Concise Syntheses of (−)- and (+)-Syringolide 1 and (−)-Δ^7-Syringolide 1

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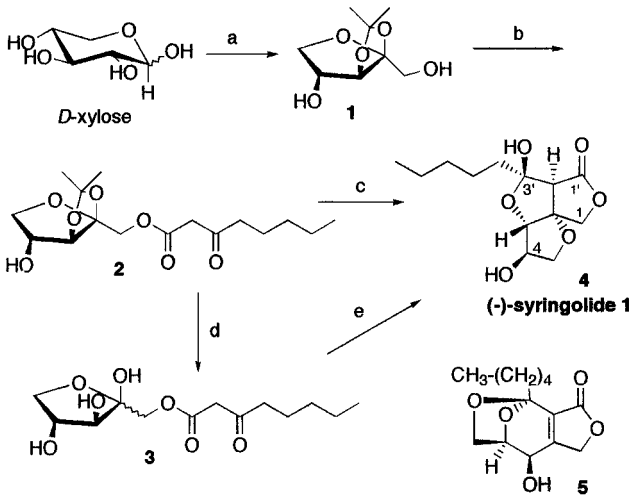
(−)- and (+)-Syringolide 1 have been synthesized from 2,3-*O*-isopropylidene-*β*-*threo*-pentulofuranose (**1**), which was readily prepared from D- or L-xylose, respectively. Condensation of **1** with 3-oxooctanoic acid and treatment of the ester with TFA:H_2O (9:1) produced syringolide 1 in 6.3% yield for the two steps. According to the same synthetic route by replacing 3-oxooctanoic acid with 3-oxo-7-octenoic acid, (−)-Δ^7-syringolide 1 was prepared in 5.8% yield. Primary *β*-keto esters of arabinulose and fructose were also prepared to test the selectivity of the biomimetic cyclization to form syringolide analogs.

Communication in the microbial world is often carried out by natural products. Signal molecules have been commonly classified as toxins, antibiotics, and hormones. The syringolides are compounds produced by the plant pathogenic bacterium *Pseudomonas syringae* pv. *tomato*, which are recognized by certain cultivars of soybean plants.[1] Recognition of the presence of a syringolide by the plant is the first step of a complex active defense reaction, the hypersensitive response. A single avirulence gene, *avrD*, in the bacterium and a single resistance gene, *Rpg4*, in the plant are both necessary and sufficient for this response which leads to the inability of the bacterium to successfully parasitize the plant.[2] We reported the isolation and structure determination of the syringolides in 1993.[3] Since then, these compounds have been synthesized in low yield from tartaric acid derivatives,[4] D-xylose[5] and substituted 2-butenolides.[6]

We proposed a biosynthesis which combined intermediates from the fatty acid biosynthetic pathway with the well known bacterial metabolite D-xylulose.[3] The biosynthesis was based on previous work by Rickards[7a] and Yamada[7b] indicating that the *Streptomyces* autoregulators were biosynthesized from esters formed from dihydroxyacetone and *β*-keto fatty acids and, furthermore, that internal Knoevenagel condensation of a *β*-keto acyl derivative of dihydroxyacetone took place readily. This provides a pathway for the first two steps of a biomimetic synthesis of syringolides. Thus, one has only to synthesize the 1-*β*-keto acyl ester of xylulose to test the biomimetic chemistry. We report here synthesis of such an ester and its conversion into syringolide 1 (**4**). We also have extended this chemistry to prepare Δ^7-syringolide 1, permitting tritium-labeling for receptor studies. Finally, we have explored the stereochemical requirements of the biomimetic syringolide cyclization with 1-*β*-keto esters of arabinulose and fructose.

Scheme 1



(a) (1) Py, reflux; (2) $CuSO_4$, acetone; (b) 3-oxooctanoic acid, DCC-DMPA CH_2Cl_2, 0°C, 48.8%; (c) TFA:H_2O (9:1), 13.0%; (d) $TiCl_4$, CH_2Cl_2, -30°C, 84.0%; (e) pH=6, H_2O, 11.6%.

The synthesis is outlined in Scheme 1. Starting with the inexpensive D-xylose, isomerization in pyridine followed by ion exchange chromatography and reaction with acetone gave the 2,3-acetonide of D-xylulose (**1**) in 20 g batches.[8] Esterification of **1** with hexanoyl Meldrum's acid[9] in refluxing toluene gave primary ester **2**, secondary ester, and diester in 39.8%, 29.3%, and 28.9% yield, respectively. The selectivity between the primary hydroxyl group and the secondary hydroxyl group was 1.4:1. Acylation of **1** with 3-oxooctanoic acid in the presence of dicyclohexylcarbodiimide improved the selectivity between the primary and secondary hydroxyls groups to 3.6:1 and afforded the primary ester **2**, secondary ester, and diester in 48.8%, 13.6% and 27.6% yield, respectively. Treatment of **2** with aqueous trifluoroacetic acid gave (−)-

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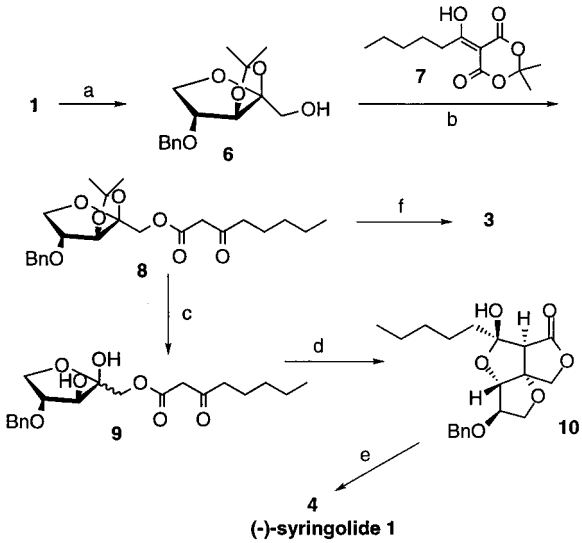
Scheme 2



(a) (1) Ph_3Cl, Py; (2) BnCl/NaH, DMF; (3) H^+, 77.0%; (b) Toluene, reflux, 97.6%; (c) TFA:H_2O (9:1), 80.0%; (d) TFA-CH_3OH, 23.3%; (e) 10% Pd/C, 100%; (f) $TiCl_4$, CH_2Cl_2, -30°C, 80.4%.

