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An Improved Synthesis of (-)-Syringolides and X-Ray Structural Characterization of Synthetic (-)-Syringolide 1

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Abstract: On treatment with 10% HF, butenolides 4a and 4b afforded enantiopure (-)-syringolides 1 (1a) and 2 (1b) respectively in much higher yields. Unprecedentedly, the cyclic acetal 5a was also converted to 1a by reacting with an excess of p-TsOH. The structure of the synthetic (-)-syringolide 1 (1a) was substantiated by an X-ray crystallographic study.

Syringolides 1 (**1a**) and 2 (**1b**), both *avirulence gene D* (*avrD*) specified hypersensitive response elicitors, were isolated from *Pseudomonas syringae* pv. *tomato* in 1993.[1] At present, no less than six total syntheses of syringolides have been reported,[2] in which some reactions of the proposed biosynthetic pathway[1b] were imitated. In this connection, the intramolecular Knoevenagel condensation, the intramolecular Michael addition and the hemiacetalization steps are common themes. Notwithstanding this success, the concluding syringolide skeleton construction via deprotection, cyclization and purification steps was usually accomplished in merely 6-23% yields, due presumably to the inherent instability of syringolides.[2] We recently reported that the optically pure butenolide **2**, prepared in several steps from 3-tri-*n*-butylstannylfuran or 3-bromofuran, was a key intermediate in the enantioselective total synthesis of the four coproducts of syringolides, namely (+)-secosyrins and (+)-syributins (Scheme 1).[3] Herein we report an improved procedure from which enantiopure (-)-syringolides 1 (**1a**) and 2 (**1b**) were afforded from **2** in acceptable total yields, thereby achieving a formal total synthesis of **1a** and **1b**. Structural confirmation of the synthetic (-)-syringolide 1 (**1a**) by an X-ray crystallographic study has also been achieved.

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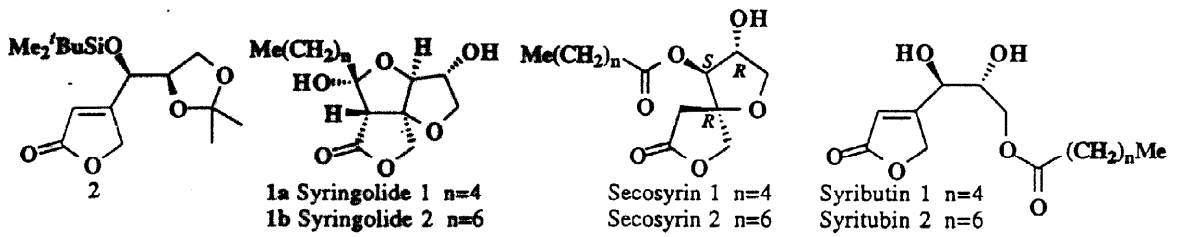
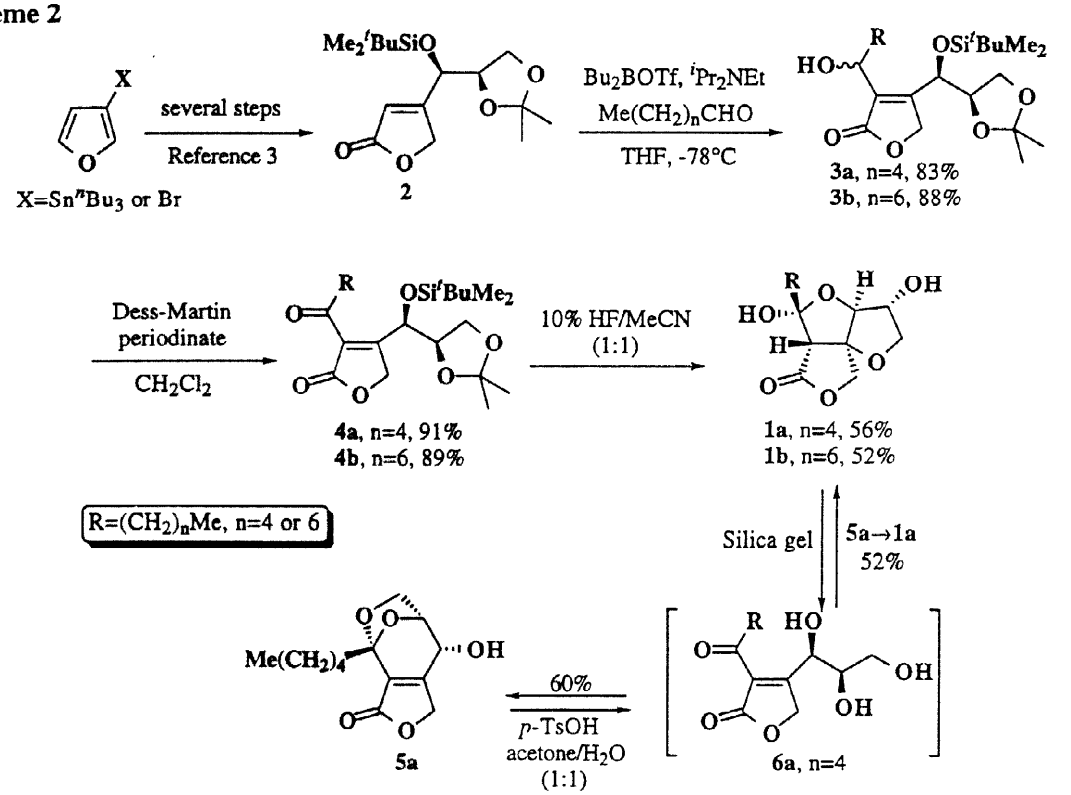
Scheme 1



