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Synthesis and Plant Growth–Inhibiting Activity of Pyridine derivatives

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A number of 3–pyridyl–2–propenoic acid derivatives, pyridines possessing a γ–butyrolactone ring and related compounds were synthesized and evaluated for their activity by using a lettuce seedling test. Most of the pyridine derivatives inhibited the growth of lettuce seedlings at concentrations ranging from 10 to 100 ppm. In the pyridine analogs of cinnamic acid, the 4–pyridine analog is more active than the 2– and 3–isomers. Of the 3–(4–pyridyl)propenoic acid derivatives examined, the *N, N*–diethyl–3–(4–pyridyl)–2–propenamide **3c–3** was the most active, which caused more than 90% inhibition of the hypocotyl and root growth at 50 ppm. Pyridine analogs with a 1,4–butanediol showed activity comparable to that of pyridyl γ–butyrolactone compounds, suggesting that the presence of the γ–butyrolactone was dispensable for the activity.

INTRODUCTION

In plants, a number of cytochrome P450 monooxygenases (P450s) involve in the biosynthesis of hormones, steroids, flavonoids, phytoalexins, lignans and lignin intermediates (Donaldson and Luster, 1991). Cinnamate 4–hydroxylase is a P450 which catalyzes the hydroxylation of *trans*–cinnamic acid into *trans*–*p*–coumaric acid, the first oxygenation step of the general phenylpropanoid metabolism in plants. This enzyme which is essential for plants has not been found in any invertebrate or vertebrate animals (Teutsch *et al.*, 1993). It might be an unexploited target for development of a new herbicide.

On the other hand, P450s are known to be selectively inhibited by various imidazole, 1,2,4–triazole, pyridine, and pyrimidine derivatives. In these heterocyclic compounds, an sp^2–nitrogen atom binds preferentially a heme iron atom of P450 active site to cause enzyme inactivation (Ortiz de Montellano and Reich, 1986). In view of the extraordinary potency of the pyridines as P450 inhibitors, we designed and synthesized a series of 3–pyridyl–2–propenoic acid derivatives, which is differing only in having a pyridine nucleus in place of a benzene ring of cinnamic acid, as an inhibitor of cinnamate 4–hydroxylase. Recently the total synthesis of novel lignans, haedoxans (Ishibashi and Taniguchi, 1989), and their derivatives (Yamauchi *et al.*, 1992) have been accomplished via γ–butyrolactone derivatives as a key intermediate in our laboratories. Using this synthetic procedure, the pyridine derivatives possessing a γ–butyrolactone ring which have been not synthesized so far were designed in expectation of obtaining a new class of biological active compounds. In the present paper, we report the synthesis and plant

growth-inhibiting activity of pyridine analogs of cinnamic acid and γ-butyrolactone.

MATERIALS AND METHODS

Synthesis

All melting points (mp) are uncorrected. ^{1}H-NMR spectra were recorded on JNM-GX400 spectrometers with tetramethylsilane as an internal standard. Gravity column chromatography was carried out with Merck kiesegel 60 F254 (0.063–0.200 mm, 70–230 mesh ASTM) and Wakogel C-300 (45–75 μm). TLC was performed on precoated 60 F254 silica gel plates (0.25 mm, 0.5 mm, or 1 mm thickness, 20×20 cm) supplied by E. Merck.

Ethyl 3-(2-pyridyl)-2-propenoate (**1a**)

To a solution of diethyl ethoxycarbonylmethylphosphonate (5.0 g, 18.7 mmol) and K_2CO_3 (5.2 g, 18.7 mmol) in water (20 ml) was added with stirring 2-pyridinecarboxaldehyde (2 g, 18.7 mmol) and the mixture was stirred for 12 hr at room temperature. The product was extracted with ethyl acetate and the ethyl acetate solution was washed with water, brine, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel by elution with hexane–ethyl acetate (8:1). Concentration of the early eluate under reduced pressure afforded 0.11 g (3.3%) of *cis* isomer (**1a-2**). NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.3 Hz), 4.21 (2H, q, J=7.3 Hz), 6.14 (1H, d, J=12.7 Hz), 6.95 (1H, d J=12.7 Hz), 7.18–7.26 (1H, m), 7.64–7.70 (2H, m), 8.59 (1H, d, J=4.9 Hz). *Trans* isomer (**1a-1**) was eluted after **1a-2** with hexane–ethyl acetate (10:1) eluate, 3.1 g (94%). NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.3 Hz), 4.27 (2H, q, J=7.3 Hz), 6.92 (1H, d, J=15.9 Hz), 7.26 (1H, d,d, J=7.8, 4.9 Hz), 7.42 (1H, d, J=7.8 Hz), 7.65–7.73 (1H, m), 8.64 (1H, d, J=3.9 Hz).

Compounds **1b** and **1c** were prepared in the same manner as **1a** with use of 3- and 4-pyridinecarboxaldehyde respectively, instead of 2-pyridine-carboxaldehyde.

Ethyl 3-(3-pyridyl)-2-propenoate (**1b**) Yield 51%. NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz), 4.28 (2H, q, J=7.0 Hz), 6.52 (1H, d, J=16.1 Hz), 7.32 (1H, d,d, J=8.0, 4.7 Hz), 7.67 (1H, d, J=16.1 Hz), 7.84 (1H, d, J=8.0 Hz), 8.60 (1H, d,d, J=4.7, 2,0 Hz), 8.75 (1H, d, J=2.0 Hz).

Ethyl 3-(4-pyridyl)-2-propenoate (**1c**) Yield 59%. Mp 64.5–65 °C. NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.3 Hz), 4.29 (2H, q, J=7.3 Hz), 6.59 (1H, d, J=16.1 Hz), 7.36 (2H, d, J=6.1 Hz), 7.59 (1H, d, J=16.1 Hz), 8.65 (2H, d, J=6.1 Hz).

