Short and Stereoselective Total Synthesis of Furano Lignans (±)-Dihydrosesamin, (±)-Lariciresinol Dimethyl Ether, (±)-Acuminatin Methyl Ether, (±)-Sanshodiol Methyl Ether, (±)-Lariciresinol, (±)-Acuminatin, and (±)-Lariciresinol Monomethyl Ether and Furofuran Lignans (±)-Sesamin, (±)-Eudesmin, (±)-Piperitol Methyl Ether, (±)-Pinoresinol, (±)-Piperitol, and (±)-Pinoresinol Monomethyl Ether by Radical Cyclization of Epoxides Using a Transition-Metal Radical Source

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Intramolecular radical cyclization of suitably substituted epoxy ethers **4a**−**g** using bis(cyclopentadienyl)titanium(III) chloride as the radical source resulted in trisubstituted tetrahydrofurano lignans and 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane lignans depending on the reaction conditions. The titanium(III) species was prepared in situ from commercially available titanocene dichloride and activated zinc dust in THF. Upon radical cyclization followed by acidic workup, epoxy olefinic ethers **4a**−**g** afforded furano lignans dihydrosesamin **1a**, lariciresinol dimethyl ether **1b**, acuminatin methyl ether **1e**, and sanshodiol methyl ether **1g** directly and lariciresinol **1h**, acuminatin **1i**, and lariciresinol monomethyl ether **1j** after removal of the benzyl protecting group by controlled hydrogenolysis of the corresponding cyclized products. The furofuran lignans sesamin **2a**, eudesmin **2b**, and piperitol methyl ether **2e** were also prepared directly by using the same precursors **4a**−**f** on radical cyclization followed by treatment with iodine and pinoresinol **2h**, piperitol **2i**, and pinoresinol monomethyl ether **2j** after controlled hydrogenolysis of the benzyl protecting group of the corresponding cyclized products. Two naturally occurring acyclic lignans, secoisolariciresinol **5h** and secoisolariciresinol dimethyl ether **5b**, have also been prepared by exhaustive hydrogenolysis of **2h** and **2b,** respectively.

Introduction

Intramolecular radical cyclization has opened the door of a new era in recent years for carbon−carbon bond formation, and it reflects its significance as a powerful tool in modern synthetic chemistry.[1] In addition to the reactive nature of carbon radicals, high regioselectivity and stereoselectivity are frequently achieved in intramolecular reactions. The number of practical methods available to conduct free-radical reactions is truly quite few. The mildness and regio- and stereoselectivities of 5-hexenyl radical cyclization have extensively been used[2] for the construction of carbocyclic as well as oxacyclic compounds leading to cyclopentane and tetrahydrofuran derivatives, respectively. A bromoalkene or a bromoalkyne derivative has been used widely as a radical precursor[3] and tin hydrides have been used as the radical initiator in radical cyclization reactions leading to five-membered cyclic compounds (Scheme 1). As the tin compounds are toxic and difficult to separate from the products, newer methods for the preparation of radical precursors as well as nontoxic radical initiator required for the intramolecular radical cyclizations are still desirable.

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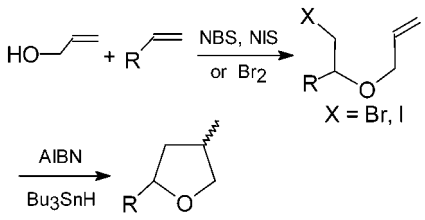
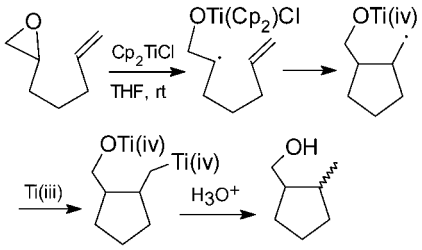
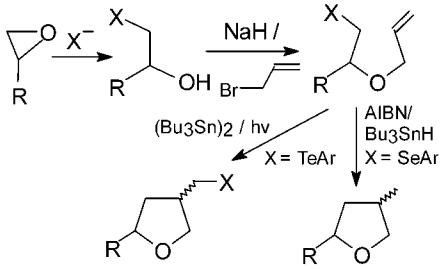
Scheme 1



Scheme 2



Scheme 3



Epoxides are vastly used as building blocks in organic synthesis due to their ready availability and facile substitution reactions with predictable stereochemistry.[4] Recently, RajanBabu and Nugent have successfully established[5] the selective one-electron reduction of an epoxide to a radical intermediate, which represents a precious synthetic tool as the intermediate radical could be trapped in subsequent reactions (Scheme 2). The use of radicals generated from an epoxide using a transition metal radical source has not been extensively explored since its discovery. Therefore, epoxides offer an excellent source of functionalized radicals.[6] The regio- and stereochemistries of the epoxide cleavage via C−O homolysis are guided by the relative stabilities of the intermediate radicals. Recently, Engman and Gupta reported[7] the epoxide ring opening by arenetellurolate or areneselenide ion and the synthesis of tetrahydrofuran derivatives by a hexabutyltin/light-induced telluride and Bu_3SnH-induced radical cyclization of selenide precursors (Scheme 3).

Lignans have drawn enormous attention of the chemists throughout the world in recent years because of their wide abundance in nature and broad range of biological activities.[8] Many of the lignans show significant antitumor, antimitotic, and antiviral effects, which include cardiovascular effects, allergenicity, activity toward insects, antimicrobial activity, etc. Pinoresinol and its monomethyl or dimethyl ether show a variety of activities as the inhibitor of cyclic AMP phosphodiesterase. Sesamin and piperitol methyl ether were found to inhibit the growth of silkworm (*Bombyx mori*) larvae. Sesamin also shows weak juvenile hormone activity in the milkweed bug (*Oncopeltus fasciatus*) and is effective in enhancing the toxicity of a wide variety of insecticides. The root and stem of *Daphne tangutica* Maxim, known as "Ai tuotuo" in Chinese herb medicine, was found to contain dihydrosesamin and is used as a remedy for rheumatism and toothache. Lariciresinol is significantly active against the P-388 lymphocytic leukaemia. The study of biological activities of lignans has been given another dimension recently by the detection of a number of lignans in man and primates.

