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Stereoselective synthesis of (+)-secosyrin 1

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ABSTRACT

A Chiron approach for the synthesis of (+)-secosyrin 1 from D-mannitol has been described. The key steps are a stereoselective Wittig reaction and an intramolecular Michael addition on the disubstituted butenolide, leading to a highly stereoselective formation of the tertiary chiral centre of (+)-secosyrin 1.

Some plant pathogens produce signal molecules (elicitors) which are recognized specifically by resistant plants and enable the plants to initiate active defense responses against these pathogens.[1] In 1993, Sims and co-workers[2] isolated Syringolides 1 and 2 (**1** and **2**, Fig. 1) from *Pseudomonas syringae* Pv. *Tomato*, which are the first known nonproteinaceous metabolites found to elicit hypersensitive responses on soybean plants carrying the resistance gene *Rpg4*.[3] Two years later, Sims and co-workers[4] reported the isolation of four structurally related metabolites from the same source, syributins 1 and 2 (**5** and **6**) and secosyrins 1 and 2 (**3** and **4**). Although these compounds are not active elicitors, they certainly display biosynthetic interest as they are co-produced with syringolides, and may provide a clue to the nature of the genes involved in the hypersensitive response.

The interesting properties of syringolides triggered extensive work regarding their biochemical evaluation in plant research.[5] Their interesting biological activity coupled with important structural features of **1** and **2** such as the spiro system with a tertiary chiral centre has attracted the attention of many synthetic organic chemists.[6] Syributins[6d,k,7] and secosyrins[7a,b,8] were also targeted by different research groups. In continuation of our interest in the synthesis of oxygenated heterocycles,[9,10] we undertook the stereoselective synthesis of (+)-secosyrin 1(**3**).

Both racemic[8c] and enantioselective approaches have been developed for secosyrins. The enantioselective approaches have utilized isopropylidene D-glyceraldehydes,[7a] diisopropyl D-tartrate,[7b,8a] D-xylulose,[8b] and D-arabinose[8d] as the chiral starting materials. Different strategies have been adopted for the construction of the tetrahydrofuran unit of compound **3**. Two of these syntheses[7a,8d] utilized Michael addition as a key step for the formation of the tetrahydrofuran unit with a stereoselectivity of not more than 5:1. Herein, we wish to present a novel approach for the (+)-secosyrin 1 (**3**) starting from D-mannitol and utilizing a highly stereoselective intramolecular Michael addition on disubstituted butenolide.

The retrosynthetic analysis (Scheme 1) showed that **3** could be obtained from the oxidation, lactonization and deprotection of olefin compound **7**. Olefin **7** could be obtained from bicyclic lactone **8**, which could be obtained from intramolecular Michael addition on disubstituted butenolide **9**. The stereoselective formation of a cis-fused bicyclic lactone was predicted[10] since it is obvious that the alternative trans ring junction between the two five-membered rings has a highly unfavourable ring strain leading to the highly stereoselective formation of the tertiary chiral centre of **8**. Compound **9** can be obtained from olefin **10**, which could be conveniently prepared from D-mannitol.

The synthesis of **3** commenced from **11** which was readily obtained by following the procedure mentioned in the literature.[11] The primary hydroxy of **11** was protected as its TBDPS ether to give **12**. The TEMPO-mediated oxidation of **12** gave **13**. A two-carbon extension of **13** was performed in a stereoselective manner by using the Wittig reaction to yield **14**. The bulky TBDPS group might have directed the formation of only the *Z*-isomer.[12] The removal of TBDPS in **14** with TBAF gave **15**, which on reaction with benzyl bromide yielded **16**. The selective isopropylidene deprotection of **16**

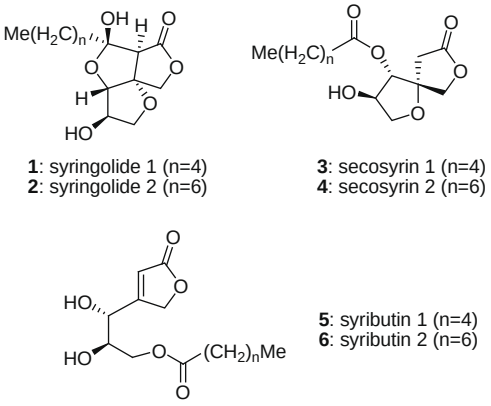

Figure 1.

