Tetrahedron 65 (2009) 1048–1058

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient synthesis of syringolides, secosyrins, and syributins through a common approach

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ARTICLE INFO

Article history:
Received 7 August 2008
Received in revised form 5 November 2008
Accepted 20 November 2008
Available online 28 November 2008

ABSTRACT

A new common synthetic approach toward the elicitors syringolides and their related natural products, secosyrins and syributins, is described here. This uses D-arabinose as starting material and efficiently delivers the targeted compounds through a sequential tandem HWE olefination–lactonization process and an IHMA reaction.

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1. Introduction

Many plant pathogens produce signal molecules (elicitors), which are specifically recognized by certain resistant plants, initiating an acute defense response.[1] Among them, Gram-negative bacteria expressing the class I homology group of avirulence gene D (*avrD*) alleles (genes cloned from *Pseudomonas syringae* pv. *tomato*) produce two relatively low molecular weight compounds, syringolides 1 and 2 (**1a** and **1b**, Fig. 1). These metabolites are the first known extracellular non-proteinaceous elicitors.[2] Soybean plants carrying the disease-resistance complementary gene *Rgp4* detect through their encoded membrane receptors the presence of syringolides when attacked by these pathogens. As a result a spontaneous hypersensitive response (HR) occurs causing a localized cell death. Accumulation of phytoalexins around the infected site is consequently induced and, overall, this defending mechanism leads to the inability of the pathogen to successfully parasitize the plant.[2]

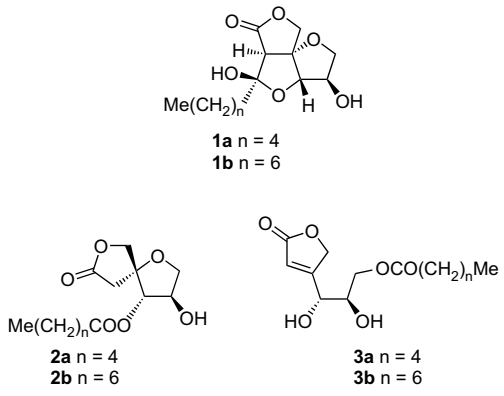

Figure 1.

Syringolides were isolated by Sims et al.[2,3] from cultivars of the plant pathogen *P. syringae* pv. *tomato*. Elucidation of their structure was accomplished by the same group using NMR experiments and confirmed by X-ray crystallography whereas their absolute configuration was initially postulated based on the assumption that they biosynthetically derive from the naturally occurring D-xylulose. Both metabolites were found to have the same main core, an oxygen-rich tricyclic *C*-glycosidic framework, indicating the latter as the critical recognition feature.

Bicyclic secosyrins 1 and 2 (**2a** and **2b**) share with syringolides the rather rare 1,7-dioxaspiro[4.4]nonane skeleton,[4] whereas monocyclic syributins 1 and 2 (**3a** and **3b**) are butenolide derivatives (Fig. 1). All these metabolites, obviously structurally and stereochemically related to **1**, were isolated from the same culture filtrates.[5] Although **2** and **3** have simpler structures and, in sharp contrast to **1**, are not active elicitors, they are of equal interest since they are co-produced with the latter. A possible biogenetic pathway connects **1** and **2** (through a reverse Claisen cleavage) and, in turn, **2** and **3** (through a tandem retro Michael reaction and 1,3-acyl migration process).

Investigation of the nature of *avrD* gene, the function of its protein expression and the receptor protein could provide a deeper understanding of the HR phenomenon. Moreover, syringolides are of particular biological interest since they behave analogously to the antigens recognized by the immune system of vertebrates. The unique properties of **1** triggered extensive work regarding their biochemical evaluation in plant research[6] and, in combination with their stimulating structures and low natural abundance, resulted in efforts toward their total syntheses.[7–13] Secosyrins[14–17] and syributins[9,16–19] have also been the synthetic target of several research

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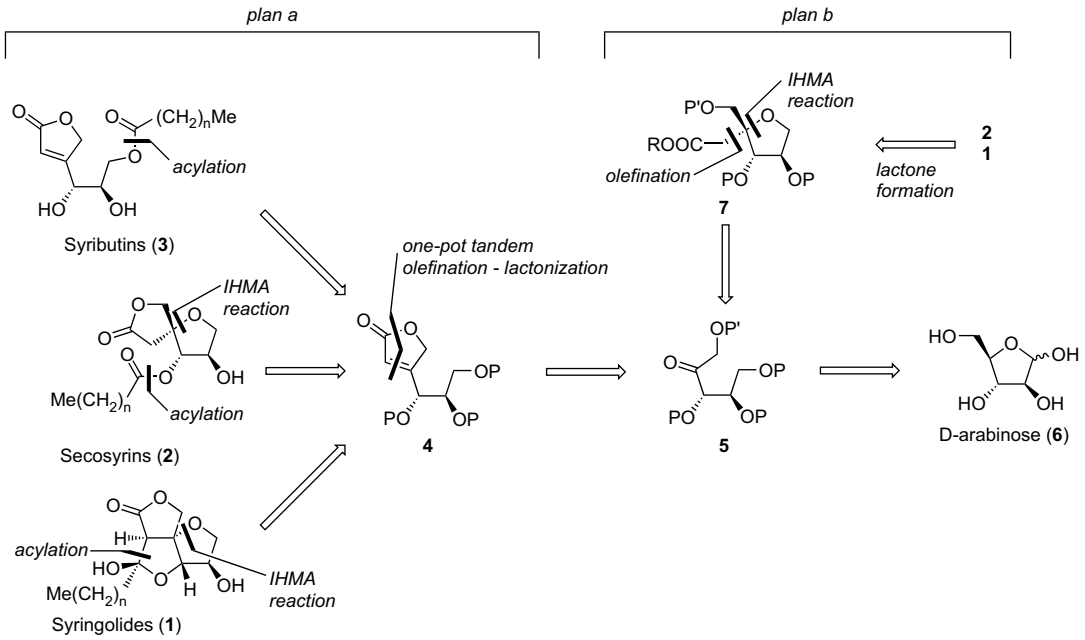
doi:10.1016/j.tet.2008.11.079



Scheme 1. Retrosynthetic analysis (P, P′=protecting groups).

groups. Chiral pool approaches were mainly adopted for the preparation of enantiopure **1**–**3**, with a preference to use various tartrates[7,15,16] or carbohydrate derivatives[20] as starting materials. Interestingly, Wong's group[11,15–18] is the only one to have presented so far a successful common strategy for the synthesis of all six natural products.

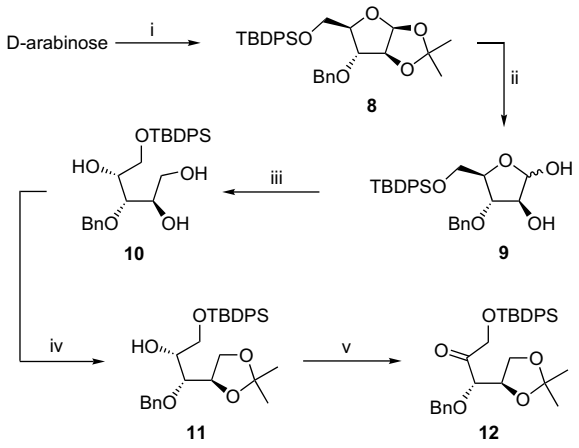
In the context of our continuous research work[21] concerning the synthesis of natural products with intriguing structures and properties, using arabinose derivatives as starting materials, we recently published[22] a new total synthesis of secosyrins 1 and 2. Herein, we wish to present in detail those results and, in addition, exhibit the application of the same flexible strategy in the preparation of syributins and syringolides.[23]

2. Results and discussion

We envisioned the synthesis of all six natural products (**1**–**3**), using butenolide derivative **4** (Scheme 1, *plan a*) as the common advanced precursor. Thus, with the acylation left for the end steps, the tetrahydrofuran ring formation is the next obvious disconnection for secosyrins and syringolides, employing an intramolecular hetero-Michael addition (IHMA) reaction for the rather difficult construction of the quaternary center. The unsaturated lactone ring could be built in a single step from ketose **5** (P′=H) via a one pot tandem olefination–lactonization process. Ketose **5** is actually a protected form of our synthetic targets biosynthetic precursor (D-xylulose). This could be easily reached from D-arabinose (**6**) applying standard functional group manipulations.

An alternative approach to the 1,7-dioxaspiro[4.4]nonane system, involving formation of the tetrahydrofuran ring before the construction of the lactone from the corresponding hydroxy-ester **7**, could be also employed (*plan b*). Although it is not possible to obtain syributins through *plan b*, the feasibility of this approach to deliver **1** and **2** was examined too.

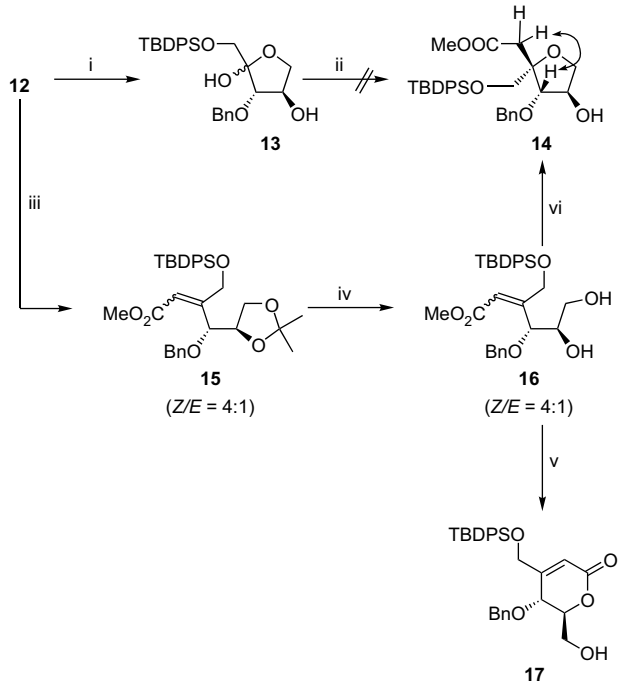
Preparation of ketone **12**, the key compound for both routes described above, was realized as outlined in Scheme 2. The known[24] fully protected β-D-arabinofuranose derivative **8** was easily reached on a multigram scale and without chromatographic purification of the intermediates, applying modifications of the



Scheme 2. Synthesis of the key ketone **12**. (i) TBDPSCl, DMAP, pyridine, 0–25 °C then 2,2-dimethoxypropane, *p*-TsOH, Me_2CO, 25 °C then NaH, BnBr, TBAI, THF, 0–25 °C, 67%; (ii) aq TFA, CH_2Cl_2, 0 °C, 87%; (iii) $NaBH_4$, MeOH, 0–25 °C, 99%; (iv) 2,2-dimethoxypropane, *p*-TsOH, Me_2CO, 25 °C, 92%; (v) CrO_3, Ac_2O, pyridine, CH_2Cl_2, 25 °C, 98%.

combined literature protocols.[24,25] Hydrolysis of the acetonide protecting group in **8** was carefully performed upon treatment with aqueous trifluoroacetic acid and the resulting lactol **9** was reduced with $NaBH_4$ to yield almost quantitatively triol **10**.[26] Selective protection of the 1,2-diol system in **10**, through the formation of the isopropylidene intermediate **11**, unmasked the C-4 hydroxyl group,[27] which under mild oxidation conditions led to the desired silyl-ketone **12**, the equivalent of our designed intermediate **5**.

Having a few grams of **12** in our hands we decided to initially investigate the possibility of constructing the tetrahydrofuran ring first (*plan b*). Thus, acidic hydrolysis of **12** was performed to obtain a mixture of anomeric ketofuranoses **13** (Scheme 3). This transformation was found to be rather problematic and either low conversion or partial decomposition after extended reaction times was observed. It was expected that **13** could directly give tetrahydrofuran derivative **14** (and/or its C_{quat} diastereoisomer) under Wittig olefination conditions, presuming a subsequent IHMA reaction[28] of the intermediate conjugated ester. However, all attempts, at heating **13** with a stable ylide in various solvents and for



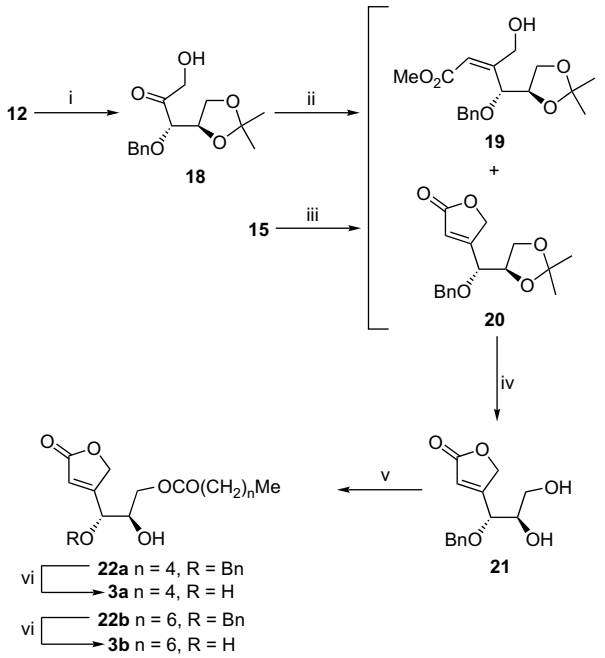
Scheme 3. Exploring synthetic *plan b*, building first the tetrahydrofuran ring. (i) aq TFA, CCl_4, −10 °C, 59%; (ii) see text; (iii) $(MeO)_2P(O)CH_2COOMe$, *n*-BuLi, THF, 0–25 °C, 90%; (iv) *p*-TsOH, MeOH, 0 °C, 79%; (v) Et_3N, $CHCl_3$, 0 °C, 14% of **17**; (vi) NaH, THF, 0 °C, 16% of **14** and 10% of **17**.

long periods, failed to give even the olefination intermediate. No such product was isolated when ketone **12** was subjected to the same reaction conditions as well.

