# (+)-Episesaminone, a *Sesamum indicum* Furofuran Lignan. Isolation and Hemisynthesis

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Several lignans from *Sesamum* sp. contain an unusual oxygen insertion between their furano and aromatic rings. As part of our ongoing studies to clarify the biosynthetic pathway to the sesame lignans, the furanoketone, (+)-episesaminone, was isolated and fully characterized in part via hemisynthesis from (+)-sesamolin.

During our ongoing studies directed toward defining how (+)-sesamolin (**1**) biosynthesis occurs in *Sesamum indicum* L. (Pedaliaceae),[1] as well as that of related lignans,[2−6] the hitherto unknown tetrahydrofuran lignan, (+)-episesaminone (**2**) (Figure 1), was isolated from commercially available unroasted and unbleached seeds, as well as from freshly harvested seed tissue. Its structure was established via a combination of $^{1}H-^{13}C$ NMR, IR, UV, and MS analyses and confirmed by total synthesis as follows: the presence of a conjugated ketone in (+)-episesaminone (**2**) was suggested from its IR (1647 $cm^{-1}$) and UV (312 nm) absorbances and was further supported from the resonance at 197.3 ppm in its $^{13}C$-NMR spectrum, which revealed an aromatic conjugated carbonyl group, with the latter confirmed by use of a $^{1}H-^{13}C$ 2D NMR HMBC experiment. The $^{1}H$-NMR spectrum showed two aromatic *o*-carbonyl protons at 7.56 ppm (1H, dd, $J$ = 8.1 Hz, $J$ = 1.7 Hz) and 7.45 ppm (1H, d, $J$ = 1.7 Hz). Additionally, the proton resonances at 7.56 and 7.45 ppm, together with those at 6.86 ppm (1H, d, $J$ = 8.1 Hz) and two methylenedioxy protons downfield at 6.05 ppm, were indicative of a 3,4-methylenedioxyphenyl (piperonyl) acetophenone system. This was additionally supported by its mass spectrum, which exhibited a base peak at *m/z* 149 and a fragment ion at *m/z* 121, corresponding to acylium ion [$ArCO^{+}$] and piperonyl ion [$Ar^{+}$] fragments, generated after carbon−carbon bond cleavage at C-7′/C-8′ and C-7′/C-1′, respectively.[7] In an analogous manner, the second piperonyl system was established by the proton resonances at 6.95, 6.84, 6.76 (aromatic protons), and 5.94 ppm ($OCH_2O$). This was further confirmed from its $^{13}C$-NMR spectrum, using both DEPT and HMBC, to determine the multiplicities and $^{3}J$ coupling relationships. That is, the methylenedioxy bridges at 5.94 and 6.05 ppm in the $^{1}H$-NMR spectrum were correlated with the two $OCH_2O$ groups at 101.13 and 102.01 ppm, respectively, thereby confirming the piperonyl structure for both aromatic substituents in the $^{13}C-^{1}H$ HETCOR NMR spectrum. The remaining assignments were made using a combination of $^{1}H$, $^{1}H-^{1}H$ COSY, $^{13}C$ (DEPT mode), and $^{13}C-^{1}H$ HETCOR NMR spectroscopic analyses, which established the tetrahydrofuran skeleton as follows: the doublet at 4.64 ppm ($J$ = 9.1 Hz) was assigned to the oxybenzylic proton H-7 in a trans configuration to H-8. Next, the multiplets centered at 4.28 and 4.10 ppm were correlated in the $^{1}H-^{1}H$ COSY NMR spectrum and assigned to the three proton resonances, viz. the protons of the methylene group at C-9′ and the methine proton at C-8′. In the same way, the multiplets at 3.76−3.66 and 2.86 ppm were correlated in the 2D $^{1}H-^{1}H$ spectrum and assigned to the hydroxymethyl group at C-9 and the methine proton at C-8. Furthermore, 2D $^{13}C-^{1}H$ HETCOR NMR spectroscopic studies confirmed the furanoketone structure by assignment of chemical shifts in the $^{13}C$-NMR spectrum relative to the corresponding $^{1}H$-NMR resonances (see Experimental Section), in a manner analogous to that used for other naturally occurring keto-lignans.[8,9] Thus, the methylenic multiplets at 4.28−4.10 ppm and 3.76−3.66 ppm displayed correlations with the methylenic carbon at 70.84 (C-9′) and the $CH_2OH$ group at 61.29 ppm (C-9), respectively, as did the multiplets at 4.18 and 2.86 ppm with the methine carbons at 49.98 ppm (C-8′) and 52.26 ppm (C-8) in the DEPT $^{13}C$-NMR spectrum. Additionally, the H-7 proton at 4.64 ppm was correlated with the methine carbon (C-7) at 83.70 ppm, thereby accounting for all of the resonances of the tetrahydrofuran skeleton. Further support for this structural determination was made by MS analysis, which displayed a molecular ion at *m/z* 370, together with fragment ions at *m/z* 203, 149, and 121 corresponding to [$ArC_5H_6O^{+}$], [$ArCO^{+}$], and [$Ar^{+}$], respectively.[7]

