FORMAL SYNTHESIS OF (-)-SYRINGOLIDE 1 STARTING FROM D-XYLOSE BASED ON A BIOMIMETIC STRATEGY

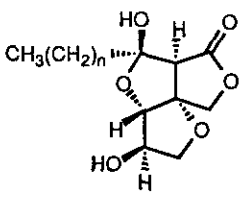
Hidemi Yoda,* Miho Kawauchi, Kunihiko Takabe, and Ken Hosoya†

Department of Molecular Science, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan

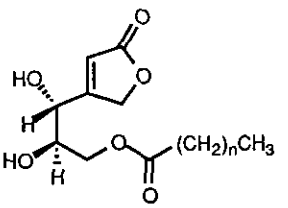
†Faculty of Textile Science, Kyoto Institute of Technology, Kyoto 606, Japan

Abstract- An expeditious and practical synthertic process for a nonproteinaceous elicitor, (-)-syringolide 1, has been developed in a short number of steps utilizing the putative biosynthetic pathway by featuring the elaboration of the protected D-xylose as a starting material.

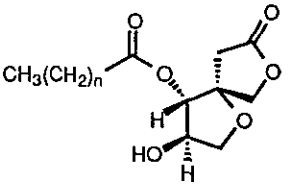
Syringolides 1 and 2 (**1** and **2**), novel nonproteinaceous elicitors, containing the oxgen-rich tricyclic core first isolated in 1993 from *Pseudomonas syringae* pv. *tomato* by Sims and co-workers[1,2] have attracted considerable attention since these compounds were shown to function as specific molecular signals which cause hypersensitive defense responses (HR) specifically in soybean plants carrying the *Rpg4* disease resistance gene.[2] These occur only in culture filtrates of bacterial cells carrying the avirulence gene D (*avrD*) and are interesting new structure that provides clues to the nature of the *avrD* gene and the function



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



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



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

Figure 1.

of its protein product. Shortly thereafter the same group also isolated four major coproducts of syringolide elicitors, syributin 1 and 2 (**3** and **4**) and secosyrin 1 and 2 (**5** and **6**), from the same medium[3] and during our synthetic studies of these substances the syntheses of **3**[4] and **5**[5] have been reported independently. The absolute stereochemistry of **1** and **2** was postulated by Sims *et al.*[1,2] based upon an assumed biosynthetic pathway involving the condensation of an appropriate β-dicarbonyl unit with D-xylulose. As shown in Figure 2, linkage of these two units was envisaged to occur either by esterification followed by intramolecular Knoevenagel condensation (route a), or alternatively by intermolecular Knoevenagel condensation followed by lactonization (route b), to yield the key butenolide intermediate.

