Oxygen insertion in *Sesamum indicum* furanofuran lignans. Diastereoselective syntheses of enzyme substrate analogues

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Abstract: The furofuran lignans in sesame seed have an unusual oxygen insertion between their furan and aryl rings. In our continuing investigations on the isolation and characterization of the enzyme(s) involved, the diastereoselective syntheses of various substrate analogues for the oxygen insertion step were developed for future substrate specificity and inhibitor studies. This synthetic strategy also provided entry to so-called furofuranone epoxy-lignans, such as salicifoliol from *Bupleurum* sp., and acuminatolide from *Helichrysum* sp.

Key words: furofuran lignans, sesame, epimers, salicifoliol, acuminatolide.

Resumé : On observe dans les lignanes furanofuraniques des graines de sésame, une insertion d'oxygène typique entre le cycle tétrahydrofuranique et le cycle aromatique. Comme avant propos à l'étude et l'isolation des enzymes responsables de la biosynthèse de la sésamoline à partir du pinorésinol, nous décrivons ici la synthèse diastéréosélective des épimères de ces intermédiaires oxygénés. Une extension de cette voie synthétique nous a fournit la possibilité d'accéder aux furolactones, le salicifoliol et l'acuminatolide.

Mots clés : lignanes furofuraniques, sésame, épimères, salicifoliol, acuminatolide.

Introduction

The furofuran lignans present in sesame (*Sesamum indicum*) seed have many important roles. They can function as potent antioxidants (1–5), either directly or through conversion to sesaminol 1 (4), thereby enhancing the quality and shelf life of sesame seed oil. Sesame lignans can also act as synergists with pyrethrum insecticides (6, 7), or as cyclic AMP phosphodi-esterase (8) and Δ-5 desaturase inhibitors in mammalian species (9). Moreover, addition of sesamin 2 to the diet reduces serum and liver cholesterol levels in rats (10) and has a hypo-cholesterolemic effect in humans (11). Dietary sesame lignans can protect against EtOH or CCl_4 induced liver damage (12), and enhance vitamin E activities (13) and the bioavailability of γ-tocopherol (14) in vivo.

Chemotaxonomic analyses of *Sesame* seed has established its major lignans as (+)-sesamin 2 and (+)-sesamolin 4 (Scheme 1) with the latter differing only by an oxygen insertion between the furofuran and piperonyl (3,4

methylenedioxyphenyl) groups. Biochemical entry to these furofuran lignans occurs via stereoselective coupling of two molecules of *E*-coniferyl alcohol 5 to give (+)-pinoresinol 3, an enzymatic conversion of particular interest being the first example of regio- and stereospecific control of bimolecular phenoxy radical coupling (15–17). Although its enzymology of formation was first delineated in *Forsythia* sp. (15–17), (+)-pinoresinol 3 biosynthesis from *E*-coniferyl alcohol 5 in *Sesame* sp. is apparently engendered in a comparable manner (unpublished data).

Depending upon the species involved, (+)-pinoresinol 3 (a central intermediate in lignan biosynthesis) can be metabolized into a wide variety of different furofuran, furano, dibenzyl butane, dibenzyl butyrolactone, and aryl (tetrahydro)naphthalene lignans (18, 19). For example, in *Forsythia intermedia*, enantiospecific reduction of (+)-pinoresinol 3 gives rise to (+)-lariciresinol 6 and (−)-secoisolariciresinol 7 (20–22), the dehydrogenation of which then affords (−)-matairesinol 8 (23). The NADPH-dependent enzyme catalyzing the sequential reductive steps leading to (−)-secoisolariciresinol 7 has been purified to apparent homogeneity, and the gene encoding the protein cloned (24).

In contrast, the lignan pathway in *Sesame* sp. converts (+)-pinoresinol 3 into (+)-sesamolin 4 via introduction of methylenedioxy bridges and an oxygen insertion between its aryl and furan rings. However, the sequence of oxidative/cyclization steps, and its associated enzymology, are as yet unknown. Scheme 2 shows plausible biosynthetic intermediates in the direct conversion of (+)-pinoresinol 3 to (+)-sesamolin 4. At this juncture, it is emphasised that the nomenclature system adopted is that of the 8,8′-linked lignans; the other recommended systems (IUPAC and CAS) were not used since they lacked any internal numbering consistency between the

Scheme 1.

1
sesaminol

2
sesamin

3
pinoresinol

4
sesamolin

5
coniferyl alcohol

6
lariciresinol

7
secoisolariciresinol

8
matairesinol
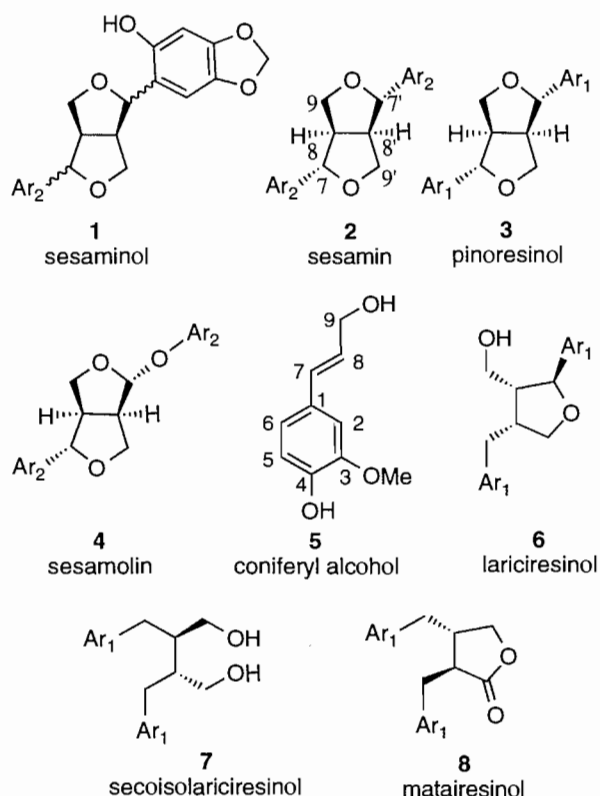
Legend: Ar_1 = 3-methoxy-4-hydroxyphenyl; Ar_2 = 3,4-methylenedioxyphenyl

different classes of lignans (and lignan-derived substances) described in this paper.

As can be seen, oxygen insertion could initially occur with (+)-pinoresinol **3** (route **a**) to give (+)-pinoresinolin **9**, with sequential methylenedioxy bridge formation to afford (+)-piperitolin **10** and (+)-sesamolin **4**, respectively. Oxygen insertion could also either follow or precede methylenedioxy bridge formation, i.e., from (+)-piperitol **11** to give (+)-sesamolinol **12** (route **b**) or from (+)-piperitol **11** to (+)-piperitolin **10** (route **c**), respectively. Perhaps, more unlikely, (+)-sesamin **2** may be directly converted into (+)-sesamolin **4** (route **d**). Synthetic methodology to pinoresinol **3** (22, 25), piperitol **11** (26), sesamin **2** (27), sesamolin **4** (27), pinoresinolin **9**, piperitolin **10**, and sesamolinol **12** (manuscript in preparation) has already been established, thus setting the stage for systematic study of the biosynthetic sequence involved.

The purpose of this investigation was to synthesize "epimers" **13–15** of the plausible aryl-*O*-furofuran biosynthetic intermediates **9**, **10**, and **12**, which differ only in their stereochemistry at C-7′ (Scheme 3). These are required to examine both the substrate specificity of the oxygen insertion reaction using epi-pinoresinol **16**, epi-piperitol **17**, and related compounds as enzyme substrate analogues, as well as determining whether they could function as inhibitors of the enzymatic transformation itself. Moreover, given our ongoing interest in the enantiospecificity of lignan biosynthetic conversions, and identification of the *precise* enzymology involved, it was important to obtain these putative substrate analogues in

