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Antifungal Activity of Morinol B Derivatives of Tetrahydropyran Sesquilignan

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The relationship between the structure of naturally occurring (7*R*,7′*R*,8*R*,8′*R*)-morinol B and its antifungal activity was examined. 3-Demethoxy morinol B showed much higher activity than the natural compound. The activity of the 4-butoxy-3-demethoxy derivative was higher than that of 3-demethoxy morinol B.

Key words: morinol B; sesquilignan; antifungal activity

The sesquilignan, morinol B, has been isolated from a Chinese herb as a mixture of enantiomers.[1)] Our previous work determined its stereochemistry by a synthetic study[2)] and then led to clarification of the effect of the stereochemistry on the antifungal activity, showing the highest activity of (7*R*,7′*R*,8*R*,8′*R*)-morinol B (**1**) after a total of 16 stereoisomers had been prepared.[3)] As the next step in this present study, the derivatives of morinol B bearing (7*R*,7′*R*,8*R*,8′*R*) stereochemistry were synthesized and their antifungal activities were examined to clarify the relationship between the structure and antifungal activity, and to design compounds having higher activity than the natural product. The insectical,[4)] antimelanogenic,[5)] antiplasmodial[6)] and anti-HIV activity,[7)] and the inhibition of LPS-induced nitric oxide production[8)] by sesquilignans have been reported. This is a first report on the structure-antifungal activity relationship of sesquilignans.

Materials and Methods

NMR data were measured by a JNM-EX400 spectrometer, using TMS as a standard (0 ppm). MS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a Horiba SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh).

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}methyl acetate (**2**).* Colorless oil, $[\alpha]_D^{20} = -23$ (*c* 0.30, $CHCl_3$). ^{1}H-NMR data agreed with those in the literature.[1)]

*(2*R*,3*R*,5*R*)-2-(3,4-Dimethoxyphenyl)-5-[(*R*)-(3,4-dimethoxyphenyl)(methoxy)methyl]-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran (**3**).* To an ice-cooled suspension of NaH (17 mg, 60% oil suspension, 0.43 mmol) in DMF (1 ml) was added a solution of (7*R*,8*R*,7′*R*,8′*R*)-morinol B[1)] (15 mg, 0.027 mmol) in DMF (1 ml). After the mixture was stirred at 0 °C for 30 min, MeI (0.50 ml, 8.0 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, and then H_2O and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 3/1) gave methyl ether derivative **3** (13 mg, 0.022 mmol, 81%) as a colorless oil, $[\alpha]_D^{20} = -30$ (*c* 0.26, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (1H, m), 1.48 (1H, m), 1.67 (1H, m), 1.82–1.98 (3H, m), 3.24 (3H, s), 3.71 (1H, dd, $J = 11.5$, 2.5 Hz), 3.77 (3H, s), 3.845 (3H, s), 3.853 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 3.95 (3H, s), 3.98 (1H, d, $J = 9.6$ Hz), 4.46 (1H, d, $J = 11.5$ Hz), 4.49 (1H, d, $J = 13.1$ Hz), 5.64 (1H, m), 6.04 (1H, d, $J = 15.6$ Hz), 6.67–6.69 (2H, m), 6.76 (1H, d, $J = 8.7$ Hz), 6.82–6.99 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 30.9, 35.4, 38.3, 41.4, 55.7, 55.9, 56.8, 68.7, 82.3, 85.5, 108.4, 108.5, 108.9, 110.3, 110.7, 111.0, 118.6, 119.7, 120.3, 120.5, 128.6, 130.6, 131.0, 133.2, 133.7, 145.1, 148.2, 148.9, 149.4. EIMS *m/z* (%) 578 (M^+, 98), 181 (100). HREIMS *m/z* M^+: calcd. for $C_{34}H_{42}O_8$, 578.2880; found, 578.2881.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-[3-(3,4-dimethoxyphenyl)propan-1-yl]tetrahydropyran-5-yl}methanol (**4**).* A reaction mixture of (7*R*,8*R*,7′*R*,8′*R*)-morinol B (**1**) (16 mg, 0.028 mmol) and 5% Pd/C (52 mg) in EtOAc (5 ml) was stirred under H_2 gas (1 atm) at ambient temperature for 24 h before filtration. The filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 4/1) to give dihydro-morinol B (**4**) (13 mg, 0.023 mmol, 82%) as a colorless oil, $[\alpha]_D^{20} = -43$ (*c* 0.21, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (1H, m), 1.07 (1H, m), 1.17 (1H, m), 1.26 (1H, m), 1.30–1.40 (2H, m), 1.82–1.94 (2H, m), 2.20 (1H, m), 2.34 (1H, m), 2.40 (1H, d, $J = 3.1$ Hz), 3.70 (1H, dd, $J = 11.7$, 2.5 Hz), 3.81–3.93 (1H, overlapped), 3.81 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 4.50 (1H, d, $J = 11.7$ Hz), 5.07 (1H, dd, $J = 9.1$, 3.1 Hz), 6.46 (1H, dd, $J = 8.1$, 1.8 Hz), 6.49 (1H, d, $J = 1.8$ Hz), 6.70 (1H, d, $J = 8.1$ Hz), 6.80 (1H, d, $J = 8.2$ Hz), 6.85 (1H, d, $J = 8.1$ Hz), 6.88–6.92 (3H, m), 6.96 (1H, d, $J = 1.7$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 28.0, 31.6, 35.1, 35.2, 36.9, 41.4, 55.85, 55.92, 68.6, 73.9, 86.4, 109.0, 110.7, 110.8, 110.95, 111.0, 111.6, 119.0, 119.8, 120.0, 133.8, 134.9, 136.3, 147.0, 148.66, 148.74, 148.9, 149.4. EIMS *m/z* (%) 566 (M^+, 100), 548 (52), 342 (71), 167 (52), 151 (82). HREIMS *m/z* M^+: calcd. for $C_{33}H_{42}O_8$, 566.2880; found, 566.2880.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-(2-propen-1-yl)tetrahydropyran-5-yl}methanol (**5**).* A solution of (2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-5-[(*R*)-(3,4-dimethoxyphenyl)(triisopropylsilyloxy)methyl]-3-(2-propen-1-yl)tetrahydropyran[2)] (61 mg, 0.10 mmol) and *n*-Bu_4NF (0.18 ml, 1 M in THF, 0.18 mmol) in THF (3 ml) was stirred at room temperature for 1 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave allyl derivative **5** (39 mg, 0.091 mmol, 91%) as a colorless oil, $[\alpha]_D^{20} = -32$ (*c* 0.77, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (1H, ddd, $J = 12.4$, 12.4, 5.1 Hz), 1.52–1.60 (2H, m), 1.80–2.00 (3H, m), 2.56 (1H, br. s), 3.70 (1H, dd, $J = 11.6$, 2.5 Hz), 3.88 (3H, s), 3.89 (6H, s), 3.92 (3H, s), 3.95 (1H, d, $J = 10.0$ Hz), 4.49 (1H, d, $J = 11.6$ Hz), 4.80

