JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Synthesis of All Stereoisomers of 3,3′-Dimethoxy-7,7′-epoxylignane-4,4′-diol and Their Plant Growth Inhibitory Activity

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Supporting Information

ABSTRACT: All stereoisomers of 3,3′-dimethoxy-7,7′-epoxylignane-4,4′-diol were synthesized to examine the effect of stereochemistry on their plant growth inhibitory activity using lettuce and Italian ryegrass. The effect of structural modifications such as dehydroxylation, methoxylation and hydroxylation at the 9- and 9′-positions of the lignans on the activity was also studied. Most of the epoxylignanes showed higher plant growth inhibitory potency against ryegrass than against lettuce, and the inhibitory activity varied depending on the configurations of each position of the tetrahydrofuran ring (7-, 7′-, 8-, and 8′-positions of the epoxylignanes). Among the 9,9′-position-modified derivatives, the dehydroxy derivatives showed the highest potency. These results suggested that the plant growth inhibitory activity should be influenced by the structure of the epoxylignanes.

KEYWORDS: *3,3′-dimethoxy-7,7′-epoxylignane-4,4′-diol, lignan, plant growth inhibitory activity, lettuce, Italian ryegrass*

INTRODUCTION

Lignans widely distributed in plants exert various biological activities such as anticancer and antioxidant activities.[1] Lariciresinol, which is a trisubstituted tetrahydrofuran lignan, has also interesting biological activities including phytotoxic activity. Our previous study of the effect of the stereochemistry of lariciresinol on plant growth regulatory activity against lettuce (*Lactuca sativa* L.) and Italian ryegrass (*Lolium multiflorum* Lam.) demonstrated that the phytotoxic activity of lariciresinol depended on its stereochemistry, that is, the importance of both the 8*S* absolute configuration and the 7,8′-*trans* relative configuration for high activity.[2] It is undoubted that lignans other than lariciresinol should also show potent phytotoxic activity, as reported for diayangambin and dihydrodiconiferyl alcohol,[3,4] and that the structural modification as well as the absolute structure of lignans should influence their phytotoxicity, but data regarding the phytotoxicity of lignans, especially in-depth discussion of the relationship between their stereochemistry and activity, are less available.

Herein we focused on the relationship between the stereochemistry of 3,3′-dimethoxy-7,7′-epoxylignane-4,4′-diol compounds, which are tetrasubstituted tetrahydrofuran lignans (Figure 1), and their plant growth regulatory activity. In addition, the effect of the structural modifications at the 9- and 9′-positions such as dehydroxylation, methoxylation and hydroxylation on the activity was also studied. Some of these lignans have been isolated and named as follows: (−)-verrucosin, **1** (**1-H**, (−)-odoratisol);[5,6] (+)-verrucosin, **4** (**2-H**);[7] (+)-fragransin A2, **7** (**3-H**);[7] (+)-*neo*-olivil, **9** (**3-OH**);[8] (+)-saucernetin diol, **13** (**5-H**);[9,10] (−)-*neo*-olivil, **18** (**6-OH**);[11] (−)-machilin-I, **22** (**8-H**);[12] nectandrin B, **25** (**9-H**);[7] and tetrahydrofuroguaiacin B, **28** (**10-H**).[10] The syntheses of **1**,[13] **7**,[13] and **13**[14,15] have been achieved, and the conversion from glucoside to **27** (**9-OH**) has been reported.[16] The other stereoisomers were synthesized for the first time in this project. In our previous studies, the constructions of all stereochemistries of 7,7′-epoxylignane have been established,[17−19] and these synthetic methods were modified to provide the stereoisomers of 3,3′-dimethoxy-7,7′-epoxylignane-4,4′-diol. This research would contribute to the collation of stereoisomer libraries of natural products.

MATERIALS AND METHODS

Chemicals. The synthetic scheme is shown in Figure 2. Reagents used for the syntheses were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), Nacalai Tesque, Inc. (Kyoto, Japan), Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and Aldrich Chemical Co (Milwaukee, WI, USA). Melting points were uncorrected. Optical rotations were measured on a SEPA-200 instrument (Horiba Ltd., Kyoto, Japan). NMR data were obtained using a Bruker AVANCE III 500 spectrometer (Bruker BioSpin K.K., Kanagawa, Japan). EIMS data were measured with a JMS-MS700 V spectrometer (JEOL Ltd., Tokyo, Japan). The silica gel used was Wakogel C-300 (Wako, 200−300 mesh). The numbering of compounds follows the nomenclature of lignans.[20] Information for compounds **1**, **4**, **7**, **9**, **10**, **12**, **13**, **15**, **16**, **18**, **19**, **22**, **25**, **27**, and **28** (**1-H**−**10-H**, **3-OH**, **4-OH**, **5-OH**, **6-OH**, and **9-OH**), which has been published,[5−8,10,11,13,14,16,21] was placed in the Supporting Information.

(7S,7′R,8S,8′S)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, ***31****:* colorless oil; $[\alpha]^{20}_{D}$ −18 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (1H, m, H-8′), 2.55 (1H, m, H-8), 2.65−3.00 (1H, br, OH), 3.08 (1H, dd, *J* = 10.3, 9.9 Hz, H-9a), 3.18−3.48 (1H, br, OH), 3.30 (1H, dd, *J* = 10.3, 4.7 Hz, H-9b), 3.55 (1H, dd, *J* = 9.6, 9.0 Hz, H-9′a), 3.72 (1H, dd, *J* = 9.6, 3.4 Hz, H-9′b), 3.84 (3H, s, 3-OCH_3), 3.88 (3H, s, 3′-OCH_3), 4.47 (1H, d, *J* = 9.4 Hz, H-7′), 5.09 (1H, d, *J* = 8.7 Hz, H-7), 5.11 (2H, s, CH_2OPh), 5.14 (2H, s, CH_2OPh), 6.82 (2H, s, H-5, H-6), 6.84 (1H, d, *J* = 8.3 Hz, H-5′), 6.89 (1H, s, H-2), 6.92 (1H, dd, *J* = 8.3, 1.9 Hz, H-6′), 7.04 (1H, d, *J* = 1.9 Hz, H-2′), 7.27−7.30 (2H, m, BnO), 7.33−7.37 (4H, m, BnO), 7.40−7.43 (4H, m, BnO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.9 (C-8), 54.9 (C-8′), 56.0 (C-9′), 56.1 (C-9), 63.0 (OCH_3), 63.7 (OCH_3), 71.10 (OCH_2Ph), 71.13 (OCH_2Ph), 81.2 (C-7), 82.5 (C-7′), 110.4 (C-2′), 110.8 (C-2), 113.9 (C-5), 114.0 (C-5′), 118.7 (C-6′), 119.0 (C-6),

Received: October 15, 2013
Revised: December 21, 2013
Accepted: December 22, 2013
Published: December 22, 2013