Fig. 1. General strategy to "oxygenated" lignans.
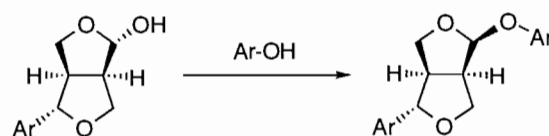
racemic form. This is because the various enantiomers can readily be separated by chiral column HPLC and, hence, provide the means to probe in detail both the enantiospecificity and diastereoselectivity of the oxygen insertion step. This approach has already been successfully applied to the study of (+)-pinoresinol **3** (15–17), (+)-lariciresinol **6**, (−)-secoisolariciresinol **7**, (−)-matairesinol **8** (20–24), and (−)-arctigenin **18** (28) biosynthesis.
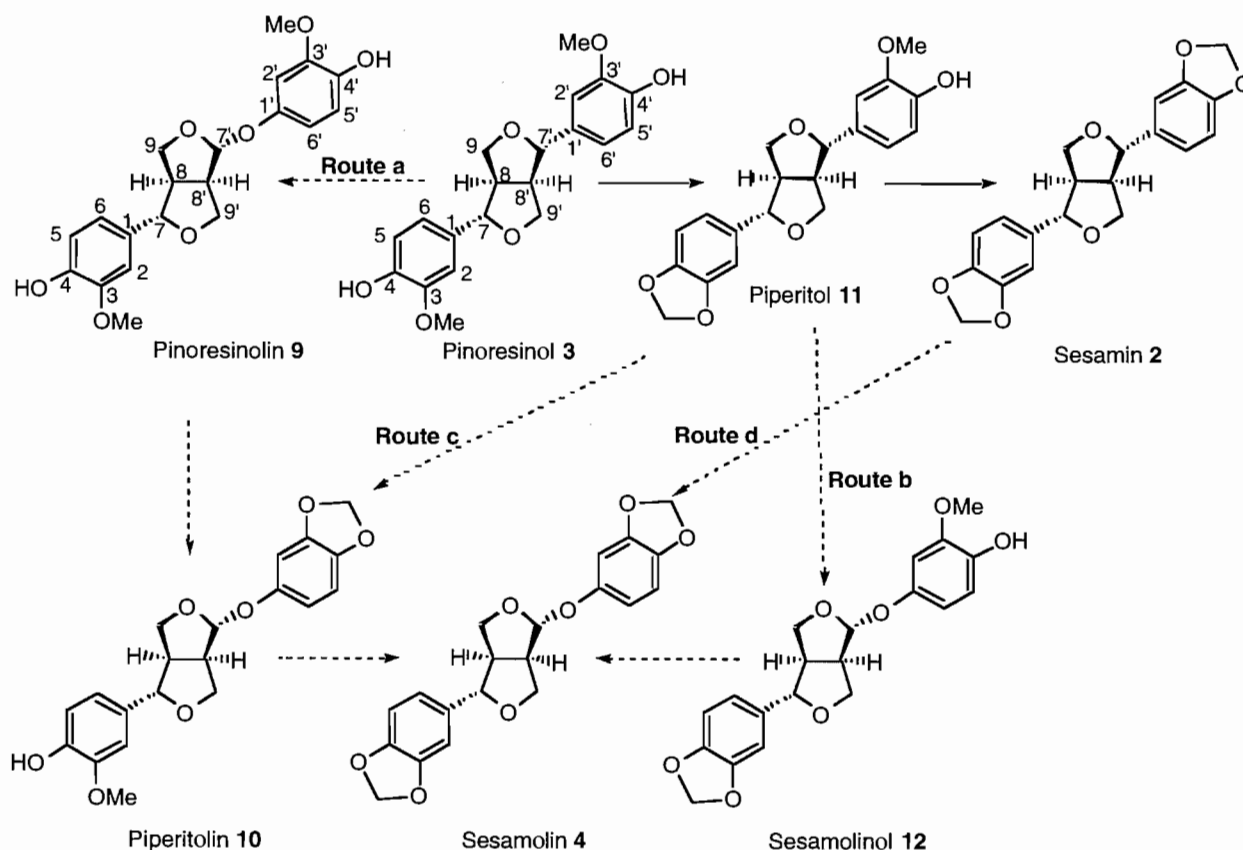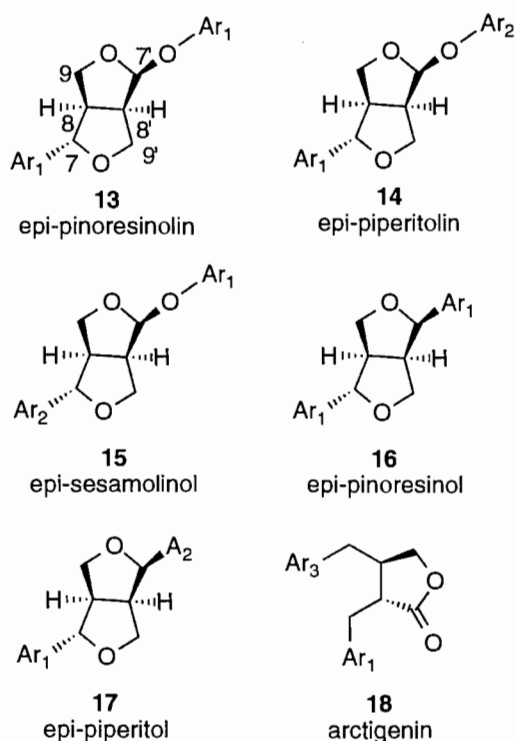
Results and discussion

The main goal of this study was to develop a facile synthesis of the "oxygenated" lignans, epi-pinoresinolin **13**, epi-piperitolin **14**, and epi-sesamolinol **15**. To achieve this goal, we envisaged the best overall strategy to be that of synthesis of lactols of the type shown above, followed by aryl alkyl ether formation with inversion of configuration at C-7′ (see Fig. 1).

We sought first to establish the validity and usefulness of the proposed approach using, as synthon, the lactol samin **19**, which can readily be obtained in either racemic (±), (+), or (−) form (27, 29, 30). For this study, (+)-samin **19** (230 mg) was first conveniently prepared by acid hydrolysis (30, 31) of (+)-sesamolin **4** (527 mg), which in turn had previously been isolated from *S. indicum* seeds (Scheme 4).

In the ^{1}H NMR spectrum of the starting material, (+)-sesamolin **4**, the H_{ax} proton at C-7′ appears as a singlet resonance at δ 5.47 (32); its absence of coupling with the adjacent bridgehead proton at H-8′ is in agreement with the projected dihedral angle of ~90°. Importantly, the corresponding H_{ax} proton at C-7′ of (+)-samin **19** also gave a singlet at δ 5.45 (data not shown), indicating that the relative stereochemistry in both molecules was the same at this position. Although the (+)-samin **19** thus generated had essentially an identical melting point, as well as IR, UV, and ^{1}H/^{13}C NMR spectra, to that reported previously (29), additional verification of the configuration of the furofuranol skeleton of **19** was determined by its conversion via oxidation with pyridinium dichromate to give the lactone, (+)-acuminatolide **20**. Its (−) antipode had previously been isolated from *Helichrysum acuminatum* (33), as well as obtained by total synthesis (27). Other than its optical rotation, (+)-acuminatolide **20** was identical in every respect to that of the natural product, thus verifying the overall configuration of (+)-samin **19** to be as shown. Moreover, to our knowledge, this is the first (hemi)synthesis of (+)-acuminatolide **20**.

With the configuration of (+)-samin **19** so defined, attention was next directed to the synthesis of (+)-epi-sesamolinol **15**. First, 4-benzyloxy-3-methoxyphenol **22** was obtained by Bayer–Villiger oxidation (34, 35) of *O*-benzyl vanillin **21** (23) via the action of *m*-chloroperoxybenzoic acid (*m*-CPBA) and subsequent NaOH hydrolysis. Phenol **22** was then condensed with (+)-samin **19**, in the presence of PPh$_3$ and DEAD (36), to give **23**, subsequent deprotection of which with H$_2$/Pd/C

Scheme 2. Proposed biosynthetic pathways from (+)-pinoresinol **3** to (+)-sesamolin **4**.

Scheme 3.

13
epi-pinoresinolin

14
epi-piperitolin

15
epi-sesamolinol

16
epi-pinoresinol

17
epi-piperitol

18
arctigenin

Legend: Ar_1 = 3-methoxy-4-hydroxyphenyl; Ar_2 = 3,4-methylenedioxyphenyl; Ar_3 = 3,4-dimethoxyphenyl

afforded (+)-epi-sesamolinol **15** in 60% overall yield. That the synthetic product so obtained had undergone an inversion of configuration at C-7′ could readily be determined by inspection of the ^{1}H NMR spectrum. The most striking change was the appearance of a doublet (J = 5.6 Hz) at 5.59 ppm, corresponding to the H_{eq} proton at C-7′ coupled to the C-8′ bridgehead proton. (This contrasts with the comparable H-7′$_{ax}$ resonance in (+)-sesamolin **4**, which has a singlet at δ 5.47 ppm.) This downfield shift of 0.15 ppm is consistent with related spectroscopic assignments for the naturally occurring lignan insecticidal agent, haedoxan A (H-7′$_{ax}$), to that of its epimeric synthetic product, isohaedoxan A (H-7′$_{eq}$), which showed a comparable downfield shift of 0.17 ppm (37). All other spectroscopic data supported epi-sesamolinol **15** to have the structure as shown. Consequently, not only does this represent the first (hemi)synthesis of (+)-epi-sesamolinol **15**, but adaptation of this approach using (±)-samin **19** gives a convenient route to racemic (±)-epi-sesamolinol **15**.

With the overall synthetic approach thus validated, attention was next directed to formation of the two other putative substrate analogues/inhibitors, epi-pinoresinolin **13** and epi-piperitolin **14**. In an analogous manner, this required synthesis of the pivotal lactol intermediate **24** (Scheme 5), which differs only from samin **19** by having a 4-benzyloxy-3-methoxyphenyl rather than a piperonyl group. Condensation of lactol **24** with either phenol **22** or its corresponding piperonyl analog would therefore afford (following deprotection) epi-pinoresinolin **13** and epi-piperitolin **14**, respectively (Schemes 5 and 6).

