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

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Abstract: Enantioselective syntheses of furan lignans (−)-dihydrerosesamin 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 nature1,4 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. Dihydrerosesamin and acuminatin are representatives of biologically active furan lignans with two identical or different aromatic moieties, respectively. Dihydrerosesamin1 was isolated from Daphne tangutica maxim and it has been used as an abortifacient and in the treatment of rheumatism and toothache. Acuminatin2 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 tetrahydrofuran lignans with two identical or different aromatic moieties, respectively. Sesamin3 was isolated from Hydrocotyle plant 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 lipoleole metabolism in rats. Methyl piperitoll 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 have been reported, there are only a few reports for the enantioselective synthesis of these lignans. To our knowledge, there is only one report8 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 synthesized13 using chiral organoselenium intermediates. A formal synthesis of (+)-sesamin in 62% ee has also been reported recently using a chiroptical 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 efforts15 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 (−)-dihydrerosesamin (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 precursor16 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-
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\(_2\)TiCl), 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.

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).

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-benzoxyl-3-methoxyphenyl) in 83 and 88% yield, respectively.

The radical initiator Cp\(_2\)TiCl was easily generated\(^{17}\) in situ from commercially available titanocene dichloride (Cp\(_2\)TiCl\(_2\)) 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 Cp₂TiCl 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 1H 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 (−)-dihydrodesamin. 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 [Lit.21 [α]D = +68.7 (c 0.40, CHCl₃)]. Under identical reaction conditions, compound 7b afforded (−)-methyl piperitol (2b) in 90% yield with opposite specific rotation compared to naturally occurring (−)-methyl piperitol24 [Lit.22 [α]D = +73.6 (c 0.35, CHCl₃), 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 Sn2 attack on the iodine-substituted carbon of II giving the stable products 2 with all the substituents equatorial. This can be explained using 1H 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 (Ar1 ≠ Ar2) 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 Cp₂TiCl.

Scheme 4  In conclusion, we have successfully achieved the enantioselective total synthesis of furan lignans (−)-dihydrodesamin 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 1H and 13C NMR spectra were recorded in CDCl₃ 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 Et₂O and THF
were dried (Na), and CH₂Cl₂ and DMSO were freshly distilled from P₂O₅ and CaH₂, 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 CHCl₃ at the concentration indicated. Elemental analyses were performed on an analytical instrument (Dr. Hans Hosi, 0A1, 468) in our analytical laboratory. High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument.

(4a)-[S]-(3,4-Dimethoxyphenyl) [(2S)-oxiran-2-yl]methanol (4a): Activated powdered 4 Å molecular sieves (150 mg, 25 wt%) in dry CH₂Cl₂ (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 CH₂Cl₂ (2 mL) [previously stirred with 4 Å molecular sieves (50 mg) for 20 min] and a solution of Ti(–PrO)₂ (0.1 mL, 0.337 mmol) in dry CH₂Cl₂ (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 BuOHH 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 CH₂Cl₂ (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 CH₂Cl₂ was removed under reduced pressure and the residue was stirred at r.t. for 8 h and carefully decomposed with ice water. After the evolution of hydrogen ceased (15 min), a solution of 50 mg, 60% dispersion, 2.06 mmol) in dry THF (7 mL) at 0–10 °C under N₂. After the evolution of hydrogen ceased (15 min), a solution of allylic alcohol 3a in dry THF (7 mL) at 0–10 °C under N₂. After the evolution of hydrogen ceased (15 min), a solution of allylic alcohol 3a (400 mg, 1.03 mmol) in dry THF (7 mL) at 0–10 °C under N₂. After the evolution of hydrogen ceased (15 min), a solution of allylic alcohol 3a (400 mg, 1.03 mmol) in dry THF (7 mL) at 0–10 °C under N₂. After the evolution of hydrogen ceased (15 min), a solution of allylic alcohol 3a (400 mg, 1.03 mmol) in dry THF (7 mL) at 0–10 °C under N₂.
IR (neat): 2944, 2895, 1672, 1606, 1503, 1488, 1444, 1249, 1039 cm⁻¹.

1H NMR (300 MHz, CDCl₃): 8 = 7.24–7.81 (m, 2 H), 3.12–3.16 (m, 1 H), 3.99 (ddd, J = 12.5, 5.6, 1.4 Hz, 1 H), 4.13 (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 = 5.8 Hz, 1 H), 6.70–6.91 (m, 6 H).

13C NMR (75 MHz, CDCl₃): δ = 54.5, 54.8, 69.8, 79.9, 101.5, 101.6, 106.1, 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.


5-[(1E)-3-[(S),(3,4-dimethoxyphenyl)oxiran-2-yl)methyl]-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).

[6]-20.5 –15.2 (c 0.8, pyridine) [Lit.3] [6] 25 –20.5 (c 0.8, CHCl₃). IR (KBr): 3409, 2916, 2848, 1610, 1504, 1488, 1442, 1247, 1039 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.55 (br s, OH), 2.32–2.38 (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 (d, 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).

13C NMR (75 MHz, CDCl₃): 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.


(2R,3S,4S)-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 colorless liquid in 61% yield (62 mg).


1H NMR (300 MHz, CDCl₃): δ = 1.59 (br s, OH), 2.32–2.41 (m, 1 H), 2.55 (dd, J = 13.4, 10.6 Hz, 1 H), 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), 3.97 (s, 3 H), 4.05 (d, 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).

13C NMR (75 MHz, CDCl₃): 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.


(−)-Acuminatin (1d): Compound 1c (40 mg, 0.089 mmol) in dry EtOAc (7 mL) was subjected to hydrogenolysis with H₂ 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 preparative TLC (20% EtOAc–light petroleum) to afford 1d as a colorless viscous liquid; yield: 64 mg (63%).
A solution of Cp₂TiCl₂ (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 I₂ (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 saturated aqueous NH₄Cl (10 mL). Most of the THF was removed under reduced pressure and the resulting residue obtained was extracted with Et₂O (4 × 50 mL). The combined ethereal extracts were washed thoroughly with 10% aq Na₂SO₃ (3 × 25 mL) and then dried (Na₂SO₄). 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%).

1H NMR (300 MHz, CDCl₃): 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, 1 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, PhOH), 5.93 (s, 2 H), 6.67–6.92 (m, 6 H).

13C NMR (75 MHz, CDCl₃): 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.


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