The most challenging and interesting part of the synthesis of furano and furofurano lignans, the two major subgroups of lignans, is the control of stereochemistry during the formation of polysubstituted furan moiety. Although a number of syntheses of these lignans have been reported,[9] there has been no investigation using intramolecular radical cyclization reaction, especially through the radicals generated from epoxides using a transition metal radical source. We report here a full account[10] for the total synthesis of furano lignans (±)-dihydrosesamin **1a**,[11,12] (±)-lariciresinol dimethyl ether **1b**,[14] (±)-lariciresinol **1h**,[15−17] (±)-acuminatin **1i**,[13] (±)-acuminatin methyl ether **1e**,[13] (±)-lariciresinol monomethyl ether **1j**,[14] and (±)-sanshodiol methyl ether **1g** and furofurano lignans (±)-sesamin **2a**,[18−22] (±)-eudesmin **2b**,[18−21] (±)-pinoresinol **2h**,[21,23,24] (±)-piperitol **2i**,[18,21,22] (±)-piperitol methyl ether **2e**,[18−20] and (±)-pinoresinol

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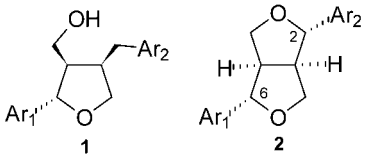
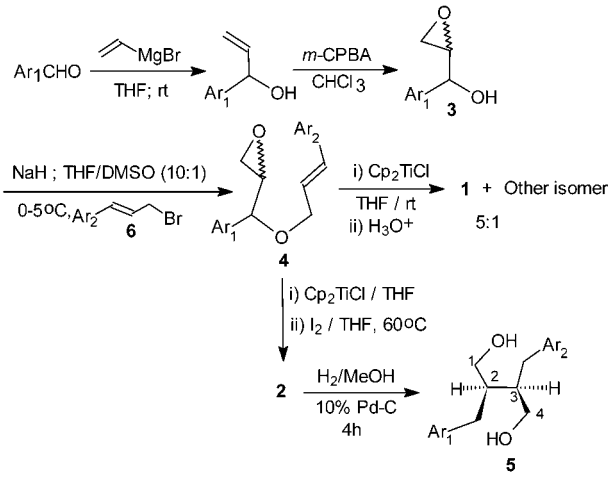
monomethyl ether **2j**[20,21] by radical cyclization of epoxides using the titanium(III) species as the radical source. Two naturally occurring acyclic lignans, secoisolariciresinol **5h**[28] and secoisolariciresinol dimethyl ether **5b**,[25−27] have also been prepared by exhaustive hydrogenolysis of the corresponding bicyclic products.



1 **2**

a, $Ar_1 = Ar_2$ = 3,4-methylenedioxy phenyl
b, $Ar_1 = Ar_2$ = 3,4-dimethoxy phenyl
c, $Ar_1 = Ar_2$ = 3-methoxy-4-benzyloxy phenyl
d, Ar_1 = 3,4-methylenedioxy phenyl, Ar_2 = 3-methoxy-4-benzyloxy phenyl
e, Ar_1 = 3,4-methylenedioxy phenyl, Ar_2 = 3,4-dimethoxy phenyl
f, Ar_1 = 3,4-dimethoxy phenyl, Ar_2 = 3-methoxy-4-benzyloxy phenyl
g, Ar_1 = 3,4-dimethoxy phenyl, Ar_2 = 3,4-methylenedioxy phenyl
h, $Ar_1 = Ar_2$ = 3-methoxy-4-hydroxy phenyl
i, Ar_1 = 3,4-methylenedioxy phenyl, Ar_2 = 3-methoxy-4-hydroxy phenyl
j, Ar_1 = 3,4-dimethoxy phenyl, Ar_2 = 3-methoxy-4-hydroxy phenyl

Scheme 4



a, $Ar_1 = Ar_2$ = 3,4-methylenedioxy phenyl
b, $Ar_1 = Ar_2$ = 3,4-dimethoxy phenyl
c, $Ar_1 = Ar_2$ = 3-methoxy-4-benzyloxy phenyl
d, Ar_1 = 3,4-methylenedioxy phenyl, Ar_2 = 3-methoxy-4-benzyloxy phenyl
e, Ar_1 = 3,4-methylenedioxy phenyl, Ar_2 = 3,4-dimethoxy phenyl
f, Ar_1 = 3,4-dimethoxy phenyl, Ar_2 = 3-methoxy-4-benzyloxy phenyl
g, Ar_1 = 3,4-dimethoxy phenyl, Ar_2 = 3,4-methylenedioxy phenyl
h, $Ar_1 = Ar_2$ = 3-methoxy-4-hydroxy phenyl
i, Ar_1 = 3,4-methylenedioxy phenyl, Ar_2 = 3-methoxy-4-hydroxy phenyl
j, Ar_1 = 3,4-dimethoxy phenyl, Ar_2 = 3-methoxy-4-hydroxy phenyl

Results and Discussion

O-Alkylation of Epoxyalcohols. The isomeric mixture (1:1) of epoxy alcohols **3a**−**g** prepared from the corresponding vinyl alcohols[29] were O-alkylated by treatment with the appropriate cinnamyl bromide **6** in the presence of NaH in THF−DMSO (10:1) to furnish **4a**−**g** (Scheme 4) as an inseparable mixture of two isomers in a ratio of 1:1. The ratio was determined, for example, for **4a**, from the distinguishable signals of the secondary proton attached to the epoxide carbon in the ^{1}H NMR spectra at δ 3.14 (m, $^1/_2$H) and 3.19 (m, $^1/_2$H). Since these isomeric mixtures could not be separated by usual chromatographic methods, the isomeric O-alkylated derivatives were used as precursors for the radical cyclization reaction finally leading to furano and furofurano lignans depending on the reaction conditions. Since some of the lignans contain free phenolic hydroxyl groups, the benzyl-protected phenols were used initially and the *O*-benzyl ether linkages were easily cleaved by controlled hydrogenolysis in the final step.

Radical Cyclization of Epoxides toward Furano Lignans Using a Titanium(III) Species as the Radical Source. For C−O homolytic cleavage of epoxides, a titanium(III) reagent, bis(cyclopentadienyl)titanium(III) chloride [Cp_2TiCl], was used at room temperature. The reagent was easily generated (eq 1) in situ from inexpensive commercially available Cp_2TiCl_2 and activated zinc dust in THF. A satisfactory reagent was prepared by stirring vigorously a red THF solution of Cp_2TiCl_2 and zinc dust for 1 h under argon atmosphere at room temperature. The red Cp_2TiCl_2 solution started to turn to green as soon as the reaction was initiated, and within a few minutes it was converted completely to a lime green solution. This green Cp_2TiCl solution was transferred to a dropping funnel through a cannula and was used for the cyclization reactions.

$$2Cp_2TiCl_2 + Zn \rightarrow 2Cp_2TiCl + ZnCl_2 \qquad (1)$$

In a preliminary experiment, 2.1 molar equiv of the green solution of Cp_2TiCl in THF was added dropwise to a THF solution of the epoxide **4a** over 25 min with constant stirring at room temperature. The initial green color of the titanium(III) species instantly discharged to red upon exposure to the epoxide. The reaction mixture, after quenching with 10% aqueous H_2SO_4 and usual workup, afforded the furan derivatives as a mixture of two isomers in a ratio of 5:1. The ratio of the two isomers was determined from the ^{1}H NMR spectrum of the crude cyclized products. For the crude product from **4a**, C-2 benzylic proton appeared as doublet at δ 4.79 (J = 6.4 Hz) for the major isomer and at δ 4.58 (J = 8.0 Hz) for the minor isomer. The major isomer was separated in moderate yield by preparative TLC, and spectral data of the major isomer **1a** were identical with those of the furano lignan dihydrosesamin. Although, theoretically, four isomers were possible, only two isomers were formed when the hydrogens on C-2 and C-3 were trans. This observation can be rationalized from our earlier results[29] and by invoking well-known conformational effects in the