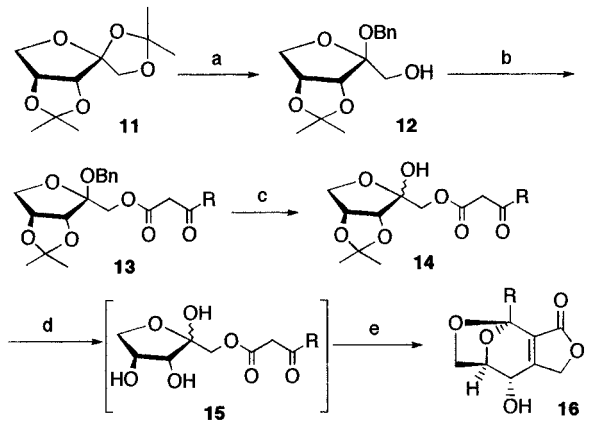
syringolide 1 (**4**) in 13.0% yield, which was identical to previously isolated material by comparison of NMR spectral data and biological activity. In our attempts to improve the yield of syringolide, we found that treatment of **2** with titanium tetrachloride at low temperature selectively removed the acetonide protecting group yielding the ester **3**. This ester had no biological activity; NMR spectra of **3** showed it to be a mixture of cyclic sugar forms. To simulate biosynthetic conditions of condensation and cyclization, we treated **3** with water of varying acidity from pH 4 to 9. The best result from these experiments provided the naturally occurring (−)-**4** after treatment at pH 6 for a week in 11.6% yield.

By replacing D-xylose with L-xylose, unnatural (+)-syringolide 1 (**4**) was similarly synthesized. It was identical to (−)-**4** by ^1H and ^{13}C NMR. The rotations of the synthetic (+) and (−) enantiomers were +74.7 and −70.0, respectively. But unexpectedly, both enantiomers of **4** showed the same specific activity as elicitors of the hypersensitive response on soybean plants harboring the *Rpg4* gene.

Cyclic ketal **5** was a byproduct found in the acidic syringolide cyclization reactions. We also have isolated **5** from cultured syringolide preparations which were acidified to pH 2 before extraction. And we have observed steady conversion of **4** to **5** in 10% MeOH/$CHCl_3$. The structure of **5** was fully elucidated by ^1H and ^{13}C NMR, assigned by $^1H-^1H$ and $^1H-^{13}C$ COSY, INAPT (selective long range $^1H-^{13}C$ spectra), and the secondary deuterium isotope shift of the ^{13}C peak which correlated to its allylic alcohol methine.

To improve the preparation of primary ester, D-xylulose acetonide (**1**) was treated with trityl chloride to selectively afford the 1-trityl derivative, which was converted to its secondary benzyl ether and then detritylated with acid to give **6** in 77.0% yield[10] (Scheme 2). Acylation of **6** with hexanoyl Meldrum's acid (**7**) in refluxing toluene gave primary β-keto ester **8** in 97.8% yield.[9] Treatment of **8** with TFA−H_2O (9:1) at room temperature yielded the deacetonized product **9** in 80.0% yield. After trying various reagents including $SnCl_4-CH_2Cl_2$, SiO_2, AcOH−H_2O (9:1), TFA−CH_2Cl_2, Py−DMF for the cyclization, finally, we found that when **9** was treated with 4% TFA in CH_3OH, the cyclized product, 4′-*O*-benzyl syringolide 1 (**10**) was obtained in 23.3% yield. It was hydrogenolyzed in the presence of 10% Pd/C catalyst to give (−)-syringolide 1 in quantitative yield. Alternatively, treatment of **8** with $TiCl_4$ at −30 °C cleaved both the acetonide and the benzyl ether to produce the ester **3** in 80.4% yield.

Scheme 3



R = *n*-C_5H_{11}. (a) TfOH, BnOH, 60.7%; (b) **7**, Toluene, reflux, 78.9%; (c) 10% Pd/C, 100%; (d) TFA:H_2O (9:1); (e) pH=6, H_2O, 18.6%.

Because of the easy availability of D-arabinose and D-fructose, we explored the behavior of the arabinose-derived ester **15**, which has opposite configuration from **3** at C-3, and fructose-derived ester **19**, which could form a larger ring with the same configuration as **3** at C-3 to test the stereochemical requirements for syringolide formation and activity. Ester **15** was prepared (Scheme 3) from **11**, the diacetonide of D-arabinulose.[8] Treatment of **11** with benzyl alcohol in the presence of catalytic amounts of trifluoromethanesulfonic acid selectively opened the 1,2-acetonide to give **12**,[11] which reacted with hexanoyl Meldrum's acid (**7**) in refluxing toluene to afford primary β-keto ester **13**. Hydrogenolysis of **13** to form **14**, followed by treatment with aqueous trifluoroacetic acid produced ester **15**. Following subjection of **15** to water of varying acidity from pH 4 to 9, only one cyclized product, **16**, was found. Ketal **16** was isomeric with **5**. Apparently, the stereochemistry at C-3 of xylulose is very important for the formation of syringolides.

β-Keto ester **19** was prepared from **17**, the diacetonide of D-fructose.[12] Esterification of **17** with **7** gave **18**, which was deprotected with $TiCl_4$ at −30 °C to give ester **19**. Unfortunately, no cyclization occurred when ester **19** was treated with water at different pH values. From this preliminary work we can conclude that cyclization of **19**, derived from a six-carbon sugar, is more difficult than cyclization of **3**, derived from a five-carbon sugar.