Interestingly, Honda[2f] had also demonstrated that **1a** and **1b** could be procured from **2** via compounds **3a**, **4a** and **3b**, **4b** albeit in only 10-11% total yields. With a sufficient quantity of butenolide **2** in hand, we had also tried to prepare **3a** and **3b** by utilizing the Baylis-Hillman reaction.[4] Unfortunately, it turned out that the bulkiness of the 3-substituent in **2** somehow impeded the attack of DABCO on the alkene.

Scheme 2



The pivotal ketones **4a** and **4b** were at length prepared by employing Honda's procedure as well.[2f] The failure of securing syringolides in good yields via various literature cyclization methodologies[2] prompted us to look for milder conditions. After several unsuccessful trials, 10% aqueous HF solution in MeCN was finally chosen to remove concomitantly both the acetonide group and the silyl group and to induce cyclization. Noteworthy is that a too dilute or a too concentrated HF aqueous solution resulted only in much longer reaction time or complex products. After stirring **4a** in 10% HF for 60 hours, the sample was analyzed on TLC plates (Merck F_{254}) with ethyl acetate-hexanes (2:1) as eluent, a single UV-invisible compound (R_f = 0.43) was detected (heated after spraying with 1% phosphomolybdic acid in EtOH solution) together with a minor polar product. However, after a normal column chromatography on silica gel (ethyl acetate - hexanes 1:1), a UV

light-visualized component (R_f = 0.53, ethyl acetate - hexanes 2:1) was instead collected as the major product, which was identified by ^{1}H-NMR spectroscopic study to be the known cyclic acetals **5a** (60% yield).[2e,2f,2g] The deviation of chromatographic results implied that silica gel might play a harmful role in promoting the rearrangement of **1a** to **5a**, via presumably the triol **6a**. Likewise, chromatography on alumina gave unsatisfactory outcome. By way of an improved work-up procedure, **1a** and **1b** were consistently realized in acceptable yields from **4a** and **4b**, respectively. Pure syringolides **1a** and **1b** form relatively air-stable needles from $CHCl_3$-hexanes. Perhaps more fascinating is the hitherto unknown *p*-TsOH-induced rearrangement of **5a** to syringolide 1 (**1a**), which was obtained in 52% yield (Scheme 2).

Single crystals of the synthetic (-)-syringolide 1 (**1a**) crystallized as colorless needles from hexanes-Et_2O and its structure was confirmed by X-ray crystallographic analysis (Figure). Noteworthy is that this is the first X-ray crystallographic results of syringolide 1 (**1a**), while X-ray crystallographic study of natural syringolide 2 (**1b**) has already been recorded in the literature.[1b]

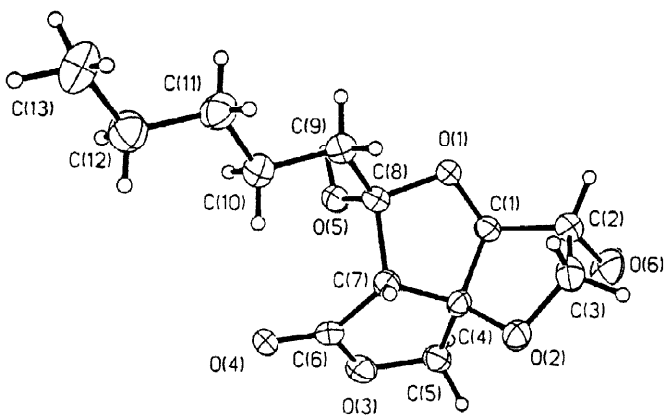


Figure: ORTEP plot of synthetic (-)-syringolide 1 (**1a**)

In conclusion, it is likely that all literature syringolide syntheses did suffer from the same low yield problem because of the chosen cyclization conditions and/or the purification step. Our work-up procedure may be useful in securing sufficient amounts of syringolides for biological evaluation.