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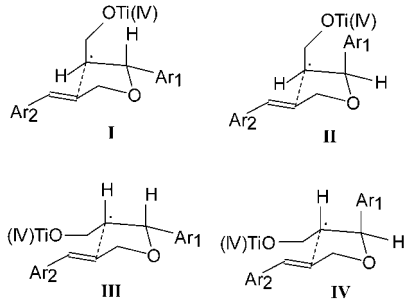
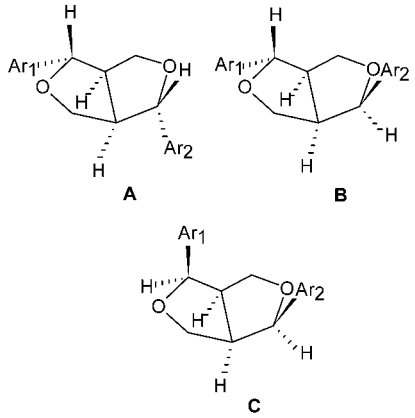


Figure 1.

intermediates,[30] although the NOE experiment (no enhancement) on C-2 H and C-3 H remained inconclusive. It is well established that the intermediate transition complex for 1,5-intramolecular addition in hex-5-enyl radical will comprise a structure somewhat similar in dimensions to cyclohexane and existing preferentially in a chairlike conformation. Consequently, in our case, for 1,5-ring closure of 2-substituted hex-5-enyl radical, four "chairlike" transition complexes, **I** and **II** where the CH_2-OTi(IV) moiety lies up and **III** and **IV** where the CH_2-OTi(IV) lies down, are possible (Figure 1). Here, the transition complexes **I** and **III** where the α-substituent is equatorially substituted should be of lower free energy compared to the axially substituted complexes **II** and **IV**. Since the α-substituent Ar and $CH_2OTi(IV)$ in the complex **III** are cis, they will have some steric interactions. It seems from the model that there might also be some steric interaction between $CH_2OTi(IV)$ and OCH_2-$CH{=}CH_2$ moieties since they come closer in the complex **III** compared to **I**. The transition complex **I** will have lower free energy than **III** and therefore lies on the pathway to the more stable product. Thus, preferential formation of trans product in **1a**−**g** derived from **i** should occur. Therefore, the radical cyclization occurs without retention of the stereochemistry of the epoxide. Since 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. Under identical cyclization conditions, the other furan derivatives were prepared as a mixture of two isomers in a ratio of 5:1 and the furano lignans lariciresinol dimethyl ether **1b**, acuminatin methyl ether **1e**, and sanshodiol methyl ether **1g** were isolated in pure forms by preparative TLC. The other furano lignans lariciresinol **1h**, acuminatin **1i**, and lariciresinol monomethyl ether **1j** were finally synthesized by hydrogenolysis of the corresponding benzyl ethers **1c**, **1d**, and **1f**, respectively, in AcOEt in the presence of 10% Pd−C.

Synthesis of Furofurano Lignans. The furofurano lignans **2a**, **2b**, and **2e** were prepared directly from the corresponding epoxyolefinic ethers **4a**, **4b**, and **4e**, respectively, through radical cyclization followed by treatment with iodine for 1h at 60 °C as the only isolated product. The minor isomer could not be isolated as it was formed in trace amount. The other furofurano lignans **2h**, **2i,** and **2j** were finally synthesized from the corresponding benzyl ethers **2c**, **2d,** and **2f**, respectively, by controlled hydrogenolysis in AcOEt in the presence of 10% Pd−C. Here, the double cyclizations furnished the furofurans in better yields and with high stereoselectivity compared to the mono cyclizations. This is probably due to the rapid cyclization at higher temperature (60 °C) leading to the highly stereoselective product, which might be facilitated by the reaction of iodine with the organo−Ti intermediate present in the reaction mixture. The second furan formation was found to be a highly controlled reaction arising from an intramolecular S_N2 attack of the alkoxide on the iodine. In the case of symmetrically substituted 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane compounds, three conformations **A**, **B**, and **C**, are possible. We are getting only one isomer of the bicyclic compounds **2a**−**f** as the sole product. This could be explained on the basis of the course of reaction.



Among these three conformers, two aromatic groups are equatorial (α) in **A**, one equatorial (α) and one axial (*β*) in **B**, and two axial (*β*) in **C**. As a part of our investigation, we hydrogenolyzed eudesmin **2b** with 10% Pd−C in methanol for 1 h to furnish lariciresinol dimethyl ether **1b** as the only product. As only one of the two rings had been broken, the unbroken ring contains one α aryl group ($Ar_1 = Ar_2$), which was equatorial in eudesmin **2b**. Since either ring of eudesmin could be broken, practically both the rings contain one equatorial aromatic group. Similar results were observed in the case of the other two furofurano lignans sesamin **2a** and pinoresinol **2h** where dihydrosesamin **1a** and lariciresinol **1h** were formed, respectively, as the sole product on partial hydrogenolysis. At this point, we can unequivocally ignore the chance of formation of the conformer **C** (sometimes referred as the dia series). Rejection of the conformer **B** (the well-known epi series) and the fact that compounds **2a**−**f** contain two equatorial aromatic moieties could be explained on the basis of ^{1}H NMR spectra. For symmetrically substituted bicyclic compounds **2a**, **2b**, and **2h**, only one doublet for both C-2 and C-6 benzylic protons was observed, for example, in **2a** at δ 4.7 (d, $J = 4.2$ Hz), in **2b** at δ 4.76 (d, $J = 4.2$ Hz), and in **2h** at δ 4.74 (d, $J = 4.2$ Hz). If one of the aromatic groups was axial (*β*) and the other one equatorial (α) (as in conformer **B**), it is expected that a different magnetic environment of the two benzylic protons at C-2 and C-6 would give two distinguishable doublets with different chemical shift values in ^{1}H NMR spectra. For unsymmetrically substituted furofurano lignans, the signals of the C-2 and C-6 benzylic protons in ^{1}H NMR spectra appeared either as one doublet or two doublets partially overlapped with each other. In case of piperitol **2i**, instead of two doublets only one doublet was observed and in case of piperitol methyl ether **2e** and pinoresinol

(30) (a)Beckwith, A. L. J.; Eaton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545. (b) Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

monomethyl ether **2j** two very close doublets were partially overlapped with each other. It is already established[20] that the variation of substituents in aromatic moieties does not change the chemical shift values of C-2 or C-6 protons. Finally, the structures of all the furofurano lignans **2a**, **2b**, **2e**, **2h**, **2i**, and **2j** were successfully confirmed by comparing their spectral data to those of the reported naturally occurring furofurano lignans.[29,31]

In continuation to our investigation, we have been able to synthesize two naturally occurring acyclic lignans. Secoisolariciresinol **5h** [2,3-bis(4′-hydroxy-3′-methoxybenzyl)butane-1,4-diol] was synthesized by treatment of pinoresinol **2h** with H_2 in the presence of 10% Pd−C in MeOH for 4 h in excellent yield. Another secolignan, secoisolariciresinol dimethyl ether **5b**, has also been synthesized in excellent yield from eudesmin **2b** following a similar exhaustive hydrogenolysis procedure.