Next, the olefination step was examined in the presence of a phosphonate derived unstable ylide using the Horner–Wadsworth–Emmons (HWE) reaction protocol.[29] To our delight an inseparable mixture of isomeric unsaturated esters **15** (*Z*/*E* ca. 4:1) was obtained in a very good yield from **12**, when *n*-BuLi was used as base.[30] It is noteworthy that at this stage it was practically impossible to confidently determine the exact stereochemistry of the newly formed double bond in **15**. This was indirectly achieved in later stages (vide infra). Removal of the isopropylidene protecting group led to **16** but again it was impossible to separate the isomeric products[31] or to securely determine their stereochemistry. Treating the mixture of diols **16** with excess Et_3N at room temperature resulted in the very slow formation of a new compound, which was found to be the six-membered unsaturated lactone **17**, and not an IHMA product. Indeed, after a period of a week, this reaction mixture was resolved by chromatography and only **17** (14%) and recovered diols **16** (76%, in a ratio of ca. 3.2:1) were obtained. This result clearly gave us the first indication that the partially consumed major isomer could only have the correct *Z* stereochemistry for the lactonization.

On the other hand when the mixture of diols **16** was exposed to an equimolar quantity of NaH, a rather complicated reaction mixture was obtained in a short time. From this mixture we were able to isolate after tedious chromatographic separations pure furan derivative **14** along with lactone **17**. The stereochemistry of the quaternary carbon center in **14** was found to be identical with the one in the targeted secosyrins.[32] Formation of the corresponding diastereoisomer of **14** during this reaction cannot be excluded. Nevertheless, the higher polarity of the unresolved products led to the speculation that they represent solely decomposition products. Analogously, the cyclization of **16** was also tested in the presence of *t*-BuOK but neither **14** nor **17** was formed.[33] The capability of the cation employed to stabilize or not the transition state probably explains the different results obtained for this IHMA reaction.

While we were able to diastereoselectively synthesize the desired derivative **14**, the low yield and the difficulties we encountered during its purification prompted us to turn our attention to the fabrication of the furan ring at a later stage (*plan a*). For this purpose ketone **12** was initially desilylated under nearly neutral conditions in order to avoid epimerization at C-3 (Scheme 4). Olefination of the obtained hydroxyketone **18** was then examined (Table 1). In contrast to the results observed with silyl-protected ketones (**12** and **13**),[34] this substrate gave the desired butenolide **20** and the *Z*-unsaturated ester **19** under the Wittig reaction conditions (entry 1) but in moderate yields. Further experimentation using the HWE protocol with different bases, concentrations, and temperature ranges allowed us to optimize the yield of **20** (entries 2–5). Concentration of starting material in the reaction mixture was found to be a crucial parameter and, unexpectedly, slightly higher values gave higher yields (entry 5). Employment of lithium hexafluoroisopropoxide[35] had a negative result (entry 6).



Scheme 4. Building first the lactone ring (*plan a*), synthesis of syributins. (i) TBAF, AcOH, THF, 0 °C, 85%; (ii) see Table 1; (iii) TBAF, AcOH, THF, 25 °C, 73% of **19**, 18% of **20**; (iv) aq AcOH, 25 °C, 95%; (v) $Me(CH_2)_4COCl$ (for **22a**) or $Me(CH_2)_6COCl$ (for **22b**), Et_3N, CH_2Cl_2, −20 °C, 81% for **22a**, 80% for **22b**; (vi) $AlCl_3$, *m*-xylene, CH_2Cl_2, −10 °C, 92% for **3a**, 90% for **3b**.

It is believed that in both cases (Wittig and HWE) the *E*-selectivity is a consequence of the free α-hydroxyl group present in **18**. This hydroxyl group forms an intramolecular hydrogen bond with the ylide carbonyl in the intermediate betaine/oxaphosphetane (or

Table 1
Olefination of ketone **18**

Entry	Method[a]	M of **18** (mmol/L)	Temp (°C)/time (h)	Yields of **20**/**19** (%)[b]
1	A	65	110/48	33/11
2	B	65	−50 to 25/24	15/17
3	C	65	0 to 25/20	27/11
4	C	65	−50 to 0/3	53/8
5	C	100	−50 to 0/3	77/4
6	D	100	−40 to 0/4	—[c]

[a] A: $Ph_3P{=}CHCO_2Me$, toluene; B: $(MeO)_2P(O)CH_2CO_2Me$, *t*-BuOK, 18-C-6, THF; C: $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF; D: $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, $(CF_3)_2CHOH$, DME.

[b] Yields refer to isolated pure compounds.

[c] Only decomposition of starting material was observed.

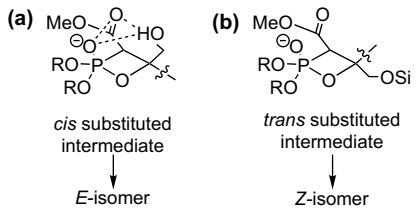


Figure 2. Favored intermediates of the HWE olefination of **18** (a) and **12** (b).

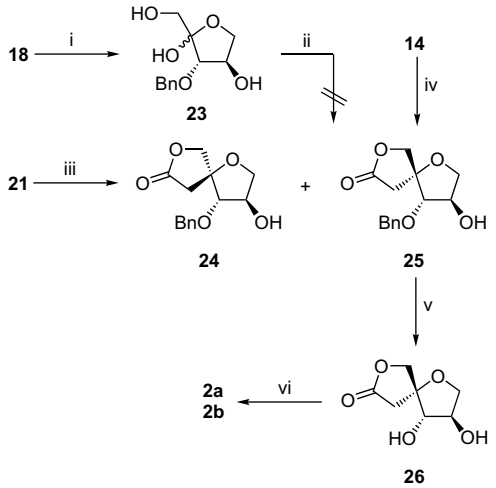
the corresponding oxy-anion) favoring the formation of the *E*-isomer of **19**. Employing a phosphonate enhances this result through a three-center interaction (Fig. 2a). Finally, the *E*-isomer spontaneously cyclizes[36] to give **20** under the specific reaction conditions. In contrast, the *Z*-isomer normally dominates when the α-hydroxyl was masked (see olefination of **12**) since this favorable interaction was absent. Additionally, in this case the bulky silyl group preferentially occupies a trans position relatively to the ester group (Fig. 2b).[37] The same products (**19** and **20**) were formed, although in the reverse distribution (ca. 4:1), when the mixture of esters **15** was desilylated, confirming once again that *Z*-isomer was the major component of the mixture.

For the completion of the synthesis of syributins, acetonide **20** was smoothly deprotected with acetic acid to afford **21** (Scheme 4). Acylation of diol **21** was performed adding hexanoyl or octanoyl chloride very slowly at low temperature to regioselectively obtain mono-esters **22a** and **22b**, respectively. Then, Lewis acid ($AlCl_3$) promoted debenzylation[38] of **22a** and **22b** led to the preparation of syributins 1 and 2 (**3a** and **3b**) in very good yields[39] without affecting the sensitive butenolide ring.

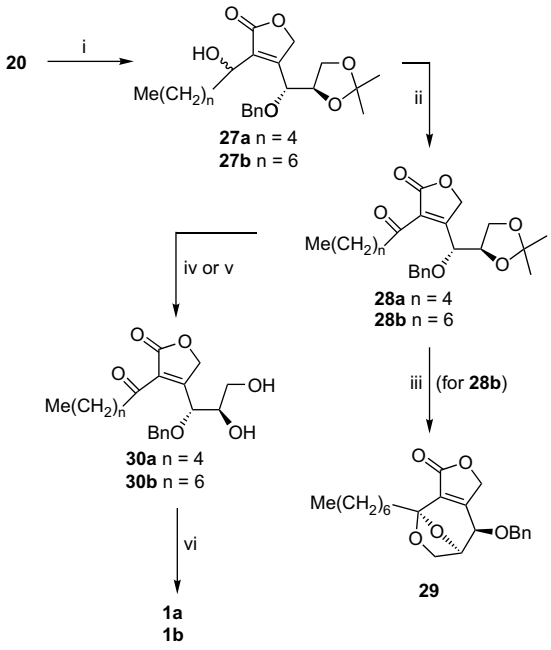
With the issue of constructing the lactone ring in a single step resolved, we then turned our attention to the formation of the spiro-system of secosyrins applying an IHMA reaction on **21** (Scheme 5). This approach had been earlier used[17] for the cyclization of an analogous intermediate[40] and proved to be fruitful in our case as well. Practically, a number of different conditions (bases, solvents, and temperatures)[41] were employed to check not only the feasibility of this ring-closure but its stereochemical outcome too. However, the best results were obtained using the conditions previously reported,[17] giving in preference the desired spiro-tetrahydrofuran system **25** along with its diastereoisomer **24** (in a ratio of ca. 4.5:1). It seems that the neighboring protective group (TBS or Bn) plays no important role regarding the diastereoselectivity of this reaction. The stereochemistry of the newly formed quaternary center was assigned by comparing the spectra data of easily separable **24** and **25** with those obtained for the analogous cyclized intermediates[17] and it was indisputably assured when **25** was hydrogenolyzed to give **26**. Finally, diol **26** was regioselectively acylated[16] with hexanoic or octanoic anhydride to afford secosyrin 1 (**2a**) and secosyrin 2 (**2b**), respectively.[39]

A straightforward pathway involving the direct formation of both rings in spiro lactone **25** (or/and **24**) from ketone **18** was also examined. The highly polar lactol **23**, the acidic hydrolysis product of **18**,[42] was treated with a large excess of the required phosphonate but none of the expected products were formed. Spiro lactone **25** was also reached with spontaneous lactonization of the intermediate hydroxy-ester formed by desilylation of furan derivative **14** (*plan b*), proving that the latter had indeed the correct stereochemistry at the quaternary center.

As was originally planned, butenolide **20** was also used as the key compound in order to investigate the synthesis of both syringolides. Thus, applying a boron triflate promoted aldol condensation[43] of **20** with hexanal or octanal led to the corresponding diastereomeric 3-hydroxyalkyl-butenolides **27a** and **27b** (Scheme 6). Subsequently, these were smoothly oxidized upon treatment with Dess–Martin periodinane to give ketones **28a** and **28b**. At this stage our fundamental concern was to determine, which is the correct order of removal of the remaining protecting groups (e.g., acetonide and benzyl). An initial attempt to achieve in one step the simultaneous removal of both groups and the subsequent rings closure using TMSI in acetonitrile gave erratic results.[44] Then, treatment of ketone **28b** with DOWEX H^+ in methanol[45] led almost exclusively to tricycloketal **29**.[46] Unfortunately, the latter slowly decomposed when treated with *p*-toluenesulfonic acid in acetone/water. This result suggested that the desired tetrahydrofuran ring-closure is facilitated only when the lactol ring can be simultaneously formed. For this reason we attempted the debenzylation of **28b** before the formation of the tetrahydrofuran ring. However, the



Scheme 5. Synthesis of secosyrins. (i) aq TFA, CH_2Cl_2, 0 °C, 80%; (ii) $(MeO)_2P(O)CH_2COOMe$, *n*-BuLi, THF, −50 to 0 °C; (iii) Et_3N, $CHCl_3$, 25 °C, 63% of **25** and 14% of **24**; (iv) TBAF, THF, 87%; (v) Pd/C, HCl, MeOH, EtOAc, 25 °C, 99%; (vi) $[Me(CH_2)_4CO]_2O$ (for **2a**) or $[Me(CH_2)_6CO]_2O$ (for **2b**), Et_3N, DMAP, THF, 0 °C, 72% for **2a**, 76% for **2b**.



Scheme 6. Synthesis of syringolides. (i) $Me(CH_2)_4CHO$ (for **27a**) or $Me(CH_2)_6CHO$ (for **27b**), Bu_2BOTf, DIPEA, CH_2Cl_2, THF, −78 to −20 °C, 88% for **27a**, 89% for **27b**; (ii) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 94% for **28a**, 93% for **28b**; (iii) DOWEX H^+, MeOH, 25 °C, 97%; (iv) $TiCl_4$, CH_2Cl_2, −30 °C, 55% for **30a**, 56% for **30b**; (v) aq AcOH, 25 °C, 80% for **30a**, 82% for **30b**; (vi) $AlCl_3$, *m*-xylene, CH_2Cl_2, −20 °C then *p*-TsOH, acetone, H_2O, 55% for **1a**, 53% for **1b**.

mild Pd catalyzed transfer hydrogenolysis protocol (1,4-cyclohexadiene protocol)[47] was unsuccessful. Aluminum chloride promoted debenzylation[38] was also investigated but gave a very complicated mixture, which after a short work up showed only traces of syringolide 2 (**1b**) in the ^{1}H NMR spectra.

