Pergamon

Tetrahedron Vol. 51, No. 32, pp. 8809-8814, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00488-2

Synthesis of (-)-Syringolides 1 and 2

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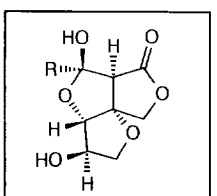
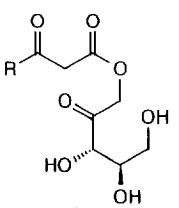
Abstract: The enantioselective synthesis of (-)-syringolides 1 and 2 which were isolated as specific elicitors produced by *Pseudomonas syringae* pv. *tomato* was accomplished in 11 steps from diethyl D-tartrate. The specific rotations of synthetic samples were in good accord with those of the natural syringolides, and synthetic syringolide 2 showed almost the same biological activity as that of natural syringolide 2.

Many plant pathogens produce signal molecules which are recognized specifically by resistant plants and enable the plants to initiate active defense responses against these pathogens.[1,2] These molecules are produced through the action of avirulence genes of the pathogens and known as specific elicitors. On the other hand, occurrence of the defense responses including the hypersensitive reaction and accumulation of phytoalexins requires the plants to have resistance genes which is postulated to encode receptors for the pathogen elicitors.[1] In 1993 Keen *et al.* isolated two *C*-glycosides possessing a new ring system as specific elicitors from *Pseudomonas syringae* pv. *tomato* and named them syringolide 1 (**1**) and syringolide 2 (**2**).[2,3] Their structures were assigned by NMR experiments, biosynthetic arguments and molecular modeling, and confirmed by X-ray crystallographic analysis. The absolute configurations of **1** and **2** were deduced from the assumption that the incorporated xylulose moiety should be the naturally occurring D-form, the normal product of D-glucose metabolism in *P. syringae*.[2] These elicitors are shown to be produced extracellularly by bacteria expressing avirulence gene D (*avrD*) and cause the hypersensitive reaction specifically in soybean plants carrying the resistance gene, *Rpg4*.[2] It is desired now to synthesize syringolide analogs which can be immobilized on a polymer support for isolating the receptor by affinity chromatography. This requires, first of all, the



1 R=*n*-C_5H_{11}
2 R=*n*-C_7H_{15}



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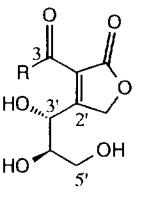

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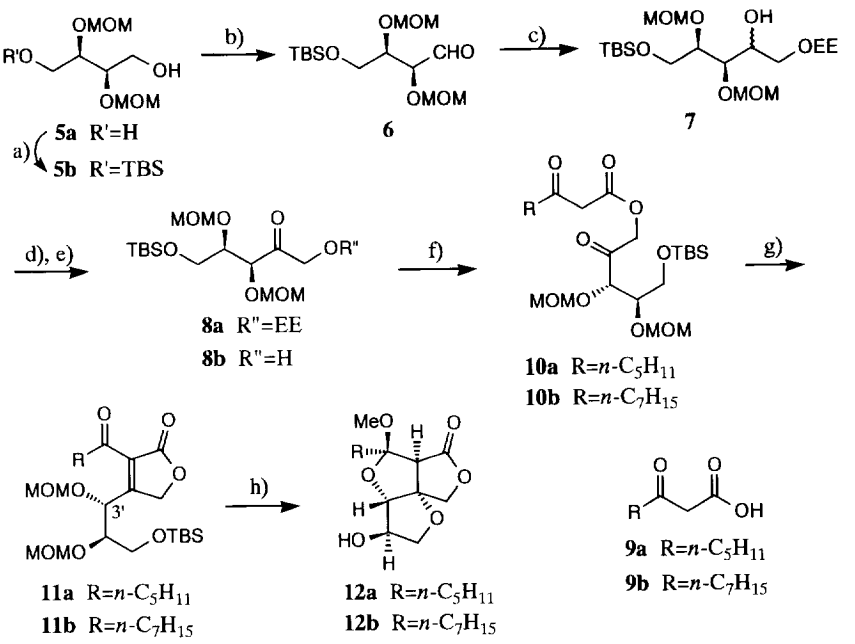