Conclusions

In conclusion, we have demonstrated the use of a radical cyclization reaction of epoxides using a transition metal radical source for the total synthesis of various furano and furofuran lignans. Although the structures of those lignans look simple, the control of stereochemistry in the cyclization step is a challenge to organic chemists. To the best of our knowledge, this radical cyclization sequence has not yet been applied to the stereoselective synthesis of lignans. Moreover, the total synthesis was completed in a very short route.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a 300 MHz spectrometer. Diethyl ether and tetrahydrofuran were dried over sodium, and dimethyl sulfoxide was freshly distilled from calcium hydride. Light petroleum of boiling range 60−80 °C and silica gel of 60−120 mesh was used for column chromatography. Elemental analyses were performed in our analytical laboratories. The epoxy alcohols **3a**−**c** were used as starting materials prepared earlier in our laboratory.[29f]

Typical Procedure for the Preparation of Epoxyolefinic Ethers. Preparation of 1-(3,4-Methylenedioxyphenyl)-1-(3-(3,4-methylenedioxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4a). To a stirred suspension of NaH (0.087 g, 60% dispersion, 3.6 mmol) in dry THF−DMSO (10:1) (5 mL) was added dropwise a solution of epoxy alcohol **3a** (0.35 g, 1.80 mmol) in dry THF (10 mL) at 0 °C under nitrogen. After the evolution of hydrogen ceased (25 min), a solution of cinnamyl bromide **6a** (0.44 g, 1.8 mmol) in THF (7 mL) was added dropwise at 0 °C over 20 min. The reaction mixture was then stirred at room temperature for 8 h and carefully decomposed with ice−water. After removal of most of the solvent under reduced pressure, the resulting residue was extracted with diethyl ether (4 × 50 mL). The combined ether extract was washed successively with water (2 × 10 mL) and brine (1 × 10 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the dark brown gummy residue obtained was purified by column chromatography over silica gel (30% ethyl acetate−light petroleum) to furnish **4a** (0.50 g, 78%) as a colorless viscous liquid: IR (neat) 2995, 2895, 1732, 1668, 1606, 1504, 1444, 1353, 1248 cm^{-1}; ^{1}H NMR δ 2.57−2.79 (m, 2H), 3.14 (m, $^1/_2$H), 3.19 (m, $^1/_2$H), 3.97−4.31 (m, 3H), 5.93 (s, OCH_2O), 5.96 (s, OCH_2O), 6.02−6.14 (m, 1H), 6.46 (dd, J = 15.9, 10.5 Hz, 1H), 6.72−6.92 (m, 6H, ArH); ^{13}C NMR δ 44.3, 45.0, 54.3, 55.2, 69.3, 70.3, 79.4, 81.8, 82.2, 100.9, 101.0, 105.6, 107.2, 107.5, 108.2, 120.5, 121.1, 123.7, 131.0, 132.3, 147.2, 147.5, 147.9. Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.75; H, 5.11.

Preparation of 1-(3,4-Dimethoxyphenyl)-1-(3-(3,4-methoxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4b). Compound **4b** was prepared from **3b** and **6b** by the same procedure as described for **4a**: yield 72%; IR (neat) 2935, 2837, 1732, 1602, 1514, 1463, 1417, 1265, 1234 cm^{-1}; ^{1}H NMR δ 2.60−2.81 (m, 2H), 3.18−3.20 (m, $^1/_2$H), 3.20−3.26 (m, $^1/_2$H), 3.80−4.37 (m, 3H), 3.87, 3.88, 3.89, 3.89 (4s, 4 × OCH_3), 6.09−6.23 (m, 1H), 6.49 (dd, J = 15.9, 8.4 Hz, 1H), 6.72−7.08 (m, 6H, ArH); ^{13}C NMR δ 44.8, 45.5, 54.8, 55.7, 56.2, 56.2, 56.3, 56.3, 70.0, 80.0, 82.6, 109.1, 110.2, 110.6, 111.4, 120.0, 120.1, 120.4, 124.1, 130.1, 131.1, 132.9, 149.3, 149.4, 149.5, 149.6. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.35; H, 6.79.

Preparation of 1-(3-Methoxy-4-benzyloxyphenyl)-1-(3-(3-methoxy-4-benzyloxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4c). Compound **4c** was prepared from **3c** and **6c** by the same procedure as described for **4a**: yield 80%; IR (neat) 2935, 2841, 1600, 1514, 1454, 1417, 1380, 1263, 1224 cm^{-1}; ^{1}H NMR δ 2.37−2.60 (m, 2H), 2.94−2.97 (m, $^1/_2$H), 2.99−3.03 (m, $^1/_2$H), 3.58−4.13 (m, 3H), 3.67, 3.68 (2s, 2 × OCH_3), 4.93, 4.94 (2s, 4H), 5.92−5.98 (m, 1H), 6.25 (dd, J = 15.8, 9.3 Hz, 1H), 6.60−6.74 (m, 6H, ArH), 7.11−7.24 (m, 10H, ArH); ^{13}C NMR δ 44.4, 45.1, 54.4, 55.3, 55.9, 69.4, 70.9, 79.4, 82.1, 109.2, 110.3, 110.6, 113.2, 113.7, 119.2, 119.8, 123.8, 127.1, 127.8, 128.5, 130.0, 131.1, 132.5, 136.9, 148.0, 148.1, 149.5, 149.5. Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.84; H, 6.35.

Preparation of 1-(3,4-Methylenedioxyphenyl)-1-(3-(3-methoxy-4-benzyloxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4d). Compound **4d** was prepared from **3a** and **6c** by the same procedure as described for **4a**: yield 81%; IR (neat) 2997, 2871, 1600, 1583, 1514, 1504, 1487, 1417, 1380, 1245 cm^{-1}; ^{1}H NMR δ 2.50−2.73 (m, 2H), 3.05−3.08 (m, $^1/_2$H), 3.10−3.15 (m, $^1/_2$H), 3.80−4.26 (m, 3H), 3.82 (s, OCH_3), 5.07 (s, 2H), 5.89 (s, 2H), 6.01−6.11 (m, 1H), 6.40 (dd, J = 15.9, 9.6 Hz, 1H), 6.71−6.90 (m, 6H, ArH), 7.18−7.36 (m, 5H, ArH); ^{13}C NMR δ 44.8, 45.4, 54.8, 55.7, 56.3, 69.9, 71.3, 79.7, 82.6, 101.5, 107.7, 108.0, 108.5, 108.7, 109.8, 114.2, 120.0, 121.0, 121.5, 124.2, 127.6, 128.2, 128.9, 130.5, 132.4, 132.5, 132.9, 137.4, 148.0, 148.3, 148.4, 150.0. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.62; H, 5.87.

