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Structure–Plant Growth Inhibitory Activity Relationship of Lariciresinol

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Supporting Information

ABSTRACT: The syntheses of 55 lariciresinol derivatives containing derivatives on the 9-position and an aryl group at both 7- and 7′-positions were successful to examine the effect of structure of (−)-lariciresinol (**1**) on plant growth regulatory activity. (−)-(7*R*,8*R*,8′*S*)-9-Dehydroxylariciresinol **9** showed activity 2-fold more potent than that of natural (−)-lariciresinol (**1**) and −95% growth inhibitory activity to negative control against rye grass root at 1 mM. The derivatives bearing hydrophobic and smaller groups at the 9-position showed higher activity. The importance of 4- and 4′-hydroxy groups and 3- and 3′-small hydrophobic groups on 7- and 7′-phenyl groups for higher activity was also suggested.

KEYWORDS: *lignan, lariciresinol, phytotoxic activity, plant growth regulation, polyphenol*

INTRODUCTION

Lariciresinol, which is a dietary lignan, is a trisubstituted five-membered tetrahydrofuran lignan possessing three chiral centers. Intrigued by the plant growth inhibitory activity of lariciresinol[1−3] and its derivative,[4] we have developed a synthetic route to all stereoisomers and examined the effect of the stereochemistry on activity, showing the importance of (7*R*,8*S*,8′*S*) and (7*S*,8*S*,8′*R*) structures for higher activity.[5] As a next step, research on the structure−activity relationship of lariciresinol was planned. The effect of stereochemistry and substituents of lignans on a remarkable range of biological activities[6] had not yet been clarified. Because of the biosynthesis of lignans as mixtures of enantiomers,[7,8] we have employed a stereoselective synthetic method to promote the biological research of lignan. Recently, we reported the structure-containing stereochemistry−activity relationships of insecticidal,[9,10] antifungal,[11−13] IgE-suppresive,[14] and cytotoxic[15] lignans. This is a first detailed research on structure-containing stereochemistry−plant growth inhibitory (phytotoxic) activity relationship (SAR) of lignan. The results of this research would contribute to development of new lead compounds for herbicides and also research on the receptor for secondary metabolites by using plant growth regulatory compounds, lariciresinol derivatives.

At the first stage of this project, all stereoisomers of 9-dehydroxy (**9**−**16**) and 9-OCH_3 (**17**−**24**) derivatives and 9-acetoxy, 9-cyano, 9-alkyl, and 9-dimethylamino derivatives bearing (7*R*,8*S*,8′*S*)-chemistry (**25**−**31**) were prepared to determine the best structure at the 9-position for the highest activity. To clarify the effect of substituents at 7- and 7′-phenyl groups on the activity, the derivatives **32**−**63** were also synthesized by employing a previously described method[5,17] with modification (Figure 1). This article describes the structure−activity relationship of all substituents on the trisubstituted tetrahydrofuran ring of lariciresinol. The results of this research would provide information for the lead compound to a natural product-based control agent.

MATERIALS AND METHODS

Chemicals. Optical rotation values were measured with a Horiba SEPA-200 instrument. NMR data were obtained with JNM-EX400 and JNM-ECS400 spectrometers, using TMS and TFA as a standard for ^{1}H NMR (0 ppm) and for ^{19}F NMR (−76.5 ppm), respectively. EI data were measured with a JMS-MS700 V spectrometer. The synthetic methods are described in Supporting Information. The numbering of compounds follows the nomenclature of lignans.[16]

*(7R,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**9**).* Colorless oil, $[\alpha]^{20}_D$ −27 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* = 7.1 Hz), 2.23 (1H, m), 2.45 (1H, dd, *J* = 13.4, 11.2 Hz), 2.56 (1H, m), 2.81 (1H, dd, *J* = 13.4, 4.7 Hz), 3.73 (1H, dd, *J* = 8.7, 5.4 Hz), 3.84 (3H, s), 3.86 (3H, s), 4.03 (1H, dd, *J* = 8.7, 6.3 Hz), 4.49 (1H, d, *J* = 7.4 Hz), 5.69 (1H, s), 5.76 (1H, s), 6.60−6.68 (2H, m), 6.79 (1H, dd, *J* = 8.0, 1.7 Hz), 6.82−6.87 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 33.5, 44.0, 45.0, 55.88, 55.90, 72.3, 87.1, 108.4, 111.4, 114.1, 114.4, 118.9, 121.3, 132.5, 134.7, 143.9, 145.0, 146.5, 146.6; MS (EI) *m*/*z* 344 (M^+, 100), 151 (83), 137 (99); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_5$ 334.1623, found 334.1618.

*(7S,8S,8′R)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**10**).* $[\alpha]^{20}_D$ +27 (*c* 1.5, $CHCl_3$).

*(7S,8R,8′R)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**11**).* Colorless oil, $[\alpha]^{20}_D$ −24 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (3H, d, *J* = 6.9 Hz), 2.13−2.18 (2H, m), 2.55 (1H, dd, *J* = 13.7, 8.7 Hz), 2.82 (1H, dd, *J* = 13.7, 5.5 Hz), 3.61 (1H, dd, *J* = 8.5, 7.4 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.18 (1H, dd, *J* = 8.5, 6.7 Hz), 5.03 (1H, d, *J* = 6.8 Hz), 5.51 (1H, s), 5.54 (1H, s), 6.67−6.70 (3H, m), 6.75 (1H, d, *J* = 1.8 Hz), 6.85 (1H, d, *J* = 7.8 Hz), 6.86 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 38.3, 43.3, 47.9, 55.86, 55.89, 73.0, 83.4, 109.0, 111.2, 113.9, 114.3, 119.2, 121.2, 132.3, 132.6, 143.9, 144.4, 146.2, 146.4; MS (EI) *m*/*z* 344 (M^+, 100), 151 (77), 137 (77); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_5$ 334.1623, found 334.1621.

*(7R,8S,8′S)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**12**).* $[\alpha]^{20}_D$ +24 (*c* 0.9, $CHCl_3$).

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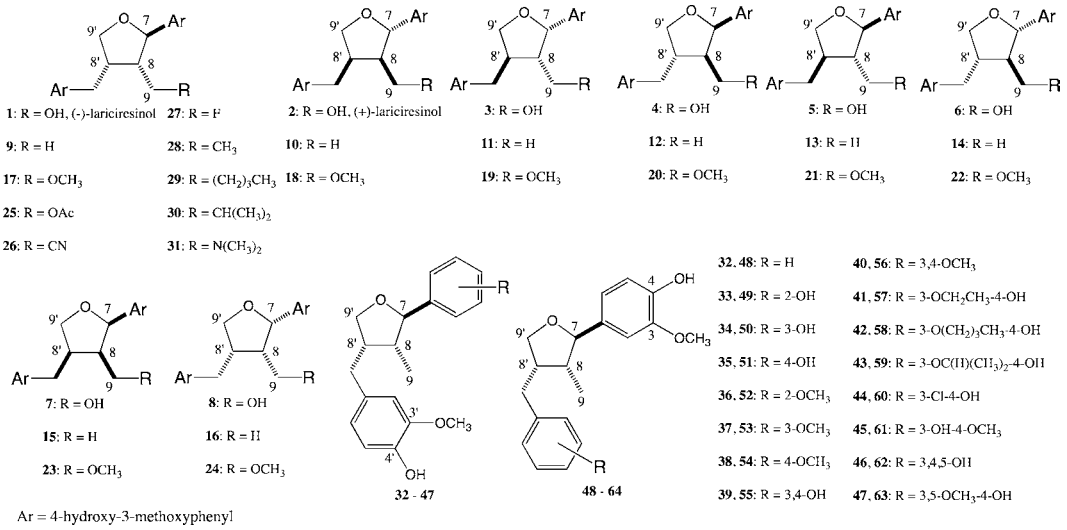

Figure 1. All stereoisomers of lariciresinol (**1**–**8**), 9-dehydroxylariciresinol (**9**–**16**), and 9-*O*-methyllariciresinol (**17**–**24**). 9-Derivatives of (−)-laricirsinol (**25**–**31**) and derivatives by substituents on the 7- and 7′-phenyl groups (**32**–**63**).

*(7R,8R,8′R)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**13**).* Colorless oil, $[\alpha]^{20}_{D}$ +45 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, d, *J* = 6.4 Hz), 1.70 (1H, m), 2.22 (1H, m), 2.53 (1H, dd, *J* = 13.7, 9.4 Hz), 2.85 (1H, dd, *J* = 13.7, 5.5 Hz), 3.80 (1H, dd, *J* = 8.3, 8.2 Hz), 3.87 (3H, s), 3.89 (3H, s), 3.99 (1H, dd, *J* = 8.3, 8.2 Hz), 4.27 (1H, d, *J* = 9.2 Hz), 5.57 (1H, s), 5.66 (1H, s), 6.66–6.68 (2H, m), 6.79–6.84 (2H, m), 6.86–6.88 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 38.2, 48.5, 49.0, 55.86, 55.88, 73.2, 88.7, 108.5, 111.0, 114.0, 114.3, 119.4, 121.2, 132.2, 133.5, 143.9, 145.1, 146.4, 146.6; MS (EI) *m*/*z* 344 (M^+, 100), 151 (51), 137 (59); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_5$, 334.1623, found 334.1623.

*(7S,8S,8′S)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**14**).* $[\alpha]^{20}_{D}$ −48 (*c* 2.0, $CHCl_3$).

*(7R,8S,8′R)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**15**).* Colorless oil, $[\alpha]^{20}_{D}$ +23 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (3H, d, *J* = 6.9 Hz), 2.31 (1H, m), 2.59 (1H, dd, *J* = 14.1, 8.4 Hz), 2.71 (1H, dd, *J* = 14.1, 7.2 Hz), 2.87 (1H, m), 3.77 (1H, dd, *J* = 10.1, 7.7 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.03 (1H, dd, *J* = 10.1, 8.3 Hz), 5.05 (1H, d, *J* = 4.6 Hz), 5.53 (1H, s), 5.56 (1H, s), 6.69–6.73 (4H, m), 6.85 (1H, d, *J* = 8.2 Hz), 6.86 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.90, 34.1, 40.6, 45.5, 55.86, 55.90, 71.1, 84.6, 108.6, 110.9, 113.9, 114.3, 118.7, 120.9, 132.2, 132.5, 143.9, 144.3, 146.2, 146.4; MS (EI) *m*/*z* 344 (M^+, 100), 151 (68), 137 (81); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_5$ 334.1623, found 334.1622.

*(7S,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxylignane-4,4′-diol (**16**).* $[\alpha]^{20}_{D}$ −23 (*c* 0.2, $CHCl_3$).

*(7R,8S,8′S)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**17**).* Colorless oil, $[\alpha]^{20}_{D}$ −20 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (1H, m), 2.48 (1H, dd, *J* = 13.6, 11.4 Hz), 2.69 (1H, m), 2.90 (1H, dd, *J* = 13.6, 4.7 Hz), 3.37 (3H, s), 3.45 (1H, dd, *J* = 9.3, 6.2 Hz), 3.58 (1H, dd, *J* = 9.3, 7.8 Hz), 3.72 (1H, dd, *J* = 8.6, 6.2 Hz), 3.83 (3H, s), 3.85 (3H, s), 4.01 (1H, dd, *J* = 8.6, 6.5 Hz), 4.75 (1H, d, *J* = 6.8 Hz), 5.71 (1H, s), 5.79 (1H, s), 6.66–6.68 (2H, m), 6.79 (1H, dd, *J* = 8.2, 1.8 Hz), 6.81–6.83 (2H, m), 6.85 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 42.6, 50.4, 55.9, 59.0, 70.6, 72.7, 82.7, 108.4, 111.3, 114.2, 114.4, 118.8, 121.3, 132.4, 134.8, 143.9, 145.0, 146.5, 146.6; MS (EI) *m*/*z* 374 (M^+, 100), 137 (66); HRMS (EI) *m*/*z* M^+ calcd for $C_{21}H_{26}O_6$ 374.1729, found 374.1721.

*(7S,8R,8′R)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**18**).* $[\alpha]^{20}_{D}$ +20 (*c* 1.7, $CHCl_3$).

