Enantioselective Syntheses of Syributin 1 and Novel C-Glycosidic Elicitors Syringolides 1 and 2

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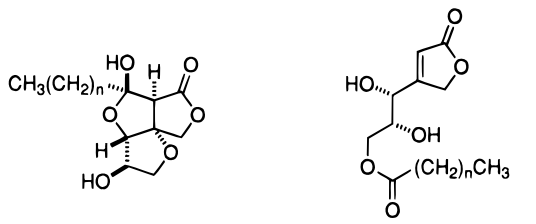
Concise enantioselective syntheses of syributin 1 (**3**) and the novel nonproteinaceous C-glycosidic elicitors syringolides 1 and 2 (**1** and **2**, respectively), isolated from *Pseudomonas syringae* pv. *tomato*, are described. Syributin 1 was synthesized in one step by the Sharpless catalytic asymmetric dihydroxylation (AD reaction) of (1′*E*)-3-(3′-(octanoyloxy)-1′-propenyl)but-2-en-4-olide (**13**) in 72% yield with >98% ee. Furthermore, alkylation of (1′*R*,2′*R*)-3-[1′-(*tert*-butyldimethylsiloxy)-2′,3′-(isopropylidenedioxy)propyl]but-2-en-4-olide (**20**), prepared from (1′*E*)-3-[3′-(*tert*-butyldimethylsiloxy)-1′-propenyl]but-2-en-4-olide (**11**) by the AD reaction, with hexanal or octanal by Jefford's procedure at the α position to the lactone carbonyl group gave adduct **21** or **22** in good yield. Oxidation of **21** or **22**, followed by removal of the protecting groups, provided syringolide 1 or 2, respectively.

Introduction

Recent progress in protein engineering has revealed the mechanisms of chemical defense in plants against attack by microbial pathogens. Disease-resistance genes control the recognition of invading pathogens and subsequent activation of defense responses. Defense responses in infected tissue are known as a hypersensitive response. The active defense reaction involves rapid, localized cell death followed by the accumulation of antimicrobial compounds called phytoalexines around the infection site. Many plant pathogens produce specific elicitor compounds that are recognized by resistant plants, thereby triggering a hypersensitive response.[1] In 1993, Sims and co-workers isolated the novel nonproteinaceous C-glycosidic elicitors syringolides 1 and 2 (**1** and **2**, respectively) from *P. syringae* pv. *tomato*.[2] These compounds are produced by bacteria expressing avirulence gene D (*avrD*) and cause a hypersensitive reaction in soybean plants carrying the resistance gene, *Rpg4*. Shortly thereafter, they also isolated four major coproducts of the syringolide elicitors, syributins 1 and 2 (**3** and **4**, respectively) and secosyrins 1 and 2 (**5** and **6**, respectively), from the same medium.[3] These compounds are not active elicitors, but are of biosynthetic interest since they are produced along with the syringolides. They are interesting new structures that provide clues to the nature of the *avrD* gene and the function of its protein product.

The structures of the syringolides were determined by NMR experiments and confirmed by X-ray crystallographic analysis.[2b] The absolute configurations were initially based on a consideration of their biosynthetic routes, which must include naturally-occurring D-xylulose as a precursor, and then unambiguously determined by total synthesis. Their low abundance in natural sources and intriguing structures have made them the target of several syntheses. Four total syntheses of syringolides



have been reported thus far. Three of these syntheses were based on the putative biosynthetic pathway, starting from D-tartrate derivatives (Wood *et al.*[4] and Kuwahara *et al.*[5]) and from D-xylulose (Henschke and Rickards[6]). Very recently, the first asymmetric synthesis of syringolide 1 (**1**) was reported by Murai *et al.*[7] who used the Sharpless catalytic asymmetric dihydroxylation (AD reaction)[8] as a key step to give the oxidation products as a mixture of four stereoisomers in 87% ee. This latter report prompted us to publish our own results on the synthesis of syringolides 1 and 2 (**1** and **2**, respectively) and syributin 1 (**3**).

Results and Discussion

Our initial retrosynthetic disconnections for these lactones **1**−**6** are outlined in Scheme 1. We thought that

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(3) Midland, S. L.; Keen, N. T.; Sims, J. J. *J. Org. Chem*. **1995**, *60*, 1118.

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(6) Henschke, J. P.; Rickards, R. W. *Tetrahedron Lett*. **1996**, *37*, 3557.

(7) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1996**, 335.

(8) (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem*. **1991**, *56*, 4585. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483 and references cited therein.

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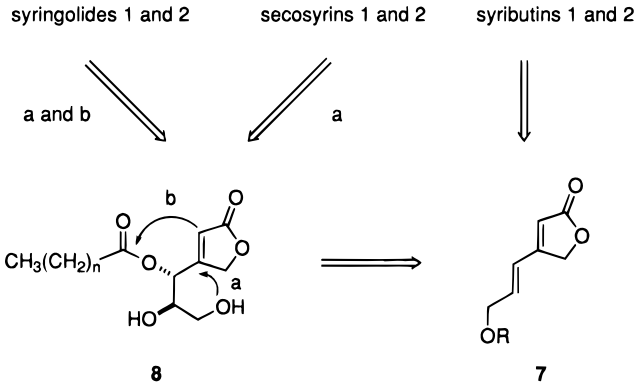
Scheme 1