Preparation of 1-(3,4-Methylenedioxyphenyl)-1-(3-(3,4-dimethoxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4e). Compound **4e** was prepared from **3a** and **6b** by the same procedure as described for **4a**: yield 80%; IR (neat) 2997, 2904, 2837, 1602, 1514, 1487, 1442, 1263 cm^{-1}; ^{1}H NMR δ 2.59−2.80 (m, 2H), 3.13−3.17 (m, $^1/_2$H), 3.18−3.23 (m, $^1/_2$H), 3.81−4.35 (m, 3H), 3.87, 3.89 (2s, 2 × OCH_3), 5.97 (s, 2H), 6.15−6.20 (m, 1H), 6.50 (dd, J = 15.9, 9.6 Hz, 1H), 6.79−6.95 (m, 6H, ArH); ^{13}C NMR δ 44.8, 45.4, 54.8, 55.7, 56.2, 69.9, 79.8, 82.7, 101.5, 107.7, 108.0, 108.5, 108.7, 109.1, 111.3, 120.2, 121.0, 121.5, 124.0, 130.0, 132.4, 133.0, 148.0, 148.3, 149.2, 149.3. Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.00; H, 5.98.

Preparation of 1-(3,4-Dimethoxyphenyl)-1-(3-(3-methoxy-4-benzyloxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4f). Compound **4f** was prepared from **3b** and **6c** by the same procedure as described for **4a**: yield 78%; IR (neat) 3060, 2933, 1651, 1593, 1514, 1504, 1463, 1454, 1417, 1382, 1263, 1232 cm^{-1}; ^{1}H NMR δ 2.60−2.80 (m, 2H), 3.16−3.20 (m, $^1/_2$H), 3.21−3.26 (m, $^1/_2$H), 3.84−4.36 (m,3H), 3.87, 3.88, 3.89 (3s, 3 × OCH_3), 5.14 (s, 2H), 6.07−6.21 (m, 1H), 6.47 (dd, J = 15.8, 8.9 Hz, 1H), 6.81−6.95 (m, 6H, ArH), 7.25−7.44 (m, 5H, ArH); ^{13}C NMR δ 44.7, 45.5, 54.8, 55.7, 56.3, 69.9, 71.4, 80.0, 82.6, 110.0, 110.4, 110.8, 111.5, 114.4, 120.0, 120.6, 124.4, 127.6, 128.2, 128.9, 130.7,131.2, 132.8, 137.5, 148.5, 149.6, 149.7, 150.2. Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.73; H, 6.54.

(31) (a) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191; **1987**, *4*, 499; **1990**, *7*, 349. (b) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1; **1995**, *12*, 183; **1997**, *14*, 43. (c) Massanet, G. M.; Pando, E.; Rodriguez-Luis, F.; Zubia, E. *Fitoterapia* **1989**, *LX*, 3.

Preparation of 1-(3,4-Dimethoxyphenyl)-1-(-3-(3,4-methylenedioxyphenyl)-2-propenyloxy)-2,3-epoxypropane (4g). Compound **4g** was prepared from **3b** and **6a** by the same procedure as described for **4a**: yield 84%; IR (neat) 2999, 2935, 2837, 1606, 1593, 1514, 1504, 1463, 1444, 1352, 1251, 1234 cm^{-1}; ^1H NMR δ 2.59−2.81 (m, 2H), 3.16−3.19 (m, $^1/_2$H), 3.21−3.25 (m, $^1/_2$H), 3.81−4.34 (m, 3H), 3.88, 3.89 (2s, 2 × OCH_3), 5.93 (s, 2H), 6.04−6.17 (m, 1H), 6.46 (dd, J = 15.8, 9.7 Hz, 1H), 6.72−6.93 (m, 6H, ArH); ^{13}C NMR δ 44.3, 45.0, 54.3, 55.2, 55.8, 69.3, 69.4, 79.5, 82.1, 100.9, 105.6, 108.1, 109.8, 110.1, 110.9, 119.5, 119.8, 121.0, 123.8, 130.6, 131.0, 132.3, 147.2, 147.9, 148.9, 149.0. Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.02; H, 6.00.

Typical Procedure for Radical Cyclization of the Epoxy Ethers 4a−g: Synthesis of Dihydrosesamin (1a). A solution of Cp_2TiCl_2 (73 mg, 0.292 mmol) in dry THF (5 mL) was stirred with activated zinc dust (58 mg, 0.89 mmol) for 1 h under argon (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl, thorough washing with water and finally with dry acetone, and then drying in vacuo). The resulting green solution was then added dropwise to a stirred solution of the epoxide **4a** (45 mg, 0.127 mmol) in dry THF (4 mL) at room temperature under argon during 30 min. The reaction mixture was stirred for an additional 1 h and decomposed with 10% H_2SO_4 (5 mL). After removal of most of the tetrahydrofuran under reduced pressure, the resulting residue was extracted with diethyl ether (4 × 25 mL). The combined ether extract was washed successively with saturated $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the brown gummy residue obtained was purified by column chromatography over silica gel (40% ethyl acetate−light petroleum) to furnish a colorless viscous liquid (41 mg, 90%) as a mixture of two isomers in a ratio of 5:1. The major isomer was separated by preparative TLC to afford **1a** (29 mg, 64%): IR (neat) 3020, 2927, 2889, 1556, 1539, 1519, 1504, 1488, 1442, 1421, 1215 cm^{-1}; ^1H NMR δ 1.61 (br s, OH), 2.32−2.37 (m, 1H), 2.53 (dd, J = 13.2, 10.3 Hz, 1H), 2.63−2.76 (m, 1H), 2.87 (dd, J = 13.2, 5.1 Hz, 1H), 3.69−3.78 (m, 2H), 3.89 (dd, J = 10.6, 6.9 Hz, 1H), 4.04 (dd, J = 8.4, 6.4 Hz, 1H), 4.79 (d, J = 6.4 Hz, 1H), 5.93 (s, OCH_2O), 5.94 (s, OCH_2O), 6.62−6.83 (m, 6H, ArH); ^{13}C NMR δ 33.3, 42.3, 52.6, 60.9, 72.9, 82.9, 100.8, 100.9, 106.3, 108.1, 108.3, 108.9, 119.0, 121.4, 134.2, 137.1, 145.9, 146.9, 147.8, 147.8.

Synthesis of Lariciresinol Dimethyl Ether (1b). Compound **1b** was prepared from **4b** by the same procedure as described for **1a**: yield 63%; IR (neat) 3440, 3016, 2937, 2910, 2837, 1712, 1593, 1514, 1465, 1419, 1261,1217 cm^{-1}; ^1H NMR δ 2.38−2.47 (m, 1H), 2.57 (dd, J = 13.3, 10.5 Hz, 1H), 2.69−2.79 (m, 1H), 2.93 (dd, J = 13.3, 5.0 Hz, 1H), 3.73−3.82 (m, 2H), 3.86−3.96 (m, 1H), 3.86, 3.87, 3.88 (4s, 4 × OCH_3), 4.06 (dd, J = 8.5, 6.6 Hz, 1H), 4.81 (d, J = 6.5 Hz, 1H), 6.71−6.88 (m, 6H, ArH); ^{13}C NMR δ 33.7, 42.8, 52.9, 56.3, 61.4, 73.3, 83.1, 109.4, 111.4, 111.8, 112.4, 118.4, 120.9, 133.3, 135.8, 147.9, 148.8, 149.4, 149.5.

