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First Discovery of Insecticidal Activity of 9,9′-Epoxylignane and Dihydroguaiaretic Acid against Houseflies and the Structure–Activity Relationship

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ABSTRACT: The insecticidal activity of (-)-(8*R*,8′*R*)-3,3′-dimethoxy-9,9′-epoxylignane-4,4′-diol (**1**) against houseflies was clarified for the first time. The activities of other stereoisomers were weaker than that of the (8*R*,8′*R*)-stereoisomer. In the course of research into structure–activity relationships involving 30 newly synthesized (8*R*,8′*R*)-derivatives, 5-fold higher activity (ED_{50} = 0.91 nmol/fly) was observed for (−)-(8*R*,8′*R*)-3,3′,4-trimethoxy-9,9′-epoxylignan-4′-ol (**21**) than for the naturally occurring compound (**1**). The activity of **1** was weaker than that of (−)-(8*R*,8′*R*)-dihydroguaiaretic acid ((−)-DGA) (**4**); however, compound **21** showed almost the same level of activity as **4**.

KEYWORDS: *lignan, 9,9′-epoxylignane, 3,4-divanillyltetrahydrofuran, dihydroguaiaretic acid, structure–activity relationship (SAR)*

INTRODUCTION

Lignans have been characterized as biologically active compounds[1,2] that can be expected to lead to new compounds for new medicines and pesticides. However, the effect of stereochemistry on biological activity has not been clarified in detail. Our efforts in lignan research are continuing to elucidate the stereochemistry–activity relationship. Tetrahydrofuran lignans, which have frequently been reported to be biosynthesized in plants,[3] are an interesting class of lignans with various biological activities. For example, antibacterial activity was observed in both 9,9′-epoxylignane (Figure 1, **1**–**3**) and 7,7′-dioxo-9,9′-epoxylignane,[4] whereas only 7,7′-dioxo-9,9′-epoxylignane showed antifungal activity.[5] We also reported the effects of the stereochemistry of trisubstituted tetrahydrofuran lignan on plant growth inhibitory activity.[6] On the other hand, dihydroguaiaretic acid (Figure 1, **4**–**6**), whose intramolecular etherification between the 9 and 9′ positions provides 9,9′-epoxylignane **1**–**3**, showed larvicidal activity against the mosquitoes *Culex pipiens*, and some of its derivatives with the substituted benzene ring killed the larvae within 30 min.[7] These results demonstrate that the stereochemistry, the bonding type of the phenylpropanoid unities, and the position of substituents on the benzene ring are important factors for determining the biological activity of tetrahydrofuran lignans and their related compounds.

Herein the insecticidal activities of stereoisomers of lignans, including disubstituted tetrahydrofuran lignan, 9,9′-epoxylignane (Figure 1, **1**–**3**), and dihydroguaiaretic acid (Figure 1, **4**–**6**), are reported, and their structure–insecticidal activity relationships are discussed. Among the three stereoisomers of 9,9′-epoxylignane, (−)-**1**[8] and *meso*-**3**[9] have been isolated from plants. The synthetic routes to (−)-**1** and (+)-**2** have been developed in our previous study.[10] However, a selective synthetic method of *meso*-**3** has not been reported. The first stereoselective preparation of *meso*-**3** is described in this paper. Moreover, 30 7-aryl derivatives of (−)-**1** were synthesized to elucidate the effect of the substituents on the insecticidal activity.

MATERIALS AND METHODS

Chemicals. Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, using TMS as a standard (0 ppm). MS data were measured with a JMS-MS700 V spectrometer, and optical rotation values were evaluated with a Jasco P-2100 polarimeter. Nomenclature of compounds follows the literature for lignans.[3] (8*R*,8′*R*)-(−)-**1** and (8*R*,8′*R*)-derivatives were synthesized according to the previously reported method from L-glutamic acid.[10] From D-glutamic acid, (8*S*,8′*S*)-(+)-**2** was obtained according to the same method.

*(8R,8′S)-3,3′-Methoxy-9,9′-epoxylignane-4,4′-diol, meso-Divanillyltetrahydrofuran (**3**).* A reaction mixture of benzyl ether **8**[9] (0.21 g, 0.39 mmol) and 20% $Pd(OH)_2/C$ (0.50 g) in THF (10 mL) was stirred under H_2 gas at the ambient temperature for 16 h before filtration. The filtrate was concentrated, and then the residue was applied to silica gel column chromatography (EtOAc/hexane = 1:1) to give *meso*-**3** (0.12 g, 0.35 mmol, 90%) as colorless crystals, mp 128–129 °C, 134–135 °C in the literature.[11] NMR data agreed with those of the literature.[11]

The (8*R*,8′*R*)-9,9′-epoxylignane derivatives **9**–**38** were synthesized from L-glutamic acid according to the previously described method.[10]

*(8R,8′R)-3′-Methoxy-9,9′-epoxylignan-4′-ol (**9**):* 2.4% from L-glutamic acid, colorless oil; $[\alpha]^{25}_{D}$ = −29 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14–2.25 (2H, m), 2.49 (1H, dd, *J* = 13.7, 8.6 Hz), 2.59 (1H, dd, *J* = 13.7, 8.2 Hz), 2.60 (1H, dd, *J* = 13.6, 6.4 Hz), 2.69 (1H, dd, *J* = 13.6, 6.4 Hz), 3.51–3.54 (2H, m), 3.82 (3H, s), 3.90 (1H, dd, *J* = 8.8, 6.9 Hz), 3.91 (1H, dd, *J* = 8.8, 6.9 Hz), 5.63 (1H, s), 6.54 (1H, d, *J* = 1.9 Hz), 6.58 (1H, dd, *J* = 8.0, 1.9 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 7.08–7.10 (2H, m), 7.18 (1H, m), 7.24–7.27 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1, 39.4, 46.4, 46.7, 55.8, 73.25, 73.33, 111.2, 114.3, 121.3, 126.1, 128.4, 128.7, 132.3, 140.4, 144.0, 146.4; MS (EI) *m*/*z* 298 (M^+, 89), 137 (100); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1568.

*(8R,8′R)-3′-Methoxy-9,9′-epoxylignane-2,4′-diol (**10**):* 0.7% from L-glutamic acid, colorless crystals; mp 121–122 °C; $[\alpha]^{25}_{D}$ = −25 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (1H, m), 2.35 (1H,

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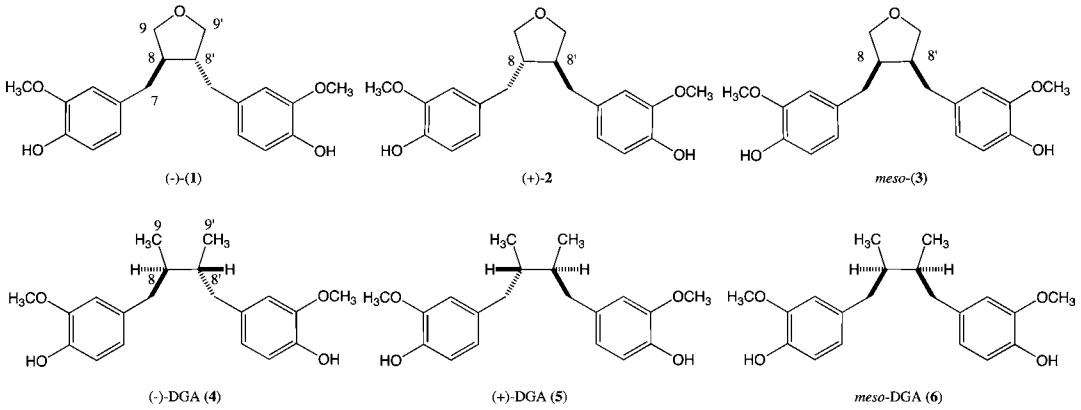

Figure 1. Stereoisomers of 9,9′-epoxylignanes and dihydroguaiaretic acid (DGA).

m), 2.48 (1H, dd, *J* = 13.8, 8.8 Hz), 2.62 (1H, dd, *J* = 13.6, 8.8 Hz), 2.64 (1H, dd, *J* = 13.8, 6.7 Hz), 2.70 (1H, dd, *J* = 13.6, 6.6 Hz), 3.54 (1H, dd, *J* = 8.7, 6.4 Hz), 3.59 (1H, dd, *J* = 8.7, 6.4 Hz), 3.80 (3H, s), 3.92 (1H, dd, *J* = 8.7, 7.2 Hz), 3.95 (1H, dd, *J* = 8.7, 7.2 Hz), 5.71 (1H, s), 6.16 (1H, s), 6.54 (1H, d, *J* = 1.9 Hz), 6.57 (1H, dd, *J* = 8.0, 1.9 Hz), 6.68 (1H, dd, *J* = 7.9, 1.0 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 6.81 (1H, dd, *J* = 7.5, 1.1 Hz), 7.00−7.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 38.9, 44.6, 46.6, 55.8, 73.2, 73.3, 111.3, 114.3, 115.3, 120.3, 121.3, 126.7, 127.5, 130.7, 132.4, 143.8, 146.4, 154.1; MS (EI) *m*/*z* 314 (M^+, 100), 138 (99); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1514.