In order to prepare tritium-labeled syringolides for the identification and purification of the syringolide receptor, we also synthesized (−)-Δ^7-syringolide 1 (**21**), a double bond analogue of **4**, according to the synthetic route shown in Scheme 1. Condensation of D-xylulose acetonide (**1**) with 3-oxo-7-octenoic acid in the presence of dicyclohexylcarbodiimide afforded ester **20** in 47.9% yield. Deprotection of **20** with aqueous TFA and cyclization with water gave **21** in 12.2% yield. Compound **21** was active in soybean leaves. It was quantitatively converted to syringolide 1 (**4**) by hydrogenation in the presence of

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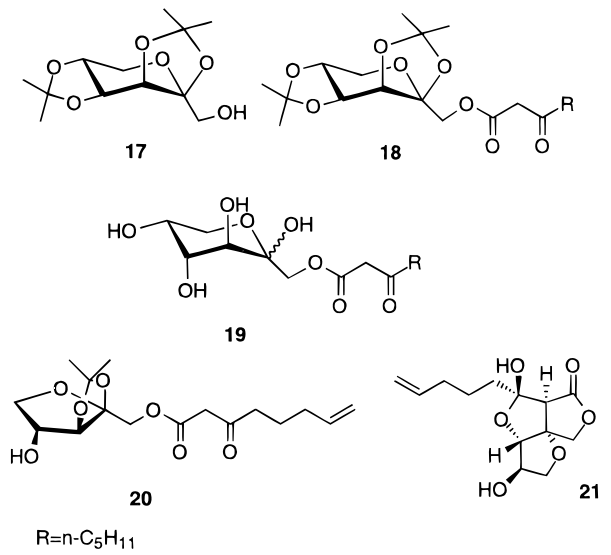

Pd/C catalyst; thus, it should be readily reduced with tritium by the same method to afford a biologically active tritiated syringolide for receptor studies.

In conclusion, we have provided a biomimetic method for the synthesis of syringolides. We have applied this method to synthesis of (−)- and (+)-syringolide 1 and (−)-Δ^7-syringolide 1 and found that each of these compounds is active as an elicitor of the hypersensitive response. We have also tested the stereochemical requirements of the syringolide cyclization reaction and found that the *threo* five-carbon sugar ester is favored for biomimetic cyclization.

Experimental Section

IR spectra were measured as films for liquids or KBr discs for solids. NMR experiments were conducted at 300 MHz ^{1}H or 75.5 MHz ^{13}C, and chemical shifts are relative to residual protonated solvent shifts. Pyridine was dried by distillation from KOH, and CH_2Cl_2 was distilled from CaH_2. All solvents were distilled before use for chromatography. Merck Kieselgel 60H No. 7736 silica gel was used for vacuum flash chromatography. Small samples were prepared using Waters silica gel Sep-Paks and, when required, HPLC on a Phenomenex Maxsil 5 (250 × 4.6 mm) silica column. Larger HPLC samples were purified using a Rainin Dynamax (25 × 2.54 cm) silica column.

2,3-*O*-Isopropylidene-*β*-D-*threo*-pentulofuranose (1). Compound **1** was prepared by isomerization of D-xylose in pyridine followed by chromatography using 75% *n*-PrOH as eluant on Dowex 1-X8 in bisulfite form and reaction of the dried xylulose with acetone.[8] **1**: ^{1}H NMR (DMSO-d_6) δ 5.08 (2H, m), 4.24 (1H, s), 4.03 (1H, ddd, J = 4.3, 2,8, 1.0 Hz), 3.95 (1H, dd, J = 9.5, 2.8 Hz), 3.67 (1H, dd, J = 9.5, 1.0 Hz), 3.51 (1H, dd, J = 11.8, 5.7 Hz), 3.43 (1H, dd, J = 11.8, 6.4 Hz), 1.34 (3H, s), 1.26 (3H, s); ^{13}C NMR (DMSO-d_6) δ 115.4, 111.3, 84.8, 74.4, 73.6, 62.3, 28.0, 27.1.

1-(3-Oxooctanoyl)-2,3-*O*-isopropylidene-*β*-D-*threo*-pentulofuranose (2). Hexanoyl Meldrum's acid (**7**) was prepared by stirring equimolar amounts of *n*-hexanoyl chloride and 2,2-dimethyl-1,3-dioxane-4,6-dione in CH_2Cl_2 at 0 °C overnight.[9] Acetonide **1** (79.8 mg, 0.42 mmol) was esterified by stirring with **7** (116.0 mg, 0.48 mmol) in refluxing toluene (10 mL) for 2.5 h. Then the solvent was removed *in vacuo*, and the residue was purified by vacuum flash chromatography with 5% acetone in chloroform to yield primary ester **2** (43.0 mg, 39.8%), secondary ester (31.6 mg, 29.3%), diester (44.5 mg, 28.9%), and recovered **1** (17.6 mg). **2**: $[\alpha]^{25}_D$ = +3.0 (*c* 1.09, CH_2Cl_2); IR(film) ν_{max} 3500, 2950, 1760, 1730, 1200, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.46 (1H, s), 4.44 (2H, m), 4.26 (1H, d, J = 2.8 Hz), 4.18 (1H, dd, J = 10.0, 2.8 Hz), 3.98 (1H, d, J = 10.0 Hz), 3.56 (1H, d, J = 15.7 Hz), 3.49 (1H, d, J = 15.7 Hz), 2.54 (2H, t, J = 7.4 Hz), 1.57∼1.62 (2H, m), 1.50 (3H, s), 1.36 (3H, s), 1.26−1.32 (4H, b), 0.89 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4, 166.4, 112.3, 112.2, 85.8, 75.5, 74.1, 65.0, 48.9, 43.5, 31.1, 27.2, 26.3, 23.1, 22.4, 13.9; DCIMS (NH_3) *m*/*z* (intensity, %), 348 (M + NH_4^+, 69.4), 331 (M + H^+, 17.0), 315 (23.7), 273 (100); HRMS calcd for $C_{16}H_{27}O_7$ 331.1757, found 331.1749. **Secondary ester**: ^{1}H NMR ($CDCl_3$) δ 5.13 (1H, d, J = 2.8 Hz), 4.51 (1H, s), 4.21 (1H, dd, J = 10.2, 2.8 Hz), 3.98 (1H, d, J = 10.2 Hz), 3.66 (2H, b), 3.42 (2H, s), 2.44 (2H, t, J = 7.4 Hz), 1.50∼1.54 (2H, m), 1.45 (3H, s), 1.31 (3H, s), 1.22∼1.23 (4H, b), 0.82 (3H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 202.8, 166.3, 114.7, 112.4, 82.8, 77.9, 71.0, 63.1, 48.8, 43.2, 31.0, 27.3, 26.6, 23.0, 22.3, 13.8.