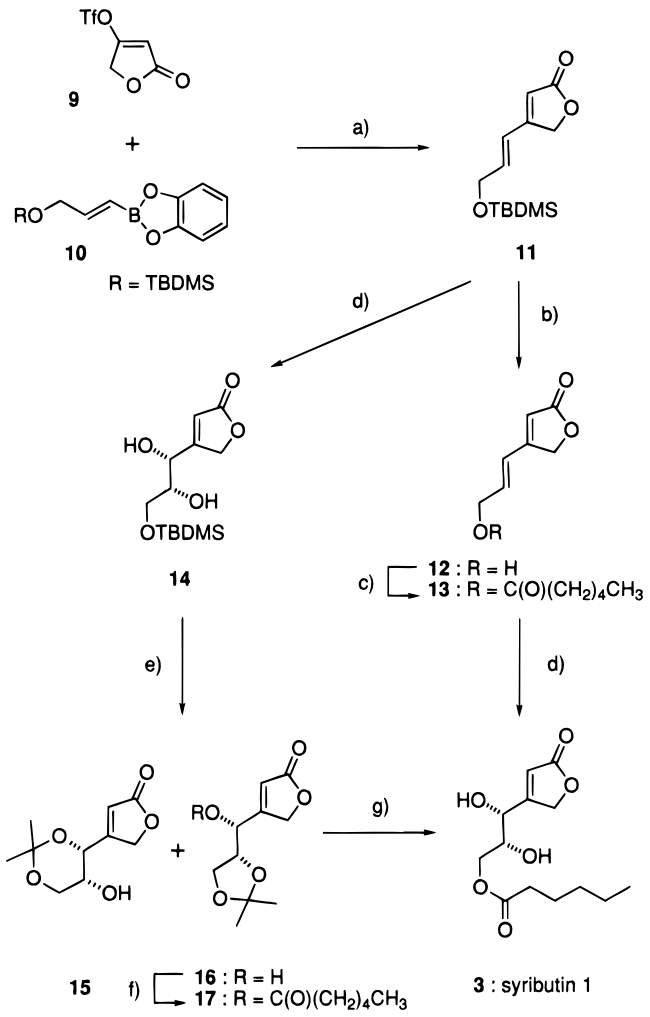
the introduction of chiral centers into the prochiral substrate **7** could be achieved by using the AD reaction[8] to give the syributins [R = $C(O)(CH_2)_4CH_3$ or $C(O)(CH_2)_6CH_3$], while the intramolecular Michael addition of the primary hydroxyl group of **8** followed by an intramolecular aldol-type reaction would give the secosyrins and the syringolides.

Thus, we embarked on the synthesis of syributin 1 (**3**) as shown in Scheme 2. Prochiral alkenyl butenolide **11**, prepared by the palladium-catalyzed cross-coupling reaction of trifluoromethanesulfonyl tetronate **9**[9] with alkenyl borane **10** according to Suzuki *et al.*,[10] was hydrolyzed with aqueous acetic acid to give alcohol **12** in 99% yield. After acylation with hexanoyl chloride, butenolide **13** was subjected to the AD reaction with AD-mix-β under standard conditions[8] to give syributin 1 (**3**), $[\alpha]^{26}_D$ +6.6 (*c* 0.6, $CHCl_3$), in 69% yield from alcohol **12**. Although the ee of the synthesized syributin 1 could not be determined at this stage, it was later shown to be >98% ee by comparison of the specific optical rotation with an authentic sample prepared by an alternative route as follows. The AD reaction of alkenyl butenolide **11** proceeded smoothly to give diol **14** in 85% yield, which, upon treatment with 2,2-dimethoxypropane and PPTS in DMF, directly gave acetonides **15** and **16** in yields of 15% and 80%, respectively. The ee of the corresponding (*S*)-(−)-MTPA ester of **16** was determined to be >98% by NMR study and also by HPLC analysis with the chiral column (CHIRALCEL OD). After acylation of **16** with hexanoyl chloride, acetonide **17** was transformed to syributin 1 (**3**), $[\alpha]^{26}_D$ +6.8 (*c* 0.5, $CHCl_3$), by treatment with 1 N HCl for 48 h at rt. The absolute configuration of **3** was determined to be the same as that of the natural compound by measurement of the exciton chirality for the corresponding 1′-*p*-bromobenzoate, which shows a positive CD curve as reported by Sims *et al.*[3]

Using acetonide **17**, we next attempted the synthesis of the syringolides and secosyrins. Acid treatment of **17** for 3 h at rt gave diol **18** in 58% yield, together with **19** (29%) and **3** (8%). Although various cyclization conditions were investigated for the conversion of **18** to **1** or **5**, such as NaH in THF, DBU in THF, $BF_3{\cdot}OEt_2$ in CH_2Cl_2, and $TiCl_4$ in CH_2Cl_2, none of the desired products were obtained, while the acyl group-rearranged product, syributin 1 (**3**), was produced predominantly (Scheme 3).

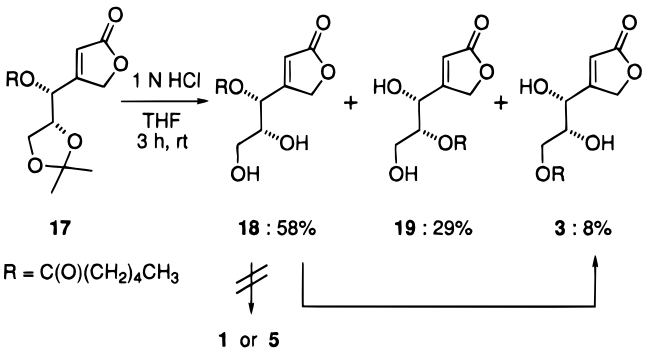
These results might support the biosynthetic pathway for syributins and secosyrins offered by Sims *et al.*[3] They proposed that secosyrins were biosynthetically produced by reverse Claisen condensation from syringolides, and

Scheme 2[a]



[a]Reagents and conditions : (a) $(Ph_3P)_2PdCl_2$, K_3PO_4, THF, 70 °C (48%); (b) AcOH-THF-H_2O (2 : 1 : 1), rt (99%); (c) $CH_3(CH_2)_4COCl$, Et_3N, CH_2Cl_2, 0 °C (96%); (d) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH-H_2O (1 : 1), 0 °C (**3** : 72%; **14** : 85%); (e) 2,2-dimethoxypropane, PPTS, DMF, rt (**15** : 15%; **16** : 80%); (f) $CH_3(CH_2)_4COCl$, Py, CH_2Cl_2, 0 °C (94%); (g) 1 N HCl, THF, rt, 48 h (quant).

Scheme 3



that syributins might be produced by 1,3-acyl migration from an intermediate like **18**, which could be derived by reverse Michael reaction from secosyrins.

Since our initial synthetic route seemed to be problematic, we decided to adopt an alternative synthetic pathway to the syringolides which involved acylation at the α position to the carbonyl group before the intramolecular Michael addition of the primary hydroxyl group.