N-n-propyl-3-(4-pyridyl)-2-propenamide (**3c-1**)

A mixture of **1c** (1.0 g, 5.6 mmol) and NaOH (0.7 g, 5.6 mmol) in 8 ml of water and 10 ml of ethanol was stirred for 24 hr at room temperature. After removal of the solvent, the residue was acidified with acetic acid. The resulting precipitates were collected by filtration and recrystallized from dimethylformamide and water affording 0.57 g (68%) of 3-(4-pyridyl)-2-propenoic acid (**2c**). To a solution of **2c** (0.2 g, 1.34 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.26 g, 1.34 mmol) and 1-hydroxy-benzotriazole (0.18 g, 1.34 mmol) in 10 ml of dichloromethane was added with stirring n-propylamine (0.08 g, 1.34 mmol). After stirring for 24 hr at room temperature, the dichloromethane solution was washed with 5% Na_2CO_3 solution, water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on

silica gel and eluted with hexane–ethyl acetate (1:2) to afford 70 mg (28%) of **3c–1**. NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.3 Hz), 1.54–1.65 (2H, m), 3.37 (2H, q, J=6.8 Hz), 5.71 (1H, broad s), 6.54 (1H, d, J=15.6 Hz), 7.34 (2H, d, J=5.9 Hz), 7.55 (1H, d, J=15.6 Hz), 8.62 (2H, d, J=5.9 Hz).

Compounds **3c–2** and **3c–3** were prepared in the same manner as that for compound **3c–1** from a corresponding amine, instead of *n*–propylamine.

N–Hexyl–3–(4–pyridyl)–2–propenamide (**3c–2**) Yield 44%. NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz), 1.23–1.40 (6H, m), 1.53–1.78 (2H, m), 3.39 (2H, q, J=6.7 Hz), 5.86 (1H, broad s), 6.56 (1H, d, J=15.6 Hz), 7.33 (2H, d, J=5.9 Hz), 7.54 (1H, d, J=15.6 Hz), 8.61 (2H, d, J=5.9 Hz).

N,N–Diethyl–3–(4–pyridyl)–2–propenamide (**3c–3**) Yield 61%. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.1 Hz), 1.28 (3H, t, J=7.1 Hz) , 3.48 (2H, q, J=7.1 Hz), 3.50 (2H, q, J=7.1 Hz) , 7.00 (1H, d, J=15.4 Hz), 7.36 (2H, d, J=5.5 Hz), 7.60 (1H, d, J=15.4 Hz), 8.62 (2H, d, J=5.5 Hz).

3–(1–Hydroxy–1–pyridylmethyl)–4–vinyldihydro–2(3H)–furanones (**5**)

To a solution of diisopropylamine (10 ml, 0.14 mol) in THF (100 ml, distilled from $LiAlH_4$) was added *n*–butyllithium (87.5 ml, 1.6 M solution in hexane) at −78 °C under nitrogen gas. After stirring for 15 minutes, a solution of β–vinyl–γ–butyrolactone (**4**, 10 g, 0.05 mol) in THF (50 ml) was added dropwise, and then the mixture was stirred at −78 °C for 30 minutes. A solution of pyridinecarboxaldehyde (11.7 g, 0.11 mol) in THF (50 ml) was added at −78 °C. After stirring at −78 °C for 1 hr, to the mixture was added saturated aqueous NH_4Cl solution (50 ml) and EtOAc (1000 ml). The organic layer was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by column chromatography (silicagel, EtOAc) gave aldols (*erythro* and *threo*). Recrystallization from EtOAc gave pure aldols **5**.

2–Pyridylaldol (**5a**) Yield 47%, white amorphous solid, mp 103–104 °C. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ 3.02 (d.d, 1H, J=2.93, 9.76, –C*H*–CH(OH)–Ar), 3.27 (d.d.d, 1H, J= 8.79, 8.79, 8.79, CH_2=CH–C*H*–), 3.88 (t, 1H, J=8.79, –C*H*$_2$O–), 4.37 (t, 1H, J=8.79, –C*H*$_2$O–), 4.56–4.62 (m, 2H, C*H*$_2$=CH–), 5.40 (d, 1H, J=4.39, –C*H*(OH)–Ar) 5.19–5.28 (m, 1H, CH_2=C*H*–), 5.46 (s, 1H, O*H*), 7.20–7.23 (m, 1H, Ar–*H*), 7.41–7.43 (m, 1H, Ar–*H*), 7.66–7.71 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 177.34, 158.82, 148.08, 137.14, 135.70, 123.06, 121.03, 117.34, 70.81, 70.12, 52.67, 39.18, *Anal.* Found: C, 66.10; H, 5.59; N, 6.33. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

3–Pyridylaldol (**5b**) Yield 52%, white amorphous solid, mp 114 °C. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ 2.80 (d.d, 1H, J=2.93, 9.28, –C*H*–CH(OH)–Ar), 3.41 (t, 1H, J=8.79, CH_2=CH C*H*), 3.89 (t, 1H, J=8.79, C*H*$_2$O), 4.39 (t, 1H, J=8.79, C*H*$_2$O), 4.70 4.74 (m, 2H, C*H*$_2$=CH–), 5.26–5.35 (m, 1H, CH_2=C*H*–), 5.48 (d, 1H, J=1.95, –C*H*(OH)–Ar), 6.40 (br.s, 1H, –O*H*), 7.24–7.34 (m, 1H, Ar–*H*), 7.77–7.80 (m, 1H, Ar–*H*), 8.36–8.41 (m, 1H, Ar–*H*), 8.49–8.54 (m, 1H, Ar–*H*), ^{13}C –NMR (100 MHz, $CDCl_3$) 176.98, 147.81, 135.57, 135.61, 134.02, 123.10, 117.53, 70.54, 67.86, 52.97, 38.81, *Anal.* Found: C, 65.96; H, 6.17; N, 6.29. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