Preparation of Lariciresinol Dibenzyl Ether (1c). Compound **1c** was prepared from **4c** by the same procedure as described for **1a**: yield 61%; IR (neat) 3018, 2935, 1649, 1539, 1512, 1456, 1259, 1215 cm^{-1}; ^1H NMR δ 2.36−2.45 (m, 1H), 2.55 (dd, J = 13.2, 10.5 Hz, 1H), 2.67−2.79 (m, 1H), 2.90 (dd, J = 13.5, 5.1 Hz, 1H), 3.71−3.81 (m, 2H), 3.86−3.95 (m, 1H), 3.87, 3.89 (2s, 2 × OCH_3), 4.05 (dd, J = 8.7, 6.6 Hz, 1H), 4.79 (d, J = 6.5 Hz, 1H), 5.12, 5.14 (2s, 2 × OCH_2Ph), 6.65−6.90 (m, 6H, ArH), 7.29−7.45 (m, 10H, ArH); ^{13}C NMR δ 33.2, 42.2, 52.4, 56.0, 60.9, 71.1, 71.1, 72.9, 82.7, 109.5, 112.5, 113.9, 114.2, 117.9, 120.4, 127.2, 127.7, 128.5, 133.6, 136.0, 137.2, 146.6, 149.7. Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.16; H, 6.80.

Preparation of Acuminatin Benzyl Ether (1d). Compound **1d** was prepared from **4d** by the same procedure as described for **1a**: yield 60%; IR (neat) 3018, 2933, 1733, 1510, 1488, 1444, 1215 cm^{-1}; ^1H NMR δ 2.33−2.42 (m, 1H), 2.54 (dd, J = 13.2, 10.5 Hz, 1H), 2.69−2.77 (m, 1H), 2.90 (dd, J = 13.2, 4.8 Hz, 1H), 3.71−3.79 (m, 2H), 3.79−3.96 (m, 1H), 3.88 (s, OCH_3), 4.04 (dd, J = 8.4, 6.6 Hz, 1H), 4.78 (d, J = 6.3 Hz, 1H), 5.13 (s, OCH_2Ph), 5.94 (s, OCH_2O), 6.65−6.84 (m, 6H, ArH), 7.29−7.45 (m, 5H, ArH); ^{13}C NMR δ 33.1, 42.2, 52.7, 56.0, 60.8, 71.1, 72.9, 82.7, 100.9, 106.2, 108.0, 112.4, 114.2, 119.0, 120.4, 127.2, 127.7, 128.4, 133.5, 136.1, 137.0, 146.6, 146.8, 147.8, 149.6. Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C,72.08; H, 6.25.

Synthesis of Acuminatin Methyl Ether (1e). Compound **1e** was prepared from **4e** by the same procedure as described for **1a**: yield 63%; IR (neat) 3018, 2937, 1591, 1516, 1489, 1466, 1443, 1215 cm^{-1}; ^1H NMR δ 1.56 (br s, OH), 2.33−2.42 (m, 1H), 2.56 (dd, J = 13.2, 10.6 Hz, 1H), 2.68−2.78 (m, 1H), 2.92 (dd, J = 13.2, 5.0 Hz, 1H), 3.72−3.95 (m, 3H), 3.86, 3.87(2s, 2 × OCH_3), 4.05 (dd, J = 8.5, 6.5 Hz, 1H), 4.79 (d, J = 6.5 Hz, 1H), 5.94 (s, OCH_2O), 6.68−6.88 (m, 6H, ArH); ^{13}C NMR δ 33.1, 42.3, 52.7, 55.9, 60.9, 72.9, 82.8, 100.9, 106.3, 108.0, 111.3, 111.9, 119.1, 120.4, 132.9, 137.0, 146.9, 147.5, 147.8, 149.0.

Preparation of Lariciresinol Methyl Benzyl Ether (1f). Compound **1f** was prepared from **4f** by the same procedure as described for **1a**: yield 60%; IR (neat) 3016, 2933, 2850, 1732, 1606, 1593, 1514, 1463, 1454, 1417, 1261, 1217 cm^{-1}; ^1H NMR δ 2.37−2.46 (m, 1H), 2.55 (dd, J = 13.2, 10.5 Hz, 1H), 2.68−2.81 (m, 1H), 2.91 (dd, J = 13.5, 5.1 Hz, 1H), 3.71−3.81 (m, 2H), 3.81−3.97 (m, 1H), 3.87, 3.88, 3.90 (3s, 3 × OCH_3), 4.06 (dd, J = 8.4, 6.3 Hz, 1H), 4.81 (d, J = 6.3 Hz, 1H), 5.12 (s, 2 × OCH_2Ph), 6.65−6.88 (m, 6H, ArH), 7.29−7.45 (m, 5H, ArH); ^{13}C NMR δ 33.2, 42.2, 52.5, 55.8, 55.9, 56.0, 60.9, 71.1, 72.9, 82.7, 108.9, 110.9, 112.5, 114.2, 118.0, 120.4, 127.2, 127.7, 128.5, 133.6, 135.4, 137.2, 146.6, 148.4, 149.0, 149.6. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.27; H, 6.87.

Synthesis of Sanshodiol Methyl Ether (1g). Compound **1g** was prepared from **4g** by the same procedure as described for **1a**: yield 62%; IR (neat) 3018, 1556, 1539, 1517, 1506, 1488, 1247, 1215 cm^{-1}; ^1H NMR δ 2.36−2.45 (m, 1H), 2.55 (dd, J = 13.5, 10.5 Hz, 1H), 2.66−2.76 (m, 1H), 2.89 (dd, J = 13.2, 5.1 Hz, 1H), 3.71−3.80 (m, 2H), 3.84−3.97 (m, 1H), 3.87, 3.88 (2s, 2 × OCH_3), 4.07 (dd, J = 8.4, 6.6 Hz, 1H), 4.82 (d, J = 6.6 Hz, 1H), 5.93 (s, OCH_2O), 6.64−6.90 (m, 6H, ArH); ^{13}C NMR δ 33.3, 42.3, 52.4, 55.9, 61.0, 72.8, 82.8, 100.8, 108.2, 108.9, 108.9, 111.0, 118.0, 121.4, 134.1, 135.4, 147.7, 147.7, 148.4, 149.1.

Synthesis of Lariciresinol (1h). Compound **1c** (30 mg, 0.05 mmol) was subjected to hydrogenolysis in ethyl acetate (5 mL) with 10% Pd−C (15 mg) at room temperature for 1.5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to furnish **1h** (19 mg, 95%) as a colorless oil: IR (neat) 3018, 1608, 1514, 1465, 1431, 1267, 1209 cm^{-1}; ^1H NMR δ 2.36−2.45 (m, 1H), 2.55 (dd, J = 13.2, 10.5 Hz, 1H), 2.67−2.79 (m, 1H), 2.92 (dd, J = 13.8, 4.8 Hz, 1H), 3.72−3.80 (m, 2H), 3.87−3.94 (m, 1H), 3.87, 3.89 (2s, 2 × OCH_3), 4.05 (dd, J = 8.4, 6.6 Hz, 1H), 4.78 (d, J = 6.6 Hz, 1H), 5.51, 5.59 (2s, 2 × PhOH), 6.68−6.89 (m, 6H, ArH); ^{13}C NMR δ 33.3, 42.4, 52.6, 55.9, 55.9, 60.9, 72.9, 82.8, 108.3, 111.2, 114.1, 114.4, 118.7, 121.2, 132.2, 134.8, 144.0, 145.0, 146.5, 146.6.

