t* (h)	Yield **19** (%)[b]
1	**a**	CO_2Et, CO_2Et	8	72	22	79[b]
2	**b**	COMe, COMe	8	72	5	93[b]
3	**c**	CN, CN	8	72	21	Quant.[d]
4	**d**[c]	CO_2Et, COMe	8	72	3	86[b]

[a] 0.4 mmol **15a–d** were reacted. [b] Yields after flash chromatography. [c] **15d** was a 4 : 6-mixture of the *E*- and the *Z*-isomer (^{1}H NMR). [d] Yield after crystallization of the crude product.



Scheme 2 Proposed reaction mechanism for the oxidative dimerization of **15**.

It is assumed that the formation of **21** proceeds as an oxidative dimerization of **15** (Scheme 2). In the first step **15** undergoes a one electron oxidation to the resonance stabilized radical **16**. This is followed by dimerization of **16B**, which proceeds with selective formation of the 5,5′-coupling product **19**. As far as we are aware, a comparable 5,5′-coupling of trisubstituted vanillidene derivatives has only been reported once[26] using equimolar amounts of [(diacetoxy)iodo]benzene (DAIB) as the oxidant.

The structures of all compounds were elucidated unambiguously using MS and NMR methods. The full assignment of all

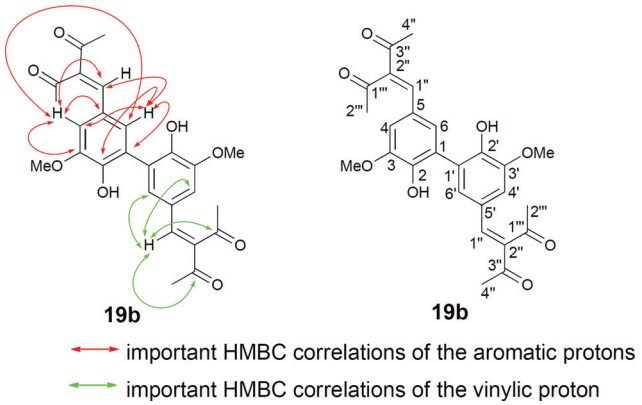


Fig. 5 Numbering of **19b** and important HMBC correlations.

^{1}H and ^{13}C chemical shifts was achieved by evaluating their COSY, HSQC and HMBC spectra. As an example, the molecular formula of compound **19b**¶ ($C_{26}H_{26}O_8$) was established by HRMS (ESI pos.) analysis of its $[M + H]^+$ at *m*/*z* 467.1700 (calculated for $C_{26}H_{27}O_8$, 467.1706). This result indicated that **19b** is a dimer originating from oxidative coupling of two substrate molecules **15b**. Furthermore, the ^{1}H NMR spectrum of **19b** exhibits two singlets corresponding to two aromatic protons and one singlet corresponding to a vinylic proton in a 1 : 1 : 1-ratio of signals suggesting – in accordance with the mass spectrum – that the product could be symmetrical (Fig. 5). A single set of 13 signals in the ^{13}C NMR spectrum of **19b** confirms the symmetrical structure of the compound. A $^{4}J_{4\text{-H},6\text{-H}}$ coupling constant of 1.6 Hz along with the HMBC correlations between 6-H and C-2, C-4, C-5 and C-1″ as well as between 4-H and C-2, C-3, C-6 and C-1″ arrange 4-H and 6-H on the same benzene ring. In addition, the HMBC correlation between 1″-H and C-4, C-6 and the two carbonyl groups revealed that the vanillidene double bonds of the two substrate molecules remain unaffected during the oxidative coupling (Fig. 5).

In summary, we have reported on the laccase-catalyzed oxidative dimerization of di- and trisubstituted vanillidene derivatives with aerial O_2 as the oxidant under mild reaction conditions. Depending on the substitution pattern of the vanillidene double bond, the formation of different products was observed. While the oxidative coupling of ferulic acid [(*E*)-**1**] resulted in the formation of dilactone **16** as the main product, the dihydrobenzo[*b*]furans **17a–e** were obtained from the dimerization of the disubstituted vanillidenes **14a–e**. With trisubstituted vanillidene β-dicarbonyls **15a–d** as substrates, the corresponding biphenyls **19a–d** were formed exclusively and with excellent yields. The advantages of the laccase-catalyzed oxidative coupling of phenols are obvious: they can be easily run using a commercially available and cheap enzyme as the catalyst which is non-toxic and environmentally benign. In addition, there is no need for a cofactor and cofactor regeneration; laccase-catalyzed processes employ O_2, which is the cheapest and most abundant oxidant, and water is the only by-product formed. The reactions can be run at room temperature in an aqueous solvent system. And last but not least the laccase-catalyzed oxidative phenolic couplings presented here compare well with other oxidants concerning selectivity and yields.