4–Pyridylaldol (**5c**) Yield 58%, white amorphous solid, mp 130 °C. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ 2.81–2.84 (m, 1H, –C*H*–CH(OH)–Ar), 3.32 (d.d.d, 1H, J=8.79, 8.79, 8.79, CH_2=CH–C*H*–), 3.65 (br.s, 1H, –O*H*), 3.90 (d.d, 1H, J=9.27, 9.27, –C*H*$_2$O–), 4.39 (d.d, 1H, J=8.79, 8.79, –C*H*$_2$O–), 4.76–4.81 (m, 2H, C*H*$_2$=CH–), 5.25–5.30 (m, 1H, CH_2=C*H*–),

5.42 (s, 1H, –*CH*(OH)–Ar), 7.28–7.36 (m, 2H, Ar–*H*), 8.51–8.58 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 177.02, 150.65, 149.38, 135.27, 120.98, 118.00, 70.75, 68.99, 52.49, 39.02, *Anal.* Found: C, 65.73; H, 5.93; N, 6.38. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.

3–[1–(tert–Butyldimethylsilyl)oxy–1–pyridylmethyl]–4–vinyldihydro–2(3H)–furanones (**6**)

To a solution of **5** (8.0 g, 0.04 mol) and imidazole (10.9 g, 0.16 mol) in DMF (200 ml) was added *tert*–butyldimeyhylsilyl chloride at room temperature. After stirring for 3 days, to the mixture was added water (100 ml) and ether (500 ml). The organic layer was sepa–rated, washed with water, brine, and dried (Na_2SO_4). Concentration followed by column chromatography (silicagel, EtOAc) gave pure silylaldol **6**.

6a Yield 82%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ–0.30 (s, 3H, –Si–CH_3), –0.03 (s, 3H, –Si–CH_3), 0.79 (s, 9H, –Si–CH_3), 2.77 (d.d, 1H, J=2.45, 9.28, –*CH*–CH(OH)–Ar), 3.30 (t, 1H, J=8.79, CH_2=CH–*CH*–), 3.66 –3.73 (m, 1H, –CH_2O–), 3.95 (t, 1H, J=8.79, –CH_2O–), 4.56 (t, 2H, J=10.25, CH_2=CH–), 5.69 (s, 1H, –*CH*(OH)–Ar) 5.74–5.81 (m, 1H, CH_2=*CH*–), 7.10–7.18 (m, 1H, Ar–*H*), 7.50–7.57 (m, 2H, Ar–*H*), 8.33–8.40 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 177.81, 159.76, 147.42, 136.89, 134.58, 122.79, 120.72, 119.44, 69.49, 52.58, 41.33, 25.90, 18.12, –4.76, –6.10, *Anal.* Found: C, 65.00; H, 7.45; N, 5.84. Calcd. for $C_{18}H_{27}NO_3Si$: C, 64.83; H, 8.16; N, 4.20%.

6b Yield 75%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ 0.02 (s, 3H, –Si–CH_3), 0.23 (s, 3H, –Si–CH_3), 1.02 (s, 9H, –Si–CH_3), 3.03 (d.d, 1H, J=3.42, 10.25, –*CH*–CH(OTBS)–Ar), 3.12–3.16 (m, 1H, CH_2=CH–*CH*–), 3.92–4.01 (m, 2H, –CH_2O–), 4.11–4.20 (m, 2H, –CH_2O), 5.26–5.43 (m, 2H, CH_2=CH–), 5.59 (d, 1H, J=1.95, –*CH*(OTBS)–Ar), 5.89–5.98 (m, 1H, CH_2=*CH*–), 7.32–7.38 (m, 1H, Ar–*H*), 7.62–7.87 (m, 1H, Ar–*H*), 8.58–8.63 (m, 1H, Ar–*H*), 8.65–8.75 (m, 1H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 176.32, 147.30, 136.07, 135.72, 134.92, 123.01, 117.36, 70.78, 70.38, 53.67, 41.47, 25.65, –3.61, –4.89, *Anal.* Found: C, 64.11; H, 8.75; N, 4.03. Calcd. for $C_{18}H_{27}NO_3Si$: C, 64.83; H, 8.16; N, 4.20%.

6c Yield 78%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ–0.19 (s, 3H, –Si–CH_3), 0.04 (s, 3H, –Si–CH_3), 0.81 (s, 9H, –Si–CH_3), 2.75–2.81 (m, 1H, –*CH*–CH(OTBS)–Ar), 3.71–3.75 (m, 1H, CH_2=CH–*CH*–), 3.80 (t, 2H, J=7.82–8.78, –CH_2O–), 3.90–3.94 (m, 2H, –CH_2O–), 5.02–5.08 (m, 2H, CH_2=CH–), 5.18 (d, 1H, J=2.93, –*CH*(OTBS)–Ar), 5.64–5.76 (m, 1H, CH_2=*CH*–), 7.32–7.38 (m, 2H, Ar–*H*), 8.40–8.51 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 174.86, 149.73, 135.76, 121.66, 120.86, 117.73, 70.91, 70.04, 53.61, 41.32, 25.61, 18.00, –4.92. *Anal.* Found: C, 63.31; H, 8.45; N, 4.15. Calcd. for $C_{18}H_{27}NO_3Si$: C, 64.83; H, 8.16; N, 4.20%.

3–[1–(tert–Butyldimethylsilyl)oxy–1–pyridylmethyl]–2–vinyl–1,4–butanediols (**7**)

To a solution of lithium aluminum hydride (1.70 g, 45 mmol) in THF (150 ml) was added **6** (9.34 g, 30 mmol) in THF (50 ml) at –10 °C under nitrogen gas. After stirring for 1 hr, to the reaction mixture was added saturated aqueous $MgSO_4$ solution (2 ml) and K_2CO_3 (8.29 g, 60 mmol). After stirring for 24 hr at room temperature, the mixture was filtered through a celite pad, and the filtrate was concentrated by *vacuo*. Concentration followed by column chromatography (silicagel, EtOAc) gave pure diols **7**.