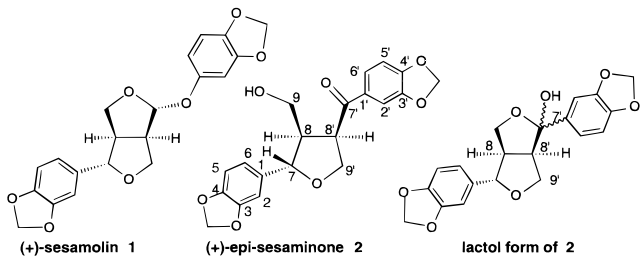


**Figure 1.** Lignans from *Sesamum indicum*.

Next, nuclear Overhauser enhancement difference experiments established a cis stereochemistry between the H-8 and H-8′ protons on the bridgehead carbons. Furthermore, since no NOE was observed between the H-7 and H-8 protons, these therefore had a trans stereochemical relationship between them. Thus, (+)-episesaminone (**2**) has the same overall stereochemistry as that of magnolenin C (**3**) from *Magnolia grandiflora*[10] (Figure 2). The absolute configuration of **2** at C-8′ was

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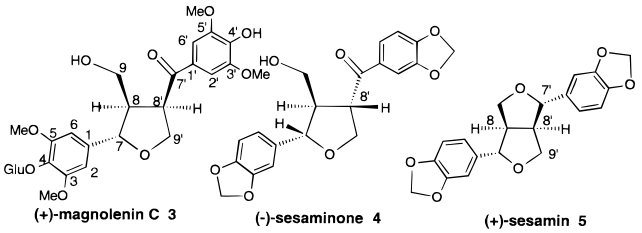



**Figure 2.** Lignan metabolites isolated from *Magnolia grandiflora* and *Sesamum indicum*, as well as from *Streptomyces* cell cultures grown on sesame-seed media.

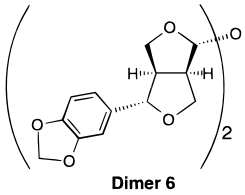
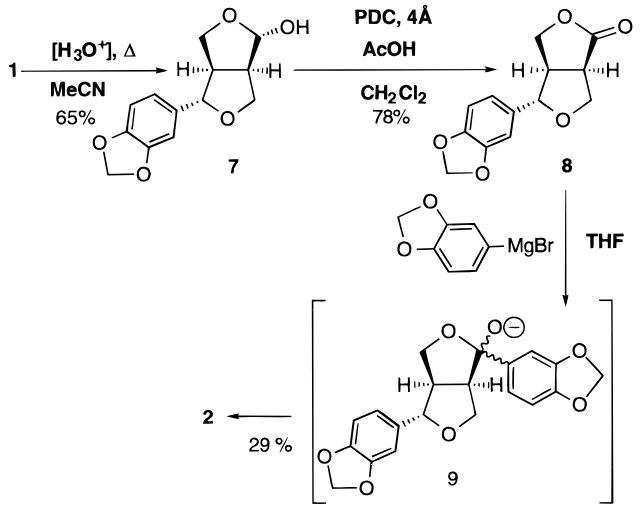