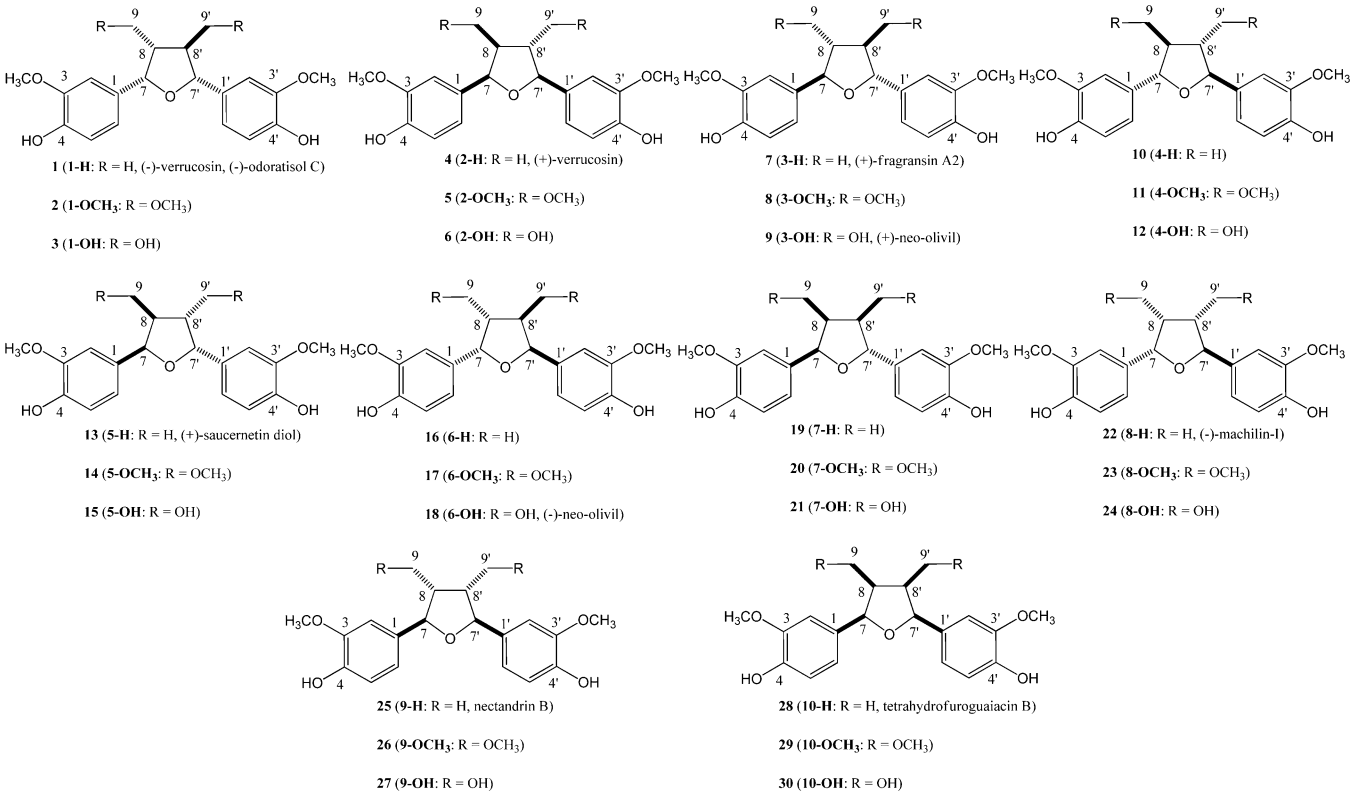

Figure 1. Chemical structures of the epoxylignanes synthesized in the present study.

127.26 (OBn), 127.33 (OBn), 127.86 (OBn), 127.88 (OBn), 128.53 (OBn), 128.55 (OBn), 132.1 (C-1), 133.2 (C-1′), 137.0 (OBn), 137.1 (OBn), 147.7 (C-4), 148.1 (C-4′), 149.5 (C-3), 149.8 (C-3′). Anal. Found: C, 73.38%; H, 6.60%. Calcd for $C_{34}H_{36}O_7$: C, 73.36%; H, 6.52%.

(7R,7′S,8R,8′R)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, ***32:*** colorless oil; $[\alpha]^{20}_D$ +18 (*c* 1.6, $CHCl_3$); NMR data agreed with those of **31**.

(7S,7′R,8S,8′S)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***2 (1-OCH₃):*** colorless oil; $[\alpha]^{20}_D$ −21 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (1H, m, H-8′), 2.63 (1H, m, H-8), 2.97 (1H, dd, *J* = 9.3, 5.8 Hz, H-9a), 3.07−3.10 (1H, overlapped, H-9b), 3.08 (3H, s, 9-OCH_3), 3.36 (3H, s, 9′-OCH_3), 3.51 (1H, dd, *J* = 9.5, 5.2 Hz, H-9′a), 3.55 (1H, dd, *J* = 9.5, 5.4 Hz, H-9′b), 3.86 (3H, s, 3-OCH_3), 3.90 (3H, s, 3′-OCH_3), 4.72 (1H, d, *J* = 8.0 Hz, H-7′), 5.10 (1H, d, *J* = 7.3 Hz, H-7), 5.70 (1H, s, ArOH), 5.74 (1H, s, ArOH), 6.89−6.92 (4H, m, H-2, H-5, H-5′, H-6), 6.99 (1H, dd, *J* = 8.2, 1.9 Hz, H-6′), 7.01 (1H, d, *J* = 1.9 Hz, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.7 (C-8), 50.6 (C-8′), 55.85 (9-OCH_3), 55.90 (9′-OCH_3), 58.6 (3′-OCH_3), 59.0 (3-OCH_3), 73.1 (C-9′, C-9), 81.6 (C-7), 82.7 (C-7′), 109.3 (C-2′), 109.5 (C-2), 114.0 (C-5), 114.2 (C-5′), 119.3 (C-6′), 119.5 (C-6), 130.9 (C-1), 133.5 (C-1′), 144.7 (C-4), 145.2 (C-4′), 146.2 (C-3), 146.5 (C-3′); MS (EI) *m*/*z* 404 (M^+, 34), 175 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_7$ (M^+) 404.1835, found 404.1834.

(7S,7′R,8S,8′S)-3,3′-Dimethoxy-7,7′-epoxylignane-4,4′,9,9′-tetraol, ***3 (1-OH):*** colorless oil; $[\alpha]^{20}_D$ −20 (*c* 1.4, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.28 (2H, s, OH), 2.28 (1H, m, H-8′), 2.56 (1H, m, H-8), 3.16 (1H, dd, *J* = 10.4, 10.0 Hz, H-9a), 3.22 (1H, dd, *J* = 10.4, 5.1 Hz, H-9b), 3.64 (1H, dd, *J* = 11.0, 6.1 Hz, H-9′a), 3.71 (1H, dd, *J* = 11.0, 4.7 Hz, H-9′b), 3.85 (3H, s, 3-OCH_3), 3.89 (3H, s, 3′-OCH_3), 4.65 (1H, d, *J* = 8.6 Hz, H-7′), 5.10 (1H, d, *J* = 7.9 Hz, H-7), 6.78 (1H, d, *J* = 8.1 Hz, H-6), 6.80−6.85 (2H, m, H-2, H-5), 6.95−6.97 (2H, m, H-5′, H-6′), 7.10 (1H, s, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5 (C-8), 54.2 (C-8′), 54.89 (OCH_3), 54.91 (OCH_3), 60.5 (C-9′), 61.0 (C-9), 76.2 (C-7), 77.1 (C-7′), 98.9 (C-2′), 99.1 (C-2), 102.5 (C-5), 102.7 (C-5′), 106.1 (C-6′), 106.3 (C-6), 115.2 (C-1), 116.9 (C-1′), 127.4 (C-4), 127.8 (C-4′), 128.8 (C-3), 129.1 (C-3′); MS (EI) *m*/*z* 376 (M^+, 51), 224 (71), 193 (81), 176 (100), 151 (62), 137 (69); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_7$ (M^+) 376.1522, found 376.1515.

(7R,7′S,8R,8′R)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***5 (2-OCH₃):*** colorless oil; $[\alpha]^{20}_D$ +21 (*c* 0.2, $CHCl_3$); NMR data agreed with those of **2**.

(7R,7′S,8R,8′R)-3,3′-Dimethoxy-7,7′-epoxylignane-4,4′,9,9′-tetraol, ***6 (2-OH):*** colorless oil; $[\alpha]^{20}_D$ +20 (*c* 0.1, MeOH); NMR data agreed with those of **3**.