Scheme 4. Hemisynthesis of (+)-epi-sesamolinol **12** and (+)-acuminatolide **20**.
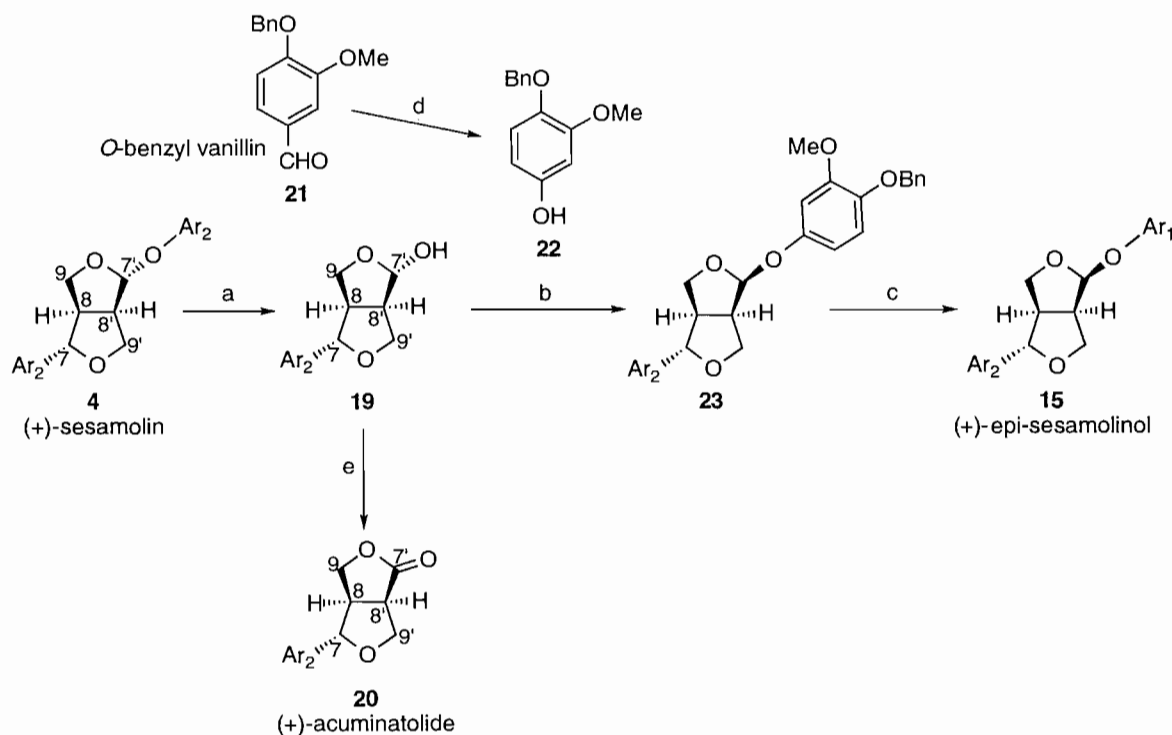
Legend: Ar_1 = 3-OMe-4-OH-Ph; Ar_2 = 3,4-OCH_2O-Ph; Bn = CH_2-Ph; a: H_3O^+, 65%; b: PPh_3, DEAD, THF, 80%; c: H_2/Pd/EtOAc, 75%; d: *m*-CPBA, CH_2Cl_2, then NaOH, MeOH, 64%; e: PDC, AcOH, 4 Å, CH_2Cl_2, 78%.

Lactol **24** was obtained from 4-vinylbutyrolactone **25** (38) as follows. Treatment of lactone **25** with LDA generated the corresponding lithiated form, which readily underwent diastereoselective addition with *O*-benzylvanillin **21**. This afforded exclusively the *trans* lactonic alcohol **26**, as a mixture of diastereoisomers in 92% yield (Scheme 5), which was used without further purification/resolution. (That the geometry of the pendant groups on the butyrolactone was indeed *trans* was based on a previous report of the configuration of the piperonyl analogue of **26**, prepared in a similar manner, which in turn was employed in the synthesis of the lignan insecticidal agents, haedoxan A, D, E, and their stereoisomers (37).)

Subsequent reduction of lactone **26** with $LiAlH_4$ and reaction of corresponding triol **27** with bromotrimethylsilane gave tetrahydrofuran **28**, presumed to possess both vinyl and hydroxymethyl substituents in a *syn* conformation, in 81% overall yield for both steps (37). Treatment of the vinyl group of alcohol **28** with OsO_4 in catalytic amount then afforded triol **29** as a mixture of diastereoisomers in 79% yield. Subsequent cleavage of its 1,2-diol by $NaIO_4$ gave the corresponding aldehyde, which underwent spontaneous cyclization, to afford lactol **24** in 84% yield. That this possessed a C-7′ H_{ax} was again established by inspection of the ^1H NMR spectrum, which displayed a 1H singlet at δ 5.35 ppm. Additionally, verification that only one stereoisomer resulted from this synthetic scheme was established via two pieces of interlocking evidence. The first involved oxidative conversion to the known lignan-derived furofuranone natural product, salicifoliol **31**, and the second by determination of the configuration of epi-pinoresin-

olin **13** via a combination of NOESY and HETCOR analyses (see later).

It had previously been established that the aerial portions of *Bupleurum salicifolium* Soland (39) contain salicifoliol **31**, in addition to the lignans (+)-pinoresinol **3**, (+)-eudesmin, and (+)-medioresinol. Thus, to verify the configuration of racemic lactol **24**, it was converted into salicifoliol **31** by oxidation with pyridinium dichromate (PDC) in the presence of AcOH and 4Å molecular sieves as before (40), with subsequent debenzylation (Scheme 5). That the synthetic product was indeed (±)-salicifoliol **31** was determined by its identical melting point to that of the natural product (101–102°C vs. 102–103°C (39)), as well as by comparison of its MS fragmentation patterns, $^1H/^{13}C$ NMR, UV, and IR spectra to those reported for (+)-salicifoliol **31**. Previous COSY experiments had shown that the pendant aryl group of salicifoliol **31** was *exo*, and that the bridgehead hydrogens were *cis* to each other. Thus, with all spectroscopic data identical to the naturally occurring product, with the exception of optical rotation, this represents the first synthesis of (±)-salicifoliol **31**. More importantly, it provided strong evidence that the configuration of lactol **24** was as shown.

With good evidence supporting the structure and configuration of lactol **24** as shown, attention was directed to the formation of (±)-epi-pinoresinolin **13** (Scheme 6). Again, *O*-benzylvanillin **21** was converted into the corresponding phenol **22**, via Bayer–Villiger oxidation with *m*-CPBA and subsequent NaOH hydrolysis. This was then reacted with lactol **24**, in the presence of PPh_3 and DEAD, to give **32**, subsequent

Scheme 5. Synthesis of (±)-lactol **24** and (±)-salicifoliol **31**.
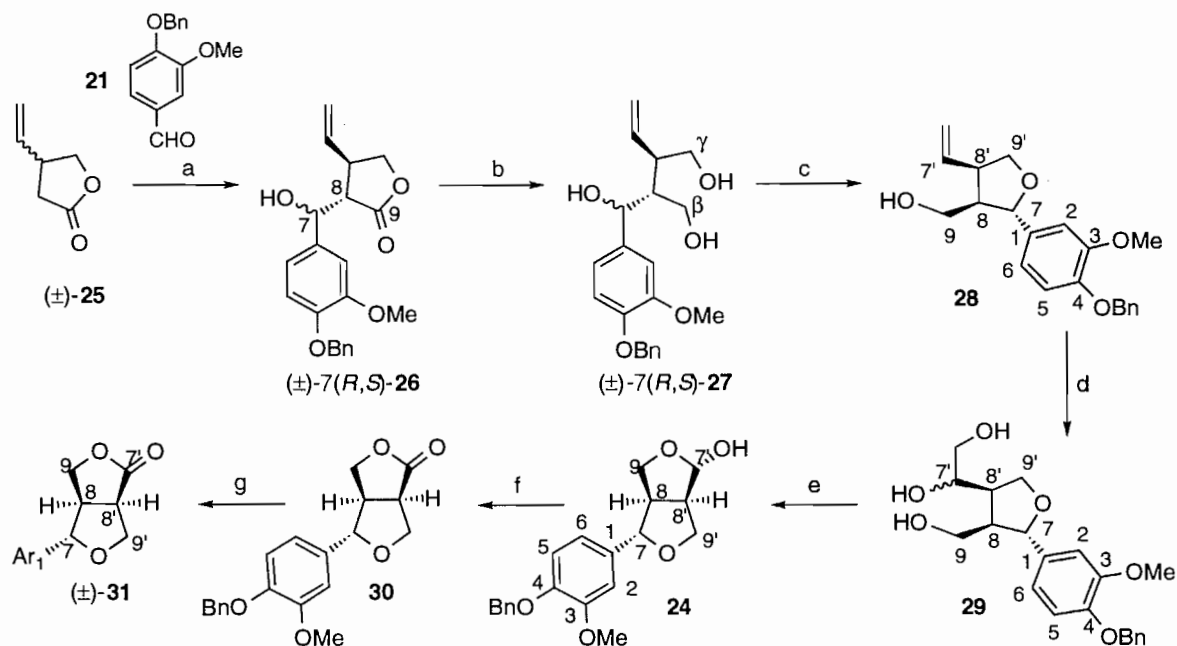
Legend: Ar₁ = 3-OMe-4-OH-Ph, Bn = CH₂-Ph; a: LDA, THF, **21**, 92%; b: LiAlH₄, THF, 89%; c: TMSBr, THF, 89%; d: OsO₄, NMO, THF/H₂O, 79%; e: NalO₄, THF, 89%; f: PDC, AcOH, 4 Å, CH₂Cl₂, 78%; g: H₂/Pd/C, EtOAc, 90%.