Scheme 1. a) NaH, TBSCl, THF; b) Swern oxidation; c) Bu_3SnCH_2OEE, *n*-BuLi, THF; d) Swern oxidation; e) PPTS, EtOH; f) **9a** or **9b**, DCC, DMAP, CH_2Cl_2; g) SiO_2, *n*-hexane-EtOAc; h) Dowex 50W-X8, MeOH.

establishment of a synthetic route to the syringolides. In this paper, we describe the synthesis of the naturally occurring enantiomers of **1** and **2**, which is applicable to the synthesis of syringolide analogs containing a binding site on their aliphatic side chains.[4]

Our synthetic plan is based on the proposed biosynthetic pathway,[2] which includes the Knoevenagel condensation of **3**, followed by conjugate addition of 5'-OH to the 2'-sp^2-carbon of the resulting α-acyl-α,β-unsaturated lactone **4** and hemiacetalization of 3'-OH to C3 carbonyl function. We expected that the asymmetry at C3' of **4** would control desirably the configurations of the newly formed stereocenters of **1** or **2**, owing to the thermodynamic stability of the *cis*-fused oxabicyclo[3.3.0]octane system incorporated in **1** and **2** as compared with the corresponding *trans*-fused system.

Our synthesis began with the monoprotection[5] of the known diol **5a** which was obtained from diethyl D-tartrate in 97% yield by protection and reduction (Scheme 1).[6] The Swern oxidation of the resulting alcohol **5b** into **6** was followed by the addition of (1-ethoxyethoxy)methyllithium prepared from Still's organotin reagent[7] to give **7** as a diastereomeric mixture. Oxidation of **7** and subsequent selective deprotection gave **8b**, a protected form of D-xylulose, *via* **8a** in 57% overall yield from **5a**. This alcohol **8b** was esterified with β-keto carboxylic acids,[8,9] **9a** or **9b**, to give **10a** or **10b**, respectively, which correspond to protected forms of **3**. The Knoevenagel condensation of **10** into **11** using various reported conditions[10] did not proceed smoothly, resulting in the formation of complex mixtures or only deprotected products. However, we noticed fortunately that a small amount of a new compound was produced during the SiO_2 column chromatographic purification of **10b**. The newly formed compound showed absorptions at 1770, 1690 and 1625 cm^{-1} which are indicative of the α-acyl-α,β-unsaturated five-membered lactone structure incorporated in **11b**. When treated with SiO_2 in *n*-

hexane-EtOAc for 15 h at room temperature, **10b** was transformed into **11b** in 56% overall yield from **8b**. Having realized the Knoevenagel condensation, we proceeded to the final stage of the synthesis which consists of three transformations: 1) deprotection; 2) conjugate addition; and 3) hemiacetalization. Although the direct conversion of **11b** into **2** using aqueous acidic conditions (30% $HClO_4$-THF, H_2SO_4-H_2O-THF, TFA-H_2O-THF, Dowex 50W-X8-H_2O-MeOH and so on) were unsuccessful, the methyl ether of **2** (*i.e.* **12b**) could be obtained in 36% yield by treating with Dowex 50-X8 or Amberlyst 15E in dry methanol for 60-72 h at room temperature.[11] Its ^1H NMR spectrum was identical with that of the authentic sample derived from natural syringolide 2.[2] Finally, **12b** was hydrolyzed by treating with *p*-TsOH in acetone-water for 16 h at room temperature to give **2** as colorless needles (m.p. 118-120.5°C), whose ^1H and ^{13}C NMR spectra were identical with those of natural syringolide 2. By the same sequence of reactions, **10a** was converted into **1** (m.p. 113-114.5°C), whose spectral properties were identical with those of natural syringolide 1. The specific rotations of **1** and **2**, $[\alpha]_D^{22}$ -83.3° (c=0.108, $CHCl_3$) and $[\alpha]_D^{22}$ -79° (c=0.26, $CHCl_3$) , respectively, were in good accord with those of natural syringolides 1 and 2, $[\alpha]_D^{24}$ -83.66° (c=0.15, $CHCl_3$) and $[\alpha]_D^{24}$ -75.91° (c=0.22, $CHCl_3$), respectively,[2] and a preliminary experiment showed that synthetic syringolide 2 had almost the same biological activity as that of natural syringolide 2.