2–Pyridyldiol (**7a**) Yield 91%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ–0.30 (s, 3H, –Si–CH_3), –0.02 (s, 3H, –Si–CH_3), 0.80 (s, 9H, –Si–CH_3), 1.90–2.00 (m, 1H,

–C*H*–CH(OH)–Ar), 2.49–2.56 (m, 1H, CH_2=CH–C*H*–), 3.14–3.17 (m, 1H, –C*H*$_2$O–), 3.64–3.74 (m, 3H, –C*H*$_2$O–), 4.97 (d, 1H, *J*=7.32, –C*H*(OH)–Ar), 5.00–5.20 (m, 2H, C*H*$_2$=CH–) 5.78–5.92 (m, 1H, CH_2=C*H*–), 7.19–7.24 (m, 1H, Ar–*H*), 7.61–7.71 (m, 1H, Ar–*H*), 8.34–8.46 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 162.72, 148.01, 13.23, 137.22, 122.65, 121.75, 116.25, 75.12, 62.08, 60.38, 58.40, 51.62, 43.68, 25.76, 14.16, –4.58. *Anal.* Found: C, 63.37; H, 9.22; N, 4.00. Calcd. for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15%.

3–Pyridyldiol (**7b**) Yield 92%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ –0.03 (s, 3H, –Si–CH$_3$), –1.02 (s, 3H, –Si–CH$_3$), 0.80 (s, 9H, –Si–CH$_3$), 1.90–2.00 (m, 1H, –C*H*–CH(OTBS)–Ar), 2.49–2.56 (m, 1H, CH_2=CH–C*H*–), 3.14–3.17 (m, 1H, –C*H*$_2$O–), 3.64–3.74 (m, 3H, –C*H*$_2$O–), 4.97 (d, 1H, *J*=7.32, –C*H*(OTBS)–Ar), 5.00–5.20 (m, 2H, C*H*$_2$=CH–), 5.78–5.92 (m, 1H, CH_2=C*H*–), 7.19–7.24 (m, 1H, Ar–*H*), 7.61–7.71 (m, 1H, Ar–*H*), 8.34–8.46 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 148.43, 148.20, 147.81, 139.58, 135.27, 123.58, 116.76, 71.97, 62.33, 58.62, 51.85, 43.97, 25.92, 18.19, –4.27, –4.95. *Anal.* Found: C, 63.90; H, 9.27; N, 3.95. Calcd. for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15%.

4–Pyridyldiol (**7c**) Yield 96%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ –0.27 (s, 3H, –Si–CH$_3$), –0.01 (s, 3H, –Si–CH$_3$), 0.82 (s, 9H, –Si–CH$_3$), 1.89–1.95 (m, 1H, –C*H*–CH(OTBS)–Ar), 2.39–2.43 (m, 1H, CH_2=CH–C*H*–), 3.30 (d.d, 2H, *J*=5.37, 11.23, –C*H*$_2$O–), 3.57–3.66 (m, 2H, –C*H*$_2$O–), 4.94 (d, 1H, *J*=5.86, –C*H*(OTBS)–Ar), 5.01 (m, 2H, C*H*$_2$=CH–), 5.75–5.84 (m, 1H, CH_2=C*H*–), 7.23–7.28 (m, 2H, Ar–*H*), 8.39–8.48 (m, 2H, Ar–*H*), ^{13}C–NMR (100 MHz, $CDCl_3$) 152.21, 149.34, 122.04, 122.03, 117.00, 72.91, 62.47, 59.16, 51.17, 43.69, 25.75, 18.07, –4.59, –4.40. *Anal.* Found: C, 63.37; H, 9.22; N, 4.00. Calcd. for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15%.

3–[1–(tert–Butyldimethylsilyl)oxy–1–pyridylmethyl]–3–hydroxymethyl–2–hydroxydihydro–2(3H)–furanols (**8**)

To a stirred solution of 7 (5 g, 15 mmol) and *N*–methylmorpholine *N*–oxide (3.5 g, 30 mmol) in acetone: *t*–butanol: H_2O=4:1:1 (150 ml) was added osmium tetraoxide (0.5 ml, 2% in water) under nitrogen gas. After stirring for 3 days, the reaction mixture was quenched by saturated aqueous Na_2SO_3 solution (5 ml). After stirring for 30 minutes, the mixture was filtered through a celite pad, and the filtrate was concentrated by *vacuo*. The residue was dissolved in EtOAc (200 ml), and to the mixture was added $NaIO_4$ (3.9 g, 180 mmol) in water (50 ml). After vigorously stirring for 24 hr, the reaction mixture was diluted with EtOAc (50 ml). The organic layer was separated, washed with water, brine, and dried (Na_2SO_4). Concentration followed by column chromatography (silicagel, EtOAc) gave pure lactols **8**.

2–Pyridyllactol (**8a**) Yield 91%, colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ –0.37 (s, 3H, –Si–CH$_3$), –0.03 (s, 3H, –Si–CH$_3$), 0.82 (s, 9H, –Si–CH$_3$), 2.27–2.29 (m, 1H, –C*H*–CH(OH)–Ar), 2.41 (br.s, 1H, –O*H*), 3.07–3.11 (m, 1H, HO–CH$_2$–C*H*–), 3.61–3.63 (m, 4H, HO–C*H*$_2$–, –C*H*$_2$O–), 3.85 (d, 1H, *J*=5.37, 11.23, –C*H*(OH)–), 4.83 (d, 1H, *J*–7.33, –C*H*(OTBS)–Ar), 5.38 (br.s, 1H, –O*H*), 7.12–7.15 (m, 1H, Ar–*H*), 7.40–7.43 (m, 1H, Ar–*H*), 7.63–7.67 (m, 1H, Ar–*H*), 8.39–8.43 (m, 1H, Ar–*H*). ^{13}C–NMR (100 MHz, $CDCl_3$) 162.40, 148.21, 137.10, 122.80, 121.25, 101.10, 74.14, 68.23, 59.49, 49.61, 46.82, 25.73, 18.00, –4.52, –4.74. *Anal.* Found: C, 61.27; H, 8.45; N, 3.97. Calcd. for $C_{17}H_{27}NO_3Si$: C, 60.14; H, 8.61; N, 4.13%.