1-(3-Oxooctanoyl)-2,3-*O*-isopropylidene-*β*-D-*threo*-pentulofuranose (2). To a stirred solution of 3-oxooctanoic acid[13] (44.0 mg, 0.28 mmol) in 5 mL of anhydrous CH_2Cl_2 at 0 °C were added DMAP (6.0 mg), DCC (108.0 mg, 0.52 mmol), and **1** (53.1 mg, 0.28 mmol), and the mixture was then stirred at 0 °C for 3 h. Precipitated urea was filtered off and the filtrate evaporated *in vacuo*. The residue was taken up in ethyl acetate and, if necessary, filtered free of any further precipitated urea. The solvent was removed by evaporation, and the residue was separated by vacuum flash chromatography washed with 5% acetone in chloroform to yield primary ester **2** (29.5 mg, 48.8%), secondary ester (8.2 mg, 13.6%), diester (23.8 mg, 27.6%), and recovered **1** (18.3 mg).

1-(3-Oxooctanoyl)-D-*threo*-pentulose (3). To a solution of 50.3 mg (0.15 mmol) of **2** in 5 mL of anhydrous CH_2Cl_2 was added 0.045 mL (2.5 equiv) of $TiCl_4$ at −30 °C under argon. The reaction mixture was stirred for 5 h and quenched by adding saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate and purified by passing through a silica Sep-Pak washed with ethyl acetate to afford **3** as a mixture of α and β cyclized forms (37.1 mg, 84.0%). IR(film) ν_{max} 3350, 2950, 1760, 1730, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.0−5.2 (m), 4.73 (1H, d, J = 11.8 Hz), 4.54 (1H, d, J = 11.8 Hz), 4.3−4.4 (m), 4.15−4.25 (m), 4.0−4.1 (m), 3.72 (dd, J = 8.6, 3.0 Hz), 3.53 (d, J = 16.6 Hz), 3.47 (d, J = 16.6 Hz), 3.6 (s), 2.8 (bs), 2.55 (t, J = 7.4 Hz), 1.6 (bm), 1.3 (bs), 0.9 (bt); ^{13}C NMR ($CDCl_3$) δ 205.0, 167.5, 167.0, 105.5, 101.4, 79.7, 785, 76.7, 76.2, 74.8, 70.8, 66.5, 65.2, 49.0, 48.9, 43.4, 43.3, 31.1, 23.1, 22.4, 13.9; DCIMS (NH_3) *m*/*z* (intensity, %), 308 (M + NH_4^+, 60.9), 290 (M^+, 67.2), 273 (100), 255 (21.9), 230 (77.5); HRMS calcd for $C_{13}H_{26}NO_7$ 308.1709, found 308.1715.

(−)-Syringolide 1 (4). The ester **2** (46.5 mg, 0.14 mmol) was stirred in 1 mL of TFA−H_2O (9:1) solution at room temperature for 2 h. Then, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extracts were dried over Na_2SO_4, filtered, and concentrated. After passing through a silica Sep-Pak washed with ethyl acetate, the residues were purified by HPLC using 40% ethyl acetate in hexane on a Maxsil 5 silica gel column to yield (−)-**4** (5.0 mg, 13.0%). $[\alpha]^{25}_D$ = −70.0 (*c* 0.25, $CHCl_3$), {lit. $[\alpha]^{24}_D$ = −83.66 (*c* 0.15, $CHCl_3$)}; ^{1}H and ^{13}C NMR spectral data were identical with those of isolated (−)-syringolide 1.[3a]

As an alternate preparation of **4**, ester **3** (22.9 mg, 0.08 mmol) was mixed with 20 mL water (pH = 6). The mixture was stirred at room temperature for one week and extracted with ethyl acetate. The extracts were dried over Na_2SO_4, filtered, and evaporated. The residues were purified by HPLC to give (−)-**4** (2.5 mg, 11.6%).

(1*R*,7*R*,8*R*)-7-Hydroxy-4,10,11-trioxa-1-pentyltricyclo[6.2.1.0^{2,6}]undec-2(6)-en-3-one (5). Tricycloketal **5** was also formed as a byproduct of acid treatment of syringolide preparations. It was purified from culture fluid or synthetic preparations by HPLC. With hexane−ethyl acetate−2-propanol (45.3:45.3:9.4) as eluant on the Dynamax silica column, **5** had a retention time of 35 min (μ = 6 mL/min). $[\alpha]^{25}_D$ = −22.31 (*c* 1.34, CH_2Cl_2); IR(film) ν_{max} 3450, 2950, 2880, 1750, 1670, 1440, 1340, 1250, 1180, 1090, 1030, 995, 940, 910, 780, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.1 (1H, d, J = 4 Hz), 5.0 (1H, dd, J = 18, 0.6 Hz), 4.8 (1H, dd, J = 18, 1.5 Hz), 4.6 (1H, ddd, J = 5.8, 4.5, 2.5 Hz), 4.1 (1H, m, J = 8.8, 2.5 Hz), 4.05 (1H, m,

(13) 3-Oxooctanoic acid was prepared by refluxing hexanoyl Meldrum's acid (**7**) with methanol and saponification of the methyl ester with KOH.

J = 8.8, 5.9, 1.3 Hz), 2.35 (1H, m), 2.1 (1H, m), 1.4 (2H, m), 1.3 (4H, m), 0.8 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 169.9, 163.0, 128.9, 104.2, 75.4, 69.0, 66.7, 63.9, 31.8, 31.1, 22.6, 22.5, 13.9; DCIMS (NH_3) m/z (intensity, %), 272(MNH_4^+, 31), 256 (15), 255 (MH^+, 100), 254 (11), 237 (5), 236 (4), 207 (5); HRMS calcd for $C_{13}H_{19}O_5$ 255.123249, found 255.1227.

