Concise Enantioselective Synthesis of Furan Lignans (–)-Dihydrosesamin and (–)-Acuminatin and Furofuran Lignans (–)-Sesamin and (–)-Methyl Piperitol by Radical Cyclization of Epoxides

Biplab Banerjee, Subhas Chandra Roy*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India
Fax +91(33)24732805; E-mail: ocscr@mahendra.iacs.res.in

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Abstract: Enantioselective syntheses of furan lignans (–)-dihydrosesamin and (–)-acuminatin and furofuran lignans (–)-sesamin and (–)-methyl piperitol were achieved in up to only three steps in 43%, 42%, 63%, and 60% overall yield, respectively, with high optical purity through stereoselective intramolecular radical cyclization of suitably substituted epoxy olefinic ethers using bis(cyclopentadienyl)titanium(III) chloride as the radical initiator. The key intermediate, chiral epoxy alcohol **4**, was prepared by the Sharpless kinetic resolution method. The titanium(III) initiator was prepared in situ from commercially available titanocene dichloride and activated zinc dust in tetrahydrofuran.

Key words: enantioselectivity, lignans, radical cyclizations, transition metals, titanium

Due to their widespread occurrence in nature[1,4] and broad range of biological activities,[2] lignans have attracted considerable interest over the years. Two major subgroups of lignans are composed of tri- and tetrasubstituted tetrahydrofurans and substituted 3,7-dioxabicyclooctanes, the synthesis of which poses interesting and often unsolved problems of stereocontrol. Because of the structural complexity and associated biological activities, lignans are challenging targets for organic chemists. Dihydrosesamin and acuminatin are representatives of biologically active furan lignans with two identical or different aromatic moieties, respectively. Dihydrosesamin[3] was isolated from *Daphne tangutica maxim* and it has been used as an abortifacient and in the treatment of rheumatism and toothache. Acuminatin[4] was isolated from *Machilus thunbergii* and *Epimedium acuminatum* and was found to exhibit diverse hepatoprotective activities, perhaps by serving as a potent antioxidant. Sesamin and methyl piperitol are representatives of biologically active symmetrical and unsymmetrical 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans, respectively. Sesamin[5] was isolated from hydrocotyle plants and was found to inhibit the growth of silkworm (*Bombyx mori*) larvae. It also shows weak juvenile hormone activity in the milkweed bug (*Oncopeltus fasciatus*) and functions as a regulator of cholesterol and linoleate metabolism in rats. Methyl piperitol[6] was isolated from *Helichrysum bracteatum* and it possesses platelet activating factor (PAF) antagonist activity. Although a number of interesting syntheses of these furan and furofuran lignans in racemic form[7] have been reported, there are only a few reports for the enantioselective synthesis of these lignans. To our knowledge, there is only one report[8] for the lengthy synthesis of optically active dihydrosesamin using a highly *erythro*-selective aldol reaction. The methods reported for enantioselective synthesis of furofuran lignans are based on the diastereoselective hetero-Diels–Alder reaction,[9] a tandem conjugate addition–aldol reaction of the thioacetal to the chiral butenolide,[10] an oxidative coupling of enantiomerically enriched β-oxo esters followed by reduction and acid-promoted cyclization,[11] and an asymmetric Strecker reaction followed by a Michael addition.[12] Recently, a furofuran lignan (+)-membrine has been synthesized[13] using chiral organoselenium intermediates. A formal synthesis of (+)-sesamin in 62% ee has also been reported recently using a chirotopical Heck reaction.[14] Further advances should seek to develop efficient asymmetric approaches that have the flexibility to allow access to different substitution patterns for the synthesis of analogues for biological testing. Therefore, our goal was to develop a short and enantioselective route, by using readily available building blocks, to synthesize different types of lignans in enantiomerically pure form. In continuation of our efforts[15] towards the synthesis of naturally occurring lignans in racemic form by radical cyclization of epoxides using a transition-metal radical initiator, we report here a full account on the enantioselective total synthesis of furan lignans (–)-dihydrosesamin (**1a**) and (–)-acuminatin (**1d**) and furofuran lignans (–)-sesamin (**2a**) and (–)-methyl piperitol (**2b**) (Figure 1) in good overall yield by employing radical technology. Lignans **1d**, **2a**, and **2b** are the enantiomers of the naturally occurring compounds (+)-acuminatin, (+)-sesamin, and (+)-methyl piperitol, respectively. To the best of our knowledge, this radical cyclization strategy has not been used before for the asymmetric synthesis of these lignans.