In conclusion, the enantioselective synthesis of syringolides 1 and 2 was achieved on the basis of the proposed biosynthetic pathway in 11 steps from diethyl D-tartrate. Synthetic studies of the syringolide analogs containing an amino functionality on the aliphatic side chain are now under way.

Experimental

All mps and bps are uncorrected. IR spectra were measured as films for oils or KBr discs for solids on a Jasco FT/IR-5000 spectrometer. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with TMS as an internal standard in $CDCl_3$ on a JEOL JNM-A500 spectrometer unless otherwise stated. High resolution mass spectra (70 eV) were measured on a Shimadzu GCMS 9020-DF spectrometer. Optical rotations were measured with a Jasco DIP-370 polarimeter. THF was purified by distilling from benzophenone ketyl. CH_2Cl_2 was purified by drying with P_2O_5 followed by distilation from CaH_2. Merck Kieselgel 60 Art 7734 was used for SiO_2 column chromatography.

(2R,3R)-2,3-bis(methoxymethoxy)-4-[(t-butyldimethylsilyl)oxy]-1-butanol **5b**. Sodium hydride (60% in mineral oil, 6.24 g, 156 mmol) was washed three times with *n*-pentane and suspended in THF (156 ml). To this mixture was added dropwise a solution of **5a** (mp 62-63°C, $[\alpha]_D^{22}$ +7.71° (c=3.40, MeOH); 29.8 g, 142 mmol) in THF (90 ml) at 0°C and the mixture was stirred for 1 h at rt. The mixture was cooled to 0°C and a solution of TBSCl (23.5 g, 156 mmol) in THF (70 ml) was added dropwise. After 30 min, the mixture was poured into sat. $NaHCO_3$ aq. and extracted with ether. The extract was washed with water, sat. $NaHCO_3$ aq. and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (150 g, *n*-hexane-EtOAc) to give 41.8 g (91%) of **5b** as an oil; $[\alpha]_D^{22}$ -1.3° (c=2.7, $CHCl_3$); ν_{max} 3470 (m), 1260 (m), 1150 (s), 1110 (s), 1030 (vs), 830 (s) cm^{-1}; δ 0.07 (6H, s), 0.89 (9H, s), 3.21-3.24 (1H, m, OH), 3.41 (3H, s), 3.43 (3H, s), 3.72-3.78 (6H, m), 4.66 (1H, d, *J*=6.5Hz), 4.70 (1H, d, *J*=6.5Hz), 4.75 (1H, d, *J*=6.5Hz), 4.77 (1H, d, *J*=6.5Hz). Anal. Calcd for $C_{14}H_{32}O_6Si$: C, 51.82; H, 9.94. Found: C, 52.18; H, 10.04.

(2S,3R)-2,3-bis(methoxymethoxy)-4-[(t-butyldimethylsilyl)oxy]butanal **6**. To a solution of $(COCl)_2$ (7.70 ml, 88.3 mmol) in CH_2Cl_2 (230 ml) was added dropwise a solution of DMSO (12.5 ml, 177 mmol) in CH_2Cl_2 (50 ml) at -78°C. After 20 min, a solution of **5b** (22.0 g, 67.9 mmol) in CH_2Cl_2 (66 ml) was added and the mixture was stirred for 2 h. To this mixture was then added a solution of Et_3N (47.3 ml, 340 mmol) in CH_2Cl_2 (94 ml) and the reaction mixture was gradually warmed to rt. The mixture was poured into sat. $NaHCO_3$ aq. and extracted with ether. The extract was washed with water (three times) and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 23.3 g of crude **6**; ν_{max} 1730 (s), 1250 (s), 1160 (s), 1110 (s),