(7R,7′R,8S,8′S)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, ***33:*** colorless oil; $[\alpha]^{20}_D$ +46 (*c* 2.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (2H, m, H-8, H-8′), 3.44 (2H, dd, *J* = 9.1, 8.8 Hz, H-9a, H-9′a), 3.63 (2H, d, *J* = 9.1 Hz, H-9b, H-9′b), 3.84 (6H, s, OCH_3), 4.22 (2H, br s, OH), 4.66 (2H, d, *J* = 9.0 Hz, H-7, H-7′), 5.09 (4H, s, OCH_2Ph), 6.76 (2H, dd, *J* = 8.3, 1.9 Hz, H-6, H-6′), 6.82 (2H, d, *J* = 8.3 Hz, H-5, H-5′), 6.92 (2H, d, *J* = 1.9 Hz, H-2, H-2′), 7.24−7.27 (2H, m, OBn), 7.30−7.33 (4H, m, OBn), 7.38−7.66 (4H, m, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.1 (OCH_3), 57.0 (C-8, C-8′), 62.6 (C-9, C-9′), 71.1 (OCH_2Bn), 83.1 (C-7, C-7′), 110.0 (C-2, C-2′), 113.9 (C-5, C-5′), 118.7 (C-6, C-6′), 127.3 (OBn), 127.6 (OBn), 127.8 (OBn), 128.5 (OBn), 134.6 (C-1), 134.8 (C-1′), 137.0 (Bn), 147.9 (C-4, C-4′), 149.8 (C-3, C-3′). Anal. Found: C, 73.40%; H, 6.53%. Calcd. for $C_{34}H_{36}O_7$: C, 73.36%; H, 6.52%.

(7S,7′S,8R,8′R)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, ***34:*** colorless oil; $[\alpha]^{20}_D$ −49 (*c* 0.9, $CHCl_3$); NMR data agreed with those of **33**.

(7R,7′R,8S,8′S)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***8 (3-OCH₃):*** colorless crystals; mp 129−130 °C; $[\alpha]^{20}_D$ +29 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (2H, m, H-8, H-8′), 3.33 (6H, s, 9-OCH_3, 9′-OCH_3), 3.45 (2H, dd, *J* = 9.5, 4.5 Hz, H-9a, H-9′a), 3.50 (2H, dd, *J* = 9.5, 5.0 Hz, H-9b, H-9′b), 3.89 (6H, s, 3-OCH_3, 3′-OCH_3), 4.96 (2H, d, *J* = 7.8 Hz, H-7, H-7′), 5.65 (2H, s, 4-OH, 4′OH), 6.87 (2H, d, *J* = 8.2 Hz, H-5, H-5′), 6.90 (2H, dd, *J* = 8.2, 1.5 Hz, H-6, H-6′), 7.00 (2H, d, *J* = 1.5 Hz, H-2, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.2 (C-8, C-8′), 56.0 (9-OCH_3, 9′-OCH_3), 59.0 (3-OCH_3, 3′-OCH_3), 72.4 (C-9, C-9′), 82.8 (C-7, C-7′), 108.8 (C-2, C-2′), 114.1(C-5, C-5′), 119.3(C-6, C-6′), 134.4 (C-1, C-1′),

dx.doi.org/10.1021/jf4046396 | J. Agric. Food Chem. 2014, 62, 651−659

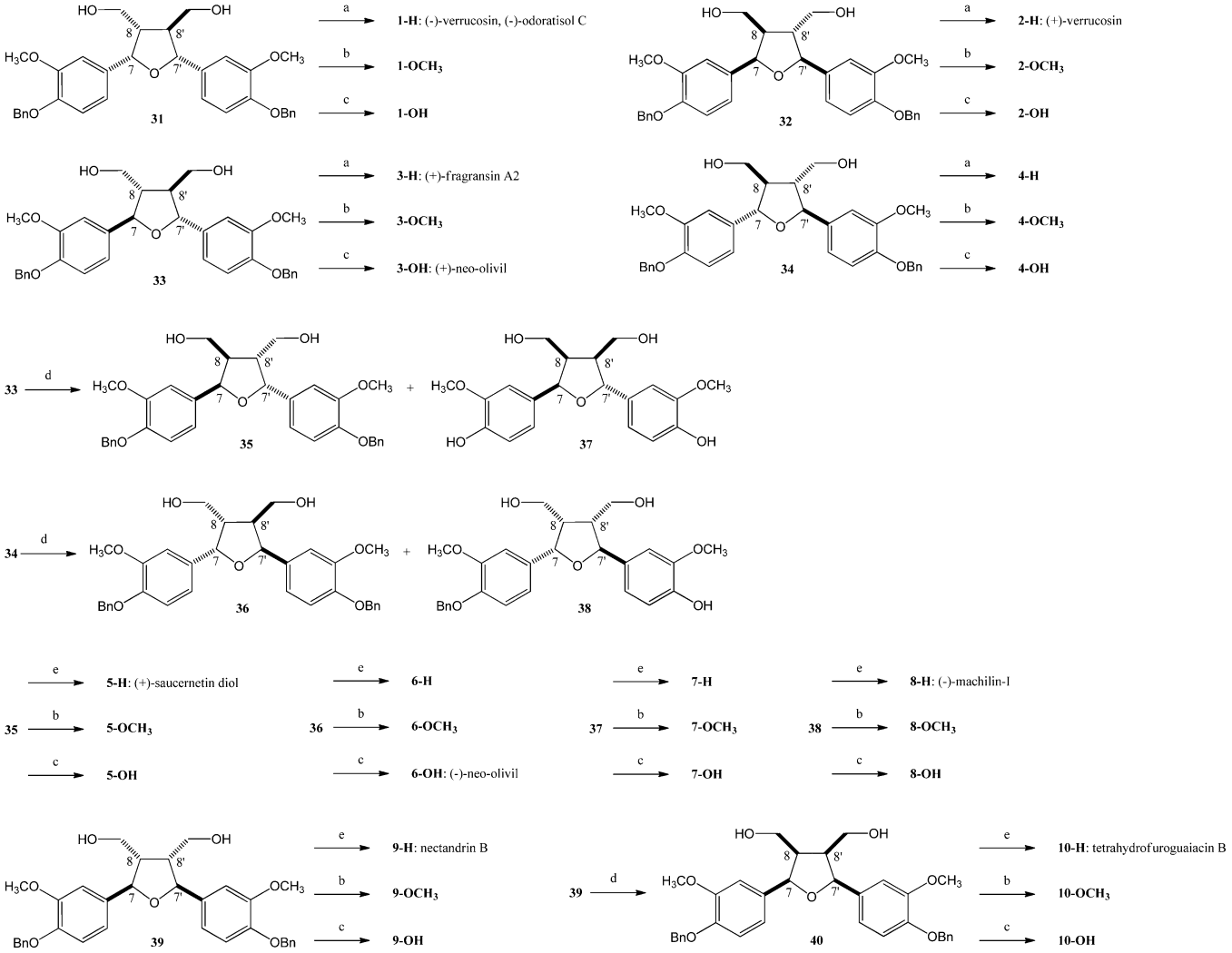

Figure 2. Synthetic schemes: (a) (1) MsCl, Et_3N, CH_2Cl_2, rt, 30 min; (2) $NaBH_4$, HMPA, 60 °C, 1.5 h; (3) H_2, 5% Pd/C, EtOAc, ambient temperature, 2 h (3 steps, **1-H**, 57%; **2-H**, 60%; **3-H**, 43%; **4-H**, 48%). (b) (1) NaH, MeI, THF, rt, 3 h; (2) H_2, 5% Pd/C, ambient temperature, 5 h (2 steps, **1-OCH$_3$**, 65%; **2-OCH$_3$**, 62%; **3-OCH$_3$**, 51%; **4-OCH$_3$**, 48%; **5-OCH$_3$**, 50%; **6-OCH$_3$**, 51%; **7-OCH$_3$**, 44%; **8-OCH$_3$**, 46%; **9-OCH$_3$**, 35%; **10-OCH$_3$**, 32%). (c) H_2, 5% Pd/C, EtOAc, ambient temperature, 6 h (**1-OH**, 59%; **2-OH**, 65%; **3-OH**, 64%; **4-OH**, 70%; **5-OH**, 57%; **6-OH**, 61%; **7-OH**, 73%; **8-OH**, 73%; **9-OH**, 46%; **10-OH**, 58%). (d) (1) MsCl, Et_3N, CH_2Cl_2, rt, 30 min; (2) NaI, DBU, DMF, 80 °C, 30 min; (3) $BH_3{\cdot}SMe_2$, THF, rt, 1 h, and then saturated aqueous $NaHCO_3$, 30% aqueous H_2O_2 (3 steps, **35**, 13%; **37**, 15%; **36**, 15%; **38**, 16%; **40**, 23%). (e) (1) MsCl, Et_3N, CH_2Cl_2, rt, 30 min; (2) super-H, THF, rt for **5-H**–**9-H**, 60 °C for **10-H**, 2.5 h; (3) H_2, 5% Pd/C, EtOAc, ambient temperature, 4 h (3 steps, **5-H**, 27%; **6-H**, 24%; **7-H**, 12%; **8-H**, 15%; **9-H**, 24%; **10-H**, 13%).