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(1H, d, $J = 17.1$ Hz), 4.84 (1H, d, $J = 10.2$ Hz), 5.03 (1H, d, $J = 9.1$ Hz), 5.45 (1H, m), 6.83–6.93 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.3, 36.5, 37.3, 41.5, 55.9, 68.5, 73.6, 85.7, 109.1, 110.6, 110.8, 111.0, 116.4, 118.8, 119.8, 133.4, 135.4, 136.4, 148.5, 148.8, 148.9, 149.2. EIMS m/z (%) 428 (M^+, 100), 204 (99), 167 (98). HREIMS m/z M^+: calcd. for $C_{25}H_{32}O_6$, 428.2199; found, 428.2200.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-[(*E*)-3-phenyl-2-propen-1-yl]tetrahydropyran-5-yl}methanol (**6**).* Colorless oil, $[\alpha]_D^{20} = -60$ (c 0.35, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (1H, ddd, $J = 12.2$, 12.2, 5.1 Hz), 1.60–1.75 (2H, m), 1.89 (1H, m), 1.92–2.04 (2H, m), 2.47 (1H, br. s), 3.73 (1H, dd, $J = 11.7$, 2.5 Hz), 3.78 (3H, s), 3.84 (3H, s), 3.89 (3H, s), 3.93 (3H, s), 3.99 (1H, d, $J = 9.8$ Hz), 4.50 (1H, d, $J = 11.7$ Hz), 5.06 (1H, d, $J = 9.2$ Hz), 5.83 (1H, m), 6.14 (1H, d, $J = 15.8$ Hz), 6.70 (1H, d, $J = 8.1$ Hz), 6.80–7.00 (5H, m), 7.12–7.19 (3H, m), 7.23–7.29 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.7, 35.5, 38.2, 41.7, 55.80, 55.84, 55.89, 55.92, 68.6, 73.7, 85.8, 108.8, 110.55, 110.60, 111.0, 118.9, 119.8, 125.8, 126.9, 127.5, 128.1, 128.4, 131.5, 133.4, 136.2, 137.4, 148.6, 148.9, 149.0, 149.3. EIMS m/z (%) 504 (M^+, 100), 167 (69). HREIMS m/z M^+: calcd. for $C_{31}H_{36}O_6$, 504.2512; found, 504.2514.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-[(*E*)-3-(3-methoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}methanol (**7**).* Colorless oil, $[\alpha]_D^{20} = -44$ (c 0.22, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (1H, ddd, $J = 12.3$, 12.3, 4.8 Hz), 1.51–1.77 (2H, m), 1.89 (1H, m), 1.91–2.08 (2H, m), 2.42 (1H, br. s), 3.73 (1H, dd, $J = 12.2$, 2.0 Hz), 3.78 (3H, s), 3.80 (3H, s), 3.84 (3H, s), 3.89 (3H, s), 3.94 (3H, s), 3.99 (1H, d, $J = 9.8$ Hz), 4.51 (1H, d, $J = 12.2$ Hz), 5.07 (1H, d, $J = 9.0$ Hz), 5.84 (1H, m), 6.11 (1H, d, $J = 15.7$ Hz), 6.60–6.77 (3H, m), 6.81–6.97 (6H, m), 7.17 (1H, dd, $J = 7.9$, 7.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.7, 35.5, 38.2, 41.7, 55.75, 55.82, 55.88, 55.90, 56.0, 68.6, 73.7, 85.8, 108.7, 110.6, 111.0, 111.4, 112.3, 118.5, 118.9, 119.8, 119.9, 127.8, 129.4, 131.4, 133.4, 136.2, 138.9, 148.6, 148.9, 149.4, 159.7. EIMS m/z (%) 534 (M^+, 100), 167 (66). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2617.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-[(*E*)-3-(4-methoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}methanol (**8**).* Colorless oil, $[\alpha]_D^{20} = -59$ (c 0.23, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 14.0 (1H, ddd, $J = 12.3$, 12.3, 5.0 Hz), 1.55–1.72 (2H, m), 1.85–2.05 (3H, m), 2.30–2.50 (1H, br.), 3.73 (1H, dd, $J = 11.8$, 2.5 Hz), 3.78 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 3.93 (3H, s), 3.99 (1H, d, $J = 9.9$ Hz), 4.50 (1H, d, $J = 11.8$ Hz), 5.05 (1H, d, $J = 9.0$ Hz), 5.69 (1H, m), 6.08 (1H, d, $J = 15.9$ Hz), 6.72 (1H, d, $J = 8.1$ Hz), 6.79 (2H, d, $J = 8.8$ Hz), 6.85–6.90 (3H, m), 6.93–6.95 (2H, m), 7.09 (2H, d, $J = 8.8$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.7, 35.5, 38.3, 41.7, 55.3, 55.81, 55.85, 55.92, 56.0, 68.6, 73.8, 85.8, 108.8, 110.6, 111.0, 113.6, 113.8, 118.9, 119.9, 125.2, 126.9, 130.3, 130.9, 133.5, 134.5, 136.3, 148.6, 149.0, 149.3, 158.7. EIMS m/z (%) 534 (M^+, 100), 165 (76). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2615.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-2-(3,4-dimethoxyphenyl)-3-[(*E*)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}methanol (**9**).* Colorless oil, $[\alpha]_D^{20} = -45$ (c 0.60, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (1H, ddd, $J = 12.3$, 12.3, 5.2 Hz), 1.63–1.75 (2H, m), 1.89 (1H, m), 1.93–2.05 (2H, m), 2.54 (1H, d, $J = 3.2$ Hz), 3.77–3.92 (1H, overlapped), 3.77 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.92 (3H, s), 3.98 (1H, d, $J = 9.7$ Hz), 4.49 (1H, d, $J = 11.7$ Hz), 5.04 (1H, d, $J = 6.0$ Hz), 5.73 (1H, m), 6.05 (1H, d, $J = 15.7$ Hz), 6.38 (2H, s), 6.69 (1H, d, $J = 8.2$ Hz), 6.77–6.96 (2H, m), 6.91–6.96 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.9, 35.7, 38.4, 41.6, 55.8, 55.9, 56.0, 56.1, 68.6, 73.9, 85.9, 109.1, 110.8, 111.2, 118.9, 120.0, 126.9, 129.8, 130.0, 131.5, 132.3, 133.2, 133.6, 136.4, 137.5, 148.6, 149.0, 149.1, 149.4, 153.3. EIMS m/z (%) 594 (M^+, 25), 576 (72), 151 (100). HREIMS m/z M^+: calcd. for $C_{34}H_{42}O_9$, 594.2829; found, 594.2822.

