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Total syntheses of (+)- and (−)-syringolides 3 and of (+)- and (−)-syributins 1, 2 and 3☆

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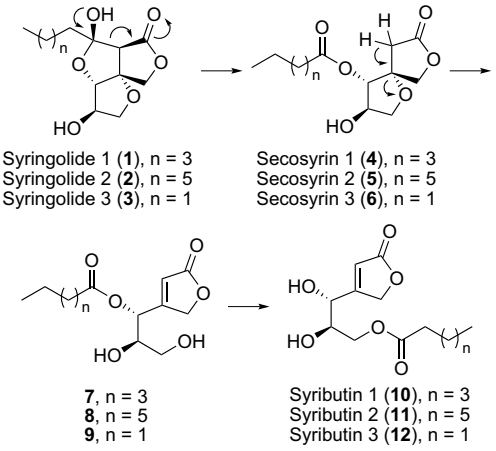
ABSTRACT

The first total syntheses of (−)-syringolide 3, (+)-syributin 3 and their unnatural enantiomers (+)-syringolide 3 and (−)-syributin 3 using a common intermediate as starting material are described. In addition, total syntheses of (−)- and (+)-syributins 1 and 2 were accomplished by means of the same methodology.

1. Introduction

The hypersensitive response (HR) of plants is an active mechanism of defense that allows them to resist pathogen infection.[2] It involves cell death in the site of infection and a complex series of biochemical changes in the plant that restrict the pathogen's proliferation. Pathogen avirulence (*avr*) genes are responsible for the biosynthesis of metabolites named elicitors that trigger the HR in plants. It is believed that complementary plant resistance (*R*) genes encode for specific receptors for the pathogen elicitors, however, most of these putative receptors have not yet been characterized and the way they interact with the elicitors and trigger the HR is not well understood.

In 1993 Sims[3] reported the isolation of syringolide 1 (**1**) and syringolide 2 (**2**), the first nonproteinaceous specific elicitors of a plant HR (Scheme 1). Syringolides 1 and 2 are bacterial signal molecules (elicitors) produced by the avirulence gene D (*avrD*) of *Pseudomonas syringae* pv. *tomato*. The syringolides elicit an HR on soybean cultivars carrying the resistance gene *Rpg4*.



Scheme 1. Proposed biosynthesis of secosyrins and syributins 1.

In 1995 Sims[4] reported the isolation and structure elucidation of secosyrin 1 (**4**), secosyrin 2 (**5**), syributin 1 (**10**), and syributin 2 (**11**). These metabolites were also isolated from *P. syringae* pathovars carrying the avirulence *avrD* gene and they are the major co-products of the syringolides 1 (**1**) and 2 (**2**). Sims proposed

☆ Portions of this work have appeared as a thesis dissertation (in Ref.1).

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a possible biosynthesis for these compounds from syringolides (Scheme 1). Reverse Claisen cleavage of **1**–**3** would furnish the corresponding secosyrins (**4**–**6**), which then would undergo a retro-Michael reaction followed by a 1,3-acyl migration of the intermediates **7**–**9** that would result in the formation of the corresponding syributins (**10**–**12**). This is supported by experiments wherein base treatment of secosyrin 1 was shown to furnish syributin[5] and by the base promoted sequential transformation of the syringolides into the corresponding secosyrins and syributins.[6] Unlike the syringolides, the syributins and secosyrins are not active elicitors of a hypersensitive response on soybean cultivars carrying the resistance gene *Rpg4*. Through a combination of NMR experiments, X-ray crystallography, and chemical methods Sims determined the structures of syringolides, secosyrins, and syributins illustrated in Scheme 1.

Yucel and co-workers[7] reported that two different classes of *avrD* alleles occur in *P. syringae* pathovars: class I and class II alleles. Class I alleles include the *avrD* allele 1 from *P. syringae* pv. *lachrimans* and the *avrD* allele from *P. syringae* pv. *tomato*. Class II alleles include the *avrD* allele 2 from *P. syringae* pv. *lachrimans* and the *avrD* allele from *P. syringae* pv. *phaseolicola*. The same year Yucel and co-workers[8] reported that the two classes of alleles direct the production of different syringolides, syributins, and secosyrins. Class I *avrD* alleles are responsible for the biosynthesis of syringolides 1 and 2 and their accompanying secosyrins 1 (**4**) and 2 (**5**) and syributins 1 (**10**) and 2 (**11**) while class II *avrD* alleles direct the production of syringolides 1 and 3 and their accompanying secosyrins 1 (**4**) and 3 (**6**) and syributins 1 (**10**) and 3 (**12**).

Syringolides and syributins **1**–**2** have attracted great deal of attention from the synthetic community. Since Wood's first report[9] there have been nine other reported total syntheses of syringolides 1 and 2[10] and two formal ones,[11] and seven total syntheses of syributins 1 and 2[5,10g,10m,11b,12] and a formal one.[13] However, syringolide 3 and syributin 3 have yet to be synthesized.

2. Results and discussion

Although simple modification of our previous approach could be used to gain access to Syringolide 3,[9] subsequent studies initially focused on a modification that finds precedent in a report by Doyle and Dyatkin.[14] The latter describes the use of regioselective intramolecular carbon–hydrogen insertion reactions to access spirolactones akin to those found in the syringolide/secosyrin core (Scheme 2). Importantly, unlike our previous approach the modified strategy was envisioned as providing direct access to either the syringolide or secosyrin ring system. Thus, in the forward sense a doubly protected acetoacetate variant of **13** could give rise to syringolide 3 (e.g., **13** to **3**, Scheme 2), whereas a differentially protected malonate variant of **13** would serve as a precursor to secosyrin upon C–H insertion, deprotection, and decarboxylation (e.g., **13** to **6**, Scheme 2). Intrigued by the potential flexibility of this approach, we prepared model substrates in both the acetoacetate and malonate series (**14a** and **14b**, respectively, Fig. 1). Disappointingly, under a variety of conditions neither of these substrates was found to undergo C–H insertion. Despite this initial failure we went forth with the preparation of more heavily functionalized substrates that were suited for eventual conversion to syringolide 3 (e.g., **13a**–**d**, Fig. 1). Unfortunately, these substrates, along with a series of TBS-enolether derivatives (not shown), were also found to deliver intractable mixtures upon exposure to a range of conditions designed to effect the desired C–H insertion.

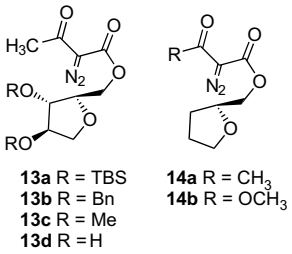
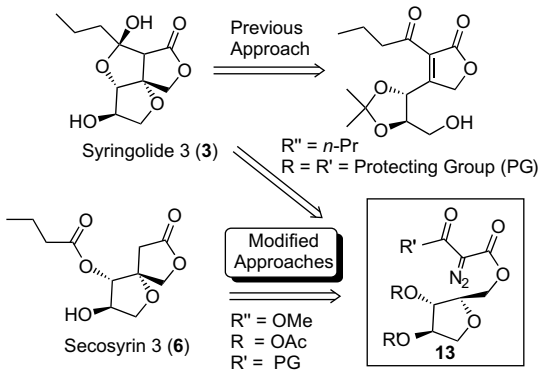


Figure 1. β-oxo-Diazoacetates for the C–H insertion approach to syringolides.