Although difficulties were initially encountered in the synthesis of **21**, treatment of butenolide **20**, prepared by

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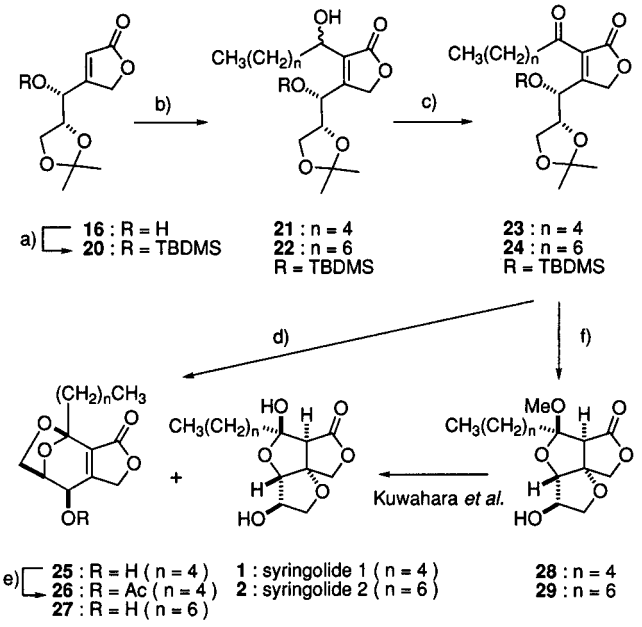
(10) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

Scheme 4[a]



[a]Reagents and conditions : (a) TBDMSCl, imidazole, DMF, rt (93%); (b) Bu_2BOTf, *i*-Pr_2NEt, $CH_3(CH_2)_nCHO$ (n = 4 or 6), THF, -78 °C (**21** : 83%; **22** : 87%); (c) Dess-Martin periodinate, CH_2Cl_2, rt (**23** : 96%; **24** : 93%); (d) 6 N HCl, THF, 6 h, rt (**1** : 10% and **25** : 44%; **2** : 12% and **27** : 40%); (e) Ac_2O, Py, rt (90%); (f) Dowex 50W-8X, MeOH, 48 h, rt (**28** : 40%; **29** : 36%).

protection of the hydroxyl group with TBDMSCl and imidazole in CH_2Cl_2, with Bu_2BOTf, *i*-Pr_2NEt, and hexanal in THF at −78 °C under the aldol reaction conditions developed by Jefford *et al.*,[11] gave aldol **21** as an inseparable diastereomeric mixture in 83% yield. Oxidation of the alcohol with Dess−Martin periodinate[12] gave ketone **23** in 96% yield, which on exposure to 6 N HCl in THF for 6 h at rt produced syringolide 1 (**1**) as colorless needles, mp 113−115 °C (lit.[2b] mp 112.5−114.5 °C, lit.[5b] 113−114.5 °C); $[\alpha]^{29}_D$ −83.3 (*c* 0.2, $CHCl_3$) [lit.[2b] $[\alpha]^{24}_D$ −83.66 (*c* 0.15, $CHCl_3$), lit.[5b] $[\alpha]^{22}_D$ −83.3 (*c* 0.108, $CHCl_3$)] in 10% yield together with acetal **25** as colorless needles, mp 83.8−85.4 °C; $[\alpha]^{29}_D$ −33.1 (*c* 0.4, $CHCl_3$) in 44% yield. The structure of acetal **25** was confirmed by further conversion into the corresponding acetate **26**, mp 73.0−74.6 °C; $[\alpha]^{29}_D$ −104.8 (*c* 0.3, $CHCl_3$) in 90% yield. On the other hand, treatment of **23** with Dowex 50W-8X in MeOH for 48 h at rt gave methyl ether **28** in 40% yield, which was also converted to syringolide 1 (**1**) according to Kuwahara *et al.*[6]

Syringolide 2 (**2**), mp 119−120 °C (lit.[2b] 123−124 °C, lit.[5b] 118−120.5 °C); $[\alpha]^{24}_D$ −79.7 (*c* 0.2, $CHCl_3$) [lit.[2b] $[\alpha]^{24}_D$ −75.91 (*c* 0.22, $CHCl_3$), lit.[5b] $[\alpha]^{22}_D$ −79 (*c* 0.26, $CHCl_3$)] was also synthesized together with acetal **27** starting from **22** *via* ketone **24** by following essentially the same synthetic routes as for **1**.

In conclusion, we have presented a concise enantioselective synthesis of syringolides 1 and 2 (**1** and **2**, respectively) and syributin 1 (**3**) in yields of 2.4% in seven steps, 3.0% in seven steps, and 32.8% in four steps, respectively, using the Sharpless catalytic asymmetric dihydroxylation as a key step. This strategy should also be applicable to the synthesis of congeners of the syributins and syringolides.

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(12) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained for a solutions in $CDCl_3$ unless otherwise noted using TMS as an internal standard.

(1′*E*)-3-[3′-(*tert*-Butyldimethylsiloxy)-1′-propenyl]but-2-en-4-olide (11). A mixture of 3-(*tert*-butyldimethylsiloxy)-1-propyne (5 g, 34.7 mmol) and catechol borane (3.7 mL, 34.7 mmol) was heated at 60 °C for 4 h under Ar. THF (80 mL) and potassium phosphate, tribasic (8.84 g, 41.6 mmol) were then added to this mixture at rt. After stirring for 5 min at the same temperature, bis(triphenylphosphine)palladium(II) dichloride (610 mg, 0.87 mmol) and a solution of trifluoromethanesulfonyl tetronate (**9**)[9] (8.1 g, 34.7 mmol) in THF (20 mL) were added, and the mixture was stirred at 70 °C for 5 h. After filtration of the insoluble material through a pad of Celite, the filtrate was washed with saturated aqueous NH_4Cl solution and brine. The solution was dried over Na_2SO_4 and evaporated to leave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (5:1, v/v) as the eluent to give alkenyl butenolide **11** (4.24 g, 48%) as colorless prisms: mp 47.3−48.5 °C (hexane−EtOAc); IR (KBr) 962, 1022, 1126, 1157, 1252, 1328, 1448, 1460, 1470, 1598, 1650, 1735, 1782 cm^{-1}; ^1H NMR δ 0.10 (s, 6H), 0.94 (s, 9H), 4.35 (m, 2H), 4.96 (d, 2H, J = 1.2 Hz), 5.91 (br s, 1H), 6.19 (dt, 1H, J = 3.7, 15.9 Hz), 6.65 (br d, 1H, J = 15.9 Hz); HRMS calcd for $C_{13}H_{22}O_3Si$ 254.1338, found 254.1338. Anal. Calcd for $C_{13}H_{22}O_3Si \cdot {}^1/_{10}\ H_2O$: C, 60.95; H, 8.73. Found: C, 60.83; H, 8.82.