145.0 (C-4, C-4′), 146.6 (C-3, C-3′); MS (EI) *m*/*z* 404 (M^+, 51), 175 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_7$ (M^+) 404.1835, found 404.1833.

*(7S,7′S,8R,8′R)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, **11** (**4-OCH$_3$**):* colorless crystals; mp 130–131 °C; $[\alpha]^{20}_D$ −29 (*c* 0.4, $CHCl_3$); NMR data agreed with those of **8**.

*(7R,7′R,8R,8′R)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, **35**, and (7R,7′R,8R,8′S)-4,4′-dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, **37**:* **35**, colorless oil; $[\alpha]^{20}_D$ +44 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50–2.70 (2H, br, OH), 2.67 (2H, m, H-8, H-8′), 3.03–3.10 (2H, m, H-9a, H-9′a), 3.46 (2H, br d, *J* = 8.0 Hz, H-9b, H-9′b), 3.87 (6H, s, OCH_3), 5.12 (4H, s, OCH_2Ph), 5.48 (2H, d, *J* = 6.8 Hz, H-7, H-7′), 6.77 (2H, d, *J* = 8.4 Hz, H-5, H-5′), 6.84–6.86 (4H, m, H-2, H-2′, H-6, H-6′), 7.29–7.30 (2H, m, OBn), 7.34–7.36 (4H, m, OBn), 7.41–7.43 (4H, m, OBn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.1 (C-8, C-8′), 56.1 (OCH_3), 62.6 (C-9, C-9′), 71.2 (OCH_2Ph), 82.5 (C-7, C-7′), 110.1 (C-2, C-2′), 114.1 (C-5, C-5′), 118.4 (C-6, C-6′), 127.28 (OBn), 127.33 (OBn), 127.9 (OBn), 128.5 (OBn), 133.6 (C-1, C-1′), 137.1 (OBn), 147.7 (C-4, C-4′), 149.7 (C-3, C-3′); MS (EI) *m*/*z* 556 (M^+, 1.5), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{34}H_{36}O_7$ (M^+) 556.2462, found 556.2470. **37**, colorless oil; $[\alpha]^{20}_D$ +66 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (2H, m, H-8, H-8′), 2.78 (2H, br s, OH), 3.28 (1H, br d, *J* = 10.2 Hz, H-9a), 3.60 (1H, dd, *J* = 10.2, 10.2 Hz, H-9b), 3.72–3.85 (2H, m, H-9′), 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.91 (1H, d, *J* = 9.0 Hz, H-7′), 5.12 (2H, s, OCH_2Ph), 5.13 (2H, s, OCH_2Ph), 5.43 (1H, d, *J* = 4.7 Hz, H-7), 6.78 (1H, dd, *J* = 8.3, 1.6 Hz, H-6), 6.82–6.86 (3H, m, H-5, H-5′, H-6′), 6.90 (1H, d, *J* = 1.8 Hz. H-2), 6.95 (1H, d, *J* = 1.6 Hz, H-2′), 7.27–7.30 (2H, m, OBn), 7.33–7.36 (4H, m, OBn), 7.41–7.42 (4H, m, OBn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.4 (C-8), 54.3 (C-8′), 56.09 (OCH_3), 56.11 (OCH_3), 59.8 (C-9′), 59.9 (C-9), 71.18 (OCH_2Ph), 71.23 (OCH_2Ph), 81.0 (C-7), 83.0 (C-7′), 109.6 (C-2′), 109.7 (C-2), 114.2 (C-5), 114.3 (C-5′), 117.9 (C-6′), 118.4 (C-6), 127.28 (OBn), 127.34 (OBn), 127.8 (OBn), 127.9 (OBn), 128.5 (OBn), 132.4 (C-1), 135.7 (C-1′), 137.15 (OBn), 137.18 (OBn), 147.4 (C-4), 147.9 (C-4′), 149.8 (C-3), 150.0 (C-3′); MS (EI) *m*/*z* 556 (M^+, 0.3), 137 (31), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{34}H_{36}O_7$ (M^+) 556.2462, found 556.2467.

*(7S,7′S,8S,8′S)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, **36**, and (7S,7′S,8S,8′R)-4,4′-dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, **38**:* **36**, colorless oil; $[\alpha]^{20}_D$ −44

dx.doi.org/10.1021/jf4046396 | J. Agric. Food Chem. 2014, 62, 651–659

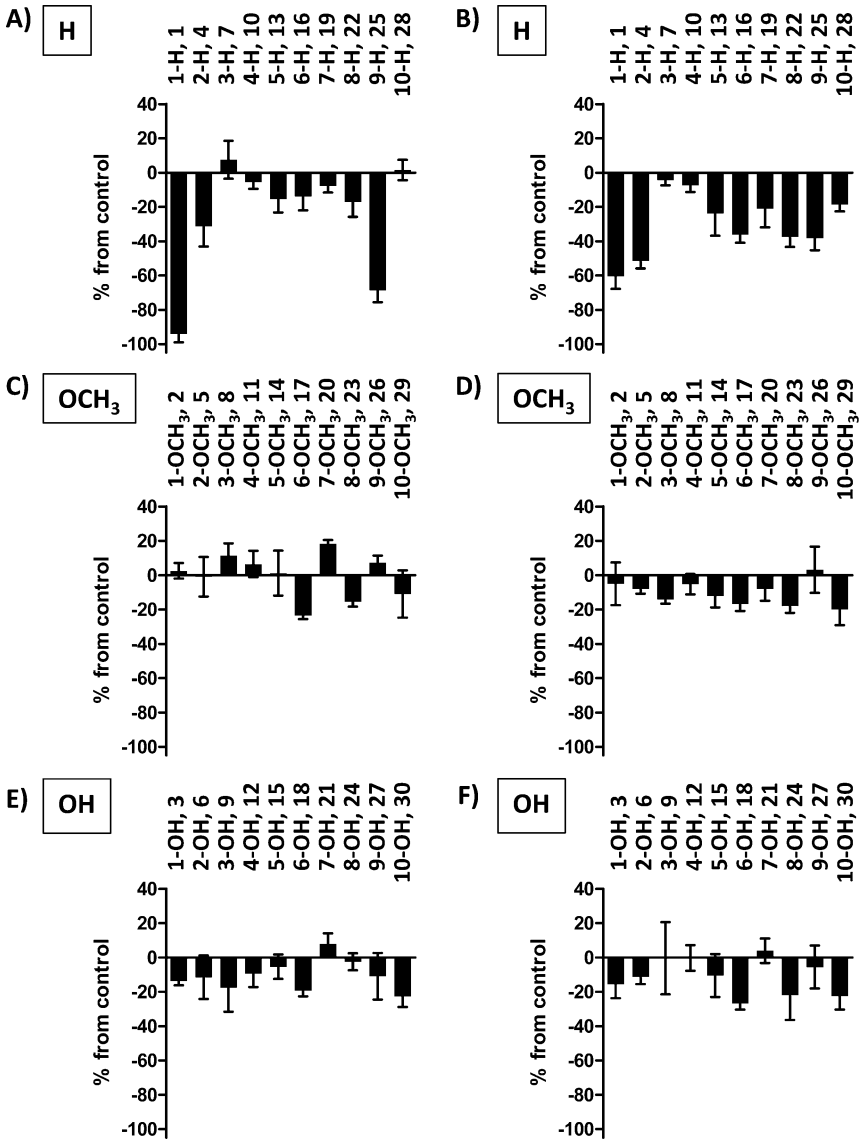

Figure 3. Plant growth inhibitory activity (percent from control) of test chemicals against root (A, C, E) and shoot (B, D, F) of lettuce when applied at the concentration of 1×10^{-3} M. Data are presented as the mean ± standard error of the mean.