Because of its mildness and its regio- and stereoselectivity, the hex-5-enyl radical cyclization has been extensively applied in the construction of oxacyclic compounds leading to tetrahydrofuran derivatives. A bromoalkene or a bromoalkyne derivative has been used widely as a radical precursor[16] and tin hydrides as the radical initiator. As the tin compounds are toxic and difficult to separate from the products, an alternative nontoxic and easily separable rad-

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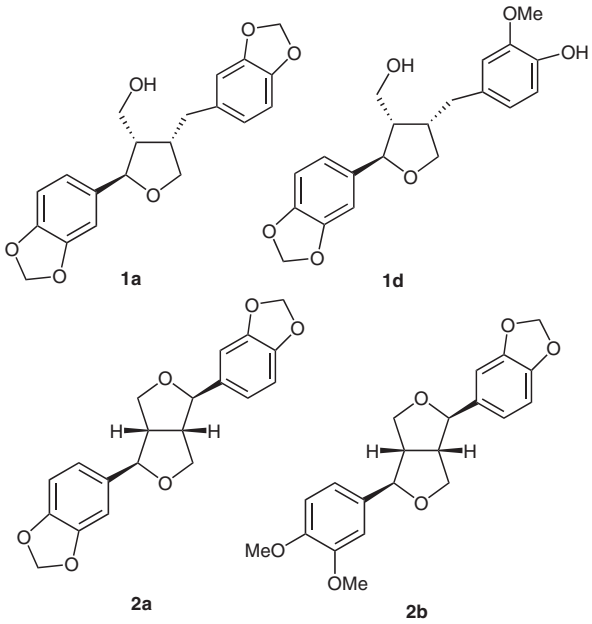
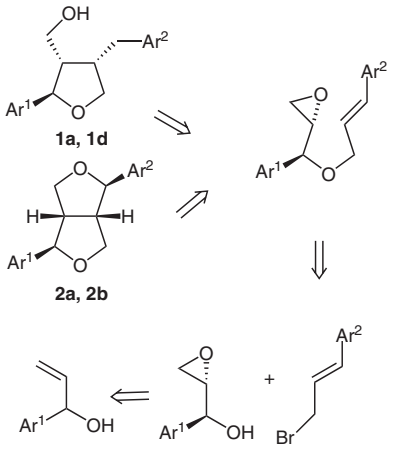


Figure 1

ical initiator for the intramolecular radical cyclizations is still desirable.

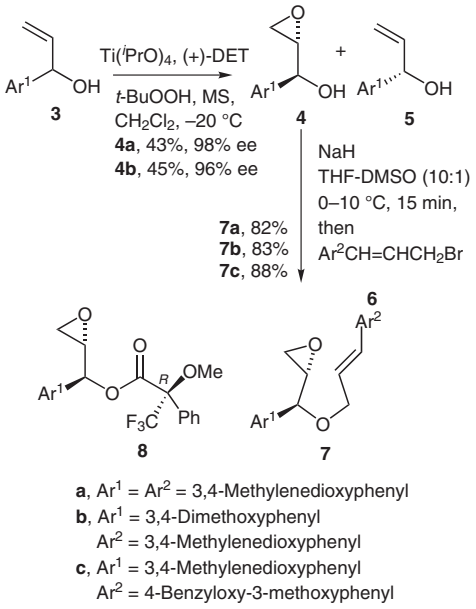
The selective one-electron reduction of an epoxide,[17] by the stoichiometric as well as catalytic one-electron transfer reagent bis(cyclopentadienyl)titanium(III) chloride (Cp_2TiCl), represents an invaluable synthetic tool as the intermediate radical can be trapped in subsequent reactions. Usually, high regioselectivity is observed as the epoxide cleavage via C–O homolysis is guided by the relative stabilities of the intermediate radicals.

From the retrosynthetic analysis shown in Scheme 1, it can be assumed that both types of lignans **1a** and **1d** and **2a** and **2b** can be synthesized by stereoselective radical cyclization of chiral epoxy olefinic ethers, which in turn can be prepared by condensation of chiral epoxy alcohols with the appropriate cinnamyl bromide.



Scheme 1 Retrosynthetic analysis

Therefore, our synthetic plan mainly relied on the preparation of chiral epoxy alcohols **4** from the corresponding allylic alcohols **3** using the Sharpless kinetic resolution method. The starting allylic alcohols **3a** and **3b** were prepared by the standard procedure from the corresponding aryl aldehyde and vinyl magnesium bromide.[18] Compound **3a** was subjected to Sharpless kinetic resolution[19] using (+)-diethyl tartrate in the presence of titanium(IV) isopropoxide [Ti(*i*-PrO)$_4$], *tert*-butyl hydroperoxide, and 4-Å molecular sieves in dry dichloromethane at –20 °C to give the corresponding chiral epoxy alcohol **4a** (Ar^1 = 3,4-methylenedioxyphenyl) in 43% yield (84% based on the recovered *S*-allylic alcohol **5a**) and with 98% ee. Similarly, alcohol **4b** (Ar^1 = 3,4-dimethoxyphenyl) was prepared in 45% yield (81% based on the recovered *S*-allylic alcohol **5b**) and with 96% ee (Scheme 2).

