Biomimetic Synthesis of *Illicium* Oligomeric Neolignans†

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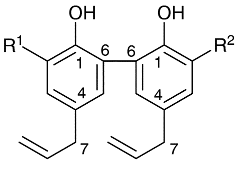
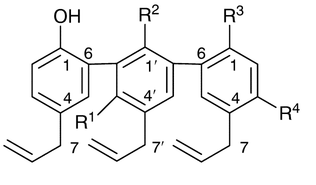
Six products have been isolated from the oxidative coupling of 4-allylphenol in the presence of Fe^{III}; the distribution of products suggests that oligomeric neolignans associated with the family *Illicium* may also be non-enzymic products of oxidative coupling.

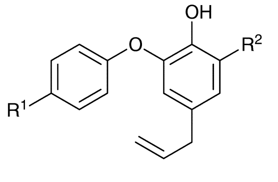
The genus *Illicium* is characterised by a variety of oligomeric neolignans which are linked through the aromatic ring (C_6): these include *ortho,ortho* (*o,o*)-linked dimers[1,2] [magnolol **1**; 2,2′-dihydroxy-3-methoxy-5,5′-di(prop-2-enyl) biphenyl **2** and dehydrodieugenol **3**], *o,o*-linked trimers[2–4] (dunnianol **4**; macrathanol **5** and simonsinol **6**), dimers and trimers involving *o*,O-linkage (isomagnolone[4] **7** and isodunnianol[1,2] **8**) and a *o,o-*/*o,p*-linked trimer **9**.[5] [A few neolignans have also been reported which are coupled through the phenylpropanoid 'tail' (C_3).][6]



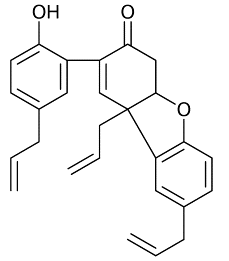
1 $R^1 = H; R^2 = H$
2 $R^1 = OMe; R^2 = H$
3 $R^1 = OMe; R^2 = OMe$



4 $R^1 = H; R^2 = OH; R^3 = OH; R^4 = H$
5 $R^1 = OH; R^2 = H; R^3 = OH; R^4 = H$
6 $R^1 = H; R^2 = OH; R^3 = H; R^4 = OH$



7 $R^1 = COEt; R^2 = H$
8 $R^1 = CH_2CH = CH_2; R^2 =$ *o*-(4-allylphenol)



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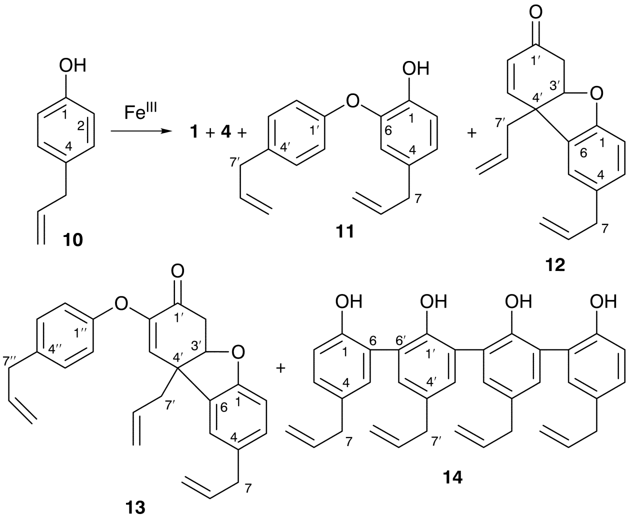
Gottlieb has proposed that oxidative coupling reactions might account for the biosynthesis of a wide range of neolignans[7] although there has been relatively little experimental work to validate this hypothesis.[8] Consequently, we decided to subject 4-allylphenol **10**, a putative biogenetic precursor to the *Illicium* neolignans, to oxidative coupling *in vitro* in order to compare the distribution of products formed with that reported *in vivo*. The oxidative coupling of phenols is a well established process[9] and Ho *et al.* have previously described a photochemical oxidative coupling of 4-allylphenol which yielded magnolol **1**[10] (magnolol has also been prepared by coupling of aromatic halides in the presence of Pd^0).[11] Anodic oxidations of 2-methoxy-4-allylphenol and 2,6-dimethoxy-4-allylphenol are reported to yield complex mixtures of dimeric products.[12,13] We herein report the results of the oxidative coupling of 4-allylphenol in the presence of Fe^{III}.