*(7S,8S,8′R)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**19**).* Colorless oil, $[\alpha]^{20}_{D}$ −41 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (1H, m), 2.49 (1H, m), 2.60 (1H, dd, *J* = 13.8, 9.2 Hz), 2.81 (1H, dd, *J* = 9.3, 6.7 Hz), 2.90 (1H, dd, *J* = 13.8, 5.5 Hz), 3.04 (1H, dd, *J* = 9.3, 7.3 Hz), 3.09 (3H, s), 3.63 (1H, dd, *J* = 8.7, 7.4 Hz), 3.86 (3H, s), 3.87 (3H, s), 4.17 (1H, dd, *J* = 8.7, 7.7 Hz), 5.11 (1H, d, *J* = 7.3 Hz), 5.61 (1H, s), 5.66 (1H, s), 6.68–6.70 (2H, m), 6.74 (1H, dd, *J* = 8.3, 1.4 Hz), 6.81 (1H, d, *J* = 1.4 Hz), 6.83 (1H, d, *J* = 8.3 Hz), 6.86 (1H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 38.7, 43.2, 48.8, 55.87, 55.89, 58.6, 72.3, 73.1, 82.1, 109.0, 111.2, 113.9, 114.3, 119.2, 121.3, 131.6, 132.0, 143.9, 144.6, 146.1, 146.4; MS (EI) *m*/*z* 374 (M^+, 100), 137 (51); HRMS (EI) *m*/*z* calcd for $C_{21}H_{26}O_6$ 374.1729, found 374.1723.

*(7R,8R,8′S)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**20**).* $[\alpha]^{20}_{D}$ +41 (*c* 0.3, $CHCl_3$).

*(7R,8S,8′R)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**21**).* Colorless oil, $[\alpha]^{20}_{D}$ +9 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (1H, m), 2.49 (1H, m), 2.63 (1H, dd, *J* = 13.8, 9.0 Hz), 2.81 (1H, dd, *J* = 13.8, 6.4 Hz), 3.28 (3H, s), 3.35 (2H, d, *J* = 5.5 Hz), 3.81 (1H, dd, *J* = 8.7, 5.9 Hz), 3.86 (3H, s), 3.89 (3H, s), 3.93 (1H, dd, *J* = 8.7, 5.9 Hz), 4.61 (1H, d, *J* = 7.8 Hz), 5.55 (1H, s), 5.64 (1H, s), 6.64–6.67 (2H, m), 6.82 (1H, d, *J* = 7.8 Hz), 6.84 (1H, dd, *J* = 8.3, 1.9 Hz), 6.88 (1H, d, *J* = 8.3 Hz), 6.91 (1H, d, *J* = 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.3, 44.4, 53.4, 55.86, 55.88, 59.0, 72.8, 83.8, 108.6, 111.2, 114.1, 114.2, 119.1, 121.4, 132.2, 134.2, 143.9, 144.9, 146.4, 146.5; MS (EI) *m*/*z* 374 (M^+, 100), 137 (50); HRMS (EI) *m*/*z* M^+ calcd for $C_{21}H_{26}O_6$ 374.1729, found 374.1723.

*(7S,8R,8′S)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**22**).* $[\alpha]^{20}_{D}$ −9 (*c* 0.5, $CHCl_3$).

*(7R,8R,8′R)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**23**).* Colorless oil, $[\alpha]^{20}_{D}$ +56 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (1H, m), 2.58 (1H, dd, *J* = 13.6, 9.4 Hz), 2.80 (1H, m), 2.89 (1H, dd, *J* = 13.6, 5.5 Hz), 3.10 (2H, d, *J* = 6.0 Hz), 3.14 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 5.07 (1H, d, *J* = 6.4 Hz), 5.52 (1H, s), 5.59 (1H, s), 6.70–6.72 (2H, m), 6.79 (1H, br. d, *J* = 8.3 Hz), 6.84 (1H, d, *J* = 7.8 Hz), 6.88 (1H, d, *J* = 8.3 Hz), 6.94 (1H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 44.6, 46.3, 55.86, 55.89, 58.6, 69.6, 72.0, 83.1, 108.8, 111.1, 113.9, 114.3, 119.1, 121.2, 131.8, 133.0, 143.8, 144.5, 146.2, 146.4; MS (EI) *m*/*z* 374 (M^+, 100), 137 (69); HRMS (EI) *m*/*z* calcd for $C_{21}H_{26}O_6$ 374.1729, found 374.1724.

*(7S,8S,8′S)-3,3′,9-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**24**).* $[\alpha]^{20}_{D}$ −56 (*c* 0.2, $CHCl_3$).

*(7R,8S,8′S)-4,4′-Dihydroxy-3,3′-dimethoxy-7,9′-epoxylignan-9-yl Acetate (**25**).* Colorless oil, $[\alpha]^{20}_{D}$ −17 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (3H, s), 2.50–2.57 (2H, m), 2.73 (1H, m), 2.83 (1H, dd, *J* = 13.6, 5.0 Hz), 3.73 (1H, dd, *J* = 8.6, 6.7 Hz), 3.87 (3H, s), 3.89 (3H, s), 4.06 (1H, dd, *J* = 8.6, 6.6 Hz), 4.18 (1H, dd, *J* = 11.2, 7.3 Hz), 4.35 (1H, dd, *J* = 11.2, 7.1 Hz), 4.76 (1H, d, *J* = 6.5 Hz), 5.55 (1H, s), 5.63 (1H, s), 6.67 (1H, d, *J* = 1.9 Hz), 6.68 (1H, d, *J* = 1.9 Hz), 6.80 (1H, dd, *J* = 8.0, 1.9 Hz), 6.83–6.85 (2H, m), 6.87 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 33.3, 42.5, 49.0, 56.0, 62.7, 72.7, 83.1, 108.4, 111.2, 114.3, 114.5, 118.9, 121.1, 131.9, 134.3,

144.1, 145.1, 146.5, 146.6, 171.0; MS (EI) m/z 402 (M^+, 100), 137 (63); HRMS (EI) m/z calcd for $C_{22}H_{26}O_7$ 402.16789, found 402.1679.

*(7R,8R,8′S)-4,4′-Dihydroxy-3,3′-dimethoxy-7,9′-epoxy-9a-homolignane-9a-nitrile (**26**).* Colorless oil, $[\alpha]^{20}_D$ −34 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44−2.56 (4H, m), 2.78 (1H, m), 2.88 (1H, dd, J = 13.4, 5.0 Hz), 3.78 (1H, dd, J = 9.0, 5.8 Hz), 3.87 (3H, s), 3.89 (3H, s), 4.10 (1H, dd, J = 9.0, 7.0 Hz), 4.69 (1H, d, J = 6.2 Hz), 5.58 (1H, s), 5.68 (1H, s), 6.67 (1H, d, J = 1.9 Hz), 6.68 (1H, d, J = 1.8 Hz), 6.79 (1H, dd, J = 8.2, 1.8 Hz), 6.84−6.86 (2H, m), 6.89 (1H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 33.2, 42.5, 47.2, 55.98, 56.00, 72.2, 84.5, 108.2, 111.2, 114.4, 114.6, 118.7, 118.9, 121.3, 130.8, 132.6, 144.3, 145.6, 146.7, 146.9; MS (EI) m/z 369 (M^+, 100), 137 (47); HRMS (EI) m/z calcd for $C_{21}H_{23}O_5N$ 369.1577, found 369.1582.

*(7R,8S,8′S)-9-Fluoro-3,3′-dimethoxy-7,9′-epoxyligane-4,4′-diol (**27**).* Colorless oil, $[\alpha]^{20}_D$ −4 (c 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (1H, m), 2.57 (1H, dd, J = 13.5, 10.9 Hz), 2.74 (1H, m), 2.90 (1H, dd, J = 13.5, 4.8 Hz), 3.71 (1H, dd, J = 8.1, 7.7 Hz), 3.85 (3H, s), 3.86 (3H, s), 4.04 (1H, dd, J = 8.1, 7.2 Hz), 4.58 (1H, m), 4.69 (1H, m), 4.84 (1H, d, J = 6.3 Hz), 5.66 (1H, s), 5.75 (1H, s), 6.65−6.70 (2H, m), 6.78−6.89 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 42.4, 50.6 (d, J = 17.3 Hz), 55.81, 55.83, 72.9, 81.8 (d, J = 169 Hz), 81.9 (d, J = 6.7 Hz), 108.1, 111.1, 114.2, 114.4, 118.6, 121.0, 131.9, 134.1, 144.0, 145.0, 146.5, 146.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −224 (m); MS (EI) m/z 362 (M^+, 18), 137 (100); HRMS (EI) m/z M^+ calcd for $C_{20}H_{23}O_5F$ 362.1529, found 362.1553.

*(7R,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxy-9a-homolignane-4,4′-diol (**28**).* Colorless oil, $[\alpha]^{20}_D$ −35 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.4 Hz), 1.44 (1H, m), 1.57 (1H, m), 2.05 (1H, m), 2.42 (1H, dd, J = 13.4, 11.7 Hz), 2.56 (1H, m), 2.82 (1H, dd, J = 13.4, 3.9 Hz), 3.79 (1H, dd, J = 8.6, 3.5 Hz), 3.88 (3H, s), 3.90 (3H, s), 3.98 (1H, dd, J = 8.6, 5.1 Hz), 4.57 (1H, d, J = 8.2 Hz), 5.50 (1H, s), 5.57 (1H, s), 6.68−6.70 (2H, m), 6.79 (1H, dd, J = 8.3, 1.9 Hz), 6.84−6.86 (2H, m), 6.87 (1H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 19.5, 32.7, 43.2, 53.0, 56.0, 72.1, 84.8, 108.6, 111.6, 114.1, 114.4, 119.3, 121.5, 132.6, 135.2, 143.9, 146.5, 146.6; MS (EI) m/z 458 (M^+, 100), 137 (65); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1781, found 358.1782.

*(7R,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxy-9a,9b,9c,9d-tetrahomolignane-4,4′- diol (**29**).* Colorless oil, $[\alpha]^{20}_D$ −30 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.9 Hz), 1.25−1.42 (7H, m), 1.49 (1H, m), 2.12 (1H, m), 2.42 (1H, dd, J = 13.3, 11.4 Hz), 2.55 (1H, m), 2.82 (1H, dd, J = 13.3, 3.7 Hz), 3.79 (1H, dd, J = 8.7, 3.5 Hz), 3.87 (3H, s), 3.88 (3H, s), 3.98 (1H, dd, J = 8.7, 5.5 Hz), 4.56 (1H, d, J = 8.2 Hz), 5.59 (1H, s), 5.66 (1H, s), 6.67−6.71 (2H, m), 6.79 (1H, dd, J = 8.3, 1.8 Hz), 6.84−6.86 (2H, m), 6.87 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 26.4, 27.8, 32.0, 32.8, 43.3, 51.1, 55.9, 72.1, 84.9, 108.6, 111.5, 114.0, 114.4, 119.3, 121.4, 132.6, 135.0, 143.8, 144.9, 146.4, 146.5; MS (EI) m/z 400 (M^+, 27), 137 (100); HRMS (EI) m/z calcd for $C_{25}H_{32}O_5$ 400.2250, found 400.2250.

*(7R,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxy-9a,9b,9b-trihomolignane-4,4′-diol (**30**).* Colorless oil, $[\alpha]^{20}_D$ −39 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 4.6 Hz), 0.89 (3H, d, J = 4.6 Hz), 1.19 (1H, m), 1.46 (1H, m), 1.68 (1H, m), 2.25 (1H, m), 2.43 (1H, dd, J = 13.3, 11.4 Hz), 2.54 (1H, m), 2.81 (1H, dd, J = 13.3, 3.7 Hz), 3.78 (1H, dd, J = 8.3, 3.5 Hz), 3.88 (3H, s), 3.89 (3H, s), 3.98 (1H, dd, J = 8.3, 5.5 Hz), 4.56 (1H, d, J = 8.3 Hz), 5.53 (1H, s), 5.61 (1H, s), 6.67−6.70 (2H, m), 6.79 (1H, dd, J = 7.8, 1.9 Hz), 6.83−6.86 (2H, m), 6.87 (1H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.2, 26.2, 33.0, 35.6, 43.3, 48.4, 55.9, 72.1, 85.0, 108.6, 111.5, 114.1, 114.4, 119.3, 121.4, 132.6, 134.8, 143.8, 145.0, 146.4, 146.5; MS (EI) m/z 386 (M^+, 93), 206 (46), 137 (100); HRMS (EI) m/z calcd for $C_{23}H_{30}O_5$ 386.2093, found 386.2091.