*(*R*)-{(2*R*,3*R*,5*R*)-2-(3,4-Dimethoxyphenyl)-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}phenylmethanol (**10**).* Colorless oil, $[\alpha]_D^{20} = -36$ (c 0.61, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (1H, ddd, $J = 12.3$, 12.3, 5.0 Hz), 1.63–1.76 (2H, m), 1.94–2.00 (3H, m), 2.36 (1H, br. s), 3.70 (1H, dd, $J = 11.8$, 2.3 Hz), 3.85 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 3.99 (1H, d, $J = 9.9$ Hz), 4.50 (1H, d, $J = 11.8$ Hz), 5.10 (1H, d, $J = 8.2$ Hz), 5.66 (1H, m), 6.06 (1H, d, $J = 15.7$ Hz), 6.66–6.70 (2H, m), 6.76 (1H, d, $J = 8.7$ Hz), 6.85–6.96 (3H, m), 7.18–7.32 (3H, m), 7.36–7.38 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.9, 35.6, 38.2, 41.6, 55.8, 55.9, 56.0, 68.6, 74.1, 85.9, 108.4, 110.5, 110.7, 111.1, 118.9, 119.9, 120.1, 125.5, 126.5, 127.7, 128.5, 128.6, 130.7, 131.2, 133.5, 143.8, 148.9, 149.0, 149.1. EIMS m/z (%) 504 (M^+, 54), 259 (100), 180 (64), 166 (87), 151 (70), 149 (96). HREIMS m/z M^+: calcd. for $C_{31}H_{36}O_6$, 504.2512; found, 504.2514.

*(*R*)-{(2*R*,3*R*,5*R*)-2-(3,4-Dimethoxyphenyl)-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}(3-methoxyphenyl)methanol (**11**).* Colorless oil, $[\alpha]_D^{20} = -42$ (c 0.72, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (1H, ddd, $J = 12.3$, 12.3, 5.1 Hz), 1.66–1.74 (2H, m), 1.91 (1H, m), 1.95 (1H, m), 2.00 (1H, m), 2.66 (1H, br. s), 3.71 (1H, dd, $J = 11.8$, 2.6 Hz), 3.73 (3H, s), 3.86 (6H, s), 3.88 (3H, s), 3.92 (3H, s), 3.98 (1H, d, $J = 9.9$ Hz), 4.49 (1H, d, $J = 11.8$ Hz), 5.06 (1H, d, $J = 8.6$ Hz), 5.68 (1H, m), 6.07 (1H, d, $J = 15.8$ Hz), 6.67–6.70 (2H, m), 6.73–6.81 (2H, m), 6.85–6.91 (2H, m), 6.93–6.96 (3H, m), 7.20 (1H, dd, $J = 8.0$, 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.8, 35.7, 38.2, 41.6, 55.2, 55.8, 55.9, 56.0, 68.6, 74.0, 85.9, 108.4, 110.7, 111.1, 111.8, 113.1, 118.8, 118.9, 119.9, 125.4, 129.4, 130.7, 131.2, 133.5, 145.5, 148.3, 148.85, 148.9, 149.0, 159.9. EIMS m/z (%) 534 (M^+, 100), 180 (54). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2618.