1030 (vs), 830 (s); δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 3.34 (3H, s), 3.45 (3H, s), 3.76 (1H, dd, *J*=7.5, 10.0Hz), 3.79 (1H, dd, *J*=6.0, 10.0Hz), 4.04 (1H, ddd, *J*=3.5, 6.0, 7.5Hz), 4.20 (1H, dd, *J*=1.0, 3.5Hz), 4.62 (2H, d, *J*=6.5Hz), 4.70 (2H, d, *J*=6.5Hz), 4.76 (1H, d, *J*=6.5Hz), 4.82 (1H, d, *J*=6.5Hz), 9.78 (1H, d, *J*=1.0Hz). This compound was used for the next step without further purification.

(3S,4R)-3,4-bis(methoxymethoxy)-5-[(t-butyldimethylsilyl)oxy]-1-(1-ethoxyethoxy)-2-pentanone **8a**. To a solution of [(1-ethoxyethoxy)methyl]tributylstannane (4.13 g, 10.5 mmol) in THF (40 ml) was added dropwise *n*-BuLi (1.61 N in *n*-hexane, 7.52 ml, 12.1 mmol) at -78°C under N_2. After 15 min, a solution of crude **6** (2.60 g, 8.07 mmol) in THF (30 ml) was added and the mixture was stirred for 1 h. The reaction was quenched by the addition of sat. NH_4Cl aq. and water, and the mixture was extracted with ether. The extract was washed with water and brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (150 g, *n*-hexane-EtOAc) to give 2.62 g (76%) of **7** as an oil; ν_{max} 3480 (m). To a solution of $(COCl)_2$ (0.98ml, 11.3 mmol) in CH_2Cl_2 (35 ml) was added a solution of DMSO (1.60 ml, 22.5 mmol) in CH_2Cl_2 (8 ml) at -78°C. After 20 min, a solution of **7** obtained above (3.20 g, 7.5 mmol) in CH_2Cl_2 (13 ml) was added and the mixture was stirred for 2 h. To this mixture was added a solution of Et_3N (6.53 ml, 46.9 mmol) in CH_2Cl_2 (13 ml) and the reaction mixture was gradually warmed to rt. The mixture was poured into sat. $NaHCO_3$ aq. and extracted with ether. The extract was washed with water (three times) and brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (50 g, *n*-hexane-EtOAc) to give 2.91 g (92%) of **8a** as an oil; $[\alpha]_D^{22}$ -17.7° (c=2.83, $CHCl_3$); ν_{max} 1740 (s), 1260 (m), 1160 (s), 1100 (vs), 1030 (vs), 830 (s); δ 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.185 and 1.190 (3H, 2t, *J*=7.0Hz), 1.35 (3H, d, *J*=5.5Hz), 3.31 (3H, s), 3.425 and 3.430 (3H, 2s), 3.46-3.54 (1H, m), 3.62-3.68 (1H, m), 3.69-3.78 (2H, m), 4.06-4.10 (1H, m), 4.42 (1H, d, *J*=18.0Hz), 4.48 (1H, br s), 4.53 (1H, d, *J*=18.0Hz), 4.58 (1H, d, *J*=6.5Hz), 4.67 and 4.68 (1H, 2d, *J*=6.5Hz), 4.725 and 4.730 (2H, 2s), 4.80-4.85 (1H, m); HRMS m/z 424.2458 (calcd for $C_{19}H_{40}O_8Si$, 424.2491).