Acknowledgements

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Notes and references

‡The activities of the laccases from *T. versicolor* or *A. bisporus* were determined following a modified procedure taken from Danieli *et al.*[14f] using a solution of ABTS [2.2′-azinobis-(-3-ethylbenzothiazolyl-6-sulfonic acid)] as the substrate. The change in absorption was followed *via* UV spectroscopy (λ = 414 nm; ε_{414} = 31 100 L mol^{-1} cm^{-1}). 1 U is equivalent to the amount of enzyme that catalyzes the conversion of 1 μmol ABTS per minute at 24 °C and corresponding pH.

§General procedure for the synthesis of biphenyls **19a–d**: A solution of a vanillidene derivative **15** in DMSO (8 mL) was added to NaOAc buffer (0.1 M, pH 5.0, 72 mL). Laccase from *T. versicolor* (4 U, 0.4 mg) was added and the reaction mixture was stirred under air at room temperature for the reaction times given in Table 3. After extraction with CH_2Cl_2 (3 × 30 mL) the combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography over silica gel to afford the biphenyl **19** in analytically pure form.

¶Selected analytical data for 5,5′-di(2,2-diacetylvinyl)-2,2′-dihydroxy-3,3′-dimethoxybiphenyl (**19b**): R_f 0.20 (CH_2Cl_2–MeOH = 40 : 1); ^{1}H NMR δ_H(300 MHz; DMSO-d$_6$) 2.23 (6H, s, 4″-H or 2‴-H), 2.35 (6H, s, 4″-H or 2‴-H), 3.80 (6H, s, OCH_3 and OCH_3′), 6.90 (2H, s, 6-H and 6′-H), 7.04 (2H, s, 4-H and 4′-H) and 7.60 (s, 2H, 1″-H); ^{13}C NMR δ_C(75 MHz; DMSO-d$_6$) 26.09 (C-4″ or C-2‴), 31.40 (C-4″ or C-2‴), 55.87 (OCH_3 and OCH_3′), 112.33 (C-4 and C-4′), 123.03 (C-5 and C-5′), 125.06 (C-1 and C-1′), 126.16 (C-6 and C-6′), 139.65 (C-2″), 140.14 (C-1″), 147.08 (C-2 and C-2′), 147.69 (C-3 and C-3′), 197.20 (C-1‴ or C-3″) and 206.37 (C-1‴ or C-3″).