*(*R*)-{(2*R*,3*R*,5*R*)-2-(3,4-Dimethoxyphenyl)-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}(4-methoxyphenyl)methanol (**12**).* Colorless oil, $[\alpha]_D^{20} = -56$ (c 0.50, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (1H, ddd, $J = 12.3$, 12.3, 4.9 Hz), 1.61–1.79 (3H, m), 1.91–2.01 (2H, m), 2.34 (1H, br. s), 3.67 (1H, dd, $J = 11.4$, 2.6 Hz), 3.73 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 3.98 (1H, d, $J = 9.7$ Hz), 4.49 (1H, d, $J = 11.4$ Hz), 5.07 (1H, d, $J = 8.8$ Hz), 5.65 (1H, m), 6.06 (1H, d, $J = 15.7$ Hz), 6.68–6.69 (2H, m), 6.76 (1H, d, $J = 8.7$ Hz), 6.83 (2H, d, $J = 8.6$ Hz), 6.86–7.00 (3H, m), 7.29 (2H, d, $J = 8.6$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.8, 35.6, 38.2, 41.7, 55.2, 55.8, 55.9, 56.0, 68.7, 73.5, 85.8, 108.4, 110.6, 111.05, 111.08, 113.9, 118.8, 119.9, 125.6, 127.6, 130.7, 131.1, 133.6, 135.8, 148.3, 148.9, 148.95, 149.03, 159.2. EIMS m/z (%) 534 (M^+, 100), 180 (64), 165 (60), 151 (62). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2618.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-phenyltetrahydropyran-5-yl}methanol (**13**).* Colorless oil, $[\alpha]_D^{20} = -40$ (c 0.23, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (1H, ddd, $J = 12.3$, 12.3, 5.0 Hz), 1.62–1.72 (2H, m), 1.91–2.07 (3H, m), 2.58 (1H, br. s), 3.77–3.84 (1H, overlapped), 3.77 (3H, s), 3.83 (3H, s), 3.841 (3H, s), 3.843 (3H, s), 4.04 (1H, d, $J = 9.8$ Hz), 4.51 (1H, d, $J = 11.8$ Hz), 5.06 (1H, d, $J = 8.5$ Hz), 5.65 (1H, m), 6.06 (1H, d, $J = 15.7$ Hz), 6.66–6.72 (3H, m), 6.75 (1H, d, $J = 8.3$ Hz), 6.86 (1H, dd, $J = 8.3$, 1.8 Hz), 6.93 (1H, d, $J = 1.8$ Hz), 7.29–7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.7, 35.5, 38.4, 41.8, 55.8, 55.86, 55.93, 68.6, 73.6, 86.0, 108.6, 109.1, 110.8, 111.2, 118.8, 118.9, 125.5, 127.4, 127.49, 127.54, 128.1, 128.47, 128.53, 131.2, 136.4, 141.0, 148.4, 148.6, 149.0. EIMS m/z (%) 504 (M^+, 91), 298 (79), 279 (55), 178 (100), 167 (56), 151 (84). HREIMS m/z M^+: calcd. for $C_{31}H_{36}O_6$, 504.2512; found, 504.2515.

*(*R*)-(3,4-Dimethoxyphenyl){(2*R*,3*R*,5*R*)-3-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(2-methoxyphenyl)tetrahydropyran-5-yl}methanol (**14**).* Colorless oil, $[\alpha]_D^{20} = -27$ (c 0.55, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (1H, ddd, $J = 12.3$, 12.3, 4.9 Hz), 1.63–1.79 (3H, m), 1.92 (1H, m), 2.22 (1H, m), 2.69 (1H, br. s), 3.72 (1H, d, $J = 11.4$ Hz), 3.79 (3H, s), 3.81 (3H, s), 3.84 (6H, s), 3.87 (3H, s), 4.49 (1H, d, $J = 11.4$ Hz), 4.57 (1H, d, $J = 9.9$ Hz), 5.10 (1H, d, $J = 7.9$ Hz), 5.69 (1H, m), 6.06 (1H, d, $J = 15.7$ Hz), 6.65–6.76 (4H, m), 6.85–6.90 (2H, m), 6.94 (1H, s), 7.03 (1H, dd, $J = 7.3$, 7.1 Hz), 7.27 (1H, dd, $J = 7.9$, 7.1 Hz), 7.48 (1H, d, $J = 7.3$ Hz). ^{13}C-NMR ($CDCl_3$) δ: 32.4, 35.5, 38.4, 41.8, 55.5, 55.8, 55.85, 55.87, 55.94, 68.8, 74.1, 108.6, 109.1, 110.7, 110.8, 111.2, 118.75, 118.81, 121.0, 126.2, 128.0, 128.9, 129.6, 130.8, 130.9, 136.7, 148.3, 148.5, 149.0, 149.3, 156.9. EIMS m/z (%) 534 (M^+, 23), 309 (100). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2623.

*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(3-methoxyphenyl)tetrahydropyran-5-yl}methanol (**15**).* Colorless oil, $[\alpha]_D^{20} = -61$ (*c* 0.12, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (1H, ddd, J = 12.3, 12.3, 4.9 Hz), 1.61–1.74 (2H, m), 1.89–2.00 (3H, m), 2.45 (1H, br. s), 3.72 (1H, dd, J = 11.7, 2.5 Hz), 3.78 (3H, s), 3.84 (6H, s), 3.85 (6H, s), 4.02 (1H, d, J = 9.7 Hz), 4.50 (1H, d, J = 11.7 Hz), 5.06 (1H, d, J = 8.8 Hz), 5.67 (1H, m), 6.07 (1H, d, J = 15.6 Hz), 6.68–6.70 (3H, m), 6.82–7.01 (6H, m), 7.31 (1H, dd, J = 7.9, 7.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.6, 35.4, 38.2, 41.7, 55.3, 55.76, 55.81, 55.9, 68.5, 73.6, 85.9, 108.5, 108.9, 110.7, 111.1, 113.1, 113.4, 118.7, 118.9, 119.9, 125.4, 129.4, 130.6, 131.2, 136.3, 142.4, 148.3, 148.5, 148.9, 149.2, 159.7. EIMS m/z (%) 534 (M^+, 100), 328 (64), 178 (57), 151 (74). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2617.

*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(4-methoxyphenyl)tetrahydropyran-5-yl}methanol (**16**).* Colorless oil, $[\alpha]_D^{20} = -55$ (*c* 0.20, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (1H, ddd, J = 12.4, 12.4, 4.8 Hz), 1.60–1.72 (2H, m), 1.86–1.99 (2H, m), 2.02 (1H, m), 2.48 (1H, br. s), 3.71 (1H, dd, J = 11.6, 2.5 Hz), 3.79 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 4.00 (1H, d, J = 10.0 Hz), 4.49 (1H, d, J = 11.6 Hz), 5.07 (1H, d, J = 9.0 Hz), 5.66 (1H, m), 6.06 (1H, d, J = 15.8 Hz), 6.69–6.72 (3H, m), 6.92 (2H, d, J = 8.6 Hz), 6.82–6.92 (3H, m), 7.34 (2H, d, J = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.9, 35.6, 38.4, 41.7, 55.3, 55.8, 68.6, 73.7, 85.5, 108.5, 110.7, 111.0, 111.1, 113.6, 113.8, 118.7, 118.9, 125.6, 128.6, 130.7, 131.1, 133.2, 136.4, 148.3, 148.5, 148.9, 149.3, 159.4. EIMS m/z (%) 534 (M^+, 100), 328 (93), 151 (71). HREIMS m/z M^+: calcd. for $C_{32}H_{38}O_7$, 534.2617; found, 534.2617.