(8R,8′R)-3′-Methoxy-9,9′-epoxylignane-3,4′-diol ***(11)****:* 0.6% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −37 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (2H, m), 2.46 (1H, dd, *J* = 13.6, 8.4 Hz), 2.49 (1H, dd, *J* = 13.6, 8.4 Hz), 2.59 (1H, dd, *J* = 13.6, 5.9 Hz), 2.62 (1H, dd, *J* = 13.6, 5.9 Hz), 3.55 (2H, dd, *J* = 8.6, 6.3 Hz), 3.79 (3H, s), 3.92 (1H, dd, *J* = 8.7, 6.8 Hz), 3.93 (1H, dd, *J* = 8.7, 6.8 Hz), 5.87 (1H, br s), 6.53−6.54 (2H, m), 6.56 (1H, dd, *J* = 9.2, 1.9 Hz), 6.60−6.65 (2H, m), 6.77 (1H, br s), 6.79 (1H, d, *J* = 7.9 Hz), 7.08 (1H, dd, *J* = 7.9, 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.8, 39.1, 46.1, 46.6, 55.9, 73.2, 73.3, 111.3, 113.2, 114.4, 115.7, 120.7, 121.3, 129.6, 132.2, 141.9, 143.9, 146.6, 156.2; MS (EI) *m*/*z* 314 (M^+, 95), 137 (100); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1526.

(8R,8′R)-3′-Methoxy-9,9′-epoxylignane-4,4′-diol ***(12)****:* 1.1% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −22 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (2H, m), 2.49 (1H, dd, *J* = 13.7, 7.5 Hz), 2.50 (1H, dd, *J* = 13.7, 7.5 Hz), 2.60 (2H, dd, *J* = 13.7, 6.1 Hz), 3.54 (1H, dd, *J* = 8.6, 6.0 Hz), 3.55 (1H, dd, *J* = 8.6, 5.9 Hz), 3.81 (3H, s), 3.93 (2H, dd, *J* = 8.6, 6.7 Hz), 5.72 (1H, br s), 6.21 (1H, br. s), 6.53 (1H, d, *J* = 1.9 Hz), 6.57 (1H, dd, *J* = 8.1, 1.9 Hz), 6.69−6.71 (2H, m), 6.80 (1H, d, *J* = 8.1 Hz), 6.90−6.92 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 39.0, 46.4, 46.5, 55.8, 73.25, 73.27, 111.2, 114.3, 115.3, 121.3, 129.7, 132.0, 132.2, 143.9, 146.5, 154.3; EIMS *m*/*z* 314 (M^+, 98), 137 (100), 107 (54); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1506.

(8R,8′R)-3′-Methoxy-9,9′-epoxylignane-3,4,4′-triol ***(13)****:* 0.6% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −39 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (2H, m), 2.42 (1H, dd, *J* = 13.7, 8.3 Hz), 2.47 (1H, dd, *J* = 13.5, 7.9 Hz), 2.54 (1H, dd, *J* = 13.7, 5.6 Hz), 2.59 (1H, dd, *J* = 13.5, 5.9 Hz), 3.52−3.56 (2H, m), 3.80 (3H, s), 3.91 (1H, dd, *J* = 6.0, 6.0 Hz), 3.93 (1H, dd, *J* = 6.2, 6.2 Hz), 5.83 (1H, br s), 6.30 (1H, br s), 6.45−6.72 (1H, br s), 6.46 (1H, br d, *J* = 8.0 Hz), 6.53 (2H, s), 6.55 (1H, br d, *J* = 8.1 Hz), 6.71 (1H, d, *J* = 8.0 Hz), 6.79 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 38.8, 46.2, 46.4, 55.9, 73.3, 111.3, 114.4, 115.2, 115.6, 120.8, 121.3, 132.2, 132.8, 142.3, 143.8, 146.5; MS (EI) *m*/*z* 330 (M^+, 95), 137 (100), 124 (98); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_5$ 330.1468, found 330.1474.

(8R,8′R)-3′-Methoxy-9,9′-epoxylignane-3,4′,5-triol ***(14)****:* 0.8% from L-glutamic acid, colorless crystals; mp 67−68 °C; $[\alpha]^{25}_D$ = −36 (*c* 0.8, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 2.17 (2H, m), 2.42 (1H, dd, *J* = 13.4, 8.6 Hz), 2.47 (1H, dd, *J* = 13.6, 8.5 Hz), 2.56 (1H, dd, *J* = 13.4, 5.8 Hz), 2.64 (1H, dd, *J* = 13.6, 5.6 Hz), 3.42 (1H, dd, *J* = 9.0, 6.6 Hz), 3.44 (1H, dd, *J* = 9.0, 6.6 Hz), 3.77−3.81 (2H, m), 3.82 (3H, s), 6.20−6.21 (3H, m), 6.62 (1H, dd, *J* = 8.0, 1.9 Hz), 6.73 (1H, d, *J* = 8.0 Hz), 6.76 (1H, d, *J* = 1.9 Hz), 7.30 (1H, s), 8.08 (2H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 39.5, 40.0, 47.3, 47.8, 56.3, 73.76, 73.81, 101.4, 108.2, 113.1, 115.7, 121.9, 133.1, 144.0, 145.7, 148.3, 159.4; MS (EI) *m*/*z* 330 (M^+, 24), 137 (100); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_5$ 330.1468, found 330.1465.

(8R,8′R)-3′-Methoxy-9,9′-epoxylignane-3,4,4′,5-tetraol ***(15)****:* 2.0% from L-glutamic acid, colorless crystals; mp 64−65 °C; $[\alpha]^{25}_D$ = −37 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 2.13 (2H, m), 2.37 (1H, dd, *J* = 13.4, 8.6 Hz), 2.44 (1H, dd, *J* = 13.4, 8.8 Hz), 2.50 (1H, dd, *J* = 13.5, 5.9 Hz), 2.61 (1H, dd, *J* = 13.5, 5.6 Hz), 3.35 (1H, dd, *J* = 8.5, 6.9 Hz), 3.46 (1H, dd, *J* = 8.8, 6.9 Hz), 3.80 (3H, s), 3.67−3.85 (2H, m), 6.27 (2H, s), 6.60 (1H, d, *J* = 8.0 Hz), 6.74 (1H, s), 6.75 (1H, d, *J* = 8.0 Hz), 7.36 (2H, br s), 7.73 (2H, br s); ^{13}C NMR (100 MHz, acetone-d_6) δ 39.45, 39.48, 47.5, 47.7, 56.3, 73.85, 73.92, 108.7, 113.0, 115.7, 122.0, 131.8, 132.9, 133.2, 145.6, 146.6, 148.2; MS (EI) *m*/*z* 346 (M^+, 50), 137 (100); HRMS (EI) *m*/*z* calcd for $C_{19}H_{22}O_6$ 346.1416, found 346.1424.

(8R,8′R)-9,9′-Epoxylignane-3,3′,4,4′,5-pentaol ***(16)****:* 0.1% from L-glutamic acid, yellowish crystals; mp 110−111 °C; $[\alpha]^{25}_D$ = −27 (*c* 0.3, acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 2.07−2.14 (2H, m), 2.33 (1H, dd, *J* = 13.5, 8.7 Hz), 2.40 (1H, dd, *J* = 13.6, 8.7 Hz), 2.53 (1H, dd, *J* = 13.5, 5.6 Hz), 2.60 (1H, dd, *J* = 13.6, 5.4 Hz), 3.37−3.60 (2H, m), 3.76 (1H, dd, *J* = 8.5, 6.8 Hz), 3.77 (1H, dd, *J* = 8.5, 6.8 Hz), 6.23 (2H, s), 6.51 (1H, dd, *J* = 8.1, 2.0 Hz), 6.67 (1H, d, *J* = 2.0 Hz), 6.72 (1H, d, *J* = 8.1 Hz), 6.90−7.50 (1H, br s), 7.66 (4H, br s); ^{13}C NMR (100 MHz, acetone-d_6) δ 39.2, 39.5, 47.7, 47.8, 73.68, 73.71, 108.5, 116.0, 116.6, 120.8, 131.8, 132.8, 133.4, 144.1, 145.8, 146.6; MS (EI) *m*/*z* 332 (M^+, 19), 139 (69), 123 (100); HRMS (EI) *m*/*z* calcd for $C_{18}H_{20}O_6$ 332.1260, found 332.1265.