(1′*E*)-3-(3′-Hydroxy-1′-propenyl)but-2-en-4-olide (12). A solution of alkenyl butenolide **11** (110 mg, 0.43 mmol) in AcOH−THF−H_2O (2 : 1 : 1, 2 mL) was stirred for 30 min at rt. After adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (1:5, v/v) as the eluent to give alcohol **12** (60 mg, 99%) as colorless prisms: mp 86.5−87 °C (hexane−Et_2O); IR (KBr) 860, 898, 968, 1024, 1103, 1163, 1238, 1315, 1338, 1452, 1597, 1655, 1734, 3460 cm^{-1}; ^1H NMR δ 2.04−2.34 (br s, 1H), 4.37 (dd, 2H, J = 1.8, 4.3 Hz), 4.98 (d, 2H, J = 1.2 Hz), 5.93 (s, 1H), 6.25 (dt, 1H, J = 4.3, 16.5 Hz), 6.69 (d, 1H, J = 16.5 Hz); HRMS calcd for $C_7H_8O_3$ 140.0473, found 140.0473. Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.87; H, 5.77.

(1′*E*)-3-(3′-(Octanoyloxy)-1′-propenyl)but-2-en-4-olide (13). To a stirred solution of alcohol **12** in CH_2Cl_2 (2 mL) were added Et_3N (0.15 mL, 1.07 mmol) and hexanoyl chloride (0.11 mL, 0.79 mmol) at 0 °C, and the resulting solution was stirred at the same temperature for 1 h under Ar. After adding saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (3:1, v/v) as the eluent to give the acylated compound **13** (163 mg, 96%) as a colorless oil: IR (thin film) 888, 968, 1000, 1036, 1108, 1152, 1247, 1326, 1383, 1450, 1600, 1658, 1748, 1780 cm^{-1}; ^1H NMR δ 0.91 (br s, 3H), 1.34 (m, 4H), 1.66 (m, 2H), 2.37 (t, 2H, J = 7.3 Hz), 4.74 (br d, 2H, J = 5.5 Hz), 4.98 (s, 2H), 5.98 (br s, 1H), 6.17 (dt, 1H, J = 5.5, 15.9 Hz), 6.63 (d, 1H, J = 15.9 Hz); HRMS calcd for $C_{13}H_{18}O_4$ 238.1204, found 238.1204.

Syributin 1 (3) from Butenolide 13. To a stirred solution of AD-mix-β (1.18 g) in 50% aqueous *t*-BuOH (4 mL) was added methanesulfonamide (40 mg, 0.42 mmol), and the mixture was stirred for 10 min at rt. After slowly adding a solution of butenolide **13** (100 mg, 0.42 mmol) in *t*-BuOH (1 mL) at 0 °C, the resulting mixture was stirred for an additional 24 h at the same temperature. The mixture was extracted with EtOAc, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (2:3, v/v) as the eluent to give syributin 1 (**3**) (82 mg, 72%) as a colorless oil: $[\alpha]^{26}_D$ +6.6 (*c* 0.6, $CHCl_3$); IR (thin film) 900, 1115, 1142, 1175, 1250, 1382, 1445, 1638, 1740, 1780, 3440 cm^{-1}; ^1H NMR δ 0.90 (t, 3H, J = 6.7 Hz), 1.31 (m, 4H), 1.62 (m, 2H), 2.35 (t, 2H, J = 7.3 Hz), 3.55 (d, 1H, J = 5.5 Hz), 3.78 (d, 1H, J = 6.1 Hz), 3.98 (m, 1H), 4.18 (dd, 1H, J =

5.5, 11.0 Hz), 4.64 (m, 1H), 4.91 and 5.00 (each dd, each 1H, J = 1.8, 18.3 Hz), 6.07 (q, 1H, J = 1.8 Hz); HRMS calcd for $C_{13}H_{18}O_4$ ($M^+ - 34$) 238.1205, found 238.1205. These data were identical to those reported previously.[3]

(1′*R*,2′*R*)-3-[3′-(*tert*-Butyldimethylsiloxy)-1′,2′-dihydroxypropyl]but-2-en-4-olide (14). This reaction was performed with 2.8 g (11.0 mmol) of silyl ether **11** and AD-mix-β (23 g) in the same manner as described for the preparation of syributin 1 (**3**) to give diol **14** (2.7 g, 85%) as colorless prisms: $[\alpha]^{21}_D$ −6.75 (*c* 0.5, $CHCl_3$); mp 68−69 °C (hexane−Et_2O); IR (KBr) 1003, 1069, 1128, 1258, 1628, 1722, 3370 cm^{-1}; ^1H NMR δ 0.12 (s, 6H), 0.92 (s, 9H), 2.75 (d, 1H, J = 7.3 Hz), 3.34 (d, 1H, J = 4.3 Hz), 3.77 (m, 1H), 3.83 (m, 2H), 4.76 (br s, 1H), 4.94 (dd, 2H, J = 1.2, 3.1 Hz), 6.04 (dd, 1H, J = 1.8, 3.1 Hz); ^{13}C NMR −5.5, 18.2, 25.8, 64.8, 70.1, 71.9, 72.4, 116.2, 170.7, 174.0; HRMS calcd for $C_9H_{15}O_5Si$ ($M^+ - 57$) 231.0690, found 231.0690. Anal. Calcd for $C_{13}H_{24}O_5Si \cdot {}^1/_{10}\ H_2O$: C, 53.8; H, 8.41. Found: C, 53.73; H, 8.34.