4-Allylphenol **10**, required for oxidative coupling studies, was obtained in 46% yield by treatment of commercially available 4-allylanisole with boron tribromide.[14] Treatment of **10** with $FeCl_3$[15] produced the dimeric *o,o*-coupled product magnolol **1** (15%), the trimeric *o,o*-coupled product dunnianol **4** (2%) and the *o*,O-coupled product isomagnolol **11** (1%). Use of $K_3Fe(CN)_6$[16] in place of $FeCl_3$ gave a better overall yield (44%) but also resulted in a qualitatively more complex mixture of dimeric, trimeric and tetrameric *o,o*-, *o*,O- and *o,p*-linked products (**1**, **4**, **11**–**14**; Scheme 1), in which **4** and **12** were the major components. All compounds were characterized by NMR (compounds **12**–**14** are reported for the first time) and ^1H and ^{13}C resonances were rigorously assigned using 2D NMR techniques (*e.g.* HSQC, HMBC, ^1H–^1H COSY), see Experimental section and Table 1.



Scheme 1

The distribution of oxidatively coupled products obtained from 4-allylphenol *in vitro*, in which it is possible to identify dimeric, trimeric and tetrameric structures formed as a result of *o,o*-, *o,p*- and *o*,O-coupling reactions, bears a striking resemblance to that reported for natural products from the genus *Illicium*, with the exception that no tetrameric neolignans have as yet been described from Nature (interestingly, however, no oligomers higher than the tetramer were isolated from *in vitro* oxidation). This similarity in chemistry, including the co-occurrence of compounds **1** and **4**, suggests that an analogous non-enzymic oxidative coupling process, operating on 4-allylphenol *in vivo*, may be sufficient to account for the formation of neolignans from the *Illiciaceae*.

Experimental

General Methods.—Chemical shifts are expressed in ppm (δ) relative to TMS as int. standard. All NMR experiments were run on a Bruker DRX 500 instrument. Two dimensional spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. MS were recorded in EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a BIO-RAD FT S-7 IR spectrometer. Column chromatography was performed using silica gel 60–200 μm (Merck).

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Table 1 ^{13}C NMR data for compounds **1**, **4**, **10** and **11**–**14**

	Compound						
Atom[a]	**1**	**4**	**10**	**11**	**12**	**13**[b]	**14**
1 (C)	151.1	151.4	153.5	145.7	157.0	156.9	151.2
2 (CH)	116.7	117.2	115.5	115.9	110.1	110.3	117.0
3 (CH)	131.2	130.0	129.7	124.6	129.4	129.5	129.8
4 (C)	133.1	133.3	132.1	132.6	131.0	131.5	133.1
5 (CH)	129.9	131.6	129.7	118.9	122.9	122.7	131.5
6 (C)	123.8	126.0	115.5 (CH)	143.4	133.2	133.5	124.8
7 (CH_2)	39.4	39.7	39.2	39.4	39.6	39.4	39.4
8 (CH_2)	137.5	137.7	137.8	137.5	137.5	137.6	137.6
9 (CH_2)	115.8	116.0	115.3	115.7	115.7	115.8	115.8
1′ (C)		147.9		155.1	195.2	189.7	147.8
2′ (CH_2)		125.0 (C)		117.9 (CH)	38.7	39.9	126.1 (C)
3′ (CH)		131.8		129.9	84.6	84.2	131.7
4′ (C)		134.0		135.2	48.4	49.1	133.9
5′ (CH)		131.8		129.9	148.4	128.3	131.7
6′ (CH)		125.0		117.9	127.1	147.6 (C)	126.0 (C)
7′ (CH_2)		39.5		39.4	40.5	41.2	39.4
8′ (CH)		137.4		137.4	132.1	132.2	137.2
9′ (CH_2)		116.3		115.9	119.6	119.8	116.1

[a] Multiplicity established from DEPT. [b] Additional peaks for compound **13**: 154.4 (C), C-1″; 117.9 (CH), C-2″; 129.5 (CH), C-3″; 135.1 (C), C-4″; 129.5 (CH), C-5″; 117.9 (CH), C-6″; 39.7 (CH_2), C-7″; 137.4 (CH), C-8″; 115.7 (CH_2), C-9″.