(*c* 1.1, $CHCl_3$). **38**, colorless oil; $[\alpha]^{20}_D$ −66 (*c* 1.2, $CHCl_3$). NMR data of **36** and **38** agreed with those of **35** and **37**, respectively.

(7R,7′R,8R,8′R)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***14 (5-OCH$_3$):*** colorless oil; $[\alpha]^{20}_D$ +21 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73 (2H, m, H-8, H-8′), 2.85 (2H, dd, *J* = 9.4, 6.7 Hz, H-9a, H-9′a), 3.13 (2H, dd, *J* = 9.4, 2.6 Hz, H-9b, H-9′b), 3.16 (6H, s, 9-OCH_3, 9′-OCH_3), 3.90 (6H, s, 3-OCH_3, 3′-OCH_3), 5.54 (2H, d, *J* = 6.6 Hz, H-7, H-7′), 5.57 (2H, s, ArOH), 6.84 (2H, dd, *J* = 8.2, 1.5 Hz, H-6, H-6′), 6.89−6.90 (4H, m, H-2, H-2′, H-5, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.4 (C-8, C-8′), 56.0 (9-OCH_3, 9′-OCH_3), 58.7 (3-OCH_3, 3′-OCH_3), 71.9 (C-9, C-9′), 82.4 (C-7, C-7′), 109.0 ((C-2, C-2′), 114.0 (C-5, C-5′), 119.3 (C-6, C-6′), 132.3 (C-1, C-1′), 144.7 (C-4, C-4′), 146.3 (C-3, C-3′); MS (EI) *m*/*z* 404 (M^+, 14), 210 (100), 194 (53), 175 (94); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_7$ (M^+) 404.1835, found 404.1831.

(7S,7′S,8S,8′S)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***17 (6-OCH$_3$):*** colorless oil; $[\alpha]^{20}_D$ −20 (*c* 0.1, $CHCl_3$); NMR data agreed with those for **14**.

(7R,7′R,8R,8′S)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***20 (7-OCH$_3$):*** colorless oil; $[\alpha]^{20}_D$ +39 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (1H, m, H-8′), 2.74 (1H, m, H-8), 3.09 (1H, dd, *J* = 9.8, 5.3 Hz, H-9a), 3.12 (3H, s, 9-OCH_3), 3.21 (1H, dd, *J* = 9.8, 4.1 Hz, H-9b), 3.30 (3H, s, 9′-OCH_3), 3.44 (1H, dd, *J* = 9.3, 5.8 Hz, H-9′a), 3.62 (1H, dd, *J* = 9.3, 8.5 Hz, H-9′b), 3.895 (3H, s, 3-OCH_3), 3.899 (3H, s, 3′-OCH_3), 4.98 (1H, d, *J* = 8.5 Hz, H-7′), 5.44 (1H, d, *J* = 6.2 Hz, H-7), 5.56 (1H, s, ArOH), 5.57 (1H, s, ArOH), 6.83 (1H, dd, *J* = 8.1, 1.5 Hz, H-6), 6.85−6.91 (3H, m, H-5, H-5′, H-6′), 6.95 (1H, d, *J* = 1.5 Hz, H-2), 7.03 (1H, d, *J* = 1.5 Hz, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.2 (C-8), 51.7 (C-8′), 56.0 (9-OCH_3, 9′-OCH_3), 58.5 (3-OCH_3), 58.8 (3′-OCH_3), 69.3 (C-9), 70.5 (C-9′), 82.7 (C-7′), 83.6 (C-7), 108.5 (C-2′), 109.1 (C-2), 113.8 (C-5), 114.1 (C-5′), 119.20 (C-6′), 119.23 (C-6), 131.8 (C-1), 135.4 (C-1′), 145.1 (C-4, C-4′), 146.3 (C-3), 146.7 (C-3′); MS (EI) *m*/*z* 404 (M^+, 28), 210 (51), 207 (63), 175 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_7$ (M^+) 404.1835, found 404.1836.

(7R,7′R,8R,8′S)-3,3′-Dimethoxy-7,7′-epoxylignane-4,4′,9,9′-tetraol, ***21 (7-OH):*** colorless oil; $[\alpha]^{20}_D$ +56 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 2.71 (2H, m, H-8, H-8′), 3.53 (1H, dd, *J* = 11.5, 8.8 Hz, H-9), 3.68 (1H, dd, *J* = 11.5, 4.5 Hz, H-9), 3.80−3.92 (2H, overlapped, H-9′, H-9′), 3.85 (3H, s, 3-OCH_3), 3.88 (3H, s, 3′-OCH_3), 4.98 (1H, d, *J* = 8.5 Hz, H-7′), 5.47 (1H, d, *J* = 5.4 Hz, H-7), 6.77−6.83 (3H, m, H-5, H-5′, H-6), 6.86 (1H, dd, *J* = 8.3, 1.8 Hz, H-6′), 6.97 (1H, d, *J* = 1.4 Hz, H-2), 7.01 (1H, d, *J* = 1.8 Hz, H-2′); ^{13}C NMR (125 MHz, CD_3OD) δ 55.4 (C-8, C-8′), 56.46 (3-OCH_3), 56.51 (3′-OCH_3), 60.0 (C-9), 60.5 (C-9′), 83.1 (C-7′), 84.7 (C-7), 110.88 (C-2′), 110.94 (C-2), 116.0 (C-5), 116.2 (C-5′), 119.8 (C-6′),

dx.doi.org/10.1021/jf4046396 | J. Agric. Food Chem. 2014, 62, 651−659

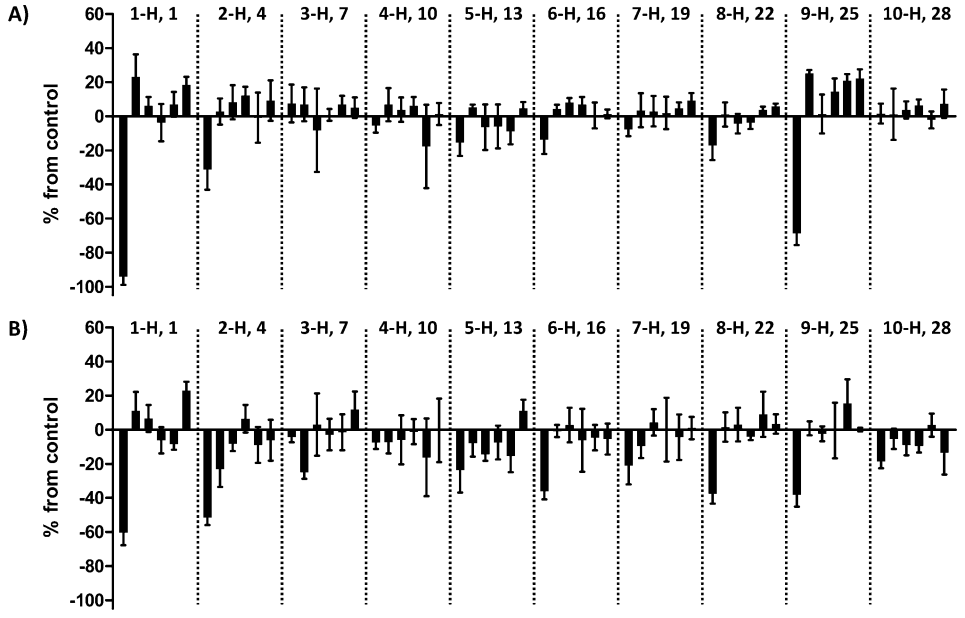

Figure 4. Plant growth inhibitory activity (percent from control) of **1-H**−**10-H** against root (A) and shoot (B) of lettuce when applied at concentrations from 1×10^{-3} to 1×10^{-8} M (from left to right for each compound). The plant growth activity of the commercial herbicide, diuron, was as follows: for root (1×10^{-3}−1×10^{-8} M), −48.5 ± 1.78%, −37.6 ± 1.48%, −9.9 ± 3.05%, −2.8 ± 5.09%, −8.2 ± 4.04%, and 0.0 ± 7.85%; for shoot (1×10^{-3}−1×10^{-8} M), −29.9 ± 5.09%, −23.7 ± 1.06%, +7.8 ± 6.67%, +13.9 ± 6.24,% +8.1 ± 6.24%, and +9.0 ± 1.55%. Data are presented as the mean ± standard error of the mean.