**Figure 3.** Dimer **6** obtained by acid hydrolysis of sesamolin **1**.

**Scheme 1.** Hemisynthesis of (+)-Episesaminone (**2**) from (+)-Sesamolin (**1**)




deduced as *R* ([α]$_D$ + 126.2°; *c* 0.127, $CHCl_3$), given that the previously reported *S* epimer,[11] (−)-sesaminone (**4**) had a negative optical rotation ([α]$_D$ − 25.0°; *c* 0.14, MeOH).

To establish unambigously the proposed structure of (+)-episesaminone (**2**), its hemisynthesis from (+)-sesamolin (**1**),[12] a readily available sesame-seed lignan together with (+)-sesamin (**5**),[13] was next developed. The approach used was based on the known chemistry of (+)-sesamolin (**1**), which can be hydrolyzed in $H_2SO_4$−EtOH to give, as the major products, the dimer **6** (Figure 3) and lactol (+)-samin (**7**).[14] Subsequent modification of this hydrolytic procedure with **1** in acetate buffer (165 mM, pH 1.0) in EtOH gave three compounds: the symmetrical dimer **6** (disaminyl ether) as the major product, as well as smaller yields (10−20%) of the required (+)-samin (**7**) and its corresponding ethoxy-ether.[15]

Further refinement of the hydrolytic procedure, however, using DOWEX-50 X 2−200 exchange resin, NaOAc buffer (165 mM, pH 1.0), and 10% HCl in $CH_3CN$ gave **7** in 65% yield (Scheme 1).

From lactol **7**, the key step to afford (+)-episesaminone (**2**) was a mono-Grignard addition to lactone **8** as shown in Scheme 1. Thus, oxidation of (+)-samin **7** with pyridinium dichromate (PDC) under acidic conditions[1,16] afforded the corresponding lactone, (+)-acuminatolide **8**[1,17] in 78% yield. Subsequent condensation of **8** with the Grignard reagent,[18] obtained from bromosesamol (1-bromo-3,4-(methylenedioxy)benzene), at room temperature, followed by hydrolysis of the intermediate lactol **9**, gave (+)-episesaminone (**2**) as shown (Scheme 1). The synthetic product was identical in all respects to naturally occurring (+)-episesaminone (**2**) (see Experimental Section), except for the optical rotation value, i.e., [α]$_D$ +120° (*c* 0.127, $CHCl_3$) versus that of the natural product **2** [[α]$_D$ +126.2° (*c* 0.127, $CHCl_3$)]. Thus, since (+)-samin **7** has a *R* configuration at C-8′,[1,14] this confirms the proposed stereochemical assignment of (+)-episesaminone (**2**).

Last, in terms of the biosynthesis of (+)-episesaminone (**2**), it can tentatively be proposed that it is formed in vivo from (+)-sesamin (**5**) (Figure 2). Given that (+)-episesaminone (**2**) can exist in its lactol form (see Figure 1) under basic conditions,[10] only a single oxidation step from (+)-sesamin **5** to **2** is required. Additionally, it should be noted that its C-8′ *S* epimer, (−)-sesaminone (**4**) (Figure 2) has been reported as present in *Streptomyces* IT-44 cell cultures grown on sesame-seed media.[11] A possible explanation for its formation is that cis (+)-episesaminone (**2**) is epimerized at C-8′ under prolonged basic treatment to give the more stable trans form **4**.

## Experimental Section

**Plant Materials.** Seeds of *S. indicum* (unroasted and unbleached) were either purchased from a local produce store or obtained from ripe pods of mature *S. indicum* plants grown in greenhouses at Washington State University.