Oxidative Coupling of **10** *in the Presence of* $FeCl_3$.—A solution of **10** in 95% EtOH (2.5 g, 10 ml) was added dropwise to an aqueous solution of $FeCl_3$ (7.03 g, 625 ml). A constant stream of air was maintained through the stirred solution for 48 h and the mixture was then acidified and extracted with Et_2O. The Et_2O layer was in turn extracted with NaOH (2 M); following acidification of the alkaline extract, a further Et_2O extract was collected which was washed, dried, concentrated under reduced pressure and subjected to gradient column chromatography to yield unreacted **10** (1.45 g), **1** (323 mg), **4** (68 mg) and **11** (29 mg).

Oxidative Coupling of **10** *in the Presence of* $K_3Fe(CN)_6$—A $K_3Fe(CN)_6$ solution (1.85 g, 6.4 ml, 0.88 M) was added dropwise over 30 min to a stirred solution of **10** (0.5 g) in aqueous Na_2CO_3 (0.8 g, 18.7 ml) at 0 °C. The reaction mixture was stirred for 3 h, then acidified and extracted with Et_2O, worked up as before and subjected to gradient column chromatography to yield unreacted **10** (107 mg), **1** (59 mg, 8%), **4** (132 mg, 11%), **11** (35 mg, 5%), **12** (94 mg, 12%), **13** (54 mg, 5%) and **14** (55 mg, 4%).

Magnolol (**1**).—Oil. IR ($CHCl_3$) ν_{max}/cm^{-1}: 3549, 3267 (br), 3082, 3011, 2907, 1639, 1497, 1215. HREIMS *m*/*z* (intensity %): 266.1305 (100) (M^+, $C_{18}H_{18}O_2$ requires 266.1307), 248 (5), 247 (6), 237 (9), 225 (15). δ_H ($CDCl_3$): 7.12 (2 H, dd, $J = 8.2$, 2.1 Hz, H-3), 7.08 (2 H, d, $J = 2.1$ Hz, H-5), 6.94 (2 H, d, $J = 8.2$ Hz, H-2), 5.95 (2 H, m, H-8), 5.05 (4 H, m, H-9), 3.35 (4 H, d, $J = 6.7$ Hz, H-7).

Dunnianol (**4**).—Solid. Mp 133.5–134.5 °C. IR ($CHCl_3$) ν_{max}/cm^{-1}: 3545, 3315 (br), 3085, 3011, 2926, 1640, 1506, 1215. HREIMS *m*/*z* (intensity %): 398.1882 (75) (M^+, $C_{27}H_{26}O_3$ requires 398.1882); 316 (13), 287 (100), 266 (29). δ_H ($CDCl_3$): 7.14 (2 H, *s*, H-3′/5′), 7.12 (2 H, d, $J = 2.1$ Hz, H-5), 7.10 (2 H, dd, $J = 8.1$, 2.1 Hz, H-3), 6.92 (2 H, d, $J = 8.1$ Hz, H-2), 5.96 (3 H, m, H-8/8′), 5.10 (6 H, m, H-9/9′), 3.36 (6 H, d, $J = 6.1$ Hz, H-7/7′).

4-*Allylphenol* (**10**).—Oil. δ_H ($CDCl_3$): 7.14 (1 H, br, s, 1-OH), 7.02 (2 H, d, $J = 8.3$ Hz, H-3/5), 6.77 (2 H, d, $J = 8.3$ Hz, H-2/6), 5.95 (1 H, m, H-8), 5.05 (2 H, m, H-9), 3.31 (2 H, d, $J = 6.7$ Hz, H-7).

Isomagnolol (**11**).—Oil IR ($CHCl_3$) ν_{max}/cm^{-1}: 3566, 3011, 2978, 2922, 1636, 1506, 1229. HREIMS *m*/*z* (intensity %); 266.1306 (100) (M^+, $C_{18}H_{18}O_2$ requires 266.1307), 175 (8), 134 (12), 133 (12). δ_H ($CDCl_3$): 7.15 (2 H, d, $J = 8.4$ Hz, H-3′/5′), 6.96 (1 H, d, $J = 8.2$ Hz, H-2), 6.93 (2 H, d, $J = 8.4$ Hz, H = 2′/6′), 6.84 (1 H, dd, $J = 8.2$, 1.8 Hz, H-3), 6.70 (1 H, d, $J = 1.8$ Hz, H-5), 5.95 (2 H, m, H-8/8′), 5.49 (1 H, s, 1-OH), 5.05 (4 H, m, H-9/9′), 3.36 (2 H, d, $J = 6.6$ Hz, H-7′), 3.24 (2 H, d, $J = 6.6$ Hz, H-7).