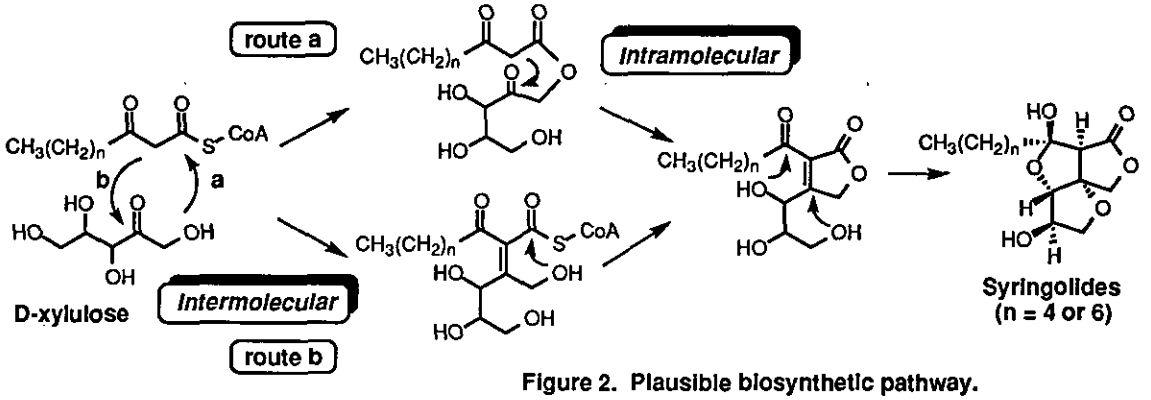
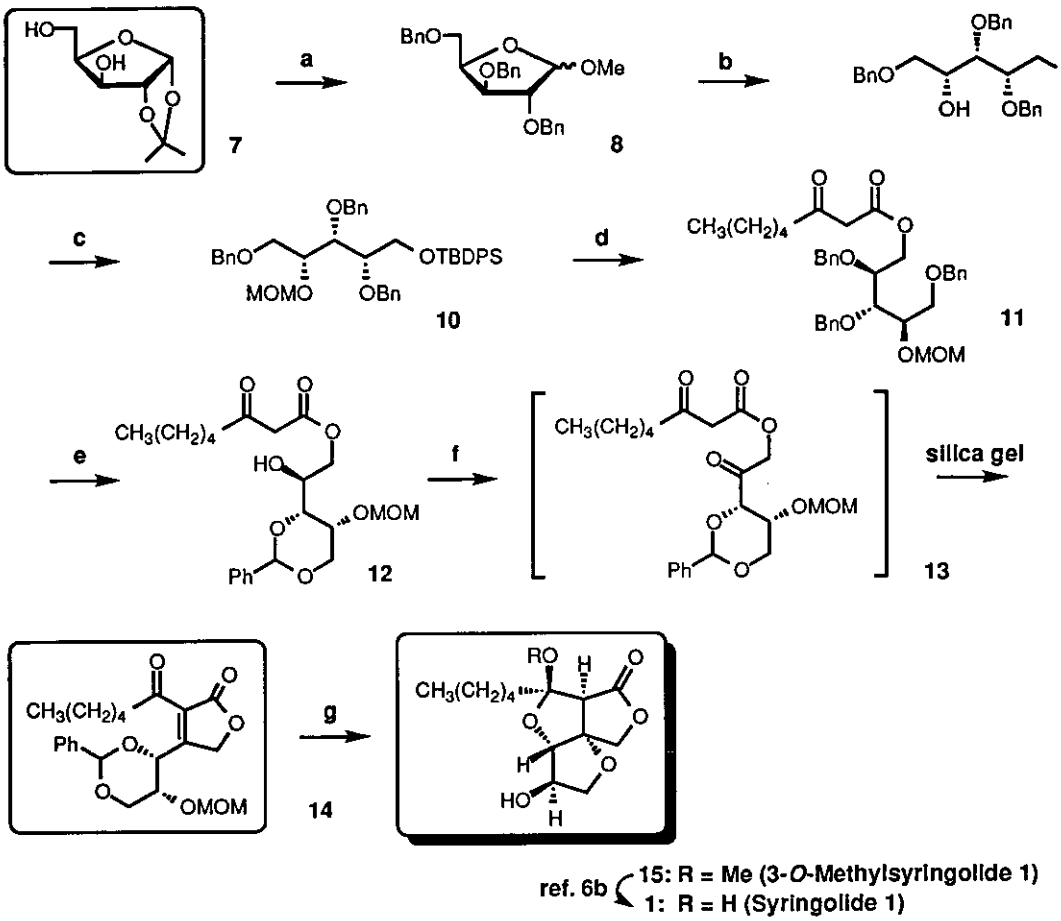


Figure 2. Plausible biosynthetic pathway.

In order to clarify the action of elicitors, the development of the new synthetic strategy and the provision of the radiolabelled compounds have been strongly required and in turn the diverse array of potentially useful activities make them inviting targets for synthesis. With these consideration in mind, herein we wish to communicate a novel and enantiomerically pure synthetic route of **1**[4,6] based on a concise biomimetic process which is readily amenable to the construction of analogs containing various aliphatic side chains. Starting from the commercially available 1,2-*O*-isopropylidene-D-xylofuranose (**7**) as shown in Scheme 1, the anomer mixture of **8** was obtained through the successive reactions of benzylation and deprotection in MeOH followed by benzylation again in high yield. Then, hydrolysis and reduction of **8** with $NaBH_4$ gave the diol (**9**), which was submitted to subsequent protection, leading to the silyl ether (**10**), $[\alpha]_D^{15}$ +7.50° (*c* 1.05, MeOH). After deprotection of the primary alcohol part, introduction of the 3-oxooctanoic acid fragment,[7] the key side chain for the synthesis of **1**, was performed effectively at this stage in the presence of DCC to afford the keto ester (**11**), $[\alpha]_D^{19}$+5.18° (*c* 1.13, MeOH), in reasonably high yield. Successive reactions of debenzylation of **11** with Pd (black) and regioselective protection of the triol