(+)-Syringolide 1. Using L-xylose to replace D-xylose, (+)-syringolide 1 was also synthesized. $[\alpha]^{25}_D$ = +74.7 (c 0.20, $CHCl_3$), ^{1}H and ^{13}C NMR spectral data were identical with those of isolated (−)-syringolide 1.

2,3-*O*-Isopropylidene-4-*O*-benzyl-*β*-D-*threo*-pentulofuranose (6). A solution of **1** (2.1435 g, 11.3 mmol) in 70 mL of anhydrous pyridine was dried by distilling off 40% of the solvent. After cooling the solution to room temperature, trityl chloride (3.1561 g, 11.3 mmol) was added, and the mixture was stirred at room temperature for three days based on TLC monitoring and then diluted with saturated aqueous $NaHCO_3$ solution (20 mL). Then the pyridine was removed at 2 mmHg, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the oily monotrityl derivative, which was filtered through silica gel, washed with 10% and 50% ethyl acetate in hexane to give fraction one containing the primary trityl ether, and fraction two containing the recovered starting material (306.9 mg), respectively. Fraction one was dissolved in DMF (15 mL) and added over 15 min to a solution of NaH (874.0 mg, 36.4 mmol) in 50 mL of DMF at 0 °C. After 1 h, benzyl chloride (2.6 mL, 22.6 mmol) was added. One hour later, the mixture was warmed to room temperature and stirred overnight and then treated with sufficient acetic acid to decompose the excess of NaH, diluted with 150 mL of water, and extracted with ethyl acetate (3 × 30 mL). The extracts were combined, dried, and evaporated to give the 4-*O*-benzyl-1-*O*-trityl derivative, which was dissolved in a mixture of 40 mL of $CHCl_3$, 20 mL of MeOH, and 5 mL of 2 N HCl. After stirring at room temperature for 3 h, the mixture was basified with saturated aqueous $NaHCO_3$, organic solvents were evaporated, and the aqueous residues were extracted with ethyl acetate (3 × 20 mL). The extracts were combined, dried over Na_2SO_4, evaporated *in vacuo*, and purified by vacuum flash chromatography with 5% ethyl acetate in hexane to afford **6** (2.0833 g, 77.0% from **1**). $[\alpha]^{25}_D$ = −13.4 (c 1.79, CH_2Cl_2); IR(film) ν_{max} 3500, 2900, 1500, 1450, 1350, 1200, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31−7.38 (5H, b), 4.62 (1H, d, J = 11.9 Hz), 4.62 (1H, s), 4.55 (1H, d, J = 11.9 Hz), 4.15 (1H, dd, J = 10.1, 2.6 Hz), 4.10 (1H, d, J = 10.1 Hz), 4.06 (1H, d, J = 2.6 Hz), 3.82 (1H, d, J = 11.9 Hz), 3.76 (1H, d, J = 11.9 Hz), 2.10 (1H, bs), 1.51 (3H, s), 1.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 137.3, 128.5, 127.9, 127.7, 114.7, 112.1, 82.6, 81.8, 71.4, 71.1, 63.5, 27.5, 26.7. DCIMS (NH_3) m/z (intensity, %), 298 ($M + NH_4^+$, 10.5), 281 ($M + H^+$, 33.6), 266 (9.9), 223 (17.8), 91 (100); HRMS calcd for $C_{15}H_{24}NO_5$ 298.1654 , found 298.1668.

1-(3-Oxooctanoyl)-2,3-*O*-isopropylidene-4-*O*-benzyl-*β*-D-*threo*-pentulofuranose (8). Hexanoyl Meldrum's acid (**7**) was prepared by stirring equimolar amounts of *n*-hexanoyl chloride and 2,2-dimethyl-1,3-dioxane-4,6-dione in CH_2Cl_2 at 0 °C overnight.[9] The protected alcohol **6** (203.4 mg, 0.73 mmol) was refluxed with **7** (248.9 mg, 1.03 mmol) in 10 mL of toluene for 2 h. Then the solvent was removed, and the residue was purified by vacuum flash chromatography using 5% ethyl acetate in hexane to give ester **8** (297.8 mg, 97.6%). $[\alpha]^{25}_D$ = −15.6 (c 1.69, CH_2Cl_2); IR(film) ν_{max} 3010, 2950, 1760, 1720, 1450, 1350, 1200, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31−7.38 (5H, m), 4.59 (1H, s), 4.56 (2H, m), 4.50 (1H, d, J = 11.9 Hz), 4.31 (1H, d, J = 11.9 Hz), 4.14 (1H, dd, J = 10.1, 2.6 Hz), 4.10 (1H, d, J = 10.1 Hz), 4.05 (1H, d, J = 2.6 Hz), 3.38 (1H, d, J = 15.7 Hz), 3.31 (1H, d, J = 15.7 Hz), 2.45 (2H, t, J = 7.4 Hz), 1.52∼1.60 (2H, m), 1.50 (3H, s), 1.37 (3H, s), 1.23∼1.35 (4H, b), 0.89 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 202.6, 166.7, 137.4, 128.5, 128.0, 127.8, 112.8, 112.3, 83.0, 82.0, 71.6, 71.3, 64.2, 48.9, 43.0, 31.2, 27.5, 26.5, 23.1, 22.4, 14.0; DCIMS (NH_3) m/z (intensity, %), 438 ($M + NH_4^+$, 100), 405 (4.7), 363 (27.7), 108 (9.5), 91 (20.2); HRMS calcd for $C_{23}H_{36}NO_7$ 438.2492, found 438.2519.