3-Pyridyllactol (**8b**) Yield 63%, white amorphous solid, mp 116 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) δ -6.64 (s, 3H, -Si-CH_3), -0.03 (s, 3H, -Si-CH_3), 0.80 (s, 9H, -Si-CH_3), 1.74 (br.s, 1H, -O*H*), 2.33-2.38 (m, 1H, -C*H*-CH(OTBS)-Ar), 3.06-3.12 (m, 1H, HO-CH_2-C*H*-,), 3.42 (d.d, 2H, *J*=8.79, 8.79, -CH_2O-), 3.63 (d.d, 2H, *J*=8.31, 8.31, HO-CH_2-), 3.89 (d.d, 1H, *J*=4.2, 11.04, -C*H*(OH)-), 4.67 (d, 1H, *J*=8.79, -C*H*(OTBS)-Ar), 5.47 (s, 1H, *H*O-CH_2-), 7.22-7.25 (m, 1H, Ar-*H*), 7.62-7.77 (m, 1H, Ar-*H*), 8.44-8.52 (m, 2H, Ar-*H*), ^{13}C-NMR (100 MHz, $CDCl_3$) 149.40, 147.94, 139.42, 134.81, 124.00, 101.73, 71.55, 68.94, 59.88, 49.46, 47.72, 26.05, 25.83, 18.17, -3.78, -4.95. *Anal.* Found: C, 59.88; H, 8.45; N, 4.08. Calcd. for $C_{17}H_{27}NO_3Si$: C, 60.14; H, 8.61; N, 4.13%.

4-Pyridyllactol (**8c**) Yield 53%, white needle solid, mp 137-138 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) δ -6.64 (s, 3H, -Si-CH_3), -0.03 (s, 3H, -Si-CH_3), 0.80 (s, 9H, -Si-CH_3), 2.27-2.31 (m, 1H, -C*H*-CH(OTBS)-Ar), 2.41-2.43 (m, 1H, HO-CH_2-C*H*-,), 3.33-3.67 (m, 4H, -CH_2O-, HO-CH_2-), 3.83-3.89 (m, 1H, -C*H*(OH)-), 4.66 (d, 1H, *J*=8.40, -C*H*(OTBS)-Ar), 5.43 (s, 1H, *H*O-CH_2-), 7.19-7.20 (m, 2H, Ar-*H*), 8.48-8.50 (m, 2H, Ar-*H*), ^{13}C-NMR (100 MHz, $CDCl_3$) 152.49, 149.49, 149.82, 121.58, 121.38, 101.65, 72.37, 68.82, 60.04, 49.05, 47.02, 25.68, 17.98, -4.12, -3.95. *Anal.* Found: C, 59.77; H, 8.45; N, 4.07. Calcd. for $C_{17}H_{27}NO_3Si$: C, 60.14; H, 8.61; N, 4.13%.

4-[1-(tert-Butyldimethylsilyl)oxy-1-pyridylmethyl]-3-hydroxymethyl-2-dihydro-2(3H)-furanones (**9**)

A vigorously stirred solution of **8** (1.74 g, 5.13 mmol) and Ag_2CO_3 celite (4.62 g, 1 mmol/0.6 g, 7.7 mmol) in benzene (50 ml) was heated under refluxing for 30 minutes. The reaction mixture was filtered through a celite pad. Concentration followed by column chromatography (silicagel, EtOAc) gave pure lactones **9**.

2-Pyridyllactone (**9a**) Yield 54%, white amorphous solid, mp 62-63 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) δ -0.27 (s, 3H, -Si-CH_3), -0.03 (s, 3H, -Si-CH_3), 0.81 (s, 9H, -Si-CH_3), 2.65-2.70 (m, 1H, -C*H*-CH(OH)-Ar), 3.12-3.19 (m, 1H, HO-CH_2-C*H*-), 3.73-3.74 (m, 2H, *H*O-CH_2-, -CH_2O-), 3.97-4.04 (m, 2H, HO-CH_2-, -CH_2O-), 4.01 (d.d, 1H, *J*=5.37, 4.40, HO-CH_2-), 5.02 (d, 1H, *J*=4.40, -C*H*(OTBS)-Ar), 7.05-7.36 (m, 1H, Ar-*H*), 7.41-7.56 (m, 1H, Ar-*H*), 7.57-7.59 (m, 1H, Ar-*H*), 8.34-8.43 (m, 1H, Ar-*H*). ^{13}C-NMR (100 MHz, $CDCl_3$) 178.45, 161.16, 148.96, 140.13, 137.39, 123.21, 121.14, 75.06, 69.99, 60.69, 59.72, 45.33, 44.91, 26.05, 18.30, -4.31, -4.82. *Anal.* Found: C, 59.97; H, 7.91; N, 4.07. Calcd. for $C_{17}H_{27}NO_4Si$: C, 60.5; H, 8.06; N, 4.15%.