Experimental

(1'*R*, 2'*R*)-3-[1'-(*tert*-Butyldimethylsiloxy)-2', 3'-(isopropylidenedioxy)propyl]-2-(1"-hydroxy hexyl)-2-buten-4-olide (3a).[2f] To a stirred solution of butenolide 2[3] (250 mg, 0.76 mmol) in THF (5 mL), ^{i}Pr$_2$NEt (0.53 mL, 3.05 mmol) was added at 0 °C and a 1.0 M CH_2Cl_2 solution of Bu_2BOTf (1.6 mL, 1.6 mmol) was added dropwise at -78 °C. The resulting solution was stirred for 30 min at the same temperature. Then hexanal (0.14 mL, 1.15 mmol) was added, and the mixture was stirred for 1 h at -20 °C. After

quenching with water (5 mL), extraction (EtOAc, 3 X 30 mL), drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by silica gel column chromatography (15 g, hexanes-ethyl acetate 6:1) to give the diastereomeric mixture **3a** (269 mg, 83%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.10 (s, 3H), 0.86-0.89 (m, 12H), 1.25-1.41 (m, 12H), 1.73 (m, 2H), 3.89 (two d, J = 6 Hz, 1H), 4.02 (m, 1H), 4.23 (m, 1H), 4.55 (m, 1H), 4.80 (d, J = 18 Hz, 1H), 4.91 (d, J = 18 Hz, 1H), 5.07 (d, J = 3 Hz, 0.6H), 5.31 (d, J = 6 Hz, 0.3H). ^{13}C NMR ($CDCl_3$) δ -5.91, -4.95, 13.97, 18.02, 22.54, 24.79, 25.16, 25.37, 25.56, 25.95, 26.15, 31.50, 31.61, 35.74, 36.49, 64.76, 65.11, 67.58, 67.69, 67.96, 68.25, 70.85, 71.02, 78.30, 110.16, 110.49, 128.72, 130.53, 159.43, 160.29, 173.02, 173.44; MS *m/z* 429 (MH^+).

(1'*R*, 2 '*R*)-3-[1'-(*tert*-Butyldimethylsiloxy)-2', 3'-(isopropylidenedioxy)propyl]-2-hexanoyl-2-buten-4-olide (4a).[2f] To a stirred solution of alcohol **3a** (200 mg, 0.47 mmol) in CH_2Cl_2 (10 mL) was added portionwise Dess-Martin periodinate (300 mg, 0.71 mmol), and the mixture was stirred for 30 min at rt under N_2. After adding saturated aqueous $NaHCO_3$ solution (5 mL), the mixture was extracted with Et_2O (3 X 40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Then the residue was purified by silica gel column chromatography (15 g, hexanes-ethyl acetate 7:1) to give ketone **4a** (180 mg, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ -0.04 (s, 3H), 0.08 (s, 3H), 0.86-0.90 (m, 12H), 1.29 (s, 3H), 1.31 (m, 4H), 1.42 (s, 3H), 1.63 (m, 2H), 2.99 (t, J = 7.3 Hz, 2H), 3.95 (dd, J = 6.0, 9.0 Hz, 2H), 4.07 (dd, J = 6.0, 9.0 Hz, 1H), 4.34 (m, 1H), 4.90 (d, J = 21.0 Hz, 1H), 5.15 (d, J = 18.0 Hz, 1H), 5.39 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -5.35, -5.00, 13.88, 17.97, 22.47, 22.88, 25.35, 25.54, 25.97, 31.17, 41.95, 65.36, 68.87, 71.25, 77.74, 110.09, 123.19, 170.66, 179.50, 197.66. MS *m/z* 427 (MH^+).