*(7R,8S,8′S)-9-(N,N-Dimethylamino)-3,3′-dimethoxy-7,9′-epoxylignane-4,4′-diol (**31**).* Colorless crystals, mp 186−188 °C, $[\alpha]^{20}_D$ −54 (c 0.2, acetone); ^{1}H NMR (400 MHz, C_5D_5N) δ 2.18 (6H, s), 2.36 (1H, dd, J = 15.5, 11.2 Hz), 2.53−2.61 (2H, m), 2.59 (1H, dd, J = 13.3, 11.2 Hz), 2.90 (1H, m), 3.11 (1H, dd, J = 13.3, 4.5 Hz), 3.72 (3H, s), 3.76 (3H, s), 3.98 (1H, dd, J = 8.4, 6.3 Hz), 4.24 (1H, dd, J = 8.4, 5.8 Hz), 5.06 (1H, d, J = 6.0 Hz), 6.89 (1H, dd, J = 8.0, 2.0 Hz), 7.00 (1H, d, J = 2.0 Hz), 7.13 (1H, dd, J = 8.0, 2.0 Hz), 7.19 (1H, dd, J = 8.0 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.27 (1H, d, J = 2.0 Hz); ^{13}C NMR (100 MHz, C_5D_5N) δ 33.2, 43.3, 45.7, 48.7, 55.80, 55.82, 57.7, 72.4, 84.2, 110.7, 113.2, 116.2, 116.5, 119.5, 121.8, 132.4, 135.7, 146.4, 147.4, 148.5, 148.6; MS (EI) m/z 387 (M^+, 59), 151 (100), 137 (76); HRMS (EI) m/z calcd for $C_{22}H_{29}O_5N$ 387.2047, found 387.2056.

*(7R,8R,8′S)-3′-Methoxy-7,9′-epoxylignan-4′-ol (**32**).* Colorless oil, $[\alpha]^{20}_D$ −16 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 6.9 Hz), 2.25 (1H, m), 2.47 (1H, dd, J = 13.3, 11.0 Hz), 2.56 (1H, m), 2.81 (1H, dd, J = 13.3, 3.9 Hz), 3.77 (1H, dd, J = 8.5, 5.3 Hz), 3.87 (3H, s), 4.05 (1H, dd, J = 8.5, 6.2 Hz), 4.58 (1H, d, J = 6.9 Hz), 5.50 (1H, s), 6.67−6.69 (2H, m), 6.84 (1H, d, J = 8.7 Hz), 7.25−7.28 (2H, m), 7.30−7.37 (3H, m); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.7, 33.4, 44.0, 45.3, 55.9, 72.4, 87.2, 111.3, 114.3, 121.3, 125.7, 127.3, 128.3, 132.5, 143.1, 143.8, 146.4; MS (EI) m/z 298 (M^+, 0.6), 137 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_3$ 298.1570, found 298.1571.

*(7R,8R,8′S)-3′-Methoxy-7,9′-epoxylignane-2,4′-diol (**33**).* Colorless oil, $[\alpha]^{20}_D$ +3 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 7.3 Hz), 2.41−2.49 (2H, m), 2.66 (1H, m), 2.87 (1H, dd, J = 13.5, 4.8 Hz), 3.69 (1H, dd, J = 9.0, 6.2 Hz), 3.88 (3H, s), 4.07 (1H, dd, J = 9.0, 7.1 Hz), 4.67 (1H, d, J = 5.9 Hz), 5.51 (1H, s), 6.67−6.69 (2H, m), 6.82−6.87 (3H, m), 6.96 (1H, dd, J = 7.3, 1.4 Hz), 7.18 (1H, ddd, J = 7.3, 7.3, 1.4 Hz), 8.43 (1H, s); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.4, 33.8, 42.7, 43.4, 55.9, 72.3, 88.5, 111.1, 114.4, 117.1, 119.5, 121.3, 124.1, 127.1, 128.9, 131.9, 144.0, 146.5, 155.7; MS (EI) m/z 314 (M^+, 0.5), 137 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1519, found 314.1528.

*(7R,8R,8′S)-3′-Methoxy-7,9′-epoxylignane-3,4′-diol (**34**).* Colorless oil, $[\alpha]^{20}_D$ −34 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 6.9 Hz), 2.24 (1H, m), 2.44 (1H, dd, J = 13.1, 11.0 Hz), 2.53 (1H, m), 2.79 (1H, dd, J = 13.1, 4.4 Hz), 3.77 (1H, ddd, J = 8.6, 5.3 Hz), 3.86 (3H, s), 4.02 (1H, dd, J = 8.6, 6.2 Hz), 4.56 (1H, d, J = 6.9 Hz), 5.54 (1H, s), 5.72 (1H, br. s), 6.64−6.67 (2H, m), 6.71 (1H, dd, J = 7.4, 1.4 Hz), 6.82−6.84 (3H, m), 7.17 (1H, dd, J = 8.3, 8.3 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.8, 33.3, 44.0, 45.1, 55.9, 72.3, 86.9, 111.3, 112.5, 114.29, 114.34, 117.9, 121.3, 129.5, 132.4, 143.8, 144.8, 146.4, 155.9; MS (EI) m/z 314 (M^+, 0.5), 137 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1519, found 314.1519.

*(7R,8R,8′S)-3′-Methoxy-7,9′-epoxylignane-4,4′-diol (**35**).* Colorless oil, $[\alpha]^{20}_D$ −18 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J = 6.9 Hz), 2.24 (1H, m), 2.44 (1H, dd, J = 13.5, 11.0 Hz), 2.56 (1H, m), 2.81 (1H, dd, J = 13.5, 4.4 Hz), 3.75 (1H, dd, J = 8.7, 5.1 Hz), 3.84 (3H, s), 4.03 (1H, dd, J = 8.7, 6.4 Hz), 4.51 (1H, d, J = 7.3 Hz), 5.62 (1H, s), 6.20 (1H, br. s), 6.65- 6.68 (2H, m), 6.73 (2H, d, J = 8.7 Hz), 6.83 (1H, d, J = 8.7 Hz), 7.15 (2H, d, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.4, 33.4, 44.0, 45.0, 55.8, 72.1, 86.9, 111.4, 114.4, 115.2, 121.3, 127.3, 132.5, 134.1, 143.8, 146.4, 155.4; MS (EI) m/z 314 (M^+, 1), 137 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1519, found 314.1518.

*(7R,8R,8′S)-2,3′-Dimethoxy-7,9′-epoxylignan-4′-ol (**36**).* Colorless oil, $[\alpha]^{20}_D$ +18 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, d, J = 7.3 Hz), 2.25 (1H, m), 2.48−2.54 (2H, m), 2.72 (1H, m), 3.76 (1H, dd, J = 8.3, 7.8 Hz), 3.82 (3H, s), 3.84 (3H, s), 4.09 (1H, dd, J = 8.3, 6.4 Hz), 5.00 (1H, d, J = 4.6 Hz), 5.54 (1H, s), 6.63−6.65 (2H, m), 6.81 (1H, d, J = 8.2 Hz), 6.84 (1H, br. d, J = 7.8 Hz), 6.93 (1H, ddd, J = 7.8, 7.8, 0.9 Hz), 7.21 (1H, ddd, J = 7.8, 7.8, 1.4 Hz), 7.35 (1H, dd, J = 7.8, 1.3 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 13.6, 33.3, 43.1, 43.4, 55.2, 55.8, 72.2, 83.0, 110.0, 111.2, 114.3, 120.3, 121.1, 126.1, 127.8, 132.1, 132.8, 143.8, 146.4, 156.2; MS (EI) m/z 328 (M^+, 78), 151 (43), 137 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1674.

*(7R,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxylignan-4′-ol (**37**).* Colorless oil; $[\alpha]^{20}_D$ −19 (c 0.1, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 7.3 Hz), 2.25 (1H, m), 2.46 (1H, dd, J = 13.0, 11.0 Hz), 2.55 (1H, m), 2.80 (1H, dd, J = 13.0, 4.6 Hz), 3.76 (1H, dd, J = 8.3, 5.5 Hz), 3.81 (3H, s), 3.87 (3H, s), 4.04 (1H, dd, J = 8.3, 6.1 Hz), 4.56 (1H, d, J = 6.4 Hz), 5.49 (1H, s), 6.66−6.88 (2H, m), 6.80 (1H, m),

6.84 (1H, d, J = 8.2 Hz), 6.88−6.91 (2H, m), 7.25 (1H, dd, J = 8.2, 7.8 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.9, 33.4, 44.0, 45.2, 55.2, 55.9, 72.4, 87.0, 111.3, 112.6, 114.3, 118.1, 121.3, 129.3, 132.5, 143.8, 144.9, 146.4, 159.7; MS (EI) m/z 328 (M^+, 40), 137 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1678.

*(7R,8R,8′S)-3′,4-Dimethoxy-7,9′-epoxylignan-4′-ol (**38**).* Colorless oil; $[\alpha]^{20}_D$ −17 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.9 Hz), 2.23 (1H, m), 2.45 (1H, dd, J = 13.3, 11.5 Hz), 2.56 (1H, m), 2.81 (1H, dd, J = 13.3, 4.6 Hz), 3.73 (1H, dd, J = 8.7, 5.0 Hz), 3.80 (3H, s), 3.86 (3H, s), 4.03 (1H, dd, J = 8.7, 6.2 Hz), 4.51 (1H, d, J = 7.3 Hz), 5.57 (1H, s), 6.67−6.69 (2H, m), 6.83 (1H, d, J = 8.7 Hz), 6.87 (2H, d, J = 7.8 Hz), 7.24 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.5, 33.5, 44.0, 45.1, 55.2, 55.8, 72.3, 86.8, 111.3, 113.7, 114.3, 121.3, 127.0, 132.5, 134.9, 143.8, 146.4, 158.9; MS (EI) m/z 328 (M^+, 60), 204 (43), 151 (42), 137 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1677.

*(7R,8R,8′S)-3′-Methoxy-7,9′-epoxylignane-3,4,4′-triol (**39**).* Colorless oil; $[\alpha]^{20}_D$ +9 (c 0.3, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.05 (3H, d, J = 6.9 Hz), 2.21 (1H, m), 2.41 (1H, dd, J = 13.5, 11.5 Hz), 2.60 (1H, m), 2.81 (1H, dd, J = 13.5, 4.9 Hz), 3.68 (1H, dd, J = 8.3, 5.1 Hz), 3.83 (3H, s), 3.95 (1H, dd, J = 8.3, 6.5 Hz), 4.39 (1H, d, J = 7.8 Hz), 4.87 (3H, s), 6.62 (1H, dd, J = 8.2, 1.8 Hz), 6.64 (1H, dd, J = 7.8, 1.8 Hz), 6.71 (1H, d, J = 7.8 Hz), 6.72 (1H, d, J = 8.2 Hz), 6.76 (2H, d, J = 1.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 12.9, 34.6, 45.7, 46.6, 56.7, 73.4, 88.9, 113.8, 114.5, 116.4, 116.5, 119.1, 122.5, 133.8, 135.4, 146.0, 146.2, 146.6, 149.3; MS (EI) m/z 330 (M^+, 2), 137 (100), 123 (55); HRMS (EI) m/z calcd for $C_{19}H_{22}O_5$ 330.1468, found 330.1479.

*(7R,8R,8′S)-3,3′,4-Trimethoxy-7,9′-epoxylignan-4′-ol (**40**).* Colorless oil; $[\alpha]^{20}_D$ −9 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, d, J = 7.3 Hz), 2.25 (1H, m), 2.46 (1H, dd, J = 13.3, 11.0 Hz), 2.57 (1H, m), 2.82 (1H, dd, J = 13.3, 4.6 Hz), 3.73 (1H, dd, J = 8.7, 5.0 Hz), 3.87 (6H, s), 3.89 (3H, s), 4.04 (1H, dd, J = 8.7, 6.4 Hz), 4.50 (1H, d, J = 7.3 Hz), 5.51 (1H, s), 6.67−6.69 (2H, m), 6.82−6.85 (3H, m), 6.87 (1H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 33.5, 44.0, 45.0, 55.9, 72.3, 87.0, 108.9, 110.8, 111.3, 114.3, 118.1, 121.3, 132.5, 135.3, 143.8, 146.4, 148.3, 148.9; MS (EI) m/z 358 (M^+, 100), 151 (47), 137 (67); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1781, found 358.1777.

