A Short and Efficient Preparation of Enantiopure Secosyrins 1 and 2

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Abstract: An alternative, short and efficient approach for the preparation of enantiopure secosyrins 1 and 2 is reported here. This uses a D-arabinose derivative as starting material and applies a HWE–IHMA strategy for the construction of the spiro-framework of target molecules.

Key words: secosyrins, D-arabinose, HWE olefination, Michael addition, total synthesis

Syringolides 1 and 2 (**1a** and **1b**, Figure 1) are natural products bearing a 1,7-dioxaspiro[4.4]nonane skeleton.[1] These unusual metabolites, which were isolated and structurally elucidated by Sims et al.,[2] are extracellular non-proteinaceous elicitors produced from the plant pathogen *Pseudomonas syringae* pv. *tomato* by the bacterial expressing avirulence gene D (*avrD*). When this pathogen attacks the soybean plants carrying the disease-resistance gene *Rgp4*, the elicitors are recognized and subsequently a spontaneous hypersensitive defense response occurs.[3] This event causes a localized cell death and consequently the accumulation of antimicrobial phytoalexins around the infected site. Bicyclic secosyrins 1 and 2 (**2a** and **2b**) and monocyclic syributins 1 and 2 (**3a** and **3b**) are structurally related, to **1**, natural products isolated from the same cultures.[4] Although **2** and **3** are not active elicitors, they are indeed of particular importance since 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).

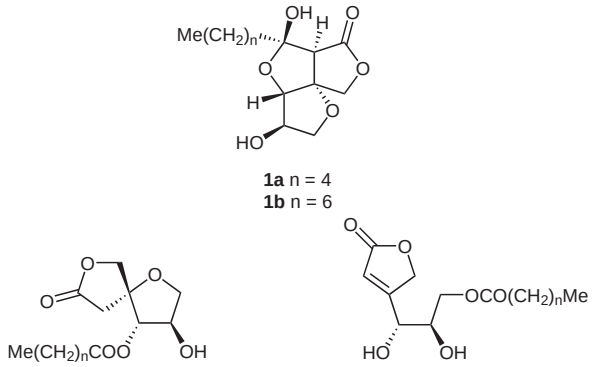

Figure 1

The interesting properties of syringolides triggered an extensive work regarding their biochemical evaluation in plant research[5] and efforts towards their total syntheses.[6] Syributins[6d,k,7] and secosyrins[7a–c,8] had also been targeted from different research groups. Specifically, enantiopure secosyrins had been prepared from isopropylidene D-glyceraldehyde,[7a] diisopropyl D-tartrate[7b,c] and D-xylulose.[8a]

In continuation of our previous research work[9] dealing with the synthesis of natural products with intriguing structures and properties using arabinose derivatives as starting materials, we embarked on the synthesis of secosyrins 1 and 2.[10]

Thus, the preparation of the required key precursor, ketone **9**, was realized starting from the readily available[11] D-arabinose derivative **4** (Scheme 1). Initially, hydrolysis of the acetonide protecting group in **4** was carefully performed upon treatment with aqueous trifluoroacetic acid and lactol **5** was obtained. Reduction of **5** with $NaBH_4$ yielded almost quantitatively triol **6**,[12] which was regioselectively reprotected to give isopropylidene intermediate **7**. Then, silyl ketone **8** was reached with mild oxidation of the free C-4 hydroxy group in **7**. At this stage, in order to avoid epimerization at C-3, **8** was desilylated under neutral conditions to afford **9**. It is noteworthy that this five-step sequence, from **4** to **9**, can be easily performed on a multigram scale and without the need of tedious chromatographic purifications.