Scheme 6. Synthesis of (±)-epi-pinoresinolin **13** and (±)-epi-piperitolin **14**.
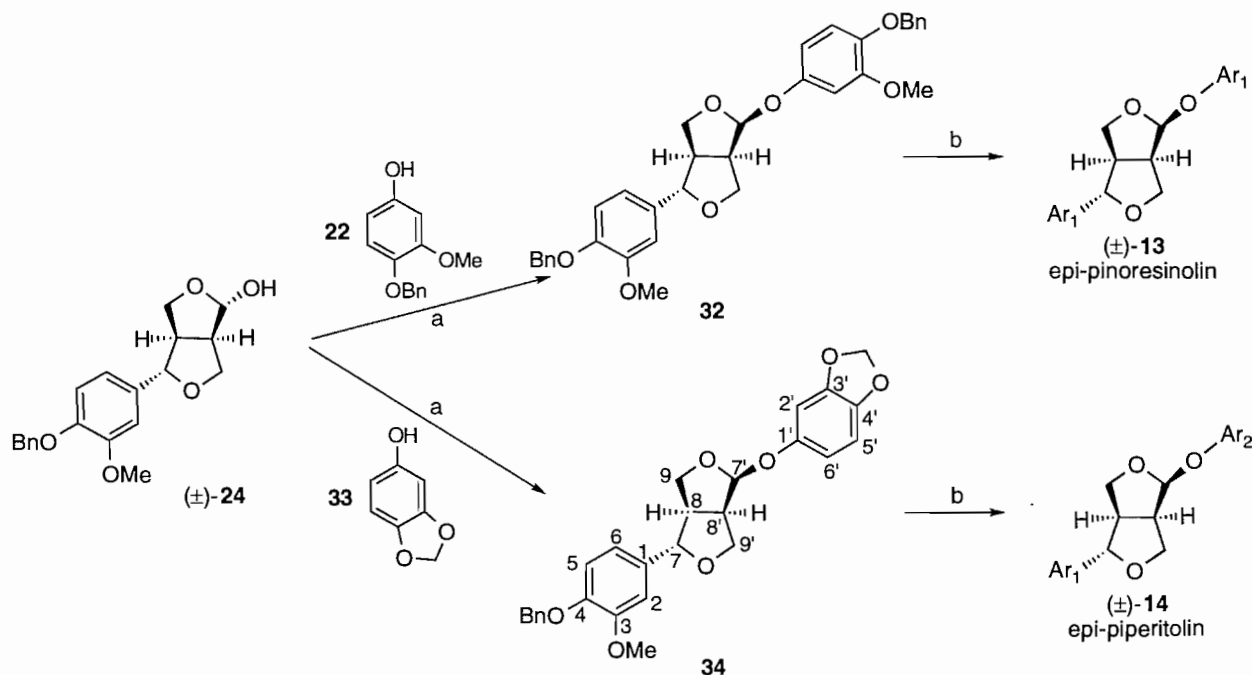
Legend: Ar₁ = 3-OMe-4-OH-Ph; Ar₂ = 3,4-OCH₂O-Ph; Bn = CH₂-Ph; a: PPh₃, DEAD, THF, **22**: 89%; **33**: 85%; b: H₂/Pd/C, EtOAc, **13**: 84%; **14**: 88%.

deprotection of which with H₂/Pd/C gave (±)-epi-pinoresino-lin **13** in 75% overall yield. Its configuration was next determined by a combination of HETCOR and NOESY spectral analyses, where the ¹H NMR signals of epi-pinoresinolin **13**

were assigned to individual protons on the basis of chemical shift, observed multiplicities, and decoupling experiments (Table 1), and all carbons (with directly attached protons) assigned using the HETCOR spectrum. Assignments of sig-

Table 1. NMR (600 MHz, ^{1}H; 150 MHz, ^{13}C; CDCl$_3$) spectral data for epi-pinoresinolin **13**.

	^{13}C	^{1}H	
Assignment	δ	δ	J (Hz)
1	132.69	—	
2	108.53	6.93	d, $J_{2,6}$ = 1.9
3	146.66[a]	—	
4	145.23[a]	—	
5	114.23	6.89	d, $J_{5,6}$ = 8.1
6	118.90	6.83	d,d, $J_{2,6}$ = 1.9, $J_{5,6}$ = 8.1
7	85.30	4.80	d, $J_{7,8}$ = 7.1
8	52.75	3.04	m, $J_{8,9ax}$= 7.6, $J_{8,9eq}$ = 4.7
9	69.30	H$_{ax}$, 4.12	m, $J_{9ax,eq}$ = 9.1
		H$_{eq}$, 4.03	
OH	—	5.43	br s
OCH$_3$	55.87	3.90	s, 3H
1′	150.80	—	
2′	101.75	6.69	d, $J_{2',6'}$ = 2.7
3′	146.83[a]	—	
4′	140.91[a]	—	
5′	114.17	6.84	d, $J_{5',6'}$ = 8.7
6′	108.41	6.64	dd, $J_{6',2'}$ = 2.7, $J_{6',5'}$ = 8.7
7′	102.83	5.60	d, $J_{7',8'}$ = 5.6
8′	51.10	3.33	$J_{8',9'ax}$ = 8.0, $J_{8',9'eq}$ = 4.1, $J_{8',8}$ = 10.0
9′	67.00	H$_{ax}$, 4.42	$J_{9'ax,eq}$ = 9.1
		H$_{eq}$, 4.17	
OH	—	5.73	br s
OCH$_3$	55.91	3.87	s

[a]Assigments are interchangeable for nonprotonated carbons.

nals derived from quaternary carbons were based on comparison with reported chemical shift data for (+)-sesamolin **4** (32).

To summarize, the NOESY spectra (mixing times 300 and 600 ms) showed a strong cross-peak between the H-8 and H-8′ proton signals suggesting that both were *cis* to each other. Moreover, the H-8 signal exhibited a correlation with the H-2 and H-6 proton resonances of the pendant aryl (Ar) group at δ 6.93 and 6.83, respectively, indicating that the 3-OMe-4-OH-phenyl group was attached to C-7 in a *cis* relationship to the H-8 and H-8′ protons. Significantly, although the NOESY spectra also displayed cross peaks between the H-7′ proton resonance and the H-2′ and H-6′ signals, none of the proton signals of the aryl group attached to the C-7′ showed any correlation to the H-8′ signal. In contrast, the H-7′ signal exhibited a correlation to the H-8′ signal, suggesting that the pendant aryl group attached to C-7′ was *trans* to the H-8 and H-8′ protons. The axial "β" configuration of the aryl group at C-7′ was again further supported by the fact that the signal of the H-7′$_{eq}$ proton was a downfield doublet ($J_{7',8'}$ = 5.6 Hz) at δ 5.6 ppm. Thus, via a combination of derivatization and spectroscopic analyses, the configuration of epi-pinoresinolin **13** was as shown.

Lastly, with the configuration of epi-pinoresinolin **13** unambiguously determined, sesamol **33** (3,4-methylenedioxy phenol) was condensed with lactol **24** to afford, after deprotection of **34**, (±)-epi-piperitol **14** in 75% overall yield.

Concluding remarks

This study provides a convenient synthetic strategy to the "oxygenated" lignans epi-pinoresinolin **13**, epi-piperitolin **14**, and epi-sesamolinol **15** in good overall yield. The configuration of each molecule was determined via a number of spectroscopic means as well as by chemical derivatization, the latter proceeding in a manner that also permitted the synthesis of furofuranone lignan-derived substances, such as acuminatolide **20** and salicifoliol **31**. Future studies will be directed to defining the enzymology of the "oxygen" insertion step, with the compounds so obtained used as substrate analogues or inhibitors.

Experimental

Unroasted and unbleached seeds of *Sesamum indicum* were purchased in a local grocery store. IR and UV spectra were recorded on Perkin–Elmer 1720-X FTIR and Lambda 6 UV/ VIS spectrophotometers, respectively. NMR studies of epi-pinoresinolin **13** were performed on a Varian UNITY*plus* (599.89 MHz, ^{1}H) spectrometer, whereas all other ^{1}H/^{13}C spectra were obtained on a Brüker AMX-300 (300.14 MHz, ^{1}H) instrument. NMR spectra were recorded in CDCl$_3$ solution with TMS as an internal reference, with chemical shifts (δ) expressed in ppm and coupling constants (J) in Hz.

NOESY spectra were recorded using the standard pulse sequence (41), with mixing times, t_m, of 300 and 600 ms. HETCOR spectra were measured using the pulse sequence previously described (42). The ^{1}H chemical shifts and coupling constants were obtained by first-order analysis of 1D spectra. EIMS were carried out using a Waters Integrity HPLC/MS, whereas HRMS employed a VG 7070 EHF mass spectrometer with a temperature source of 250°C at 70 eV with Ar_1 = 3-methoxy-4-hydroxyphenyl and Ar_2 = 3,4-methylenedioxyphenyl for fragment interpretation. Solvents were either HPLC grade (CH_3CN, MeOH, AcOH, CH_2Cl_2, THF) or ACS grade (EtOAc, hexanes) and were obtained from Baker. Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were distilled over $LiAlH_4$–triphenylmethane and CaH_2, and column and analytical thin-layer chromatographic separations were performed using silica gel 60 (230–400 mesh) and AL SI G/UV 254 (Whatman), respectively.