(3S,4R)-3,4-bis(methoxymethoxy)-5-[(t-butyldimethylsilyl)oxy]-1-hydroxy-2-pentanone **8b**. A mixture of **8a** (2.91 g, 6.90 mmol) and PPTS (0.17 g, 0.690 mmol) in ethanol was stirred for 2.5 h at rt. The mixture was poured into sat. $NaHCO_3$ aq. and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (40 g, *n*-hexane-EtOAc) to give 2.20 g (90%) of **8b** as an oil; $[\alpha]_D^{22}$ -9.21° (c=3.18, $CHCl_3$); ν_{max} 3480 (s), 1725 (s), 1250 (s), 1150 (s), 1100 (vs), 1020 (vs), 830 (s); δ 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 3.04 (1H, t, *J*=5.0Hz, OH), 3.30 (3H, s), 3.43 (3H, s), 3.70 (1H, dd, *J*=8.0, 10.0Hz), 3.76 (1H, dd, *J*=5.5, 10.0Hz), 4.01 (1H, ddd, *J*=3.0, 5.5, 8.0Hz), 4.43 (1H, d, *J*=3.0Hz), 4.50 (1H, dd, *J*=5.0, 19.5Hz), 4.56 (1H, d, *J*=7.0Hz), 4.58 (1H, dd, *J*=5.0, 19.5Hz), 4.65 (1H, d, *J*=7.0Hz), 4.74 (2H, s); HRMS m/z 352.1931 (calcd for $C_{15}H_{32}O_7Si$, 352.1916).

3-Oxodecanoic acid **9a**. Sodium hydride (60% in mineral oil, 3.50 g, 87.5 mmol) was washed three times with *n*-pentane and suspended in THF (100 ml). To this suspension was added dropwise a solution of methyl acetoacetate (10.0 g, 86.2 ml) in THF (150 ml) at 0°C. After 30 min, *n*-BuLi (1.66 N in *n*-hexane, 55.0 ml, 91.3 mmol) was added and the mixture was stirred for 30 min. To this mixture was added 1-iodohexane (13.67 ml, 92.6 mmol) and the mixture was stirred for 4 h at rt. The mixture was poured into 3 N HCl (42 ml) and extracted with ether. The extract was washed with $Na_2S_2O_3$ aq. and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 14.3 g (83%) of methyl 3-oxodecanoate, bp 94-99°C (1 mmHg); ν_{max} 1750 (s), 1720 (s), 1660 (m). This ester (3 g, 15 mmol) was dissolved in ethanol (30 ml), mixed with 3 N KOH (12.5 ml, 37.5 mmol) and stirred for 6 h at rt. The mixture was diluted with EtOAc, neutralized with a solution of oxalic acid (3.35 g, 37.2 mmol) in water (33 ml) and extracted with EtOAc. The extract was washed with brine (two times), dried ($MgSO_4$) and concentrated *in vacuo* to give **9a** as a colorless solid, which was purified by washing with *n*-hexane to give 1.35 g (48%) of pure **9a**, mp 81-82°C; ν_{max} ~3100 (m, br), 1725 (s), 1705 (s); δ 0.88 (3H, t, *J*=7.0Hz), 1.22-1.34 (8H, m), 1.55-1.66 (2H, m), 2.56

(2H, t, *J*=7.5Hz), 3.53 (2H, s); HRMS m/z 142.1340 (M^+ - CO_2) (calcd for $C_9H_{18}O$, 142.1357).

3-Oxooctanoic acid **9b**. In the same manner as described for the preparation of **9a**, 10 g (86.1 mmol) of methyl acetoacetate and 17.1 g (92.9 mmol) of 1-iodobutane gave 3.42 g (25%) of **9b** *via* methyl 3-oxooctanoate (bp 70-74°C, 1 mmHg), mp 72-73°C; ν_{max} ~3100 (m, br), 1725 (s), 1700 (s); δ 0.90 (3H, t, *J*=7.0Hz), 1.24-1.36 (4H, m), 1.63 (2H, quin, *J*=7.5Hz), 2.57 (2H, t, *J*=7.5Hz), 3.53 (2H, s); HRMS m/z 158.0965 (calcd for $C_8H_{14}O_3$, 158.0942).