1-(3-Oxooctanoyl)-4-*O*-benzyl-D-*threo*-pentulose (9). The acetonide of ester **8** (58.0 mg , 0.14 mmol) was hydrolyzed by mixing with 3 mL of TFA−H_2O (9:1) and stirring at rt for 2 h. Then the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was purified by vacuum flash chromatography using 40% ethyl acetate in hexane to elute **9** as a mixture of α and *β* cyclized forms (42.7 mg, 80.0%). IR(KBr) ν_{max} 3300, 2950, 1760, 1720, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3−7.4 (m), 5.1 (m), 4.9 (m), 4.72 (d, J = 11.7 Hz), 4.64 (s), 4.57 (d, J = 11.7 Hz), 4.2 (m), 4.1 (m), 4.04 (d, J = 11.4 Hz), 3.84 (dd, J = 8.6, 2.9 Hz), 3.5−3.7 (m), 2.49 (t, J = 7.3 Hz), 1.55 (m), 1.27 (m), 0.9 (t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 204.7, 167.6, 166.9, 137.6, 128.6, 128.5, 127.9, 127.8, 105.6, 101.6, 83.5, 83.3, 77.6, 77.3, 71.9, 71.7, 69.6, 66.6, 65.1, 49.1, 49.0, 43.3, 31.1, 23.1, 22.4. 13.9; DCIMS (NH_3) m/z (intensity, %), 398 ($M + NH_4^+$, 30.1), 380 ($M + NH_4^+ - H_2O$, 34.6), 363 (40.9), 240 (100), 132 (44.3), 108 (81.1), 91 (53.4); HRMS calcd for $C_{20}H_{30}NO_6$ 380.2073, found 380.2073.

4′-*O*-Benzylsyringolide 1 (10). The cyclization of ester **9** (23.9 mg, 0.06 mmol) was accomplished by stirring with 5 mL of absolute CH_3OH and 0.2 mL of TFA at room temperature for three days. Then, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The extracts were dried over Na_2SO_4, filtered, and evaporated. The residues were purified by HPLC using 12% ethyl acetate in hexane on a Maxsil 5 silica gel column to give **10** (5.3 mg, 23.3%). $[\alpha]^{25}_D$ = −52.1 (c 1.06, CH_2Cl_2); IR(KBr) ν_{max} 3350, 3010, 2950, 1760, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30−7.39 (5H, m), 4.69 (1H, d, J = 10.3 Hz), 4.67 (1H, s), 4.58 (2H, s), 4.45 (1H, d, J = 10.3 Hz), 4.19 (1H, d, J = 10.5 Hz), 4.02 (1H, d, J = 2.9 Hz), 3.76 (1H, dd, J = 10.5, 2.9 Hz), 3.09 (1H, s), 1.91 (2H, t, J = 6.9 Hz), 1.40−1.55 (2H, m), 1.26∼1.34 (4H, bm), 0.90 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 137.6, 128.6, 128.0, 127.6, 108.3, 97.7, 89.3, 81.3, 74.8, 71.8, 71.2, 59.2, 38.9, 31.6, 23.2, 22.5, 14.0; FABMS (NBA) m/z (intensity, %), 363 ($M + H^+$, 20.9), 345 (100), 255 (19.9); HRMS calcd for $C_{20}H_{27}O_6$ 363.1808, found 363.1787.

(−)-Syringolide 1 (4). To a solution of **10** (5.3 mg) in 2 mL of ethyl acetate was added 10% Pd/C catalyst (2.0 mg). The mixture was stirred under H_2 atmosphere at rt for 3 h. Then, the catalyst was removed by filtration, and the solvent was evaporated to afford **4** in almost quantative yield. Synthetic and isolated (−)-syringolide 1 samples had identical ^{1}H and ^{13}C NMR spectra.[3a]

1-(3-Oxooctanoyl)-D-*threo*-pentulose (3). To a solution of **8** (95.5 mg, 0.23 mmol) in 5 mL of anhyd CH_2Cl_2 at −30 °C was added $TiCl_4$ (63 mL, 2.5 equiv) under argon. The reaction was stirred 5 h at this temperature and then quenched with saturated aqueous NH_4Cl. The product was extracted with ethyl acetate, concentrated, and passed through a silica Sep-Pak using ethyl acetate as eluant to give deprotected primary ester **3** (53.0 mg, 80.4%).

Benzyl 3, 4-Isopropylidene-*β*-D-*erythro*-pentulofuranoside (12). Diacetonide **11** was prepared by pyridine isomerization of D-arabinose followed by bisulfite ion exchange chromatography and acetonization.[8] A solution of **11** (798.5 mg, 3.47 mmol) and TfOH (50 mL, 0.57 mmol) in benzyl alcohol (5.5 mL) was stirred at 0 °C for 5 h. The reaction was made basic with saturated aqueous $NaHCO_3$ at the same temperature and extracted with ethyl acetate. The extracts were concentrated and evacuated to 2 mmHg to remove unreacted benzyl alcohol. The residue was then purified by vacuum flash chromatography using 10% ethyl acetate in hexane to afford benzyl ketal **12** (590.1 mg, 60.7%). $[\alpha]^{25}_D$ = −53.9 (c 1.86, $CHCl_3$); IR(film) ν_{max} 3500, 3100, 1490, 1380, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37−7.33 (5H, m), 4.87 (1H, dd, J = 5.9, 3.7 Hz), 4.62 (1H, d, J = 5.9 Hz), 4.57 (1H, d, J = 13.0 Hz), 4.56 (1H, d, J = 13.0 Hz), 4.06 (1H, d, J = 10.4 Hz), 3.95 (1H, d, J = 12.3 Hz), 3.88 (1H, d, J = 12.3 Hz), 3.87 (1H, dd, J = 10.4, 3.7 Hz), 1.52 (3H, s), 1.34 (3H, s); ^{13}C NMR ($CDCl_3$) δ 138.1, 128.5, 127.7, 126.9, 112.7, 109.2, 84.8, 80.3, 71.7, 63.2, 59.5, 26.2, 24.6; DCIMS (NH_3) m/z (intensity, %), 298 ($M + NH_4^+$, 10.7), 280 ($M + NH_4^+ - H_2O$, 3.0), 190 (100), 173 (26.2), 131 (20.9), 91 (30.4); HRMS calcd for $C_{15}H_{24}NO_5$ 298.1654, found 298.1656.