(+)-Samin 19

This was synthesized as outlined (30, 31) but modified as follows. A suspension of (+)-sesamolin 4 (527 mg, 1.42 mmol), DOWEX 50 X2-200 (545 mg), NaOAc (150 mg, 1.83 mmol), and HCl 10% (1 mL) in CH_3CN (10 mL) was stirred under reflux for 2 h. The suspension was then cooled to room temperature, the resin removed by filtration, and the filtrate evaporated in vacuo, to give a dry solid. The resulting residue was dissolved in a minimum amount of $CHCl_3$ and subjected to silica gel column chromatography, eluted with hexanes:EtOAc 3:1 to 1:1, to give (+)-samin 19 (230.8 mg, 65%); mp 108–109°C (EtOAc:cyclohexane) (lit. (31) mp 106°C; (29) mp 108–109°C); $[\alpha]_D$ +104.65 (c 0.516, $CHCl_3$) (lit. $[\alpha]_D$ (30) +103); IR ($CHCl_3$) ν_{max}: 3400 (br, OH), 1610, 1505, 1490, 1446, 1245 cm^{-1}; MS m/e (relative %): 250 (M$^+$, 86), 232 (M – H_2O^+, 6), 194 (M – $C_2O_2^+$, 38), 176 (54), 149 (Ar_2CO^+, 100), 135 ($Ar_2CH_2^+$, 58), 122 (Ar_2H^+, 22); HRMS; calcd. for $C_{13}H_{14}O_5$: 250.0841 (M$^+$), found: 250.0805; for ^{1}H and ^{13}C NMR spectral analyses: see ref. 29.

(+)-Acuminatolide 20

To a solution of (+)-samin 19 (80 mg, 0.32 mmol) in dry CH_2Cl_2 (50 mL) was added pyridinium dichromate (PDC) (4 equiv., 481 mg), AcOH (1 equiv., 20 µL), and 4Å molecular sieves (500 mg). The resulting suspension was stirred for 6 h at room temperature (r.t.), then filtered through a plug of silica gel and the filtrate removed in vacuo to give a yellow solid. The residue was dissolved in a minimum amount of $CHCl_3$ and subjected to silica gel column chromatography, eluted with hexanes:EtOAc (2:1), to give 20 (61.84 mg, 78%); mp 118°C (EtOAc:hexanes) (lit. (27, 33) mp 118–119°C); $[\alpha]_D$ +100.2 (c 0.11, $CHCl_3$) (lit. $[\alpha]_D$ (27) –103.82 (c 0.31, $CHCl_3$); $[\alpha]_D$ (33) –37 (c 0.11, $CHCl_3$)); IR ($CHCl_3$) ν_{max}: 1775 (C=O), 1610, 1510, 1500 (C=CAr), 1245 (C-O) cm^{-1}; ^{1}H NMR δ: 6.80 (br s, 1H, H-2), 6.70 (br s, 2H, H-5 and H-6), 5.95 (s, 2H, OCH_2O), 4.57 (d, 1H, $J_{7,8}$ = 6.8, H-7), 4.46 (dd, 1H, $J_{9eq,9ax}$ = 6.8, $J_{8,9eq}$ = 9.7, H-9eq), 4.35–4.25 (m, 2H, H-9′ax and H-9ax), 4.14 (dd, 1H, $J_{9'eq,9'ax}$ = 3.6, $J_{8',9'eq}$ = 9.3, H-9′eq), 3.40 (ddd, 1H, $J_{7,8'}$ = 3.6, $J_{8',9eq}$ = 9.3, $J_{8',8}$ = 9.0, H-8′), 3.05 (m, 1H, H-8); ^{13}C NMR δ: 178.16 (C-7′), 148.11 (C-3), 147.60 (C-4), 132.73 (C-1), 119.57 (C-6), 108.22 (C-5), 106.27 (C-2), 101.19 (OCH_2O), 85.92 (C-7), 69.93 and 69.77 (C-9/C-9′), 48.86 (C-8), 46.58 (C-8′) ppm; MS m/e (relative

%): 248 (M$^+$, 100), 218 (M – CH_2O^+, 22), 163 (83), 150 (Ar_2CHO^+, 80), 149 (Ar_2CO^+, 100), 135 ($Ar_2CH_2^+$, 82), 121 (Ar_2^+, 38); HRMS, calcd. for $C_{13}H_{12}O_5$: 248.0685 (M$^+$); found: 248.0683.

4-Benzyloxy-3-methoxy phenol 22

Phenol 22 (139.5 mg, 0.64 mmol) was prepared from O-benzylvanillin 21 (242 mg, 1 mmol) (23) in 64% overall yield exactly as described (34, 35).

O-Benzyl-epi-sesamolinol 23

To a solution of (+)-samin 19 (29.8 mg, 0.12 mmol) in dry THF (10 mL), PPh$_3$ (31.6 mg, 0.12 mmol), and protected phenol 22 (26.2 mg, 0.12 mmol) was added diethylazodicarboxylate (DEAD) (19 µL, 1 equiv.). The mixture was stirred at r.t. for 24 h and the solvent removed in vacuo. The residue was next subjected to silica gel column chromatography, eluted with hexanes:EtOAc 3:1 (v/v), to give O-benzyl epi-sesamolinol 23 (44.8 mg, 80%). IR ($CHCl_3$) ν_{max}: 1600, 1510, 1450 (C=CAr), 1250, 1220 (C-O) cm^{-1}; ^{1}H NMR δ: 7.50–7.20 (m, 5H, Bn), 6.90–6.55 (m, 6H, CHAr), 5.94 (s, 2H, OCH_2O), 5.62 (d, 1H, $J_{7',8'}$ = 5.6, H-7′), 5.10 (s, 2H, CH_2Ph), 4.80 (d, 1H, $J_{7,8}$ = 6.8, H-7), 4.45–4.38 (m, 1H, H-9′ax), 4.20–4.10 (m, 1H, H-9′eq), 4.15–4.10 (m, 1H, H-9ax), 4.05–3.95 (m, 1H, H-9eq), 3.87 (s, 3H, OCH_3), 3.35–3.25 (m, 1H, H-8′), 3.05–2.90 (m, 1H, H-8); ^{13}C NMR δ: 151.95, 151.14, 150.56, 147.92, 147.13 (C-3, C-4, C-1′, C-3′, C-4′), 134.79 (Cq/Bn), 143.31 (C-1), 128.42, 128.38, 127.37 (CH/Bn), 119.42 (C-6), 115.27 (C-5′), 108.13 (C-5), 107.03 (C-6′), 106.39 (C-2), 102.65 (C-7′), 102.41 (C-2′), 101.02 (OCH_2O), 85.31 (C-7), 71.83 (CH_2Ph), 69.40 (C-9′), 67.08 (C-9), 55.93 (OCH_3), 52.85 (C-8), 51.09 (C-8′); MS m/e (relative %): 462 (M$^+$, 5), 243 (20), 230 (70), 203 (30), 165 (15), 149 (Ar_2CO^+, 15), 135 ($Ar_2CH_2^+$, 100), 121 (Ar_2^+, 70), 105 (15); HRMS, calcd. for $C_{27}H_{26}O_7$: 462.1679; found: 462.1671.

(+)-Epi-sesamolinol 15

(+)-O-Benzyl epi-sesamolinol 23 (59.2 mg, 0.13 mmol) in EtOAc (5 mL) was treated with Pd/C 10% (15 mg). The solution was then stirred for 3 h under H_2 atmosphere, following which it was filtered over a short path silica gel column eluted with EtOAc. The filtrate was removed in vacuo, and the resulting residue purified by silica gel column chromatography, eluted with EtOAc:hexanes 2:1 (v/v), to give (+)-epi-sesamolinol 15 (29 mg, 75%). $[\alpha]_D$ +182 (c 0.996 g/100 mL in $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3425 (br, OH), 1613, 1510, 1490, 1448 (C=CAr), 1234, 1196 cm^{-1}; UV λ_{max}: 230, 285 nm; ^{1}H NMR δ: 6.90–6.70 (m, 6H), 5.95 (s, 2H, OCH_2O), 5.59 (d, 1H, $J_{7',8'}$ = 5.6, H-7′), 5.38 (br s, 1H, OH), 4.78 (d, 1H, $J_{7,8}$ = 7, H-7), 4.50–4.35 (m, 1H, H-9′ax), 4.20–4.10 (m, 1H, H-9′eq), 4.10–4.08 (m, 1H, H-9ax), 4.05–3.95 (m, 1H, H-9eq), 3.87 (s, 3H, OCH_3), 3.35–3.20 (m, 1H, H-8′), 3.05-2.95 (m, 1H, H-8); ^{13}C NMR δ: 150.69 (C-1′), 147.88 (C-3), 147.07 (C-4), 146.80 (C-3′), 140.82 (C-4′), 134.90 (C-1), 119.36 (C-6), 114.13 (C-5′), 108.56 (C-5), 108.26 (C-6′), 106.54 (C-2), 101.92 (C-7′), 101.15 (OCH_2O), 100.98 (C-2′), 85.44 (C-7), 69.47 (C-9), 67.23 (C-9′), 56.08 (OCH_3), 53.08 (C-8′), 51.26 (C-8); MS m/e (relative %): 372 (M$^+$, 5), 273 (5), 233 (28), 203 ($Ar_2C_5H_6O^+$, 45), 149 (Ar_2CHO^+, 30), 140 (70), 135 ($Ar_2CH_2^+$, 100), 121 (Ar_2^+, 25), 105 (18); HRMS, calcd. for $C_{20}H_{20}O_7$: 372.1209; found: 372.1194.