Synthesis of Acuminatin (1i). Compound **1i** was prepared from **1d** by the procedure as described for **1h**: yield 95%; IR (neat) 3018, 1514, 1488, 1215, 1039 cm^{-1}; ^1H NMR δ 2.33−2.42 (m, 1H), 2.54 (dd, J = 13.2, 10.5 Hz, 1H), 2.66−2.79 (m, 1H), 2.90 (dd, J = 13.5, 5.1 Hz, 1H), 3.72−3.80 (m, 2H), 3.83−3.97 (m, 1H), 3.87 (s, OCH_3), 4.04 (dd, J = 8.4, 6.3 Hz, 1H), 4.78 (d, J = 6.3 Hz, 1H), 5.50 (s, PhOH), 5.94 (s, OCH_2O), 6.65−6.91 (m, 6H, ArH); ^{13}C NMR δ 33.2, 42.4, 52.7, 55.9, 60.9, 72.9, 82.8, 100.9, 106.3, 108.0, 111.1, 114.3, 119.0, 121.2, 132.2, 137.0, 143.9, 146.5, 146.8, 147.8.

Synthesis of Lariciresinol Monomethyl Ether (1j). Compound **1j** was prepared from **1f** by the procedure as described for **1h**: yield 95%; IR (neat) 3018, 2922, 2850, 1704, 1685, 1652, 1514, 1461, 1419, 1263, cm^{-1}; ^1H NMR δ 2.37−2.47 (m, 1H), 2.55 (dd, J = 13.0, 10.8 Hz, 1H), 2.68−2.77 (m, 1H), 2.92 (dd, J = 13.5, 5.1 Hz, 1H), 3.73−3.79 (m, 2H), 3.82−3.96 (m, 1H), 3.87, 3.87, 3.88(3s, 3 × OCH_3), 4.06 (dd, J = 8.4, 6.6 Hz, 1H), 4.81 (d, J = 6.6 Hz, 1H), 5.48 (s, PhOH), 6.65−6.94 (m, 6H, ArH); ^{13}C NMR δ 33.4, 42.5, 52.6, 55.5, 55.9, 61.1,

73.0, 82.8, 109.1, 109.4, 111.1, 114.4, 118.1, 121.2, 132.3, 135.5, 144.1, 146.5, 148.5, 149.2.

Typical Procedure for the Preparation of Furofurano Lignans 2a−f: Synthesis of Sesamin (2a). A solution of Cp_2TiCl_2 (73 mg, 0.292 mmol) in dry THF (5 mL) was stirred with activated zinc dust (58 mg, 0.89 mmol) for 1 h under argon. The resulting green solution was then added dropwise to a stirred solution of the epoxide **4a** (45 mg, 0.127 mmol) in dry THF (4 mL) at 60 °C under argon during 10 min. After 10 min, a solution of iodine (42 mg, 0.165 mmol) in THF (1 mL) was added by a syringe. The reaction mixture was kept at 60 °C with constant stirring for further 1 h and then decomposed by saturated aqueous ammonium chloride solution (10 mL). Most of THF was removed under reduced pressure, and the residue obtained was extracted with diethyl ether (4 × 50 mL). The combined ether extract was thoroughly washed with 10% aqueous $Na_2S_2O_3$ (3 × 25 mL) and brine (1 × 20 mL) and then dried (Na_2SO_4). Solvent was removed under reduced pressure, and the dark mass obtained was purified by column chromatography over silica gel (20% ethyl acetate in light petroleum) to afford **2a** (42 mg, 93%) as crystalline solid: mp 123−124 °C; IR (KBr) 2966, 2850, 1604, 1500, 1442, 1365, 1251 cm^{-1}; ^1H NMR δ 3.02−3.06 (m, 2H), 3.86 (dd, J = 9.0, 3.6 Hz, 2H), 4.23 (dd, J = 9.0, 7.0 Hz, 2H), 4.70 (d, J = 4.2 Hz, 2H), 5.92 (s, 2 × OCH_2O), 6.75−6.83 (m, 6H, ArH); ^{13}C NMR δ 53.3, 70.7, 84.8, 100.1, 105.5, 107.2, 118.3, 134.0, 146.1, 147.0.

Synthesis of Eudesmin (2b). Compound **2b** was prepared from **4b** by the procedure as described for **2a**: yield 90%; crystalline solid; mp 100 °C; IR (KBr) 2954, 2935, 2837, 1712, 1589, 1515, 1465, 1450, 1411, 1367, 1257, 1238 cm^{-1}; ^1H NMR δ 3.10−3.13 (m, 2H), 3.87−3.98 (m, 2H), 3.87, 3.90 (2s, 4 × OCH_3), 4.26 (dd, J = 9, 7 Hz, 2H), 4.76 (d, J = 4.2 Hz, 2H), 6.83−6.91(m, 6H, ArH); ^{13}C NMR δ 54.5, 56.3, 56.3, 72.1, 86.1, 109.8, 111.6, 118.6, 134.0, 149.1, 149.6.

Preparation of Pinoresinol Dibenzyl Ether (2c). Compound **2c** was prepared from **4c** by the procedure as described for **2a**: yield 87%; crystalline solid; mp 108−110 °C; IR (KBr) 3018, 1593, 1514, 1465, 1419, 1382, 1263, 1215 cm^{-1}; ^1H NMR δ 3.10−3.12 (m, 2H), 3.85−3.89 (m, 2H), 3.91 (s, 2 × OCH_3), 4.24 (dd, J = 9.0, 7.0 Hz, 2H), 4.74 (d, J = 3.9 Hz, 2H), 5.15 (s, 2 × OCH_2Ph), 6.78−6.93 (m, 6H, ArH), 7.26−7.45 (m, 10H, ArH); ^{13}C NMR δ 54.0, 56.0, 71.0, 71.7, 85.7, 109.7, 113.9, 118.2, 127.2, 127.8, 128.5, 134.0, 137.0, 147.7, 149.8. Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.81; H, 6.36. Found: C, 75.77; H, 6.34.

Preparation of Piperitol Benzyl Ether (2d). Compound **2d** was prepared from **4d** by the procedure as described for **2a**: yield 86%; IR (neat) 2933, 2871, 1714, 1606, 1593, 1514, 1504, 1487, 1454, 1384, 1249 cm^{-1}; ^1H NMR δ 3.05−3.08 (m, 2H), 3.84−3.90 (m, 2H), 3.90 (s, OCH_3), 4.20−4.26 (m, 2H), 4.72 (d, J = 3.3 Hz, 2H), 5.14 (s, 2H, OCH_2Ph), 5.95 (s, 2H, OCH_2O), 6.78−6.92 (m, 6H, ArH), 7.25−7.44 (m, 5H, ArH); ^{13}C NMR δ 54.1, 54.3, 56.0, 71.1, 71.7, 71.7, 85.7, 85.8, 101.1, 106.5, 108.2, 109.8, 113.9, 118.2, 119.3, 127.2, 127.8, 128.5, 134.1, 135.1, 137.1, 147.1, 147.7, 147.9, 149.9. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.51; H, 5.82.