3-Pyridyllactone (**9b**) Yield 99%, white amorphous solid, mp 94-95 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) δ -0.03 (s, 3H, -Si-CH_3), -0.49 (s, 3H, -Si-CH_3), 0.80 (s, 9H, -Si-CH_3), 3.17-3.21 (m, 1H, -C*H*-CH(OTBS)-Ar), 3.64-3.65 (m, 1H, HO-CH_2-C*H*-,), 4.10 (d.d, 2H, *J*=8.91, 8.91, -CH_2O-), 4.36 (d.d, 1H, *J*=8.91, 8.91, HO-CH_2-), 4.50 (d.d, 1H, *J*=8.91, 8.91, HO-CH_2-), 4.58 (d.d, 1H, *J*=3.40, 10.25, *H*O-CH_2-), 5.48 (d, 1H, *J*=8.91, -C*H*(OTBS)-Ar), 7.71-7.74 (m, 1H, Ar-*H*), 8.03-8.13 (m, 1H, Ar-*H*), 8.91-8.96 (m, 2H, Ar-*H*), ^{13}C-NMR (100 MHz, $CDCl_3$) 179.16, 149.48, 147.78, 137.55, 134.50, 123.74, 71.37, 69.61, 59.75, 46.55, 44.85, 25.52, 17.73, -4.07, -5.02. *Anal.* Found: C, 61.28; H, 8.00; N, 4.01. Calcd. for $C_{17}H_{27}NO_4Si$: C, 60.5; H, 8.06; N, 4.15%.

4-Pyridyllactone (**9c**) Yield 79%, white amorphous solid, mp 151-152 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, TMS) δ -0.42 (s, 3H, -Si-CH_3), -0.02 (s, 3H, -Si-CH_3), 0.77 (s, 9H, -Si-CH_3), 2.67-2.64 (m, 1H, -C*H*-CH(OTBS)-Ar), 2.93-2.95 (m, 1H, HO-CH_2-C*H*-), 3.55 5.43 (br.s, 1H, *H*O-CH_2-), 3.68 (d.d, 1H, *J*=8.30, 8.30, HO-CH_2-), 3.89-4.01 (m, 2H,

–CH_2O–) 4.88 (d, 1H, J=7.80, –CH(OTBS)–Ar), 7.16–7.18 (m, 2H, Ar–H), 8.47–8.49 (m, 2H, Ar–H), ^{13}C–NMR (100 MHz, $CDCl_3$) 178.83, 151.10, 150.08, 121.60, 121.35, 72.81, 69.74, 59.94, 46.20, 44.80, 25.63, 17.88, -4.05, -4.50. *Anal.* Found: C, 60.66; H, 8.00; N, 4.07. Calcd. for $C_{17}H_{27}NO_4Si$: C, 60.5; H, 8.06; N, 4.15%.

4–[1–(tert–Butyldimethylsilyl)oxy–1–pyridylmethyl]–3–methylenedihydro–2(3 H)–furanones (**10**)

To a solution of **9** (240 mg, 0.71 mmol) and triethylamine (0.2 ml, 1.42 mmol) in benzene (50 ml) was added methanesulfonyl chloride (0.1 ml, 1.07 mmol) at 0 °C. After stirring for 3 hr at room temperature, to the mixture was added saturated aqueous citric acid solution (1 ml) and EtOAc (50 ml). The organic layer was separated, washed with water, saturated aqueous $NaHCO_3$ solution, brine, and dried (Na_2SO_4). Concentration followed by column chromatography (silicagel, EtOAc) gave pure methylenelactones **10**.

2–Pyridylmethylenelactone (**10a**) Yield 45%, colorless amorphous solid, mp 68–69 °C. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ–0.27 (s, 3H, –Si–CH_3), –0.03 (s, 3H, –Si–CH_3), 0.80 (s, 9H, –Si–CH_3), 3.39–3.41 (m, 1H, –CH–CH(OH)–Ar), 4.21–4.30 (m, 2H, –CH_2O–), 4.86 (d, 1H, J=5.86, –CH(OTBS)–Ar), 4.87 (s, 1H, CH_2=C–), 6.09 (s, 1H, CH_2=C–), 7.12–7.15 (m, 1H, Ar–H), 7.29–7.31 (m, 1H, Ar–H), 7.60–7.64 (m, 1H, Ar–H), 8.45–8.46 (m, 1H, Ar–H). ^{13}C–NMR (100 MHz, $CDCl_3$) 170.98, 160.64, 149.20, 136.56, 134.36, 124.36, 123.06, 121.84, 77.40, 68.56, 45.78, 25.92, 18.18. *Anal.* Found: C, 63.91; H, 7.89; N, 4.05. Calcd. for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38%.

3–Pyridylmethylenelactone (**10b**) Yield 50%: colorless oil. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ–0.28 (s, 3H, –Si–CH_3), –0.28 (s, 3H, –Si–CH_3), 0.80 (s, 9H, –Si–CH_3), 3.20–3.21 (m, 1H, –CH–CH(OTBS)–Ar), 4.14–4.22 (m, 2H, –CH_2O–), 4.77 (d, 1H, J=5.86, –CH(OTBS)–Ar), 6.24 (s, 1H, CH_2=C–), 6.25 (s, 1H, CH_2=C–), 7.21–7.25 (m, 1H, Ar–H), 7.56–7.57 (m, 1H, Ar–H), 8.91–8.96 (m, 2H, Ar–H), ^{13}C–NMR (100 MHz, $CDCl_3$) 170.42, 149.73, 148.40, 136.44, 164.55, 134.22, 125.28, 123.36, 74.55, 67.84, 46.95, 25.78, 18.09, –4.36, –4.91. *Anal.* Found: C, 61.37; H, 8.01; N, 4.44. Calcd. for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38%.