(3S,4R)-3,4-bis(methoxymethoxy)-4-[(t-butyldimethylsilyl)oxy]-2-oxopentyl 3-oxodecanoate **10b**. To a mixture of **8b** (8.10 g, 23.1 mmol) and DCC (6.53 g, 31.7 mmol) in CH_2Cl_2 (162 ml) was added **9b** (5.89 g, 31.7 mmol) and DMAP (0.28 g, 2.3 mmol) at 0°C. After 1 h, the mixture was filtered through a Celite pad. The filtrate was diluted with water and extracted with EtOAc. The extract was washed two times with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 13.0 g of crude **10b**; ν_{max} 1760 (s), 1740 (s), 1720 (s), 1690 (w), 1660 (w), 1625 (w), 1160 (s), 1100 (s), 1020 (s), 840 (s); δ 0.06 (3H, s), 0.07 (3H, s), 0.88 (3H, t, *J*= 7.0Hz), 0.89 (9H, s), 1.22-1.34 (8H, m), 1.55-1.64 (2H, m), 2.61 (2H, t, *J*=7.5Hz), 3.32 (3H, s), 3.44 (3H, s), 3.54 (2H, s), 3.70 (1H, dd, *J*=8.5, 10.0Hz), 3.77 (1H, dd, *J*=5.0, 10.0Hz), 3.95 (1H, ddd, *J*=3.0, 5.5, 8.5Hz), 4.38 (1H, d, *J*=3.0Hz), 4.59 (1H, d, *J*=7.5Hz), 4.67 (1H, d, *J*=7.5Hz), 4.74 (1H, d, *J*=7.5Hz), 4.78 (1H, d, *J*=7.5Hz), 5.01 (1H, d, *J*=17.5Hz), 5.19 (1H, d, *J*=17.5Hz). This compound was employed for the next step without further purification.

(1'R,2'R)-3-{1',2'-bis(methoxymethoxy)-3'-[(t-butyldimethylsilyl)oxy]propyl}-2-octanoyl-2-buten-4-olide **11b**. A mixture of **10b** (13.0 g, 25.1 mmol) and SiO_2 (195 g) in *n*-hexane-EtOAc (8:1, 650 ml) was stirred 15 h at rt. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (180 g, *n*-hexane-EtOAc) to give 6.42 g (56 % from **8b**) of **11b** as an oil; $[\alpha]_D^{22}$ -27.5° (c=2.51, $CHCl_3$); ν_{max} 1770 (s), 1690 (m), 1625 (m), 1250 (m), 1160 (s), 1100 (s), 1020 (s), 920 (m), 830 (s); δ 0.08 (3H, s), 0.12 (3H, s), 0.88 (3H, t, *J*=7.0Hz), 0.92 (9H, s), 1.23-1.36 (8H, m), 1.58-1.64 (2H, m), 2.90-3.02 (2H, m), 3.24 (3H, s), 3.37 (3H, s), 3,78 (1H, dd, *J*=7.5, 10.0Hz), 3.82 (1H, dd, *J*=6.0, 10.0Hz), 4.01 (1H, ddd, *J*=2.5, 6.0, 7.5Hz), 4.52 (1H, d, *J*=7.0Hz), 4.64 (1H, d, *J*=7.0Hz), 4.66 (1H, d, *J*=7.0Hz), 4.68 (1H, d, *J*=7.0Hz), 4.98 (1H, d, *J*=19.5Hz), 5.11 (1H, dd, *J*=1.5, 19.5Hz), 5,48 (1H, dd, *J*=1.5, 2.5Hz); HRMS m/z 502.2949 (calcd for $C_{25}H_{46}O_8Si$, 502.2960).