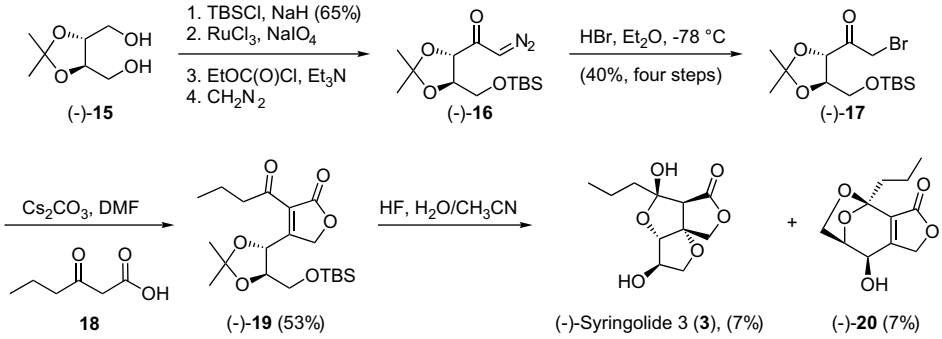
Scheme 2. Retrosynthetic analysis for syringolide 3 and secosyrin 3.

Given the difficulties encountered with our modified approach we returned to our previous strategy and targeted (+)- and (−)-syringolide 3 (**3**) as well as (+)-syributins 1–3 (**10**–**12**). Toward (−)-**3**, known (−)-2,3-*O*-isopropilidene-L-threitol [(−)-**15**][9] was monosilylated and then transformed into α-bromoketone (−)-**17** via a four-step procedure without purification of the intermediates (Scheme 3). Specifically, diol (−)-**15** was treated with TBSCl and NaH to furnish a monoprotected alcohol,[15] which was then oxidized to the corresponding carboxylic acid using the catalytic $RuCl_3$ procedure of Sharpless.[16] This acid was treated first with ethyl chloroformate and triethylamine and then with excess diazomethane[17] to furnish (−)-**16**, the common intermediate for the synthesis of (−)-syringolides and (+)-syributins (Schemes 3 and 4). Halogenation[17] of (−)-**16** with anhydrous ethereal HBr provided (−)-**17** in 40% overall yield from (−)-**15**. Acylation of (−)-**17** with the cesium salt[18] of β-ketoacid **18**[19] furnished the desired butenolide (−)-**19**[20] in 53% yield after an intramolecular Knoevenagel condensation in the same pot of the expected ester intermediate.

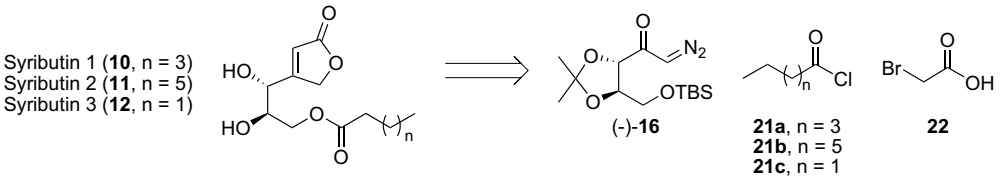
The final step of the synthesis involved complete deprotection of butenolide (−)-**19** using 10% aqueous HF in CH_3CN[10i] to furnish the desired (−)-syringolide 3 (**3**) in 7% yield, along with the side product (−)-**20** in 7% yield. There is no published data for (−)-syringolide 3, however, spectroscopic data for this compound is similar to that for (−)-syringolides 1 and 2[3] and consistent with the proposed structure, furthermore X-ray crystallographic analysis of (−)-**3** (Fig. 2) confirms that this compound has the same relative stereochemical configuration as syringolides 1 and 2.[21]

The total synthesis of (+)-syringolide 3 was accomplished in the same manner as for the corresponding (−)-syringolide 3 by replacing (−)-**15** with (+)-**15**. Thus, α-bromoketone (+)-**17** was obtained in 35% overall yield form the monosilylated derivative of (+)-**15** and was treated with the β-ketoacid **18** to give butenolide (+)-**19** in 51% yield. Deprotection of this butenolide furnished the corresponding syringolide (+)-**3** in 10% yield, along with the side product (+)-**20** in 10% yield.

The total synthesis of (+)-syributins 1, 2, and 3 (**10**, **11**, and **12**, respectively) is described in Scheme 5. Bromoacetate (−)-**23** was obtained in 64% yield by O–H insertion of the rhodium(II)



Scheme 3. Total synthesis of (−)-syringolide 3.



Scheme 4. Syributins: retrosynthetic analysis.

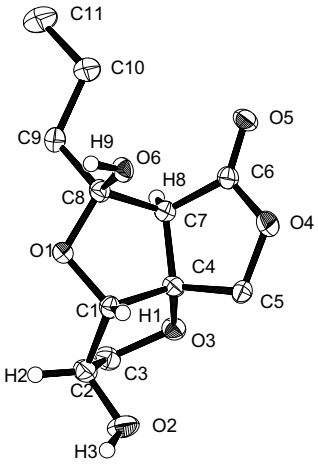
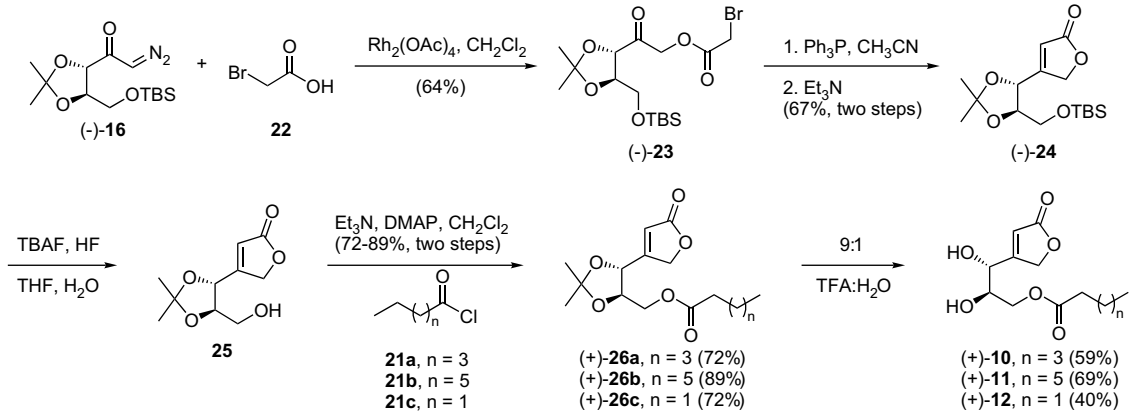


Figure 2. ORTEP plot of syringolide 3.

67% yield. Desilylation of (−)-**24** followed by acylation of the resulting primary alcohol **25**[23] with acid chlorides **21a–c** furnished esters (+)-**26a–c**[23] in 72–89% overall yields. Removal of the isopropylidene protecting group under acidic conditions[12b] resulted in the formation of the desired syributins 1 [(+)-**10**], 2 [(+)-**11**], and 3 [(+)-**12**] in 40–69% yields. Spectroscopic data for (+)-syributins 1 and 2 were identical to that reported in the literature.[5,10g,12a] There is no published data for (+)-syributin 3, however, spectroscopic data for this compound is similar to that for (+)-syributins 1 and 2 and consistent with the proposed structure.

The total syntheses of (−)-syributins 1, 2, and 3 were performed in the same manner as for the corresponding (+)-syributins by replacing (−)-**16** with (+)-**16**. Thus, diazo decomposition of α-diazoketone (+)-**16** in the presence of acid **22** produced ester (+)-**23** in 55% yield. Two-step intramolecular Wittig olefination of (+)-**23** furnished butenolide (+)-**24** in 68% yield. Deprotection of (+)-**24** gave alcohol **25**, which was acylated with acid chlorides



Scheme 5. Total synthesis of (+)-syributins 1, 2 and 3.

stabilized carbene derived from the α-diazoketone (−)-**16** into the acid **22**. A two-step intramolecular Wittig olefination[22] adding first triphenylphosphine and later triethylamine to a solution of bromoacetate (−)-**23** provided the expected butenolide (−)-**24** in **21a–c** to produce esters (−)-**26a–c** in 39–70% overall yields. Removal of the isopropylidene protecting group in acidic conditions resulted in the formation of the desired syributins 1 [(−)-**10**], 2 [(−)-**11**], and 3 [(−)-**12**] in 58–65% yields.