120.2 (C-6), 132.3 (C-1), 135.6 (C-1′), 146.8 (C-4), 147.3 (C-4′), 148.9 (C-3), 149.2 (C-3′); MS (EI) *m*/*z* 376 (M^+, 49), 193 (79), 175 (86), 151 (100), 137 (84); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_7$ (M^+) 376.1522, found 376.1519.

(7S,7′S,8S,8′R)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***23 (8-OCH$_3$):*** colorless oil; $[\alpha]^{20}_D$ −39 (*c* 0.2, $CHCl_3$); NMR data agreed with those of **20**.

(7S,7′S,8S,8′R)-3,3′-Dimethoxy-7,7′-epoxylignane-4,4′,9,9′-tetraol, ***24 (8-OH):*** colorless oil; $[\alpha]^{20}_D$ −56 (*c* 0.1, MeOH); NMR data agreed with those of **21**.

(7R,7′S,8S,8′R)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, ***39:*** colorless crystals; mp 79−80 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (2H, m, H-8, H-8′), 3.19 (2H, br s, OH), 3.75 (2H, dd, *J* = 11.4, 2.6 Hz, H-9, H-9′), 3.87 (6H, s, OCH_3), 3.89 (2H, dd, *J* = 11.4, 3.9 Hz, H-9, H-9′), 4.62 (2H, d, *J* = 7.3 Hz, H-7, H-7′), 5.14 (4H, s, OCH_2Ph), 6.85 (2H, d, *J* = 8.3 Hz, H-5, H-5′), 6.89 (2H, dd, *J* = 8.3, 1.8 Hz, H-6, H-6′), 6.99 (2H, d, *J* = 1.8 Hz), 7.28−7.30 (2H, m, OBn), 7.34−7.37 (4H, m, OBn), 7.42−7.43 (4H, m, OBn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.6 (C-8, C-8′), 56.0 (OCH_3), 60.4 (C-9, C-9′), 71.1 (OCH_2Ph), 82.1 (C-7, C-7′), 110.4 (C-2, C-2′), 114.0 (C-5, C-5′), 118.8 (C-6, C-6′), 127.3 (OBn), 127.8 (OBn), 128.5 (OBn), 134.3 (C-1, C-1′), 137.1 (OBn), 148.0 (C-4, C-4′), 149.8 (C-3, C-3′). Anal. Found: C, 73.40%; H, 6.34%. Calcd for $C_{34}H_{36}O_7$: C, 73.36%; H, 6.52%.

(7R,7′S,8S,8′R)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***26 (9-OCH$_3$):*** colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (2H, m, H-8, H-8′), 3.34 (6H, s, 9-OCH_3, 9′-OCH_3), 3.50 (2H, dd, *J* = 9.5, 5.0 Hz, H-9a, H-9′s), 3.57 (2H, dd, *J* = 9.5, 6.3 Hz, H-9b, H-9′b), 3.84 (6H, s, 3-OCH_3, 3′-OCH_3), 4.82 (2H, d, *J* = 6.6 Hz, H-7, H-7′), 5.71 (2H, s, 4-OH, 4′-OH), 6.87 (2H, d, *J* = 8.0 Hz, H-5, H-5′), 6.92 (2H, dd, *J* = 8.0, 1.8 Hz, H-6, H-6′), 6.96 (2H, d, *J* = 1.8 Hz, H-2, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.0 (C-8, C-8′), 55.8 (9-OCH_3, 9′-OCH_3), 58.9 (3-OCH_3, 3′-OCH_3), 70.6 (C-9, C-9′), 82.9 (C-7, C-7′), 109.3 (C-2, C-2′), 114.2 (C-5, C-5′), 119.4 (C-6, C-6′), 134.0 (C-1, C-1′), 145.1 (C-4, C-4′), 146.5 (C-3, C-3′); MS (EI) *m*/*z* 404 (M^+, 30), 210 (73), 194 (54), 175 (100), 151 (52); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_7$ (M^+) 404.1835, found 404.1835.

(7R,7′S,8R,8′S)-4,4′-Dibenzyloxy-3,3′-dimethoxy-7,7′-epoxylignane-9,9′-diol, ***40:*** colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (2H, br s, OH), 2.90 (2H, m, H-8, H-8′), 3.35 (2H, dd, *J* = 11.2, 3.7 Hz, H-9a, H-9′a), 3.43 (2H, dd, *J* = 11.2, 9.9 Hz, H-9b, H-9′b), 3.88 (6H, s, OCH_3), 5.11 (2H, d, *J* = 6.9 Hz, H-7, H-7′), 5.14 (4H, s, OCH_2Ph), 6.87 (4H, s, H-5, H-5′, H-6, H-6′), 6.95 (2H, s, H-2, H-2′), 7.28−7.31 (2H, m, OBn), 7.34−7.37 (4H, m, OBn), 7.42−7.44 (4H, m, OBn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.0 (C-8, C-8′), 56.0 (OCH_3), 60.9 (C-9, C-9′), 71.2 (OCH_2Ph), 80.9 (C-7, C-7′), 109.9 (C-2, C-2′), 114.1 (C-5, C-5′), 118.2 (C-6, C-6′), 127.3 (OBn), 127.9 (OBn), 128.6 (OBn), 132.1 (C-1, C-1′), 137.1 (OBn), 147.5 (C-4, C-4′), 149.6 (C-3, C-3′); MS (EI) *m*/*z* 556 (M^+, 0.4), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{34}H_{36}O_7$ (M^+) 556.2462, found 556.2464.

(7R,7′S,8R,8′S)-3,3′,9,9′-Tetramethoxy-7,7′-epoxylignane-4,4′-diol, ***29 (10-OCH$_3$):*** colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (2H, m, H-8, H-8′), 3.03 (2H, dd, *J* = 9.6, 6.1 Hz, H-9a, H-9′a), 3.05 (6H, s, 9-OCH_3, 9′-OCH_3), 3.26 (2H, dd, *J* = 9.6, 6.2 Hz, H-9b, H-9′b), 3.91 (6H, s, 3-OCH_3, 3′-OCH_3), 5.17 (2H, d, *J* = 7.0 Hz, H-7, H-7′), 5.59 (2H, s, 4-OH, 4′-OH), 6.91 (2H, d, *J* = 8.1 Hz, H-5, H-5′), 6.97 (2H, dd, *J* = 8.1, 1.4 Hz, H-6, H-6′), 7.07 (2H, d, *J* = 1.4 Hz, H-2, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.5 (C-8, C-8′), 55.9 (9-OCH_3, 9′-OCH_3), 58.4 (3-OCH_3, 3′-OCH_3), 70.2 (C-9, C-9′), 81.5 (C-7, C-7′), 109.5 (C-2, C-2′), 113.9 (C-5, C-5′), 119.5 (C-6, C-6′), 131.2 (C-1, C-1′), 144.6 (C-4, C-4′), 146.1 (C-3, C-3′); MS (EI) *m*/*z* 404 (M^+, 32), 175 (100); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_7$ (M^+) 404.1835, found 404.1831.