**General Experimental Procedure.** Solvents were either HPLC grade ($CH_3CN$, MeOH, AcOH, $CH_2Cl_2$, THF) or ACS grade (EtOAc, Hexanes) from Baker. Tetrahydrofuran (THF) and methylene chloride ($CH_2Cl_2$) were distilled over $LiAlH_4$−triphenylmethane and $CaH_2$, respectively. Column and analytical TLC separations (Al Si G/UV 254) were performed using Si gel 60 (230−400 mesh) (Whatman). IR spectra were recorded on a Perkin-Elmer 1720-X FTIR spectrometer, whereas NMR spectra were obtained using either Bruker AMX300 (for $^1H$, $^{13}C$, and 2D NMR) or Varian 500VXR (for NOE measurements) spectrometers. All spectra were recorded in $CDCl_3$ using TMS as internal reference, with chemical shifts ($\delta$) expressed in parts per million and coupling constants (*J*) in Hertz. UV and ORD spectra were recorded on a Perkin-Elmer Lambda 6 UV/vis spectrophotometer and a JASCO 181 polarimeter at $\lambda$ 289 nm (Na), respectively. HPLC separations were carried out in the reversed-phase mode [Waters $C_{18}$ Nova-Pak, 150 × 3.9 mm i.d., 4 $\mu$m], eluted with MeOH−$H_2O$ in a linear gradient of 3:7 → 7:3 over 60 min with detection at 280 nm. EIMS analyses were carried out with an HPLC−MS (Integrity Waters), using a reversed-phase column (Waters $C_{18}$ Nova-Pak, 150 × 2 mm i.d., 4 $\mu$m) eluted with a linear solvent gradient A: $H_2O$ (3% v/v acetic acid) and B: $CH_3CN$; as follows: 8:2 → 7:3 in 10 min, then 7:3 → 1:1 in 25 min; MS analyses TIC (Total Intensity Chromatogram) were performed from *m*/*z* 80 to 700 at a rate of 1 scan $s^{-1}$, with an optimal temperature of the nebulizer at 80 °C

using (+)-sesamin (**5**) as a reference. Interpretation of fragmentation patterns were calculated where Ar = 3,4-methylenedioxyphenyl.[7] HRMS analyses employed a VG 7070 EHF mass spectrometer at 70 eV.

**Isolation of (+)-Episesaminone (2).** Commercially available *S. indicum* seeds (1.28 kg, unroasted) were homogenized in a Waring blender containing MeOH (1 L) and extracted exhaustively with hot MeOH (11 × 1 L) at 50 °C. The resulting MeOH solubles (12 L) were combined, cooled to 0 °C for 45 min, then filtered with the filtrate concentrated in vacuo to give an oily residue. This residue was suspended in MeOH−$H_2O$ (1:1, 150 mL), then sequentially extracted with hexanes (2 × 400 mL) and EtOAc (4 × 500 mL). The EtOAc solubles were combined and concentrated (15 mL), to which MeOH (150 mL) was next added. The resulting precipitate (3.24 g) was removed by filtration to give a crude mixture of (+)-sesamin (**5**) and (+)-sesamolin (**1**),[9,19] with the filtrate concentrated to afford a yellow gum (12.3 g). The latter was dissolved in a minimal amount of EtOAc and applied to a Si gel column (300 g) eluted with a hexane−EtOAc gradient (5:1 to 1:1; 150 mL each). Fractions 6−7 (25 mL each) and 8−9 contained (+)-sesamin (**5**) (536 mg)[13] and (+)-sesamolin (**1**) (279 mg),[9] respectively. Fractions 13−15 were evaporated to dryness, reconstituted in $CHCl_3$, then subjected to preparative TLC eluted with 3% (v/v) MeOH in $CHCl_3$ to give (+)-episesamin (2 mg) (C-7′ epimer of **5**),[7] (+)-kobusin (1.5 mg),[20] and a more polar fraction. The latter was subjected to analytical HPLC separation [$C_{18}$ reversed-phase, eluted with MeOH−$H_2O$, linear gradient 3:7 → 7:3 in 60 min] to give (+)-piperitol (2 mg)[21] and (+)-sesamolinol (1 mg).[22] Fractions 17−20 (58 mg) were pooled and purified by preparative TLC ($CHCl_3$−MeOH 5:1) to give two fractions, purification of which by analytical HPLC as before gave (+)-sesamolinol (1.5 mg)[22] and (+)-episesaminone (**2**) (1 mg), respectively. Fractions 21−24 (88 mg) were chromatographed on Si gel eluted with 5% (v/v) MeOH in $CHCl_3$ to afford (+)-pinoresinol (23 mg)[23] and *trans*-ferulic acid (7 mg).