3. Conclusions

The first total syntheses of (−)-syringolide 3, (+)-syributin 3 and their unnatural enantiomers (+)-syringolide 3 and (−)-syributin 3 were successfully completed using a common intermediate. In addition, total syntheses of (−)- and (+)-syributins 1 and 2 were achieved using the same methodology.

4. Experimental

4.1. General

Unless stated otherwise, reactions were performed in flame dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received. Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230–400 mesh) purchased from Bodman. In general, the chromatography guidelines reported by Still and coworkers[24] were followed. All melting points were obtained on a Thomas *Hoover* capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500, Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.2 ppm), or acetone (^1H, δ 2.05 ppm; ^{13}C, δ 29.8 ppm).[25] High resolution mass spectra were performed at the University of Illinois at Urbana-Champaign Mass Spectrometry Center. High performance liquid chromatography (HPLC) was performed on a Waters 510 solvent delivery system using a Rainin Microsorb 80-–199-C5 column, or a Rainin Dynamax SD-200 solvent delivery system with a Rainin Microsorb 80-–120-C5 column. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University.

4.2. C–H insertion approach

4.2.1. Representative synthetic procedures.

4.2.1.1. Diazotransfer reaction.

4.2.1.1.1. Diazoacetoacetate 13a. Triethylamine (400 μL, 2.87 mol, 3.05 equiv) was added dropwise to a stirred (0 °C) solution of corresponding acetoacetate[1] (421 mg, 0.94 mmol, 1 equiv) and *p*-ABSA (275 mg, 1.14 mmol, 1.21 equiv) in CH_3CN (5 mL). After allowing to warm to room temperature and stirring overnight, the reaction mixture was concentrated in vacuo, triturated with 1:1 Et_2O/petroleum ether (10 mL), filtered and reconcentrated to a yellow oil. Silica gel chromatography employing 9:4 hexanes/EtOAc as eluant furnished **13a** (401 mg, 90% yield) as a yellow oil. An analytical sample (yellow oil) was obtained by selecting fractions from the flash chromatography: FTIR (thin film/NaCl) 2953 (s), 2930 (s), 2886 (m), 2858 (m), 2138 (s), 1721 (s), 1663 (s), 1472 (m), 1463 (m), 1364 (m), 1314 (s), 1251 (s), 1156 (m), 1113 (s), 1078 (s), 1069 (s), 1013 (m), 915 (w), 837 (s), 811 (m), 777 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 4.34 (dd, *J*=11.3, 5.6 Hz, 1H), 4.31 (dd, *J*=11.1, 6.7 Hz, 1H), 4.05–4.03 (m, 1H), 3.98 (dd, *J*=9.2, 3.7 Hz, 1H), 3.96–3.93 (m, 2H), 3.78 (d, *J*=9.1 Hz, 1H), 2.47 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 161.2, 84.1, 80.0, 78.6, 74.7, 65.5, 28.5, 25.8, 25.7, 18.0, −4.5, −4.6, −4.7, −4.8; HRMS (EI) *m*/*z* 473.2501 [calcd for $C_{21}H_{41}N_2O_6Si_2$ (M+H) 473.2503].

4.2.1.2. C–H insertion reaction attempts. To a suspension of $Rh_2(OAc)_4$ (9.7 mg, 0.02 mmol, 0.9% equiv) in CH_2Cl_2 (45 mL) at reflux was added dropwise (over a 10 h period via syringe pump) a solution of a diazoacetate **13** or **14** (2.46 mmol, 1 equiv) in CH_2Cl_2 (12 mL). After allowing to cool to room temperature and concentrating in vacuo, the resultant oil was analyzed by ^1H NMR showing to be an intractable mixture, which did not contain the desired spirolactone product.

*4.2.2. Diazoacetoacetates prepared as **13a**.*

*4.2.2.1. (+)-Diazoacetoacetate **13b**.* Yield: 3.103 g, 89%. Analytical sample (yellowish oil): $[\alpha]_D^{20}$ +20.96 (*c* 1.04, $CHCl_3$); FTIR (thin film/NaCl) 3088 (w), 3063 (w), 3030 (w), 3006 (w), 2922 (w), 2866 (w), 2141 (s), 1717 (s), 1657 (s), 1496 (w), 1454 (m), 1364 (m), 1312 (s), 1250 (m), 1208 (w), 1157 (m), 1076 (s), 1027 (m), 965 (m), 740 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 7.38–7.29 (m, 10H), 4.56 (d, *J*=11.8 Hz, 1H), 4.54 (d, *J*=11.9 Hz, 1H), 4.50 (d, *J*=11.8 Hz, 1H), 4.47 (d, *J*=12.2 Hz, 1H), 4.38 (dd, *J*=11.2, 4.4 Hz, 1H), 4.33 (dd, *J*=11.3, 6.4 Hz, 1H), 4.09 (m, 2H), 4.05 (d, *J*=10.3 Hz, 1H), 3.94 (dd, *J*=10.1, 4.3 Hz, 1H), 3.90 (d, *J*=3.1 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 161.2, 137.6, 137.4, 128.6, 128.1, 128.0, 127.8, 84.3, 82.6, 81.5, 72.0, 71.8, 71.5, 64.8, 28.4; HRMS (FAB) *m*/*z* 425.1712 [calcd for $C_{23}H_{25}N_2O_6$ (M+H) 425.1713].

*4.2.2.2. Diazoacetoacetate **13c**.* Yield: 1.613 g, 78%. Analytical sample (yellow oil): FTIR (thin film/NaCl) 2984 (w), 2932 (m), 2902 (m), 2825 (w), 2142 (s), 1717 (s), 1657 (s), 1457 (w), 1365 (m), 1312 (s), 1249 (m), 1195 (w), 1156 (m), 1106 (m), 1074 (s), 965 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.40 (dd, *J*=11.8, 4.4 Hz, 1H), 4.35 (dd, *J*=11.7, 6.0 Hz, 1H), 4.02–3.97 (m, 2H), 3.86 (dd, *J*=10.0, 4.0 Hz, 1H), 3.82–3.81 (m, 1H), 3.62 (d, *J*=3.3 Hz, 1H), 3.40 (s, 3H), 3.34 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 161.1, 86.4, 84.3, 81.3, 71.2, 64.8, 57.6, 56.8, 28.2; HRMS (EI) *m*/*z* 273.1098 [calcd for $C_{11}H_{17}N_2O_6$ (M+H) 273.1087].

*4.2.2.3. (+)-Diazoacetoacetate **13d**.* Slightly modified procedure, which includes transient protection of the diol functionality:

4.2.2.3.1. Diol protection. 2-Methoxypropene (1.6 mL, 16.71 mmol, 3.98 equiv) was added dropwise to a stirred solution of the corresponding acetoacetate[1] (917 mg, 4.20 mmol, 1 equiv) and $POCl_3$ (ca. 1 μL, 0.01 mmol, 0.3% equiv) in THF (10 mL). The reaction mixture was stirred at room temperature for 1 h, quenched by adding triethylamine and concentrated in vacuo to a turbid yellow oil, which was used without purification.

4.2.2.3.2. Diazotransfer. Triethylamine (1.8 mL, 12.91 mmol, 3.07 equiv) was added dropwise to a stirred (0 °C) solution of the crude product of the previous reaction and *p*-ABSA (1.244 g, 5.18 mmol, 1.23 equiv) in CH_3CN (10 mL). After allowing to warm to room temperature and stirring for 1 h, the reaction mixture was concentrated in vacuo, triturated with 1:1 Et_2O/petroleum ether (20 mL), filtered and reconcentrated to a yellow oil, which was used without purification.