Examining again the reverse order of deprotections, we then treated **28b** with *p*-toluenesulfonic acid in acetone/water. Surprisingly, this experiment was similarly disappointing. However, more encouraging was the removal of the acetonide with $TiCl_4$ giving in moderate yields the desired diols **30a** and **30b** from **28a** and **28b**, respectively.[48] Even better results were obtained when the deprotection was performed with aqueous acetic acid furnishing the same diols in good yields. In these latter cases (reactions employing either $TiCl_4$ or AcOH) formation of a ketal-like product (e.g., **29**) was not observed. At the final steps, diols **30a** and **30b** were debenzylated with $AlCl_3$/*m*-xylene to give initially a very complicated mixture.[49] This was resolved upon treatment with *p*-toluenesulfonic acid in acetone/water to yield the targeted tricycles, syringolide 1 (**1a**) and syringolide 2 (**1b**), as crystalline solids.[39]

3. Conclusions

In summary, we have presented a detailed study of the preparation of syringolides (**1a** and **1b**) and their natural related metabolites secosyrins (**2a** and **2b**) and syributins (**3a** and **3b**). As a result, a convenient alternative synthesis of enantiopure **1**–**3** was realized using a common synthetic strategy. This starts from the known and readily available D-arabinose derived chiron **8** and leads to the targeted natural products in good overall yields. Briefly, it employs the stepwise construction of the spiro-framework present in the desired products, following a well defined sequential HWE olefination/lactonization—IHMA pathway. Additionally, useful information regarding the formation of the butenolide ring and the correct assembly of the syringolide tricyclic could be deduced from the present in depth investigation.

4. Experimental

4.1. General

All commercially available grade quality reagents were used without further purification. All solvents were purified by standard procedures before use. Dry solvents were obtained by the literature methods and stored over molecular sieves. All reactions were conducted under nitrogen atmosphere. All reactions were monitored on commercial available pre-coated TLC plates (layer thickness 0.25 mm) of Kieselgel 60 F_{254}. Compounds were visualized by use of a UV lamp or/and *p*-anisaldehyde ethanolic solution and warming. Column chromatography was performed in the usual way using Merck 60 (40–60 μm) silica gel. NMR spectra were recorded on a 300 or a 400 MHz spectrometer (^{1}H: 300/400 MHz, ^{13}C: 75/100 MHz) in $CDCl_3$, unless otherwise stated. Chemical shifts are given in parts per million and *J* in hertz using solvent or tetramethylsilane as an internal reference. IR spectra were recorded on an FTIR instrument as indicated. Mass spectra were obtained by electro spray technique, positive mode (ES-MS) or MALDI-FTMS.

4.2. Procedures

*4.2.1. 4-O-Benzyl-5-O-tert-butyldiphenylsilyl-1,2-O-isopopylidene β-D-arabinofuranose (**8**)*

TBDPSCl (9.5 mL, 37 mmol) was added dropwise in a solution of D-arabinose (5 g, 33 mmol) and DMAP (410 mg, 3.3 mmol) in dry pyridine (100 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 48 h. Then, MeOH (80 mL) was added and the solvents were removed under reduced pressure at 40 °C. The obtained residue was re-dissolved in a mixture of toluene/EtOH (10 mL, 4:1 v/v) and the solvents were again removed under reduced pressure. This was repeated three times and the final residue was dissolved in $CHCl_3$ (80 mL). This solution was washed with a 0.5 M HCl solution (20 mL), water (20 mL) and brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure gave a thick oil, which was dissolved in the minimum volume of a mixture of hexane/EtOAc (2:1 v/v) and passed through a short pad of silica gel to yield crude 5-*O*-*tert*-butyldiphenylsilyl-D-arabinofuranose as a colorless syrup. A solution of this lactol, 2,2-dimethoxypropane (60 mL) and *p*-toluenesulfonic acid monohydrate (560 mg, 3 mmol) in acetone (60 mL) was stirred at 25 °C for 3 h. MeOH (60 mL) was then added and the resulting mixture was diluted with $CHCl_3$ (100 mL), neutralized with saturated aqueous sodium bicarbonate solution and dried ($NaSO_4$). Removal of the solvents under reduced pressure gave crude 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuranose as a colorless oil. A solution of this acetonide in dry THF (50 mL) was added dropwise to a suspension of NaH (80% in mineral oil, 1.88 g, 62 mmol) in dry THF (250 mL) at 0 °C. After the resulting slurry was vigorously stirred for 1 h, BnBr (4.4 mL, 38 mmol) was added dropwise at 0 °C, followed by the addition of TBAI (350 mg, 0.9 mmol). The mixture was stirred at 25 °C overnight. Then, it was quenched by the addition of a saturated aqueous solution of ammonium chloride (25 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were washed with brine (50 mL), dried ($NaSO_4$) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (10:1 v/v) to give 11.6 g of benzyl ether **8** (67% overall from D-arabinose), as a colorless oil. R_f (hexane/EtOAc 3:1 v/v) 0.45; $[\alpha]_D^{25}$ +1.3 (*c* 1.5, $CHCl_3$) [lit.[24] $[\alpha]_D^{25}$ +1.0 (*c* 1.0, $CHCl_3$)]; IR (neat): 3071, 2933, 2859 cm^{-1}; ^{1}H NMR spectra were identical with that reported in the literature;[24] ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.5 (C-*i*Ar_{Bn}), 135.6, 133.2 (C-*i*Ar_{TBDPS}), 133.1 (C-*i*Ar_{TBDPS}), 129.72, 129.66, 128.5, 127.8, 127.7, 112.4 (CMe_2), 105.7 (C-1), 85.2 (C-4), 85.1 (C-2), 82.9 (C-3), 71.7 (CH_2Ph), 63.4 (C-5), 27.0 (CMe_2), 26.8 (CMe_3), 26.1 (CMe_2), 19.2 (CMe_3). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{31}H_{38}O_5SiNa$ [(M+Na)$^+$]: 541.2381. Found: 541.2384.

*4.2.2. 4-O-Benzyl-5-O-tert-butyldiphenylsilyl-D-arabinofuranose (**9**)*

A 90% aqueous solution of TFA (27.5 mL) was added dropwise to a solution of acetonide **8** (3.73 g, 7.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After 1 h, the mixture was neutralized by the careful addition of a saturated aqueous sodium bicarbonate solution (approximately 200 mL). The aqueous phase was extracted with CH_2Cl_2 (2×100 mL), the combined organic phases were washed with brine (25 mL), dried (Na_2SO_4) and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 3.0 g of lactol **9** (87%), as a colorless oil (mixture of anomers, ca. 1:1). R_f (hexane/EtOAc 2:1 v/v) 0.37; IR (neat): 3419, 3071, 2932, 2858 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68–7.59 (m, 8H, H-*o*Ar_{TBDPS}), 7.48–7.31 (m, 22H, ArH), 5.35–5.29 (m, 2H, H-1), 4.69 and 4.57 (ABq, *J*=11.6 Hz, 2H, CH_2Ph), 4.68 and 4.54 (ABq, *J*=11.6 Hz, 2H, CH_2Ph), 4.33 (br s, 1H, 1×H-3), 4.21–4.03 (m, 6H, 2×H-3 and 1×H-3 and 2×H-4 and 1×H-5), 3.97 (br d, *J*=9.8 Hz, 1H, 1×H-5), 3.86–3.80 (m, 2H, 2×H-5′), 3.65 (d, *J*=11.0 Hz, 1H, OH), 3.58 (d, *J*=11.0 Hz, 2H, OH), 3.43 (d, *J*=9.2 Hz, 1H, OH), 1.05 (s, 9H, CMe_3), 1.03 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6 (C-*i*Ar_{Bn}), 136.8 (C-*i*Ar_{Bn}), 135.6, 135.5, 132.1 (C-*i*Ar_{TBDPS}), 132.0 (C-*i*Ar_{TBDPS}), 130.07, 130.02, 128.6, 128.4, 128.1, 127.9, 127.8, 127.7, 103.8 (C-1$_\beta$), 97.4 (C-1$_\alpha$), 84.4 (C-4), 84.2 (C-4), 83.2 (C-3), 82.4 (C-3), 76.5 (C-2), 76.4 (C-2), 72.2 (CH_2Ph), 71.8 (CH_2Ph), 64.7 (C-5), 64.1 (C-5), 26.7 (CMe_3), 26.6 (CMe_3), 19.1 (CMe_3), 18.9 (CMe_3). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{28}H_{34}O_5SiNa$ [(M+Na)$^+$]: 501.2068. Found: 501.2070.

*4.2.3. (2R,3S,4R)-3-(Benzyloxy)-5-tert-butyldiphenylsilyloxy-pentane-1,2,4-triol (**10**)*

$NaBH_4$ (475 mg, 12.6 mmol) was added to a solution of lactol **9** (3.0 g, 6.27 mmol) in MeOH (90 mL) at 0 °C and the resulting suspension was stirred at 25 °C overnight. Then, a few drops of glacial acetic acid and EtOAc (150 mL) were added and the mixture was washed with saturated aqueous sodium bicarbonate solution (2×25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 2.98 g of triol **10** (99%), as a colorless syrup. R_f (hexane/EtOAc 2:1 v/v) 0.28; $[\alpha]_D^{25}$ −5.2 (*c* 1.5, $CHCl_3$) [lit.[26] $[\alpha]_D^{25}$ −5.0 (*c* 1.16, $CHCl_3$)]; IR (neat): 3419, 3071, 2931, 2858 cm^{-1}; ^1H NMR and ^{13}C NMR spectra were identical with those reported in the literature.[26] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{28}H_{36}O_5SiNa$ [(M+Na)$^+$]: 503.2224. Found: 503.2225.

*4.2.4. (2R,3R,4R)-3-Benzyloxy-1-tert-butyldiphenylsilyloxy-4,5-isopropylidenedioxy-2-pentol (**11**)*

A solution of triol **10** (2.23 g, 4.6 mmol), 2,2-dimethoxypropane (9.1 mL), and *p*-toluenesulfonic acid monohydrate (70 mg, 0.4 mmol) in acetone (9.1 mL) was stirred at 25 °C for 24 h. Methanol (25 mL) was added and the mixture was diluted with $CHCl_3$ (50 mL), neutralized with saturated aqueous sodium bicarbonate solution and dried ($NaSO_4$). After evaporation of the solvents under reduced pressure, the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (10:1 v/v) to give 2.20 g of acetonide **11** (92%), as an amorphous white solid. R_f (hexane/EtOAc 3:1 v/v) 0.61; mp 115–117 °C (lit.[26] 115–117 °C); $[\alpha]_D^{25}$ +6.7 (*c* 1.0, $CHCl_3$) [lit.[26] $[\alpha]_D^{25}$ +6.86 (*c* 1.02, $CHCl_3$)]; IR (neat): 3486, 3071, 2932, 2858 cm^{-1}; ^1H NMR and ^{13}C NMR spectra were identical with those reported in the literature.[26] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{31}H_{40}O_5SiNa$ [(M+Na)$^+$]: 543.2537. Found: 543.2540.

*4.2.5. (3S,4R)-3-Benzyloxy-1-tert-butyldiphenylsilyloxy-4,5-isopropylidenedioxy-pentan-2-one (**12**)*

A solution of alcohol **11** (1.74 g, 3.34 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a suspension of CrO_3 (0.77 g, 7.7 mmol) and dry pyridine (1.25 mL, 15.4 mmol) in dry CH_2Cl_2 (40 mL). Then, Ac_2O (0.7 mL, 7.3 mmol) was added. After stirring at 25 °C for 3 h, the reaction mixture was directly charged on a short pad of silica gel. Elution with EtOAc afforded the impure product. Traces of pyridine were removed by co-evaporation with toluene (2×10 mL) and the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (10:1 v/v) to give 1.70 g of ketone **12** (98%), as a colorless oil. R_f (hexane/EtOAc 5:1 v/v) 0.44; $[\alpha]_D^{25}$ −34.4 (*c* 2.6, $CHCl_3$); IR (neat): 3071, 2933, 2892, 2858, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.66–7.63 (m 4H, H-*o*Ar_{TBDPS}), 7.47–7.35 (m, 6H, H-*p*Ar_{TBDPS} and H-*m*Ar_{TBDPS}), 7.28–7.26 (m, 3H, H-*o*Ar_{Bn} and H-*p*Ar_{Bn}), 7.18–7.15 (m, 2H, H-*o*Ar_{Bn}), 4.58 and 4.50 (ABq, *J*=18.9 Hz, 2H, H-1), 4.49 and 4.34 (ABq, *J*=12.2 Hz, 2H, CH_2Ph), 4.22 (dd, *J*=11.6, 6.1 Hz, 1H, H-3), 3.94–3.87 (m, 2H, H-4 and H-5a), 3.76 (dd, *J*=8.6, 6.7 Hz, 1H, H-5b), 1.33 (s, 3H, CMe_2), 1.29 (s, 3H, CMe_2), 1.08 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.2 (C-2), 136.9 (C-*i*Ar_{Bn}), 135.6, 132.9 (C-*i*Ar_{TBDPS}), 132.8 (C-*i*Ar_{TBDPS}), 129.9, 128.4, 128.0, 127.7, 109.6 (*C*Me_2), 82.5 (C-3), 76.0 (C-4), 73.3 (*C*H_2Ph), 68.9 (C-1), 65.5 (C-5), 26.7 (C*Me*$_3$), 26.1 (C*Me*$_2$), 25.3 (C*Me*$_2$), 19.2, (*C*Me_3). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{31}H_{38}O_5SiNa$ [(M+Na)$^+$]: 541.2381. Found: 541.2383.