*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(4-trifluoromethoxyphenyl)tetrahydropyran-5-yl}methanol (**17**).* Colorless oil, $[\alpha]_D^{20} = -38$ (*c* 0.68, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (1H, ddd, J = 12.3, 12.3, 4.9 Hz), 1.63 (1H, m), 1.71 (1H, m), 1.91–1.98 (3H, m), 2.38 (1H, br. s), 3.78–3.85 (1H, overlapped), 3.78 (3H, s), 3.83 (3H, s), 3.845 (3H, s), 3.850 (3H, s), 4.06 (1H, d, J = 9.8 Hz), 4.51 (1H, d, J = 11.7 Hz), 5.04 (1H, d, J = 9.2 Hz), 5.65 (1H, m), 6.07 (1H, d, J = 15.7 Hz), 6.68–6.71 (3H, m), 6.76 (1H, d, J = 8.2 Hz), 6.86 (1H, d, J = 8.2 Hz), 6.93 (1H, s), 7.24 (2H, d, J = 8.3 Hz), 7.44 (2H, d, J = 8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 31.5, 35.3, 38.5, 41.7, 55.8, 55.9, 56.0, 68.6, 73.5, 85.1, 108.7, 109.0, 110.8, 111.2, 118.8, 119.0, 120.1 (J = 174.7 Hz), 121.0, 125.0, 128.9, 130.6, 131.5, 136.2, 139.8, 148.5, 148.7, 148.9, 149.0, 149.4. EIMS m/z (%) 588 (M^+, 40), 178 (93), 167 (100). HREIMS m/z M^+: calcd. for $C_{32}H_{35}O_7F_3$, 588.2335; found, 588.2337.

*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-2-(4-ethylphenyl)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}methanol (**18**).* Colorless oil, $[\alpha]_D^{20} = -37$ (*c* 0.50, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.6 Hz), 1.42 (1H, ddd, J = 12.2, 12.2, 5.2 Hz), 1.64–1.74 (2H, m), 1.88 (1H, m), 1.97 (1H, m), 2.08 (1H, m), 2.52 (1H, br. s), 2.66 (2H, q, J = 7.6 Hz), 3.71 (1H, dd, J = 11.6, 2.6 Hz), 3.78 (3H, s), 3.83 (3H, s), 3.85 (6H, s), 4.01 (1H, d, J = 9.9 Hz), 4.48 (1H, d, J = 11.6 Hz), 5.07 (1H, d, J = 8.8 Hz), 5.69 (1H, m), 6.07 (1H, d, J = 15.7 Hz), 6.68–6.76 (4H, m), 6.87 (1H, dd, J = 8.2, 1.8 Hz), 6.93 (1H, d, J = 1.8 Hz), 7.20–7.22 (2H, m), 7.23–7.3 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.6, 28.6, 31.8, 35.5, 38.2, 41.7, 55.8, 55.87, 55.94, 68.6, 73.8, 85.8, 108.7, 109.1, 110.8, 111.2, 118.7, 118.9, 125.6, 127.4, 128.0, 130.7, 131.2, 136.4, 138.1, 144.1, 148.4, 148.5, 149.0, 149.3. EIMS m/z (%) 532 (M^+, 19), 514 (96), 307 (100). HREIMS m/z M^+: calcd. for $C_{33}H_{40}O_6$, 532.2825; found, 532.2827.