4.2.2.3.3. Diol deprotection. To a solution of the crude product of the previous reaction in MeOH (20 mL) was added *p*-TsOH monohydrate (81 mg, 0.43 mmol, 0.10 equiv). The reaction mixture was stirred at room temperature for 15 min, quenched by adding triethylamine and concentrated in vacuo to a yellow oil. Silica gel chromatography employing EtOAc as eluant furnished (+)-**13d** (938 mg, 91% yield) as a yellow oil. An analytical sample (yellowish oil) was obtained by a second flash chromatography using 13:1 CH_2Cl_2/MeOH as eluant: $[\alpha]_D^{20}$ +21.97 (*c* 0.58, MeOH); FTIR (thin film/NaCl) 3413 (br m), 2928 (w), 2147 (s), 1718 (s), 1652 (m), 1368

(m), 1317 (s), 1251 (m), 1156 (m), 1072 (s), 969 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (d, J=5.3 Hz, 2H), 4.25 (m, 1H), 4.09–4.04 (m, 2H), 3.98 (q, J=4.8 Hz, 1H), 3.88 (dd, J=10.0, 2.1 Hz, 1H), 2.48 (s, 3H), 1.70 (br s, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 189.8, 161.9, 84.2, 79.8, 78.4, 74.4, 66.0, 28.2; HRMS (EI) m/z 245.0775 [calcd for $C_9H_{13}N_2O_6$ (M+H) 245.0774].

4.2.2.4. Diazoacetoacetate ***14a***. Yield: 3.857 g, 88%. Analytical sample (yellow oil): $[\alpha]_D^{20}$ +20.96 (c 1.04, $CHCl_3$); FTIR (thin film/NaCl) 3088 (w), 3063 (w), 3030 (w), 3006 (w), 2922 (w), 2866 (w), 2141 (s), 1717 (s), 1657 (s), 1496 (w), 1454 (m), 1364 (m), 1312 (s), 1250 (m), 1208 (w), 1157 (m), 1076 (s), 1027 (m), 965 (m), 740 (m), 699 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 7.38–7.29 (m, 10H), 4.56 (d, J=11.8 Hz, 1H), 4.54 (d, J=11.9 Hz, 1H), 4.50 (d, J=11.8 Hz, 1H), 4.47 (d, J=12.2 Hz, 1H), 4.38 (dd, J=11.2, 4.4 Hz, 1H), 4.33 (dd, J=11.3, 6.4 Hz, 1H), 4.09 (m, 2H), 4.05 (d, J=10.3 Hz, 1H), 3.94 (dd, J=10.1, 4.3 Hz, 1H), 3.90 (d, J=3.1 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 161.2, 137.6, 137.4, 128.6, 128.1, 128.0, 127.8, 84.3, 82.6, 81.5, 72.0, 71.8, 71.5, 64.8, 28.4; HRMS (FAB) m/z 425.1712 [calcd for $C_{23}H_{25}N_2O_6$ (M+H) 425.1713].

4.2.2.5. Diazomalonate ***14b***. Yield: 1.406 g, 68%. Analytical sample (yellow oil): FTIR (thin film/NaCl) 2965 (s), 2875 (m), 2137 (s), 1761 (s), 1738 (s), 1694 (s), 1438 (s), 1387 (s), 1325 (s), 1237 (s), 1183 (s), 1081 (s), 1019 (m), 992 (m), 923 (w), 761 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, J=11.0, 3.4 Hz, 1H), 4.21–4.14 (m, 2H), 3.87 (dd, J=15.1, 7.0 Hz, 1H), 3.83 (s, 3H), 3.79 (dd, J=14.3, 7.3 Hz, 1H), 2.01 (m, 1H), 1.90 (m, 2H), 1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 160.7, 76.2, 68.4, 67.1, 52.4, 27.8, 25.6; HRMS (EI) m/z 229.0825 [calcd for $C_9H_{13}N_2O_5$ (M+H) 229.0824].

4.3. Common intermediate synthesis

*4.3.1. α-Diazoketone (+)-**16***. To a stirred biphasic solution of mono-TBS protected (+)-2,3-*O*-isopropilidene-L-threitol (5.532 g, 20.01 mmol, 1 equiv), CCl_4 (40 mL), CH_3CN (40 mL), and water (60 mL) were added sodium periodate (12.894 g, 60.28 mmol, 3.01 equiv) and $RuCl_3$ hydrate (210 mg, 0.93 mmol, 0.05 equiv).[16b] After vigorously stirring the reaction mixture overnight, water (165 mL) and CH_2Cl_2 (120 mL) were added. The phases were separated and the aqueous one was extracted with CH_2Cl_2 (2×180 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to furnish the corresponding carboxylic acid as a purple oil (3.914 g, 67% yield), which was used without purification.

Triethylamine (2.2 mL, 15.78 mmol) and ethyl chloroformate (1.4 mL, 14.64 mmol) were sequentially added to a stirred (−10 °C) solution of the crude carboxylic acid (3.914 g, 13.48 mmol) in THF (17 ml). After 10 min of stirring, a white precipitate formed. CAUTION, diazomethane is toxic and potentially explosive.[26,27] Excess diazomethane in Et_2O (ca. 0.3 M, 146 mL, 43.8 mmol) was added at −10 °C and the resultant mixture was stirred (0 °C) for 30 min. The reaction mixture was allowed to warm to room temperature, quenched with 0.1 M aqueous acetic acid (40.5 mL) and stirred until the deep yellow color of diazomethane was no longer present. The biphasic mixture was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (2×81 mL). The aqueous washings were extracted with CH_2Cl_2 (81 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was chromatographed on silica gel employing 4:1 hexanes/EtOAc as eluant to furnish (+)-**16** (2.958 g, 70% yield) as a yellow oil. An analytical sample (yellow oil) was obtained by HPLC employing 9:1 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ +19 (c 1.01, $CHCl_3$); FTIR (thin film/NaCl) 3129 (m), 2992 (m), 2957 (s), 2934 (s), 2856 (s), 2114 (m), 1622 (m), 1471 (w), 1460 (m), 1454 (m), 1381 (s), 1361 (s), 1254 (s), 1078 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (s, 1H), 4.34 (d, J=7.6 Hz, 1H), 4.08–4.05 (m, 1H), 3.93 (dd, J=11.5, 2.4 Hz, 1H), 3.77 (dd, J=11.5, 4.1 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 110.9, 80.3, 79.3, 62.9, 52.8, 27.0, 26.4, 26.0, 18.5, −5.2, −5.3; HRMS (CI, isobutane) m/z 315.1753 [calcd for $C_{14}H_{27}N_2O_4Si$ (M+H) 315.1740].

*4.3.2. α-Diazoketone (−)-**16*** This compound was prepared in the same manner as its enantiomer (+)-**16** and was used without purification. An analytical sample (yellow oil) was prepared by flash column chromatography followed by HPLC employing 9:1 hexanes/EtOAc as eluant in both cases: $[\alpha]_D^{20}$ −20 (c 1.02, $CHCl_3$); FTIR (thin film/NaCl) 3128 (m), 2992 (m), 2956 (s), 2930 (s), 2856 (s), 2118 (m), 1621 (s), 1472 (w), 1460 (m), 1453 (m), 1380 (s), 1361 (s), 1254 (s), 1078 (s), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (s, 1H), 4.36 (d, J=7.7 Hz, 1H), 4.09–4.08 (m, 1H), 3.95 (dd, J=11.4, 2.6 Hz, 1H), 3.79 (dd, J=11.2, 4.0 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 111.0, 80.4, 79.4, 62.9, 52.9, 27.0, 26.5, 26.1, 18.5, −5.1, −5.3; HRMS (CI, isobutane) m/z 315.1740 [calcd for $C_{14}H_{27}N_2O_4Si$ (M+H) 315.1740].