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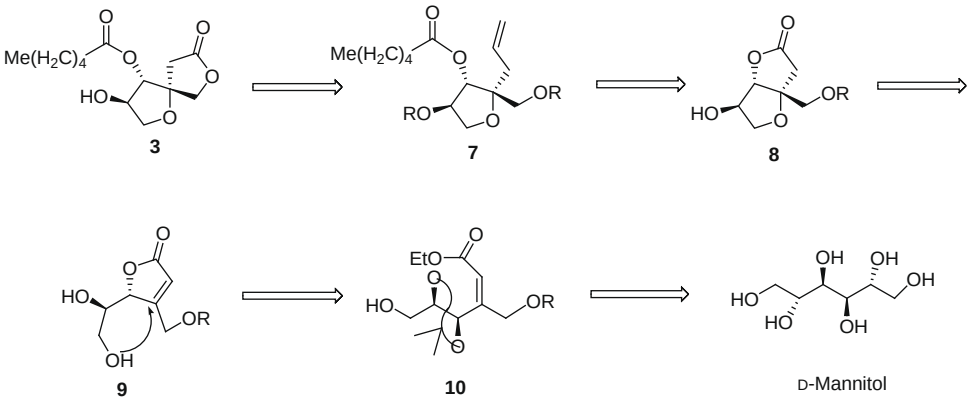
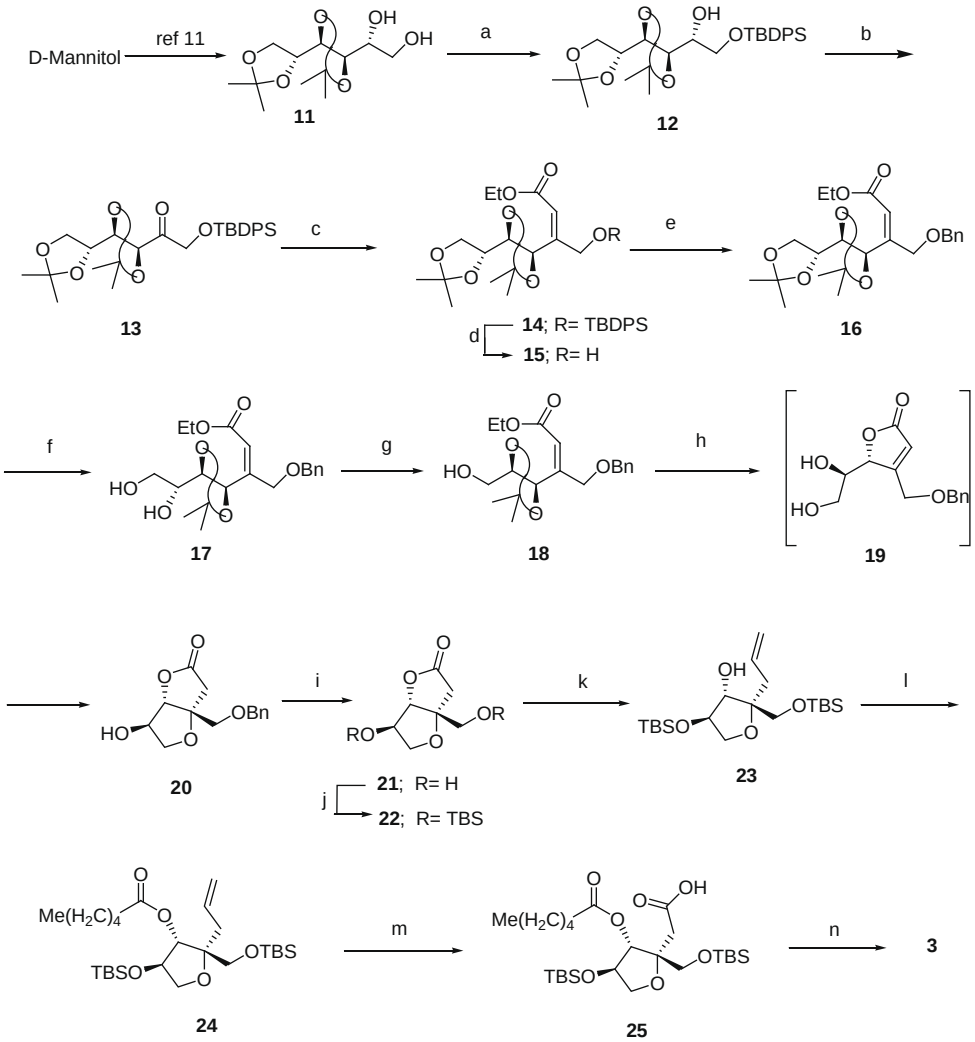