(1′*R*,2′*R*)-3-[2′-Hydroxy-1′,3′-(isopropylidenedioxy)propyl]but-2-en-4-olide (15) and (1′*R*,2′*R*)-3-[1′-Hydroxy-2′,3′-(isopropylidenedioxy)propyl]but-2-en-4-olide (16). To a stirred solution of diol **14** (910 mg, 3.16 mmol) in DMF (5 mL) were added 2,2-dimethoxypropane (1.17 mL, 9.48 mmol) and PPTS (79 mg, 0.32 mmol), and the resulting mixture was stirred for 12 h at rt. After adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (1:2, v/v) as the eluent. The first fraction gave compound **16** (542 mg, 80%) as a colorless oil: $[\alpha]^{25}_D$ −13.5 (*c* 0.3, $CHCl_3$); IR (thin film) 856, 890, 1030, 1068, 1144, 1214, 1256, 1375, 1383, 1446, 1640, 1745, 3450 cm^{-1}; ^1H NMR δ 1.38 and 1.48 (each s, each 3H), 2.67 (d, 1H, J = 6.1 Hz), 3.93 (dd, 1H, J = 5.5, 8.6 Hz), 4.13 (dd, 1H, J = 6.1 Hz, 8.6 Hz), 4.25 (ddd, 1H, J = 4.9, 5.5, 6.1 Hz), 4.57 (ddd, 1H, J = 1.8, 4.9, 6.1 Hz), 4.88 and 4.96 (each dd, each 1H, J = 1.8, 18.9 Hz), 6.03 (q, 1H, J = 1.8 Hz); ^{13}C NMR 24.1, 26.1, 65.4, 68.7, 71.9, 76.8, 110.0, 116.3, 169.6, 173.8; HRMS calcd for $C_9H_{11}O_5$ ($M^+ - 15$) 199.0606, found 199.0606. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.90; H, 6.57. The second fraction gave compound **15** (102 mg, 15%) as colorless prisms: $[\alpha]^{25}_D$ −67.0 (*c* 0.5, $CHCl_3$); mp 120−121.5 °C (hexane−Et_2O); IR (KBr) 1020, 1070, 1140, 1210, 1390, 1650, 1740, 3460 cm^{-1}; ^1H NMR δ 1.48 and 1.52 (each s, each 3H), 2.87 (d, 1H, J = 11.6 Hz), 3.58 (dd, 1H, J = 1.8, 11.6 Hz), 3.88 and 4.18 (each dd, each 1H, J = 1.8, 12.2 Hz), 4.84−4.98 (m, 3H), 6.04 (q, 1H, J = 1.8 Hz); HRMS calcd for $C_9H_{11}O_5$ ($M^+ - 15$) 199.0706, found 199.0607. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.92; H, 6.64.

(1′*R*,2′*R*)-3-[2′,3′-(Isopropylidenedioxy)-1′-(hexanoyloxy)propyl]but-2-en-4-olide (17). To a stirred solution of alcohol **16** (30 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) were added pyridine (17 μL, 0.21 mmol) and hexanoyl chloride (24 μL, 0.17 mmol) at 0 °C. After stirring for 12 h at rt under Ar, saturated aqueous NH_4Cl solution was added to the solution, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (5:1, v/v) as the eluent to give ester **17** (41 mg, 94%) as a colorless oil: $[\alpha]^{26}_D$ −24.3 (*c* 0.4, $CHCl_3$); IR (thin film) 855, 880, 1070, 1095, 1113, 1152, 1374, 1384, 1640, 1753, 1786 cm^{-1}; ^1H NMR δ 0.91 (t, 3H, J = 6.7 Hz), 1.23−1.38 (m, 9H), 1.44 (s, 3H), 1.57−1.73 (m, 2H), 2.40 (t, 2H, J = 7.9 Hz), 3.81 (dd, 1H, J = 5.5, 8.5 Hz), 4.37 (ddd, 1H, J = 4.3, 5.5, 6.7 Hz), 4.84 and 4.93 (each dd, each 1H, J = 1.8, 17.7 Hz), 5.80 (br s, 1H, J = 3.7 Hz), 6.05 (q, 1H, J = 1.8 Hz); ^{13}C NMR 13.7, 22.1, 24.3, 24.7, 25.8, 31.0, 33.8, 65.2, 69.0, 71.6, 75.4, 110.2, 117.7, 164.5, 172.5; HRMS calcd for $C_{15}H_{21}O_6$ ($M^+ - 15$) 297.1337, found 297.1337.

Syributin 1 (3) from Acetonide 17. A solution of acetonide **17** (41 mg, 0.13 mmol) in 1 N HCl−THF (1:1, 0.6 mL) was stirred for 48 h at rt. After adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (2:3, v/v) as the eluent to give syributin 1 (**3**) (35.7 mg, quant) as a colorless oil: $[\alpha]^{26}_D$ +6.8 (*c* 0.5, $CHCl_3$). The spectroscopic data of this compound were identical to those reported previously[3] and those for syributin 1 synthesized from butenolide **13**.

Hydrolysis of Acetonide (17). A solution of acetonide **17** (270 mg, 0.87 mmol) in 1 N HCl−THF (1:1, 4 mL) was stirred for 3 h at rt. After adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (1:2, v/v) as the eluent. The first fraction gave a mixture of diols **18** and **19** (204 mg, 87%). The ratio of **18**/**19** was determined to be 2:1 by ^1H NMR analysis. Recrystallization from hexane−Et_2O gave **18** as an amorphous solid: ^1H NMR δ 0.91 (t, 3H, J = 7.3 Hz), 1.34 (m, 4H), 1.66 (m, 2H), 2.06 (br s, 1H), 2.42 (t, 2H, J = 7.3 Hz), 2.57 (br s, 1H), 3.67 (m, 2H), 3.98 (m, 1H), 4.89 and 4.99 (each dd, each 1H, J = 1.8, 17.7 Hz), 5.80 (br d, 1H, J = 4.3 Hz), 6.06 (q, 1H, J = 1.8 Hz); HRMS calcd for $C_{13}H_{19}O_5$ ($M^+ - 17$) 255.1233, found 255.1233. Mother liquid contained **19**: ^1H NMR δ 0.89 (t, 3H, J = 6.7 Hz), 1.31 (m, 4H), 1.61 (m, 2H), 2.29 (br s, 1H), 2.35 (t, 2H, J = 7.9 Hz), 3.55 (br s, 1H), 3.92 (m, 2H), 4.85 and 4.96 (each dd, each 1H, J = 1.2, 17.7 Hz), 4.97 (m, 1H), 5.08 (m, 1H), 6.08 (q, 1H, J = 1.2 Hz). This compound was isolated as a mixture with a trace of **18**, and further purification could not be achieved. The second fraction gave syributin 1 (**3**) (19 mg, 8%) as a colorless oil.