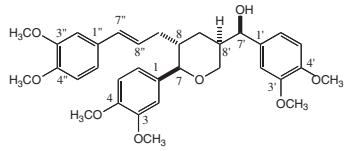
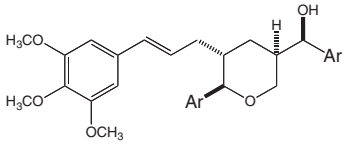
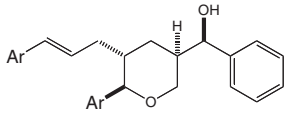
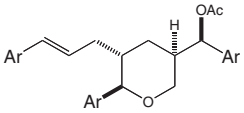
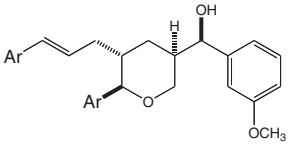
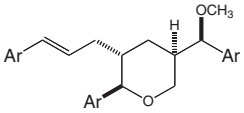
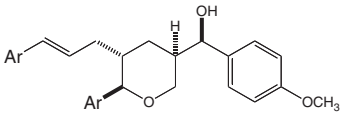
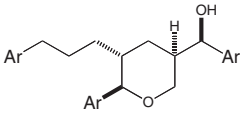
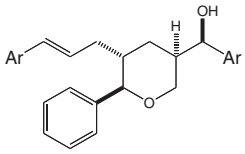
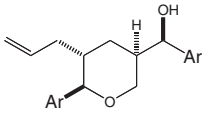
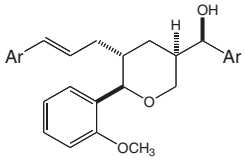
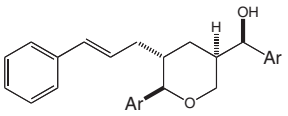
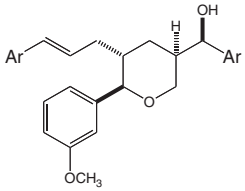
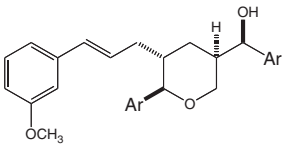
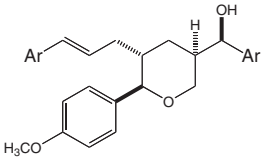
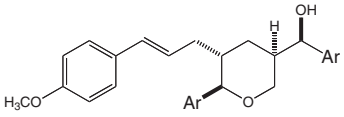
*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(4-hydroxyphenyl)tetrahydropyran-5-yl}methanol (**19**).* To an ice-cooled solution of a diastereomeric mixture of acetate **I** (1.58 g, 1.88 mmol), which was prepared by the previously described method[2] with modification, and Et_3N (0.29 ml, 2.1 mmol) in CH_2Cl_2 (5 ml) was added MsCl (0.16 ml, 2.1 mmol), and then the reaction mixture was stirred at 0 °C for 30 min before additions of H_2O and CH_2Cl_2. The organic solution was separated washed with sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration gave a crude mesylate. A reaction mixture of this crude mesylate and K_2CO_3 (2.60 g, 18.8 mmol) in MeOH (10 ml) was stirred at room temperature for 16 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave diastereomerically pure phenol **II** (0.40 g, 0.74 mmol, 39%) as a colorless oil, $[\alpha]_D^{20} = +7$ (*c* 2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.93–1.03 (21H, m), 1.21 (1H, ddd, J = 12.3, 12.3, 4.3 Hz), 1.37 (1H, m), 1.49 (1H, m), 1.72–1.84 (3H, m), 3.67 (1H, dd, J = 11.4, 2.4 Hz), 3.87 (6H, s), 3.92 (1H, d, J = 9.6 Hz), 4.58 (1H, d, J = 11.4 Hz), 4.75 (1H, d, J = 6.8 Hz), 4.78 (1H, d, J = 9.7 Hz), 5.07 (1H, d, J = 9.9 Hz), 5.37 (1H, m), 6.17 (1H, s), 6.72 (2H, d, J = 8.5 Hz), 6.78 (1H, d, J = 8.1 Hz), 6.84 (1H, dd, J = 8.1, 1.2 Hz), 6.91 (1H, d, J = 1.2 Hz), 7.18 (2H, d, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 12.6, 18.0, 18.1, 30.6, 36.4, 37.9, 43.7, 55.78, 55.84, 68.5, 73.9, 85.5, 109.7, 110.3, 115.3, 116.3, 119.5, 128.6, 133.0, 135.5, 137.1, 148.3, 148.9, 155.6. EIMS m/z (%) 540 (M^+, 6), 497 (96), 323 (100). HREIMS m/z M^+: calcd. for $C_{33}H_{48}O_5Si$, 540.3271; found, 540.3273. Phenol **II** was converted to **19** by the previously described method.[2] **19**: Colorless oil, $[\alpha]_D^{20} = -49$ (*c* 0.25, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (1H, ddd, J = 12.3, 12.3, 6.1 Hz), 1.63–1.72 (2H, m), 1.91–1.97 (3H, m), 2.66 (1H, br. s), 3.78–3.86 (1H, overlapped), 3.78 (3H, s), 3.83 (3H, s), 3.86 (6H, s), 3.98 (1H, d, J = 9.9 Hz), 4.54 (1H, d, J = 11.3 Hz), 5.05 (1H, d, J = 8.7 Hz), 5.68 (1H, m), 5.62–5.70 (1H, br.), 6.06 (1H, d, J = 15.6 Hz), 6.70–6.80 (6H, m), 6.87 (1H, d, J = 7.9 Hz), 6.93 (1H, s), 7.17–7.24 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 31.8, 35.6, 38.3, 41.7, 55.8, 68.6, 73.7, 85.6, 108.6, 109.1, 110.8, 111.2, 115.4, 118.8, 118.9, 125.5, 128.8, 130.7, 131.1, 132.9, 136.3, 148.3, 148.5, 148.9, 149.3, 155.7. EIMS m/z (%) 520 (M^+, 100), 314 (80), 151 (58). HREIMS m/z M^+: calcd. for $C_{31}H_{36}O_7$, 520.2461; found, 520.2461.

*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(4-ethoxyyphenyl)tetrahydropyran-5-yl}methanol (**20**).* Colorless oil, $[\alpha]_D^{20} = -50$ (*c* 0.39, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.40–1.43 (1H, overlapped), 1.41 (3H, t, J = 7.0 Hz), 1.65–1.72 (2H, m), 1.89–1.98 (3H, m), 2.51 (1H, br. s), 3.72 (1H, d, J = 11.5 Hz), 3.78 (3H, s), 3.84 (3H, s), 3.85 (6H, s), 3.98 (1H, d, J = 10.3 Hz), 4.03 (2H, q, J = 7.0 Hz), 4.49 (1H, d, J = 11.5 Hz), 5.06 (1H, d, J = 6.9 Hz), 5.66 (1H, m), 6.05 (1H, d, J = 15.7 Hz), 6.69–6.77 (3H, m), 6.82–6.93 (3H, m), 6.90 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.9, 31.9, 35.6, 38.4, 41.7, 55.8, 63.4, 68.6, 73.7, 85.6, 108.5, 109.0, 110.7, 111.1, 114.4, 118.7, 118.9, 125.6, 128.6, 130.7, 131.0, 133.0, 136.4, 148.3, 148.5, 149.0, 149.3, 158.7. EIMS m/z (%) 548 (M^+, 100), 342 (62), 177 (75), 151 (85). HREIMS m/z M^+: calcd. for $C_{33}H_{40}O_7$, 548.2774; found, 548.2775.