*(7R,8R,8′S)-3-Ethoxy-3′-methoxy-7,9′-epoxylignane-4,4′-diol (**41**).* Colorless oil; $[\alpha]^{20}_D$ −19 (c 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.9 Hz), 1.42 (3H, t, J = 6.8 Hz), 2.22 (1H, m), 2.44 (1H, dd, J = 13.3, 11.5 Hz), 2.55 (1H, m), 2.80 (1H, dd, J = 13.3, 4.6 Hz), 3.73 (1H, dd, J = 8.6, 5.5 Hz), 3.84 (3H, s), 4.02 (1H, dd, J = 8.6, 6.2 Hz), 4.10 (2H, q, J = 6.8 Hz), 4.48 (1H, d, J = 7.4 Hz), 5.69 (1H, s), 5.76 (1H, s), 6.65−6.68 (2H, m), 6.78 (1H, dd, J = 8.2, 1.8 Hz), 6.82−6.85 (2H, m), 6.87 (1H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 14.8, 33.4, 43.9, 45.0, 55.8, 64.4, 72.2, 87.0, 109.2, 111.3, 113.9, 114.3, 118.7, 121.2, 132.4, 134.5, 143.8, 145.0, 145.7, 146.4; MS (EI) m/z 358 (M^+, 100), 165 (45), 151 (56), 137 (77); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1781, found 358.1782.

*(7R,8R,8′S)-3-Butoxy-3′-methoxy-7,9′-epoxylignane-4,4′-diol (**42**).* Colorless crystals, mp 64−65 °C, $[\alpha]^{20}_D$ −21 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.6 Hz), 1.08 (3H, d, J = 7.3 Hz), 1.50 (2H, m), 1.80 (2H, m), 2.22 (1H, m), 2.45 (1H, dd, J = 13.3, 11.5 Hz), 2.56 (1H, m), 2.81 (1H, dd, J = 13.3, 4.6 Hz), 3.72 (1H, dd, J = 8.7, 5.1 Hz), 3.88 (3H, s), 4.02 (1H, dd, J = 8.7, 6.4 Hz), 4.05 (2H, t, J = 6.4 Hz), 4.47 (1H, d, J = 7.4 Hz), 5.49 (1H, s), 5.60 (1H, s), 6.66−6.69 (2H, m), 6.79 (1H, dd, J = 8.3, 1.9 Hz), 6.840 (1H, d, J = 8.7 Hz), 6.843 (1H, d, J = 1.9 Hz), 6.88 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 13.8, 19.2, 31.3, 33.6, 44.0, 45.0, 55.9, 68.6, 72.3, 87.1, 109.1, 111.3, 113.9, 114.3, 118.7, 121.3, 132.6, 134.6, 143.8, 145.0, 145.9, 146.4; MS (EI) m/z 386 (M^+, 93), 149 (58), 137 (100); HRMS (EI) m/z calcd for $C_{23}H_{30}O_5$ 386.2094, found 386.2099.

*(7R,8R,8′S)-3-Isopropoxy-3′-methoxy-7,9′-epoxylignane-4,4′-diol (**43**).* Colorless oil; $[\alpha]^{20}_D$ −7 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.8 Hz), 1.35 (3H, d, J = 6.0 Hz), 1.36 (3H, d, J = 6.0 Hz), 2.21 (1H, m), 2.45 (1H, dd, J = 13.3, 11.0 Hz), 2.55 (1H, m), 2.80 (1H, dd, J = 13.3, 4.6 Hz), 3.72 (1H, dd, J = 8.6, 5.0 Hz), 3.87 (3H, s), 4.01 (1H, dd, J = 8.6, 6.2 Hz), 4.47 (1H, d, J = 7.3 Hz), 4.60 (1H, m), 5.54 (1H, s), 5.68 (1H, s), 6.66−6.69 (2H, s), 6.79 (1H, dd, J = 8.2, 1.8 Hz), 6.84 (1H, d, J = 8.2 Hz), 6.85 (1H, d, J = 1.8 Hz), 6.88 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 22.16, 22.20, 33.5, 43.9, 45.1, 55.8, 71.6, 72.2, 87.0, 111.1, 111.3, 114.1, 114.3, 118.8, 121.3, 132.5, 134.6, 143.8, 144.4, 145.9, 146.4; MS (EI) m/z 372 (M^+, 100), 151 (40), 137 (91); HRMS (EI) m/z calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1932.

*(7R,8R,8′S)-3-Chloro-3′-methoxy-7,9′-epoxylignane-4,4′-diol (**44**).* Colorless oil; $[\alpha]^{20}_D$ −16 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 7.3 Hz), 2.20 (1H, m), 2.44 (1H, dd, J = 13.2, 11.5 Hz), 2.54 (1H, m), 2.80 (1H, dd, J = 13.2, 5.5 Hz), 3.74 (1H, dd, J = 8.6, 5.5 Hz), 3.88 (3H, s), 4.02 (1H, dd, J = 8.6, 6.3 Hz), 4.48 (1H, d, J = 7.3 Hz), 5.51 (1H, s), 5.56 (1H, s), 6.67−6.69 (2H, m), 6.84 (1H, d, J = 8.7 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.11 (1H, dd, J = 8.7, 1.9 Hz), 7.30 (1H, d, J = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 33.4, 43.9, 45.2, 55.9, 72.3, 86.2, 111.3, 114.3, 116.0, 119.8, 121.3, 126.0, 126.3, 132.4, 136.3, 143.8, 146.4, 150.5; MS (EI) m/z 348 (M^+, 88), 151 (49), 137 (100); HRMS (EI) m/z calcd for $C_{19}H_{21}O_4Cl$ 348.1129, found 348.1123.

*(7R,8R,8′S)-3′,4-Dimethoxy-7,9′-epoxylignane-3,4′-diol (**45**).* Colorless oil; $[\alpha]^{20}_D$ −18 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.9 Hz), 2.22 (1H, m), 2.44 (1H, dd, J = 13.3, 11.0 Hz), 2.54 (1H, m), 2.79 (1H, dd, J = 13.3, 4.1 Hz), 3.73 (1H, dd, J = 8.6, 5.3 Hz), 3.859 (3H, s), 3.863 (3H, s), 4.01 (1H, dd, J = 8.6, 5.9 Hz), 4.48 (1H, d, J = 6.8 Hz), 5.57 (1H, s), 5.69 (1H, s), 6.65−6.68 (2H, m), 6.79−6.81 (2H, m), 6.83 (1H, d, J = 8.7 Hz), 6.91 (1H, br. s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 33.4, 44.0, 45.0, 55.9, 60.4, 72.2, 86.8, 110.3, 111.3, 112.1, 114.3, 117.4, 121.3, 132.6, 136.3, 143.8, 145.5, 145.8, 146.4; MS (EI) m/z 344 (M^+, 100), 151 (71), 137 (82); HRMS (EI) m/z calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.2621.

*(7R,8R,8′S)-3′-Methoxy-7,9′-epoxylignane-3,4,4′,5-tetraol (**46**).* Colorless oil; $[\alpha]^{20}_D$ −30 (c 0.6, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.05 (3H, d, J = 6.9 Hz), 2.20 (1H, m), 2.40 (1H, dd, J = 13.2, 11.8 Hz), 2.58 (1H, m), 2.79 (1H, dd, J = 13.2, 5.1 Hz), 3.67 (1H, dd, J = 8.2, 5.0 Hz), 3.82 (3H, s), 3.94 (1H, dd, J = 8.2, 6.4 Hz), 4.34 (1H, d, J = 7.8 Hz), 4.85 (4H, s), 6.33 (2H, s), 6.62 (1H, dd, J = 7.9, 1.4 Hz), 6.71 (1H, d, J = 7.9 Hz), 6.75 (1H, d, J = 1.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 13.0, 34.5, 45.6, 46.5, 56.7, 73.4, 89.0, 106.4, 113.8, 116.5, 122.5, 133.8, 135.0, 146.0, 147.2, 149.2; MS (EI) m/z 346 (M^+, 3), 329 (69), 181 (42), 137 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_6$ 346.1417, found 346.1426.

*(7R,8R,8′S)-3,3′,5-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**47**).* Colorless crystals, mp 135−136 °C; $[\alpha]^{20}_D$ −16 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 7.3 Hz), 2.23 (1H, m), 2.45 (1H, dd, J = 13.3, 11.0 Hz), 2.56 (1H, m), 2.82 (1H, dd, J = 13.3, 4.6 Hz), 3.73 (1H, dd, J = 8.4, 5.5 Hz), 3.88 (3H, s), 3.89 (6H, s), 4.04 (1H, dd, J = 8.4, 6.2 Hz), 4.48 (1H, d, J = 7.3 Hz), 5.48 (1H, s), 5.52 (1H, s), 6.55 (2H, s), 6.68−6.69 (2H, m), 6.84 (1H, d, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 33.5, 43.9, 45.0, 55.9, 56.3, 72.3, 87.3, 102.4, 111.3, 114.3, 121.3, 132.5, 133.9, 143.8, 146.4, 146.9; MS (EI) m/z 374 (M^+, 100), 257 (55), 149 (44), 137 (64); HRMS (EI) m/z calcd for $C_{21}H_{26}O_6$ 374.1730, found 374.1722.

*(7R,8R,8′S)-3-Methoxy-7,9′-epoxylignan-4-ol (**48**).* Colorless oil; $[\alpha]^{20}_D$ −14 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 6.9 Hz), 2.23 (1H, m), 2.53 (1H, dd, J = 13.0, 11.0 Hz), 2.62 (1H, m), 2.87 (1H, dd, J = 13.0, 4.4 Hz), 3.72 (1H, dd, J = 8.7, 5.5 Hz), 3.86 (3H, s), 4.03 (1H, dd, J = 8.7, 6.5 Hz), 4.49 (1H, d, J = 7.4 Hz), 5.67 (1H, s), 6.79 (1H, dd, J = 8.1, 2.1 Hz), 6.85−6.87 (2H, m), 7.17−7.21 (3H, m), 7.27−7.31 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 33.9, 43.6, 44.9, 55.8, 72.3, 87.1, 108.3, 114.0, 118.8, 126.0, 128.4, 128.7, 134.6, 140.7, 144.9, 146.5; MS (EI) m/z 298 (M^+, 82), 152 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_3$ 298.1570, found 298.1574.

*(7R,8R,8′S)-3-Methoxy-7,9′-epoxylignane-2′,4-diol (**49**).* Colorless oil; $[\alpha]^{20}_D$ −42 (c 0.4, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.08 (3H, d, J = 7.1 Hz), 2.23 (1H, m), 2.50 (1H, dd, J = 13.0, 11.6 Hz), 2.74 (1H, m), 2.88 (1H, dd, J = 13.0, 4.4 Hz), 3.75 (1H, dd, J = 8.3, 4.7 Hz), 3.84 (3H, s), 3.96 (1H, dd, J = 8.3, 6.3 Hz), 4.48 (1H, d, J = 7.9 Hz), 4.89 (2H, s), 6.73−6.76 (4H, m), 6.89 (1H, br. s), 7.01

(1H, dd, J = 7.7, 7.7 Hz), 7.06 (1H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 16.8, 31.1, 34.1, 43.9, 60.9, 76.1, 98.2, 103.4, 103.5, 107.6, 108.0, 115.7, 115.8, 119.1, 122.7, 134.6, 136.5, 144.0; MS (EI) m/z 314 (M^+, 100), 189 (51), 149 (74), 107 (70); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1519, found 314.1523.