*4.2.6. (3S,4R)-3-Benzyloxy-2-tert-butyldiphenylsilyloxymethyl-tetrahydrofuran-2,4-diol (**13**)*

A 90% aqueous solution of TFA (1.1 mL) was added dropwise to a solution of acetonide **12** (78 mg, 0.15 mmol) in CCl_4 (0.11 mL) at −10 °C. The reaction mixture was stirred at the same temperature for 30 min. Then, H_2O (0.5 mL) was added, the mixture was neutralized by the addition of solid sodium carbonate and extracted with $CHCl_3$ (3×5 mL). The combined organic phases were dried (Na_2SO_4), the solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (4:1 v/v) to give 42 mg of lactols **13** (59%, ratio of ca. 3:1), as a colorless thick oil. R_f (hexane/EtOAc 2:1 v/v) 0.25; IR (neat): 3445, 3071, 2931, 2858 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, for the major isomer): δ 7.71–7.62 (m, 4H, H-*o*Ar_{TBDPS}), 7.46–7.27 (m, 11H, H-*p*Ar_{TBDPS} and H-*m*Ar_{TBDPS} and H-Ar_{Bn}), 4.77 and 4.66 (ABq, *J*=11.6 Hz, 2H, CH_2Ph), 4.45 (br s, 1H, H-4), 4.23 (br d, *J*=8.5 Hz, 1H, H-3), 4.11 (dd, *J*=9.8, 3.0 Hz, 1H, H-5a), 3.95 (s, 1H, OH), 3.88 (d, *J*=9.8 Hz, 1H, H-5b), 3.81 and 3.57 (ABq, *J*=11.0 Hz, 2H, CH_2OSi), 2.31 (br s, 1H, OH), 1.06 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz, for the major isomer): δ 135.70, 135.65 (C-*i*Ar_{Bn}), 132.4 (C-*i*Ar_{TBDPS}), 132.5 (C-*i*Ar_{TBDPS}), 130.0, 128.7, 128.4, 128.0, 127.9, 127.8, 103.6 (C-2), 84.6 (C-3), 74.7 (C-4), 73.6 (C-5), 73.2 (*C*H_2Ph), 67.2 (C-1), 26.8 (C*Me*$_3$), 19.1 (*C*Me_3). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{28}H_{34}O_5SiNa$ [(M+Na)$^+$]: 501.2068. Found: 501.2070.

*4.2.7. Methyl 2-((2R,3S)-3-benzyloxy-2-tert-butyldiphenylsilyloxymethyl-4-hydroxy-tetrahydrofuran-2-yl)acetate (**14**)*

A solution of diols **16a** and **16b** (64 mg, 0.12 mmol, ratio of ca. 4:1) in dry THF (5 mL) was added dropwise to a suspension of NaH (80% in mineral oil, 4 mg, 0.13 mmol) in dry THF (5 mL) at 0 °C. After 4 h at 0 °C, the mixture was neutralized by the addition of a few drops of AcOH and extracted with Et_2O (3×3 mL). The combined organic phases were washed with saturated aqueous solution of sodium bicarbonate (3 mL), brine (3 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure yielded a residue, which was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give, in the order of elution, 10 mg of furan derivative **14** (16%) and 6 mg of lactone **17** (10%). Compound **14**: oil; R_f (hexane/EtOAc 1:1 v/v) 0.61; $[\alpha]_D^{25}$ +30.6 (*c* 0.3, $CHCl_3$); IR (neat): 3440, 3068, 2931, 2858, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.73–7.69 (m, 4H, H-*o*Ar_{TBDPS}), 7.46–7.42 (m, 6H, H-*p*Ar_{TBDPS} and H-*m*Ar_{TBDPS}), 7.38–7.26 (m, 5H, H-Ar_{Bn}), 4.66 and 4.47 (ABq, *J*=11.4 Hz, 2H, CH_2Ph), 4.20 (d, *J*=10.6 Hz, 1H, C*H*HOSi), 4.20 (br s, 1H, H-3′), 4.11 (d, *J*=1.7 Hz, 1H, H-4′), 3.99 (dd, *J*=9.8, 2.4 Hz, 1H, H-5′a), 3.90 (d, *J*=9.8 Hz, 1H, H-5′b), 3.72 (d, *J*=10.6 Hz, 1H, CH*H*OSi), 3.38 (s, 3H, OCH_3), 2.70 and 2.42 (ABq, *J*=16.5 Hz, 2H, H-2), 1.59 (br s, 1H, OH), 1.08 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2 (C-1), 137.7 (C-*i*Ar_{Bn}), 135.7, 132.2 (C-*i*Ar_{TBDPS}), 130.02, 129.96, 128.3, 127.9, 127.8, 127.7, 127.4, 86.9 (C-2′), 86.3 (C-3′), 75.1 (C-4′), 73.6 (C-5′), 73.1 (*C*H_2Ph), 68.5 (C-1″), 51.1 (OCH_3), 36.9 (C-2), 26.8 (C*Me*$_3$), 19.2 (*C*Me_3). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{31}H_{38}O_6SiNa$ [(M+Na)$^+$]: 557.2330. Found: 557.2333.

*4.2.8. (Z)- and (E)-Methyl (4R,5R)-4-benzyloxy-3-tert-butyldiphenylsilyloxymethyl-5,6-isopropylidenedioxy-hex-2-enoate (**15a** and **15b**)*

A 15% solution of *n*-BuLi in hexanes (0.15 mL, 0.35 mmol) was added dropwise to a solution of $(MeO)_2P(O)CH_2COOMe$ (0.06 mL, 0.37 mmol) in dry THF (1 mL) at 0 °C. The mixture was kept for 30 min at the same temperature before the dropwise addition of a solution of ketone **12** (78 mg, 0.15 mmol) in dry THF (1 mL). After stirring at 25 °C for 20 h, a saturated aqueous solution of ammonium chloride (2 mL) was added and the resulting slurry was extracted with EtOAc (3×5 mL). The combined organic phases were washed with brine (5 mL) and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (10:1 v/v) to give 78 mg of inseparable unsaturated esters **15a** and **15b** (90%, ratio of ca. 4:1), as a colorless oil. Compound **15a**: R_f (hexane/EtOAc 6:1 v/v) 0.38; IR (neat, for the mixture): 3071,

2932, 2858, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.66–7.63 (m, 4H, H-*o*Ar_{TBDPS}), 7.44–7.32 (m, 6H, H-*p*Ar_{TBDPS} and H-*m*Ar_{TBDPS}), 7.25–7.23 (m, 3H, H-*o*Ar_{Bn} and H-*p*Ar_{Bn}), 7.15–7.12 (m, 2H, H-*m*Ar_{Bn}), 6.47 (s, 1H, H-2), 5.29 (d, *J*=5.3 Hz, 1H, H-4), 4.55 and 4.49 (ABq, *J*=9.2 Hz, 2H, CH_2OSi), 4.35 and 4.26 (ABq, *J*=11.8 Hz, 2H, C*H*$_2$Ph), 4.18 (q, *J*=5.5 Hz, 1H, H-5), 3.77 (dd, *J*=7.0, 4.6 Hz, 2H, H-6), 3.71 (s, 3H, OCH_3), 1.29 (s, 6H, CMe_2), 1.09 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8 (C-1), 158.4 (C-3), 137.6 (C-*i*Ar_{Bn}), 135.4, 132.9 (C-*i*Ar_{TBDPS}), 129.8, 128.1, 127.8, 127.5, 116.7 (C-2), 109.8 (*C*Me$_2$), 77.8 (C-4), 76.1 (C-5), 71.6 (*C*H$_2$Ph), 65.5 (CH_2OSi), 62.9 (C-6), 51.3 (OCH_3), 26.8 (C*Me*$_3$), 26.1 (C*Me*$_2$), 25.8 (C*Me*$_2$), 19.2 (*C*Me$_3$). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{34}H_{42}O_6SiNa$ [(M+Na)$^+$]: 597.2643. Found: 597.2642. Compound **15b**: ^1H NMR ($CDCl_3$, 300 MHz, selected peaks): δ 6.05 (s, 1H, C-2), 5.19 (d, *J*=15.3 Hz, 1H, H-4), 3.61 (s, 3H, OCH_3), 1.39 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2), 1.04 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz, selected peaks): δ 166.0 (C-1), 156.3 (C-3), 137.8, 135.5, 132.9, 117.9 (C-2), 110.0 (*C*Me$_2$), 78.2 (C-4), 76.0 (C-5), 71.2 (*C*H$_2$Ph), 65.7 (CH_2OSi), 61.1 (C-6), 51.2 (OCH_3), 26.7 (C*Me*$_3$), 26.3 (C*Me*$_2$), 25.6 (C*Me*$_2$), 19.1 (*C*Me$_3$).

4.2.9. (Z)- and (E)-Methyl (4R,5R)-4-benzyloxy-3-tert-butyldiphenylsilyloxymethyl-5,6-dihydroxy-hex-2-enoate (*16a* and *16b*)

p-Toluenesulfonic acid monohydrate (2 mg, 0.01 mmol) was added to solution of a 4:1 mixture of acetonides **15a** and **15b** (57 mg, 0.1 mmol) in MeOH (5 mL), at 0 °C. After 24 h at the same temperature solid sodium bicarbonate was added, followed by brine (5 mL). The mixture was extracted with EtOAc (3×5 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 42 mg of inseparable diols **16a** and **16b** (79%, ratio of ca. 4:1), as a colorless oil. Compound **16a**: R_f (hexane/EtOAc 1:1 v/v) 0.39; IR (neat, for the mixture): 3445, 3071, 2932, 2858, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.67–7.62 (m, 4H, H-*o*Ar_{TBDPS}), 7.46–7.30 (m, 6H, H-*p*Ar_{TBDPS} and H-*m*Ar_{TBDPS}), 7.27–7.25 (m, 3H, H-*o*Ar_{Bn} and H-*p*Ar_{Bn}), 7.08–7.04 (m, 2H, H-*o*Ar_{Bn}), 6.55 (s, 1H, H-2), 5.21 (d, *J*=6.1 Hz, 1H, H-4), 4.44 (br s, 2H, H-3′), 4.28 and 4.21 (ABq, *J*=11.0 Hz, 2H, C*H*$_2$Ph), 3.75 (s, 3H, OCH_3), 3.65–3.58 (m, 1H, H-5), 3.53–3.51 (m, 2H, H-6), 2.72 (br s, 2H, OH), 1.10 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.5 (C-1), 158.2 (C-3), 136.9 (C-*i*Ar_{TBDPS}), 135.41, 135.35, 132.6 (C-*i*Ar_{Bn}), 129.9, 128.3, 128.0, 127.9, 127.8, 117.7 (C-2), 77.1 (C-4), 73.2 (*C*H$_2$Ph), 72.1 (C-5), 62.8 (C-3′), 62.6 (C-6), 51.7 (OCH_3), 26.8 (C*Me*$_3$), 19.2 (*C*Me$_3$). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{31}H_{38}O_6SiNa$ [(M+Na)$^+$]: 557.2330. Found: 557.2327. Compound **16b**: ^1H NMR ($CDCl_3$, 300 MHz, selected peaks): δ 6.05 (s, 1H, H-2), 3.62 (s, 3H, OCH_3), 1.04 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz, selected peaks): δ 165.9 (C-1), 155.8 (C-8), 137.1 (C-*i*Ar_{TBDPS}), 132.2 (C-*i*Ar_{Bn}), 129.8, 117.1 (C-2), 78.7 (C-4), 72.7 (*C*H$_2$Ph), 71.6 (C-5), 64.2 (C-3′), 61.4 (C-6), 51.2 (OCH_3), 26.5 (C*Me*$_3$), 19.1 (*C*Me$_3$).

4.2.10. (5R,6S)-5-Benzyloxy-4-tert-butyldiphenylsilyloxymethyl-6-hydroxymethyl-5,6-dihydro-2H-pyran-2-one (*17*)

Et_3N (0.44 mL, 3.2 mmol) was added to a solution of diols **16a** and **16b** (53 mg, 0.1 mmol, ratio of ca. 4:1) in $CHCl_3$ (7 mL) at 0 °C. After stirring at 0 °C for 7 days, the solvents were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 40 mg of unreacted starting material (**16a** and **16b** in a ratio of ca. 3.2:1, 76%) and 7 mg of lactone **17** (14%), as a colorless oil. Compound **17**: R_f (hexane/EtOAc 1:1 v/v) 0.47; $[\alpha]_D^{25}$ −40.4 (*c* 0.7, $CHCl_3$); IR (neat): 3425, 3071, 2931, 2858, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64–7.60 (m, 4H, H-*o*Ar_{TBDPS}), 7.48–7.37 (m, 6H, H-*p*Ar_{TBDPS} and H-*m*Ar_{TBDPS}), 7.24–7.21 (m, 3H, H-*o*Ar_{Bn} and H-*p*Ar_{Bn}), 7.13–7.10 (m, 2H, H-*m*Ar_{Bn}), 6.33 (br s, 1H, H-3), 4.46 and 4.41 (ABq, *J*=11.6 Hz, 2H, C*H*$_2$Ph), 4.41–4.38 (m, 1H, H-5), 4.28 and 4.20 (ABq, *J*=17.7, 1.8 Hz, 2H, H-4′), 4.03 (dd, *J*=11.6, 7.3 Hz, 1H, H-6′a), 3.97 (d, *J*=2.5 Hz, 1H, H-6), 3.89 (dd, *J*=11.6, 6.1 Hz, 1H, H-6′b), 2.40 (br s, 1H, OH), 1.08 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.5 (C-4), 156.6 (C-2), 136.6 (C-*i*Ar_{TBDPS}), 135.4, 132.4 (C-*i*Ar_{Bn}), 132.3, 130.0, 128.5, 128.3, 128.0, 127.9, 116.5 (C-3), 80.2 (C-5), 72.8 (*C*H$_2$Ph), 67.2 (C-6), 63.4 (C-4′), 60.8 (C-6′), 26.7 (C*Me*$_3$), 19.1 (*C*Me$_3$). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{30}H_{34}O_5SiNa$ [(M+Na)$^+$]: 525.2068. Found: 525.2070.