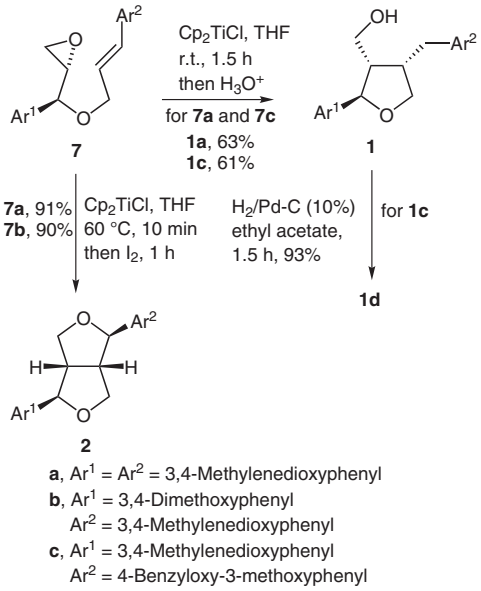


Scheme 2 Synthesis of epoxy ethers

The enantiomeric excess was determined by ^{1}H NMR spectroscopic analysis of the corresponding Mosher esters[20] **8a** and **8b** derived from **4a** and **4b**, respectively, with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. The chiral epoxy alcohol **4a** was treated with bromide **6a** (Ar^2 = 3,4-methylenedioxyphenyl) in the presence of sodium hydride in tetrahydrofuran–dimethyl sulfoxide (10:1) to afford the epoxy olefinic ether **7a** in 82% yield. Similarly, ethers **7b** and **7c** were prepared from bromides **6b** (Ar^2 = 3,4-methylenedioxyphenyl) and **6c** (Ar^2 = 4-benzyloxy-3-methyloxyphenyl) in 83 and 88% yield, respectively.

The radical initiator Cp_2TiCl was easily generated[17] in situ from commercially available titanocene dichloride (Cp_2TiCl_2) and activated zinc dust in tetrahydrofuran; a satisfactory reagent was prepared by vigorously stirring the red solution for one hour under an argon atmosphere at room temperature.

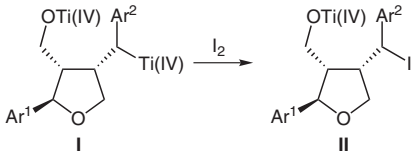
The epoxy olefinic ether **7a** on treatment with Cp_2TiCl in tetrahydrofuran at room temperature for 1.5 h, followed by acidic workup, gave the cyclized product **1a** together with a minor isomer in a ratio of 5:1 in 87% yield (Scheme 3). Similarly, the epoxy olefinic ether **7c** under identical reaction conditions afforded the cyclized product **1c** together with a minor isomer in a 5:1 ratio in 85% yield.



Scheme 3 Radical cyclization of epoxy ethers

The ratio of the two isomers was determined from the C-2 benzylic proton that appeared in the ^{1}H NMR spectra as a doublet at δ 4.80 (J = 6.2 Hz) for the major isomer and at δ 4.60 (J = 8.0 Hz) for the minor isomer in the crude product mixture obtained from **7a**, and as a doublet at δ 4.79 (J = 6.6 Hz) for the major isomer and at δ 4.61 (J = 7.9 Hz) for the minor isomer in the crude product mixture obtained from **7c**. The major isomers **1a** and **1c** were separated by preparative TLC (20% EtOAc–light petroleum) in 63% and 61% yield, respectively. The specific rotation of the major isomer **1a** was nearly identical with that of naturally occurring (–)-dihydrosesamin.[3,8] The benzyl ether **1c** on catalytic hydrogenolysis over 10% palladium on charcoal in ethyl acetate afforded (–)-acuminatin (**1d**) in 93% yield, the specific rotation of which was opposite to natural (+)-acuminatin[21] {Lit.[21] $[\alpha]_D^{25}$ +11.1 (*c* 0.09, $CHCl_3$)}. To our knowledge, this is the first report for the synthesis of optically active (–)-acuminatin. Because neither the minor isomer nor a derivative formed by reaction of its hydroxy group could be separated chromatographically in pure form, its stereochemistry remains uncertain. The reasons for the high diastereoselectivity observed in the radical cyclizations have already been explained thoroughly by our group[15] during the synthesis of lignans in racemic forms.