1 (*a*) N. G. Lewis and L. B. Davin, in *Comprehensive Natural Products Chemistry*, ed. D. Barton, K. Nakanishi and O. Meth-Cohn, Elsevier, London, 1999, vol. 1, p. 639; (*b*) N. G. Lewis and S. Sarkanen, *Lignin and Lignan Biosynthesis*, American Chemical Society, Washington, DC, 1996, p. 1.
2 N. G. Lewis, L. B. Davin and S. Sarkanen, in *Comprehensive Natural Products Chemistry*, ed. D. Barton, K. Nakanishi and O. Meth-Cohn, Elsevier, Oxford, 1999, vol. 3, p. 617.
3 (*a*) C. T. Brett, G. Wende, A. C. Smith and K. W. Waldron, *J. Sci. Food Agric.*, 1999, **79**, 421; (*b*) J. Ralph, S. Quideau, J. H. Grabber and R. D. Hatfield, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3485.
4 (*a*) D. Dobberstein and M. Bunzel, *J. Sci. Food Agric.*, 2010, **90**, 1802; (*b*) M. Bunzel, J. Ralph, P. Brüning and H. Steinhart, *J. Agric. Food Chem.*, 2006, **54**, 6409; (*c*) L. Saulnier and J.-F. Thibault, *J. Sci. Food Agric.*, 1999, **79**, 396.
5 M. F. Andreasen, A.-K. Landbo, L. P. Christensen, A. Hansen and A. S. Meyer, *J. Agric. Food Chem.*, 2001, **49**, 4090.
6 S. K. Manna, J. S. Bose, V. Gangan, N. Raviprakash, T. Navaneetha, P. B. Raghavendra, B. Babajan, C. S. Kumar and S. K. Jain, *J. Biol. Chem.*, 2010, **285**, 22318.
7 (*a*) G. Lessene and K. S. Feldman, in *Modern Arene Chemistry*, ed. D. Astruc, Wiley-VCH, Weinheim, 2002, ch. 14, p. 479; (*b*) T. Pal and A. Pal, *Curr. Sci.*, 1996, **71**, 106; (*c*) T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657; (*d*) H. Musso, *Angew. Chem., Int. Ed.*, 1963, **2**, 723.
8 (*a*) S. Riva, *Trends Biotechnol.*, 2006, **24**, 219; (*b*) A. M. Mayer and R. C. Staples, *Phytochemistry*, 2002, **60**, 551; (*c*) C. F. Thurston, *Microbiology*, 1994, **140**, 19–26.
9 (*a*) E. I. Solomon, A. J. Augustine and J. Yoon, *Dalton Trans.*, 2008, 3921; (*b*) H. Claus, *Arch. Microbiol.*, 2003, **179**, 145.
10 P. Anastas and P. Tundo, *Green Chemistry: Challenging Perspectives*, Oxford University Press, 2000.
11 (*a*) D. Monti, G. Ottolina, G. Carrea and S. Riva, *Chem. Rev.*, 2011, **111**, 4111; (*b*) F. Hollmann, I. W. C. E. Arends, K. Buehler, A. Schallmey and B. Bühler, *Green Chem.*, 2011, **13**, 226; (*c*) S. Witayakran and A. J. Ragauskas, *Adv. Synth. Catal.*, 2009, **351**, 1187.
12 (*a*) H. Leutbecher, M.-A. Constantin, S. Mika, J. Conrad and U. Beifuss, *Tetrahedron Lett.*, 2011, **52**, 604; (*b*) C. Asta, J. Conrad, S. Mika and

U. Beifuss, *Green Chem.*, 2011, **13**, 3066; (*c*) A. Wells, M. Teria and T. Eve, *Biochem. Soc. Trans.*, 2006, **34**, 304; (*d*) I. W. C. E. Arends, Y.-X. Li, R. Ausan and R. A. Sheldon, *Tetrahedron*, 2006, **62**, 6659; (*e*) F. d'Acunzo, P. Baiocco and C. Galli, *New J. Chem.*, 2003, **27**, 329; (*f*) E. Fritz-Langhals and B. Kunath, *Tetrahedron Lett.*, 1998, **39**, 5955; (*g*) A. Potthast, T. Rosenau, C. L. Chen and J. S. Gratzl, *J. Mol. Catal. A: Chem.*, 1996, **108**, 5.

13 (*a*) S. Hajdok, J. Conrad and U. Beifuss, *J. Org. Chem.*, 2012, **77**, 445; (*b*) H. Leutbecher, G. Greiner, R. Amann, A. Stolz, U. Beifuss and J. Conrad, *Org. Biomol. Chem.*, 2011, **9**, 2667; (*c*) S. Hajdok, J. Conrad, H. Leutbecher, S. Strobel, T. Schleid and U. Beifuss, *J. Org. Chem.*, 2009, **74**, 7230; (*d*) H. Leutbecher, S. Hajdok, C. Braunberger, M. Neumann, S. Mika, J. Conrad and U. Beifuss, *Green Chem.*, 2009, **11**, 676; (*e*) S. Hajdok, H. Leutbecher, G. Greiner, J. Conrad and U. Beifuss, *Tetrahedron Lett.*, 2007, **48**, 5073; (*f*) S. Witayakran and A. J. Ragauskas, *Green Chem.*, 2007, **9**, 475; (*g*) H. Leutbecher, J. Conrad, I. Klaiber and U. Beifuss, *Synlett*, 2005, 3126.