4.2.11. (3S,4R)-3-Benzyloxy-1-hydroxy-4,5-isopropylidenedioxy-pentan-2-one (*18*)

A solution of TBAF in THF (1 M, 1.1 mL, 1.1 mmol) was added to a solution of AcOH (65 μL, 1.1 mmol) in THF (10 mL). The resulting mixture was added dropwise to a solution of silyl ether **12** (518 mg, 1 mmol) in THF (25 mL) at 0 °C. After 1 h, EtOAc (30 mL) was added and the mixture was washed with brine (30 mL). The aqueous phase was back-extracted with EtOAc (2×30 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (3:1 v/v) to give 238 mg of alcohol **18** (85%), as a colorless oil. R_f (hexane/EtOAc 3:1 v/v) 0.20; $[\alpha]_D^{25}$ −53.6 (*c* 3.4, $CHCl_3$); IR (neat): 3445, 2987, 2935, 2892, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.32 (m, 5H, ArH), 4.69 and 4.61 (ABq, *J*=19.7 Hz, 2H, C*H*$_2$Ph), 4.51 and 4.43 (ABq, *J*=20.1 Hz, 2H, H-1), 4.34 (dd, *J*=11.0, 6.1 Hz, 1H, H-3), 4.06–4.00 (m, 2H, H-4 and H-5a), 3.90 (dd, *J*=8.6, 6.7 Hz, 1H, H-5b), 2.91 (br s, 1H, OH), 1.43 (s, 3H, C*Me*$_2$), 1.33 (s, 3H, C*Me*$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.4 (C-2), 136.5 (C-*i*Ar), 128.4 (C-*o*Ar), 128.1 (C-*p*Ar), 127.9 (C-*m*Ar), 109.7 (*C*Me$_2$), 82.5 (C-3), 76.1 (C-4), 73.8 (*C*H$_2$Ph), 67.7 (C-1), 65.3 (C-5), 25.9 (C*Me*$_2$), 25.1 (C*Me*$_2$). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{15}H_{20}O_5Na$ [(M+Na)$^+$]: 303.1203. Found: 303.1201.

4.2.12. (Z)-Methyl (4R,5R)-4-benzyloxy-3-hydroxymethyl-5,6-isopropylidenedioxy-hex-2-enoate (*19*) and 4-((1′R,2′R)-1′-benzyloxy-2′,3′-isopropylidenedioxy-propyl)-furan-2(5H)-one (*20*)

*4.2.12.1. HWE reaction of **18**.* A 15% solution of *n*-BuLi in hexanes (0.33 mL, 0.76 mmol) was added dropwise to a solution of $(MeO)_2P(O)CH_2COOMe$ (0.15 mL, 0.93 mmol) in dry THF (3 mL) at −50 °C. The mixture was stirred for 30 min while the temperature was left to rise to −10 °C. Then, it was re-cooled to −50 °C and a solution of hydroxyketone **18** (126 mg, 0.45 mmol) in dry THF (3 mL) was added dropwise. The resulting slurry was stirred for 3 h while the temperature was left to rise to −10 °C. A saturated aqueous solution of ammonium chloride (15 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The combined organic phases were washed with brine (15 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. The obtained residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (6:1 v/v) to give, in the order of elution, 6 mg of alcohol **19** (4%) and 105 mg of lactone **20** (77%). Compound **19**: oil; R_f (hexane/EtOAc 3:1 v/v) 0.21; $[\alpha]_D^{25}$ −21.8 (*c* 0.7, $CHCl_3$); IR (neat): 3468, 2987, 2935, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.29 (m, 5H, ArH), 6.16 (br s, 1H, H-2), 5.34 (d, *J*=3.7 Hz, 1H, H-4), 4.56 and 4.45 (ABq, *J*=12.1 Hz, 2H, C*H*$_2$Ph), 4.47 and 4.17 (ABq, *J*=14.6 Hz, 2H, C*H*$_2$OH), 4.33 (td, *J*=6.7, 3.7 Hz, 1H, H-5), 4.02 (t, *J*=7.6 Hz, 1H, H-6a), 3.92 (t, *J*=7.6 Hz, 1H, H-6b), 3.70 (s, 3H, *Me*O), 2.37 (br s, 1H, OH), 1.45 (s, 3H, C*Me*$_2$), 1.36 (s, 3H, C*Me*$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4 (C-1), 158.8 (C-3), 137.5 (C-*i*Ar), 128.3 (C-*o*Ar), 127.8 (C-*p*Ar), 127.7 (C-*m*Ar), 118.8 (C-2), 110.1 (*C*Me$_2$), 78.1 (C-4), 75.7 (C-5), 72.4 (*C*H$_2$Ph), 65.9 (CH_2OH), 62.7 (C-6), 51.4 (*Me*O), 26.0 (C*Me*$_2$), 25.8 (C*Me*$_2$). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{18}H_{24}O_6Na$ [(M+Na)$^+$]: 359.1465. Found: 359.1466. Compound **20**: oil; R_f (hexane/EtOAc 3:1 v/v) 0.17; $[\alpha]_D^{25}$ −48.3 (*c* 1.6, $CHCl_3$); IR

(neat): 2987, 2936, 2890, 1780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.30 (m, 5H, ArH), 6.07 (s, 1H, H-3), 4.93 and 4.85 (dABq, J=18.0, 1.8 Hz, 2H, CH_2Ph), 4.67 and 4.51 (ABq, J=12.2 Hz, 2H, H-5), 4.43 (d, J=4.9 Hz, 1H, H-1′), 4.33 (ddd, J=7.0, 6.1, 4.9 Hz, 1H, H-2′), 4.03 (dd, J=8.6, 7.0 Hz, 1H, H-3′a), 3.82 (dd, J=8.6, 6.1 Hz, 1H, H-3′b), 1.40 (s, 3H, CMe_2), 1.34 (s, 3H, CMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.9 (C-2), 166.6 (C-4), 136.7 (C-*i*Ar), 128.7 (C-*o*Ar), 128.3 (C-*p*Ar), 127.9 (C-*m*Ar), 118.6 (C-3), 110.1 (*C*Me_2), 76.10 (C-1′), 75.2 (*C*H_2Ph), 72.5 (C-2′), 72.1 (C-5), 65.2 (C-3′), 26.0 (CMe_2), 24.9 (CMe_2). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{17}H_{20}O_5Na$ [(M+Na)$^+$]: 327.1203. Found: 327.1201.

*4.2.12.2. Wittig reaction of **18**.* Methyl (triphenylphosphoranylidene)acetate (60 mg, 0.18 mmol) was added to a solution of hydroxyketone **18** (42 mg, 0.15 mmol) in dry toluene (20 mL). The mixture was heated at reflux for 48 h. Then, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (6:1 v/v) to give 5 mg of alcohol **19** (10%) and 15 mg of lactone **20** (33%).

*4.2.12.3. Desilylation of **15a** and **15b**.* A solution of TBAF in THF (1 M, 0.1 mL, 0.1 mmol) was added to a solution of AcOH (6 μL, 0.1 mmol) in THF (4 mL). The resulting mixture was added dropwise to a solution of silyl ethers **15a** and **15b** (52 mg, 0.09 mmol, ratio of ca. 4:1) in THF (4 mL) at 0 °C. After 24 h at 25 °C the mixture was neutralized with saturated aqueous sodium bicarbonate solution and extracted with EtOAc (3×5 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (6:1 v/v) to give 22 mg of alcohol **19** (73%) and 5 mg of lactone **20** (18%).

*4.2.13. 4-((1′R,2′R)-1′-Benzyloxy-2′,3′-dihydroxypropyl)-furan-2(5H)-one (**21**)*

A solution of acetonide **20** (152 mg, 0.5 mmol) in 80% aqueous AcOH (1 mL) was stirred at room temperature for 2 days. Then, the reaction mixture was diluted with EtOAc (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate (2×10 mL). The combined aqueous phases were back-extracted with EtOAc (10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 126 mg of diol **21** (95%), as a colorless oil. R_f (hexane/EtOAc 1:2 v/v) 0.18; $[\alpha]_D^{25}$ +64.7 (*c* 0.8, $CHCl_3$); IR (neat): 3406, 2926, 2860, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.28 (m, 5H, ArH), 6.09 (s, 1H, H-3), 4.90 (s, 2H, CH_2Ph), 4.62 and 4.50 (ABq, J=11.6 Hz, 2H, H-5), 4.45 (d, J=4.3 Hz, 1H, H-1′), 3.80–3.76 (m, 1H, H-2′), 3.68 (dd, J=11.6, 3.7 Hz, 1H, H-3′a), 3.58 (dd, J=11.6, 6.1 Hz, 1H, H-3′b), 3.41 (br s, 1H, OH), 2.87 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6 (C-2), 167.9 (C-4), 136.5 (C-*i*Ar), 128.7 (C-*o*Ar), 128.4 (C-*p*Ar), 128.0 (C-*m*Ar), 118.0 (C-3), 76.0 (C-1′), 73.0 (*C*H_2Ph), 72.6 (C-5), 72.1 (C-2′), 62.7 (C-3′). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{14}H_{16}O_5Na$ [(M+Na)$^+$]: 287.0890. Found: 287.0891.

*4.2.14. (2R,3R)-3-Benzyloxy-2-hydroxy-3-(5′-oxo-2′,5′-dihydrofuran-3′-yl)-propyl hexanoate (**22a**)*

Et_3N (60 μL, 0.43 mmol) was added to a solution of diol **21** (106 mg, 0.4 mmol) in dry CH_2Cl_2 (15 mL) at −20 °C. Then, hexanoyl chloride (60 μL, 0.43 mmol) was added dropwise (1 h) and the mixture was stirred at the same temperature. After 2 h, brine was added (5 mL) and the mixture was extracted with Et_2O (2×25 mL). The combined organic phases were dried (Na_2SO_4), the solvents were removed under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (4:1 v/v) to give 117 mg of ester **22a** (81%), as a colorless oil. R_f (hexane/EtOAc 1:1 v/v) 0.48; $[\alpha]_D^{25}$ −27.0 (*c* 0.4, $CHCl_3$); IR (neat): 3454, 2945, 2931, 2872, 1780, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.28 (m, 5H, ArH), 6.11 (s, 1H, H-4′), 4.94 (s, 2H, CH_2Ph), 4.67 and 4.47 (ABq, J=11.6 Hz, 2H, H-2′), 4.40 (d, J=3.7 Hz, 1H, H-3), 4.19 and 4.13 (dABq, J=11.6, 4.9 Hz, 2H, H-1), 3.98–3.91 (m, 1H, H-2), 2.67 (d, J=6.4 Hz, 1H, OH), 2.28 (t, J=7.7 Hz, 2H, H-2″), 1.59 (p, J=7.3 Hz, 2H, H-3″), 1.30–1.22 (m, 4H, H-4″ and H-5″), 0.89 (t, J=6.7 Hz, 3H, H-6″); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.9 (C-1″), 172.9 (C-5′), 166.8 (C-3′), 136.2 (C-*i*Ar), 128.7 (C-*o*Ar), 128.6 (C-*p*Ar), 128.1 (C-*m*Ar), 118.6 (C-4′), 74.9 (C-3), 72.5 (C-2), 71.8 (C-2′), 71.3 (*C*H_2Ph), 64.4 (C-1), 33.9 (C-2″), 31.2 (C-4″), 24.4 (C-3″), 22.2 (C-5″), 13.9 (C-6″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{20}H_{26}O_6Na$ [(M+Na)$^+$]: 385.1622. Found: 385.1622.

*4.2.15. Syributin 1 (**3a**)*

A solution of benzyl ether **22a** (72 mg, 0.2 mmol) in a 2:1 mixture of dry CH_2Cl_2 and *m*-xylene (6 mL) was added to a suspension of $AlCl_3$ (80 mg, 0.6 mmol) in CH_2Cl_2 (4 mL) at −20 °C. The reaction mixture was vigorously stirred at 0 °C for 6 h. Then, iced water (2 mL) was added and extracted with Et_2O (2×25 mL). The combined organic phases were washed with brine (10 mL) and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (3:1 v/v) to give 50 mg of syributin 1 (**3a**, 92%) as a colorless oil. $[\alpha]_D^{25}$ +6.1 (*c* 0.9, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +6.09 (*c* 0.8, $CHCl_3$)]; IR, ^1H NMR and ^{13}C NMR spectra were identical with those reported in the literature.[16] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{13}H_{20}O_6Na$ [(M+Na)$^+$]: 295.1152. Found: 295.1153.

