A SHORT AND EFFICIENT SYNTHETIC PROCESS TO ENANTIOMERICALLY PURE (+)-SYRIBUTIN 1

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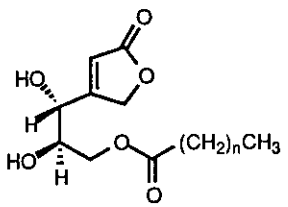
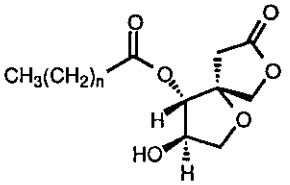
Abstract- For the synthesis of (+)-syributin 1 produced by bacteria which expresses the *avrD* gene, a simple and practical synthetic route is described in a short number of steps and high overall yield featuring the elaboration of D-arabinofuranose derivative.

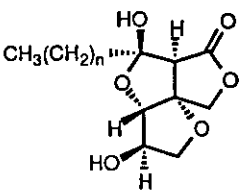
Structurally unusual metabolites, syributin 1 and 2 (**1** and **2**) and secosyrin 1 and 2 (**3** and **4**) produced by Gram-negative bacteria, are first isolated in 1995 by Sims and co-workers.[1] These compounds express the class I homology group of the avirulence gene D (*avrD*) alleles, genes from *Pseudomonas syringae* involved with formation of bacteria signal molecules or elicitors,[2] and occur only in culture filtrates of bacterial cells carrying the *avrD* gene. In connection with these metabolites we have recently accomplished the formal synthesis of syringolide 1 (**5**),[3] the only known nonproteinaceous specific elicitor of the hypersensitive defense responses (HR) carrying the *Rpg4* disease resistance gene, which is also isolated



1: Syributin 1 (n=4)
2: Syributin 2 (n=6)



3: Secosyrin 1 (n=4)
4: Secosyrin 2 (n=6)

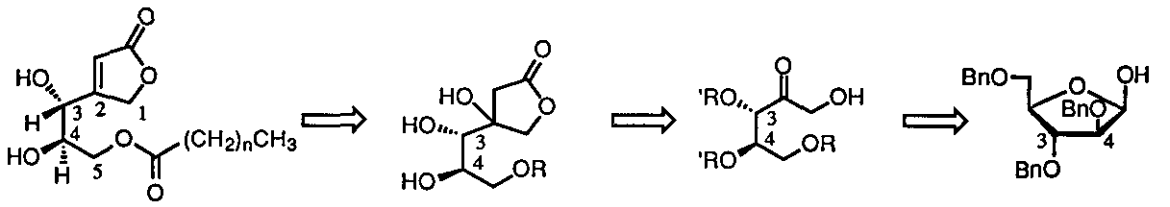


5: Syringolide 1 (n=4)
6: Syringolide 2 (n=6)

Figure 1.

from the same medium.[4] The syributins and secosyrins are not active elicitors, but are of biosynthetic interest since they are produced along with the syringolides. They are interesting new structures that provide clues to the nature of the *avrD* gene and the function of its protein product.

During our synthetic studies of these substances the first asymmetric syntheses of **1**[3f] and **3**[5] were reported by different groups and the absolute configuration of the natural syributin 1 was determined as shown in Figure 1. Herein we wish to describe an expeditious and practical route for the synthesis of **1** by featuring the elaboration of the naturally occurring D-arabinofuranose based on the retrosynthetic pathway described in Scheme 1.



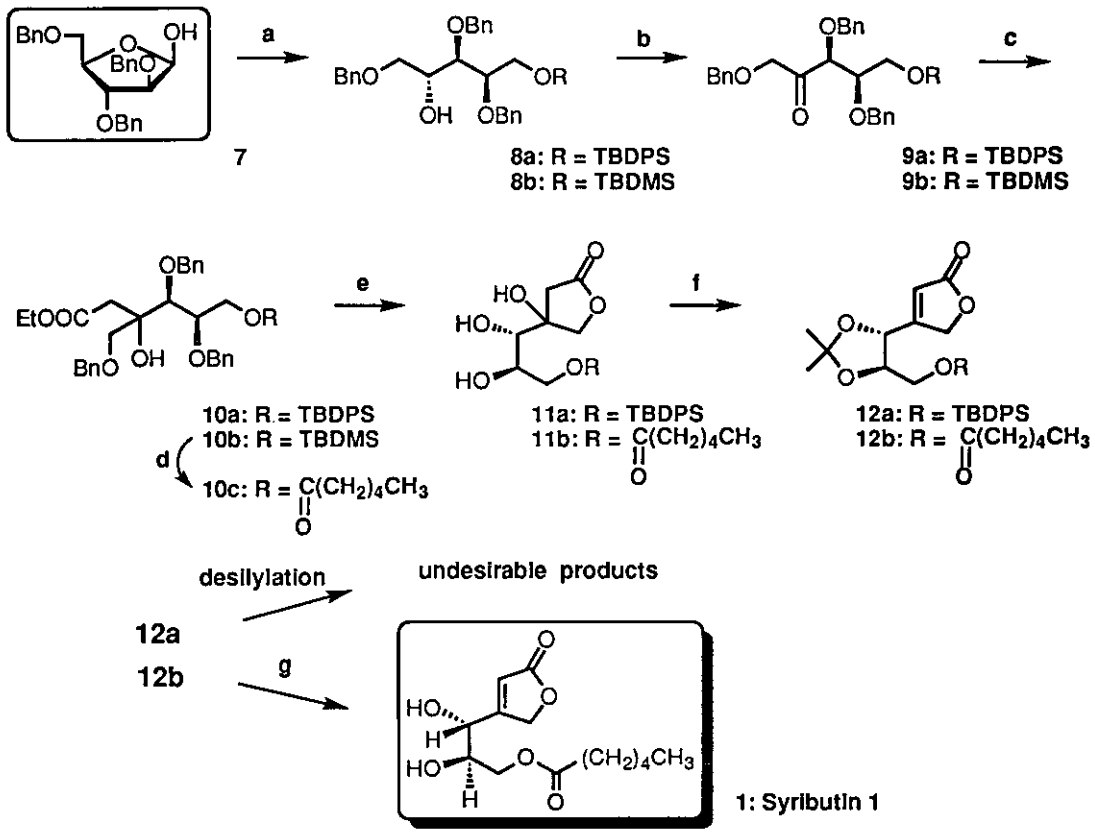
1: Syributin 1 (n=4)
2: Syributin 2 (n=6)