(1′*R*,2′*R*)-3-[1′(*tert*-Butyldimethylsiloxy)-2′,3′-(isopropylidenedioxy)propyl]but-2-en-4-olide (20). To a stirred solution of alcohol **16** (330 mg, 1.54 mmol) in DMF (3 mL) were added imidazole (420 mg, 6.17 mmol) and TBDMSCl (470 mg, 3.08 mmol) at 0 °C, and the resulting mixture was stirred for 20 h at rt under Ar. After adding saturated aqueous NH_4Cl solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (4:1, v/v) as the eluent to give silyl ether **20** (470 mg, 93%) as a colorless oil: $[\alpha]^{23}_D$ −4.0 (*c* 1.0, $CHCl_3$); IR (thin film) 840, 1070, 1135, 1215, 1255, 1370, 1470, 1640, 1750, 1780 cm^{-1}; ^1H NMR δ 0.07 and 0.11 (each s, each 3H), 0.98 (s, 9H), 1.34 and 1.40 (each s, each 3H), 3.77 (dd, 1H, J = 6.1, 8.5 Hz), 4.02 (dd, 1H, J = 6.7, 8.5 Hz), 4.23 (ddd, 1H, J = 4.9, 6.1, 6.7 Hz), 4.75 (d, 1H, J = 4.9 Hz), 4.84 and 4.98 (each dd, each 1H, J = 1.8, 18.9 Hz), 6.04 (q, 1H, J = 1.8 Hz); HRMS calcd for $C_{15}H_{25}O_5Si$ ($M^+ - 15$) 313.1471, found 313.1472. Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.50; H, 8.59. Found: C, 58.21; H, 8.61.

(1′*R*,2′*R*)-3-[1′-(*tert*-Butyldimethylsiloxy)-2′,3′-(isopropylidenedioxy)propyl]-2-(1″-hydroxyhexyl)]-2-buten-4-olide (21). To a stirred solution of butenolide **20** (500 mg, 1.52 mmol) in THF (10 mL) was added *i*-Pr_2NEt (1.06 mL, 6.10 mmol) at 0 °C. After cooling to −78 °C, a 1.0 M CH_2Cl_2 solution of Bu_2BOTf (3.05 mL, 3.05 mmol) was added dropwise, and the resulting mixture was stirred for 30 min at the same temperature. Hexanal (0.28 mL, 2.29 mmol) was added to the mixture, which was then stirred for 30 min at −20 °C. After adding cold water, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (6:1, v/v) as the eluent to give alcohol **21** (538 mg, 83%) as a diastereomeric mixture (colorless oil): IR (thin film) 970, 1070, 1130, 1255, 1370, 1465, 1665, 1745, 3460 cm^{-1}; ^1H NMR δ 0.04−0.11 (each s, each 3H), 0.88−1.93 (m, 12H), 1.24−1.58 (m, 12H), 1.67−1.84 (m, 2H), 2.73 and 3.43 (each dd, each 0.5H, J = 3.7, 7.9 Hz), 3.90 and 4.03 (each m, each 1H), 4.23 (m, 1H), 4.55 (m, 1H), 4.81 and 4.92 (each m, each 1H), 5.07 and 5.32 (each dd, J = 3.7, 4.3 Hz); HRMS calcd for $C_{21}H_{37}O_6Si$ ($M^+ - 15$) 413.2358, found 413.2358. Anal. Calcd for $C_{22}H_{40}O_6Si$: C, 61.65; H, 9.41. Found: C, 61.37; H, 9.42.

(1′*R*,2′*R*)-3-[1′-(*tert*-Butyldimethylsiloxy)-2′,3′-(isopropylidenedioxy)propyl]-2-hexanoyl-2-buten-4-olide (23). To a stirred solution of alcohol **21** (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added portionwise Dess−Martin periodinate (99 mg, 0.23 mmol), and the mixture was stirred for 30 min

at rt under Ar. After adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted with Et_2O. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (7:1, v/v) as the eluent to give ketone **23** (19 mg, 96%) as a colorless oil: $[\alpha]^{24}_D$ −122.8 (*c* 0.2, $CHCl_3$); IR (thin film) 780, 840, 870, 1010, 1070, 1130, 1250, 1625, 1690, 1770 cm^{-1}; ^1H NMR δ 0.03 and 0.10 (each s, each 3H), 0.84−0.94 (m, 12H), 1.27−1.38 (m, 4H), 1.33 and 1.38 (each s, each 3H), 1.62 (m, 2H), 3.00 (t, 2H, J = 7.3 Hz), 3.96 (dd, 1H, J = 5.5, 6.7 Hz), 4.34 (ddd, 1H, J = 2.4, 5.5, 6.7 Hz), 4.92 and 5.16 (each d, each 1H, J = 19.5 Hz), 5.40 (dd, 1H, J = 1.2, 2.4 Hz); ^{13}C NMR −5.3, −4.9, 13.9, 18.1, 22.5, 23.0, 25.4, 25.6, 26.1, 31.3, 42.0, 65.4, 68.9, 71.3, 77.8, 110.2, 123.3, 170.7, 179.5, 197.7; HRMS calcd for $C_{21}H_{35}O_6Si$ (M^+ − 15) 411.2203, found 411.2203. Anal. Calcd for $C_{22}H_{38}O_6Si$: C, 61.94; H, 8.98. Found: C, 61.70; H, 8.85.