*(7R,8R,8′S)-3-Methoxy-7,9′-epoxylignane-3′,4-diol (**50**).* Colorless crystals, mp 50−52 °C; $[\alpha]^{20}_D$ −38 (c 0.6, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.05 (3H, d, J = 6.9 Hz), 2.24 (1H, m), 2.44 (1H, dd, J = 13.4, 11.2 Hz), 2.62 (1H, m), 2.81 (1H, dd, J = 13.4, 4.8 Hz), 3.68 (1H, dd, J = 8.4, 5.0 Hz), 3.83 (3H, s), 3.99 (1H, dd, J = 8.4, 6.4 Hz), 4.46 (1H, d, J = 7.8 Hz), 4.90 (2H, s), 6.59−6.68 (3H, m), 6.76 (2H, s), 6.89 (1H, s), 7.08 (1H, dd, J = 7.8, 7.8 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 22.1, 32.5, 33.8, 43.8, 60.6, 76.0, 98.0, 101.4, 103.3, 104.1, 107.4, 108.5, 117.9, 122.5, 131.0, 134.5, 136.4, 146.0; MS (EI) m/z 314 (M^+, 23), 192 (100), 137 (41); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1519, found 314.1522.

*(7R,8R,8′S)-3-Methoxy-7,9′-epoxylignane-4′,4-diol (**51**).* Colorless oil; $[\alpha]^{20}_D$ −40 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 7.0 Hz), 2.23 (1H, m), 2.46 (1H, dd, J = 13.2, 11.1 Hz), 2.56 (1H, m), 2.80 (1H, dd, J = 13.2, 4.5 Hz), 3.71 (1H, dd, J = 8.4, 5.5 Hz), 3.88 (3H, s), 4.03 (1H, dd, J = 8.4, 6.6 Hz), 4.49 (1H, d, J = 7.2 Hz), 5.06 (1H, br. s), 5.58 (1H, s), 6.74 (2H, d, J = 8.3 Hz), 6.79 (1H, dd, J = 8.2, 1.9 Hz), 6.84 (1H, d, J = 1.9 Hz), 6.87 (1H, d, J = 8.2 Hz), 7.03 (2H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.7, 33.0, 43.9, 45.0, 55.9, 72.3, 87.2, 108.3, 114.0, 115.3, 118.9, 129.8, 132.7, 134.6, 144.9, 146.5, 153.9; MS (EI) m/z 314 (M^+, 100), 151 (53), 121 (81), 107 (91); HRMS (EI) m/z calcd for $C_{19}H_{22}O_4$ 314.1519, found 314.1520.

*(7R,8R,8′S)-2′,3-Dimethoxy-7,9′-epoxylignan-4-ol (**52**).* Colorless oil; $[\alpha]^{20}_D$ −32 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 6.9 Hz), 2.22 (1H, m), 2.53 (1H, dd, J = 13.2, 11.1 Hz), 2.65 (1H, m), 2.89 (1H, dd, J = 13.2, 4.2 Hz), 3.74 (1H, dd, J = 8.5, 5.2 Hz), 3.81 (3H, s), 3.86 (3H, s), 4.00 (1H, dd, J = 8.5, 6.3 Hz), 4.49 (1H, d, J = 7.5 Hz), 5.69 (1H, s), 6.79 (1H, dd, J = 8.1, 1.8 Hz), 6.83−6.87 (3H, m), 6.89 (1H, dd, J = 7.3, 0.9 Hz), 7.13 (1H, dd, J = 7.3, 1.4 Hz), 7.20 (1H, ddd, J = 7.3, 7.3, 1.4 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.6, 28.3, 42.2, 45.3, 55.3, 55.9, 72.5, 87.0, 108.4, 110.3, 114.0, 118.9, 120.4, 127.3, 129.1, 130.3, 134.9, 144.9, 146.5, 157.5; MS (EI) m/z 328 (M^+, 100), 220 (43), 151 (45), 121 (86); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1671.

*(7R,8R,8′S)-3,3′-Dimethoxy-7,9′-epoxylignan-4-ol (**53**).* Colorless oil; $[\alpha]^{20}_D$ −35 (c 0.2, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 7.2 Hz), 2.24 (1H, m), 2.51 (1H, dd, J = 13.2, 11.0 Hz), 2.62 (1H, m), 2.85 (1H, dd, J = 13.2, 4.5 Hz), 3.72 (1H, dd, J = 8.7, 5.5 Hz), 3.80 (3H, s), 3.89 (3H, s), 4.05 (1H, dd, J = 8.7, 6.2 Hz), 4.48 (1H, d, J = 7.3 Hz), 5.60 (1H, s), 6.74 (1H, br. s), 6.76−6.80 (3H, m), 6.84−6.88 (2H, m), 7.21 (1H, dd, J = 7.9, 7.9 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.7, 34.0, 43.6, 45.0, 55.2, 55.9, 72.4, 87.1, 108.2, 111.2, 114.0, 114.6, 118.9, 121.2, 129.4, 134.7, 142.4, 144.9, 146.5, 159.7; MS (EI) m/z 328 (M^+, 100), 134 (47), 121 (92); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1674.

*(7R,8R,8′S)-3,4′-Dimethoxy-7,9′-epoxylignan-4-ol (**54**).* Colorless oil; $[\alpha]^{20}_D$ −22 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 6.9 Hz), 2.22 (1H, m), 2.47 (1H, dd, J = 13.2, 11.0 Hz), 2.57 (1H, m), 2.81 (1H, dd, J = 13.2, 4.8 Hz), 3.71 (1H, dd, J = 8.6, 5.5 Hz), 3.78 (3H, s), 3.86 (3H, s), 4.01 (1H, dd, J = 8.6, 6.3 Hz), 4.48 (1H, d, J = 7.2 Hz), 5.74 (1H, s), 6.68−6.86 (5H, m), 7.09 (2H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 12.7, 33.0, 43.8, 45.0, 55.2, 55.9, 72.3, 87.1, 108.3, 113.9, 114.1, 118.8, 129.6, 132.7, 134.7, 144.9, 146.6, 157.9; MS (EI) m/z 328 (M^+, 20), 206 (98), 122 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1675.

*(7R,8R,8′S)-3-Methoxy-7,9′-epoxylignane-3′,4,4′-triol (**55**).* Colorless crystals, mp 110−111 °C; $[\alpha]^{20}_D$ −28 (c 1.1, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.05 (3H, d, J = 7.0 Hz), 2.17 (1H, m), 2.39 (1H, dd, J = 13.3, 11.0 Hz), 2.55 (1H, m), 2.73 (1H, dd, J = 13.3, 5.0 Hz), 3.63 (1H, J = 8.3, 5.9 Hz), 3.82 (3H, s), 3.97 (1H, dd, J = 8.3, 6.6 Hz), 4.43 (1H, d, J = 7.0 Hz), 6.55 (1H, d, J = 8.0 Hz), 6.70 (1H, s), 6.74 (1H, d, J = 8.0 Hz), 6.78 (2H, s), 6.94 (1H, s), 7.46 (1H, br. s), 7.71 (2H, br. s); ^{13}C NMR (100 MHz, acetone-d_6) δ 12.9, 33.7, 44.5, 45.9, 56.2, 72.6, 87.8, 110.2, 115.3, 116.0, 116.6, 119.4, 120.8, 133.5, 135.8, 144.0, 145.8, 146.6, 148.2; MS (EI) m/z 330 (M^+, 84), 149 (61), 137 (89), 123 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_5$ 330.1468, found 330.14771.

*(7R,8R,8′S)-3,3′,4′-Trimethoxy-7,9′-epoxylignan-4-ol (**56**).* Colorless oil; $[\alpha]^{20}_D$ −25 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, d, J = 6.9 Hz), 2.24 (1H, m), 2.47 (1H, dd, J = 12.8, 11.6 Hz), 2.58 (1H, m), 2.84 (1H, dd, J = 12.8, 4.7 Hz), 3.73 (1H, dd, J = 8.1, 5.4 Hz), 3.86 (3H, s), 3.87 (6H, s), 4.04 (1H, dd, J = 8.1, 7.1 Hz), 4.49 (1H, d, J = 7.3 Hz), 5.69 (1H, s), 6.71−6.74 (2H, m), 6.79−6.81 (2H, m), 6.86−6.88 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 33.5, 43.9, 45.1, 55.86, 55.90, 72.3, 87.1, 108.3, 111.2, 112.0, 114.1, 118.9, 120.6, 133.2, 134.6, 144.9, 146.6, 147.3, 148.8; MS (EI) m/z 358 (M^+, 67), 151 (100); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1781, found 358.1779.

*(7R,8R,8′S)-3′-Ethoxy-3-methoxy-7,9′-epoxylignane-4,4′-diol (**57**).* Colorless oil; $[\alpha]^{20}_D$ −25 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 7.1 Hz), 1.44 (3H, t, J = 6.9 Hz), 2.23 (1H, m), 2.44 (1H, dd, J = 13.3, 11.8 Hz), 2.55 (1H, m), 2.80 (1H, dd, J = 13.3, 4.9 Hz), 3.72 (1H, dd, J = 8.6, 5.4 Hz), 3.89 (3H, s), 4.02 (1H, dd, J = 8.6, 6.4 Hz), 4.09 (2H, q, J = 6.9 Hz), 4.48 (1H, d, J = 7.3 Hz), 5.57 (1H, s), 5.61 (1H, s), 6.66−6.67 (2H, m), 6.78 (1H, dd, J = 8.2, 1.5 Hz), 6.84 (1H, d, J = 8.6 Hz), 6.85−6.86 (1H, overlapped), 6.87 (1H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 14.9, 33.6, 44.0, 45.1, 55.9, 64.4, 72.3, 87.1, 108.2, 112.2, 114.0, 114.3, 118.9, 121.2, 132.5, 134.7, 143.9, 144.9, 145.7, 146.5; MS (EI) m/z 358 (M^+, 100), 165 (41), 151 (80); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1781, found 358.1781.

*(7R,8R,8′S)-3′-Butoxy-3-methoxy-7,9′-epoxylignane-4,4′-diol (**58**).* Colorless oil; $[\alpha]^{20}_D$ −15 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.3 Hz), 1.09 (3H, d, J = 7.1 Hz), 1.50 (2H, m), 1.80 (2H, m), 2.23 (1H, m), 2.44 (1H, dd, J = 13.3, 11.2 Hz), 2.55 (1H, m), 2.80 (1H, dd, J = 13.3, 4.5 Hz), 3.73 (1H, dd, J = 8.6, 5.3 Hz), 3.88 (3H, s), 4.01−4.05 (1H, overlapped), 4.02 (2H, t, J = 6.6 Hz), 4.48 (1H, d, J = 7.4 Hz), 5.56 (1H, s), 5.64 (1H, s), 6.65−6.67 (2H, m), 6.79 (1H, dd, J = 8.0, 1.9 Hz), 6.83−6.88 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 15.6, 19.3, 31.4, 35.0, 35.3, 40.5, 46.0, 55.8, 63.1, 68.5, 111.2, 112.1, 113.9, 121.5, 121.7, 132.8, 133.2, 143.6, 143.8, 145.8, 146.3; MS (EI) m/z 386 (M^+, 100), 220 (44), 151 (50), 123 (49); HRMS (EI) m/z calcd for $C_{23}H_{30}O_5$ 386.2094, found 386.2093.

*(7R,8R,8′S)-3′-Isopropoxy-3-methoxy-7,9′-epoxylignane-4,4′-diol (**59**).* Colorless oil; $[\alpha]^{20}_D$ −24 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, d, J = 7.1 Hz), 1.348 (3H, d, J = 6.0 Hz), 1.355 (3H, d, J = 6.0 Hz), 2.22 (1H, m), 2.43 (1H, dd, J = 13.5, 11.2 Hz), 2.55 (1H, m), 2.79 (1H, dd, J = 13.5, 4.7 Hz), 3.72 (1H, dd, J = 8.6, 5.5 Hz), 3.88 (3H, s), 4.03 (1H, dd, J = 8.6, 6.4 Hz), 4.48 (1H, d, J = 7.3 Hz), 4.56 (1H, m), 5.61 (1H, s), 5.64 (1H, s), 6.65 (1H, dd, J = 8.3, 1.6 Hz), 6.69 (1H, d, J = 1.6 Hz), 6.79 (1H, dd, J = 8.1, 1.6 Hz), 6.84 (1H, d, J = 8.1 Hz), 6.85−6.86 (1H, overlapped), 6.86 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 22.2, 33.6, 44.0, 45.0, 55.9, 71.6, 72.3, 87.1, 108.3, 114.08, 114.13, 114.5, 118.9, 121.4, 132.4, 134.8, 144.5, 144.9, 145.0, 146.6; MS (EI) m/z 372 (M^+, 100), 151 (41), 137 (40), 123 (56); HRMS (EI) m/z calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1933.