*4.2.16. (2R,3R)-3-Benzyloxy-2-hydroxy-3-(5′-oxo-2′,5′-dihydrofuran-3′-yl)-propyl octanoate (**22b**)*

Following the procedure described for **22a**, diol **21** (106 mg, 0.4 mmol) gave using octanoyl chloride 120 mg of ester **22b** (80%) as a colorless oil. R_f (hexane/EtOAc 1:1 v/v) 0.47; $[\alpha]_D^{25}$ −27.0 (*c* 0.9, $CHCl_3$); IR (neat): 3453, 2940, 2928, 2857, 1780, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.27 (m, 5H, ArH), 6.10 (s, 1H, H-4′), 4.94 (s, 2H, CH_2Ph), 4.67 and 4.47 (ABq, J=11.6 Hz, 2H, H-2′), 4.40 (d, J=3.7 Hz, 1H, H-3), 4.19 and 4.13 (dABq, J=11.6, 4.9 Hz, 2H, H-1), 3.98–3.94 (m, 1H, H-2), 3.00 (br s, 1H, OH), 2.27 (t, J=7.3 Hz, 2H, H-2″), 1.60–1.56 (m, 2H, H-3″), 1.33–1.23 (m, 8H, H-4″-H-7″), 0.88 (t, J=6.4 Hz, 3H, H-8″); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.8 (C-1″), 173.0 (C-5′), 166.9 (C-3′), 136.2 (C-*i*Ar), 128.7 (C-*o*Ar), 128.5 (C-*p*Ar), 128.1 (C-*m*Ar), 118.5 (C-4′), 75.0 (C-3), 72.4 (*C*H_2Ph), 71.9 (C-2), 71.2 (C-2′), 64.4 (C-1), 33.9 (C-2″), 31.5 (C-6″), 29.0 (C-5″), 28.8 (C-4″), 24.7 (C-3″), 22.5 (C-7″), 14.0 (C-8″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{22}H_{30}O_6Na$ [(M+Na)$^+$]: 413.1935. Found: 413.1933.

*4.2.17. Syributin 2 (**3b**)*

Following the procedure described for **3a**, benzyl ether **22b** (78 mg, 0.2 mmol) gave 54 mg of syributin 2 (**3b**, 90%), as a colorless oil. $[\alpha]_D^{25}$ +7.1 (*c* 0.6, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +7.03 (*c* 0.6, $CHCl_3$)]; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those reported in the literature.[16] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{15}H_{24}O_6Na$ [(M+Na)$^+$]: 323.1465. Found: 323.1464.

*4.2.18. (3S,4R)-3-Benzyloxy-2-hydroxymethyl-tetrahydrofuran-2,4-diol (**23**)*

A 90% aqueous solution of TFA (0.26 mL) was dropwise added at 0 °C to a solution of hydroxyketone **18** (31 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL). After 90 min, the solution was neutralized by the addition of saturated aqueous sodium bicarbonate. The aqueous phase was extracted with CH_2Cl_2 (2×3 mL) and the combined organic layers

were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel with a mixture of hexanes/ethyl acetate (1:1 v/v) to give 21 mg of lactols **23** (80%, ratio of ca. 3:1) as a colorless syrup. R_f (hexane/EtOAc 1:3 v/v) 0.10; IR (neat for the mixture): 3391, 2927, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, for the major isomer): δ 7.36–7.32 (m, 5H, ArH), 4.75 and 4.67 (ABq, J=11.6 Hz, 2H, CH_2Ph), 4.34 (br s, 1H, OH), 4.29 (br d, J=4.9 Hz, 1H, OH), 4.23 (d, J=3.7 Hz, 1H, H-3), 4.13–4.08 (m, 1H, H-4), 4.01 (br d, J=9.0 Hz, 1H, OH), 3.91–3.74 (m, 2H, H-5), 3.72 and 3.59 (ABq, J=11.9 Hz, 2H, H-2′); ^{13}C NMR ($CDCl_3$, 75 MHz, for the major isomer): δ 136.6 (C-*i*Ar), 128.4 (C-*o*Ar), 128.0 (C-*p*Ar), 127.7 (C-*m*Ar), 103.9 (C-2), 84.2 (C-3), 74.7 (C-4), 73.5 (C-5), 72.9 (*C*H_2Ph), 65.2 (C-2′). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{12}H_{16}O_5Na$ [(M+Na)$^+$]: 263.0890. Found: 263.0891.

*4.2.19. (3R,4S,5R)-4-Benzyloxy-3-hydroxy-1,7-dioxaspiro[4.4]-nonan-8-one (**25**) and (3R,4S,5S)-4-benzyloxy-3-hydroxy-1,7-dioxaspiro[4.4]nonan-8-one (**24**)*

*4.2.19.1. IHMA reaction of **21**.* Et_3N (1.4 mL, 1 mmol) was added to a solution of diol **21** (90 mg, 0.34 mmol) in $CHCl_3$ (1.5 mL). The mixture was stirred at room temperature for 4 days. Then, EtOAc (10 mL) was added and the mixture was washed with brine (2×10 mL). The organic phase was dried (Na_2SO_4) and the solvents were removed under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (3:1 v/v) to give, in the order of elution, 44 mg of spiro-derivative **25** (63%) and 10 mg of spiro-derivative **24** (14%) and 20 mg of unreacted starting material **21**. Compound **24**: solid, R_f [hexane/EtOAc 1:1 v/v (three times development)] 0.44; mp 75–77 °C; $[\alpha]_D^{25}$ −3.7 (*c* 0.7, $CHCl_3$); IR (neat): 3418, 2928, 2890, 1779 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.30 (m, 5H, ArH), 4.72 and 4.56 (ABq, J=12.2 Hz, 2H, CH_2Ph), 4.53 and 4.32 (ABq, J=10.4 Hz, 2H, H-6), 4.42 (br s, 1H, H-4), 4.17 (dd, J=9.8, 4.3 Hz, 1H, H-3), 3.90 (d, J=1.8 Hz, 1H, H-2a), 3.83 (dd, J=9.8, 1.8 Hz, 1H, H-2b), 2.76 and 2.68 (ABq, J=18.3 Hz, 2H, H-9), 2.05 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.8 (C-8), 137.0 (C-*i*Ar), 128.7 (C-*o*Ar), 128.3 (C-*p*Ar), 127.7 (C-*m*Ar), 87.4 (C-4), 86.9 (C-5), 74.5 (C-3), 73.9 (*C*H_2Ph), 73.8 (C-6), 72.4 (C-2), 40.0 (C-9). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{14}H_{16}O_5Na$ [(M+Na)$^+$]: 287.0890. Found: 287.0892. Compound **25**: oil; R_f [hexane/EtOAc 1:1 v/v (three times development)] 0.50; $[\alpha]_D^{25}$ −5.3 (*c* 0.8, MeOH); IR (neat): 3445, 2930, 2910, 1779 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.31 (m, 5H, ArH), 4.76 and 4.60 (ABq, J=12.2 Hz, 2H, CH_2Ph), 4.45–4.41 (m, 1H, H-4), 4.37 and 4.28 (ABq, J=10.4 Hz, 2H, H-6), 4.11 (dd, J=10.4, 4.9 Hz, 1H, H-3), 3.83 (dd, J=10.4, 2.5 Hz, 1H, H-2a), 3.82 (d, J=1.8 Hz, 1H, H-2b), 2.98 and 2.56 (ABq, J=18.3 Hz, 2H, H-9), 2.74 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.7 (C-8), 137.1 (C-*i*Ar), 128.7 (C-*o*Ar), 128.2 (C-*p*Ar), 127.7 (C-*m*Ar), 87.4 (C-5), 86.2 (C-4), 76.5 (C-3), 74.7 (*C*H_2Ph), 73.3 (C-6), 72.5 (C-2), 35.4 (C-9). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{14}H_{16}O_5Na$ [(M+Na)$^+$]: 287.0890. Found: 287.0891.

*4.2.19.2. Desilylation of **14**.* A solution of TBAF in THF (1 M, 0.11 mL, 0.11 mmol) was added dropwise to a solution of silyl ether **14** (54 mg, 0.1 mmol) in THF (4 mL) at 0 °C. After 8 h at 25 °C the mixture was quenched with saturated aqueous ammonium chloride solution (2 mL) and extracted with EtOAc (2×5 mL). The combined organic phases were washed with brine (3 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (3:1 v/v) to give 23 mg of lactone **25** (87%).

*4.2.20. (3R,4S,5R)-3,4-Dihydroxy-1,7-dioxaspiro[4.4]nonan-8-one (**26**)*

A 10% methanolic solution of HCl (60 μL) was added to a solution of benzyl ether 25 (78 mg, 0.3 mmol) in EtOAc (6 mL) followed by a catalytic amount of 5% Pd/C (10 mg). The reaction mixture was vigorously stirred at room temperature for 90 min. Then, it was filtered through Celite® with the aid of EtOAc (10 mL). The solvents were removed under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel with a mixture of EtOAc/MeOH (50:1 v/v) to give 52 mg of diol **26** (99%) as colorless needles. Mp 108 °C (lit.[16] 107–108 °C); $[\alpha]_D^{25}$ +75.9 (*c* 0.3, MeOH) [lit.[16] $[\alpha]_D^{25}$ +75.3 (*c* 0.22, MeOH)]; IR, ^1H NMR and ^{13}C NMR spectra were identical with those reported in the literature.[16] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_7H_{10}O_5Na$ [(M+Na)$^+$]: 197.0420. Found: 197.0420.

*4.2.21. Secosyrin 1 (**2a**)*

Diol **26** (26 mg, 0.5 mmol) gave, following a known procedure,[16] 29 mg of secosyrin 1 (**2a**, 72%), as a colorless oil. $[\alpha]_D^{25}$ +40.0 (*c* 1.0, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +40.2 (*c* 1.1, $CHCl_3$)]; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those reported in the literature.[16] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{13}H_{20}O_6Na$ [(M+Na)$^+$]: 295.1152. Found: 295.1150.

*4.2.22. Secosyrin 2 (**2b**)*

Diol **26** (26 mg, 0.5 mmol) gave, following a known procedure,[16] 34 mg of secosyrin 2 (**2b**, 76%), as a colorless oil. $[\alpha]_D^{25}$ +42.5 (*c* 0.5, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +42.3 (*c* 0.5, $CHCl_3$)]; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those reported in the literature.[17] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{15}H_{24}O_6Na$ [(M+Na)$^+$]: 323.1465. Found: 323.1468.

*4.2.23. 4-((1′R,2′R)-1′-Benzyloxy-2′,3′-isopropylidenedioxy-propyl)-3-(1″-hydroxyhexyl)-furan-2(5H)-one (**27a**)*

DIPEA (280 μL, 1.63 mmol) was added to a solution of lactone **20** (124 mg, 0.41 mmol) in dry THF (3 mL) at 0 °C. This mixture was cooled to −78 °C and a 1 M solution in CH_2Cl_2 of Bu_2BOTf (0.8 mL, 0.8 mmol) was added. The resulting mixture was stirred at −78 °C for 1 h, then hexanal (73 μL, 0.61 mmol) was added and it was left at −20 °C for 1 h. Iced water (20 mL) was used to quench the reaction. The obtained slurry was extracted with EtOAc (3×15 mL) and the combined organic phases were washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the volatiles under reduced pressure yielded a residue, which was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (4:1 v/v) to give 146 mg of alcohols **27a** (88%, mixture of diastereoisomers in a ratio of ca. 9:1) as a colorless oil. R_f (hexane/EtOAc 3:1 v/v) 0.25; IR (neat): 3473, 2934, 2872, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, for the major diastereoisomer): δ 7.35–7.30 (m, 5H, ArH), 4.93 and 4.79 (ABq, J=18.0 Hz, 2H, H-5), 4.82 (d, J=3.9 Hz, 1H, H-1′), 4.64 and 4.48 (ABq, J=12.0 Hz, 2H, CH_2Ph), 4.57–4.50 (m, 1H, H-1″), 4.33–4.27 (m, 1H, H-2″), 4.05–4.00 (m, 1H, H-3′a), 3.93 (dd, J=8.6, 6.1 Hz, 1H, H-3′b), 2.97 (br d, J=8.9 Hz, 1H, OH), 1.72–1.67 (m, 2H, H-2″), 1.41 (s, 3H, CMe_2), 1.35–1.25 (m, 6H, H-3″-H-5″), 1.34 (s, 3H, CMe_2), 0.89 (t, J=6.5 Hz, 3H, H-6″); ^{13}C NMR ($CDCl_3$, 75 MHz, for the major diasteroisomer): δ 173.2 (C-2), 158.3 (C-4), 136.9 (C-*i*Ar), 131.4 (C-3), 128.5 (C-*o*Ar), 128.1 (C-*p*Ar), 127.6 (C-*m*Ar), 110.1 (*C*Me_2), 77.2 (C-2′), 73.6 (C-1′), 72.2 (C-5), 70.8 (*C*H_2Ph), 67.5 (C-3′), 65.3 (C-1″), 36.5 (C-2″), 31.4 (C-4″), 26.0 (CMe_2), 25.3 (C-3″), 25.2 (CMe_2), 22.5 (C-5″), 13.9 (C-6″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{23}H_{32}O_6Na$ [(M+Na)$^+$]: 427.2091. Found: 427.2090.