(1'*R*, 2 '*R*)-3-[1'-(*tert*-Butyldimethylsiloxy)-2', 3'-(isopropylidenedioxy)propyl]-2-(1''-hydroxy octyl)-2-buten-4-olide (3b).[2f] This reaction was performed with butenolide **2** (250 mg, 0.76 mmol) and 1-octanal (0.18 mL, 1.15 mmol) in the same manner as described for the preparation of alcohol **3a** to give alcohol **3b** (305 mg, 88%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.02-0.09 (m, 6H), 0.83-0.89 (m, 12H), 1.25-1.38 (m, 16H), 1.73 (m, 2H), 3.90 (m, 0.65H), 4.00 (m, 1.35H), 4.22 (m, 1H), 4.55 (m, 1H), 4.87 (m, 2H), 5.07 (d, J = 3.6 Hz, 0.57H), 5.29 (d, J = 4.5 Hz, 0.33H). ^{13}C NMR ($CDCl_3$) δ -5.22, -4.98, 14.00, 17.99, 22.56, 24.79, 25.14, 25.40, 25.54, 25.65, 25.93, 26.12, 29.15, 29.26, 29.35, 31.71, 35.78, 36.51, 64.77, 65.10, 67.63, 67.87, 68.20, 70.84, 71.00, 78.32, 110.10, 110.42, 128.67, 130.41, 159.57, 160.39, 173.05, 173.45. MS *m/z* 457 (MH^+).

(1'*R*, 2 '*R*)-3-[1'-(*tert*-Butyldimethylsiloxy)-2', 3'-(isopropylidenedioxy)propyl]-2-octanoyl-2-buten-4-olide (4b).[2f] This reaction was performed with alcohol **3b** (500 mg, 1.18mmol) and Dess-Martin periodinate (600 mg, 1.42 mmol) in the same manner as described for the preparation of ketone **4a** to give ketone **4b** (445 mg, 89%) as a colorless oil: ^1H NMR ($CDCl_3$) δ -0.03 (s, 3H), 0.10 (s, 3H), 0.90 (m, 12H), 1.28-1.43 (m, 16H), 1.61 (m, 2H), 3.01 (t, J = 7.5 Hz, 2H), 3.97 (dd, J = 6.0, 9.0 Hz, 1H), 4.09 (dd, J = 6.0, 9.0 Hz, 1H), 4.35 (m, 1H), 4.93 (d, J = 18 Hz, 1H), 5.17 (dd, J = 1.2, 21 Hz, 1H), 5.40 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -5.34, -5.00, 14.05, 17.98, 22.58, 23.22, 25.36, 25.55, 25.98, 29.00, 29.09, 31.65, 42.00, 65.37, 68.88, 71.24, 77.77, 110.10, 123.23, 170.65, 179.45, 197.67. MS *m/z* 455 (MH^+).

(-)-Syringolide 1 (1a). To a stirred solution of ketone **4a** (43 mg, 0.1 mmol) in MeCN (4 mL) inside a polyethylene bottle was added 10% HF (4 mL) and the mixture was stirred for 70 h at rt. After neutralized with saturated $NaHCO_3$ solution to *p*H 7, the mixture was extracted with EtOAc, washed with water (1 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was filtered rapidly on silica gel (2 g, EtOAc) to give the crude product, which after washing with hexanes (2 x 1 mL) gave pure syringolide 1 (**1a**) (15.3 mg, 56%): mp 111-112.5°C, lit[1b] mp 112.5-114.5°C, $[\alpha]_D^{20}$ = -81.3 (*c* 0.38, $CHCl_3$), lit[1b] $[\alpha]_D^{24}$ = -83.66 (*c* 0.15, $CHCl_3$); ^1H NMR (acetone-d_6) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.33-1.37 (m, 4H), 1.52 (m, 1H), 1.66 (m, 1H), 1.92 (t, *J* = 7.8 Hz, 2H), 3.13 (s, 1H), 3.79 (dd, *J* = 3.0, 10.2 Hz, 1H), 3.99 (dd, *J* = 0.9, 9.9 Hz, 1H), 4.18 (m, 1H), 4.36 (d, *J* = 10.2 Hz, 1H), 4.40 (d, *J* = 3.9 Hz, 1H), 4.52 (s, 1H), 4.71(d, *J* = 10.5 Hz, 1H), 5.45 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 14.05, 22.82, 29.04, 32.27, 38.81, 59.46, 74.48, 74.76, 75.55, 91.51, 98.70, 108.59, 173.42. MS *m/z* 273 (MH^+).