Lactone 26

To a solution of LDA (3.18 mmol, 1.1 equiv.), freshly prepared from diisopropyl amine (0.42 mL) and 1.6 M n-BuLi in hexanes (1.99 mL) at $-15°C$, in dry THF (10 mL) under argon at $-78°C$ (acetone – Dry Ice bath), was added dropwise 4-vinyl butyrolactone **25** (323.5 mg, 2.88 mmol, 1 equiv.) in dry THF (6 mL) over 30 min. The resulting mixture was stirred at $-78°C$ for 30 min, following which O-benzylvanillin **21** (578.5 mg, 2.39 mmol) in dry THF (5 mL) was added dropwise over 30 min with the mixture allowed to stir at $-78°C$ for an additional 3.5 h. A saturated solution of $NH_4Cl_{(aq)}$ (0.5 mL) was added, and the resulting mixture was then allowed to warm to r.t. The mixture was sequentially extracted with diethyl ether (2×15 mL) and EtOAc (2×15 mL), with the combined organic layers dried (Na_2SO_4), evaporated in vacuo, and the resulting residue chromatographed on a silica gel column, eluted with hexanes:EtOAc 2:1 (v/v), to give the diastereoisomeric lactone **26** (779.7 mg, 92%) mixture, which was not resolved further. IR (CHCl$_3$) ν_{max}: 3492 (br, OH), 1762 (C=O), 1593, 1515, 1455 (C=CAr) cm^{-1}; ^{1}H NMR δ: 7.40–7.18 (m, 5H, Bn), 6.88–6.85 (m, 3H, CHAr), 5.30–5.15 (m, 1H, =CH), 4.85–4.55 (m, 1H, CHOH), 4.35–4.15 (m, 2H, =CH$_2$), 4.15–3.90 (m, 2H, CH$_2$OCO), 3.74 (s, 3H, OCH$_3$), 3.25–3.10 and 2.85–2.70 (m, 1H, =CH-CH), 2.70–2.55 (m, 1H, CO-CH); ^{13}C NMR δ: 177.72, 177.46 (CO), 149.17, 149.07, 147.42, 146.76 (Cq-O/Ar), 136.69, 136.65 (Cq/Bn), 135.78, 134.46 (CH$_2$=CH), 134.26, 131.92 (Cq/Ar), 128.04, 127.38, 126.92 (CH/Bn), 118.84, 117.46 (CH/Ar), 113.36, 113.16 (CH/Ar), 116.96, 116.38 (CH$_2$=), 110.05, 109.27 (CH/Ar), 72.90, 69.93 (CHOH), 70.44, 70.35 (CH$_2$O), 70.42 (CH$_2$Ph), 55.97 (OCH$_3$), 55.47, 51.58 (CH$_2$CO), 41.96, 38.58 (CH-CH=); MS m/e (relative %): 354 (M$^+$, 90), 337 (65), 336 (27), 315 (30), 243 (100), 151 (Ar$_1$CO$^+$, 80), 123 (Ar$_1^+$, 50); HRMS, calcd. for C$_{21}$H$_{22}$O$_5$: 354.1467; found: 354.1486.

Triol 27

To a solution of LiAlH$_4$ (51.2 mg, 1.5 equiv.) in dry THF (10 mL) at $0°C$, under an atmosphere of argon, was added dropwise a solution of lactone **26** (302.1 mg, 0.85 mmol) in dry THF (15 mL). The temperature was next raised to $50°C$, this being maintained for an additional 1.5 h. After cooling to r.t., the solution was neutralized with saturated $NH_4Cl_{(aq)}$ and extracted with CHCl$_3$ (3×10 mL). The organic solubles were combined, dried (Na_2SO_4), evaporated to dryness in vacuo, and the resulting residue purified by chromatography on silica gel, eluted sequentially with hexanes:EtOAc 2:1 (v/v) and EtOAc, to give the diastereoisomeric triol **27** (258 mg, 89%) mixture, which was not resolved further. IR (CHCl$_3$) ν_{max}: 3310 (br, OH), 1640 (C=C), 1606, 1593, 1510, 1455 (C=C, C=CAr), 1261, 1219 (C-O) cm^{-1}; ^{1}H NMR δ: 7.35–7.20 (m, 5H, Bn), 6.90–6.80 and 6.80–6.70 (m, 3H, CHAr), 5.90–5.50 (m, 1H, =CH), 5.20–5.00 (m, 2H, =CH$_2$), 5.07 (s, 1H) and 5.06 (s, 1H, CH$_2$-Ph), 5.00–4.70 (m, 1H, CHOH), 3.81 (s, 3H, OCH$_3$), 3.80–3.30 (m, 4H, CH$_2$OH), 2.60–2.20 (m, 1H, CH-CHOH), 2.10–1.60 (m, 1H, =CH-CH); ^{13}C NMR δ: 149.29, 149.20 (C-4), 146.99, 146.90 (C-3), 138.52, 138.40 (CH=), 136.86, 136.05 (C-1, Cq/Bn), 128.32, 127.67, 127.15 (CH/Bn), 118.40, 117.95 (C-6), 117.24, 116.30 (CH$_2$=), 113.59, 113.46 (C-5), 109.87, 109.49 (C-2), 74.55, 72.16 (CHOH), 70.82 (CH$_2$-Ph), 63.06, 62.50, 59.96, 59.53 ($2 \times$ CH$_2$OH), 55.77 (OCH$_3$), 50.06, 48.07 (=CH-CH), 44.87, 43.05 (CH-

CHOH); MS m/e (relative %): 340 (M$^+$ – H$_2$O$^+$, 19), 322 (100), 291 (19), 275 (34), 231 (85), 201 (81), 167 (87), 149 (79), 128 (81); HRMS, calcd. for C$_{21}$H$_{26}$O$_5$: 340.1675 (M – H$_2$O$^+$); found: 340.1686.

Tetrahydrofuran 28

To a solution of the diastereoisomeric triol mixture **27** (189 mg, 0.55 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added TMSBr (140 µL, 2 equiv.). The resulting solution was then stirred at r.t. for 15 min, neutralized with saturated $NaHCO_{3(aq)}$ (0.5 mL), dried (Na_2SO_4), with the organic solvent evaporated in vacuo and the residue subjected to silica gel column chromatography, eluted with hexanes:EtOAc 2:1 (v/v), to give tetrahydrofuran **28** (159.3 mg, 89%). IR (CHCl$_3$) ν_{max}: 3300 (br, OH), 1640 (C=C), 1606, 1594, 1515, 1465 (C=CAr), 1263, 1225 (C-O) cm^{-1}; ^{1}H NMR δ: 7.45–7.30 (m, 5H, Bn), 6.93 (d, 1H, J = 1.7, CHAr), 6.84–6.78 (m, 1H, CHAr), 5.97–5.90 (m, 1H, =CH), 5.22–5.14 (m, 2H, =CH$_2$), 5.16 (s, 2H, CH$_2$-Ph), 4.70 (d, 1H, J = 7.3, ArCHO), 4.23 and 3.83 (dd, 2H, J = 6.7, 8.6, CH$_2$OC), 3.90 (s, 3H, OCH$_3$), 3.75–3.69 (m, 1H) and 3.64–3.60 (m, 1H, CH$_2$OH), 3.15–3.05 (m, 1H, =CH-CH), 2.40–2.30 (m, 1H, CH-CH$_2$OH); ^{13}C NMR δ: 149.63 (C-4), 147.49 (C-3), 137.07 (Cq/Bn), 135.57 (CH=), 135.38 (C-1), 128.44, 127.73, 127.19 (CH/Bn), 118.10 (C-6), 117.32 (CH$_2$=), 113.72 (C-5), 109.47 (C-2), 82.41 (C-7), 72.61 (C-9'), 70.94 (CH$_2$-Ph), 60.76 (C-9), 55.90 (OCH$_3$), 53.41 (C-8), 45.62 (C-8'); MS m/e (relative %): 322 (M – H$_2$O$^+$, 100), 293 (10), 268 (5), 231 (95), 201 (73), 171 (55), 149 (63), 123 (Ar$_1^+$, 65); HRMS, calcd. for C$_{21}$H$_{24}$O$_4$ (M – H$_2$O$^+$): 322.1569; found: 322.1558.