Benzyl 1-(3-Oxooctanoyl)-3,4-isopropylidene-*β*-D-*erythro*-pentulofuranoside (13). A mixture of **12** (427.4 mg, 1.53

mmol) and hexanoyl Meldrum's acid (**7**, 480.8 mg, 1.99 mmol) was refluxed in 15 mL of toluene overnight, and then the solvent was removed and the residue was purified by vacuum flash chromatography using 20% ethyl acetate in hexane as eluant to give ester **13** (505.6 mg, 78.9%). $[\alpha]^{25}_D = -47.1$ (*c* 1.22, $CHCl_3$); IR(KBr) ν_{max} 3100, 2900, 1760, 1720, 1490, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.28 (5H, m), 4.87 (1H, dd, J = 3.8, 5.5Hz), 4.75 (1H, d, J = 11.9 Hz), 4.53 (3H, m), 4.25 (1H, d, J = 11.9 Hz), 4.02 (1H, d, J = 10.3 Hz), 3.88 (1H, dd, J = 3.8, 10.3 Hz), 3.48 (2H, s), 2.53 (2H, t, J = 7.4 Hz), 1.57 (2H, m), 1.50 (3H, s), 1.33 (3H, s), 1.27 (4H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 202.5, 166.8, 137.7, 128.4, 127.8, 127.7, 112.7, 107.6, 84.6, 80.3, 71.9, 63.5, 60.1, 49.1, 42.8, 31.2, 26.3, 24.9, 23.1, 22.4, 13.9; DCIMS (NH_3) *m*/*z* (intensity, %), 438 (M + NH_4^+, 32.6), 313 (100), 271 (13.8), 91 (20.5); HRMS calcd for $C_{23}H_{36}NO_7$ 438.2492, found 438.2500.

1-(3-Oxooctanoyl)-3,4-isopropylidene-D-*erythro*-pentulofuranose (14). To a solution of **13** (111.9 mg) in 5 mL of ethyl acetate was added 10% Pd/C catalyst (40.3 mg). The mixture was stirred under H_2 atmosphere at rt overnight. Then the catalyst was removed by filtration, and the solvent was evaporated to give **14** in almost quantative yield. IR(KBr) ν_{max} 3500, 2950, 1760, 1720, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (1H, dd, J = 3.6, 5.9 Hz), 4.59 (1H, d, J = 11.6 Hz), 4.50 (1H, d, J = 5.9 Hz), 4.28 (1H, d, J = 11.6 Hz), 4.05 (1H, dd, J = 3.6, 10.6 Hz), 3.96 (1H, d, J = 10.6 Hz), 3.54 (2H, s), 2.50 (2H, t, J = 7.4 Hz), 1.54 (2H, m), 1.43 (3H, s), 1.28 (3H, s), 1.26 (4H, m), 0.85 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 204.3, 166.9, 112.8, 104.2, 84.9, 80.6, 71.6, 65.8, 49.1, 43.1, 31.1, 26.2, 24.8, 23.1, 22.4, 13.9; DCIMS (NH_3) *m*/*z* (intensity, %), 348 (M + NH_4^+, 47.6), 330 (M + NH_4^+ − H_2O, 3.7), 313 (100), 190 (12.4); HRMS calcd for $C_{16}H_{30}NO_7$ 348.2022, found 348.2025.

(1*R*,7*S*,8*R*)-7-Hydroxy-4,10,11-trioxa-1-pentyltricyclo[6.2.1.0^{2,6}]undec-2(6)-en-3-one (16). The ester **14** (115.2 mg, 0.35 mmol) was treated with 1 mL of TFA−H_2O (9:1) for 15 min to deacetonize. Then the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The crude reaction extracts were dried over Na_2SO_4, filtered, and evaporated to give 95.0 mg of oily product **15** which was then stirred with 90 mL of water (pH = 6) for one week. Then the mixture was extracted with ethyl acetate and purified by HPLC using 2-propanol/EtOAc/hexanes (9.4:45.3:45.3) on a Dynamax silica gel column (μ = 6 mL/min, t_R = 78 min) to yield **16** (16.5 mg, 18.6%). $[\alpha]^{25}_D = +26.3$ (*c* 0.43, CH_2Cl_2); IR(KBr) ν_{max} 3450, 2950, 1750, 1620, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.97 (1H, d, J = 17.7 Hz), 4.82 (1H, d, J = 17.7 Hz), 4.78 (1H, bs), 4.14 (1H, dd, J = 8.4, 7.2 Hz), 4.08 (1H, s), 3.41 (1H, dd, J = 8.4, 2.4 Hz), 2.27 (1H, m), 2.15 (1H, m), 1.50 (2H, m), 1.37 (4H, m), 0.90 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 168.9, 158.4, 130.4, 104.1, 77.8, 69.1, 66.3, 64.3, 31.8, 30.9, 22.5, 22.4, 13.9; DCIMS (NH_3) *m*/*z* (intensity, %), 272 (M + NH_4^+, 66.5), 255 (M + H^+, 100), 207 (15.2); HRMS calcd for $C_{13}H_{19}O_5$ 255.1232, found 255.1229.