*(R)-{(2R,3R,5R)-2-(4-Butoxyphenyl)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]tetrahydropyran-5-yl}(3,4-dimethoxyphenyl)methanol (**21**).* Colorless oil, $[\alpha]_D^{20} = -43$ (*c* 0.30, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J = 7.3 Hz), 1.42 (1H, ddd, J = 12.3, 12.3, 4.8 Hz), 1.51 (2H, m), 1.62–1.75 (2H, m), 1.77 (2H, m), 1.85–2.10 (3H, m), 2.56 (1H, br. s), 3.70 (1H, dd, J = 11.6, 1.4 Hz), 3.78 (3H, s), 3.83 (3H, s), 3.85 (6H, s), 3.94–4.00 (3H, m), 4.48 (1H, d, J = 11.6 Hz), 5.06 (1H, d, J = 9.0 Hz), 5.66 (1H, m), 6.06 (1H, d, J = 15.7 Hz), 6.69–6.77 (3H, m), 6.82–6.93 (5H, m), 7.31 (2H, d, J = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 19.2, 31.3, 31.9, 35.6, 38.3, 41.7, 55.78, 55.82, 55.9, 67.7, 68.6, 73.7, 85.6, 108.6, 111.1, 114.4, 118.7, 118.8, 125.6, 128.5, 131.0, 132.9, 136.4, 148.3, 148.5, 149.3, 158.9. EIMS m/z (%) 576 (M^+, 31), 558 (100), 380 (57), 351 (53), 177 (98), 151 (78). HREIMS m/z M^+: calcd. for $C_{35}H_{44}O_7$, 576.3087; found, 576.3085.

*(R)-(3,4-Dimethoxyphenyl){(2R,3R,5R)-3-[(E)-3-(3,4-dimethoxyphenyl)-2-propen-1-yl]-2-(4-isopropoxyphenyl)tetrahydropyran-5-yl}methanol (**22**).* Colorless oil, $[\alpha]_D^{20} = -50$ (*c* 0.46, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J = 5.9 Hz), 1.34 (3H, d, J = 6.0 Hz), 1.41 (1H, ddd, J = 12.3, 12.3, 3.7 Hz), 1.63–1.73 (2H, m), 1.89 (1H, m), 1.96 (1H, m), 2.04 (1H, m), 2.60 (1H, br. s), 3.77 (1H, dd, J = 11.7, 2.7 Hz), 3.78 (3H, s), 3.83 (3H, s), 3.85 (6H, s), 3.98 (1H, d, J = 9.9 Hz), 4.49 (1H, d, J = 11.7 Hz), 4.54 (1H, m), 5.06 (1H, d, J = 9.0 Hz), 5.67 (1H, m), 6.06 (1H, d, J = 15.7 Hz), 6.67–6.77 (3H, m), 6.84–6.94 (3H, m), 6.90 (2H, d, J = 8.6 Hz), 7.31 (2H, d, J = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.05, 22.08, 31.9, 35.6, 38.3, 41.8,

Table 1. Growth Rate (% ± σ, n = 3) of *Alternaria alternata* at 0.50 mM of the (7*R*,7′*R*,8*R*,8′*R*)-Morinol B Derivatives
The area of the mycelial colony was measured. Ar = 3,4-dimethoxyphenyl

Compound No.	Structure	Growth %	Compound No.	Structure	Growth %
1	 (7*R*,7′*R*,8*R*,8′*R*)-morinol B	43 ± 0.43	**9**		41 ± 1.7
			10		40 ± 3.2
2		77 ± 0.63	**11**		67 ± 4.3
3		55 ± 4.0	**12**		72 ± 6.2
4		42 ± 1.4	**13**		45 ± 1.7
5		77 ± 9.2	**14**		39 ± 3.3
6		38 + 1.0	**15**		56 + 3.4
7		44 + 1.8	**16**		0
8		41 ± 1.7			

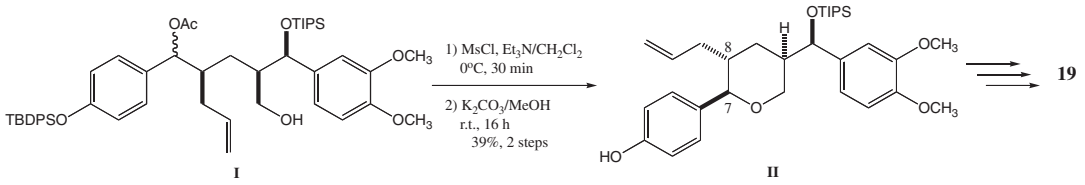
55.8, 55.9, 56.0, 68.6, 70.0, 73.7, 85.6, 108.7, 109.1, 110.8, 111.2, 115.9, 118.8, 118.9, 125.7, 128.6, 130.8, 131.1, 136.5, 148.4, 148.6, 149.0, 149.3, 157.7. EIMS *m/z* (%) 562 (M^+, 70), 544 (100), 347 (75), 285 (69), 177 (98), 151 (98). HREIMS *m/z* M^+: calcd. for $C_{34}H_{42}O_7$, 562.2930; found, 562.2933.

Organisms. The phytopathogenic fungi, *Colletotrichum lagenarium race 2.1*, *Bipolaris oryzae race 1.1*, *Fusarium solani race 3.3*, and *Alternaria alternata race 1.1*, had been isolated from a farm at Ehime University and were kindly presented by Dr. Ohguchi. Each fungus was cultured on potato dextrose agar (PDA, Sigma-Aldrich, Canada).

Antifungal assay. The antimicrobial assay was performed by the same method as that described in the literature.[9)]

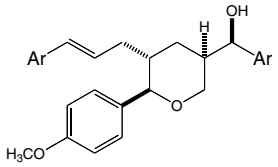
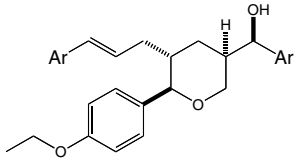
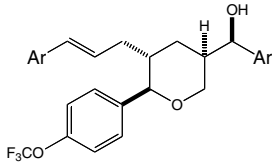
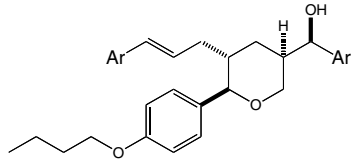
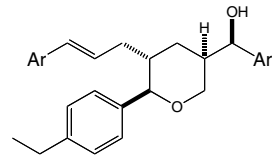
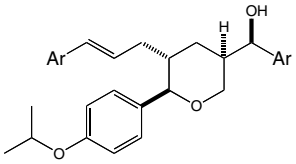
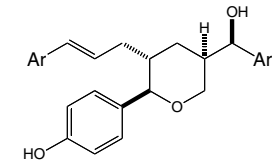
Results and Discussions