*4.2.24. 4-((1′R,2′R)-1′-Benzyloxy-2′,3′-isopropylidenedioxy-propyl)-3-hexanoylfuran-2(5H)-one (**28a**)*

Dess–Martin periodinane (573 mg, 1.35 mmol) was added in portions in a solution of diastereoisomeric alcohols **27a** (121 mg, 0.3 mmol) in CH_2Cl_2 (6 mL) at 25 °C. The mixture was stirred for 3 h and then saturated aqueous solution of sodium bicarbonate (20 mL) was added and it was extracted with ether (3×25 mL). The combined organic phases were washed with brine (20 mL) and

dried (Na_2SO_4). Evaporation of the volatiles under reduced pressure yielded a residue, which was purified by flash column chromatography on silica gel with a mixture of hexane/EtOAc (4:1 v/v) to give 113 mg of ketone **28a** (94%) as a colorless oil. R_f (hexane/EtOAc 3:1 v/v) 0.48; $[\alpha]_D^{20}$ −51.4 (*c* 1.8, $CHCl_3$); IR (neat): 2933, 2890, 1766, 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz,): δ 7.35–7.27 (m, 5H, ArH), 5.14 and 4.85 (ABq, *J*=20.1, 2H, H-5), 5.12 (d, *J*=2.4 Hz, 1H, H-1′), 4.53 (s, 2H, CH_2Ph), 4.38 (dt, *J*=1.8, 6.4 Hz, 1H, H-2′), 4.10–4.00 (m, 2H, H-3′), 3.03 (dt, *J*=18.0, 7.3 Hz, 1H, H-2″a), 2.91 (dt, *J*=18.0, 7.3 Hz, 1H, H-2″b), 1.65–1.56 (m, 2H, H-3″), 1.45 (s, 3H, CMe_2), 1.36–1.30 (m, 4H, H-4″, H-5″), 1.31 (s, 3H, CMe_2), 0.91 (t, *J*=6.7 Hz, 3H, H-6″); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.4 (C-1″), 177.5 (C-2), 170.3 (C-4), 136.5 (C-*i*Ar), 128.5 (C-*o*Ar), 128.3 (C-*p*Ar), 127.8 (C-*m*Ar), 125.3 (C-3), 110.2 (*C*Me$_2$), 77.0 (C-2′), 74.8 (C-1′), 73.5 (C-5), 71.1 (*C*H$_2$Ph), 65.5 (C-3′), 41.8 (C-2″), 31.1 (C-3″), 25.8 (CMe_2), 25.3 (CMe_2), 22.7 (C-4″), 22.4 (C-5″), 13.8 (C-6″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{23}H_{30}O_6Na$ [(M+Na)$^+$]: 425.1935. Found: 425.1935.

4.2.25. *4-((1′R,2′R)-1′-Benzyloxy-2′,3′-dihydroxypropyl)-3-hexanoylfuran-2(5H)-one (**30a**)*

4.2.25.1. $TiCl_4$ promoted deprotection. Protected diol **28a** (20 mg, 0.05 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under an Ar atmosphere. This was cooled to −30 °C and a 1 M solution of $TiCl_4$ in dichloromethane (150 μL, 0.15 mmol) was slowly added. The mixture was left to stir for 5 h at the same temperature and then quenched by the addition of a saturated aqueous solution of ammonium chloride (1 mL). The resulting slurry was vigorously stirred at 25 °C for 15 min. Then, EtOAc (10 mL) was added, the organic phase was dried ($MgSO_4$) and the solvents were removed under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel with a mixture of heptane/EtOAc (1:1 v/v) to give diol **30a** (10 mg, 55%) as a pale yellow oil. R_f (hexane/EtOAc 1:1 v/v) 0.14; $[\alpha]_D^{20}$ −40.6 (*c* 0.3, $CHCl_3$); IR (neat): 3441, 2956, 2871, 1761, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): δ 7.38–7.31 (m, 3H, ArH), 7.28–7.24 (m, 2H, ArH), 5.21 (d, *J*=3.5 Hz, 1H, H-1′), 5.14 and 4.87 (ABq, *J*=19.9 Hz, 2H, H-5), 4.53 (s, 2H, CH_2Ph), 3.89 (br s, 1H, H-2′), 3.78–3.68 (m, 2H, H-3′), 3.07–2.86 (m, 3H, H-2″, 1×OH), 2.35 (br s, 1H, 1×OH), 1.60 (quintet, 2H, H-3″), 1.37–1.28 (m, 4H, H-4″, H-5″), 0.90 (t, *J*=7.0 Hz, 3H, H-6″); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1 (C-1″), 177.0 (C-2), 170.2 (C-4), 136.1 (C-*i*Ar), 128.83 (C-*o*Ar), 128.81 (C-*p*Ar), 128.3 (C-*m*Ar), 126.1 (C-3), 76.5 (C-2′), 73.9 (C-1′), 73.4 (C-5), 70.9 (*C*H$_2$Bn), 63.4 (C-3′), 42.0 (C-2″), 31.2 (C-3″), 22.9 (C-4″), 22.5 (C-5″), 13.9 (C-6″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{20}H_{26}O_6Na$ [(M+Na)$^+$]: 385.1622. Found: 385.1620.

4.2.25.2. AcOH promoted deprotection. Protected diol **28a** (100 mg, 0.25 mmol) was dissolved in 80% aqueous AcOH (3 mL). This mixture was stirred at 20 °C for 4 h. Then, EtOAc was added (10 mL) and it was carefully quenched by the addition of saturated aqueous solution of sodium hydrogencarbonate (until pH 7). The resulting slurry was extracted with EtOAc (3×15 mL) and the combined organic phases were washed with brine (10 mL). Evaporation under reduced pressure of the solvent left a residue, which was purified by flash column chromatography on silica gel with a mixture of heptane/EtOAc (1:1 v/v) to give diol **30a** (72 mg, 80%) as a pale yellow oil.

4.2.26. *Syringolide 1 (**1a**)*

A solution of diol **30a** (36 mg, 0.1 mmol) in a 2:1 mixture of dry CH_2Cl_2 and *m*-xylene (3 mL) was added to a suspension of $AlCl_3$ (67 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at −20 °C. The reaction mixture was vigorously stirred at 0 °C for 4 h. Iced water (2 mL) was added and the mixture was left to stir vigorously until it warmed up to 20 °C. Then it was extracted with EtOAc (2×10 mL). The combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). The solvents were evaporated under reduced pressure and the resulting residue was passed very fast through a small column containing silica gel using neat EtOAc as eluant. The solvent was evaporated under reduced pressure and the residue was re-dissolved in acetone/H_2O (3 mL, 1:1 v/v), *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol) was added and the mixture was stirred at 25 °C for 3 days. Solid sodium bicarbonate was used to neutralize the reaction. The mixture was left to vigorously stir for 2 h and subsequently it was extracted with EtOAc (2×15 mL). The combined organic phases were washed with brine (5 mL) and the solvents were removed under reduced pressure at 25 °C. The obtained residue gave upon the addition of a mixture of $CHCl_3$/hexane syringolide 1 (**1a**, 15 mg, 55%), as colorless needles. Mp 112–113 °C (lit.[2] 112.5–114.5 °C); $[\alpha]_D^{25}$ −81.0 (*c* 0.4, $CHCl_3$) [lit.[11] $[\alpha]_D^{20}$ −81.3 (*c* 0.38, $CHCl_3$)]; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those reported in the literature.[9] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{13}H_{20}O_6Na$ [(M+Na)$^+$]: 295.1152. Found: 295.1154.

4.2.27. *4-((1′R,2′R)-1′-Benzyloxy-2′,3′-isopropylidenedioxypropyl)-3-(1″-hydroxyoctyl)-furan-2(5H)-one (**27b**)*

Following the procedure described for **27a**, lactone **20** (122 mg, 0.4 mmol) gave with octanal 154 mg of alcohols **27b** (89%, mixture of diastereoisomers in a ratio of ca. 8:1) as a colorless oil. R_f (hexane/EtOAc 3:1 v/v) 0.23; IR (neat): 3473, 2928, 2857, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, for the major diasteroisomer): δ 7.35–7.30 (m, 5H, ArH), 4.93 and 4.80 (ABq, *J*=17.7 Hz, 2H, H-5), 4.79 (d, *J*=4.3 Hz, 1H, H-1′), 4.63 and 4.50 (ABq, *J*=11.6 Hz, 2H, CH_2Ph), 4.56–4.50 (m, 1H, H-1″), 4.32–4.27 (m, 1H, H-2′), 4.05–4.00 (m, 1H, H-3′a), 3.94 (dd, *J*=8.5, 6.1 Hz, 1H, H-3′b), 2.81 (br s, 1H, OH), 1.73–1.67 (m, 2H, H-2″), 1.42 (s, 3H, CMe_2), 1.35–1.24 (m, 10H, H-3″, H-4″, H-5″, H-6″, H-7″), 1.34 (s, 3H, CMe_2), 0.88 (t, *J*=6.7 Hz, 3H, H-8″); ^{13}C NMR ($CDCl_3$, 75 MHz, for the major diasteroisomer): δ 173.2 (C-2), 158.1 (C-4), 136.8 (C-*i*Ar), 131.4 (C-3), 128.5 (C-*o*Ar), 128.1 (C-*p*Ar), 127.6 (C-*m*Ar), 110.2 (*C*Me$_2$), 77.2 (C-2′), 73.6 (C-1′), 72.3 (C-5), 70.8 (*C*H$_2$Ph), 67.6 (C-3′), 65.3 (C-1″), 36.6 (C-2″), 31.7 (C-6″), 29.3 (C-5″), 26.1 (C-3″), 25.7 (CMe_2), 25.2 (CMe_2), 22.5 (C-7″), 14.0 (C-8″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{25}H_{36}O_6Na$ [(M+Na)$^+$]: 455.2404. Found: 455.2407.

4.2.28. *4-((1′R,2′R)-1′-Benzyloxy-2′,3′-isopropylidenedioxypropyl)-3-octanoylfuran-2(5H)-one (**28b**)*

Following the procedure described for **28a** a mixture of alcohols **27b** (140 mg, 0.32 mmol) gave 128 mg of ketone **28b** (93%) as a colorless oil. R_f (hexane/EtOAc 3:1 v/v) 0.47; $[\alpha]_D^{20}$ −115.7 (*c* 0.9, $CHCl_3$); IR (neat): 2930, 2858, 1767, 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz,): δ 7.36–7.25 (m, 5H, ArH), 5.14 and 4.84 (ABq, *J*=20.1, 2H, H-5), 5.12 (d, *J*=2.4 Hz, 1H, H-1′), 4.53 (s, 2H, CH_2Ph), 4.37 (dt, *J*=2.4, 6.1 Hz, 1H, H-2′), 4.11–4.00 (m, 2H, H-3′), 3.03 (dt, *J*=18.0, 7.3 Hz, 1H, H-2″a), 2.91 (dt, *J*=18.0, 7.3 Hz, 1H, H-2″b), 1.64–1.55 (m, 2H, H-4″), 1.45 (s, 3H, CMe_2), 1.35–1.27 (m, 8H, H-3″, H-5″, H-6″, H-7″), 1.31 (s, 3H, CMe_2), 0.89 (t, *J*=6.7 Hz, 3H, H-8″); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.5 (C-1″), 177.5 (C-2), 170.4 (C-4), 136.6 (C-*i*Ar), 128.9 (C-*o*Ar), 128.3 (C-*p*Ar), 127.8 (C-*m*Ar), 125.4 (C-3), 110.3 (*C*Me$_2$), 77.1 (C-2′), 74.9 (C-1′), 73.6 (C-5), 71.1 (*C*H$_2$Ph), 65.6 (C-3′), 42.0 (C-2″), 31.7 (C-6″), 29.1 (C-4″), 29.0 (C-5″), 25.9 (CMe_2), 25.3 (CMe_2), 23.1 (C-3″), 22.6 (C-7″), 14.0 (C-8″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{25}H_{34}O_6Na$ [(M+Na)$^+$]: 453.2248. Found: 425.2251.

4.2.29. *(1R,7R,8R)-7-Benzyloxy-4,10,11-trioxa-1-heptyltricyclo[6.2.1.0^{2,6}]undec-2(6)-en-3-one (**29**)*

Protected diol **28b** (21 mg, 0.05 mmol) was dissolved in MeOH (2 mL) and Dowex® 50 W-X8 (250 mg) was added. The mixture was stirred at 25 °C for 20 h. Then, it was filtered and the resin was washed with MeOH (1 mL). The solvent was evaporated under

reduced pressure and the obtained residue was purified by flash column chromatography on silica gel with a mixture of heptane/EtOAc (4:1 v/v) to give 18 mg (97%) of tricycloketal **29** as a colorless oil. R_f (hexane/EtOAc 7:3 v/v) 0.42; $[\alpha]_D^{20}$ −20.7 (*c* 0.4, $CHCl_3$); IR (neat): 3028, 2956, 2852, 1740, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): δ 7.41–7.37 (m, 3H, ArH), 7.32–7.29 (m, 2H, ArH), 4.85 (dd, *J*=17.8, 2.0 Hz, 1H, H-5a), 4.75 (br s, 1H, H-7), 4.66–4.58 (m, 3H, H-8 and CH_2Ph), 4.51 (dd, *J*=17.8, 1.4 Hz, 1H, H-5b), 4.09–4.05 (m, 1H, H-9a), 3.99–3.95 (m, 1H, H-9b), 2.31–2.24 (m, 1H, H-1′a), 2.06–1.99 (m, 1H, H-1′b), 1.62–1.54 (m, 2H, H-3′), 1.43–1.25 (m, 8H, H-2′, H-4′, H-5′, H-6′), 0.86 (t, *J*=6.9 Hz, 3H, H-7′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0 (C-3), 161.0 (C-6), 136.9 (C-*i*Ar), 129.3 (C-2), 128.9 (C-*o*Ar), 128.7 (C-*p*Ar), 128.0 (C-*m*Ar), 104.3 (C-1), 77.2 (C-8), 73.5 (C-5), 73.0 (C-7), 68.6 (CH_2Ph), 64.1 (C-9), 31.7 (C-5′), 31.1 (C-3′), 29.6 (C-1′), 29.1 (C-4′), 22.9 (C-2′), 22.6 (C-6′), 14.1 (C-7′). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{22}H_{28}O_5Na$ [(M+Na)$^+$]: 395.1829. Found: 395.1833.