Synthesis of Piperitol Methyl Ether (2e). Compound **2e** was prepared from **4e** by the procedure as described for **2a**: yield 88%; IR (neat) 2935, 1714, 1606, 1593, 1514, 1504, 1488, 1463, 1342, 1238 cm^{-1}; ^1H NMR δ 3.05−3.11 (m, 2H), 3.87−3.89 (m, 2H), 3.87, 3.89 (2s, 2 × OCH_3), 4.21−4.27 (m, 2H), 4.73 (d, J = 3.7 Hz, 1H), 4.74 (d, J = 4.0 Hz, 1H), 5.94 (s, OCH_2O), 6.76−6.90 (m, 6H, ArH); ^{13}C NMR δ 54.5, 54.7, 56.3, 56.4, 72.1, 72.2, 86.1, 86.2, 101.4, 106.9, 108.5, 109.7, 111.6, 118.6, 119.7, 134.0, 135.5, 147.5, 148.3, 149.1, 149.6.

Preparation of Pinoresinol Methyl Benzyl Ether (2f). Compound **2f** was prepared from **4f** by the procedure as described for **2a**: yield 85%; IR (neat) 2933, 1714, 1606, 1591, 1514, 1463, 1454, 1417, 1382, 1234 cm^{-1}; ^1H NMR δ 3.08−3.11 (m, 2H), 3.86−3.93 (m, 2H), 3.86, 3.89, 3.90 (3s, 3 × OCH_3), 4.25 (dd, J = 8.8, 6.6 Hz, 2H), 4.75 (d, J = 3.0 Hz, 2H), 5.14 (s, OCH_2Ph), 6.78−6.93 (m, 6H, ArH), 7.25−7.43 (m, 5H, ArH); ^{13}C NMR δ 54.5, 54.5, 56.3, 56.3, 56.5, 71.5, 72.1, 72.2, 86.1, 109.7, 110.4, 111.6, 114.5, 118.6, 118.6, 127.6, 128.2, 128.9, 134.0, 134.6, 137.5, 148.2, 149.1, 149.6, 150.3. Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.84; H, 6.48.

Synthesis of Pinoresinol (2h). Compound **2c** (50 mg, 0.093 mmol) was subjected to hydrogenolysis in ethyl acetate (5 mL) with 10% Pd−C (20 mg) at room temperature for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to furnish **2h** (32 mg**,** 96%) as a viscous oil: IR (neat) 3018, 2966, 2856, 1712, 1612, 1515, 1465, 1431, 1363, 1269, 1215 cm^{-1}; ^1H NMR δ 3.08−3.12 (m, 2H), 3.82−3.88 (m, 2H), 3.90 (s, 2 × OCH_3), 4.24 (dd, J = 9, 6.6 Hz, 2H), 4.74 (d, J = 4.2 Hz, 2H), 5.60 (s, PhOH), 6.80−6.90 (m, 6H, ArH); ^{13}C NMR δ 54.1, 56.0, 71.6, 85.9, 108.6, 114.2, 119.0, 133.0, 145.2, 146.6.

Synthesis of Piperitol (2i). Compound **2i** was prepared from **2d** by the procedure as described for **2h**: yield 93%; IR (neat) 3018, 2937, 2885, 1716, 1701, 1610, 1514, 1489, 1442, 1373, 1215 cm^{-1}; ^1H NMR δ 3.05−3.11 (m, 2H), 3.83−3.89 (m, 2H), 3.91 (s, 1 × OCH_3), 4.21−4.27 (m, 2H), 4.73 (d, J = 3.0 Hz, 2H), 5.62 (s, PhOH), 5.95 (s, OCH_2O), 6.77−6.91 (m, 6H, ArH); ^{13}C NMR δ 54.1, 54.3, 55.9, 71.6, 71.7, 85.8, 85.8, 101.0, 106.5, 108.1, 108.5, 114.2, 118.9, 119.3, 132.8, 135.1, 145.2, 146.7, 147.1, 147.9.

Synthesis of Pinoresinol Monomethyl Ether (2j). Compound **2j** was prepared from **2f** by the procedure as described for **2h**: yield 95%; IR (neat) 3018, 2964, 2869, 1733, 1714, 1701, 1608, 1515, 1465, 1423, 1365, 1265, 1215 cm^{-1}; ^1H NMR δ 3.10−3.11 (m, 2H), 3.81−3.90 (m, 2H), 3.87, 3.90, 3.91 (3s, 3 × OCH_3), 4.25 (dd, J = 9, 6.8 Hz, 2H), 4.74 (d, J = 4.56 Hz, 1H), 4.76 (d, J = 4.53 Hz, 1H), 5.60 (s, PhOH), 6.80−6.90 (m, 6H, ArH); ^{13}C NMR δ 54.1, 56.0, 71.6, 85.8, 85.9, 108.6, 109.2, 111.0, 114.2, 118.2, 119.0, 132.9, 133.5, 145.2, 146.7, 148.6, 149.2.

Synthesis of Secoisolariciresinol (5h). A solution of the bicyclic compound **2h** (30 mg, 0.084 mmol) in MeOH (5 mL) was subjected to hydrogenolysis in the presence of 10% Pd−C (20 mg) for 3 h at room temperature. The catalyst was filtered off, and the solvent was removed under reduced pressure to furnish **5h** (28 mg, 92%) as a colorless liquid: IR (neat) 3543, 3020, 2931, 1606, 1514, 1465, 1429, 1267, 1215 cm^{-1}; ^1H NMR δ 1.58 (br s, OH), 1.86 (m, 2H), 2.69 (ddd, J = 30.3, 13.8, 6.6 Hz, 4H), 3.49 (dd, J = 11.4, 4.2 Hz, 2H), 3.75−3.80 (m, 2H), 3.75 (s, 6H, 2 × OCH_3), 5.42 (s, 2H, 2 × PhOH), 6.51−6.57 (m, 4H, ArH), 6.73−6.75 (m, 2H, ArH); ^{13}C NMR δ 35.9, 43.8, 55.8, 61.0, 111.3, 114.1, 121.7, 132.4, 143.8, 146.4.

Synthesis of Secoisolariciresinol Dimethyl Ether (5b). Compound **5b** was obtained from **2b** by the same procedure as described for **5h** in 90% yield as a crystalline solid: mp 121−123 °C; IR (KBr) 3485, 3286, 2920, 1606, 1589, 1515, 1465, 1417, 1261 cm^{-1}; ^1H NMR δ 1.88 (m, 2H), 2.70 (ddd, J = 29.2, 13.7, 6.3 Hz, 4H), 3.55 (dd, J = 11.3, 4.2 Hz, 2H), 3.75−3.97 (m, 2H), 3.83, 3.85 (2s, 2 × OCH_3), 6.65−6.78 (m, ArH, 6H); ^{13}C NMR δ 36.1, 44.2, 56.3, 61.2, 111.6, 112.6, 121.4, 133.4, 147.8, 149.3.

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