4.4. Syringolide synthesis

4.4.1. Representative synthetic procedures.

*4.4.1.1. α-Bromoketone (+)-**17***. A ca. 1 M solution of HBr in MeOH was prepared by adding MeOH (0.85 mL, 20.98 mmol, 2.90 equiv) to a stirred (0 °C) solution of acetyl bromide (1.04 mL, 14.07 mmol, 1.95 equiv) in Et_2O (14 mL). The HBr solution was added dropwise to a stirred (−78 °C) solution of (+)-**16** (2.272 g, 7.23 mol, 1 equiv) in Et_2O (12 mL). Gas evolution was immediately noted upon addition of the HBr solution. After stirring at −78 °C for 30 min, saturated aqueous $NaHCO_3$ (48 mL) was added. After allowing to warm to room temperature, the biphasic mixture was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (2×48 mL) and brine (60 mL). The aqueous washings were extracted with CH_2Cl_2 (48 mL) and then the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was chromatographed on silica gel employing 9:1 hexanes/EtOAc as eluant to furnish (+)-**17** (1.955 g, 74% yield) as a yellowish oil. An analytical sample (colorless oil) was obtained by a second flash chromatography employing 9:1 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ +16 (c 1.33, $CHCl_3$); FTIR (thin film/NaCl) 2989 (w), 2954 (s), 2930 (s), 2885 (m), 2858 (m), 1733 (m), 1472 (w), 1463 (w), 1383 (m), 1374 (m), 1254 (s), 1216 (m), 1146 (s), 1096 (s), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (d, J=7.5 Hz, 1H), 4.28 (d, J=13.7 Hz, 1H), 4.24 (d, J=13.7 Hz, 1H), 4.14 (app. dt, J=7.4, 3.7 Hz, 1H), 3.89 (dd, J=11.3, 3.4 Hz, 1H), 3.79 (dd, J=11.3, 3.6 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 110.9, 79.5, 79.1, 62.4, 32.3, 26.7, 26.3, 25.8, 18.2, −5.4, −5.5; HRMS (CI, isobutane) m/z 369.0910 [calcd for $C_{14}H_{21}{}^{81}BrO_4Si$ (M+H) 369.0920].

*4.4.1.2. Butenolide (+)-**19***. To a stirred solution of β-ketoacid **18** (598 mg, 4.59 mmol, 1.11 equiv) and α-bromoketone (+)-**17** (1.517 g, 4.13 mmol, 1 equiv) in DMF (4.8 mL) was added in small portions over a 10 min period solid Cs_2CO_3 (1.723 g, 5.29 mmol, 1.28 equiv). The reaction mixture was stirred at room temperature for 30 min and then diluted with water and EtOAc (16 mL ea.). The aqueous layer was acidified to pH 1 with 1 N HCl and extracted with EtOAc (3×32 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to a brown oil. Silica gel chromatography employing 9:1 hexanes/EtOAc as eluant furnished (+)-**19** (836 mg, 51% yield) as a yellow oil. An analytical sample (yellow oil) was prepared by flash column chromatography followed by HPLC employing 9:1 hexanes/EtOAc as eluant in both cases: $[\alpha]_D^{20}$ +39.74 (c 1.16, $CHCl_3$); FTIR (thin film/NaCl) 2958 (m),

2932 (m), 2881 (w), 2858 (m), 1769 (s), 1694 (m), 1633 (w), 1472 (w), 1463 (w), 1381 (m), 1373 (m), 1252 (m), 1090 (m), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J=7.5 Hz, 1H), 5.05 (d, J=19.4 Hz, 1H), 4.88 (d, J=20.0 Hz, 1H), 3.94–3.86 (m, 3H), 2.96 (dt, J=18.2, 7.3 Hz, 1H), 2.91 (dt, J=18.2, 7.4 Hz, 1H), 1.64 (sext., J=7.4 Hz, 2H), 1.45 (s, 6H), 0.96 (t, J=7.3 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 173.1, 170.5, 126.9, 111.1, 83.0, 73.5, 69.3, 63.6, 44.0, 27.1, 27.0, 26.0, 18.5, 16.8, 13.7, −5.1, −5.2; HRMS (CI, isobutane) m/z 399.2192 [calcd for $C_{20}H_{35}SiO_6$ (M+H) 399.2203].

*4.4.1.3. (+)-Syringolide 3 and acetal (+)-**20**.* To a stirred solution of butenolide (+)-**19c** (836 mg, 2.10 mmol, 1 equiv) in CH_3CN (85 mL) was added 10% aqueous HF (85 mL). The reaction mixture was stirred at room temperature for 36 h and then neutralized to pH 7 with saturated aqueous $NaHCO_3$ and extracted with EtOAc (4×170 mL). The organic phases were washed with brine (170 mL) and then they were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to a brown syrup. Silica gel chromatography employing 1:1 CH_2Cl_2/EtOAc as eluant furnished two products: (+)-syringolide 3 [(+)-**3**] (50 mg, 10% yield, eluted second) as a white solid and (+)-**20** (47 mg, 10% yield, eluted first) as a yellowish oil.

An analytical sample of (+)-**3** (white solid) was prepared by HPLC employing 5:6 CH_2Cl_2/EtOAc as eluant: mp 118–120 °C; $[\alpha]_D^{20}$ +98.46 (c 0.13, $CHCl_3$); FTIR (thin film/NaCl) 3396 (br m), 2963 (m), 2937 (m), 2922 (w), 2876 (m), 1755 (s), 1467 (w), 1385 (m), 1198 (m), 1053 (m), 1029 (s), 973 (m) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 5.35 (s, 1H), 4.67 (d, J=10.2 Hz, 1H), 4.48 (s, 1H), 4.32 (d, J=10.4 Hz, 1H), 4.31 (s, 1H), 4.14 (s, 1H), 3.95 (d, J=10.2 Hz, 1H), 3.82 (d, J=9.8 Hz, 1H), 3.08 (s, 1H), 1.87 (t, J=7.9 Hz, 2H), 1.66–1.57 (m, 1H), 1.55–1.47 (m, 1H), 0.87 (t, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 172.7, 108.7, 99.0, 92.2, 75.6, 75.4, 74.9, 59.7, 41.6, 17.8, 14.4; HRMS (CI, isobutane) m/z 245.1028 [calcd for $C_{11}H_{16}O_6$ (M+H) 245.1025].

An analytical sample of (+)-**20** (colorless oil) was prepared by HPLC employing 5:6 CH_2Cl_2/EtOAc as eluant: $[\alpha]_D^{20}$ +33.5 (c 0.83, $CHCl_3$); FTIR (thin film/NaCl) 3416 (m), 2965 (m), 2933 (w), 1737 (s), 1657 (w), 1433 (w), 1376 (w), 1339 (m), 1246 (w), 1180 (m), 1025 (m), 990 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (d, J=4.4 Hz, 1H), 4.99 (d, J=18.2 Hz, 1H), 4.77 (d, J=18.2 Hz, 1H), 4.64 (ddd, J=6.3, 4.5, 1.9 Hz, 1H), 4.10 (dd, J=8.8, 2.0 Hz, 1H), 4.05–4.02 (m, 1H), 3.14 (br s, 1H), 2.25 (ddd, J=14.3, 11.0, 4.9 Hz, 1H), 2.04 (ddd, J=14.2, 10.9, 5.3 Hz, 1H), 1.52–1.38 (m, 2H), 0.97 (t, J=7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 163.0, 129.2, 104.3, 75.7, 69.2, 66.9, 64.0, 33.3, 16.4, 14.4; HRMS (CI, isobutane) m/z 227.0912 [calcd for $C_{11}H_{15}O_5$ (M+H) 227.0919].