4.2.30. 4-((1′*R*,2′*R*)-1′-Benzyloxy-2′,3′-dihydroxypropyl)-3-octanoylfuran-2(5*H*)-one (**30b**)

4.2.30.1. $TiCl_4$ promoted deprotection. Following the procedure described for **30a** protected diol **28b** (22 mg, 0.05 mmol) gave diol **30b** (11 mg, 56%) as a pale yellow oil. R_f (hexane/EtOAc 1:3 v/v) 0.13; $[\alpha]_D^{20}$ −44.6 (*c* 0.3, $CHCl_3$); IR (neat): 3418, 2954, 2927, 2857, 1763, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz,): δ 7.38–7.31 (m, 3H, ArH), 7.28–7.23 (m, 2H, ArH), 5.21 (d, *J*=3.5 Hz, 1H, H-1′), 5.14 and 4.87 (ABq, *J*=19.9 Hz, 2H, H-5), 4.54 (s, 2H, CH_2Ph), 3.89 (br s, 1H, H-2′), 3.78–3.68 (m, 2H, H-3′), 3.07–2.86 (m, 3H, H-2″, 1×OH), 2.33 (br s, 1H, 1×OH), 1.61–1.58 (m, 2H, H-4″), 1.32–1.25 (m, 8H, H-3″, H-5″, H-6″, H-7″), 0.88 (t, *J*=7.0 Hz, 3H, H-8″); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.2 (C-1″), 176.9 (C-2), 170.1 (C-4), 136.1 (C-*i*Ar), 128.83 (C-*o*Ar), 128.81 (C-*p*Ar), 128.3 (C-*m*Ar), 126.1 (C-3), 76.5 (C-2′), 73.9 (C-1′), 73.4 (C-5), 70.9 (CH_2Bn), 63.4 (C-3′), 42.0 (C-2″), 31.7 (C-6″), 29.1 (C-4″), 29.0 (C-5″), 23.1 (C-3″), 22.6 (C-7″), 14.1 (C-8″). HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{22}H_{30}O_6Na$ [(M+Na)$^+$]: 413.1935. Found: 413.1938.

4.2.30.2. AcOH promoted deprotection. Following the procedure described for **30a** protected diol **28b** (100 mg, 0.23 mmol) gave diol **30a** (74 mg, 82%) as a pale yellow oil.

4.2.31. Syringolide 2 (**1b**)

Following the procedure described for **1a** diol **30b** (40 mg, 0.1 mmol) gave syringolide 2 (**2b**, 16 mg, 53%), as colorless needles. Mp 122–123 °C (lit.[2] 123–124 °C); $[\alpha]_D^{25}$ −76.4 (*c* 0.35, $CHCl_3$) [lit.[11] $[\alpha]_D^{20}$ −74.7 (*c* 0.1, $CHCl_3$)]; IR, ^1H NMR, and ^{13}C NMR spectra were identical with those reported in the literature.[7a,9] HRMS (MALDI-FTMS): *m*/*e* calcd for $C_{15}H_{24}O_6Na$ [(M+Na)$^+$]: 323.1465. Found: 323.1464.

References and notes

1. Bent, A. F.; Kunkel, B. N.; Dahlbeck, D.; Brown, K. L.; Schmidt, R.; Giraudat, J.; Leung, J.; Staskawicz, B. J. *Science* **1994**, *265*, 1856–1860 and references cited therein.
2. Midland, S. L.; Keen, N. T.; Sims, J. J.; Midland, M. M.; Stayton, M. M.; Burton, V.; Smith, M. J.; Mazzola, E. P.; Graham, K. J.; Clardy, J. *J. Org. Chem.* **1993**, *58*, 2940–2945 and references cited therein.
3. Smith, M. J.; Mazzola, E. P.; Sims, J. J.; Midland, S. L.; Keen, N. T.; Burton, V.; Stayton, M. M. *Tetrahedron Lett.* **1993**, *34*, 223–226.
4. Wong, H. N. C. *Eur. J. Org. Chem.* **1999**, 1757–1765.
5. Midland, S. L.; Keen, N. T.; Sims, J. J. *J. Org. Chem.* **1995**, *60*, 1118–1119.
6. Selected recent publications: (a) Keith, L. W.; Boyd, C.; Keen, N. T.; Partridge, J. E. *Mol. Plant-Microbe Interact.* **1997**, *10*, 416–422; (b) Ji, C.; Okinaka, Y.; Takeuchi, Y.; Tsurushima, T.; Buzzell, R. I.; Sims, J. J.; Midland, S. L.; Slaymaker, D.; Yoshikawa, M.; Yamaoka, N.; Keen, N. T. *Plant Cell* **1997**, *9*, 1425–1433; (c) Ji, C.; Boyd, C.; Slaymaker, D.; Okinaka, Y.; Takeuchi, Y.; Midland, S. L.; Sims, J. J.; Herman, E.; Keen, N. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3306–3311; (d) Tsurushima, T.; Ji, C.; Okinaka, Y.; Takeuchi, Y.; Sims, J. J.; Midland, S. L.; Yoshikawa, M.; Yamaoka, N.; Keen, N. T. In *Developments in Plant Pathology*; Kohmoto, K., Yoder, O. C., Eds.; Springer: 1998; Vol. 13, pp 139–140; (e) Okinaka, Y.; Yang, C.-H.; Herman, E.; Kinney, A.; Keen, N. T. *Mol. Plant-Microbe Interact.* **2002**, *15*, 1213–1218; (f) Slaymaker, D. H.; Keen, N. T. *Plant Sci.* **2004**, *166*, 387–396; (g) Hagihara, T.; Hashi, M.; Takeuchi, Y.; Yamaoka, N. *Planta* **2004**, *218*, 606–614; (h) Slaymaker, D. H.; Hoppey, C. M. *Plant Sci.* **2006**, *170*, 54–60.
7. (a) Wood, J. L.; Jeong, S.; Salcedo, A.; Jenkins, J. *J. Org. Chem.* **1995**, *60*, 286–287; (b) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron Lett.* **1995**, *36*, 3201–3202; (c) Kuwahara, S.; Moriguchi, M.; Miyagawa, K.; Konno, M.; Kodama, O. *Tetrahedron* **1995**, *51*, 8809–8814.
8. (a) Henschke, J. P.; Rickards, R. W. *Tetrahedron Lett.* **1996**, *37*, 3557–3560; (b) Zeng, C.-M.; Midland, S. L.; Keen, N. T.; Sims, J. J. *J. Org. Chem.* **1997**, *62*, 4780–4784; (c) Yoda, H.; Kawauchi, M.; Takabe, K.; Ken, H. *Heterocycles* **1997**, *45*, 1895–1898.
9. Honda, T.; Mizutani, H.; Kanai, K. *J. Org. Chem.* **1996**, *61*, 9374–9378.
10. (a) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1996**, 335–336; (b) Ishihara, J.; Sugimoto, T.; Murai, A. *Tetrahedron* **1997**, *53*, 16029–16040.
11. Yu, P.; Wang, Q.-G.; Mak, T. C. W.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1783–1788.
12. Chênevert, R.; Dasser, M. *Can. J. Chem.* **2000**, *78*, 275–279.
13. Chênevert, R.; Dasser, M. *J. Org. Chem.* **2000**, *65*, 4529–4531.
14. (a) Carda, M.; Castillo, E.; Rodriguez, S.; Falomir, E.; Alberto Marco, J. *Tetrahedron Lett.* **1998**, *39*, 8895–8896; (b) Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465–467.
15. Mukai, C.; Moharram, S. M.; Hanaoka, M. *Tetrahedron Lett.* **1997**, *38*, 2511–2512.
16. Mukai, C.; Moharram, S. M.; Azukizawa, S.; Hanaoka, M. *J. Org. Chem.* **1997**, *62*, 8095–8103.
17. Yu, P.; Yang, Y.; Zhang, Z. Y.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 6359–6366.
18. Wong, H. N. C. *Pure Appl. Chem.* **1996**, *68*, 335–344.
19. (a) Yoda, H.; Kawauchi, M.; Takabe, K.; Hosoya, K. *Heterocycles* **1997**, *45*, 1903–1906; (b) Di Florio, R.; Rizzacasa, M. A. *Aust. J. Chem.* **2000**, *53*, 327–331; (c) Krishna, P. R.; Narsingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773–4775.
20. Refs. 8, 12, 14a, 19a.
21. (a) Koumbis, A. E.; Dieti, K. M.; Vikentiou, M. G.; Gallos, J. K. *Tetrahedron Lett.* **2003**, *44*, 2513–2516; (b) Gallos, J. K.; Stathakis, C. I.; Kotoulas, S. S.; Koumbis, A. E. *J. Org. Chem.* **2005**, *70*, 6884–6890; (c) Koumbis, A. E.; Chronopoulos, D. *Tetrahedron Lett.* **2005**, *46*, 4353–4355; (d) Koumbis, A. E.; Kaitaidis, A. D.; Kotoulas, S. S. *Tetrahedron Lett.* **2006**, *47*, 8479–8481; (e) Koumbis, A. E.; Kotoulas, S. S.; Gallos, J. K. *Tetrahedron* **2007**, *63*, 2235–2243.
22. Koumbis, A. E.; Varvogli, A.-A. C. *Synlett* **2006**, 3340–3342.
23. Preliminary results of this work were presented in: (a) 1st European Chemistry Congress, Budapest, Hungary, August 2006, p 329 (N-PO-94); (b) 2nd Hellenic Symposium on Organic Synthesis, Athens, Greece, April 2007, p 53 (L17).
24. Pakulski, Z.; Zamojksi, A. *Tetrahedron* **1995**, *51*, 871–908.
25. Dahlman, O.; Garegg, P. J.; Mayer, H.; Schramek, S. *Acta Chem. Scand. Ser. B* **1986**, *40*, 15–20.
26. Intermediates **10** and **11** have been previously prepared from D-mannitol, following a different synthetic scheme: (a) Toyota, M.; Hirota, M.; Hirano, H.; Ihara, M. *Org. Lett.* **2000**, *2*, 2031–2034; (b) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875–878.
27. Sugar numbering.
28. Wang, E. S.; Choy, Y. M.; Wong, H. N. C. *Tetrahedron* **1996**, *52*, 12137–12158.
29. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
30. Using NaH and *t*-BuOK as bases resulted in the formation of these esters in almost the same ratios but in much lower yields.
31. As expected the ratio of *Z*/*E* isomers remained the same (ca. 4:1).
32. Structural assignment was based on NOE studies, which revealed the indicated crucial effects (see Scheme 3).
33. Only slow decomposition of starting material was observed.
34. Obviously, the bulkiness of the TBDPS group played a decisive role regarding the inactivity of these substrates.
35. Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281–4283.
36. Bonadies, F.; Cardilli, A.; Lattanzi, A.; Pesci, S.; Scettri, A. *Tetrahedron Lett.* **1995**, *36*, 2839–2840; (b) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; Garcia, N.; Escola, M. A.; Basabe, P.; Conde, A.; Moro, R. F.; Urones, J. G. *Synthesis* **2005**, 3301–3310.
37. Analogous conclusions could be reached by examining the opened formed intermediates (*erythro* and *threo*).
38. Ono, M.; Saotome, C.; Akita, H. *Tetrahedron: Asymmetry* **1996**, *7*, 2595–2602.
39. These compounds were found to have identical physical and spectra data with those reported in the literature.
40. The 3-*O*-TBS derivative instead of 3-*O*-benzyl one (**21**).
41. Triethylamine, *t*-BuOK, NaH, DBU, DBN in THF, $CHCl_3$, DME were used.
42. It was observed that ketone **18** slowly decomposes, even when stored at −20 °C, giving lactol **23**.
43. Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1595–1596.
44. This approach gave directly **1a** and **1b** in good overall yields (45–55%) only when 4–5 mg scale experiments were employed. Using bigger quantities of starting material resulted in an unexplained dramatic drop of the yields. Commercially available TMSI or the in situ generated one (from TMSCl and NaI) was employed.
45. Practically, we observed no reaction when THF/H_2O or acetone/H_2O was used as solvent.
46. No tetrahydrofuran-type product was found after careful investigation of the reaction mixture.
47. Jung, M. E.; Usui, Y.; Vu, C. T. *Tetrahedron Lett.* **1987**, *28*, 5977–5980.
48. A simultaneous debenzylation (see Ref. 8b) did not occur.
49. Free triol, lactol, ketal, and desired syringolide were the major components of this mixture as it was judged by the ^1H NMR spectra and LC-MS analysis.