Triol 29

To a solution of tetrahydrofuran **28** (144 mg, 0.45 mmol) in THF (3 mL) was added OsO$_4$ (2.5% equiv., 108 µL of a 2.5% soln. in t-BuOH) and N-methylmorpholine-N-oxide (NMO) (1.4 equiv., 124 µL of a 60% soln. in H$_2$O). The suspension was stirred for 2 days at r.t., following which it was extracted with CHCl$_3$ (3×10 mL). The organic solubles were combined, dried (Na_2SO_4), the solvent removed in vacuo, and the resulting residue chromatographed on silica gel, eluted with hexanes:EtOAc 2:1 (v/v), to give the triol **29** (132.1 mg, 79%). IR (CHCl$_3$) ν_{max}: 3390 (br, OH), 1607, 1594, 1515, 1455 (C=CAr), 1263, 1217 (C-O) cm^{-1}; ^{1}H NMR δ: 7.40–7.20 (m, 5H, Bn), 6.90–6.70 (m, 3H, CHAr), 5.14 (s, 2H, CH$_2$-Ph), 4.79 (d, J = 6.4) and 4.51 (d, J = 3.8, 1H, OCH-Ar), 4.10–3.90 (m, 1H, CHOH-CH$_2$OH), 3.90–3.30 (m, 6H, CH$_2$OH and CH$_2$O), 3.83 (s, 3H, OCH$_3$), 2.60–2.30 (m, 1H, CHCHOH), 2.60–2.35 and 2.30–2.20 (m, 1H, CHCH$_2$OH); ^{13}C NMR δ: 149.51 (C-4), 147.47 (C-3), 136.84 (Cq/Bn), 135.07, 134.98 (C-1), 128.38, 127.73, 127.20 (CH/Bn), 117.96, 117.81 (C-6), 113.62 (C-5), 109.41 (C-2), 82.81, 82.11 (C-7), 70.87 (CH$_2$-Ph), 70.46, 70.35 (CHOH), 68.93, 68.25 (C-7') 65.71, 65.39 (CH$_2$OH), 60.67, 59.53 (C-9), 55.91 (OCH$_3$), 51.15, 50.74 (C-8), 43.86, 42.54 (C-8'); MS m/e (relative %): 374 (M$^+$, 83), 356 (80), 338 (50), 295 (50), 283 (20), 265 (90), 175 (78), 151 (Ar$_1$CO$^+$, 80), 123 (Ar$_1^+$, 100), 107 (90); HRMS, calcd. for C$_{21}$H$_{26}$O$_6$: 374.1726; found: 374.1741.

Furanofuran-1-ol 24

To a solution of triol **29** (125.1 mg, 0.334 mmol) in MeOH (3 mL) at $0°C$ was added dropwise a solution of NaIO$_4$ (85.7 mg, 1.2 equiv.) in MeOH–H$_2$O (6.5 mL, 10:3) over 10 min. The

temperature was raised to r.t., with the mixture allowed to stir for an additional 12 h, and then filtered. The resulting filtrate was extracted with $CHCl_3$ (3×10 mL) with the organic layers combined and dried (Na_2SO_4), and the solution evaporated to dryness in vacuo. The residue was subjected to chromatography on silica gel, eluted with hexanes:EtOAc 2:1 (v/v), to give the furanofuranol **24** (101.8 mg, 89%). IR ($CHCl_3$) ν_{max}: 3410 (br, OH), 1594, 1515, 1455 (C=CAr) cm^{-1}; ^{1}H NMR δ: 7.45–7.20 (m, 5H, Bn), 6.95 (d, 1H, $J_{2,6}$ = 1.7, H-2), 6.75–6.65 (m, 2H, H-5, H-6), 5.16 (s, 2H, CH_2-Ph), 5.35 (s, 1H, H-7'), 4.38 (d, 1H, $J_{7,8}$ = 7.1, H-7), 4.39 (dd, 1H, $J_{9ax,9eq}$ = 7, $J_{8,9ax}$ = 8.9, H-9ax), 4.25-4.10 (m, 1H, H-9'ax), 3.95–3.85 (m, 1H, H-9'eq), 3.56 (dd, 1H, $J_{9ax,9eq}$ = 7, $J_{8,9eq}$ = 9.1, H-9 eq), 3.91 (s, 3H, OCH_3), 3.76 (br s, 1H, OH), 3.11–2.87 (m, 2H, H-8, H-8'); ^{13}C NMR δ: 149.78 (C-3), 147.82 (C-4), 136.99 (Cq/Bn), 133.51 (C-1), 128.47, 127.78, 127.20 (CH/Bn), 118.47 (C-6), 113.69 (C-5), 109.61 (C-2), 102.02 (C-7'), 85.79 (C-7), 71.21 (C-9), 70.93 (CH$_2$Ph), 69.13 (C-9'), 55.95 (OCH$_3$), 53.51 (C-8'), 52.52 (C-8); MS m/e (relative %): 342 (M$^+$, 20), 251 (10), 223 (10), 193 (5), 151 (Ar$_1$CO$^+$, 6), 137 (Ar$_1$CH$_2^+$, 5), 123 (Ar$_1^+$, 5), 91 (100); HRMS, calcd. for $C_{20}H_{22}O_5$: 342.1467; found: 342.1475.

Furolactone 30

To a solution of **24** (34.41 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) was added pyridinium dichromate (PDC) (4 equiv., 151.4 mg), AcOH (1 equiv., 5.76 μL), and 4Å molecular sieves (150 mg). Following stirring for 6 h at r.t., the suspension was filtered through a short-path silica gel plug and the filtrate removed in vacuo to give a residue that was then subjected to silica gel column chromatography, eluted with hexanes:EtOAc 2:1 (v/v), to give **30** (26.7 mg, 78%); mp 114–115°C; IR ($CHCl_3$) ν_{max}: 1772 (C=O), 1594, 1516, 1456 (C=CAr), 1244 (C-O) cm^{-1}; ^{1}H NMR δ: 7.45–7.25 (m, 5H, Bn), 6.93 (d, 1H, J = 1.8, H-2), 6.87 (d, 1H, $J_{5,6}$ = 8.2, H-5), 6.79 (dd, 1H, $J_{2,6}$ = 1.8, $J_{5,6}$ = 8.2, H-6), 5.17 (s, 2H, Ar-CH_2), 4.62 (d, 1H, $J_{7,8}$ = 6.7, H-7), 4.50 (dd, 1H, $J_{9eq,8}$ = 9.8, $J_{9eq,9ax}$ = 6.8, H-9 eq), 4.40–4.30 (m, 2H, H-9ax and H-9'ax), 4.20 (dd, 1H, $J_{8',9'eq}$ = 9.2, $J_{9'eq,9'ax}$ = 3.8, H-9' eq), 3.92 (s, 3H, OCH_3), 3.45 (ddd, 1H, $J_{8',9'ax}$ = 9.2, $J_{8',8}$ = 9.2, $J_{8',9'eq}$ = 3.8, H-8'), 3.15–3.10 (m, 1H, H-8); ^{13}C NMR δ: 178.13 (C-7'), 149.94 (C-4), 148.17 (C-5), 136.81 (Cq/Bn), 131.81 (C-1), 128.49, 127.82, 127.13 (CH/Bn), 118.29 (C-6), 113.70 (C-5), 109.43 (C-2), 85.89 (C-7), 70.89 (CH$_2$Ph), 69.93 and 69.77 (C-9 and C-9'), 55.98 (OCH$_3$), 48.03 (C-8'), 45.92 (C-8); MS m/e (relative %): 340 (M$^+$, 100), 250 (20), 221 (45), 149 (48); HRMS, calcd. for $C_{20}H_{20}O_5$: 340.1311; found: 340.1319.

(±)-Salicifoliol 31

To a solution of **30** (26.7 mg, 0.078 mmol) in EtOAc (5 mL) was added Pd/C 10% (15 mg). The suspension was then stirred under an H_2 atmosphere, as described for epi-(+)-sesamolinol **15**, with salicifoliol **31** purified by silica gel column chromatography, eluted with hexanes:EtOAc (2:1 → 1:1 (v/v)), to give **31** (17.66 mg, 90%); mp 101–102°C (lit. (39) mp 102–103°C); IR ($CHCl_3$) ν_{max}: 3417 (br, OH), 1768 (C=O), 1605, 1519, 1466 (C=CAr), 1241 (C-O) cm^{-1}; UV λ_{max}: 234, 278 nm; ^{1}H NMR δ: 6.93 (d, 1H, J = 6.9, H-5), 6.89 (d, 1H, J = 1.6, H-2), 6.80 (dd, 1H, $J_{2,6}$ = 1.6, $J_{5,6}$ = 8, H-6), 5.74 (s, 1H, OH), 4.61 (d, 1H, $J_{7,8}$ = 6.9, H-7), 4.51 (dd, 1H, $J_{9eq,8}$ = 9.8, $J_{9eq,9ax}$ = 6.8, H-9ax), 4.40–4.30 (m, 1H, H-9eq and H-9'ax), 4.19 (dd, 1H, $J_{8',9'eq}$ = 9.2, $J_{9'eq,9'ax}$ = 3.8, H-9' eq), 3.90 (s, 3H, OCH_3), 3.43 (ddd, $J_{8',9'eq}$ = 9.2, $J_{8',8}$ = 9.2, $J_{8',9'ax}$ = 3.8, 1H, H-8'), 3.18–3.08 (m, 1H, H-8); ^{13}C NMR δ: 178.32 (C-7'), 146.98 (C-3), 145.88 (C-4), 130.63 (C-1), 119.15 (C-6), 114.47 (C-5), 105.51 (C-2), 86.13 (C-7), 70.01 and 69.91 (C-9/C-9'), 56.02 (OCH$_3$), 48.21 (H-8), 45.99 (H-8'); MS m/e (relative %): 250 (M$^+$, 100), 233 (10), 219 (15), 205 (Ar$_1$C$_5$H$_6$O$^+$, 10), 165 (50), 152 (Ar$_1$CHO$^+$, 90), 151 (Ar$_1$CO$^+$, 100), 137 (Ar$_1$CH$_2^+$, 95), 123 (Ar$_1^+$, 50), 109 (75); HRMS, calcd. for $C_{14}H_{14}O_5$: 250.0841; found: 250.0843.