(8R,8′R)-2,3′-Dimethoxy-9,9′-epoxylignan-4′-ol ***(17)****:* 1.7% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −27 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (1H, m), 2.30 (1H, m), 2.46 (1H, dd, *J* = 13.7, 8.8 Hz), 2.59−2.65 (2H, m), 2.72 (1H, dd, *J* = 13.4, 6.8 Hz), 3.49−3.55 (2H, m), 3.76 (3H, s), 3.82 (3H, s), 3.90 (2H, dd, *J* = 8.1, 7.6 Hz), 5.56 (1H, s), 6.52 (1H, br s), 6.56 (1H, br d, *J* = 8.1 Hz), 6.78 (1H, d, *J* = 7.5 Hz), 6.80 (1H, d, *J* = 8.1 Hz), 6.86 (1H, dd, *J* = 7.5, 7.2 Hz), 7.05 (1H, d, *J* = 7.2 Hz), 7.18 (1H, dd, *J* = 7.5, 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 33.8, 39.0, 44.5, 46.7, 55.1, 55.8, 73.3, 73.5, 110.2, 111.2, 114.2, 120.3, 121.3, 127.4, 128.8, 130.4, 132.6, 143.8, 146.3, 157.5; MS (EI) *m*/*z* 328 (M^+, 100), 138 (74); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1679.

(8R,8′R)-3,3′-Dimethoxy-9,9′-epoxylignan-4′-ol ***(18)****:* 1.4% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −35 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (2H, m), 2.50 (1H, dd, *J* = 13.7, 8.4 Hz), 2.56 (1H, dd, *J* = 13.6, 8.3 Hz), 2.60 (1H, dd, *J* = 13.7, 4.9 Hz), 2.66 (1H, dd, *J* = 13.6, 6.4 Hz), 3.52 (2H, dd, *J* = 7.4, 7.4 Hz), 3.77 (3H, s), 3.83 (3H, s), 3.88−3.93 (2H, m), 5.58 (1H, s), 6.54 (1H, d, *J* = 2.0 Hz), 6.59 (1H, d, *J* = 8.0 Hz), 6.63 (1H, s), 6.68 (1H, d, *J* = 7.6 Hz), 6.73 (1H, dd, *J* = 8.1, 2.0 Hz), 6.80 (1H, d, *J* = 8.1 Hz), 7.17 (1H, dd, *J* = 8.0, 7.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 39.1, 39.5, 46.3, 46.7,

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55.1, 55.8, 73.3, 73.4, 111.1, 111.3, 114.3, 114.5, 121.1, 121.3, 129.4, 132.3, 142.0, 144.0, 146.4, 159.7; MS (EI) m/z 328 (M^+, 95), 137 (79), 122 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1673.

(8R,8′R)-3′,4-Dimethoxy-9,9′-epoxylignan-4′-ol (**19**): 1.0% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -34$ (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (2H, m), 2.49 (1H, dd, J = 13.7, 8.3 Hz), 2.53 (1H, dd, J = 13.7, 8.2 Hz), 2.60 (1H, dd, J = 13.7, 6.1 Hz), 2.63 (1H, dd, J = 13.7, 6.4 Hz), 3.51 (1H, dd, J = 8.7, 6.1 Hz), 3.52 (1H, dd, J = 8.7, 6.1 Hz), 3.78 (3H, s), 3.83 (3H, s), 3.89 (1H, dd, J = 8.7, 6.7 Hz), 3.90 (1H, dd, J = 8.7, 6.7 Hz), 5.55 (1H, s), 6.53 (1H, d, J = 1.9 Hz), 6.59 (1H, dd, J = 8.1, 1.9 Hz), 6.78−6.81 (3H, m), 6.98−7.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 39.1, 46.56, 46.63 55.2, 55.8, 73.28, 73.33, 111.1, 113.8, 114.2, 121.3, 129.6, 132.3, 132.4, 143.9, 146.4, 157.9; MS (EI) m/z 328 (M^+, 85), 137 (79), 121 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1668.

(8R,8′R)-2,3′,4-Trimethoxy-9,9′-epoxylignan-4′-ol (**20**): 2.6% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -28$ (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (1H, m), 2.26 (1H, m), 2.46 (1H, dd, J = 13.8, 8.6 Hz), 2.55 (1H, dd, J = 13.8, 8.0 Hz), 2.61 (1H, dd, J = 13.8, 6.5 Hz), 2.65 (1H, dd, J = 13.8, 6.8 Hz), 3.50 (1H, dd, J = 8.6, 8.6 Hz), 3.52 (1H, dd, J = 8.6, 8.6 Hz), 3.73 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 3.88 (1H, dd, J = 8.6, 6.7 Hz), 3.90 (1H, dd, J = 8.6, 6.7 Hz), 5.61 (1H s), 6.37−6.39 (2H, m), 6.52 (1H, d, J = 1.7 Hz), 6.57 (1H, dd, J = 7.9, 1.7 Hz), 6.78 (1H, d, J = 7.9 Hz), 6.93 (1H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 39.1, 44.6, 46.6, 55.1, 55.3, 55.8, 73.3, 73.5, 98.3, 103.7, 111.1, 114.1, 121.2, 121.3, 130.5, 132.6, 143.8, 146.3, 158.3, 159.3; MS (EI) m/z 358 (M^+, 59), 151 (100); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1778.

(8R,8′R)-3,3′,4-Trimethoxy-9,9′-epoxylignan-4′-ol (**21**): 0.9% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -38$ (c 0.7, MeOH); NMR data agreed with those of the literature.[12]

(8R,8′R)-3,3′,5-Trimethoxy-9,9′-epoxylignan-4′-ol (**22**): 0.4% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -30$ (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (2H, m), 2.51 (1H, dd, J = 13.6, 8.1 Hz), 2.53 (1H, dd, J = 13.6, 8.0 Hz), 2.61 (2H, dd, J = 13.6, 6.4 Hz), 3.53 (2H, dd, J = 8.0, 5.9 Hz), 3.76 (6H, s), 3.84 (3H, s), 3.91 (1H, dd, J = 8.0, 7.1 Hz), 3.93 (1H, dd, J = 8.0, 7.1 Hz), 5.57 (1H, br s), 6.24 (2H, d, J = 2.2 Hz), 6.29 (1H, dd, J = 2.2, 2.2 Hz), 6.55 (1H, d, J = 1.8 Hz), 6.59 (1H, dd, J = 8.0, 1.8 Hz), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1, 39.8, 46.2, 46.7, 55.2, 55.8, 73.3, 73.4, 97.9, 106.8, 111.1, 114.2, 121.3, 132.3, 142.7, 143.9, 146.4, 160.7; MS (EI) m/z 358 (M^+, 32), 152 (100); HRMS (EI) m/z calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1773.

(8R,8′R)-3′-Methoxy-3,4-methylenedioxy-9,9′-epoxylignan-4′-ol (**23**): 1.1% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -47$ (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (2H, m), 2.50 (1H, dd, J = 13.7, 8.1 Hz), 2.51 (1H, dd, J = 13.7, 8.1 Hz), 2.58 (1H, dd, J = 13.7, 6.0 Hz), 2.59 (1H, dd, J = 13.7, 6.2 Hz), 3.50 (1H, dd, J = 8.8, 5.9 Hz), 3.52 (1H, dd, J = 8.8, 5.8 Hz), 3.84 (3H, s), 3.90 (1H, dd, J = 9.1, 6.7 Hz), 3.91 (1H, dd, J = 9.1, 6.7 Hz), 5.60 (1H, s), 5.91 (2H, s), 6.53 (1H, dd, J = 8.0, 1.3 Hz), 6.54 (1H, d, J = 1.3 Hz), 6.55 (1H, d, J = 2.0 Hz), 6.59 (1H, dd, J = 7.4, 2.0 Hz), 6.69 (1H, d, J = 7.4 Hz), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 39.15, 39.17, 46.5, 46.6, 55.8, 73.27, 73.31, 100.9, 108.1, 109.0, 111.2, 114.3, 121.3, 121.5, 132.3, 134.2, 144.0, 145.8, 146.4, 147.6; MS (EI) m/z 342 (M^+, 79), 137 (100); HRMS (EI) m/z calcd for $C_{20}H_{22}O_5$ 342.1465, found 342.1476.