(-)-Syringolide 2 (1b). In the same manner as described above, ketone **4b** (40 mg, 0.088 mmol) yielded syringolide 2 (**1b**) (13.6 mg, 52%): mp 120-122°C, lit[1b] mp 123-124°C, $[\alpha]_D^{20}$ = -74.7 (*c* 0.10, $CHCl_3$), lit[1b] $[\alpha]_D^{24}$ = -75.91 (*c* 0.22, $CHCl_3$). ^1H NMR (acetone-d_6) δ 0.90 (m, 3H), 1.30 (m, 8H), 1.50 (m, 1H) 1.60 (m, 1H), 1.90 (m, 2H), 3.09 (s, 1H), 3.82 (dd, *J* = 2.7, 9.9 Hz, 1H), 3.96 (dd, *J* = 0.9, 9.9 Hz, 1H), 4.14 (d, *J* = 2.4 Hz, 1H), 4.32 (d, *J* = 10.5 Hz, 1H), 4.48 (s, 1H), 4.67 (d, *J* = 10.2 Hz, 1H), 5.43 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 14.10, 22.96, 29.03, 32.20, 38.88, 59.45, 74.48, 74.76, 75.53, 91.52, 98.70, 108.57, 173.36; ^{13}C NMR ($CDCl_3$) δ 14.05, 22.59, 23.50, 29.09, 29.40, 31.71, 38.82, 59.10, 74.24, 74.70, 91.41, 97.62, 108.22, 172.41. MS *m/z* 301 (MH^+).

Acetal 5a.[2e-g] To a stirred solution of ketone **4a** (40 mg, 0.094 mmol) in MeCN (3 mL) inside a polyethylene bottle was added 10% HF (3 mL), and the resulting solution was stirred for 43 h at rt. After neutralized with saturated $NaHCO_3$ solution (*p*H = 7), the mixture was extracted with EtOAc (3 X 30 mL). The extract was washed with brine (1 X 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was isolated by column chromatography on silica gel (10 g, hexanes-ethyl acetate 1:1) gave **5a** as major product (14.3 mg, 60%): $[\alpha]^{20}_D$ = -29.6 (*c* 1.0 $CHCl_3$), lit. $[\alpha]^{29}_D$ = -33.1 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.24-1.46 (m, 6H), 2.05 (m, 1H), 2.24 (m, 1H), 3.31 (br d, *J* = 6.0 Hz, 1H), 4.03 (ddd, *J* = 1.3, 5.8, 8.7 Hz, 1H), 4.09 (dd, *J* = 2.4, 8.7 Hz, 1H), 4.63 (m, 1H), 4.76 (dd, *J* = 1.2, 18 Hz, 1H), 4.99 (d, *J* = 18.3 Hz, 1H), 5.08 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.92, 22.45, 22.51, 31.07, 31.79, 63.85, 66.62, 69.02, 75.42, 104.19, 128.84, 163.00, 169.93. MS *m/z* 255 (MH^+). Further elution with the same solvent system provided the minor product syringolide 1 (**1a**) (2.2 mg, 8.6%).

From **5a**[2e-g] to **(-)-syringolide 1 (1a).** To a solution of **5a** (14 mg, 0.055mmol) in acetone/water (1:1, 2 mL) was added *p*-TsOH·H_2O (105 mg, 0.55 mmol). After 50 h, the mixture was neutralized with $NaHCO_3$ aqueous solution. Extraction (EtOAc, 3 X 20 mL) was followed by washing with water (1 X 3 mL), drying ($MgSO_4$) and solvent evaporation, giving essentially pure syringolide 1 (**1a**) (7.8 mg, 52%), which was further purified in the same manner as described above. The spectroscopic data of **1a** prepared this way were identical to those reported previously.[1,2]

Crystal data of synthetic (-)-**syringolide 1 (1a)**. $C_{13}H_{20}O_6$ = 272.29, monoclinic, space group $P2_1$ (No. 4), a = 8.073(2) Å, b = 5.802(1) Å, c = 14.691(3) Å, β = 95.66(3)°, V = 684.8(2) Å^3, Z = 2, D_c = 1.316 Mg/m^3, $F(000)$ = 290, Mo K_α radiation λ = 0.71073 Å. Intensity data were collected with AFC7R Rigaku diffractometer. 1431 reflections collected in the range $2.54 < \theta < 24.99°$, $0 \le h \le 9$, $0 \le k \le 6$, $-17 \le l \le 17$; 1334 independent (R_{int} = 0.0141), 1334 observed [$I > 2\sigma(I)$]. Anisotropic displacement parameters were used for nonhydrogen atoms. The hydrogen atoms were located by difference Fourier map and refined isotropically. The final agreement was R_1 = 0.0415. Tables of fractional atomic coordinates, atomic displacement parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom.

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References and Notes

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