(7R,7′S,8R,8′S)-3,3′-Dimethoxy-7,7′-epoxylignane-4,4′,9,9′-tetraol, ***30 (10-OH):*** colorless oil; ^{1}H NMR (500 MHz, CD_3OD) δ 2.91 (2H, m, H-8, H-8′), 3.29 (2H, dd, *J* = 11.2, 4.2 Hz, H-9a, H-9′a), 3.44 (2H, dd, *J* = 11.2, 10.2 Hz, H-9b, H-9′b), 4.84 (6H, s, OCH_3), 5.13 (2H, d, *J* = 6.9 Hz, H-7, H-7′), 6.82 (2H, d, *J* = 8.1 Hz, H-5, H-5′), 6.89 (2H, dd, *J* = 8.1, 1.7 Hz, H-6, H-6′), 7.02 (2H, d, *J* = 1.7 Hz, H-2, H-2′); ^{13}C NMR (125 MHz, CD_3OD) δ 49.4 (C-8, C-8′), 56.4 (OCH_3), 61.4 (C-9, C-9′), 82.6 (C-7, C-7′), 111.1 (C-2, C-2′), 116.1 (C-5, C-5′), 120.0 (C-6, C-6′), 131.9 (C-1, C-1′), 146.9 (C-4, C-4′), 148.9 (C-3, C-3′); MS (EI) *m*/*z* 376 (M^+, 43), 224 (54), 193 (81), 175 (100), 151 (66), 137 (69); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_7$ (M^+) 376.1522, found 376.1523.

Evaluation of Plant Growth Inhibitory Activity. For all of the synthesized epoxylignane derivatives, their plant growth inhibitory activities were evaluated using lettuce (*L. sativa* L., green-wave (Takii Seed Co. Ltd., Kyoto, Japan)) and Italian ryegrass (*L. multiflorum* Lam., wase-fudo (Takii Seed Co. Ltd., Kyoto, Japan)), according to our earlier paper.[2] Briefly, 30 seeds of each plant were placed on a filter paper (in a 90 mm Petri dish) moisturized with 3 mL of water

dx.doi.org/10.1021/jf4046396 | J. Agric. Food Chem. 2014, 62, 651−659

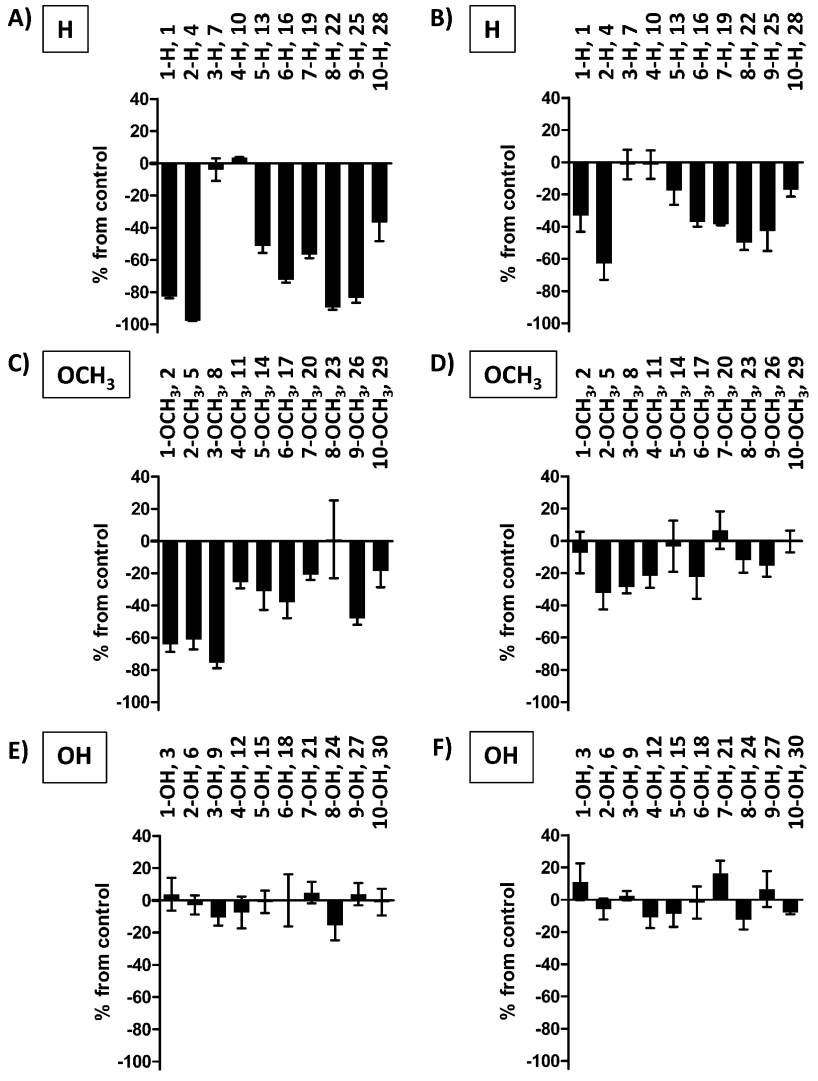

Figure 5. Plant growth inhibitory activity (percent from control) of test chemicals against root (A, C, E) and shoot (B, D, F) of ryegrass when applied at the concentration of 1×10^{-3} M. Data are presented as the mean ± standard error of the mean.

containing each sample at the concentration of 1.0 mM. After they were incubated in the dark at 20 °C for 3 and 5 days for lettuce and grass, respectively, the lengths of their roots and shoots were measured using a ruler. Experiments were performed in triplicate, and statistical analyses were conducted by one-way ANOVA followed by Tukey's multiple-comparison test using PRISM software (Graphpad Software, San Diego, CA, USA).

For compounds **1-H** and **2-H**, the germination rates of lettuce and grass seeds were recorded 3 days after seeding.

RESULTS AND DISCUSSION

The intermediates **31**−**34** and **39** were synthesized according to the previously described method with modification.[17−19] The mesylation of the two hydroxyl groups, followed by reduction, gave dimethyl compounds. To obtain **1-H**, **2-H**, **3-H**, and **4-H**, $NaBH_4$ in hexamethylphosphoramide (HMPA) was employed for the corresponding mesylates. On the other hand, lithium triethylborohydride (superhydride) was used for reduction of mesylate from the intermediate **39**, giving **9-H**. To prepare the intermediates **35** and **37**, compound **33** was selected as a starting compound. After conversion of **33** to the corresponding conjugated diene by elimination, hydroboration was tried to give two stereoisomers **35** and **37**. By the same procedure, **36** and **38** were obtained from diol **34**. The intermediate **40** was obtained by the isomerization of **39** using elimination followed by hydroboration. The intermediates **35**−**38** and **40** were subjected to mesylations followed by superhydride reductions, giving **5-H**, **6-H**, **7-H**, **8-H**, and **10-H**, respectively.

Among 10 stereoisomers of **H**-type epoxylignane (**1-H**−**10-H**), the compounds with the configurations of 7*S*,7′*R*,8*R*,8′*R* (**1-H**) and 7*R*,7′*S*,8*R*,8′*S* (**9-H**) suppressed the growth of lettuce root to −94 and −69%, respectively, whereas the other stereoisomers showed less activity (from −25 to +7.5%) (Figure 3A). Against the lettuce shoot (Figure 3B), −60 and −52% inhibitions relative to the control were observed for **1-H** and **2-H**, respectively. On the other hand, **5-H**, **6-H**, **7-H**, **8-H**, and **9-H** suppressed the shoot growth moderately (from −20 to −40%), but statistically insignificant relative to the control. The application of **3-H**, **4-H**, and **10-H** did not influence the lettuce shoot growth. With these results taken together, **1-H** showed the highest potency against lettuce. Introduction of the methoxy and hydroxyl groups to the 9 and 9′ carbon atoms (**1-OCH_3**−**10-OCH_3** and **1-OH**−**10-OH**) induced the absolute values of the growth rate below 25% (Figure 3C−F), demonstrating that the modification of the 9 and 9′ carbon atoms with the methoxy and hydroxyl groups influences the