(8R,8′R)-3,3′,4,5-Tetramethoxy-9,9′-epoxylignan-4′-ol (**24**): 0.3% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -26$ (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (2H, m), 2.52 (1H, dd, J = 13.7, 8.2 Hz), 2.56−2.61 (2H, m), 2.62 (1H, dd, J = 13.7, 8.2 Hz), 3.54 (1H, dd, J = 8.5, 2.0 Hz), 3.56 (1H, dd, J = 8.5, 2.1 Hz), 3.82 (9H, s), 3.83 (3H, s), 3.93 (1H, dd, J = 8.5, 6.1 Hz), 3.94 (1H, dd, J = 8.5, 6.1 Hz), 5.62 (1H, br s), 6.27 (2H, s), 6.55 (1H, d, J = 1.4 Hz), 6.60 (1H, dd, J = 8.1, 1.4 Hz), 6.81 (1H, d, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 40.0, 46.3, 46.6, 55.8, 56.1, 60.9, 73.2, 73.3, 105.5, 111.1, 114.2, 121.3, 132.2, 136.2, 136.3, 144.0, 146.5, 153.1; MS (EI) m/z 388 (M^+, 92), 182 (100); HRMS (EI) m/z calcd for $C_{22}H_{28}O_6$ 388.1886, found 388.1886.

(8R,8′R)-4-Ethoxy-3,3′-dimethoxy-9,9′-epoxylignan-4′-ol (**25**): 1.5% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -32$ (c 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7.1 Hz), 2.18 (2H, m), 2.517 (1H, dd, J = 13.7, 8.2 Hz), 2.524 (1H, dd, J = 13.8, 8.2 Hz), 2.61 (1H, dd, J = 13.7, 6.3 Hz), 2.62 (1H, dd, J = 13.8, 6.2 Hz), 3.525 (1H, dd, J = 8.6, 6.0 Hz), 3.526 (1H, dd, J = 8.6, 6.6 Hz), 3.826 (3H, s), 3.830 (3H, s), 3.91 (2H, dd, J = 8.6, 6.7 Hz), 4.06 (2H, q, J = 7.1 Hz), 5.55 (1H, s), 6.55 (1H, d, J = 2.0 Hz), 6.58 (1H, d, J = 2.0 Hz), 6.596 (1H, dd, J = 8.0, 2.0 Hz), 6.603 (1H, dd, J = 8.0, 2.0 Hz), 6.76 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9, 39.1, 39.2, 46.5, 46.7, 55.8, 55.9, 64.4, 73.28, 73.32, 111.2, 112.3, 112.8, 114.2, 120.6, 121.3, 132.3, 133.1, 144.0, 146.5, 146.7, 149.2; MS (EI) m/z 372 (M^+, 100), 137 (80); HRMS (EI) m/z calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1938.

(8R,8′R)-4-Isopropoxy-3,3′-dimethoxy-9,9′-epoxylignan-4′-ol (**26**): 2.1% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -33$ (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, d, J = 6.2 Hz), 2.19 (2H, m), 2.52 (1H, dd, J = 13.7, 8.2 Hz), 2.53 (1H, dd, J = 13.7, 8.1 Hz), 2.62 (2H, dd, J = 13.7, 5.7 Hz), 3.53 (1H, dd, J = 8.6, 6.2 Hz), 3.54 (1H, dd, J = 8.5, 6.3 Hz), 3.81 (3H, s), 3.83 (3H, s), 3.91 (1H, dd, J = 8.6, 6.7 Hz), 3.92 (1H, dd, J = 8.5, 6.7 Hz), 4.47 (1H, m), 5.58 (1H, s), 6.56 (1H, d, J = 1.9 Hz), 6.59−6.63 (3H, m), 6.79 (1H, d, J = 7.4 Hz), 6.80 (1H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.2, 39.10, 39.13, 46.5, 46.7, 55.8, 55.9, 71.5, 73.27, 73.34, 111.2, 112.6, 114.2, 116.0, 120.6, 121.3, 132.3, 133.5, 143.9, 145.6, 146.4, 150.3; MS (EI) m/z 386 (M^+, 100), 344 (73), 137 (81); HRMS (EI) m/z calcd for $C_{23}H_{30}O_5$ 386.2094, found 386.2093.

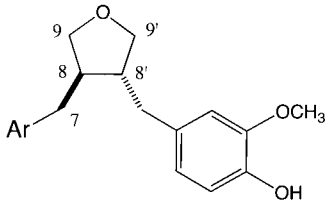
(8R,8′R)-4-Butoxy-3-methoxy-3′-methoxy-9,9′-epoxylignan-4′-ol (**27**): 2.3% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -35$ (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.7 Hz), 1.49 (2H, m), 1.81 (2H, m), 2.18 (2H, m), 2.53 (1H dd, J = 13.7, 8.2 Hz), 2.54 (1H, dd, J = 13.7, 8.2 Hz), 2.62 (2H, dd, J = 13.7, 6.2 Hz), 3.53 (1H, dd, J = 7.7, 6.1 Hz), 3.54 (1H, dd, J = 7.7, 6.1 Hz), 3.82 (3H, s), 3.83 (3H, s), 3.91 (2H, dd, J = 7.7, 6.9 Hz), 3.98 (2H, t, J = 7.7 Hz), 5.59 (1H, s), 6.54 (1H, d, J = 2.0 Hz), 6.58 (1H, d, J = 2.0 Hz), 6.60 (1H, dd, J = 8.1, 2.0 Hz), 6.61 (1H, dd, J = 8.2, 2.0 Hz), 6.76 (1H, d, J = 8.1 Hz), 6.80 (1H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.3, 31.3, 39.07, 39.14, 46.5, 46.7, 55.8, 56.0, 68.8, 73.28, 73.32, 111.1, 112.4, 112.9, 114.2, 120.6, 121.3, 132.3, 133.0, 143.9, 146.4., 146.9, 149.3; MS (EI) m/z 400 (M^+, 91), 137 (100); HRMS (EI) m/z calcd for $C_{24}H_{32}O_5$ 400.2250, found 400.2245.

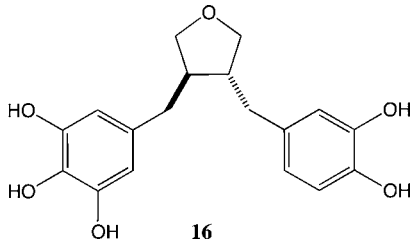
(8R,8′R)-3-Ethoxy-3′,4-dimethoxy-9,9′-epoxylignan-4′-ol (**28**). 1.8% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -34$ (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, t, J = 7.1 Hz), 2.18 (2H, m), 2.52 (1H, dd, J = 13.7, 8.2 Hz), 2.61 (1H, dd, J = 13.7, 6.2 Hz), 3.53 (2H, dd, J = 8.7, 5.7 Hz), 3.83 (3H, s), 3.84 (3H, s), 3.91 (2H, dd, J = 8.7, 5.7 Hz), 4.04 (2H, q, J = 7.1 Hz), 5.57 (1H, s), 6.54 (1H, d, J = 1.8 Hz), 6.58 (1H, d, J = 1.8 Hz), 6.59 (1H, dd, J = 8.0, 1.8 Hz), 6.61 (1H, dd, J = 8.2, 1.8 Hz), 6.76 (1H, d, J = 8.2 Hz), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 39.1, 39.2, 46.5, 46.6, 55.8, 56.0, 64.3, 73.29, 73.31, 111.1, 111.4, 113.4, 114.2, 120.6, 121.3, 132.3, 132.9, 143.9, 146.4, 147.6, 148.1; MS (EI) m/z 372 (M^+, 100), 165 (67), 137 (82); HRMS (EI) m/z calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1941.

(8R,8′R)-3-Isopropoxy-3′,4-dimethoxy-9,9′-epoxylignan-4′-ol (**29**): 2.5% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -30$ (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (6H, d, J = 6.0 Hz), 2.17 (2H, m), 2.51 (1H, dd, J = 13.6, 8.4 Hz), 2.52 (1H, dd, J = 13.7, 8.4 Hz), 2.61 (1H, dd, J = 13.6, 5.7 Hz), 2.62 (1H, dd, J = 13.7, 5.8 Hz), 3.53 (2H, dd, J = 8.7, 6.0 Hz), 3.82 (3H s), 3.84 (3H, s), 3.90 (1H, dd, J = 8.7, 6.9 Hz), 3.91 (1H, dd, J = 8.7, 6.7 Hz), 4.47 (1H, m), 5.59 (1H, s), 6.56 (1H, d, J = 1.9 Hz), 6.60 (1H, dd, J = 8.0, 1.9 Hz), 6.63 (1H, dd, J = 8.7, 2.1 Hz), 6.64 (1H d, J = 2.1 Hz), 6.76 (1H, d, J = 8.7 Hz), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.2, 38.9, 39.1, 46.67, 46.69, 55.8, 56.0, 71.5, 73.29, 73.34, 111.2, 112.0, 114.2, 116.9, 121.2, 121.3, 132.3, 132.9, 143.9, 146.4, 147.0, 148.9; MS (EI) m/z 386 (M^+, 99), 138 (100); HRMS (EI) m/z calcd for $C_{23}H_{30}O_5$ 386.2094, found 386.2091.