1-(3-Oxooctanoyl)-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (18). Diacetonide **17** (322.5 mg, 1.24 mmol), which was prepared from D-fructose by isomerization in pyridine followed by acetonization,[12] was esterified by stirring with hexanoyl Meldrum's acid (**7**, 374.1 mg, 1.55 mmol) in refluxing toluene (15 mL) for 3 h. Then the solvent was removed *in vacuo*, and the residue was purified by vacuum flash chromatography with 20% ethyl acetate in hexane to give **18** (463.3 mg, 93.4%). $[\alpha]^{25}_D = -23.1$ (*c* 2.11, $CHCl_3$); IR(KBr) ν_{max} 2950, 1760, 1720, 1380, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.59 (1H, dd, J = 2.5, 7.9 Hz), 4.42 (1H, d, J = 11.7 Hz), 4.29 (1H, d, J = 2.5 Hz), 4.22 (1H, dd, J = 1.8, 7.9 Hz), 4.13 (1H, d, J = 11.7 Hz), 3.88 (1H, dd, J = 1.8, 13.0 Hz), 3.75 (1H, d, J = 13.0 Hz), 3.47 (2H, s), 2.53 (2H, t, J = 7.4 Hz), 1.58 (2H, m), 1.53 (3H, s), 1.47 (3H, s), 1.37 (3H, s), 1.33 (3H, s), 1.29 (4H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 202.4, 166.6, 109.1, 108.8, 101.3, 70.7, 70.5, 70.0, 66.0, 61.3, 49.1, 42.9, 31.1, 26.5, 25.9, 25.2, 24.1, 23.1, 22.4, 13.9; DCIMS (NH_3) *m*/*z* (intensity, %), 418 (M + NH_4^+, 100), 401 (M + H^+, 13.8), 385 (31.8), 360 (8.6), 343 (26.4), 278 (10.4); HRMS calcd for $C_{20}H_{33}O_8$ 401.2175, found 401.2185.

1-(3-Oxo-7-octenoyl)-2,3-*O*-isopropylidene-β-D-*threo*-pentulofuranose (20). To a solution of **1** (219.0 mg, 1.15 mmol), 3-oxooctenoic acid (152.2 mg, 0.98 mmol),[14] and DMAP (31.5 mg, 0.26 mmol) in 50 mL of anhyd CH_2Cl_2 was added DCC (305.2 mg, 1.48 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Precipitated urea was filtered off, and the filtrate was evaporated to dryness. The residue was taken up in ethyl acetate and filtered free of any further precipitated urea. The solvent was removed by evaporation, and the residue was purified by vacuum flash chromatography using 5% acetone in chloroform to yield the desired primary monoester **20** (104.2 mg , 47.9%), secondary monoester (35.0 mg, 16.1%), diester (66.7 mg, 21.6%), and recovered **1** (93.0 mg). **20**: $[\alpha]^{25}_D = +2.2$ (*c* 1.11, CH_2Cl_2); IR(film) ν_{max} 3500, 2950, 1780, 1730, 1200, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.74 (1H, m), 5.01 (2H, m), 4.46 (1H, s), 4.46 (1H, d, J = 11.8 Hz), 4.41 (1H, d, J = 11.8 Hz), 4.26 (1H, d, J = 2.7 Hz), 4.19 (1H, dd, J = 9.4, 2.7 Hz), 3.98 (1H, d, J = 9.4 Hz), 3.55 (1H, d, J = 15.6 Hz), 3.49 (1H, d, J = 15.6 Hz), 2.56 (2H, t, J = 7.3 Hz), 2.07 (2H, bq, J = 7.0 Hz), 1.71 (2H, m), 1.51 (3H, s), 1.36 (3H, s); ^{13}C NMR ($CDCl_3$) δ 203.2, 166.5, 137.6, 115.5, 112.4, 112.1, 85.4, 75.1, 74.0, 64.6, 48.9, 42.3, 32.7, 27.2, 26.3, 22.3; DCIMS (NH_3) *m*/*z* (intensity, %), 346 (M + NH_4^+, 100), 329 (M + H^+, 12.9), 313 (14.0), 288 (8.0), 271 (70.3), 208 (27.0); HRMS calcd for $C_{16}H_{28}NO_7$ 346.1866, found 346.1871.

(−)-Δ^7-Syringolide 1 (21). Primary ester **20** (56.6 mg, 0.17 mmol) was stirred with 2 mL of TFA−H_2O (9:1) at rt for 2 h. Then the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 15 mL). The extracts were combined, dried over Na_2SO_4, filtered, and evaporated. After prechromatography on a silica Sep-Pak using ethyl acetate as eluant, the residues were purified by HPLC with 40% ethyl acetate in hexanes on a Maxsil 5 silica gel column to isolate **21** (5.6 mg, 12.2%). $[\alpha]^{25}_D = -69.4$ (*c* 0.50, $CHCl_3$); IR(KBr) ν_{max} 3350, 2950, 1760, 1070 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.79 (1H, m), 5.41 (1H, s), 5.00 (1H, d, J = 17.1 Hz), 4.92 (1H, d, J = 10.2 Hz), 4.66 (1H, d, J = 10.3 Hz), 4.47 (1H, s), 4.35 (bs), 4.31 (1H, d, J = 10.3 Hz), 4.13 (1H, d, J = 2.8 Hz), 3.94 (1H, d, J = 10.0 Hz), 3.81 (1H, dd, J = 10.0, 2.8 Hz), 3.09 (1H, s), 2.05 (m), 1.89 (2H, t, J = 8.0 Hz), 1.58−1.70 (2H, m); ^{13}C NMR (acetone-d_6) δ 171.8, 138.5, 114.2, 107.8, 98.1, 91.4, 74.7, 74.5, 74.0, 58.9, 38.1, 33.5, 22.9; DCIMS (NH_3) *m*/*z* (intensity, %), 288 (M + NH_4^+, 11.0), 270 (M^+, 12.5), 253 (23.1), 228 (100), 184 (99.2), 167 (73.6); HRMS calcd for $C_{13}H_{22}NO_6$ 288.1447, found 288.1452.

(−)-Syringolide 1 (4). To a solution of **21** (2 mg) in ethyl acetate (2 mL) was added 10% Pd/C catalyst (0.5 mg). This mixture was stirred at rt for 3 h under hydrogen atmosphere and then filtered. Evaporation of the solvent from the filtrate afforded **4** in nearly quantitative yield based on ^1H NMR analysis.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **2**, **5**, **6**, **8**, **10**, **12**−**14**, **16**, **18**, **20**, and **21** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) 3-Oxooctenoic acid was prepared using 5-hexenoyl chloride to replace hexanoyl chloride.[13] The 5-hexenoyl chloride was prepared from 5-hexen-1-ol by oxidation using PDC in DMF followed by chlorination with $SOCl_2$.