3-*O*-Methylsyringolide 1 (28). To a stirred solution of ketone **23** (350 mg, 0.82 mmol) in MeOH (30 mL) was added Dowex 50W-8X (35 g), and the mixture was stirred for 48 h at rt. After filtration of the mixture, the filtrate was concentrated to leave an oily product that was dissolved in EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel with hexane−EtOAc (1:1, v/v) as the eluent to give 3-*O*-methylsyringolide 1 (**28**) (95 mg, 40%) as a colorless oil: $[\alpha]^{24}_D$ −95.9 (*c* 0.9, $CHCl_3$); IR (thin film) 915, 980, 1020, 1085, 1185, 1250, 1295, 1380, 1465, 1770, 3450 cm^{-1}; ^1H NMR δ 0.90 (t, 3H, J = 6.7 Hz), 1.33 (m, 5H), 1.77 (m, 1H), 1.92 (m, 1H), 2.60 (br s, 1H), 3.09 (s, 1H), 3.24 (s, 3H), 3.82 (dd, 1H, J = 3.1, 10.4 Hz), 4.04 (dd, 1H, J = 1.2, 10.4 Hz), 4.24−4.31 (m, 2H), 4.42 and 4.64 (each d, each 1H, J = 10.4 Hz); HRMS calcd for $C_{14}H_{22}O_6$ 286.1412, found 286.1413. These data were identical to those reported previously.[5]

Syringolide 1 (1). A solution of ketone **23** (300 mg, 0.70 mmol) in 6 N HCl−THF (1:1, 6 mL) was stirred for 10 h at rt. After adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (1:1, v/v) gave acetal **25** (70 mg, 44%) as colorless needles: $[\alpha]^{29}_D$ −33.1 (*c* 0.4, $CHCl_3$); mp 83.8−85.4 °C (hexane−Et_2O); IR (KBr) 900, 940, 987, 1016, 1058, 1092, 1174, 1228, 1325, 1342, 1367, 1445, 1666, 1740, 3460 cm^{-1}; ^1H NMR δ 0.89 (t, 3H, J = 6.9 Hz), 1.26−1.53 (m, 6H), 2.06 (m, 1H), 2.29 (m, 1H), 4.05 (ddd, 1H, J = 1.3, 5.8, 8.7 Hz), 4.10 (dd, 1H, J = 2.5, 8.7 Hz), 4.64 (m, 1H), 4.76 (dd, 1H, J = 1.5, 18.1 Hz), 4.99 (d, 1H, J = 18.1 Hz), 5.11 (br d, 1H, J = 4.0 Hz); ^{13}C NMR 14.0, 22.5, 22.6, 31.2, 31.9, 63.9, 66.8, 69.0, 75.5, 104.3, 129.1, 162.8, 170.0; MS *m*/*z* 254. Further elution with the same solvent system provided syringolide 1 (**1**) (19.2 mg, 10%) as colorless needles: $[\alpha]^{29}_D$ −83.3 (*c* 0.2, $CHCl_3$); mp 113−115 °C (hexane−Et_2O); IR (KBr) 914, 972, 992, 1044, 1066, 1152, 1170, 1198, 1258, 1278, 1308, 1397, 1467, 1755, 3410 cm^{-1}; ^1H NMR (acetone-d_6) δ 0.89 (t, 3H, J = 6.7 Hz), 1.32 (m, 4H), 1.43−1.71 (m, 2H), 1.89 (t, 2H, J = 7.9 Hz), 3.09 (s, 1H), 3.83 (dd, 1H, J = 2.4, 10.4 Hz), 3.95 (dd, 1H, J = 1.2, 10.4 Hz), 4.15 (m, 1H), 4.32 (br s, 1H), 4.33 (d, 1H, J = 10.4 Hz), 4.49 (br s, 1H), 4.67 (d, 1H, J = 10.4 Hz), 5.36 (d, 1H, J = 1.8 Hz); ^{13}C NMR 14.5, 23.4, 24.3, 32.9, 39.7, 60.0, 75.2, 75.7, 75.9, 92.5, 99.2, 109.1, 172.9; HRMS calcd for $C_{13}H_{18}O_5$ (M^+ − 18) 254.1155, found 254.1157. These data were identical to those reported previously.[2b,5]

Acetylation of Acetal 25. A solution of acetal **25** (25 mg, 0.09 mmol), acetic anhydride (60 μL, 0.55 mmol), and pyridine (90 μL, 1.1 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 10 h. The mixture was diluted with CH_2Cl_2 and the organic layer washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with hexane−EtOAc (4:1, v/v) gave acetate **26** (26 mg, 90%) as colorless needles: $[\alpha]^{29}_D$ −104.8 (*c* 0.3, $CHCl_3$); mp 73.0−74.6 °C (hexane−Et_2O); IR (KBr) 930, 1000, 1035, 1070, 1234, 1340, 1375, 1445, 1666, 1748, 1760 cm^{-1}; ^1H NMR δ 0.89 (t, 3H, J = 6.9 Hz), 1.23−1.53 (m, 6H), 2.04−2.16 (m, 1H), 2.16 (s, 3H), 2.26−2.36 (m, 1H), 4.03 (dd, 1H, J = 2.3, 8.7 Hz), 4.10 (ddt, 1H, J = 1.2, 5.9, 8.7 Hz), 4.68 (d, 1H, J = 18.3 Hz), 4.77 (d, 1H, J = 18.1 Hz), 4.79 (m, 1H), 5.88 (d, 1H, J = 4.5 Hz); ^{13}C NMR 14.0, 20.6, 22.4, 22.5, 31.0, 31.8, 64.7, 68.8, 68.9, 73.0, 104.6, 131.4, 158.1, 168.6, 170.4; HRMS calcd for $C_{15}H_{20}O_6$ 296.1262, found 296.1259.

(1′*R*,2′*R*)-3-[1′-(*tert*-Butyldimethylsiloxy)-2′,3′-(isopropylidenedioxy)propyl]-2-(1"-hydroxyoctyl)-2-buten-4-olide (22). This reaction was performed with 500 mg (1.52 mmol) of butenolide **20** and 1-octanal (0.36 mL, 2.29 mmol) in the same manner as described for the preparation of alcohol **21** to give alcohol **22** (602 mg, 87%) as a colorless oil: IR (thin film) 838, 892, 970, 1000, 1128, 1155, 1218, 1256, 1340, 1370, 1380, 1464, 1666, 1750, 3470 cm^{-1}; ^1H NMR δ 0.04 (s, 3.8H), 0.06 (s, 2.2H), 0.11 (s, 6H), 0.85−0.92 (m, 12H), 1.23−1.41 (m, 16H), 1.74 (m, 2H), 2.69 (d, 0.63H, J = 4.3, 7.3 Hz), 3.42 (d, 0.37H, J = 4.3, 7.3 Hz), 3.90 (m, 0.74H), 4.02 (m, 1.26H), 4.23 (m, 1H), 4.56 (m, 1H), 4.86 (m, 2H), 5.06 (br d, 0.63H, J = 4.3 Hz), 5.32 (br d, 0.37H, J = 4.3 Hz); HRMS calcd for $C_{23}H_{41}O_6Si$ (M^+ − 15) 441.2672, found 441.2682. Anal. Calcd for $C_{24}H_{44}O_6Si$: C, 63.12; H, 9.71. Found: C, 62.82; H, 9.75.