The (7*R*,7′*R*,8*R*,8′*R*)-morinol B derivatives were synthesized by the previously described method.[2)] The antifungal activities of the derivatives were initially examined by using phytopathogenic fungus *Alternaria alternata* at 0.50 mM (Table 1). To check the role of the benzylic hydroxy group in the activity, acetate **2** and methyl ether **3** were examined. The activities of these derivatives were slightly weaker than that of natural product **1**. On the other hand, the activity level of olefin reductive derivative **4** was same as that of **1**. These facts indicate that the benzylic hydroxy group was important for the higher activity and that the 7″–8″ double bond of



Scheme 1. Preparation of the Intermediate for the Synthesis of **19**.

Table 2. Growth Rate (% ± σ, n = 3) of *Alternaria alternata* at 3.9 μM of 3-Demethoxy (7*R*,7′*R*,8*R*,8′*R*)-Morinol B Derivatives The area of the mycelial colony was measured. Ar = 3,4-dimethoxyphenyl

Compound		Growth %	Compound		Growth %
No.	Structure		No.	Structure	
16		74 ± 0.97	**20**		57 ± 3.2
17		73 ± 2.8	**21**		50 ± 1.8
18		72 ± 3.8	**22**		77 ± 4.4
19		77 ± 2.5			

the cinnamyl structure was not important for the activity. Derivative **5** lacking the benzene ring at the 1″–6″ positions resulted in a decrease in the activity. This fact suggests that this benzene ring was important, however, the methoxy groups on this 7″-phenyl ring of **1** did not play an important role in the activity, because the activities of phenyl derivative **6**, 3″-methoxy derivative **7**, and 4″-methoxy derivative **8** were same as that of **1**. Since the 3″,4″,5″-trimethoxy derivative **9** also showed same level of activity as that of **1**, the increase of methoxy group on the 7″-phenyl group did not affect the activity. In respect of the substituents on the 7′ phenyl group, derivative **10** lacking two methoxy groups showed the same level of activity as that of **1**, although the activities of derivatives **11** and **12** lacking one methoxy group were weaker. In the case of the substituents on the 7-phenyl group, 4-methoxy derivative **16** showed the highest activity, whose growth rate was 0% at 0.50 mM. Although the activities of derivative **13** lacking substituents, 2-methoxy derivative **14**, and 3-methoxy derivative **15** were at almost the same level as that of **1**, these activity levels were weaker than that of 4-methoxy derivative **16**. It could be assumed that the 3-methoxy group of morinol B reduced the activity.

In the next step, the 3-demethoxy derivatives, which had a different substituent at the 4 position of **16**, were synthesized and their activities were examined to elucidate the important factor at the 4 position. 4-Hydroxy derivative **19** was synthesized from a diastereomeric mixture of hydroxy acetate **I**, which had been prepared by the previously described method[2] with modification. The treatment of **I** with mesyl chloride and triethylamine, and then by K_2CO_3 in MeOH gave phenol **II** as a single isomer (Scheme 1). The coupling constant at the 7 position was 9.6 Hz, showing diaxial stereochemistry between the 7 and 8 positions. The *tert*-butyldiphenylsilyl ether in this reaction was cleaved in the presence of the secondary tri-isopropylsilyl ether. Phenol **II** was converted to **19** by the previously described method.[2]

The antifungal activities of the 3-demethoxy derivatives at 3.9 μM are shown in Table 2. 4-Methoxy derivative **16** showed 74% growth rate. 4-Hydroxy derivative **19**, 4-trifluoromethoxy derivative **17**, and 4-ethyl derivative **18** showed the same levels of activity as that of **16**. These facts indicate that hydrophilic and electron withdrawing groups and the oxygen atom at the 4 position did not affect the activity. On the other hand,

the longer alkoxy derivative at the 4 position increased the activity. Thus, the activities of 4-ethoxy derivative **20** and 4-butoxy derivative **21** were higher than that of **16**. However, the activity of bulky 4-isopropoxy derivative **22** was the same as that of **16**. 4-Butoxy derivative **21** showed the highest activity in this study, having higher activity than that of thiabendazol (71% of growth rate at 3.9 μM). A linear and longer alkoxy group was necessary at the 4 position of morinol B for this higher activity. Derivative **21** did not show the antifungal activity against the other phytopathogenic fungi, *Colletotrichum lagenarium*, *Bipolaris oryzae*, and *Fusarium solani*.

The relationship between the structure of (7*R*,7′*R*,8*R*,8′*R*)-morinol B (**1**) and its antifungal activity was clarified. It was revealed that the 3-methoxy group of **1** inhibited the higher activity. Since the natural lignans and sesquilignans bearing a 4-methoxy phenyl group were known, it would be possibility to isolate compound **16** from its natural source in the future. Although the mechanism for antifungal activity was not identified in this study, the morinol derivatives seem to have affected the characteristic enzyme or metabolic pathway for *Alternaria alternata*, because other fungi were not affected by the morinol derivatives. The possibility for identifying the characteristic enzyme for *Alternaria alternata* by employing morinol derivatives was suggested. The discovery of morinol derivatives having higher activity than that of **1** might lead to the development of new fungicides. The structure-antifungal activity relationship of lignan has previously been examined.[9–11] The tetra-substituted tetrahydrofuran lignan[9] and di-benzoylbutyrolactone lignan[10] respectively showed activity against *Colletotrichum lagenarium* and *Bipolaris oryzae*. On the other hand, the butane type of lignan[11] was effective against *Alternaria alternata* at the same level as that of sesquilignan morinol B and its derivatives. Some morinol B derivatives showed higher antifungal activity than that of the butane type of lignan.

Acknowledgments

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