4–Pyridylmethylenelactone (**10c**) Yield 88%, white amorphous solid, mp 79–80 °C. ^{1}H–NMR (400 MHz, $CDCl_3$, TMS) δ–0.34 (s, 3H, –Si–CH_3), 0.03 (s, 3H, –Si–CH_3), 0.90 (s, 9H, –Si–CH_3), 3.15–3.16 (m, 1H, –CH–CH(OTBS)–Ar), 4.15–4.24 (m, 2H, –CH_2O–) 4.70 (d, 1H, J=5.40, –CH(OTBS)–Ar), 5.21 (d, 1H, J=0.98, CH_2=C–), 6.23 (d, 1H, J=1.46, CH_2=C–), 7.14–7.15 (m, 2H, Ar–H), 8.53–8.54 (m, 2H, Ar–H), ^{13}C–NMR (100 MHz, $CDCl_3$) 170.26, 149.94, 149.71, 133.72, 125.29, 121.63, 75.46, 67.76, 46.53, 25.64, 18.01, 1.02, –4.50, –4.32. *Anal.* Found: C, 61.55; H, 8.32; N, 4.31. Calcd. for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38%.

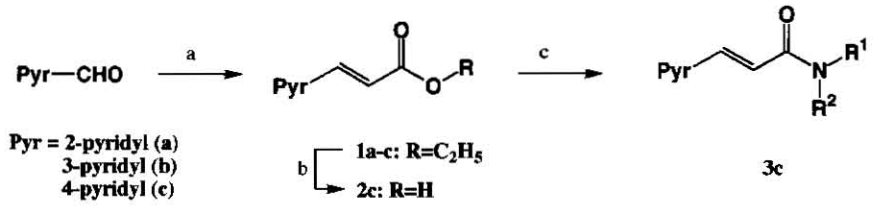
Lettuce seedling tests

Lettuce (*Lactuca sativa* L. cv. Sacramento) seedling tests were performed by the same method as described previously (Kikuchi *et al.*, 1990). The inhibitory activity of compounds was evaluated after 4 days by inspecting the rate of growth of the hypocotyls and roots. The inhibitory rates were determined by percentage of the averaged lengths of hypocotyls and roots of treated plants to those of controls and indicated according to the following scale: **0**$<$10%$\leq$**1**$<$30%$\leq$**2**$<$50%$\leq$**3**$<$70%$\leq$**4**$<$90%$\leq$**5**

RESULTS AND DISCUSSIONS

Synthesis

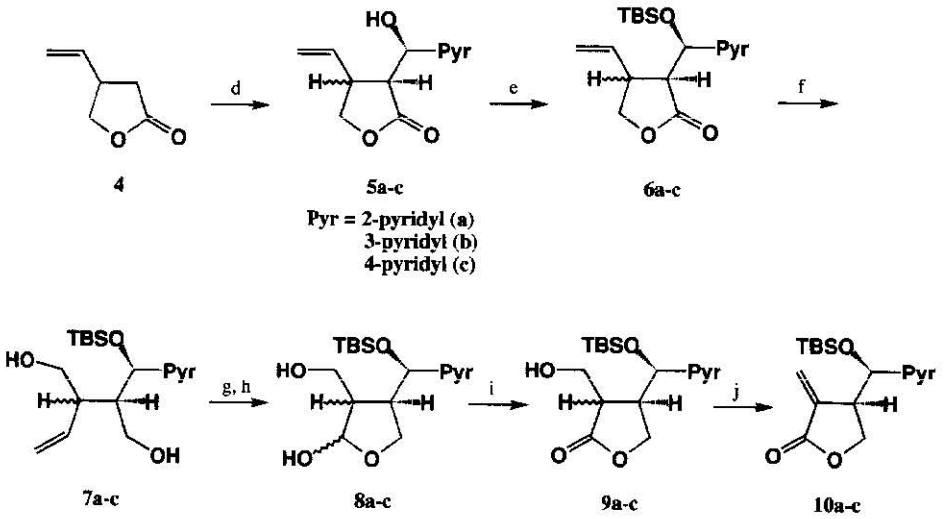
The synthesis of ethyl 3-pyridyl-2-propenoates (**1a–c**) was accomplished by the reaction of 2-, 3-, and 4-pyridinecarboxaldehydes with diethyl ethoxycarbonylmethylphosphonate using potassium carbonate as a base. In the 2-pyridyl analog **1a**, *trans* isomer **1a–1** produced with a small amount of *cis* isomer **1a–2** which was separated by column chromatography on silica gel. Confirmation of the structure of stereoisomers of **1a–1** and **1a–2** was provided from ^{1}H-NMR spectra; the coupling constants between 2-*H* and 3-*H* of **1a–1** and **1a–2** were observed as 15.9 and 12.7 Hz, respectively. In the 3- and 4-pyridyl analogs, *cis* isomers were not detected in the reaction mixture by TLC. The ethyl ester **1c** was hydrolyzed to its corresponding carboxylic acid **2c**, which was treated with alkylamines in the presence of water-soluble carbodiimide and 1-hydroxybenzotriazole to give amides **3c** (Scheme 1).



a) diethyl ethoxycarbonylmethylphosphonate, K_2CO_3, H_2O;
b) NaOH, EtOH, H_2O;
c) amine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl, 1-hydroxybenzotriazole, CH_2Cl_2

Scheme 1. Synthesis of pyridylpropenoic acid derivatives

The general synthetic pathway for the preparation of the pyridine derivatives possessing a γ-butyrolactone ring is shown in Scheme 2. β-Vinyl-γ-butyrolactone **4** was prepared according to the procedure reported (Kondo and Mori, 1974). The lithium enolate of **4** generated with 1.2 equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C was treated with 2-, 3-, and 4-pyridinecarboxaldehydes to give a mixture of *erythro* and *threo* aldol products in 87–90% yields in the respective ratio of *c.a.* 1:1, which was calculated based on their NMR spectra. Recrystallization from ethyl acetate afforded pure *erythro* **5a–c**. After protecting a secondary hydroxyl group with *t*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole, the silyl ethers **6a-c** were reduced with lithium aluminum hydride giving diols **7a–c** quantitatively. Dihydroxylation of **7a–c** by using a catalytic amount of osmium tetraoxide and



d) LDA, Pyr-CHO, THF; e) TBSCl, imidazole, DMF; f) $LiAlH_4$, THF;
g) cat. OsO_4, NMO, acetone:*t*-BuOH:H_2O=4:1:1; h) $NaIO_4$, aq. EtOAc
i) Ag_2CO_3–Celite, benzene; j) mesyl chloride, Et_3N, benzene.