3-O-methylsyringolide 2 **12b**. A mixture of **11b** (0.190 g, 0.378 mmol) and Dowex 50W-X8 (20 g) in dry methanol (35 ml) was stirred for 34 h at rt. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was mixed with sat. $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (8 g, hexane-EtOAc) to give 42.3 mg (36%) of **12b** as an oil; $[\alpha]_D^{22}$ -31.5° (c=0.575, $CHCl_3$); ν_{max} 3480 (m), 1765 (vs), 1190 (m), 1085 (s), 1040 (s); δ 0.89 (3H, t, *J*=7.0Hz), 1.23-1.35 (8H, m), 1.51-1.60 (2H, m), 1.78 (ddd, *J*=5.0, 12.0, 14.5Hz), 1.94 (1H, ddd, *J*=5.0, 12.5, 14.5Hz), 3.08 (1H, s), 3.24 (3H, s), 3.85 (1H, dd, *J*=3.5, 10.5Hz), 4.03 (1H, dd, *J*=1.5, 10.5Hz), 4.29-4.31 (2H, m), 4.41 (1H, d, *J*=10.0Hz), 4.63 (1H, d, *J*=10.0Hz); HRMS m/z 314.1688 (calcd for $C_{16}H_{26}O_6$, 314.1728).

(2S,3R,2'R,3'S,4'R)-syringolide 2 **2**. To a solution of **12b** (0.151 g, 0.479 mmol) in acetone-water (1:5, 3 ml) was added *p*-TsOH·H_2O (0.991 g, 4.79 mmol). After 16 h, the mixture was poured into sat. $NaHCO_3$ aq. and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ aq., water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude **2** as a yellow solid, which was washed five times with *n*-pentane-ether (2.5:1) to give 73.2 mg (51%) of **2**. This was further purified by SiO_2 columm chromatography and recrystallization from *n*-heptane-acetone to give pure **2** as colorless needles, mp 118-120.5°C; $[\alpha]_D^{22}$ -79° (c=0.26, $CHCl_3$) ; ν_{max} (KBr) 3410 (m), 1755 (s), 1390 (m), 1200 (m), 1050 (m), 1025 (m), 975 (m); ^1H NMR δ 0.88 (3H, t, *J*=7.0Hz), 1.23-1.37 (8H, m), 1.40-1.56 (2H, m), 1.72 (1H, br, OH), 1.89-1.95 (2H, m), 2.51 (1H, s, OH), 3.08 (1H, s), 3.85 (1H, dd, *J*=3.0, 10.5Hz), 4.04 (1H, d, *J*=10.5Hz), 4.31 (1H, br s),

4.46 (1H, d, *J*=10.5Hz), 4.55 (1H, s), 4.72 (1H, d, *J*=10.5Hz); ^{13}C NMR δ 14.04, 22.59, 23.47, 29.08, 29.38, 31.70, 38.86, 59.09, 74.26, 74.65, 74.74, 91.42, 97.62, 108.21, 172.23. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.94; H, 8.08.

(1'R,2'R)-3-{1',2'-bis(methoxymethoxy)-3'-[(t-butyldimethylsilyl)oxy]propyl}-2-hexanoyl-2-buten-4-olide **11a**. In the same manner as described for the preparation of **11b**, 4.50 g (12.8 mol) of **8a** yielded 3.16 g (51% from **8b**) of **11a** as an oil *via* **10a**; $[\alpha]_D^{22}$ -57.2° (c=3.07, $CHCl_3$); ν_{max} 1770 (s), 1690 (m), 1625 (w), 1260 (m), 1160 (s), 1100 (s), 1025 (vs), 840 (s); δ 0.08 (3H, s), 0.12 (3H, s), 0.90 (3H, t, *J*=7.0Hz), 0.92 (9H, s), 1.28-1.36 (4H, m), 1.59-1.65 (2H, quin, *J*=7.5Hz), 2.93 (1H, dd, *J*=7.5, 17.5Hz), 2.99 (1H, dd, *J*=7.5, 17.5Hz), 3.24 (3H, s), 3.37 (3H, s), 3.78 (1H, dd, *J*=7.5, 10.0Hz), 3.82 (1H, dd, *J*=6.0, 10.0Hz), 4.02 (1H, ddd, *J*=2.5, 6.0, 7.5Hz), 4.52 (1H, d, *J*=7.0Hz), 4.65 (1H, d, *J*=7.0Hz), 4.66 (1H, d, *J*=7.0Hz), 4.68 (1H, d, *J*=7.0Hz), 4.98 (1H, d, *J*=20.0Hz), 5.11 (1H, d, *J*=20.0Hz), 5.49 (1H, d, *J*=2.5Hz). Anal. Calcd for $C_{23}H_{42}O_8Si$: C, 58.20; H, 8.92. Found: C, 57.81; H, 8.88.