Having a few grams of **9** in our hands, we then sought to explore the possibility of constructing the lactone ring in one step. Indeed, after some experimentation we were pleased to discover that when **9** was subjected to phosphonate-mediated olefination (Horner–Wadsworth–Emmons reaction, HWE)[13] butenolide **10** was isolated in a very good overall yield. Careful investigation of the reaction mixture revealed that a small amount of *Z*-alkene **11** was also produced. Formation of the *E*-isomer of **11** is possibly favored due to presence of the α-hydroxyl group. Obviously, under these conditions the initially produced *E*-alkene gives directly **10**, which bears the required lactone ring of target molecules.[14a]

For the completion of secosyrins synthesis, butenolide **10** was used to reach diol **12** upon removal of the acetonide moiety. The construction of the second ring and assemble of the spiro system was achieved through an intramolecular hetero-Michael addition (IHMA).[15] This approach had been earlier used[7a] for the cyclization of an analogous intermediate[16] and proved to be fruitful in our case as well.

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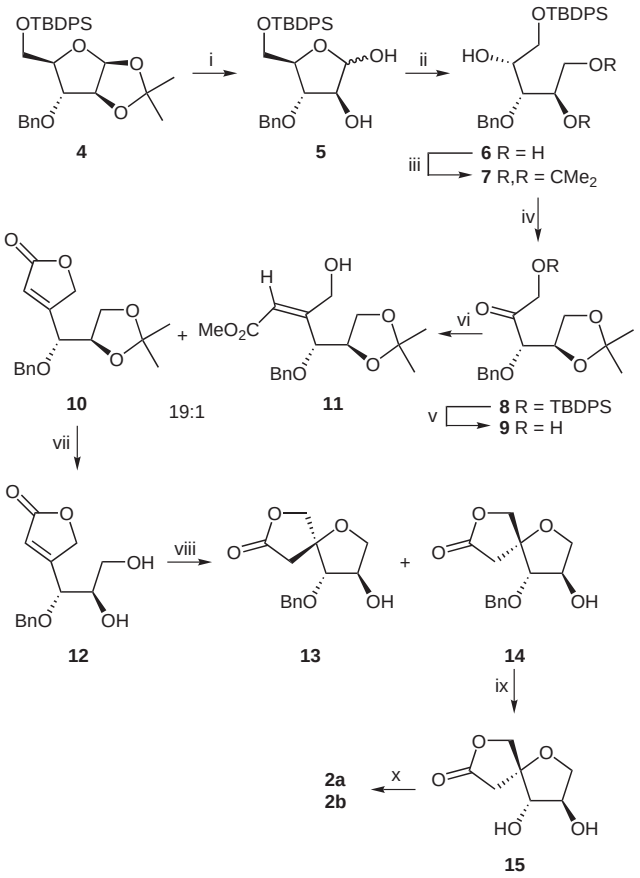

Scheme 1 *Reagents and conditions*: i) 90% TFA in H_2O, CH_2Cl_2, 0 °C, 87%; ii) $NaBH_4$, MeOH, 0 °C to r.t., 99%; iii) $MeC(OMe)_2Me$, acetone, PTSA, r.t., 92%; iv) CrO_3, pyridine, Ac_2O, r.t., 98%; v) TBAF, AcOH, THF, 0 °C, 85%; vi) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF, –50 °C to 0 °C, **10**: 77%, **11**: 4%; vii) PTSA, MeOH, 0 °C, 95%; viii) Et_3N, $CHCl_3$, 0 °C, **13**: 14%, **14**: 63%; ix) H_2, Pd/C, r.t., 99%; x) $[Me(CH_2)_4CO]_2O$ (for **2a**) or $[Me(CH_2)_6CO]_2O$ (for **2b**), DMAP, THF, 0 °C to r.t., **2a**: 72%, **2b**: 76%.