Compound **12**.—Oil. IR ($CHCl_3$) ν_{max}/cm^{-1}: 3013, 2905, 1686, 1639, 1487, 1250. HREIMS *m*/*z* (intensity %): 266.1305 (91) (M^+, $C_{18}H_{18}O_2$ requires 266.1307), 239 (13), 225 (100), 197 (16), 184 (14), δ_H ($CDCl_3$): 7.02 (1 H, d, $J = 1.7$ Hz, H-5), 6.99 (1 H, dd, $J = 8.2$, 1.7 Hz, H-3), 6.72 (1 H, d, $J = 8.2$ Hz, H-2), 6.49 (1 H, dd, $J = 10.2$, 1.8 Hz, H-5′), 5.99 (1 H, d, $J = 10.2$ Hz, H-6′), 5.94 (1 H, m, H-8), 5.78 (1 H, m, H-8′), 5.19 (2 H, m, H-9′), 5.07 (2 H, m, H-9), 4.80 (1 H, m, H-3′), 3.33 (2 H, d, $J = 6.7$ Hz, H-7), 3.00 (1 H, dd, $J = 17.6$, 2.8 Hz, H-2′), 2.79 (1 H, dd, $J = 14.2$, 6.7 Hz, H-7′), 2.74 (1 H, dd, $J = 17.6$, 4.2 Hz, H-2′), 2.66 (1 H, dd, $J = 14.2$, 8.1 Hz, H-7′).

Compound **13**.—Oil. IR ($CHCl_3$) ν_{max}/cm^{-1}: 3078, 3011, 2914, 1697, 1643, 1607, 1502, 1225. HREIMS *m*/*z* (intensity %): 398.1882 (100) (M^+, $C_{27}H_{26}O_3$ requires 398.1882), 357 (8). δ_H ($CDCl_3$): 7.05 (2 H, d, $J = 8.4$ Hz, H-3″/5″), 7.00 (1 H, d, $J = 8.1$, H-3), 6.92 (1 H, s, H-5), 6.78 (1 H, d, $J = 8.1$ Hz, H-2), 6.73 (2 H, d, $J = 8.4$ Hz, H-2″/6″), 5.95 (2 H, m, H-8/8″), 5.85 (1 H, m, H-8′), 5.81 (1 H, s, H-5′), 5.22 (2 H, m, H-9′), 5.04 (4 H, m, H-9/9″), 4.76 (1 H, m, H-3′), 3.31 (4 H, d, $J = 6.6$, H-7/7″), 3.17 (1 H, dd, $J = 17.6$, 2.9 Hz, H-2′), 2.92 (1 H, dd, $J = 17.6$, 5.0 Hz, H-2′), 2.78 (1 H, dd, $J = 14.2$, 6.9 Hz, H-7′), 2.63 (1 H, dd, $J = 14.2$, 8.0 Hz, H-7′).

Compound **14**.—Pink solid. mp 168 °C. IR ($CHCl_3$) ν_{max}/cm^{-1}: 3528, 3275 (br), 3082, 3011, 2914, 1636, 1497, 1229. HREIMS *m*/*z* (intensity %): 530.2457 (100) (M^+, $C_{36}H_{34}O_4$ requires 530.2457). δ_H ($CDCl_3$): 7.20 (2 H, dd, $J = 2.2$ Hz, H-3′), 7.17 (2 H, d, $J = 2.2$ Hz, H-5′), 7.12 (2 H, d, $J = 2.2$ Hz, H-5), 7.09 (2 H, dd, $J = 8.2$, 2.2 Hz, H-3), 6.89 (2 H, d, $J = 8.2$ Hz, H-2), 5.95 (4 H, m, H-8/8′), 5.07 (8 H, m, H-9/9′), 3.41 (2 H, d, $J = 6.7$ Hz, H-7′), 3.36 (4 H, d, $J = 6.7$ Hz, H-7).

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