*(7R,8R,8′S)-3′-Chloro-3-methoxy-7,9′-epoxylignane-4,4′-diol (**60**).* Colorless crystals, mp 146−147 °C; $[\alpha]^{20}_D$ −21 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J = 7.0 Hz), 2.23 (1H, m), 2.45 (1H, dd, J = 13.6, 11.1 Hz), 2.54 (1H, m), 2.78 (1H, dd, J = 13.6, 4.6 Hz), 3.69 (1H, dd, J = 8.6, 5.5 Hz), 3.87 (3H, s), 4.06 (1H, dd, J = 8.6, 6.3 Hz), 4.48 (1H, d, J = 7.3 Hz), 5.66 (1H, s), 5.72 (1H, s), 6.79 (1H, br. d, J = 6.5 Hz), 6.85−6.91 (3H, m), 6.97 (1H, d, J = 8.2 Hz), 7.14 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 32.8, 43.7, 44.9, 55.9, 72.1, 87.1, 108.3, 114.1, 116.3, 118.9, 119.8, 128.6, 129.0, 133.8, 134.4, 145.0, 146.6, 149.7; MS (EI) m/z 348 (M^+, 85), 220 (48), 151 (92), 141 (100); HRMS (EI) m/z calcd for $C_{19}H_{21}O_4Cl$ 348.1129, found 348.1133.

*(7R,8R,8′S)-3,4′-Dimethoxy-7,9′-epoxylignane-3′,4-diol (**61**).* Colorless crystals, mp 113−114 °C; $[\alpha]^{20}_D$ −21 (c 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, J = 7.0 Hz), 2.21 (1H, m), 2.42 (1H, dd, J = 13.4, 11.3 Hz), 2.56 (1H, m), 2.76 (1H, dd, J = 13.4, 4.5 Hz), 3.70 (1H, dd, J = 8.0, 6.1 Hz), 3.83 (3H, s), 3.85 (3H, s), 4.03

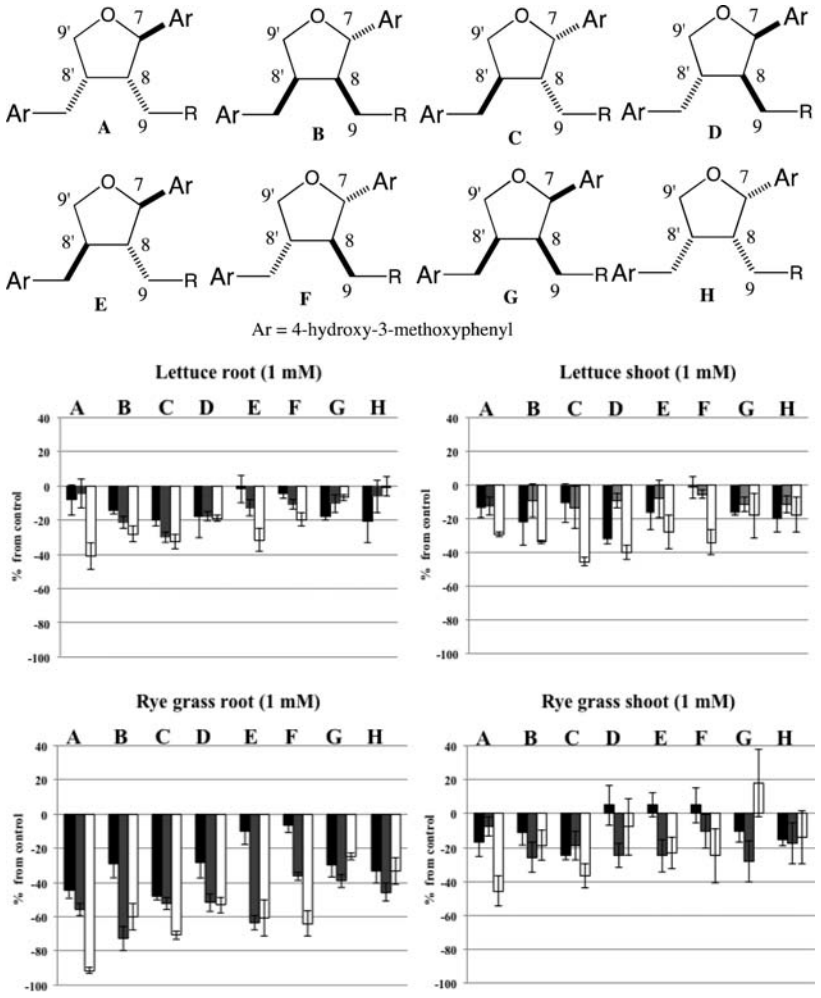

Figure 2. Plant growth regulatory activities of all stereoisomers of 9-OH (**1**–**8**), 9-OCH_3 (**17**–**24**), and 9-H (**9**–**16**) lariciresinol derivatives against lettuce and rye grass at 1 mM. **A**: R = OH (**1**), R = OCH_3 (**17**), R = H (**9**). **B**: R = OH (**2**), R = OCH_3 (**18**), R = H (**10**). **C**: R = OH (**3**), R = OCH_3 (**19**), R = H (**11**). **D**: R = OH (**4**), R = OCH_3 (**20**), R = H (**12**). **E**: R = OH (**5**), R = OCH_3 (**21**), R = H (**13**). **F**: R = OH (**6**), R = OCH_3 (**22**), R = H (**14**). **G**: R = OH (**7**), R = OCH_3 (**23**), R = H (**15**). **H**: R = OH (**8**), R = OCH_3 (**24**), R = H (**16**).

(1H, dd, J = 8.0, 6.8 Hz), 4.48 (1H, d, J = 7.2 Hz), 5.76 (1H, s), 5.79 (1H, s), 6.65 (1H, d, J = 8.0 Hz), 6.75–6.79 (3H, m), 6.84–6.86 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 33.2, 43.6, 44.9, 55.88, 55.95, 72.4, 87.2, 108.3, 110.7, 114.1, 114.9, 118.9, 120.1, 133.9, 134.7, 144.9, 145.0, 145.6, 146.6; MS (EI) m/z 344 (M^+, 100), 151 (71), 137 (97); HRMS (EI) m/z calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.2611.

(7R,8R,8′S)-3-Methoxy-7,9′-epoxylignane-,3′,4,4′,5′-tetraol (**62**). Colorless crystals, mp 116–117 °C; $[\alpha]^{20}_D$ −27 (c 0.5, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.04 (3H, d, J = 7.1 Hz), 2.14 (1H, m), 2.33 (1H, dd, J = 13.3, 10.9 Hz), 2.53 (1H, m), 2.67 (1H, dd, J = 13.3, 5.1 Hz), 3.63 (1H, dd, J = 8.2, 5.9 Hz), 3.819 (3H, s), 3.824 (3H, s), 3.98 (1H, dd, J = 8.2, 6.5 Hz), 4.42 (1H, d, J = 7.0 Hz), 6.26 (2H, s), 6.76 (1H, br. s), 6.77 (2H, s), 6.93 (1H, s), 7.20 (1H, br. s), 7.47 (1H, br. s), 7.74 (1H, br. s); ^{13}C NMR (100 MHz, acetone-d_6) δ 12.8, 33.9, 44.4, 45.9, 56.1, 72.6, 87.7, 108.3, 110.1, 115.2, 119.3, 132.9, 135.8, 146.4, 146.5, 148.0, 148.1; MS (EI) m/z 346 (M^+, 30), 259 (100); HRMS (EI) m/z calcd for $C_{19}H_{22}O_6$ 346.1417, found 346.1419.

(7R,8R,8′S)-3,3′,5′-Trimethoxy-7,9′-epoxylignane-4,4′-diol (**63**). Colorless oil; $[\alpha]^{20}_D$ −24 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.9 Hz), 2.27 (1H, m), 2.56 (1H, dd, J = 13.3, 11.8 Hz), 2.68 (1H, m), 3.02 (1H, dd, J = 13.3, 3.7 Hz), 3.82 (1H, dd, J = 8.7, 4.1 Hz), 3.85 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.98 (1H, dd, J = 8.7, 5.9 Hz), 4.50 (1H, d, J = 8.2 Hz), 5.74 (2H, s), 6.58 (1H, s), 6.80 (1H, d, J = 8.0 Hz), 6.86 (2H, s), 6.87 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz,$CDCl_3$) δ 12.2, 33.9, 42.6, 45.5, 55.9, 56.4, 60.6, 71.8, 86.8, 108.3, 109.0, 114.1, 119.0, 130.9, 134.5, 138.0, 145.0, 146.6, 146.7; MS (EI) m/z 374 (M^+, 16), 373 (100), 167 (54), 151 (42); HRMS (EI) m/z calcd for $C_{21}H_{26}O_6$ 374.1730, found 374.1727.

Evaluation of Plant Growth Regulatory Activity. The plant growth regulatory activity of all stereoisomers of lariciresinol was evaluated using lettuce (*Lactuca sativa* L. Green-wave (Takii Seed Co. Ltd., Kyoto, Japan)) and Italian ryegrass (*Lolium multiflorum* Lam. Wase-fudo (Takii Seed Co. Ltd.)). A sheet of filter paper (diameter = 90 mm) was placed in a 90-mm Petri dish and wetted with 500 μL of test sample solution dissolved in acetone at concentrations from 6.0×10^{-3} to 6.0×10^{-8} M. After the filter paper had dried, 3 mL of water was poured into the dish to adjust the final concentration from 1.0×10^{-3} to 1.0×10^{-8} M. Thirty seeds of each plant were placed on the filter paper, and the Petri dishes were sealed with Parafilm. The Petri dishes were then incubated in the dark at 20 °C. The lengths of roots and shoots were measured after 3 days for lettuce and after 5 days for ryegrass by using an ordinary ruler. The root and shoot lengths of the control were ca. 3 and 1 cm for lettuce and 4 and 3 cm for ryegrass, respectively. Data are presented as percentage differences from the control; positive and negative values present stimulation and inhibition of plant growth, respectively. Experiments were performed in triplicate or more for each sample (n = 3–7). Statistical analyses were conducted by one-way ANOVA followed by Tukey's multiple-comparison test using PRISM software (Graphpad Software, San Diego, CA), and values of $p < 0.05$ were considered to be statistically significant.

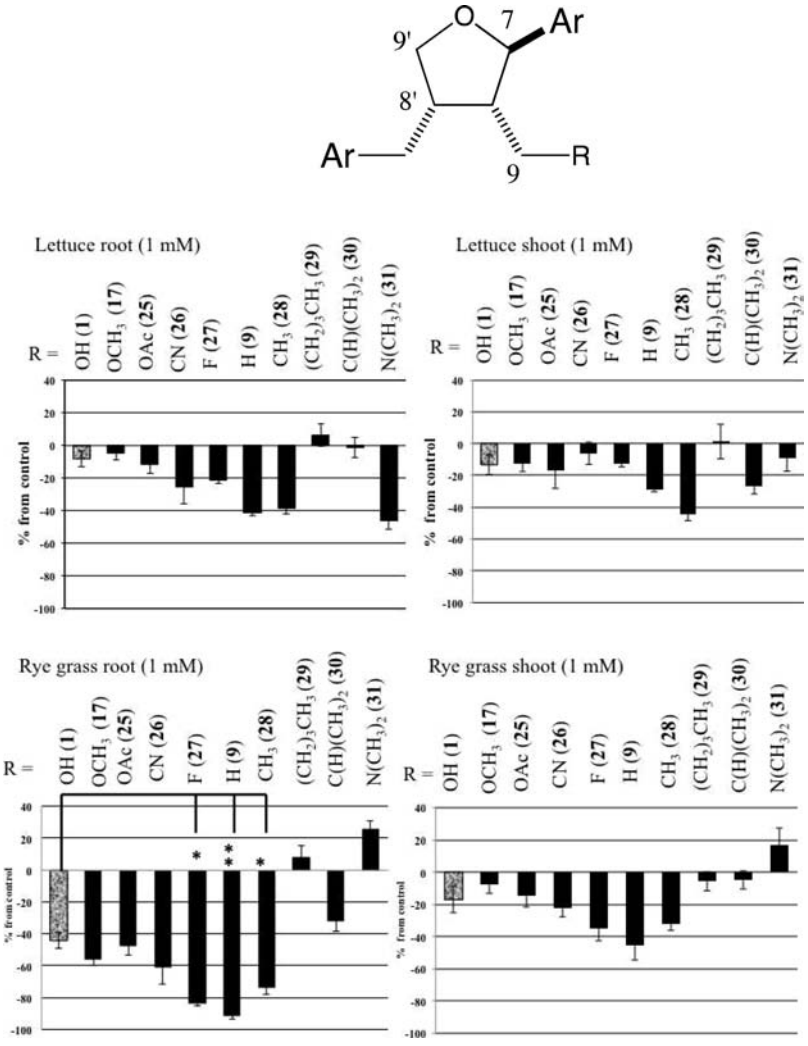

Figure 3. Plant growth regulatory activities of 9-derivatives of (−)-(7*R*,8*S*/*R*,8′*S*)-lariciresinol, *$p < 0.05$, **$p < 0.01$.