Scheme 2. Synthesis of pyridine derivatives with a γ–butyrolactone ring

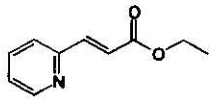
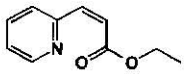
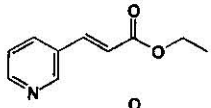
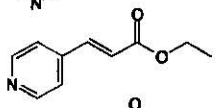
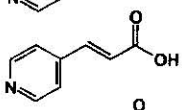
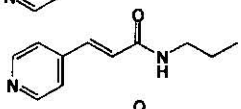
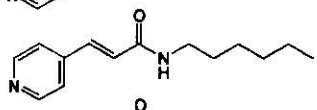
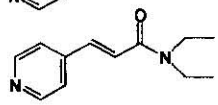
N–methylmorpholine *N*–oxide as a reoxidant and successive periodate oxidation afforded lactols **8a–c**. The lactols **8a–c** were oxidized with silver carbonate–celite to lactones **9a–c**, which were treated with methanesulfonyl chloride in the presence of triethylamine to give **10a–c**. The mesylated **9a–c** could not be isolated in this reaction, where the mesyl group eliminated without base to result in **10a–c**.

Plant-growth inhibiting activity

Table 1 shows the effects of a number of 3–pyridyl–2–propenoic acid derivatives on the growth of lettuce seedlings. The pyridine analogs of ethyl cinnamate (**1a–1c**) irrespective of the position of a nitrogen atom inhibited the growth of lettuce seedlings at 50 ppm. In the 2–pyridyl analogs, there was little difference in activity between *cis* and *trans* isomer. Among the ester analogs, the 4–pyridine isomer **1c** showed the highest activity, which inhibited the growth of hypocotyl and root at 10 ppm. The activity of 3–(4–pyridyl) –2–propenoic acid (**2c**) is less than that of the ester analog **1c**. In contrast to the ester analogs, compound **2c** had little effect on the hypocotyl growth. Since the 4–pyridine analog showed considerably higher activity than other isomers, further modification was made in the compound **1c** by replacing the ester group with an amide group. The *N*–propylamide **3c–1** had low inhibitory activity on comparison with the ester analog **1c**. The activity of amide analogs was found to fall off with increasing size of the *N*–alkyl substituent (**3c–2**), while the additional introduction of an alkyl group at the nitrogen

atom (**3c–3**) increased the activity. Compound **3c–3** at 50 ppm caused greater than 90% inhibition of the hypocotyl and root growth compared to the control, however, the activity rapidly decreased at 10 ppm. *N, N*–Diethyl cinnamamide at 50 ppm had no activity on the growth of hypocotyl (data not shown), indicating that the presence of a nitrogen atom at the 4–position of the benzene ring was essential for the activity. Although it remains to be seen whether or not compounds **1c** and **3c–3** inhibited cinnamate 4–hydroxylase in the lettuce seedlings, 3–(4–pyridyl)–2–propenoic acid derivatives might be a lead for the development of a new herbicide.

Table 1. Effects of pyridine derivatives on the growth of lettuce seedlings

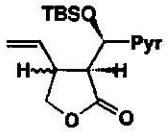
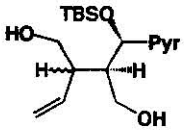
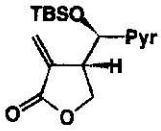
Compound	Growth rate			
	Hypocotyl		Root	
Conc. (ppm)	50	10	50	10
1a-1 	2	0	2	0
1a-2 	2	0	2	1
1b 	2	1	2	0
1c 	3	2	4	3
2c 	1	0	3	2
3c-1 	3	2	3	1
3c-2 	2	1	1	1
3c-3 	5	2	5	2

The bioassay data for pyridine derivatives with a γ–butyrolactone and related compounds on the growth of lettuce seedlings are given in Table 2. In a series of pyridine analogs with a vinyllactone (**6a–6c**), the 3– and 4–pyridine analogs (**6b** and **6c**) at 10 ppm

inhibited the growth of hypocotyl and root more than 30% compared to the control, whereas the 2-pyridine analog **6a** showed low activity even at 100 ppm. In contrast, all of the pyridine analogs with a 1,4-butanediol (**7a–7c**) and a methylenelactone (**10a–10c**) substituent had almost the same activity. It is noteworthy that the presence of the γ-butyrolactone was dispensable for the activity.

The design of inhibitors targeted at the P450 enzymes which are involved in essential physiological functions in plants would be appear to be a promising field for future research. Further studies on this new series of pyridines are in progress.

Table 2. Effects of pyridine derivatives with a γ-lactone ring and related compounds on the growth of lettuce seedlings

Compound		Growth rate					
		Hypocotyl			Root		
	Conc. (ppm)	100	10	1	100	10	1
	2-pyridyl (**6a**)	2	0	0	0	0	0
	3-pyridyl (**6b**)	4	2	1	4	2	2
	4-pyridyl (**6c**)	4	2	1	4	2	0
	2-pyridyl (**7a**)	4	2	0	3	2	0
	3-pyridyl (**7b**)	3	0	0	3	2	0
	4-pyridyl (**7c**)	4	0	0	3	2	0
	2-pyridyl (**10a**)	3	2	0	4	2	0
	3-pyridyl (**10b**)	3	2	0	4	2	0
	4-pyridyl (**10c**)	4	0	0	4	2	1

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