(8R,8′R)-3-Butoxy-4-methoxy-3′-methoxy-9,9′-epoxylignan-4′-ol (**30**): 1.6% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -30$ (c 0.5,

Table 1. Insecticidal Activities of Stereoisomers of 8,8′-Epoxylignane and Derivatives of (−)-1 against Houseflies (n = 3)[a]





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no.	Ar or structure	ED_{50} (nmol/fly)	no.	Ar or structure	ED_{50} (nmol/fly)
(−)-**1**	Ar = Ph(4-OH-3-OMe)	4.84 ± 0.71	**23**	Ar = Ph(3,4-OCH_2O)	3.40 ± 0.98
(+)-**2**	(8*S*,8′*S*), Ar = Ph(4-OH-3-OMe)	>6.93 (45%)	**24**	Ar = Ph(3,4,5-OMe)	5.02 ± 0.40
meso-**3**	*meso*, Ar = Ph(4-OH-3-OMe)	>6.93 (40%)	**25**	Ar = Ph(3-OMe-4-OEt)	1.07 ± 0.20
9	Ar = Ph	4.87 ± 1.25	**26**	Ar = Ph(3-OMe-4-OPr-i)	1.64 ± 0.41
10	Ar = Ph(2-OH)	1.80 ± 0.11	**27**	Ar = Ph(3-OMe-4-OBu)	3.35 ± 0.55
11	Ar = Ph(3-OH)	2.37 ± 0.78	**28**	Ar = Ph(3-OEt-4-OMe)	3.68 ± 0.29
12	Ar = Ph(4-OH)	4.23 ± 0.93	**29**	Ar = Ph(3-OPr-i-4-OMe)	>6.93 (36%)
13	Ar = Ph(3,4-OH)	4.05 ± 0.01	**30**	Ar = Ph(3-OBu-4-OMe)	3.59 ± 0.27
14	Ar = Ph(3,5-OH)	6.99 ± 1.45	**31**	Ar = Ph(3-Et-4-OMe)	2.45 ± 0.14
15	Ar = Ph(3,4,5-OH)	>6.93 (40%)	**32**	Ar = Ph(3-OMe-4-Et)	1.89 ± 0.09
16	pentanol	>6.93 (20%)	**33**	Ar = Ph(3,4-Me)	2.95 ± 0.38
17	Ar = Ph(2-OMe)	4.76 ± 2.25	**34**	Ar = Ph(3-OH-4-OMe)	4.44 ± 0.52
18	Ar = Ph(3-OMe)	2.53 ± 0.25	**35**	Ar = Ph(3-OEt-4-OH)	3.75 ± 0.86
19	Ar = Ph(4-OMe)	2.98 ± 0.33	**36**	Ar = Ph(2-OH-4,5-OMe)	>6.93 (47%)
20	Ar = Ph(2,4-OMe)	2.79 ± 0.59	**37**	Ar = Ph(3,5-OMe-4-OH)	3.36 ± 0.32
21	Ar = Ph(3,4-OMe)	0.91 ± 0.19	**38**	Ar = Ph(4-NMe_2)	4.53 ± 0.39
22	Ar = Ph(3,5-OMe)	2.73 ± 0.34			

[a]Imidacloprid (positive control): ED_{50} = 10.1 ± 0.90 pmol/fly.

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.4 Hz), 1.50 (2H, m), 1.82 (2H, m), 2.18 (2H, m), 2.52 (2H, dd, J = 13.7, 7.8 Hz), 2.61 (1H, dd, J = 13.7, 6.2 Hz), 2.62 (1H, dd, J = 13.7, 6.4 Hz), 3.53 (2H, d, J = 8.5, 5.8 Hz), 3.83 (6H, s), 3.91 (2H, dd, J = 8.5, 6.7 Hz), 3.96 (2H, t, J = 7.4 Hz), 5.55 (1H, s), 6.54 (1H, d, J = 1.8 Hz), 6.58−6.62 (3H, m), 6.75 (1H, d, J = 7.8 Hz), 6.80 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.3, 31.4, 39.1, 39.2, 46.6, 46.7, 55.8, 56.1, 68.7, 73.29, 73.32, 111.1, 111.7, 113.7, 114.2, 120.6, 121.3, 132.3, 133.0, 143.9, 146.4, 147.8, 148.5; MS (EI) m/z 400 (M^+, 100), 137 (77); HRMS (EI) m/z calcd for $C_{24}H_{32}O_5$ 400.2250, found 400.2248.

(8R,8′R)-3-Ethyl-3′,4-dimethoxy-9,9′-epoxylignan-4′-ol (**31**): 2.7% from L-glutamic acid, colorless crystals; mp 56−57 °C; $[\alpha]^{25}_D$ = −32 (c 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, t, J = 7.5 Hz), 2.18 (2H, m), 2.51 (1H, dd, J = 13.7, 8.6 Hz), 2.51−2.65 (5H, m), 3.52 (1H, dd, J = 8.7, 6.1 Hz), 3.53 (1H, dd, J = 8.6, 6.3 Hz), 3.79 (3H, s), 3.83 (3H, s), 3.90 (1H, dd, J = 8.7, 6.7 Hz), 3.91 (1H, dd, J = 8.7, 6.6 Hz), 5.56 (1H, br s), 6.55 (1H,d, J = 1.8 Hz), 6.59 (1H, dd, J = 7.9, 1.8 Hz), 6.71 (1H, d, J = 8.8 Hz), 6.80 (1H, d, J = 7.9 Hz), 6.86−6.87 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 23.3, 38.6, 39.1, 46.6, 46.7, 55.3, 55.8, 73.3, 73.4, 110.0, 111.0, 114.2, 121.3, 126.7, 129.4, 132.1, 132.4, 132.5, 143.9, 146.4, 155.7; MS (EI) m/z (%) 356 (M^+, 100), 149 (91); HRMS (EI) m/z calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1989.

(8R,8′R)-3,3′-Dimethoxy-4a,4b-dihomo-9,9′-epoxylignan-4′-ol (**32**): 1.6% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −38 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, t, J = 7.5 Hz), 2.20 (2H, m), 2.52 (1H, dd, J = 13.8, 8.2 Hz), 2.56−2.62 (4H, m), 2.65 (1H, dd, J = 13.8, 6.3 Hz), 3.53 (1H, dd, J = 8.7, 5.9 Hz), 3.55 (1H, dd, J = 8.7, 5.9 Hz), 3.78 (3H, s), 3.82 (3H, s), 3.92 (1H, dd, J = 8.7, 4.4 Hz), 3.93 (1H, dd, J = 8.7, 4.5 Hz), 5.55 (1H, s), 6.52 (1H, d, J = 1.5 Hz), 6.53 (1H, d, J = 1.8 Hz), 6.59 (1H, dd, J = 7.8, 1.8 Hz), 6.63 (1H, dd, J = 7.6, 1.5 Hz), 6.80 (1H, d, J = 7.8 Hz), 7.02 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.9, 39.2, 39.5, 46.4, 46.7, 55.2, 55.8, 73.3, 73.4, 110.7, 111.1, 114.2, 120.6, 121.3, 128.7, 130.3, 132.3, 139.1, 143.9, 146.4, 157.3; MS (EI) m/z 356 (M^+, 99), 150 (100), 137 (58); HRMS (EI) m/z calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.1991.

(8R,8′R)-3′-Methoxy-3a,4a-dihomo-9,9′-epoxylignan-4′-ol (**33**): 1.9% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −34 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.15−2.22 (2H, m), 2.22 (6H, s), 2.50 (1H, dd, J = 13.7, 8.2 Hz), 2.51 (1H, dd, J = 13.7, 8.1 Hz), 2.63 (1H, dd, J = 13.7, 3.1 Hz), 2.64 (1H, dd, J = 13.7, 3.1 Hz), 3.52 (1H, dd, J = 8.7, 6.1 Hz), 3.53 (1H, dd, J = 8.7, 6.1 Hz), 3.83 (3H, s), 3.90 (1H, dd, J = 8.7, 5.3 Hz), 3.92 (1H, dd, J = 8.7, 5.2 Hz), 5.58 (1H, s), 6.54 (1H, d, J = 1.8 Hz), 6.59 (1H, dd, J = 8.1, 1.8 Hz), 6.80 (1H, d, J = 8.1 Hz), 6.82 (1H, br d, J = 7.5 Hz), 6.84 (1H, br s), 7.01 (1H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.9, 39.0, 39.2, 46.5, 46.8, 55.9, 73.4, 73.5, 111.2, 114.3, 121.4, 126.1, 129.7, 130.1, 132.4, 134.3, 136.6, 137.8, 144.0, 146.5; MS (EI) m/z 326 (M^+, 100), 138 (98), 120 (62); HRMS (EI) m/z calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1876.