**(+)-Episesaminone (2).** (+)-[3*R*-(3α,4α,5β)]-1,3-Benzodioxol-5-yl[1-(1,3-benzodioxol-5-yl)-2-(hydroxymethyl)tetrahydro-1*H*,3*H*-3-furanyl]methanone: IR ($CHCl_3$) $\nu_{max}$ 3600−3200 (OH), 1647 (C=O), 1604, 1505, 1444, 1409 (C=C Ar), 1251 (C−O) $cm^{-1}$; UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 230 (4.76), 280 (3.75), 312 (2.87) nm; $[\alpha]_D$ +126.2° (*c* 0.127, $CHCl_3$); MS *m/z* 370 [$M^+$] (38), 352 [$M - H_2O^+$] (5), 243 (5), 203 [$ArC_5H_6O^+$] (25), 194 (40), 176 (48), 152 (50), 150 [$ArCHO^+$] (45), 149 [$ArCO^+$] (100), 121 [$Ar^+$] (40); HRMS *m/z* 370.1044 (calcd for $C_{20}H_{18}O_7$, 370.1053); $^1$H-NMR δ 7.56 (1H, dd, *J* = 8.1 Hz, *J* = 1.7 Hz, H-6′), 7.45 (1H, d, *J* = 1.7 Hz, H-2′); 6.95 (1H, d, *J* = 1.65 Hz, H-2), 6.86 (1H, d, *J* = 8.1 Hz, H-5′), 6.84 (1H, dd, *J* = 7.94 Hz, *J* = 1.65 Hz, H-6), 6.76 (1H, d, *J* = 7.94 Hz, H-5), 6.05 (2H, s, O*C*$H_2$−O), 5.94 (2H, s, O*C*$H_2$−O), 4.64 (1H, d, *J* = 9.1 Hz, H-7), 4.28 (1H, m, H-9′eq), 4.10 (2H, m, H-9′ax + H-8′), 3.76 (1H, m) and 3.66 (1H, m, H-9), 2.86 (1H, m, H-8); $^{13}$C-NMR (DEPT mode) δ 197.30 (s, C-7′), 152.18 (s, C-4′), 148.44 (s, C-3′), 147.98 (s, C-4), 147.45 (s, C-3), 134.42 (s, C-1), 131.14 (s, C-1′), 124.93 (d, C-6′), 119.08 (d, C-6), 108.30 (d, C-5), 108.09 (d, C-2′), 107.93 (d, C-5′), 107.14 (d, C-2), 102.01 (t, O*C*$H_2$O), 101.13 (t, O*C*$H_2$O), 83.70 (d, C-7), 70.84 (t, C-9′), 61.29 (t, C-9), 52.26 (d, C-8), 49.98 (d, C-8′) ppm.

**Ripe Pod Extraction.** Mature (9−12 weeks' growth) *S. indicum* greenhouse grown plants were harvested, with the intact seeds (50 g) carefully removed, and immediately homogenized in a Waring blender containing MeOH (200 mL) and then extracted with hot MeOH (50 °C, 3 × 200 mL). The resulting MeOH extracts (800 mL) were combined, filtered under reduced pressure over a short path of sea sand, and the filtrate evaporated to dryness in vacuo. The resulting residue was subjected to column chromatography on Si gel (60 g) using hexane−EtOAc 3:1 as solvent to give (+)-sesamolin (**1**) (20 mg) and (+)-sesamin (**5**) (10 mg).[9] Further elution with hexane−EtOAc 1:1 gave two fractions; HPLC−MS of the latter fraction gave a single component at the same retention time as **2** with identical UV and MS spectra to those of the synthetic (+)-episesaminone (**2**).