Scheme 1.

7: D-Arabinofuranose derivative

Reduction of the commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**7**) cleavaged the cyclic hemiacetal to open the ring and protection of the resulting diol afforded the mono-silyl ethers (**8a**: *tert*-butyldiphenylsilyl (TBDPS) and **8b**: *tert*-butyldimethylsilyl (TBDMS)) in both high yields. Then, oxidation of the secondary alcohol with PCC proceeded smoothly to yield the carbonyl compounds (**9**), which were in turn submitted to condensation with ethyl acetate, leading to the corresponding esters (**10**).[6] Compound (**10a**) thus obtained was effected by deprotection with Pd (black), followed by favorably simultaneous ring-closure to form the desired triol-lactone (**11a**) in high yield. Acetal protection of **11a** and elimination of the tertiary hydroxyl group with CF_3SO_2Cl under basic conditions effectively resulted in the preparation of the corresponding butenolide (**12a**). Subsequent deprotection of the silyl group in **12a** under a variety of conditions suffered from the formation of the side-reaction products derived from isomerization of the acetonide group[3f] and/or conjugate addition to the butenolide function. The use of benzaldehyde dimethylacetal for the protection of **11a** also failed to deprotect the silyl ether moiety selectively.

After detailed investigations, introduction of the hexanoyl group to the primary alcohol part prior to elimination of the tertiary hydroxyl group of **11** turned out to be crucial for this synthesis. Thus, exchange of the TBDMS group in **10b** to a hexanoyl function was easily performed, and then **12b**, $[\alpha]_D^{27}$+14.07°



Scheme 2. Reagents and conditions: (a) 1, $NaBH_4$, EtOH; 99%; 2, TBDPSCl, imidazole, DMF; 98% (**8a**); TBDMSCl, Et_3N, cat. DMAP, CH_2Cl_2; 93% (**8b**); (b) PCC, MS4A, CH_2Cl_2; 92% (**9a**); 80% (**9b**); (c) CH_2=C(OLi)OEt, -78 °C; 92% (**10a**); 86% (**10b**); (d) 1, cat. *p*-TsOH, MeOH; 90%; 2, $CH_3(CH_2)_4COOH$, DCC, cat. DMAP, CH_2Cl_2; 98%; (e) Pd (black), 4.4% HCOOH-MeOH, 40 °C; 94% (**11a**); 80% (**11b**); (f) 1, $Me_2C(OMe)_2$, acetone, cat. *p*-TsOH, 95% (from **11a**); 94% (from **11b**); 2, CF_3SO_2Cl, Et_3N, DMAP, CH_2Cl_2; 97% (**12a**); 78% (**12b**); (g) TFA-H_2O (9:1), THF; 70%.

(c 0.92, $CHCl_3$), obtained according to the same procedure (diol protection and elimination of the tertiary hydroxyl group) as mentioned above, was subjected to the selective cleavage of the acetonide protection with TFA-H_2O (9:1) to complete the enantiomerically pure synthesis of (+)-syributin 1 (**1**), $[\alpha]_D^{27}$+11.93° (c 0.48, $CHCl_3$) [lit.[3f] synthetic **1**, $[\alpha]_D^{26}$+6.8° (c 0.5, $CHCl_3$)][7] in 23% overall yield. The spectral data of the synthetic **1** were also completely identical with those of reported natural compound.[1]

This process is readily amenable to the construction of analogs containing various aliphatic side chains and it is clear that the simplicity of this synthetic approach and the high yield of the final product display the attractiveness and will serve to clarify the action of elicitors and catch clues to the nature of the *avrD* gene.

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6. Although the diastereomer with respect to the quaternary stereogenic center was formed, the product ratio was not determined. No racemized compound was not detected.
7. It is not clear at present the reasons for such a difference of its specific rotation, since we confirmed the absence of the other impurities in our compound.

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