4.4.2. Additional spectroscopic and analytical data.

*4.4.2.1. α-Bromoketone (−)-**17**.* This compound was prepared in the same manner as its enantiomer (+)-**17** [40% overall yield from (−)-**15**]. An analytical sample (colorless oil) was prepared by flash column chromatography employing 9:1 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ −17 (c 0.95, $CHCl_3$); FTIR (thin film/NaCl) 2988 (w), 2954 (s), 2930 (s), 2885 (m), 2858 (m), 1733 (m), 1472 (w), 1463 (w), 1383 (m), 1374 (m), 1254 (s), 1216 (m), 1146 (s), 1096 (s), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (d, J=7.5 Hz, 1H), 4.28 (d, J=13.7 Hz, 1H), 4.24 (d, J=13.7 Hz, 1H), 4.14 (app. dt, J=7.4, 3.7 Hz, 1H), 3.89 (dd, J=11.3, 3.4 Hz, 1H), 3.79 (dd, J=11.3, 3.6 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 111.3, 79.9, 79.4, 62.7, 32.5, 27.0, 26.5, 26.1, 18.6, −5.1, −5.3; HRMS (CI, isobutane) m/z 369.0910 [calcd for $C_{14}H_{21}{}^{81}BrO_4Si$ (M+H) 369.0920].

*4.4.2.2. Butenolide (−)-**19**.* This compound was prepared in the same manner as its enantiomer (+)-**19** (910.7 mg, 53% yield). An analytical sample (yellow oil): $[\alpha]_D^{20}$ −36.74 (c 0.89, $CHCl_3$); FTIR (thin film/NaCl) 2959 (m), 2932 (m), 2881 (m), 2858 (m), 1769 (s), 1694 (m), 1633 (w), 1472 (w), 1463 (w), 1381 (m), 1373 (m), 1252 (m), 1090 (m), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J=7.9 Hz, 1H), 5.06 (d, J=19.9 Hz, 1H), 4.87 (d, J=19.0 Hz, 1H), 3.93–3.85 (m, 3H), 2.96 (dt, J=18.2, 7.3 Hz, 1H), 2.91 (dt, J=18.2, 7.4 Hz, 1H), 1.64 (sext., J=7.4 Hz, 2H), 1.45 (s, 6H), 0.95 (t, J=7.4 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 173.2, 170.5, 126.8, 111.1, 83.0, 73.5, 69.3, 63.6, 44.0, 27.1, 27.0, 26.0, 18.5, 16.7, 13.7, −5.2, −5.3; HRMS (CI, isobutane) m/z 399.2192 [calcd for $C_{20}H_{35}SiO_6$ (M+H) 399.2203].

*4.4.2.3. (−)-Syringolide 3 and acetal (−)-**20**.* These compounds were prepared in the same manner as their enantiomers (+)-**3** and (+)-**20** (41.8 and 36.8 mg, respectively; i.e., 7% yield ea.). Recrystallization of (−)-syringolide 3 [(−)-**3**] from heptane produced crystals suitable for a single-crystal X-ray analysis, which established the illustrated relative stereochemical configuration.[21]

Analytical sample of (−)-**3** (white solid): mp 120–122 °C; $[\alpha]_D^{20}$ −97.74 (c 0.09, $CHCl_3$); FTIR (thin film/NaCl) 3358 (br m), 2961 (m), 2933 (m), 2917 (m), 2874 (w), 2848 (w), 1759 (s), 1466 (w), 1380 (m), 1191 (m), 1151 (m), 1077 (m), 1025 (s), 975 (m) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 5.35 (s, 1H), 4.67 (d, J=10.2 Hz, 1H), 4.49 (s, 1H), 4.32 (d, J=10.5 Hz, 1H), 4.31 (br s, 1H), 4.15 (s, 1H), 3.95 (d, J=9.6 Hz, 1H), 3.82 (d, J=10.3 Hz, 1H), 3.08 (s, 1H), 1.87 (t, J=8.1 Hz, 2H), 1.66–1.57 (m, 1H), 1.55–1.46 (m, 1H), 0.92 (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 172.7, 108.7, 99.0, 92.3, 75.6, 75.4, 74.9, 59.7, 41.7, 17.8, 14.4; HRMS (CI, isobutane) m/z 245.1031 [calcd for $C_{11}H_{16}O_6$ (M+H) 245.1025].

Analytical sample of (−)-**20** (colorless oil): $[\alpha]_D^{20}$ −33.40 (c 0.94, $CHCl_3$); FTIR (thin film/NaCl) 3418 (br m), 2965 (m), 2933 (w), 2879 (w), 1736 (s), 1658 (w), 1434 (w), 1377 (w), 1339 (m), 1245 (w), 1179 (m), 1086 (m), 1023 (m), 990 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.10 (d, J=3.1 Hz, 1H), 4.99 (d, J=18.3 Hz, 1H), 4.76 (dd, J=18.0, 1.0 Hz, 1H), 4.64 (m, 1H), 4.10 (dd, J=8.6, 2.3 Hz, 1H), 4.05–4.02 (m, 1H), 2.99 (br s, 1H), 2.26 (ddd, J=14.4, 10.9, 5.5 Hz, 1H), 2.05 (ddd, J=14.1, 10.7, 5.2 Hz, 1H), 1.53–1.38 (m, 2H), 0.98 (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 163.5, 129.0, 104.3, 75.5, 69.4, 66.8, 64.0, 33.3, 16.5, 14.4; HRMS (CI, isobutane) m/z 227.0914 [calcd for $C_{11}H_{15}O_5$ (M+H) 227.0919].

4.5. Syributin synthesis

4.5.1. Representative synthetic procedures.

*4.5.1.1. Bromoacetate (−)-**23**.* To a solution of bromoacetic acid (451 mg, 3.25 mmol, 1.01 equiv) and α-diazoketone (−)-**16** (1.011 g, 3.22 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added $Rh_2(OAc)_4$ (1.8 mg, 0.004 mmol, 0.13% equiv). The reaction mixture was heated to reflux for 40 min and then concentrated in vacuo to a green oil. Silica gel chromatography employing 4:1 hexanes/EtOAc as eluant furnished (−)-**23** (882 mg, 64% yield) as a yellow oil. An analytical sample (colorless oil) was obtained by a second flash chromatography using 9:1 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ −15.60 (c 1.03, $CHCl_3$); FTIR (thin film/NaCl) 2988 (m), 2953 (s), 2930 (s), 2885 (s), 2857 (s), 1739 (s), 1472 (m), 1463 (m), 1408 (m), 1383 (s), 1374 (s), 1096 (s), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (d, J=17.8 Hz, 1H), 5.00 (d, J=17.9 Hz, 1H), 4.48 (d, J=8.1 Hz, 1H), 4.14 (dt, J=7.8, 3.2 Hz, 1H), 3.96 (s, 2H), 3.91 (dd, J=11.9, 3.0 Hz, 1H), 3.74 (dd, J=11.4, 3.4 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 166.7, 111.4, 79.7, 79.1, 67.6, 62.4, 26.8, 26.4, 26.0, 25.0, 18.5, −5.2, −5.4; HRMS (CI, isobutane) m/z 425.0996 [calcd for $C_{16}H_{30}{}^{79}BrO_6Si$ (M+H) 425.0995].

*4.5.1.2. Butenolide (−)-**24**.* A solution of bromoacetate (−)-**23** (791 mg, 1.86 mmol, 1 equiv) and triphenylphosphine (537 mg,

2.05 mmol, 1.10 equiv) in CH_3CN (17 mL) was stirred at ca. 65 °C (oil bath) for 3 h. Triethylamine (0.8 mL, 5.74 mmol, 3.09 equiv) was added dropwise to the solution and the reaction mixture was stirred at ca. 65 °C for another 3 h. The reaction mixture was allowed to cool to room temperature and then concentrated in vacuo to a brown semisolid. The residue was taken in EtOAc and filtered through a pad of silica gel to remove the precipitate. The filtrate was concentrated in vacuo to a brown semisolid, which was chromatographed on silica gel employing 4:1 hexanes/EtOAc as eluant to furnish (−)-**24** (409 mg, 67% yield) as a yellow oil. An analytical sample (yellowish oil) was obtained by a second flash chromatography employing 4:1 hexanes/EtOAc as eluant. Spectroscopic data for this material was identical to that reported in the literature[5]: $[\alpha]_D^{20}$ −5.46 (*c* 1.08, $CHCl_3$).