RESULTS AND DISCUSSION

All stereoisomers of 9-dehydroxylariciresinol (**9**−**16**) and 9-*O*-methyllariciresinol (**17**−**24**) were synthesized from the corresponding stereoisomers of 4-*O*,4′-*O*-benzyllariciresinol.[5,17] The 9-derivatives of (−)-lariciresinol **25**−**31** were also synthesized from 4-*O*,4′-*O*-benzyl-(−)-lariciresinol (**64**). The previously described synthetic method[17] was modified to prepare the 7-phenyl derivatives **32**−**47** and 7′-phenyl derivatives **48**−**63**.

All synthesized compounds were applied to the plant growth regulatory test at 1 mM. As a first attempt, all stereoisomers of 9-*O*-CH_3 (**17**−**24**) and 9-dehydroxy (R = H, **9**−**16**) derivatives were tested on lettuce and rye grass by comparing 9-OH compounds (**1**−**8**) containing natural (−)- and (+)-lariciresinol (**1** and **2**) (Figure 2). These compounds were more effective against rye grass in the growth inhibition of root than against shoot of rye grass or root and shoot of lettuce. In the experiment with 9-*O*-CH_3 stereoisomers, stereoisomers **B**, **D**, **E**, and **F** were 2−12-fold more effective than the corresponding 9-OH compounds; on the other hand, stereoisomers **A**, **C**, and both *cis* stereoisomers **G** and **H** showed the same level of activities as that of the corresponding 9-OH compounds. Except for both *cis* stereoisomers **G** and **H**, all stereoisomers **A**−**F** of 9-dehydroxy derivatives (R = H) showed higher growth inhibitory activity than that of corresponding 9-OH compounds against rye grass root (1.5−12-fold). Comparing 9-*O*-CH_3 derivatives with 9-dehydroxy derivatives (R = H), the 9-dehydroxy derivatives (R = H) of stereoisomers **A**, **C**, and **F** were 1.5−2-fold more favorable than the corresponding 9-*O*-CH_3 derivatives; on the other hand, the activities of 9-*O*-CH_3 and 9-dehydroxy derivatives (R = H) bearing the stereochemistry of **B**, **D**, **E**, **G**, and **H** were comparable. Against rye grass root, one of the 9-dehydroxy stereoisomers (R = H), (7*R*,8*S*,8′*S*)-stereoisomer **A** (**9**), showed the highest activity, exhibiting −95% growth inhibitory activity. Among the 9-dehydroxy derivatives, the activities of both *cis*-stereoisomers **G** and **H** (**15** and **16**) were smallest (−30% inhibition). The (7*R*,8*S*,8′*S*)-9-dehydroxy stereoisomer **A** (**9**) showed also highest growth inhibitory activity against rye grass shoot and lettuce root, although the activity was less potent (40−50% inhibition) than against rye grass root. The (7*S*,8*R*,8′*R*)-9-dehydroxy stereoisomer **C** (**11**) was most potent against lettuce shoot growth inhibitory activity, showing 50% growth inhibitory activity. Dilution experiments of all derivatives from 10^{-4} to 10^{-6} M showed less than 5% growth inhibition compared to negative control.

To perform further research on the effect of the 9-substituent, the activities of 9-derivative of (7*R*,8*S*/*R*,8′*S*)-stereoisomers **17**−**31** were compared with that of (−)-laricir-

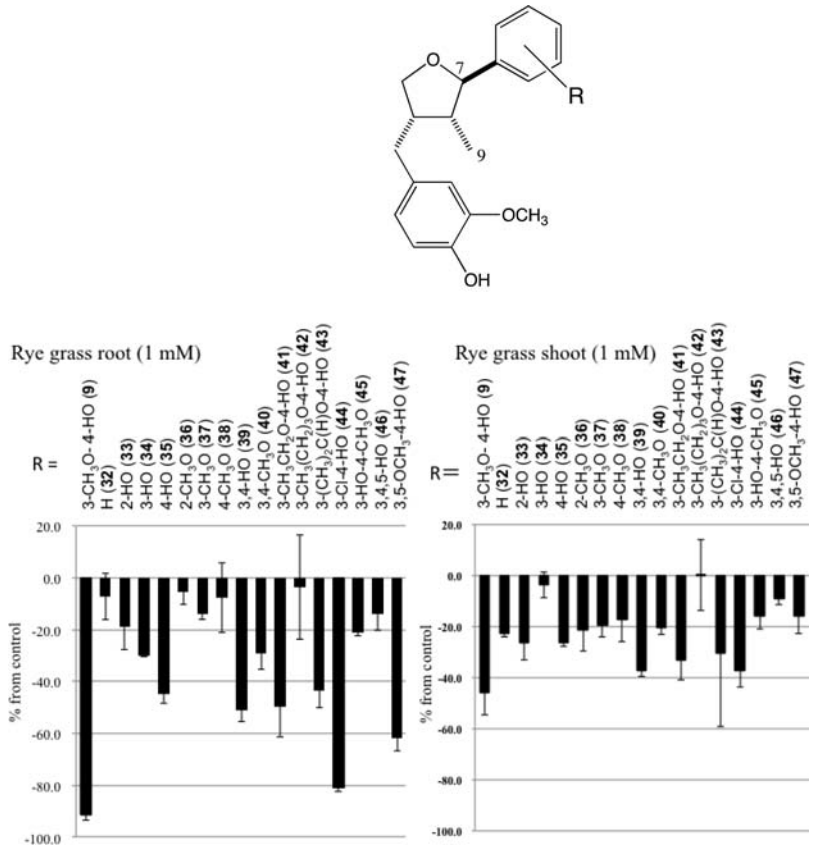

Figure 4. Plant growth regulatory activities of 7-aryl derivatives of (7*R*,8*R*,8′*S*)-9-dehydroxylariciresinol.

esinol, (7*R*,8*S*,8′*S*)-9-OH compound (**1**), at 1 mM (Figure 3). A higher inhibitory effect was observed against rye grass root. The activities of 9-methoxy (**17**), 9-acetoxy (**25**), and 9-nitrile (**26**) derivatives were almost comparable to that of natural 9-OH compound (**1**). The 9-F (**27**), 9-H (9-dehydroxy, **9**), and 9-CH_3 (**28**) derivatives suppressed the root growth of rye grass to −70% to −90% with significant difference compared with natural compound **1**. The activity of 9-isopropyl derivative **30** was less potent than that of natural compound **1**, showing −20% suppression. Suppressive activity of 9-butyl (**29**) and 9-$N(CH_3)_2$ (**31**) derivatives was not observed; however, 9-$N(CH_3)_2$ derivative (**31**) promoted the growth of rye grass root and shoot a little, which phenomena disappeared by dilution experiment from 10^{-4} to 10^{-6} M. Against rye grass shoot, the same tendency as against rye grass root was observed, assuming that the small hydrophobic group at the 9-position is effective for higher activity. In the case of lettuce root, 9-H (9-dehydroxy, **9**), 9-CH_3 (**28**), and 9-$N(CH_3)_2$ (**31**) derivatives were more effective with −40% growth inhibition; on the other hand, 9-CH_3 derivative (**28**) was most potent against growth suppression of lettuce shoot, −40% growth inhibitory activity being observed. Dilution experiments of all derivatives from 10^{-4} to 10^{-6} M showed less than 5% growth inhibition compared to negative control.

Since higher activity was observed in the 9-dehydroxy derivative (R = H) against rye grass root in this 9-derivative research, the activities of 7- and 7′-derivatives of 9-dehydroxylariciresinol derivatives were tested to examine the effect of substituents of the benzene ring on the activity against rye grass. Figure 4 displays the results of growth inhibitory activity tests of 7-aryl-9-dehydroxy derivatives (**32**−**47**) against rye grass at 1 mM. The activities of 7-(4-HOPh) **35**, 7-(3,4-HOPh) **39**, 7-(3-CH_3CH_2O-4-HOPh) **41**, 7-(3-$(CH_3)_2C(H)$-O-4-HOPh) **43**, 7-(3-Cl-4-HOPh) **44**, and 7-(3,5-CH_3O-4-HOPh) **47** derivatives showed more than −40% growth inhibitory activity against rye root; on the other hand, 7-(2-HOPh) **33**, 7-(3-HOPh) **34**, 7-(3-HO-4-CH_3OPh) **45** derivatives, and other derivatives without a hydroxy group (**36**−**38** and **40**) exhibited less than −30% growth inhibitory activity, suggesting that a 4-hydroxy group on the 7-aryl group is necessary to keep higher activity. Even if the 4-hydroxy group is present on the 7-phenyl group, the presence of a longer alkoxy group at the 3-position and hydroxy groups at both the 3- and 5-positions decreased the activity, 7-(3-$CH_3(CH_2)_3O$-4-HOPh) **42** and 7-(3,4,5-HOPh) **46** derivatives being less potent. It could be assumed that the higher hydrophobicity and higher hydrophilic property on the 7-phenyl group is disadvantageous for higher activity. The activity of 7-(3-Cl-4-HOPh)-9-dehydroxy derivative **44** was comparable to that of 7-(3-CH_3O-4-HOPh)-9-dehydroxy derivative **9**, suggesting that the activity level does not depend on the electron density, but that the presence of a small hydrophobic group at the 3-position and a 4-hydroxy group on the 7-phenyl group is important for higher activity. The activities of all derivatives against rye grass shoot were weak, showing less than −40% growth inhibition.