(8R,8′R)-3′,4-Dimethoxy-9,9′-epoxylignane-3,4′-diol (**34**): 0.3% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D$ = −33 (c 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.17 (2H, m), 2.48 (1H, dd, J = 17.8, 8.4 Hz), 2.49 (1H, dd, J = 17.8, 8.2 Hz), 2.59 (1H, dd, J = 13.7, 6.9 Hz), 2.60 (1H, dd, J = 13.7, 6.6 Hz), 3.50 (1H, dd, J = 8.6, 6.2 Hz), 3.52 (1H, dd, J = 8.6, 6.2 Hz), 3.84 (3H, s), 3.85 (3H, s), 3.89 (1H, dd, J = 9.1, 6.7 Hz), 3.91 (1H, dd, J = 9.1, 6.7 Hz), 5.58 (1H, s), 5.67 (1H, s), 6.55 (1H, dd, J = 8.2, 2.1 Hz), 6.56 (1H, d, J = 2.0 Hz), 6.59 (1H, dd, J = 8.0, 2.0 Hz), 6.68 (1H, d, J = 2.1 Hz), 6.72 (1H, d, J = 8.2 Hz), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.8, 39.1, 46.5, 46.7, 55.8, 56.0, 73.3, 73.4, 110.6, 111.2, 114.3, 114.9, 120.0, 121.3, 132.4, 133.7, 143.9, 145.0, 145.5, 146.4; MS (EI) m/z 344 (M^+, 67), 138 (100); HRMS (EI) m/z calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1617.

(8R,8′R)-3-Ethoxy-3′-methoxy-9,9′-epoxylignane-4,4′-diol (**35**): 0.9% from L-glutamic acid, colorless crystals; mp 88−89 °C; $[\alpha]^{25}_D$ = −39 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 7.0 Hz), 2.16 (2H, m), 2.50 (2H, dd, J = 13.7, 7.9 Hz), 2.566 (1H, dd, J = 13.7, 6.5 Hz), 2.571 (1H, dd, J = 13.7, 6.5 Hz), 3.53 (2H, dd, J = 8.7, 5.8 Hz), 3.80 (3H, s), 3.91 (2H, dd, J = 8.7, 6.5 Hz), 4.01 (2H, q, J

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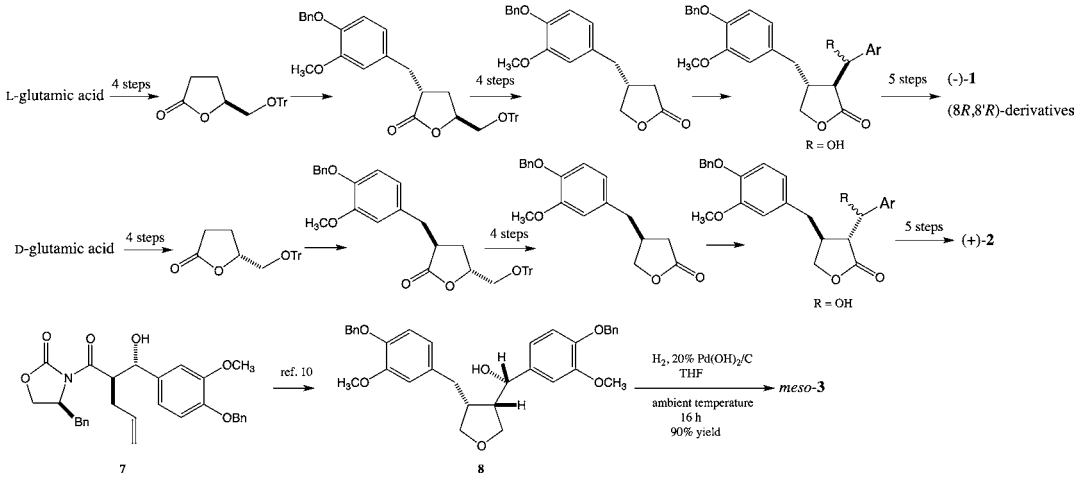

Figure 2. Stereoselective syntheses of (−)-9,9′-epoxylignane (**1**),[10] (+)-9,9′-epoxylignane (**2**), and *meso*-9,9′-epoxylignane (**3**).

= 7.0 Hz), 5.76 (1H, s), 5.79 (1H, s), 6.50 (2H, d, *J* = 1.9 Hz), 6.57 (2H, d, *J* = 8.0 Hz), 6.79 (2H, dd, *J* = 8.0, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 39.11, 39.12, 46.4, 46.5, 55.7, 64.4, 73.3, 111.2, 112.1, 114.16, 114.23, 121.2, 121.3, 132.16, 132.24, 144.0, 144.1, 145.8, 146.5; MS (EI) *m*/*z* 358 (M^+, 100), 151 (51), 137 (78); HRMS (EI) *m*/*z* calcd for $C_{21}H_{26}O_5$, 358.1781, found 358.1778.

(8R,8′R)-3′,4,5-Trimethoxy-9,9′-epoxylignane-2,4′-diol (**36**): 1.6% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -35$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (2H, m), 2.52−2.59 (3H, m), 2.61 (1H, dd, *J* = 13.9, 7.0 Hz), 3.54 (1H, dd, *J* = 8.4, 5.9 Hz), 3.59 (1H, dd, *J* = 8.4, 5.6 Hz), 3.79 (6H, s), 3.83 (3H, s), 3.89 (1H, dd, *J* = 8.4, 6.7 Hz), 3.98 (1H, dd, *J* = 8.4, 8.4 Hz), 5.19 (1H, s), 5.60 (1H, s), 6.35 (1H, s), 6.50 (1H, s), 6.56 (1H, br s), 6.61 (1H, br d, *J* = 8.0 Hz), 6.80 (1H, br d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3, 39.2, 44.9, 46.6, 55.8, 55.9, 56.6, 73.1, 73.4, 100.9, 111.1, 114.16, 114.23, 117.2, 121.3, 132.3, 142.8, 143.9, 146.4, 147.6, 148.1; MS (EI) *m*/*z* 374 (M^+, 100), 167 (79); HRMS (EI) *m*/*z* calcd for $C_{21}H_{26}O_6$ 374.1730, found 374.1730.

(8R,8′R)-3,3′,5-Trimethoxy-9,9′-epoxylignane-4,4′-diol (**37**): 0.3% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -37$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (2H, m), 2.52 (1H, dd, *J* = 13.7, 8.0 Hz), 2.55−2.61 (3H, m), 3.54 (1H, dd, *J* = 8.6, 5.8 Hz), 3.55 (1H, dd, *J* = 8.6, 5.8 Hz), 3.81 (3H, s), 3.83 (6H, s), 3.92 (1H, dd, *J* = 8.6, 6.4 Hz), 3.93 (1H, dd, *J* = 8.6, 6.4 Hz), 5.47 (1H, br s), 5.61 (1H, br s), 6.26 (2H, s), 6.51 (1H, d, *J* = 1.9 Hz), 6.59 (1H, dd, *J* = 8.0, 1.9 Hz), 6.80 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 39.8, 46.5, 55.8, 56.3, 73.2, 73.3, 105.3, 111.1, 114.2, 121.3, 131.5, 132.3, 133.1, 144.0, 146.5, 147.0; MS (EI) *m*/*z* 374 (M^+, 65), 168 (100); HRMS (EI) *m*/*z* calcd for $C_{21}H_{26}O_6$ 374.1730, found 374.1729.