*4.5.1.3. Butyrate (+)-**26c**.* A solution of 1 M TBAF in THF (506 μL, 0.506 mmol, 1.07 equiv) and 48% HF (44 μL, aqueous) was added to a solution of butenolide (−)-**24** (155 mg, 0.47 mmol, 1 equiv) in THF (6 mL). The reaction mixture was stirred at room temperature for 8 h, at which point the butenolide (−)-**24** could not be detected by TLC analysis. The reaction mixture was then diluted with water (6 mL) and extracted with EtOAc (3×12 mL). The organic phases were washed with water (12 mL) and then they were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to furnish alcohol **25** as a beige syrup, which was used without purification. To a stirred (0 °C) solution of alcohol **25** in CH_2Cl_2 (6 mL) were sequentially added DMAP (ca. 1 mg, 0.01 mmol, 1.7% equiv), triethylamine (80 μL, 0.57 mmol, 1.22 equiv), and butyryl chloride (54 μL, 0.52 mmol, 1.10 equiv). After allowing to warm to room temperature and stirring overnight, the reaction mixture was diluted with water (6 mL) and extracted with EtOAc (3×12 mL). The organic extracts were washed with water (12 mL) and brine (12 mL) and then they were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to a brown oil. Silica gel chromatography employing 3:1 hexanes/EtOAc as eluant furnished (+)-**26c** (96 mg, 72% yield) as a yellowish oil. An analytical sample (yellowish oil) was obtained by a second flash chromatography using 3:1 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ +10.14 (*c* 1.12, $CHCl_3$); FTIR (thin film/NaCl) 2985 (w), 2968 (w), 2938 (w), 2877 (w), 1781 (s), 1747 (s), 1645 (w), 1453 (m), 1382 (m), 1375 (m), 1170 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.11 (q, *J*=1.6 Hz, 1H), 4.94 (dd, *J*=18.4, 1.9 Hz, 1H), 4.87 (ddd, *J*=18.2, 1.8, 1.0 Hz, 1H), 4.73 (d, *J*=7.9 Hz, 1H), 4.32 (dd, *J*=12.0, 4.7 Hz, 1H), 4.27 (dd, *J*=12.0, 4.7 Hz, 1H), 4.95 (app. dt, *J*=8.1, 4.7 Hz, 1H), 2.34 (t, *J*=7.4 Hz, 2H), 1.67 (sext., *J*=7.4 Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 0.96 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 172.7, 166.0, 116.8, 111.0, 78.1, 74.6, 70.8, 62.6, 35.8, 26.6, 26.5, 18.3, 13.6; HRMS (CI, isobutane) *m*/*z* 285.1337 [calcd for $C_{14}H_{21}O_6$ (M+H) 285.1338].

*4.5.1.4. (+)-Syributin **3** [(+)-**12**].* Butyrate (+)-**26c** (88 mg, 0.31 mmol) was treated with a 9:1 TFA/H_2O solution (3 mL). The resulting mixture was stirred at room temperature for 15 min, at which point the butyrate (+)-**26c** could no longer be detected by TLC analysis. The reaction mixture was diluted with water (5 mL), neutralized to pH 7 with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×15 mL). The organic extracts were washed with brine (10 mL) and then they were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to a yellowish oil. Silica gel chromatography employing 2:3 hexanes/EtOAc as eluant furnished (+)-syributin 3 (30 mg, 40% yield) as a yellowish oil. An analytical sample (colorless oil) was obtained by a second flash chromatography using 2:3 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ +6.14 (*c* 0.76, $CHCl_3$); FTIR (thin film/NaCl) 3415 (br m), 2966 (w), 2936 (w), 2877 (w), 1780 (w), 1737 (s), 1638 (w), 1181 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (d, *J*=1.9 Hz, 1H), 4.97 (dd, *J*=18.1, 1.5 Hz, 1H), 4.91 (dd, *J*=18.0, 1.2 Hz, 1H), 4.64 (s, 1H), 4.28 (dd, *J*=11.6, 5.4 Hz, 1H), 4.18 (dd, *J*=11.2, 6.4 Hz, 1H), 3.97 (app. td, *J*=5.8, 2.7 Hz, 1H), 3.43 (br s, 2H), 2.33 (t, *J*=7.5 Hz, 2H), 1.64 (sext., *J*=7.4 Hz, 2H), 0.94 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 174.2, 170.4, 116.7, 72.2, 71.6, 69.1, 64.8, 36.2, 18.5, 13.7; HRMS (CI, isobutane) *m*/*z* 245.1022 [calcd for $C_{11}H_{17}O_6$ (M+H) 245.1025].

4.5.2. Additional spectroscopic and analytical data.

4.5.2.1. Common intermediates.

4.5.2.1.1. Bromoacetate (+)-23. This compound was prepared in the same manner as its enantiomer (−)-**23** (1.5393 g, 55% yield). An analytical sample of (yellowish oil) was prepared by flash column chromatography employing 85:15 hexanes/EtOAc as eluant: $[\alpha]_D^{20}$ +14.22 (*c* 1.05, $CHCl_3$); FTIR (thin film/NaCl) 2988 (w), 2954 (m), 2931 (m), 2885 (m), 2858 (m), 1739 (s), 1472 (m), 1463 (m), 1409 (m), 1383 (m), 1374 (m), 1096 (s), 838 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (d, *J*=17.6 Hz, 1H), 5.00 (d, *J*=17.8 Hz, 1H), 4.48 (d, *J*=8.0 Hz, 1H), 4.14 (dt, *J*=7.6, 3.2 Hz, 1H), 3.96 (s, 2H), 3.91 (dd, *J*=11.4, 2.9 Hz, 1H), 3.74 (dd, *J*=11.9, 3.4 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 166.8, 111.4, 79.7, 79.1, 67.7, 62.3, 26.9, 26.4, 26.1, 25.1, 18.5, −5.2, −5.3; HRMS (CI, isobutane) *m*/*z* 425.0992 [calcd for $C_{16}H_{30}{}^{79}BrO_6Si$ (M+H) 425.0995].

4.5.2.1.2. Butenolide (+)-24. This compound was prepared in the same manner as its enantiomer (−)-**24** (304.6 mg, 68% yield). An analytical sample (colorless oil) was prepared by flash column chromatography employing 85:15 hexanes/EtOAc as eluant. Spectroscopic data for this material was identical to that reported in the literature for its enantiomer[5] but with opposite optical rotation: $[\alpha]_D^{20}$ +6.02 (*c* 1.13, $CHCl_3$).

*4.5.2.2. Esters prepared as (+)-**26c**.*

4.5.2.2.1. Hexanoate (+)-26a. Yield: 51 mg, 72%. Spectroscopic data for this material was identical to that reported in the literature[5]: $[\alpha]_D^{20}$ +11.20 (*c* 1.12, $CHCl_3$).

4.5.2.2.2. Hexanoate (−)-26a. Yield: 63.7 mg, 39%. Spectroscopic data for this material was identical to that reported in the literature for its enantiomer[5] but with opposite optical rotation: $[\alpha]_D^{20}$ −11.77 (*c* 0.88, $CHCl_3$).

4.5.2.2.3. Octanoate (+)-26b. Yield: 145 mg, 89%. Spectroscopic data for this material was identical to that reported in the literature[5]: $[\alpha]_D^{20}$ +10.68 (*c* 1.11, $CHCl_3$).