(1′*R*,2′*R*)-3-[1′-(*tert*-Butyldimethylsiloxy)-2′,3′-(isopropylidenedioxy)propyl]-2-octanoyl-2-buten-4-olide (24). This reaction was performed with 500 mg (1.18 mmol) of alcohol **22** and Dess−Martin periodinate (600 mg, 1.42 mmol) in the same manner as described for the preparation of ketone **23** to give ketone **24** (465 mg, 93%) as a colorless oil: $[\alpha]^{26}_D$ −126.0 (*c* 1.1, $CHCl_3$); IR (thin film) 780, 840, 870, 1010, 1070, 1130, 1220, 1255, 1370, 1380, 1440, 1460, 1625, 1690, 1770 cm^{-1}; ^1H NMR δ 0.03 and 0.10 (each s, each 3H), 0.84−0.93 (m, 12H), 1.22−1.37 (m, 11H), 1.43 (s, 3H), 1.52−1.69 (m, 2H), 3.00 (t, 2H, J = 7.3 Hz), 3.96 (dd, 1H, J = 5.5, 7.9 Hz), 4.08 (dd, 1H, J = 6.7, 7.9 Hz), 4.34 (ddd, 1H, J = 2.4, 5.5, 6.7 Hz), 4.92 (d, 1H, J = 20.1 Hz), 5.16 (dd, 1H, J = 1.2, 20.1 Hz), 5.40 (t, 1H, J = 1.2 Hz); ^{13}C NMR −5.3, −4.9, 14.1, 18.1, 22.7, 23.3, 25.4, 25.6, 26.1, 29.1, 29.2, 31.7, 42.1, 65.5, 69.0, 71.4, 77.8, 110.2, 123.3, 170.7, 179.5, 197.7; HRMS calcd for $C_{23}H_{39}O_6Si$ (M^+ − 15) 439.2516, found 439.2518. Anal. Calcd for $C_{24}H_{42}O_6Si$: C, 63.40, H; 9.31. Found: C, 63.20, H; 9.33.

3-*O*-Methylsyringolide 2 (29). This reaction was performed with 400 mg (0.88 mmol) of ketone **24** and Dowex 50W-8X (40 g) in the same manner as described for the preparation of 3-*O*-methylsyringolide 1 (**28**) to give 3-*O*-methylsyringolide 2 (**29**) (99 mg, 36%) as colorless needles: $[\alpha]^{25}_D$ −103.6 (*c* 0.2, $CHCl_3$); mp 94−95 °C (hexane−Et_2O); IR (KBr) 976, 1044, 1084, 1186, 1296, 1380, 1665, 1770, 3450 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.7 Hz), 1.30 (m, 9H), 1.56 (m, 1H), 1.68 (d, 1H, J = 4.9 Hz), 1.78 (m, 1H), 1.94 (m, 1H), 3.09 (s, 1H), 3.24 (s, 3H), 3.84 (dd, 1H, J = 3.1, 10.4 Hz), 4.04 (dd, 1H, J = 1.8, 10.4 Hz), 4.30 (br s, 2H), 4.42 and 4.64 (each d, each 1H, J = 10.4 Hz); HRMS calcd for $C_{16}H_{26}O_6$ 314.1730, found 314.1747. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 60.83; H, 8.30. These data were identical to those reported previously.[5]

Syringolide 2 (2). This reaction was performed with 300 mg (0.66 mmol) of ketone **24** and 6 N HCl-THF (1:1, 6 mL) in the same manner as described for the preparation of syringolide 1 (**1**) to give syringolide 2 (**2**) (23 mg, 12%) and acetal **27** (75 mg, 40%) as colorless needles, respectively. Syringolide 2 (**2**): $[\alpha]^{24}_D$ −79.7 (*c* 0.2, $CHCl_3$); mp 119−120 °C; IR (KBr) 972, 1025, 1050, 1074, 1171, 1200, 1266, 1387, 1400, 1468, 1755, 3410 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.7 Hz), 1.29 (m, 8H), 1.49 (m, 2H), 1.76 (br s, 1H), 1.92 (t, 2H, J = 7.9 Hz), 2.57 (br s, 1H), 3.08 (s, 1H), 3.84 (dd, 1H, J = 3.1, 10.4 Hz), 4.04 (dd, 1H, J = 1.2, 10.4 Hz), 4.35 (m, 1H), 4.46 and 4.72 (each d, each 1H, J = 10.4 Hz), 4.55 (br s, 1H); ^{13}C NMR 14.2, 22.7, 23.6, 29.2, 29.5, 31.9, 39.0, 59.2, 74.4, 74.8, 74.9, 91.5, 97.7, 108.3, 172.3; HRMS calcd for $C_{15}H_{22}O_5$ (M^+ − 18) 282.1466, found 282.1433. Anal. Calcd for $C_{15}H_{24}O_6 \cdot {}^1/_6\ H_2O$: C, 59.39; H, 8.09. Found: C, 59.10; H, 7.91. These data were identical to those reported previously.[2b,5] Acetal **27**: IR (KBr) 970, 1040, 1095, 1185, 1265, 1470, 1655, 1760, 3450 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.9 Hz), 1.18-1.45 (m, 6H), 2.06 (m, 1H), 2.30 (m, 1H), 4.06 (m, 2H), 4.65 (m, 1H), 4.75 (dd, 1H, J = 1.5 and 18.1 Hz), 4.97 (d, 1H, J = 18.1 Hz), 5.09 (br d, 1H, J = 4.0 Hz); MS *m*/*z* 282.

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