Scheme 1.

was performed using aq H_2SO_4 in EtOH to afford **17**, which on treatment with $NaIO_4$ followed by reduction of the resulting aldehyde using $NaBH_4$ gave **18**. Compound **18** was treated with PTSA in aq acetone to cleave the isopropylidene, and the crude concentrated reaction mixture was treated with excess $NaHCO_3$ in ethyl acetate for 2 days. Stereoselective intramolecular Michael addition



Scheme 2. Reagents and conditions: (a) TBDPSCl, Imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 90%; (b) NaOCl, TEMPO free radical, TBAI (cat. amount), NaBr, EtOAc, toluene, H_2O, $NaHCO_3$, 0 °C, 2 h, 94%; (c) $PPh_3CHCO_2C_2H_5$, toluene, reflux, 5 h, 78%; (d) TBAF, THF, 0 °C to rt, 12 h, 70%; (e) BnBr, Ag_2O, 4 Å molecular sieves, CH_2Cl_2, rt, 24 h, 80%; (f) aq H_2SO_4, EtOH, rt, 10 h, 70%; (g) (i) $NaIO_4$, CH_2Cl_2, 0 °C to rt 3 h; (ii) $NaBH_4$, MeOH, 0 °C to rt, 2 h, 86% for two steps; (h) PTSA, acetone/water (3:2), rt, 5 h, then $NaHCO_3$, EtOAc, rt, 2 days, 70%; (i) H_2, 10% Pd/C, EtOAc, rt, 12 h, 95%, (j) TBSOTf, 2,6-lutidine, THF, −78 °C to rt, 4 h, 86%; (k) (i) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 97%; (ii) PPh_3CH_3I, KO^tBu, THF, 0 °C to rt, 15 min, 80%; (l) hexanoic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 98%; (m) $NaIO_4$, $RuCl_3$. H_2O (cat. amount), Na_2HPO_4. $2H_2O$, H_2O, CCl_4, MeCN, rt, 18 h, 62%; (n) TFA, TFAA, rt, 1 h then TBAF, rt, 2 days, 73%.

on intermediate **19** had taken place to give *syn*-bicyclic lactone **20** in 70% yield.[13,14] The deprotection of the benzyl group in **20** using H_2, Pd/C gave **21**, which was converted to its disilyl ether **22**. The bicyclic lactone formation helped not only in creating the tertiary chiral centre, but also in selectively protecting the hyroxyls. The reduction of **22** with DIBAL-H and one carbon homologation yielded **23**. The acylation of **23** with hexanoic anhydride gave ester **24**. The RuO_4-mediated oxidative cleavage of a double bond in **24** gave acid **25**. Finally, the lactonization of **25** with trifluoroacetic anhydride/trifluoroacetic acid and the subsequent deprotection of more robust secondary OTBS with TBAF have been carried out in one pot to give compound **3**. The spectral and physical properties of **3** are in good agreement with the reported values.[7a] $[\alpha]_D^{26}$ +42.7 (*c* 0.275, $CHCl_3$) lit.[7a] $[\alpha]_D^{20}$ +40.2 (*c* 1.1, $CHCl_3$) (Scheme 2).

In conclusion, we have demonstrated the total synthesis of (+)-secosyrin 1 (**3**) through a chiral pool strategy using D-mannitol in a highly stereoselective fashion. The above-mentioned strategy is useful in making related skeletons and analogues.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.106.