(8R,8′R)-4-Dimethylamino-3′-methoxy-9,9′-epoxylignan-4′-ol (**38**): 0.03% from L-glutamic acid, colorless oil; $[\alpha]^{25}_D = -36$ (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (2H, m), 2.48 (1H, dd, *J* = 13.9, 6.0 Hz), 2.51 (1H, dd, *J* = 13.9, 6.0 Hz), 2.62 (1H, dd, *J* = 13.9, 6.0 Hz), 2.64 (1H, dd, *J* = 13.9, 5.7 Hz), 2.91 (6H, s), 3.51 (1H, dd, *J* = 8.7, 8.7 Hz), 3.53 (1H, dd, *J* = 8.7, 8.7 Hz), 3.84 (3H, s), 3.89 (1H, dd, *J* = 8.7, 6.7 Hz), 3.91 (1H, dd, *J* = 8.7, 6.7 Hz), 5.47 (1H, br s), 6.56 (1H, br s), 6.60 (1H, br d, *J* = 8.1 Hz), 6.66 (2H, d, *J* = 8.7 Hz), 6.81 (1H, d, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 39.1, 40.8, 46.71, 46.74, 55.9, 73.3, 73.4, 111.2, 112.9, 114.2, 121.3, 128.4, 129.3, 132.5, 143.8, 146.4, 149.1; MS (EI) *m*/*z* 341 (M^+, 65), 134 (100); HRMS (EI) *m*/*z* calcd for $C_{21}H_{27}O_3N$ 341.1990, found 341.1996.

Hydrophobicity. Values for log*P* (*P* is the partition coefficient in a 1-octanol/water system) were calculated as the hydrophobicity parameter of the lignan derivatives by using the ChemBioDraw ultra ver. 11.0 program.

Insects. The houseflies used in this experiment were of the Takatsuki strain. They were maintained at 25 °C under a photoperiod of 12 h of light. Eggs of the *C. pipiens* mosquito were purchased from Sumika Technoservice Co. (Hyogo, Japan) and reared. The larvae were maintained at 25 °C under a photopeiod of 12 h of light and 12 h of darkness.

Evaluation of Insecticidal Activity against Housefly. For evaluating the insecticidal activity, 0.22 μL of 50% ethanol solutions containing a test chemical at various concentrations was injected into the dorsal side of the thorax of male adult houseflies anesthetized using carbon dioxide. Symptoms of the flies were observed 1 h after injection, and the dead, unconscious, and paralyzed flies were counted as the affected ones. The values of 50% effective dose, ED_{50}, were determined using probit transformation[13] and are listed in Table 1. The pED_{50} was calculated as $-\log ED_{50}$.

Evaluation of Larvicidal Activity against *C. pipiens*. Five microliters of a DMSO solution containing each test chemical at various concentrations was added to 1 mL of water, into which 10 third-instar larvae were released. Twenty larvae (10 × 2 tubes) were used at each concentration. The lethal concentration for inducing death in 50% of mosquito larvae [LC_{50} (M)] 24 h after application of the compound was calculated by a probit analysis.[13] The insecticidal assay was performed in triplicate. DMSO at a concentration of 0.5% demonstrated no adverse effect on the mosquitoes.

RESULTS AND DISCUSSION

Preparation of Stereoisomers. To evaluate the biological activities of all stereoisomers of 9,9′-epoxylignane, (−)-(8*R*,8*R*′)-**1** and (+)-(8*S*,8*S*′)-**2** were synthesized by using the stereochemistry of L-glutamic acid and D-glutamic acid, respectively, according to the method described previously.[10] The chiral center of L- or D-glutamic acid was relayed to another position, determining the (−)-form is of (8*R*, 8*R*′) stereochemistry and the (+)-form is of (8*S*, 8*S*′) stereochemistry. To obtain *meso*-**3**, hydroxy lactone **8**, which has been obtained from compound **7**,[10] was treated with H_2 in the presence of $Pd(OH)_2/C$. NMR data agreed with those in the literature. A synthetic method to give both (±)-**1** and *meso*-**3** by the same process has also been reported.[11] This is a first stereoselective synthetic method of obtaining *meso*-**3** by employing Evans's *anti* aldol condensation (Figure 2).

Insecticidal Activity of 9,9′-Epoxylignane against Houseflies. The insecticidal activities of (−)-**1**, (+)-**2**, and *meso*-**3** against houseflies are shown in Table 1. In the preliminary test, we compared the ED_{50} values evaluated 1 h after injection with those evaluated 24 h after injection for some compounds, and we found no significant differences between them. However, the natural component (−)-(**1**) displayed the highest activity, indicating that the stereochemistry of 9,9′-

epoxylignane affects the insecticidal activity a little and that the (8*R*,8′*R*)-form is the most effective for this activity. To elucidate the structure−activity relationship, the derivatives **9**−**38** bearing the same stereochemistry as (−)-**1** were synthesized from L-glutamic acid, which gives (8*R*,8′*R*) stereochemistry, by employing the method described previously,[10] and their activities were examined. The observation that the same level of activity occurred in the phenyl derivative **9** as in (−)-**1** prompted us to further our research to discover compounds that exhibit higher activity than the natural compound (−)-**1**. Among the hydroxy derivatives **10**−**16** and **34**−**37**, the 2-hydroxy derivative **10** showed about 2-fold higher activity than (−)-**1**, the activity of which was decreased by conversion to the 2-methoxy derivative **17**, showing the same level of activity as (−)-**1**. The 2-hydroxy derivative **10** and the 3-hydroxy derivative **11** showed higher activity than the 4-hydroxy derivative. The 4-hydroxy derivative **12** and the 3,4-dihydroxy derivative **13** displayed almost the same levels of activity as (−)-**1**, whereas, on the other hand, the activities of the 3,5-dihydroxy derivative **14**, the 3,4,5-trisubstituted derivative **15**, and the pentanol derivative **16** were less potent than that of (−)-**1**. Specifically, the activities of **15** and **16** were very weak. It can be suggested that the presence of multiple hydrophilic groups on the 7-aromatic ring is not effective for obtaining higher activity. In a comparison of the activities of derivatives bearing both a hydroxy group and an alkoxy group, derivatives **34**−**37** showed the same level of activity as the natural (−)-**1** except for **36**. The monomethoxy derivatives and the dimethoxy derivatives showed higher activity than (−)-**1**, except for the 2-methoxy derivative **17**. Compared with (−)-**1**, the 3,4-dimethoxy derivative **21** appeared to exhibit about 5-fold higher activity. The 3,4,5-trimethoxy derivative **24** and the 3,4-methylenedioxy derivative **23** showed ED_{50} values similar to that of (−)-**1** and were less potent than the 3,4-dimethoxy derivative **21**. The 2,4-dimethoxy derivative **20** and the 3,5-dimethoxy derivative **22** showed higher activities than (−)-**1** and were less potent than the 3,4-dimethoxy derivative **21**. It seems that the position of the two methoxy groups and the steric condition influence the activity and that the presence of a hydrophobic group is important for higher activity (**13** vs **21**, **14** vs **22**, and **15** vs **24**). Because the 2-hydroxy derivative **10** and the 3,4-dimethoxy derivative **21** showed potent activities, we designed the 2-hydroxy-4,5-dimethoxy derivative **36**, but in this case lower activity than (−)-(**1**) was observed. For further investigation of steric effects, the derivatives **25**−**30** were employed. Compared with the 3,4-dimethoxy derivative **21**, the derivatives bearing a longer and bulkier substituent on the 4-position, such as the 3-methoxy-4-isopropoxy derivative **26** and the 3-methoxy-4-butoxy derivative **27**, showed less potent activities, although the 3-methoxy-4-ethoxy derivative **25** showed the same level of activity as **21**. This tendency was obvious in those derivatives bearing longer and bulkier groups on the 3-position of **21**. The activities of derivatives **28**−**30** were weaker than that of **21**. Specifically, the activity of the bulky 3-isopropoxy-4-methoxy derivative **29** was too low to acquire an ED_{50} value. The less potent activities of the 3-ethyl-4-methoxy derivative **31** and the 3-methoxy-4-ethyl derivative **32** compared with that of the 3,4-dimethoxy derivative **21** confirmed the importance of both oxygen atoms at the 3- and 4-positions for the higher activity. The 3,4-dimethyl derivative **33** displayed higher activity than (−)-**1**, yet was less potent than the 3,4-dimethoxy derivative **21**, indicating that the presence of methoxy groups at the 3- and 4-positions is more favorable than methyl groups for obtaining higher activity. The 4-dimethylamino derivative **38** was also examined to check the influence of electron donor groups and bulky groups at the 4-position, and we found that the activity was at the same level as (−)-**1**. The relationship between the Clog*P* values and the pED_{50} values is shown in Figure 3. The hydrophobic

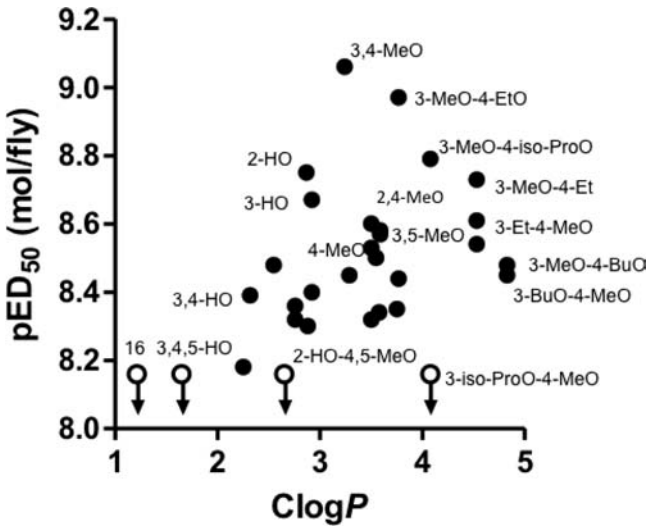

Figure 3. Relationship between Clog*P* and pED_{50}.

compounds display higher activity, but bulkier groups decrease the activity, and the position of the substituents influences the activity. The most potent 9,9′-epoxylignane derivative in this research was the 3,4-dimethoxy derivative **21**. The houseflies treated with (−)-**1** and **21** showed paralysis and tremble, suggesting action to the excitatory receptor for acetylcholine.