In addition, the epoxy olefinic ether **7a** was treated with Cp_2TiCl in tetrahydrofuran at 60 °C, and the resulting solution was stirred with an excess of iodine at the same temperature for 1 h to give (–)-sesamin (**2a**) as the only isolated product in 91% yield, the specific rotation of which was opposite to naturally occurring (+)-sesamin[22] {Lit.[23] $[\alpha]_D^{22}$ +68.7 (*c* 0.40, $CHCl_3$)}. Under identical reaction conditions, compound **7b** afforded (–)-methyl piperitol (**2b**) in 90% yield with opposite specific rotation compared to naturally occurring (+)-methyl piperitol[24] {Lit.[6a] $[\alpha]_D^{22}$ +73.6 (*c* 0.35, $CHCl_3$)}, also known as Kobusin. Here, double cyclizations furnished the furofurans in better yields and with higher stereoselectivity compared to the monocyclizations. This could be accounted for by rapid cyclization at a higher temperature (60 °C) leading to the highly stereoselective product, which might be facilitated by the reaction of iodine with the organotitanium intermediate **I** present in the reaction mixture to give intermediate **II** (Scheme 4). The second furan moiety formation was found to be a highly controlled reaction arising from an intramolecular S_N2 attack on the iodine-substituted carbon of **II** giving the stable products **2** with all the substituents equatorial. This can be explained using ^{1}H NMR spectra; for example, for symmetrical **2a**, only one doublet at δ 4.71 (J = 4.3 Hz) for both C-2 and C-6 benzylic protons was observed, but for unsymmetrically substituted furofuran lignans ($Ar^1 \neq Ar^2$) such as (–)-methyl piperitol (**2b**), two doublets at δ 4.72 (J = 3.9 Hz) and 4.74 (J = 4.1 Hz) for the C-2 and C-6 benzylic protons, partially overlapped with each other, were observed. Other one-electron reduction reagents, such as samarium(II) iodide, might influence the opening of epoxides to undergo radical cyclization reactions, but we were interested only in Cp_2TiCl.



Scheme 4

In conclusion, we have successfully achieved the enantioselective total synthesis of furan lignans (–)-dihydrosesamin and (–)-acuminatin and furofuran lignans (–)-sesamin and (–)-methyl piperitol by radical cyclization of epoxides using a transition-metal radical source in up to only three steps in respectable overall yields and with high optical purity. To the best of our knowledge, radical cyclizations of epoxides used for the concise enantioselective synthesis of lignans have not yet been reported in the literature.

The compounds described are all optically active. Melting points were determined in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 300 MHz and 75 MHz spectrometers (Bruker), respectively, using TMS as the internal standard. IR spectra of solids (KBr) and liquids (neat) were recorded on a Shimadzu FTIR-8300 instrument. The Et_2O and THF

were dried (Na), and CH_2Cl_2 and DMSO were freshly distilled from P_2O_5 and CaH_2, respectively. Light petroleum (bp 60–80 °C) and silica gel (60–120 mesh) were used for column chromatography. Preparative TLC was performed using Merck precoated silica 60 F254 plates (0.2 mm). Optical rotations were determined on a polarimeter (JASCO, P-1020) at the sodium D line using spectroscopic grade $CHCl_3$ at the concentration indicated. Elemental analyses were performed on an analytical instrument (Dr. Hans Hosli, 0A1, 468) in our analytical laboratory. High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument.

(*S*)-1,3-Benzodioxol-5-yl[(2*S*)-oxiran-2-yl]methanol (4a):
Activated powdered 4-Å molecular sieves (150 mg, 25 wt%) in dry CH_2Cl_2 (5 mL) were placed in a flame-dried, 50-mL, two-necked round-bottom flask under an argon atmosphere. The apparatus was cooled to –20 °C and a solution of (+)-DET (104 mg, 0.505 mmol) in dry CH_2Cl_2 (2 mL) [previously stirred with 4-Å molecular sieves (50 mg) for 20 min] and a solution of Ti(*i*-PrO)$_4$ (0.1 mL, 0.337 mmol) in dry CH_2Cl_2 (2 mL) [previously stirred with 4-Å molecular sieves (50 mg) for 20 min] were cannulated sequentially into the reaction flask with stirring. After 20 min, 5.5 M *t*-BuOOH in decane (0.61 mL) was added to the mixture and it was stirred at –20 °C for another 0.5 h. Then, a solution of allylic alcohol **3a** (600 mg, 3.37 mmol) in dry CH_2Cl_2 (4 mL) [previously stirred with 4-Å molecular sieves (75 mg) for 20 min] was cannulated into the mixture and the stirring was continued for further 4 h. Finally, an aqueous solution of 30% tartaric acid (3.4 mL) was added, the mixture was stirred for 0.5 h, and the temperature was allowed to warm to 0 °C. Most of the CH_2Cl_2 was removed under reduced pressure and the residue was stirred at 0 °C for 0.5 h with 30% aq NaOH (3.5 mL) saturated with NaCl. The resulting mixture was filtered through celite using Et_2O and the filtrate was placed in a separatory funnel and the organic layer was separated. The aqueous layer was extracted with Et_2O (1 × 30 mL) and the combined ethereal extracts were washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography (silica gel, 30% EtOAc–light petroleum) to give pure epoxide **4a** as a colorless viscous liquid [yield: 280 mg (43%)] with 98% ee [by ^{1}H NMR spectroscopic analysis of the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester **8** prepared following a standard procedure[20]] together with the unreacted *S*-allylic alcohol **5a** [yield: 290 mg (48%)].