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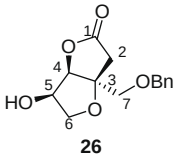
12. The ^1H NMR of the column-filtered product showed exclusive formation of *Z*-isomer. Generally, the *E*-isomer of **14** undergoes spontaneous lactonization upon deprotection of the TBDPS group. No lactonization of **14** was observed upon deprotection of the TBDPS group, thus confirming the *Z*-isomer. *Z*-isomer was further confirmed by the isolation of intermediate lactone **19** in 88% yield prior to base-induced Michael addition.
*NMR data of compound **14***: ^1H NMR(300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.16 (s, 3H), 1.27–1.37 (m, 12H), 3.65 (dd, *J* = 4.5 Hz, 9.1 Hz, 1H), 3.86–3.96 (m, 1H) 4.03–4.23 (m, 4H), 4.25(d, *J* = 17.4 Hz, 1H), 4.46 (dd, *J* = 1.9 Hz, 17.4 Hz, 1H), 5.61 (d, *J* = 9.1 Hz, 1H), 6.36 (s, 1H), 7.32–7.45 (m, 6H), 7.59–7.66 (m, 4H).
NMR data of compound **19**: ^1H NMR(400 MHz, $CDCl_3$) δ = 2.34 (br s, 1H), 2.77 (br s, 1H), 3.81 (m, 2H), 4.03 (br s, 1H), 4.37, 4.43 (AB-q, *J* = 14.9 Hz, 2H), 4.59, 4.63 (AB-q, *J* = 11.8 Hz, 2H), 5.09 (s, 1H), 6.08 (d, *J* = 1.5 Hz, 1H), 7.28–7.43 (m, 5H).
13. *Analytical data of compound* **20**: Colourless liquid, $[\alpha]_D^{28}$ +8.4 (*c* 2.2, $CHCl_3$); IR(Neat) 3423, 2924, 2858, 1781, 1452, 1037 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.58 (s, 2H), 3.56, 3.74 (AB-q, *J* = 9.8 Hz, 2H), 3.63 (d, *J* = 10.9 Hz, 1H) 3.95–4.04 (m, 2H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.56, 4.70 (AB-q, *J* = 11.7 Hz, 2H), 4.69 (s, 1H), 7.26–7.4 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 37.4, 71.1, 73.7, 74.1, 74.6, 87.2, 88.8, 127.8, 128.2, 128.5, 136.3, 174.2; ESIMS: 287 $[M+Na]^+$; ESI-HRMS: calcd for $C_{14}H_{16}O_5Na$ $[M+Na]^+$ = 287.0895, found: 287.0899.
14. (a) In batches of around 1 g (2.9 mmol) of **18**, about 4% of diastereomeric **26** was also isolated and its structure was confirmed by its ^1H NMR coupling constants and NOE experiment. Compound **26** showed a coupling constant of 4.9 Hz for H4 and H5 protons (due to *syn* orientation), which was further confirmed by the NOE between H4 and H7 protons and H4 and H5 protons (due to the *syn* orientation of protons), thus confirming the compound **26**. No compound with *trans* ring junction was isolated.



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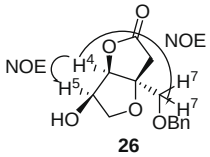
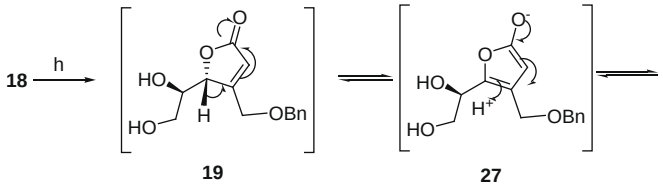
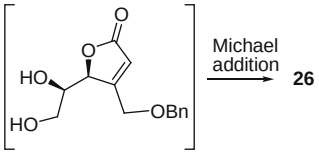


26

Compound **26** formation can be explained by the epimerization of intermediate **19** to **28** via oxy-furan intermediate **27** followed by Michael addition of **28**.





(b) *Analytical data of compound **26***: White solid, mp 85 °C, $[\alpha]_D^{28}$ −1.5 (*c* 0.65, $CHCl_3$); IR(Neat) 3446, 1776, 1636, 1075 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.69, 2.82 (AB-q, *J* = 18.5 Hz, 2H) 3.50, 3.54 (AB-q, *J* = 10.2 Hz, 2H), 3.70 (dd, *J* = 7.2 Hz, 9.4 Hz, 1H), 4.12 (dd, *J* = 6.0 Hz, 9.4 Hz, 1H), 4.41–4.50 (m, 1H) 4.54, 4.60 (AB-q, *J* = 11.7 Hz, 2H), 4.81 (d, *J* = 4.9 Hz), 7.27–7.41 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 38.5, 71.2, 71.6, 71.6, 73.6, 83.6, 86.5, 127.7, 128.1, 128.6, 137.2, 174.8; ESIMS: 287 $[M+Na]^+$.