Figure 5 illustrates the relationship between the structure of the 7′-phenyl group and growth inhibitory activity against rye grass root and shoot by using 7′-aryl-9-dehydroxylariciresinol derivatives (**48**−**63**). For monosubstituted derivatives, only the 7′-(3′-hydroxyphenyl) derivative showed a little lower potency compared to that of 7′-(3′-CH_3O-4′-HOPh) derivative **9**,

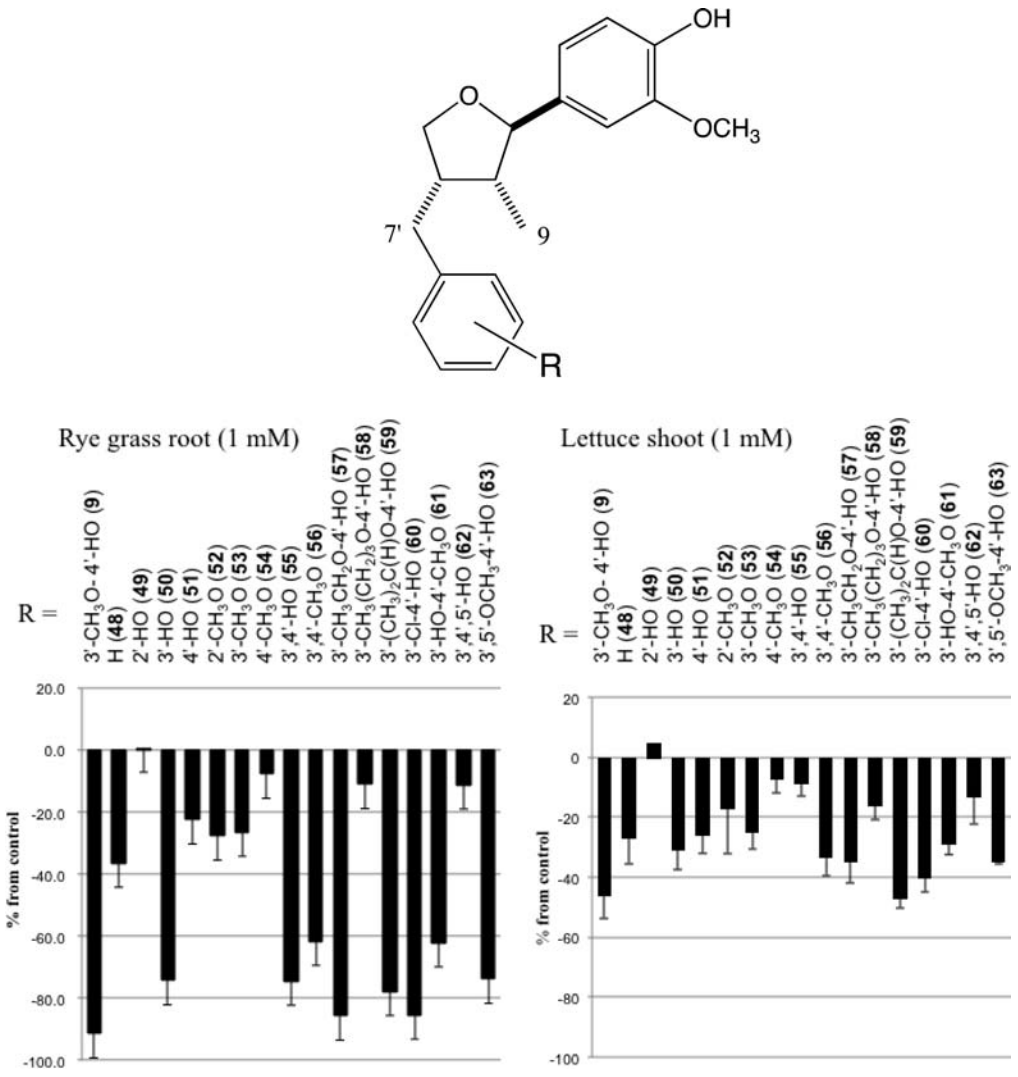

Figure 5. Plant growth regulatory activities of 7′-aryl derivatives of (7*R*,8*R*,8′*S*)-9-dehydroxylariciresinol.

showing −70% growth inhibitory rate. The growth inhibitory activities of the other monohydroxy and methoxy derivatives (**49**, **51**−**54**) and phenyl derivative **48** were 0 to −30%, suggesting the importance of two substituents at both the 3′- and 4′-positions for higher activity. In the treatment of 3′,4′-disubstituted derivatives, 7′-(3′,4′-HOPh) **55**, 7′-(3′,4′-CH_3OPh) **56**, 7′-(3′-CH_3CH_2O-4′-HOPh) **57**, 7′-(3′-$(CH_3)_2$C(H)O-4′-HOPh) **59**, 7′-(3′-Cl-4′-HOPh) **60**, and 7′-(3′-HO-4′-CH_3OPh) **61** displayed higher growth inhibition (−60% to −80%); however, the activity of a derivative bearing a longer and more hydrophobic group at the 3′-position was lower, 7′-(3′-$CH_3(CH_2)_3$O-4′-HOPh) **58** showing only −10% growth inhibitory activity. The results of treatment by trisubstituted derivatives **62** and **63** suggested that a more hydrophilic derivative is unfavorable for higher activity and the more hydrophobic group on the 7′-phenyl group is tolerable for the activity. Thus, 7′-(3′,4′,5′-HOPh) derivative **62** (−10% growth inhibition) was less potent than that of 7′-(3′,5′-CH_3O-4′-HOPh) derivative **63** (−70% growth inhibition). The growth inhibitory activities against rye grass shoot were weaker (0 to −40%) than against rye grass root. Application of 7′-(3′-CH_3CH_2O-4′-HOPh) derivative **57** and 7′-(3′-Cl-4′-HOPh) derivative **60** to rye grass showed activity comparable to that of 7′-(3′-CH_3O-4′-HOPh) derivative **9** against root. Although the presence of a smaller hydrophobic group at the 3′-position and a hydroxy group at the 4′-position is important for higher activity as on the 7-phenyl group, many 7′-phenyl derivatives showed activity higher than that of 7-phenyl derivatives.

In summary, we synthesized all stereoisomers of 9-dehydroxy derivatives and 9-OCH_3 derivatives of lariciresinol and performed the plant growth regulatory activity test to determine that (−)-(7*R*,8*R*,8′*S*)-9-dehydroxy derivative **9** showed 2-fold higher activity (−90% growth inhibition at 1 mM) compared to that of natural (−)-lariciresinol (**1**) against rye grass root. When the other seven synthesized 9-derivatives of (−)-(7*R*,8*R*,8′*S*)-lariciresinol were subjected to the biological test, (−)-(7*R*,8*R*,8′*S*)-9-dehydroxy derivative **9** showed the highest activity. As a next stage, sixteen 7-aryl-9-dehydroxy derivatives and sixteen 7′-aryl-9-dehydroxy derivatives were synthesized and subjected to the growth regulatory activity test against rye grass root to show the activities of 7-(3-Cl-4-HOPh)-9-dehydroxy derivative **44**, 7′-(3′-CH_3CH_2O-4′-HOPh)-9-dehydroxy derivative **57**, and 7′-(3′-Cl-4′-HOPh)-9-dehydroxy derivative **60**, which were comparable to that of (−)-(7*R*,8*R*,8′*S*)-9-dehydroxy derivative **9**. The importance of hydroxy groups on the 4- and 4′-positions and a small hydrophobic group at the 3- and 3′-positions was suggested. Although phytotoxic lignans have been reported,[1−4,18−22] the

structure-containing stereochemistry−plant growth regulatory (phytotoxic) activity relationship of lignan was clarified by employing lariciresinol derivatives for the first time. The information in this article would contribute to development of a new lead compound to regulate plant growth based on the natural lignan structure.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic method of compounds is available free of charge via Internet at http://pubs.acs.org.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Nakano, H.; Fujii, Y.; Yamada, K.; Kosemura, S.; Yamamura, S.; Hasegawa, K.; Suzuki, T. Isolation and identification of plant growth inhibitors as candidate(s) for allelopathic substance(s), from aqueous leachate from mesquite (*Prosopis juliflora* (Sw.) DC.) leaves. *Plant Growth Regul.* **2002**, *37*, 113−117.

(2) Cutillo, F.; Abrosca, B. D.; Greca, M. D.; Fiorentino, A.; Zarrelli, A. Lignans and neolignans from *Brassica fruticulosa*: effects on seed germination and plant growth. *J. Agric. Food Chem.* **2003**, *51*, 6165−6172.

(3) D'Abrosca, B.; DellaGreca, M.; Fiorentino, A.; Monaco, P.; Previtera, L.; Simoner, A. M.; Zarrelli, A. Potential allelochemicals from *Sambucus nigra*. *Phytochemistry* **2001**, *58*, 1073−10081.

(4) DellaGreca, M.; Mancino, A.; Previtera, L.; Zarrelli, A.; Zuppolini, S. Lignans from Phillyrea angustifolia L. *Phytochem. Lett.* **2011**, *4*, 118−121.

(5) Nishiwaki, H.; Kumamoto, M.; Shuto, Y.; Yamauchi, S. Stereoselective syntheses of all stereoisomers of lariciresinol and their plant growth inhibitory activities. *J. Agric. Food Chem.* **2011**, *59*, 13089−13095.

(6) Ayres, D. C.; Loike, J. D. Biological and clinical properties of podophyllotoxin and other lignans. In *Lignans*; Cambridge University Press: Cambridge, U.K., 1990; pp 85−112.

(7) Suzuki, S.; Umezawa, T.; Shimada, M. Stereochemical diversity in lignan biosynthesis of Arctium lappa L. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1262−1269.

(8) Sicilia, T.; Niemeyer, H. B.; Honig, D. M.; Metzler, M. Identification and stereochemical characterization of lignans in flaxseed and pumpkin seeds. *J. Agric. Food Chem.* **2003**, *51*, 1181−1188.

(9) Nishiwaki, H.; Hasebe, A.; Kawaguchi, Y.; Akamatsu, M.; Shuto, Y.; Yamauchi, S. Larvicidal activity of (−)-dihydroguaiaretic acid derivatives against *Culex pipiens*. *Biosci. Biotechnol. Biochem.* **2011**, *75*, 1735−1739.

(10) Wukirsari, T.; Nishiwaki, H.; Hasebe, A.; Shuto, Y.; Yamauchi, S. First discovery of insecticidal activity of 9,9′-epoxylignane and dihydroguaiaretic acid against houseflies and the structure-activity relationship. *J. Agric. Food Chem.* **2013**, *61*, 4318−4325.

(11) Masuda, K.; Nishiwaki, H.; Akiyama, K.; Yamauchi, S.; Maruyama, M.; Sugahara, T.; Kishida, T. Antifungal activity of morinol B derivatives of tetrahydropyran sesquilignan. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 2071−2076.

(12) Nishiwaki, H.; Ouchi, M.; Matsugi, J.; Akiyama, K.; Sugahara, T.; Kishida, T.; Yamauchi, S. Effect of substituents at phenyl group of 7,7′-dioxo-9,9′-epoxylignane on antifungal activity. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6740−6744.

(13) Hasebe, A.; Nishiwaki, H.; Akiyama, K.; Sugahara, T.; Kishida, T.; Yamauchi, S. Quantitative structure−activity relationship analysis of antifungal (+)-dihydro-guaiaretic acid using 7-phenyl derivatives. *J. Agric. Food Chem.* **2013**, *61*, 8548−8555.

(14) Kawahara, S.; Iwata, I.; Fujita, E.; Yamawaki, M.; Nishiwaki, H.; Sugahara, T.; Yamauchi, S.; Akiyama, K.; Kishida, T. IgE-suppressive activity of (−)-matairesinol and its structure-activity relationship. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 1878−1883.

(15) Yamauchi, S.; Kawahara, S.; Wukirsari, T.; Nishiwaki, H.; Nishi, K.; Sugahara, T.; Akiyama, K.; Kishida, T. Structure−cytotoxic activity relationship of sesquilignan, morinol A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4923−4930.

(16) Moss, G. P. Nomenclature of lignans and neolignans (IUPAC recommendations 2000). *Pure Appl. Chem.* **2000**, *72*, 1493−1523.

(17) Yamauchi, S.; Sugahara, T.; Matsugi, J.; Someya, T.; Masuda, T.; Kishida, T.; Akiyama, K.; Maruyama, M. Effect of the benzylic structure of lignan on antioxidant activity. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 2283−2290.

(18) Agnes, M. R.; Franck, E. D.; Julie, R. M.; Rita, M. M. Phytotoxic Lignans of *Leucophyllum frutescens*. *Nat. Toxins* **1999**, *7*, 39−43.

(19) Francisco, M.; Adriana, L.; Rosa, M. V.; Ascensión, T.; José, M. G. M. Bioactive lignans from a cultivar of *Helianthus annuus*. *J. Agric. Food Chem.* **2004**, *52*, 6443−6447.

(20) Ana, L. A.; Martha, M.-R.; Rocío, C.-O.; Clara, G.-S.; Perla, N. S.-M.; Blanca, E. H.-B.; Rachel, M. Allelochemicals from *Stauranthus perforatus*, a Rutaceous tree of the Yucatan Peninsula, Mexico. *Pytochemistry* **2005**, *66*, 487−494.

(21) D'abrosca, B.; Dellagreca, M.; Fiorentino, A.; Golino, A.; Monaco, P.; Zarrelli, A. Isolation and characterization of new lignans from the leaves of *Cetrum parwui*. *Nat. Prod. Res.* **2006**, *20*, 293−298.

(22) Satake, H.; Ono, E.; Murata, J. Recent advances in the metabolic engineering of lignan biosynthesis pathway for the production of transgenic plant-based food and supplements. *J. Agric. Food Chem.* **2013**, *61*, 11721−11729.

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