Insecticidal Activity of DGA against Houseflies. To evaluate the effects of the tetrahydrofuran structure on insecticidal activity against houseflies, dihydroguaiaretic acid, which is a "butane-type" of lignan, and its derivatives[7] were employed for biological tests against houseflies (Table 2). The activity of (−)-DGA (**4**), which exhibits (8*R*,8′*R*) stereochemistry, displayed the lowest ED_{50} value. (+)-DGA (**5**) and *meso*-DGA (**6**) showed weaker activity than (−)-DGA. This observation means that the (8*R*,8′*R*) stereochemistry of both tetrahydrofuran and butane lignan should be important in terms of their higher activities. The activity of (−)-DGA (**4**) was higher than that of (−)-**1** and was almost the same level as that of **21**, which showed the highest activity among the 9,9′-epoxylignane derivatives. The 7-phenyl derivative **39**, the 2-hydroxy derivative **40**, and the 3-hydroxy derivative **41** of (−)-DGA showed the same level of activity as that of the corresponding 9,9′-epoxylignane derivatives **9**−**11**, whereas, on the other hand, the activities of the other hydroxy derivatives of (−)-DGA **42**−**45** were more potent than those of the corresponding 9,9′-epoxylignane derivatives **12**−**15**. Both pentanol derivatives **16** and **46** showed the lowest activities. On the other hand, the activities of the 3-methoxy 9,9′-epoxylignane derivative **18** and of 4-methoxy 9,9′-epoxylignane **19** were higher than the those of the corresponding (−)-DGA derivatives **48** and **49**. The 2-methoxy derivatives of 9,9′-epoxylignane **17** showed the same levels of activity as the corresponding (−)-DGA derivatives **47**. The 3,4-dimethoxy derivative of 9,9′-epoxylignane **21**, the ED_{50} value of which was almost the same as that of natural (−)-DGA, was more potent

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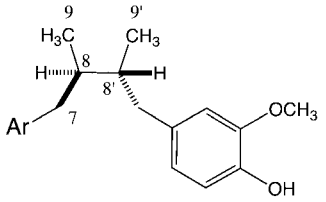
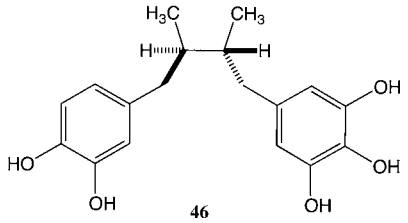
Table 2. Insecticidal Activities of Stereoisomers of Dihydroguaiaretic Acid 4−6 and Derivatives of 4 against Houseflies (n = 3)[a]





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no.	Ar or structure	ED_{50} (nmol/fly)	no.	Ar or structure	ED_{50} (nmol/fly)
4	3-MeO-4-HOPh ((−)-DGA)	1.65 ± 0.35	**46**	pentanol	>6.93 (13%)
5	(+)-DGA	4.02 ± 0.97	**47**	Ph(2-OMe)	2.37 ± 1.04
6	*meso*-DGA	4.99 ± 0.85	**48**	Ph(3-OMe)	5.24 ± 0.96
39	Ph	6.75 ± 2.47	**49**	Ph(4-OMe)	>3.48 (22%)
40	Ph(2-OH)	1.97 ± 0.10	**50**	Ph(3,4-OMe)	5.10 ± 1.68
41	Ph(3-OH)	1.67 ± 0.53	**51**	Ph(3,4-OCH_2O)	>2.77 (27%)
42	Ph(4-OH)	1.72 ± 0.16	**52**	Ph(3-OH-4-OMe)	3.24 ± 1.00
43	Ph(3,4-OH)	1.82 ± 0.49	**53**	Ph(3-OEt-4-OH)	1.94 ± 0.54
44	Ph(3,5-OH)	3.43 ± 0.61	**54**	Ph(3,5-OMe-4-OH)	2.71 ± 0.64
45	Ph(3,4,5-OH)	1.76 ± 0.54			

[a]Imidacloprid (positive control): ED_{50} = 10.1 ± 0.90 pmol/fly.

than the 3,4-dimethoxy derivative of (−)-DGA **50**. As for those derivatives bearing both hydroxy groups and alkoxy groups, **52** and **53**, the same levels of activity as the corresponding 9,9′-epoxylignanes **35** and **36** were observed, yet the trisubstituted derivative of (−)-DGA **54** was more potent than the corresponding 9,9′-epoxylignane **37**. Which lignan structure is more favorable for insecticidal activity against houseflies depends on the substituent on the 7-phenyl group in the case of tetrahydrofuran lignan and butane lignan. The activities of (−)-DGA and its derivatives against houseflies were also shown for the first time. The paralysis and tremble occurring in houseflies treated by (−)-DGA seemed to be an action to the excitatory receptor, the same as by 9,9′-epoxylignane.

Larvicidal Activities of 9,9′-Epoxylignane. In our previous study concerning the larvicidal activities of (−)-DGA derivatives against *C. pipiens*, the 3-hydroxy derivative **41** and the 4-hydroxy derivative **42** induced acute paralytic activity,[7] whereas the 3-hydroxy derivative **11** and the 4-hydroxy derivative **12** of 9,9′-epoxylignane did not show such activity, displaying weaker activity than the corresponding butane-type of lignan after 24 h (LC_{50} **11**, 39.6 ± 4.98 × 10^{-5} M; **12**, 38.1 ± 5.45 × 10^{-5} M). The larvicidal activities (LC_{50}) of three stereoisomers of 9,9′-epoxylignane (−)-**1**, (+)-**2**, and *meso*-**3** were 7.15 ± 0.72 × 10^{-5}, 10.6 ± 1.47 × 10^{-5}, and 12.3 ± 1.99 × 10^{-5} M, respectively, and these activities were weaker than those of the corresponding DGA stereoisomers **4**−**6**. These results suggest that the butane structure is more effective for larvicidal activity than the tetrahydrofuran ring.

In summary, the insecticidal activities of 9,9′-epoxylignane and DGA against houseflies were first examined. Although the insecticidal activities against houseflies of the sesquilignan,[14] which acts on the GABA receptor,[15] and the podophyllotoxin type[16] compound, which is known as a cytotoxic compound, are already known, this is a first report concerning simple epoxy and butane type lignans. It seemed that 9,9′-epoxylignane and DGA act on the excitatory receptor. To compare the effects of the stereochemistry of 9,9′-epoxylignane, *meso*-9,9′-epoxylignane was stereoselectively prepared for the first time. Because the (−)-(8*R*,8′*R*)-isomer (**1**) showed the highest activity, 30 7-phenyl derivatives bearing (8*R*,8′*R*) stereochemistry were synthesized. We found that the 3,4-dimethoxy derivative **21** showed 5-fold higher activity (ED_{50} = 0.91 nmol/fly) compared with the natural (−)-**1**. The presence of longer and bulkier substituents at the 3- and 4-positions decreased the activity. The importance of both oxygen atoms of the 3,4-methoxy groups of **21** in terms of obtaining higher activity was confirmed. The activity level of the 3,4-dimethoxy 9,9′-epoxylignane derivative **21** was the same as that of the naturally occurring butane-type lignan, (−)-DGA (**4**). This experiment also showed that the biological activities of lignans depend on the linkage of the phenyl propane, the oxidation patterns of the main structure, and the stereochemistry. New lead compounds for medicine and pesticides could be discovered and new biological activities could be added to the chemical library by continuing research into the biological activities of each lignan.

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Notes

The authors declare no competing financial interest.

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