14 (*a*) M.-A. Constantin, J. Conrad, E. Merisor, K. Koschorreck, V. B. Urlacher and U. Beifuss, *J. Org. Chem.*, 2012, **77**, 4528; (*b*) M.-A. Constantin, J. Conrad and U. Beifuss, *Tetrahedron Lett.*, 2012, **53**, 3254; (*c*) B. Pickel, M.-A. Constantin, J. Pfannstiel, J. Conrad, U. Beifuss and A. Schaller, *Angew. Chem., Int. Ed.*, 2010, **49**, 202; (*d*) S. Ncanana, L. Baratto, L. Roncaglia and S. Riva, *Adv. Synth. Catal.*, 2007, **349**, 1507; (*e*) C. Ponzoni, E. Beneventi, M. R. Cramarossa, S. Raimondi, G. Trevisi, U. M. Pagnoni, S. Riva and L. Forti, *Adv. Synth. Catal.*, 2007, **349**, 1497; (*f*) S. Nicotra, A. Intra, G. Ottolina, S. Riva and B. Danieli, *Tetrahedron: Asymmetry*, 2004, **15**, 2927.

15 (*a*) A. Hirata, Y. Murakami, T. Atsumi, M. Shoji, T. Ogiwara, K. Shibuya, S. Ito, I. Yokoe and S. Fujisawa, *In vivo*, 2005, **19**, 849; (*b*) E. Kim, H. K. Lee, E.-I. Hwang, S.-U. Kim, W. S. Lee and S. Lee, *Synth. Commun.*, 2005, **35**, 1231; (*c*) S. Quideau and J. Ralph, *J. Chem. Soc., Perkin Trans. 1*, 1993, 653; (*d*) N. J. Cartwright and R. D. Haworth, *J. Chem. Soc.*, 1944, 535.

16 (*a*) L. Ou, L.-Y. Kong, X.-M. Zhang and M. Niwa, *Biol. Pharm. Bull.*, 2003, **26**, 1511; (*b*) E. Larsen, M. F. Andreasen and L. P. Christensen, *J. Agric. Food Chem.*, 2001, **49**, 3471; (*c*) H. Yeo, J. H. Lee and J. Kim, *Arch. Pharmacal Res.*, 1999, **22**, 306.

17 F. Carunchio, C. Crescenzi, A. M. Girelli, A. Messina and A. M. Tarola, *Talanta*, 2001, **55**, 189.

18 (*a*) D. L. A. Rakotondramanana, M. Delomenede, M. Baltas, H. Duran, F. Bedos-Belval, P. Rasoanaivo, A. Negre-Salvayre and H. Gornitzka, *Bioorg. Med. Chem.*, 2007, **15**, 6018; (*b*) L. Pieters, S. Van Dyck, M. Gao, R. Bai, E. Hamel, A. Vlietinck and G. Lemiere, *J. Med. Chem.*, 1999, **42**, 5475; (*c*) G. Lemiere, M. Gao, A. De Groot, R. Dommisse, J. Lepoivre, L. Pieters and V. Buss, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1775; (*d*) S. Antus, A. Gottsegen, P. Kolonits and H. Wagner, *Liebigs Ann. Chem.*, 1989, 593.

19 E. Bolzacchini, C. Canevali, F. Morazzoni, M. Orlandi, B. Rindone and R. Scotti, *J. Chem. Soc., Dalton Trans.*, 1997, 4695.

20 T. Masuda, K. Yamada, T. Maekawa, Y. Takeda and H. Yamaguchi, *Food Sci. Technol. Res.*, 2006, **12**, 173.

21 (*a*) J. Ralph, M. T. G. Conesa and G. Williamson, *J. Agric. Food Chem.*, 1998, **46**, 2531; (*b*) F. Choccara, S. Poli, B. Rindone, T. Pilati, G. Brunow, P. Pietikäinen and H. Setälä, *Acta Chem. Scand.*, 1993, **47**, 610; (*c*) T. Yoshihara, K. Yamaguchi and S. Sakamura, *Agric. Biol. Chem.*, 1983, **47**, 217.

22 C. Wallace and S. C. Fry, *Phytochemistry*, 1999, **52**, 769.

23 E. M. Guanti, K. Ncokazi, T. J. Egan, J. Gut, P. J. Rosenthal, R. Bhampidipati, A. Kopinathan, P. J. Smith and K. Chibale, *J. Med. Chem.*, 2011, **54**, 3637.

24 S. A. DiBiase, B. A. Lipisko, A. Haag, R. A. Wolak and G. W. Gokel, *J. Org. Chem.*, 1979, **44**, 4640.

25 L. F. Tietze and U. Beifuss, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 2, p. 341.

26 G. Wells, A. Seaton and M. F. G. Stevens, *J. Med. Chem.*, 2000, **43**, 1550.