Practically, a number of different conditions (bases, solvents and temperatures) were employed to check not only the feasibility of this ring-closure but its stereoselective outcome as well. However, the best results were obtained using the conditions previously reported,[7a] giving in preference the spiro-tetrahydrofuran system **14** along with its diastereoisomer **13** (in a ratio of ca. 4.5:1).[14b] It seems that the role of the neighboring protective group (TBS or Bn) is not crucial for the diastereoselectivity of this reaction. Stereochemistry of the newly formed quaternary center was assigned comparing the spectra data of easily separable **13** and **14** with those obtained for the analogous cyclized intermediates.[7a] However, it was indisputably assured when **14** was hydrogenolyzed to give diol **15**[17] {for **15**: $[\alpha]_D^{25}$ +75.0 (*c* 0.2, MeOH), lit.[7c] $[\alpha]_D^{25}$ +75.3 (*c* 0.22, MeOH)}. Finally, **15** was regioselectively acylated[7c] with hexanoic or octanoic anhydride to afford secosyrin 1 (**2a**) and secosyrin 2 (**2b**), respectively[18] {for **2a**: $[\alpha]_D^{25}$ +40.0 (*c* 1.0, $CHCl_3$), lit.[7a] $[\alpha]_D^{20}$ +40.2 (*c* 1.1, $CHCl_3$), for **2b**: $[\alpha]_D^{25}$ +42.5 (*c* 0.5, $CHCl_3$), lit.[7a] $[\alpha]_D^{20}$ +42.3 (*c* 0.5, $CHCl_3$)}.

In conclusion, we present herein an alternative and efficient approach for the preparation of enantiopure secosyrins 1 and 2. This synthetic scheme uses a readily available D-arabinose derivative as the starting material, it involves ten easily executed steps and delivers the targeted natural products in overall yields higher than 20% for both.[19] Moreover, the stereoselective construction of the 1,7-dioxaspiro[4.4]nonane framework through the HWE–IHMA strategy could be proved significantly versatile for the synthesis of analogous systems.

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(14) (a) Compound **10**: oil; $[\alpha]_D^{25}$ –48.3 (*c* 1.6, $CHCl_3$). IR (neat): 3032, 2987, 2936, 2890, 1780, 1641, 1455, 1372, 1259, 1213, 1071, 1029, 888, 852, 739, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 5 H), 6.07 (s, 1 H), 4.93 and 4.85 (dABq, *J* = 18.0, 1.8 Hz, 2 H), 4.67 and 4.51 (ABq, *J* = 12.2 Hz, 2 H), 4.43 (d, *J* = 4.9 Hz, 1 H), 4.33 (ddd, *J* = 7.0, 6.1, 4.9 Hz, 1 H), 4.03 (dd, *J* = 8.6, 7.0 Hz, 1 H), 3.82 (dd, *J* = 8.6, 6.1 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 166.6, 136.7, 128.7, 128.3, 127.9, 118.6, 110.1, 76.10, 75.2, 72.5, 72.1, 65.2, 26.0, 24.9. HRMS (MALDI-FTMS): *m/e* calcd for $C_{17}H_{20}O_5Na$ $[M + Na]^+$: 327.1208; found: 327.1207. (b) Compound **14**: oil; $[\alpha]_D^{25}$ –5.3 (*c* 0.8, MeOH). IR (neat): 3445, 2930, 2910, 1779, 1456, 1398, 1207, 1077, 1012, 741, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 5 H), 4.76 and 4.60 (ABq, *J* = 12.2 Hz, 2 H), 4.45–4.41 (m, 1 H), 4.37 and 4.28 (ABq, *J* = 10.4 Hz, 2 H), 4.11 (dd, *J* = 10.4, 4.9 Hz, 1 H), 3.83 (dd, *J* = 10.4, 2.5 Hz, 1 H), 3.82 (d, *J* = 1.8 Hz, 1 H), 2.98 and 2.56 (ABq, *J* = 18.3 Hz, 2 H), 2.74 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 137.1, 128.7, 128.2, 127.7, 87.4, 86.2, 76.5, 74.7, 73.3, 72.5, 35.4. HRMS (MALDI-FTMS): *m/e* calcd for $C_{14}H_{16}O_5Na$ $[M + Na]^+$: 287.0895; found: 287.0894.

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(16) The 3-*O*-TBS derivative instead of the 3-*O*-benzyl derivative (**12**).

(17) Compound **15** was found to have identical physical and spectra data with those reported in ref. 7c.

(18) Compounds **2a** and **2b** were found to have physical and spectral data identical to those reported in ref. 7a.

(19) To the best of our knowledge, these are the highest overall yields reported so far for the total synthesis of both secosyrins.

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