3-O-Methylsyringolide 1 **12a**. In the same manner as described for the preparation of **12b**, 1.00 g (2.11 mol) of **11a** yielded 184 mg (30%) of **12a** as an oil; $[\alpha]_D^{22}$ -88.4° (c=0.690, $CHCl_3$); ν_{max} 3450 (m), 1770 (s), 1185 (m), 1085 (m), 1040 (s); δ 0.90 (3H, t, *J*=7.0Hz), 1.29-1.37 (5H, m), 1.52-1.62 (1H, m), 1.78 (1H, ddd, *J*=5.0, 12.0, 14.5Hz), 1.93 (1H, ddd, *J*=5.0, 12.5, 14.5Hz), 2.10 (1H, br, OH), 3.09 (1H, s), 3.24 (3H, s), 3.84 (1H, dd, *J*=2.5, 10.5Hz), 4.04 (1H, d, *J*=10.5Hz), 4.29-4.32 (2H, m), 4.42 (1H, d, *J*=10.5Hz), 4.64 (1H, d, *J*=10.5Hz); HRMS m/z 286.1396 (calcd for $C_{14}H_{22}O_6$, 286.1416).

(2S,3R,2'R,3'S,4'R)-Syringolide 1 **1**. In the same manner as described for the preparation of **2**, 95.7 mg (0.335 mol) of **12a** gave 41.5 mg (46%) of **1** as colorless needles, mp 113-114.5°C; $[\alpha]_D^{22}$ -83.3° (c=0.108, $CHCl_3$); ν_{max} (KBr) 3410 (m), 1755 (s), 1390 (m), 1200 (m), 1065 (m), 1045 (m), 975 (m); ^{1}H NMR (acetone-d_6) δ 0.89 (3H, t, *J*=7.0 Hz), 1.27-1.37 (4H, m), 1.44-1.54 (1H, m), 1.57-1.67 (1H, m), 1.85-1.92 (2H, m), 3.09 (1H, s), 3.83 (1H, dd, *J*=3.0, 10.0 Hz), 3.95 (1H, dd, *J*=1.5, 10.0 Hz), 4.15 (1H, br s), 4.33 (1H, d, *J*=10.0 Hz), 4.33 (1H, br, OH), 4.49 (1H, br s), 4.67 (1H, d, *J*=10.0 Hz), 5.37 (1H, d, *J*=2.0 Hz, OH); ^{13}C NMR (acetone-d_6) δ 14.27, 23.19, 24.08, 32.66, 39.46, 59.77, 74.96, 75.45, 75.66, 92.30, 99.02, 108.86, 172.70. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.18; H, 7.35.

Acknowledgements: We are grateful to Dr. S. Kawasaki (National Institute of Agrobiological Resorces) for bioassay. Our thanks are due to Prof. J. J. Sims (University of California, Riverside) for copies of NMR spectra of the natural syringolides. We thank Mr. N. Awai (Ibaraki Universaity) for HRMS measurements. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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10. Compound **10** and its fully or partially deprotected derivatives were subjected to the following reaction conditions: 1) piperidine-AcOH, benzene; 2) piperidine, EtOH; 3) TFA, MeOH; 4) $TiCl_4$-Py, CCl_4; 5) $ZnCl_2$-Py, ether; 6) K_2CO_3, CH_3CN; and 7) *t*-BuOK, THF.
11. As was expected, other stereoisomers were not obtained. If the conjugate addition takes place from the β-side of the double bond of **11b**, the resulting adduct will not lead to the tricyclic structure through acetalization, because the relationship between the two five-membered rings formed through the β-side addition and acetalization is *trans*.

(*Received in Japan* 24 *May* 1995; *accepted* 15 *June* 1995)