Hydrolysis of **1** to give the known (+)-samin **7**,[13] subsequent conversion to (+)-acuminatolide (**8**), and complete physical and spectroscopic data of **7** and **8** are described elsewhere.[1]

**Dimer 6:** IR ($CHCl_3$) $\nu_{max}$ 1503, 1443 (C=CAr), 1248 (C−O) $cm^{-1}$; UV ($CHCl_3$) $\lambda_{max}$ (log $\epsilon$) 243 (3.8), 288 (3.9), 337 (1.32) nm; mp 188−189 °C (MeOH), (lit.[14] 191−192 °C); $[\alpha]_D$ +160.1° (*c* 1.37, $CHCl_3$) (lit.[14] $[\alpha]_D$ +143° (*c* 1.74, $CHCl_3$)); MS *m/z* 482 [$M^+$] (5), 233 [$C_{13}H_{13}O_4^+$] (10), 203 [$ArC_5H_6O^+$] (15), 189 (5), 163 (10), 150 [$ArCHO^+$] (95), 149 [$ArCO^+$] (100), 135 [$ArCH_2^+$] (90), 121 [$Ar^+$] (20); HRMS 482.1581 (calcd for $C_{26}H_{26}O_9$, 482.1517); $^1$H-NMR δ 6.90−6.75 (m, 6H, H-2, H-5 and H-6), 5.96 (s, 4H, O*C*$H_2$O), 5.29 (s, 2H, H-7′), 4.37 (d, *J* = 8.4 Hz, 2H, H-7), 4.38 (dd, *J* = 9.2 Hz, *J* = 7.8 Hz, 2H) and 4.05−3.95 (m, 4H) and 3.58 (dd, *J* = 9.2 Hz, *J* = 7.8 Hz, 2H, H-9 and H-9′), 3.05−2.95 (m, 2H, H-8′), 2.90−2.85 (m, 2H, H-8); $^{13}$C-NMR (DEPT mode) δ 148.06 (s, C-3), 147.39 (s, C-4), 134.63 (d, C-1), 119.78 (d, C-6), 108.25 (d, C-5), 106.65 (d, C-2), 102.96 (d, C-7′), 101.17 (t, O*C*$H_2$O), 87.06 (d, C-7), 71.44 (t, C-9), 69.43 (t, C-9′), 52.84, 52.77 (d, C-8 and C-8′) ppm.

**Synthesis of (+)-Episesaminone (2).** A suspension of magnesium turnings (5.2 mg, 1.2 equiv) and 1-bromo-3,4-(methylenedioxy)benzene (1.1 equiv, 23.5 mL) in dry THF (5 mL) was heated under argon until reflux began, this being maintained for 3 h. The resulting suspension was cooled to room temperature and added dropwise to a solution of **8** (44 mg, 0.177 mmol) in dry THF (50 mL). After being stirred for 12 h, the solvent was removed in vacuo, with the resulting residue subjected to column chromatography (hexane−EtOAc, 3:1 then 1:1) to give **2** (18.4 mg, yield 29%, conversion 47% based on starting material) and unreacted starting material **8** (18 mg). The $[\alpha]_D$ (120°; *c* 0.127, $CHCl_3$), MS, HRMS, $^1$H and $^{13}$C NMR, IR, and UV spectra were identical with naturally occurring (+)-episesaminone (**2**) except for the optical rotation value, i.e., $[\alpha]_D$ +120° (*c* 0.127, $CHCl_3$) versus that of the natural product **2** {$[\alpha]_D$ +126.2° (*c* 0.127, $CHCl_3$) see above}.

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