dx.doi.org/10.1021/jf4046396 | J. Agric. Food Chem. 2014, 62, 651−659

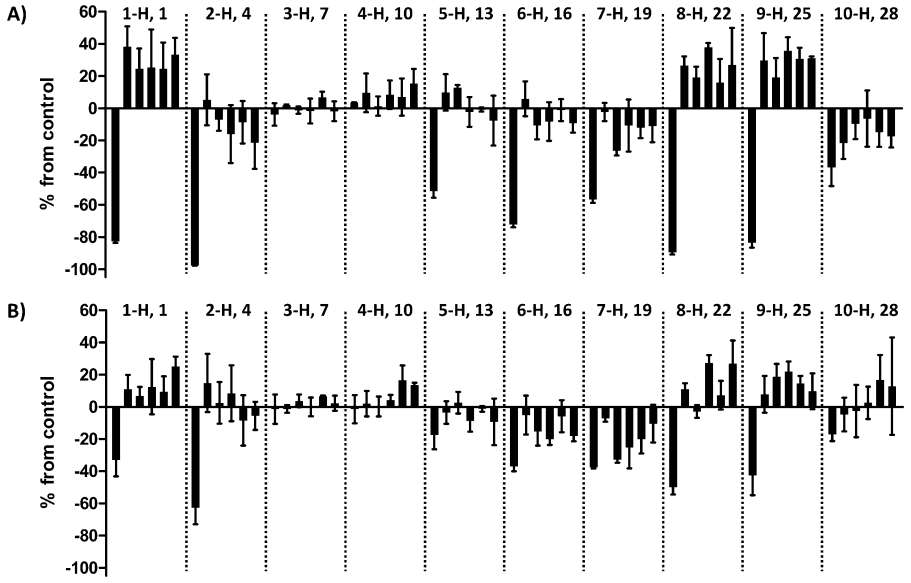

Figure 6. Plant growth inhibitory activity (precent from control) of **1-H**−**10-H** against root (A) and shoot (B) of ryegrass when applied at concentrations from 1×10^{-3} to 1×10^{-8} M (from left to right for each compound). The plant growth activity of the commercial herbicide, diuron, was as follows: for root (1×10^{-3}−1×10^{-8} M), −78.2 ± 3.79%, −49.8 ± 2.47%, −21.8 ± 8.69%, −4.83 ± 1.29%, −0.02 ± 6.1%3, and −9.70 ± 8.83%; for shoot (1×10^{-3}−1×10^{-8} M), −66.7 ± 8.15%, −32.9 ± 6.29%, −24.1 ± 8.59%, −21.9 ± 3.19%, −15.8 ± 5.54%, and −25.4 ± 5.52%. Data are presented as the mean ± standard error of the mean.

activity adversely. At the dose-dependent assay for evaluating the influence on the lettuce growth of the **H**-type epoxylignane compounds, the compounds did not influence the root growth at the diluted concentrations (Figure 4A). The inhibitory activity of **2-H** against the lettuce shoot decreased depending on the dilution of the concentration, but no significant activity was observed for the other compounds at the tested concentrations (Figure 4B).

Ryegrass root was found to be more sensitive to the epoxylignanes than lettuce root (Figure 5). Among the **H**-type epoxylignanes, not only the compounds **1-H** and **9H**, which were active to the lettuce root, but also **2-H**, **5-H**, **6-H**, **7-H**, and **8-H** suppressed the growth of the grass root below −50%, whereas **3-H** and its enantiomer **4-H**, which have the configuration of all *R* and all *S*, respectively, did not show any inhibitory activity (Figure 5A). Among these epoxylignanes, compound **2-H** with the 7*R*,7′*S*,8*S*,8′*S* configuration was the most potent compound, which could suppress the growth of the root almost completely at 1×10^{-3} M. The order of the sensitivity of the grass shoot to the **H**-type epoxylignanes was likely to be similar to that of the sensitivity of the grass root, although the sensitivity of the shoot was relatively less than that of the root (Figure 5A vs 5B). Introduction of the methoxy group induced less activity except the compounds with the configuration of all *R* and all *S*; especially the inhibitory activity of the all *R* configuration compound **3-H**, which showed no activity to the grass shoot, was strengthened up to −76% from control by attaching the methoxy group (**3-OCH$_3$**, Figure 5C). The inhibitory activity against the grass shoot of the compounds having the methoxy group was weak (Figure 5D). The compounds having the hydroxyl group did not influence the growth of grass root as well as shoot (Figure 5E,F). At the dose-dependent assay for evaluating the influence on the grass of the **H**-type epoxylignane compounds, compounds **1-H**, **8-H**, and **9-H** showed a promotive effect on the growth of grass root at diluted concentrations (Figure 6).

The phytotoxicity of all stereoisomers of lariciresinol has been evaluated in our previous paper,[2] in which (−)-lariciresinol and its 7*S*,8*S*,8′*R* stereoisomer have been found to inhibit the growth of Italian ryegrass as well as suppress the germination of the ryegrass seed to some extent. The most potent compound in the present study, **2-H**, inhibited the root growth of ryegrass almost completely, demonstrating that lariciresinol, which suppressed the growth of ryegrass root to around 50%, was less potent than **2-H**. Lariciresinol has the hydroxyl group at the 9-position, and all of the **OH**-type epoxylignanes in the present study were slightly potent, suggesting that hydrophilic features of the compounds having a hydroxyl group at the 9-position should be adverse to the root growth of ryegrass. Because the substitution patterns on the epoxylignanes synthesized in this study are basically different from that of lariciresinol, the effects of the conformations of each compound on the phytotoxicity were not compared.

The germination rate of the lettuce seed applied by **1-H**, which showed the highest inhibitory activity against the lettuce root (Figure 3), was 92.5 ± 1.12% (mean ± SEM, $n = 3$), which was almost the same as the control (95.7 ± 2.15%, $n = 3$). Also, the germination rate of the ryegrass seed applied by **2-H**, which almost completely suppressed the growth of the ryegrass root (Figure 5), was 87.3 ± 2.07% ($n = 3$), which was a little smaller than that of the control (94.7 ± 2.78%, $n = 3$), suggesting that these potent epoxylignanes should not suppress the germination process of the seed, unlike lariciresinol,[2] but influence the development and growth process other than germination. Because the inhibitory effects of the compounds on the shoot of both lettuce and grass were similar (in Figures 3B and 5B, **3-H** and **4-H** were ineffective, but the others suppressed the growth to some degree), the target sites would be the same in both species, although the mode of action of these compounds remains unknown.

Among the epoxylignanes that have been isolated in the previous studies, the antifungal activity[5] and disruption of ion homeostasis of (−)-verrucosin (**1-H**)[22] have been reported.

dx.doi.org/10.1021/jf4046396 | J. Agric. Food Chem. 2014, 62, 651−659

Nectandrin B (**9-H**) was found to activate AMP-activated protein kinase[10,23] and endothelial nitric-oxide synthase phosphorylation,[24] to show neuroprotective effects,[25,26] antifungal,[27] and glucocorticoid receptor binding activity,[28] and to inhibit proliferation,[29,30] hydroxysteroid dehydrogenase,[30] aromatase,[30] topoisomerase,[31] melanin biosynthesis,[32] prostaglandin,[33] and platelet aggregation induction.[34] Tetrahydrofuroguaiacin B (**10-H**) also activated AMP-activated protein kinase.[10] The target sites in the plants of the epoxylignanes synthesized in the present study are still unclear, but the targets should strictly recognize the stereochemistry of the compounds, and the affinity to the target sites may be different among the stereoisomers, because these stereoisomers should have the same physicochemical properties such as hydrophobicity (Clog P) and acidity (pK_a), indicating that the potency of the systemic translocation to the target site would be similar.

In summary, stereoisomers of tetrasubstituted tetrahydrofuran type epoxylignanes were synthesized to evaluate their plant growth inhibitory activity, and it was suggested that the structures of these epoxylignanes should be strictly recognized by the targets in the plants. As seen in the recent reviews for lignans,[35,36] studies on the effect of its fine chemical structure of lignans on their biological activities should be performed routinely. To retrieve the information of the target sites of the epoxylignanes, the structure–activity relationship results in the present study should be useful, and the probe compound will be designed on the basis of the stereochemical structure of the highest potency compound in the future.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

Part of this study was performed at the INCS (Johoku station) of Ehime University. We are grateful to Marutomo Co. for financial support.

Notes

The authors declare no competing financial interest.

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