Scheme 1. Reagents and conditions: (a) 1, NaH, BnBr, THF; 93%; 2, conc. HCl, MeOH; 93%; 3, NaH, BnBr, THF; 98%; (b) 1, 80% CH_3COOH, 100 °C; 91%; 2, $NaBH_4$, EtOH; 96%; (c) 1, TBDPSCl, imidazole, DMF; 92%; 2, MOMCl, diisopropylethylamine, CH_2Cl_2; 97%; (d) 1, Bu_4NF, THF; 98%; 2, 3-oxooctanoic acid, DCC, cat. DMAP, CH_2Cl_2, 92%; (e) 1, Pd (black), 4.4% HCOOH-MeOH, 40 °C; 94%; 2, $PhCH(OMe)_2$, cat. *p*-TsOH; 60%; (f) 1, PCC, MS4A, CH_2Cl_2; 2, silica gel column chromatography (hexane-ethyl acetate); 27% (overall yield); (g) Dowex 50W-X8, MeOH; 40%.

intermediate with benzaldehyde dimethylacetal provided the corresponding alcohol (**12**), $[\alpha]_D^{27}$-15.23° (*c* 1.27, MeOH). Accompanying formation of the five-membered acetalization product was not observed in this reaction. In the subsequent oxidation of **12**, some difficulty was encountered. After detailed investigations, the use of PCC was proved to be superior to other Swern or Dess-Martin periodinane oxidation method in terms of the oxidized product yield. Furthermore it became apparent that the following silica gel chromatography to isolate the product cleanly resulted in the direct preparation of the butenolide (**14**), $[\alpha]_D^{28}$-117.69° (*c* 0.18, MeOH), which was envisaged to occur through intramolecular Knoevenagel condensation of **13** under the same process mentioned in the putative biosynthetic pathway (Figure 2, route

a). Finally, **14** was subjected to the tandem cyclization reactions of Michael addition and acetalization with ion-exchange resin to construct the tricyclic core,[8] leading to the total synthesis of 3-*O*-methylsyringolide (**15**), $[\alpha]_D^{26}$-89.40° (*c* 0.77, $CHCl_3$) [lit.,[6b] $[\alpha]_D^{28}$-88.4° (*c* 0.690, $CHCl_3$)]. The spectral data of the synthetic **15** were completely identical with reported values in all respects.

Since conversion of **15** into **1** has been easily accomplished by the preceding report,[6b] the present work formally constitutes a novel and practical synthesis of syringolide 1.

The process described here utilizing the biomimetic route from D-xylose provides a new synthetic strategy and represents a short and easily accessible pathway to this elicitor.

REFERENCES

1. M. J. Smith, E. P. Mozzola, J. J. Sims, S. L. Midland, N. T. Keen, V. Burton, and M. M. Stayton, *Tetrahedron Lett.*, 1993, **34**, 223.
2. S. L. Midland, N. T. Keen, J. J. Sims, M. M. Midland, M. M. Stayton, V. Burton, M. J. Smith, E. P. Mozzola, K. J. Graham, and J. Clardy, *J. Org. Chem.*, 1993, **58**, 2940.
3. S. L. Midland, N. T. Keen, and J. J. Sims, *J. Org. Chem.*, 1995, **60**, 1118.
4. T. Honda, H. Mizutani, and K. Kanai, *J. Org. Chem.*, 1996, **61**, 9374.
5. C. Mukai, S. M. Moharram, and M. Hanaoka, *Tetrahedron Lett.*, 1997, **38**, 2511.
6. In addition to three putative biosynthetic methods starting from D-tartarate derivatives[6a,b] and D-xylulose,[6c] three asymmetric syntheses of syringolide 1 and/or 2 were reported.[4,6d,e]: (a) J. L. Wood, S. Jeong, A. Salcedo, and J. Jenkins, *J. Org. Chem.*, 1995, **60**, 286. (b) S. Kuwahara, M. Moriguchi, K. Miyagawa, M. Konno, and O. Kodama, *Tetrahedron Lett.*, 1995, **36**, 3201; *idem*, *Tetrahedron*, 1995, **51**, 8809. (c) J. P. Henschke and R. W. Rickards, *Tetrahedron Lett.*, 1996, **37**, 3557. (d) J. Ishihara, T. Sugimoto, and A. Murai, *Synlett*, 1996, 335. (e) C.-m. Zeng, S. L. Midland, N. T. Keen, and J. J. Sims, *J. Org. Chem.*, 1997, **62**, 4780.
7. 3-Oxooctanoic acid was prepared from the successive reactions through Aldol condensation of ethyl acetate with n-capronaldehyde and Jones oxidation followed by hydrolysis with KOH in 33% overall yield.
8. It has been documented that the conjugate addition takes place from its α-face of the butenolide (**14**) to give the sole product with the desired contiguous configurations because of the *trans*-relationship between the two five-membered rings formed through addition and acetalization.[6b]

Received, 16th July, 1997