Furofuran 32

To a solution of lactol **24** (101.1 mg, 0.3 mmol) in dry THF (30 mL), PPh$_3$ (79 mg, 0.3 mmol), and 4-benzyloxy-3-methoxyphenol **22** (65.4 mg, 0.3 mmol) was added diethylazodicarboxylate (DEAD) (47.5 μL, 1 equiv.), and the mixture was allowed to stir at r.t. for an additional 24 h. The solvent was then removed in vacuo and the residue subjected to silica gel column chromatography, eluted with hexanes:EtOAc (3:1 → 2:1 (v/v)), to give the furofuran lignan **32** (147.9 mg, 89%). IR ($CHCl_3$) ν_{max}: 1597, 1510, 1455 (C=CAr) cm^{-1}; ^{1}H NMR δ: 7.43–7.25 (m, 10H, Bn), 6.95 (d, 1H, $J_{2,6}$ = 1.5 , H-2), 6.85–6.70 (m, 2H, CHAr), 6.70 (d, 1H, $J_{2',6'}$ = 2.7, H-2'), 6.60 (dd, 1H, J = 2.7, H-6'), 5.59 (d, 1H, J = 5.6, H-7'), 5.13 (s, 2H, CH_2Ph), 5.08 (s, 2H, CH_2Ph), 4.78 (d, 1H, $J_{7,8'}$ = 6.9, H-7), 4.38 (dd, 1H, $J_{9'ax,8'}$ = 9.1, $J_{9'eq,9'ax}$ = 4.7, H-9'ax), 4.20–4.00 (m, 2H, H-9'eq and H-9ax), 3.95 (dd, $J_{8,9eq}$ = 9.1, $J_{9eq,9ax}$ = 4.7, H-9eq), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.35-3.20 (m, 1H, H-8'), 3.04 (m, 1H, H-8); ^{13}C NMR δ: 151.95 (C-1'), 150.53 (C-3'), 149.72 (C-3), 147.63 (C-4), 143.27 (C-4'), 137.31 (Cq/Bn), 137.02 (Cq/Bn), 133.92 (C-1), 128.47, 128.42, 127.71, 127.70, 127.35, 127.20 (CH/Bn), 118.17 (C-6), 115.53 (C-5), 113.80 (C-5'), 109.63 (C-6'), 107.06 (C-2), 102.63 (C-7'), 102.47 (C-2'), 85.21 (C-7), 71.82 (CH$_2$Ph), 70.96 (CH$_2$Ph), 69.38 (C-9), 67.04 (C-9'), 55.93 (OCH$_3$), 55.92 (OCH$_3$), 52.78 (C-8), 51.15 (C-8'); MS m/e (relative %): 554 (M$^+$, 5), 464 (3), 445 (2), 429 (2), 325 (10), 295 (30), 243 (50), 230 (100), 139 (75); HRMS, calcd. for $C_{34}H_{34}O_7$: 554.2304; found: 554.2318.

(±)-Epi-pinoresinolin 13

To a solution of the protected furolignan **32** (69.7 mg, 0.125 mmol) in EtOAc (5 mL) was added Pd/C 10% (20 mg). The solution was then stirred for 3 h under an H_2 atmosphere, as for epi-sesamolinol **15**, to give epi-pinoresinolin **13** (39.4 mg, 84%). IR ($CHCl_3$) ν_{max}: 3410 (br, OH), 1613, 1511, 1452 (C=CAr) cm^{-1}; ^{1}H and ^{13}C NMR spectra (see Table 1); MS m/e (relative %): 374 (M$^+$, 35), 275 (22), 235 (90), 205 (Ar$_1$C$_5$H$_6$O$^+$, 95), 137 (Ar$_1$CH$_2^+$, 100); HRMS, calcd. for $C_{20}H_{22}O_7$: 374.1366; found: 374.1387.

Furofuran 34

The furanofuranol **24** (17.7 mg, 0.05 mmol) was treated with sesamol **33** (7.01 mg, 0.05 mmol) as described above to give **34** (20.3 mg, 85%). IR ($CHCl_3$) ν_{max}: 1600, 1508, 1466 (C=CAr), 1245, 1217 (C-O) cm^{-1}; ^{1}H NMR δ: 7.45–7.20 (m, 5H, Bn), 6.90–6.50 (m, 6H, CHAr), 5.93 (s, 2H, OCH_2O), 5.56 (d, 1H, $J_{7',8'}$ = 5.6, H-7'), 5.15 (m, 2H, CH_2Ph), 4.77 (d, 1H, $J_{7,8}$ = 7, H-7), 4.38 (dd, 1H, $J_{9'ax,8'}$ = 9.1, $J_{9'eq,9'ax}$ = 4.2, H-9'ax), 4.20–4.05 (m, 2H, H-9'eq and H-9ax), 3.97 (dd, 1H, $J_{8,9eq}$ = 9.1, $J_{9eq,9ax}$ = 4.8, H-9eq), 3.91 (s, 3H, OCH_3), 3.38–

3.25 (m, 1H, H-8'), 3.10–2.95 (m, 1H, H-8); ^{13}C NMR δ: 152.15 (C-1'), 149.75 (C-3'), 148.03 (C-3), 147.68 (C-4), 143.55 (C-4'), 136.95 (Cq/Bn), 133.87 (C-1), 128.46, 127.74, 127.16 (CH/Bn), 118.13 (C-6), 113.75 (C-5), 109.58 (C-6'), 108.93 (C-5'), 107.95 (C-2), 102.94 (C-7'), 101.18 (OCH$_2$O), 100.14 (C-2'), 85.17 (C-7), 70.95 (CH$_2$Ph), 69.30 (C-9), 66.96 (C-9'), 55.95 (OCH$_3$), 52.70 (C-8), 51.11 (C-8'); MS m/e (relative %): 462 (M$^+$, 15), 325 (30), 295 (70), 243 (55), 227 (100), 203 (Ar$_2$C$_5$H$_6$O$^+$, 30), 179 (12), 137 (Ar$_1$CH$_2$$^+$, 55), 107 (15); HRMS, calcd. for C$_{27}$H$_{26}$O$_7$: 462.1678; found: 462.1671.

(±)-Epi-piperitolin 14

O-Benzyl piperitolin 34 (59.2 mg, 0.128 mmol) in EtOAc (5 mL) was treated with Pd/C 10% (15 mg), as described for furofuran 32, to give (±)-14 (41.4 mg, 95 %); mp 116–117°C; IR (CHCl$_3$) ν_{max}: 3446 (br, OH), 1612, 1547, 1488 (C=CAr), 1271, 1243 (C-O) cm^{-1}; UV λ_{max}: 230, 285 nm; ^{1}H NMR δ: 6.90 (d, 1H, $J_{2,6}$ = 1.8, H-2), 6.81 (dd, 1H, $J_{6,2}$ = 1.8, $J_{5,6}$ = 8.1, H-6), 6.8 (d, 1H, $J_{5,6}$ = 8.1, H-5), 6.72 (d, 1H, $J_{5',6'}$ = 8.4, H-5'), 6.69 (d, 1H, $J_{2',6}$ = 2.4, H-2'), 6.56 (dd, 1H, $J_{2',6'}$ = 2.4, $J_{5',6'}$ = 8.4, H-6'), 5.92 (s, 2H, OCH$_2$O), 5.74 (s, 1H, OH), 5.55 (d, 1H, $J_{7',8'}$ = 5.6, H-7'), 4.47 (d, 1H, $J_{7,8}$ = 7, H-7), 4.40–4.36 (m, 1H, H-9'ax), 4.17–4.07 (m, 2H, H-9'eq and H-9ax), 4.02–3.95 (m, 1H, H-9eq), 3.89 (s, 3H, OCH3), 3.33–3.28 (m, 1H, H-8'), 3.06–3.00 (m, 1H, H-8); ^{13}C NMR δ: 152.28 (C-1'), 148.15 (C-3'), 146.77 (C-3), 145.33 (C-4'), 142.79 (C-4'), 132.79 (C-1), 118.99 (C-6), 114.34 (C-5), 109.14 (C-6'), 108.64 (C-2), 108.04 (C-5'), 103.07 (C-7'), 100.23 (OCH$_2$O), 85.48 (C-7), 69.40 (C-9), 67.04 (C-9'), 55.97 (OCH$_3$), 52.87 (C-8'), 51.22 (C-8); MS m/e (relative %): 372 (M$^+$, 15), 261 (5), 235 (60), 205 (Ar$_1$C$_5$H$_6$O$^+$, 65), 187 (5), 161 (Ar$_1$C$_3$H$_4$$^+$, 5), 159 (4), 153 (Ar$_2CHO^+$, 30), 151 (Ar$_1CHO^+$, 50), 138 (90), 137 (Ar$_2CH_2$$^+$, 100), 115 (30), 107 (60); HRMS, calcd. for C$_{20}$H$_{20}$O$_7$: 372.1209; found: 372.1219.

Acknowledgments

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