4a
$[\alpha]_D^{31}$ +70.5 (*c* 1.1, $CHCl_3$).

IR (neat): 3417, 2993, 2900, 1610, 1504, 1488, 1444, 1247, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (br s, O*H*), 2.77 (t, *J* = 4.9 Hz, 1 H), 2.95 (dd, *J* = 4.8, 2.6 Hz, 1 H), 3.16–3.19 (m, 1 H), 4.83 (d, *J* = 2.3 Hz, 1 H), 5.96 (s, 2 H), 6.78–6.89 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.1, 55.5, 71.2, 101.5, 107.4, 108.6, 120.4, 133.9, 147.8, 148.2.

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.86; H, 5.19. Found: C, 61.73; H, 5.12.

(*S*)-(3,4-Dimethoxyphenyl)[(2*S*)-oxiran-2-yl]methanol (4b):
Compound **4b** was prepared from **3b** following the same procedure as described for **4a** and was formed as a viscous liquid in 45% yield (290 mg) with 96% ee together with the unreacted *S*-allylic alcohol **5b** (270 mg, 45%).

4b
$[\alpha]_D^{31}$ +75.8 (*c* 1.0, $CHCl_3$).

IR (neat): 3492, 2941, 2841, 1633, 1593, 1519, 1464, 1454, 1421, 1142, 1022 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (br s, O*H*), 2.81 (t, *J* = 4.7 Hz, 1 H), 2.98 (dd, *J* = 4.9, 2.7 Hz, 1 H), 3.23–3.26 (m, 1 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.90 (d, *J* = 2.1 Hz, 1 H), 6.87–6.98 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.3, 55.5, 56.1, 56.2, 71.4, 109.9, 111.4, 119.1, 132.7, 149.1, 149.3.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.75; H, 6.60.

(*R*)-(+)-[(*S*)-1,3-Benzodioxol-5-yl][(2*S*)-oxiran-2-yl]methyl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (8a):
To a solution of **4a** (30 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was added (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (43.6 mg, 0.18 mmol), DCC (37 mg, 0.18 mmol), and a catalytic amount of DMAP (3.7 mg, 0.03 mmol). The mixture was stirred overnight at r.t. The solid was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography (silica gel, 10% EtOAc–light petroleum) to afford **8a** as a viscous liquid; yield: 54.8 mg (89%).

IR (neat): 3018, 2918, 2848, 1753, 1504, 1490, 1446 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63 (dd, *J* = 5.1, 2.5 Hz, 1 H), 2.73 (t app, *J* = 4.2 Hz, 1 H), 3.18–3.22 (m, 1 H), 3.47 (s, 3 H), 5.98 (s, 2 H), 6.04 (d, *J* = 3.6 Hz, 1 H), 6.79–6.90 (m, 3 H), 7.33–7.46 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.1, 52.3, 55.2, 75.0, 101.2, 107.7, 108.2, 108.3, 121.5, 121.9, 125.0, 127.2, 128.1, 128.2, 128.3, 129.4, 129.6, 147.8, 148.1, 165.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}F_3O_6$: 411.1055; found: 411.1017.

(*R*)-(+)-[(*S*)-(3,4-Dimethoxyphenyl)][(2*S*)-oxiran-2-yl]methyl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (8b):
Ester **8b** was prepared from **4b** following the same procedure as described for **8a** and was formed as a viscous liquid in 90% yield (55 mg).

IR (neat): 3020, 2933, 2848, 1753, 1517, 1465, 1168, 1026 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65 (dd, *J* = 5.0, 2.4 Hz, 1 H), 2.75 (dd, *J* = 4.8, 3.8 Hz, 1 H), 3.23–3.27 (m, 1 H), 3.48 (s, 3 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 6.08 (d, *J* = 3.6 Hz, 1 H), 6.85–6.99 (m, 3 H), 7.31–7.45 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.4, 52.5, 55.4, 55.8, 55.9, 75.5, 110.6, 111.1, 111.2, 120.3, 121.4, 125.2, 127.3, 127.4, 128.3, 129.6, 129.7, 132.2, 149.2, 149.7, 165.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}F_3O_6$: 427.1368; found: 427.1324.