4.5.2.2.4. Octanoate (−)-26b. Yield: 186.5 mg, 59%. Spectroscopic data for this material was identical to that reported in the literature for its enantiomer[5] but with opposite optical rotation: $[\alpha]_D^{20}$ −10.53 (*c* 0.66, $CHCl_3$).

4.5.2.2.5. Butyrate (−)-26c. Yield: 175.2 mg, 70%. Analytical sample (yellowish oil): $[\alpha]_D^{20}$ −11.83 (*c* 1.73, $CHCl_3$); FTIR (thin film/NaCl) 2985 (w), 2968 (w), 2938 (w), 2878 (w), 1781 (s), 1750 (s), 1646 (w), 1457 (m), 1383 (m), 1374 (m), 1168 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.91 (d, *J*=18.1 Hz, 1H), 4.84 (d, *J*=17.6 Hz, 1H), 4.71 (d, *J*=8.4 Hz, 1H), 4.30 (dd, *J*=12.0, 4.3 Hz, 1H), 4.24 (dd, *J*=12.1, 4.6 Hz, 1H), 4.08 (app. dt, *J*=8.6, 4.4 Hz, 1H), 2.31 (t, *J*=7.4 Hz, 2H), 1.64 (sext., *J*=7.5 Hz, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 0.93 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 172.8, 166.0, 117.0, 111.2, 78.2, 74.7, 70.9, 62.8, 36.0, 26.7, 26.6, 18.4, 13.7; HRMS (CI, isobutane) *m*/*z* 285.1340 [calcd for $C_{14}H_{21}O_6$ (M+H) 285.1338].

*4.5.2.3. Syributins obtained as (+)-syributin 3 [(+)-**12**].*

4.5.2.3.1. (+)-Syributin 1 [(+)-10]. Yield: 47 mg, 59%. Analytical sample (yellowish oil): $[\alpha]_D^{20}$ +7.18 (*c* 0.59, $CHCl_3$); FTIR (thin film/NaCl) 3400 (br m), 2955 (m), 2928 (m), 2870 (m), 1780 (m), 1729 (s), 1638 (w), 1170 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.97 (d, *J*=17.9 Hz, 1H), 4.91 (d, *J*=18.0 Hz, 1H), 4.63 (br s, 1H), 4.29 (dd, *J*=11.6, 5.3 Hz, 1H), 4.18 (dd, *J*=11.5, 6.5 Hz, 1H), 3.96 (br s, 1H), 3.35 (br s, 2H), 2.35 (t, *J*=7.4 Hz, 2H), 1.62 (quint., *J*=7.4 Hz, 2H), 1.35–1.24 (m, 4H), 0.89 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 174.1,

170.2, 116.8, 72.1, 71.6, 69.0, 64.8, 34.2, 31.4, 24.7, 22.4, 14.0; HRMS (CI, isobutane) m/z 273.1334 [calcd for $C_{13}H_{21}O_6$ (M+H) 273.1338].

4.5.2.3.2. (−)-Syributin 1 [(−)-10]. Yield: 42 mg, 58%. Analytical sample (yellowish oil): $[\alpha]_D^{20}$ −6.44 (*c* 0.87, $CHCl_3$); FTIR (thin film/NaCl) 3400 (br m), 2957 (m), 2930 (m), 2871 (m), 1781 (m), 1738 (s), 1729 (s), 1639 (w), 1172 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.97 (d, J=18.5 Hz, 1H), 4.91 (d, J=17.8 Hz, 1H), 4.63 (br s, 1H), 4.27 (dd, J=12.0, 5.2 Hz, 1H), 4.17 (dd, J=11.9, 6.7 Hz, 1H), 3.96 (br s, 1H), 3.74 (br s, 1H), 3.52 (br s, 1H), 2.34 (t, J=7.6 Hz, 2H), 1.61 (quint., J=7.4 Hz, 2H), 1.33–1.24 (m, 4H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 174.3, 170.6, 116.7, 72.2, 71.5, 69.0, 64.8, 34.2, 31.4, 24.7, 22.4, 14.1; HRMS (CI, isobutane) m/z 273.1340 [calcd for $C_{13}H_{21}O_6$ (M+H) 273.1338].

4.5.2.3.3. (+)-Syributin 2 [(+)-11]. Yield: 74 mg, 69%. Analytical sample (yellowish oil): $[\alpha]_D^{20}$ +7.05 (*c* 0.78, $CHCl_3$); FTIR (thin film/NaCl) 3388 (br m), 2954 (m), 2926 (m), 2855 (m), 1780 (m), 1740 (s), 1731 (s), 1721 (s), 1639 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.97 (dd, J=18.0, 1.7 Hz, 1H), 4.91 (d, J=17.4 Hz, 1H), 4.61 (d, J=3.0 Hz, 1H), 4.35 (dd, J=11.7, 4.9 Hz, 1H), 4.18 (dd, J=11.8, 6.4 Hz, 1H), 3.95 (ddd, J=6.3, 5.1, 3.3 Hz, 1H), 2.37 (t, J=7.4 Hz, 2H), 1.66–1.60 (m, 2H), 1.30–1.27 (m, 8H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 174.5, 170.9, 116.6, 72.3, 71.5, 69.0, 64.7, 34.3, 31.8, 29.2, 29.0, 25.0, 22.7, 14.2; HRMS (CI, isobutane) m/z 301.1651 [calcd for $C_{15}H_{25}O_6$ (M+H) 301.1651].

4.5.2.3.4. (−)-Syributin 2 [(−)-11]. Yield: 17.4 mg, 65%. Analytical sample (colorless oil): $[\alpha]_D^{20}$ −6.75 (*c* 0.59, $CHCl_3$); FTIR (thin film/NaCl) 3388 (s), 2957 (m), 2931 (m), 2856 (w), 1779 (m), 1737 (s), 1713 (s), 1639 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.97 (d, J=17.9 Hz, 1H), 4.91 (d, J=17.4 Hz, 1H), 4.62 (s, 1H), 4.35 (dd, J=11.8, 4.6 Hz, 1H), 4.17 (dd, J=11.8, 6.4 Hz, 1H), 3.96–3.94 (m, 2H), 2.37 (t, J=7.6 Hz, 2H), 1.66–1.60 (m, 2H), 1.30–1.27 (m, 8H), 0.88 (t, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 174.4, 170.7, 116.6, 72.2, 71.5, 69.0, 64.7, 34.3, 31.8, 29.2, 29.0, 25.0, 22.7, 14.2; HRMS (CI, isobutane) m/z 301.1646 [calcd for $C_{15}H_{25}O_6$ (M+H) 301.1651].

4.5.2.3.5. (−)-Syributin 3 [(−)-12]. Yield: 15.9 mg. 58%. Analytical sample (yellowish oil): $[\alpha]_D^{20}$ −6.33 (*c* 0.68, $CHCl_3$); FTIR (thin film/NaCl) 3400 (br m), 2965 (w), 2934 (w), 2876 (w), 1780 (w), 1737 (s), 1730 (s), 1640 (w), 1178 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (q, J=1.5 Hz, 1H), 4.97 (dd, J=17.8, 1.7 Hz, 1H), 4.91 (ddd, J=17.6, 2.1, 1.1 Hz, 1H), 4.62 (d, J=2.8 Hz, 1H), 4.35 (dd, J=11.8, 5.4 Hz, 1H), 4.18 (dd, J=11.8, 6.4 Hz, 1H), 3.95 (ddd, J=7.4, 6.3, 3.3 Hz, 1H), 2.36 (t, J=7.4 Hz, 2H), 1.67 (sext., J=7.5 Hz, 2H), 0.97 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 174.3, 170.5, 116.7, 72.2, 71.5, 69.0, 64.8, 36.1, 18.5, 13.8; HRMS (CI, isobutane) m/z 245.1025 [calcd for $C_{11}H_{17}O_6$ (M+H) 245.1025].

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