5-[(1*E*)-3-{(*S*)-1,3-benzodioxol-5-yl[(2*S*)-oxiran-2-yl]methoxy}prop-1-enyl]-1,3-benzodioxole (7a):
To a stirred suspension of NaH (50 mg, 60% dispersion, 2.06 mmol) in dry THF–DMSO (10:1, 4 mL) was added dropwise a solution of epoxy alcohol **4a** (200 mg, 1.03 mmol) in dry THF (7mL) at 0–10 °C under N_2. After the evolution of hydrogen ceased (15 min), a solution of cinnamyl bromide **6a** (300 mg, 1.24 mmol) in THF (6 mL) was added dropwise at 0 °C over 25 min. The mixture was then stirred at r.t. for 8 h and carefully decomposed with ice water. After removal of most of the THF under reduced pressure, the resulting residue was extracted with Et_2O (4 × 50 mL). The combined ethereal extracts were washed with H_2O (2 × 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the dark brown residue obtained was purified by column chromatography (silica gel, 30% EtOAc–light petroleum) to give **7a** as a colorless viscous liquid; yield: 300 mg (82%).

$[\alpha]_D^{27.7}$ +60.5 (*c* 1.8, $CHCl_3$).

IR (neat): 2994, 2895, 1672, 1606, 1503, 1488, 1444, 1249, 1039 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.74–2.81 (m, 2 H), 3.12–3.16 (m, 1 H), 3.99 (ddd, *J* = 12.4, 6.6, 1.3 Hz, 1 H), 4.12 (ddd, *J* = 12.5, 5.6, 1.4 Hz, 1 H), 4.31 (d, *J* = 4.0 Hz, 1 H), 5.86 (s, 2 H), 5.89 (s, 2 H), 6.02–6.12 (m, 1 H), 6.44 (d, *J* = 15.8 Hz, 1 H), 6.70–6.91 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.5, 54.8, 69.8, 79.9, 101.5, 101.6, 106.2, 108.0, 108.6, 108.7, 121.5, 121.6, 124.3, 131.5, 132.5, 132.8, 147.7, 148.0, 148.3, 148.4.

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.80; H, 5.1. Found: C, 67.72; H 5.11.

5-[(1*E*)-3-{(*S*)-(3,4-dimethoxyphenyl)[(2*S*)-oxiran-2-yl]methoxy}prop-1-enyl]-1,3-benzodioxole (7b):
Compound **7b** was prepared from **4b** by condensation with **6b** following the same procedure as described for **7a** and was formed as a viscous liquid in 83% yield (293 mg).

$[\alpha]_D^{27.7}$ +52.8 (*c* 0.6, $CHCl_3$).

IR (neat): 2997, 2902, 1677, 1604, 1504, 1444, 1250 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.74–2.82 (m, 2 H), 3.16–3.20 (m, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 4.01 (ddd, *J* = 12.5, 6.5, 1.2 Hz, 1 H), 4.13 (ddd, *J* = 12.4, 5.8, 1.3 Hz, 1 H), 4.33 (d, *J* = 4.2 Hz, 1 H), 5.94 (s, 2 H), 6.04–6.13 (m, 1 H), 6.45 (d, *J* = 15.8 Hz, 1 H), 6.72–6.92 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.5, 54.8, 56.3, 69.8, 80.0, 101.3, 106.1, 108.6, 110.2, 110.5, 111.3, 120.3, 121.5, 124.3, 131.0, 131.4, 132.8, 147.7, 148.3, 149.4, 149.5.

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 6.51. Found: C, 67.98; H, 6.50.

5-{(*S*)-{[(2*E*)-3-(4-benzyloxy-3-methoxyphenyl)prop-2-enyl]oxy}[(2*S*)-oxiran-2-yl]methyl}-1,3-benzodioxole (7c):
Compound **7c** was prepared from **4a** by condensation with **6c** following the same procedure as described for **7a** and was formed as a viscous liquid in 88% yield (420 mg).

$[\alpha]_D^{27.7}$ +42.3 (*c* 2.0, $CHCl_3$).

IR (neat): 2918, 2871, 1602, 1585, 1514, 1504, 1487, 1444, 1247, 1137, 1037 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.76–2.81 (m, 2 H), 3.12–3.16 (m, 1 H), 3.90 (s, 3 H), 4.00 (dd, *J* = 12.1, 6.3 Hz, 1 H), 4.13 (dd, *J* = 12.3, 5.7 Hz, 1 H), 4.33 (d, *J* = 4.0 Hz, 1 H), 5.15 (s, 2 H), 5.97 (s, 2 H), 6.06–6.16 (m, 1 H), 6.45 (d, *J* = 15.8 Hz, 1 H), 6.81–6.94 (m, 6 H), 7.26–7.44 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.4, 54.8, 56.3, 69.9, 71.4, 79.8, 101.4, 108.0, 108.5, 109.9, 114.4, 120.0, 121.4, 124.3, 127.6, 127.7, 128.2, 128.3, 128.9, 132.1, 132.3, 132.9, 137.1, 148.0, 148.3, 149.2, 149.6.

Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.43; H, 5.86.

(–)-Dihydrosesamin (1a):
A solution of Cp_2TiCl_2 (155 mg, 0.62 mmol) in dry THF (8 mL) was stirred with activated Zn dust (115 mg, 1.77 mmol) for 1 h under argon [activated Zn dust was prepared by washing commercially available Zn dust (20 g) with 4 M HCl (60 mL), followed by thorough washing with H_2O, and finally with dry acetone, and then drying in vacuo]. The resulting green solution was then added dropwise to a stirred solution of epoxide **7a** (100 mg, 0.282 mmol) in dry THF (7 mL) at r.t. under argon over a period of 30 min. The mixture was stirred for an additional 1 h and decomposed with 10% H_2SO_4 (10 mL). After removal of most of the THF under reduced pressure, the resulting residue was extracted with Et_2O (4 × 30 mL) and the combined ethereal extracts were washed successively with sat. aq $NaHCO_3$ (1 × 15 mL) and brine (1 × 15 mL), and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the brown residue obtained was purified by column chromatography (silica gel, 40% EtOAc–light petroleum) to give a colorless viscous liquid (88 mg, 87%) as a mixture of two isomers in a ratio of 5:1. The minor isomer could not be separated in pure form. It was always contaminated with the major isomer. The major isomer was separated by preparative TLC (20% EtOAc–light petroleum) to afford **1a** as a crystalline solid; yield: 64 mg (63%).

mp 97–99 °C (Lit.[3] 98–99 °C)

$[\alpha]_D^{26.5}$ –15.2 (*c* 0.8, pyridine) {Lit.[3] $[\alpha]_D^{25}$ –15.9 (*c* 0.67, pyridine)}.

IR (KBr): 3409, 2916, 2848, 1610, 1504, 1488, 1442, 1247, 1039 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.55 (br s, O*H*), 2.33–2.38 (m, 1 H), 2.54 (dd, *J* = 13.4, 10.5 Hz, 1 H), 2.61–2.75 (m, 1 H), 2.88 (dd, *J* = 13.4, 5.2 Hz, 1 H), 3.69–3.79 (m, 2 H), 3.90 (dd, *J* = 10.5, 6.7 Hz 1 H), 4.06 (dd, *J* = 8.5, 6.6 Hz 1 H), 4.80 (d, *J* = 6.2 Hz, 1 H), 5.93 (s, 2 H), 5.94 (s, 2 H), 6.63–6.85 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.2, 42.3, 52.7, 61.0, 73.0, 82.9, 100.9, 101.0, 106.3, 108.0, 108.2, 108.9, 119.0, 121.4, 134.1, 137.1, 146.0, 146.9, 147.8, 147.9.

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.65. Found: C, 67.32; H, 5.61.

[(2*R*,3*S*,4*S*)-4-(4-benzyloxy-3-methoxybenzyl)-2-(1,3-benzodioxol-5-yl)tetrahydrofuran-3-yl]methanol (1c):
Compound **7c** was subjected to the radical cyclization reaction following the same procedure as described for **1a** to give a mixture of two isomers as a colorless viscous liquid in a ratio of 5:1. The minor isomer could not be separated in pure form. It was always contaminated with the major isomer. The major isomer was separated by preparative TLC (20% EtOAc–light petroleum) to afford **1c** as a viscous liquid in 61% yield (62 mg).

$[\alpha]_D^{27}$ –20.5 (*c* 0.8, $CHCl_3$).

IR (neat): 3018, 2887, 1605, 1510, 1488, 1215 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.59 (br s, O*H*), 2.32–2.41 (m, 1 H), 2.55 (dd, *J* = 13.4, 10.6 Hz, 1H), 2.67–2.79 (m, 1 H), 2.91 (dd, *J* = 13.3, 5.1 Hz, 1 H), 3.71–3.80 (m, 2 H), 3.86–3.95 (m, 1 H), 3.87 (s, 3 H), 4.05 (dd, *J* = 8.7, 6.4 Hz, 1 H), 4.79 (d, *J* = 6.6 Hz, 1 H), 5.12 (s, 2 H), 5.94 (s, 2 H), 6.64–6.84 (m, 6 H), 7.26–7.45 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.1, 42.3, 52.7, 55.7, 60.9, 71.1, 73.0, 82.8, 101.0, 106.3, 108.0, 112.5, 114.2, 119.1, 120.4, 120.6, 127.2, 127.8, 128.5, 133.6, 136.1, 137.0, 137.2, 146.6, 146.9, 147.8, 149.6.

Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.21; H, 6.26.

(–)-Acuminatin (1d):
Compound **1c** (40 mg, 0.089 mmol) in dry EtOAc (7 mL) was subjected to hydrogenolysis with H_2 and 10% Pd/C (25 mg) at r.t. and with constant stirring for 1.5 h. The catalyst was then filtered off, the filtrate was concentrated under reduced pressure, and the residue obtained was purified by column chromatography (silica gel, 40% EtOAc–light petroleum) to give **1d** as a colorless viscous liquid; yield: (30 mg, 93%).

$[\alpha]_D^{26.5}$ –10.6 (*c* 0.5, $CHCl_3$).

IR (neat): 3018, 2939, 1604, 1514, 1488, 1442, 1215 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32–2.40 (m, 1 H), 2.53 (dd, *J* = 13.5, 10.8, Hz, 1 H), 2.68–2.76 (m, 1 H), 2.91 (dd, *J* = 13.2, 5.3 Hz, 1 H), 3.71–3.81 (m, 2 H), 3.83–3.94 (m, 1 H), 3.86 (s, 3 H), 4.05 (dd, *J* = 8.7, 6.6 Hz, 1 H), 4.77 (d, *J* = 6.5 Hz, 1 H), 5.50 (s, PhO*H*), 5.93 (s, 2 H), 6.67–6.92 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.3, 42.4, 52.8, 56.0, 60.8, 73.0, 82.8, 101.0, 106.6, 108.0, 111.2, 114.4, 119.1, 121.3, 132.2, 137.1, 144.0, 146.5, 146.9, 147.8.

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.92; H, 6.15.

(–)-Sesamin (2a):

A solution of Cp_2TiCl_2 (155 mg, 0.619 mmol) in dry THF (8 mL) was stirred with activated Zinc dust (115 mg, 1.77 mmol) for 1 h under argon. The resulting green solution was then added dropwise to a stirred solution of epoxide **7a** (100 mg, 0.28 mmol) in dry THF (7 mL) at 60 °C under argon over a period of 10 min. After 10 min, a solution of I_2 (97 mg, 0.38 mmol) in THF (2 mL) was added via syringe. The mixture was kept at 60 °C with constant stirring for a further 1 h and then decomposed with sat. aq NH_4Cl (10 mL). Most of the THF was removed under reduced pressure and the resulting residue obtained was extracted with Et_2O (4 × 50 mL). The combined ethereal extracts were thoroughly washed with 10% aq $Na_2S_2O_3$ (3 × 25 mL) and brine (1 × 20 mL), and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the dark mass obtained was purified by column chromatography (silica gel, 20% EtOAc–light petroleum) to give **2a** as a crystalline solid; yield: 91 mg (91%).

mp 122–124°C (Lit.[22a] 123–124.5 °C).

$[\alpha]_D^{26}$ –66.8 (*c* 0.30, $CHCl_3$).

IR (KBr): 2918, 2850, 1608, 1502, 1488, 1442, 1245, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03–3.07 (m, 2 H), 3.88 (dd, *J* = 9.2, 3.5 Hz, 2 H), 4.25 (dd, *J* = 9.1, 6.8 Hz, 2 H), 4.71 (d, *J* = 4.3 Hz, 2 H), 5.95 (s, 4 H), 6.77–6.84 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.3, 70.6, 84.7, 100.0, 105.4, 107.1, 118.3, 134.0, 146.0, 146.9.

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.80; H, 5.12. Found: C, 67.74; H, 5.10.

(–)-Methyl Piperitol (2b):

(–)-Methyl piperitol (**2b**) was prepared from **7b** by following the same procedure as described for **2a** and was formed as a viscous liquid in 90% yield (90 mg).

$[\alpha]_D^{25}$ –71.5 (*c* 0.40, $CHCl_3$).

IR (neat): 2916, 2848, 1606, 1504, 1490, 1442, 1249, 1039 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.06–3.12 (m, 2 H), 3.80–3.97 (m, 2 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 4.22–4.28 (m, 2 H), 4.72 (d, *J* = 3.9 Hz, 1 H), 4.74 (d, *J* = 4.1 Hz, 1 H), 5.95 (s, 2 H), 6.77–6.91 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.6, 54.8, 56.3, 56.5, 72.1, 72.2, 86.2, 86.3, 101.5, 106.9, 108.6, 109.8, 111.6, 118.7, 119.8, 134.0, 135.6, 147.5, 148.4, 149.1, 149.7.

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 6.51. Found: C, 68.01; H, 6.50.

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