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First Total Synthesis of (+)-Secosyrin 1

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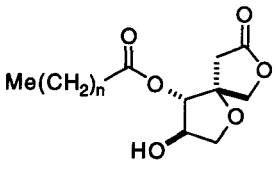
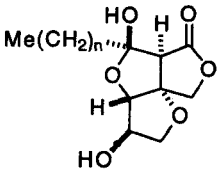
Abstract: The first total synthesis of (+)-secosyrin 1, isolated from *P. syringae.* pv. *tomato*, was accomplished in a stereoselective manner from diisopropyl D-tartrate. This synthesis unambiguously established the stereochemistry of (+)-secosyrin 1. © 1997 Elsevier Science Ltd.

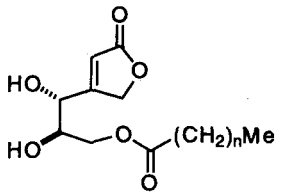
Secosyrins 1 and 2 (**1** and **2**) have a 1,7-dioxaspiro[4.4]nonane framework and are coproducts of novel nonproteinaceous C-glycoside elicitors syringolides 1 and 2 (**3** and **4**), isolated from *P. syringae* pv. *tomato*.[1] Monocyclic syributins 1 and 2 (**5** and **6**) were also isolated from the same medium.[1b] Although these simpler four products (**1**, **2**, **5**, and **6**) are not active elicitors in sharp contrast to structurally more complex syringolides, they are of particular interest for understanding their biosynthetic pathway. Syringolides have so far been synthesized by five groups[2] and the first synthesis of syributin 1 (**5**)[2e] has been recorded lately. We describe herein the first stereoselective total synthesis of (+)-secosyrin 1 (**1**) from diisopropyl D-tartrate in a stereoselective fashion, which enabled us to establish its stereochemistry unambiguously.



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

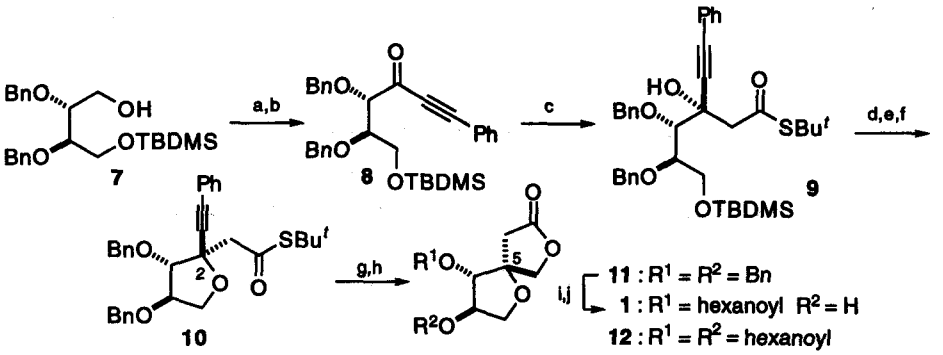


3 : syringolide 1(n = 4)
4 : syringolide 2(n = 6)



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

The hydroxy compound **7**,[3] derived from diisopropyl tartrate, was successively exposed to oxidation, acetylide addition, and oxidation conditions to give the ynone derivative **8**. The aldol reaction of **8** with the lithium enolate of *tert*-butyl thioacetate effected stereoselective introduction of C_2-component to yield **9** in 94% yield. It became apparent that the stereochemistry[4] of the newly constructed quaternary carbon center of **9** was not in accordance with that of **1**. Tetrahydrofuran ring formation accompanying isomerization of the quaternary chiral center was realized by taking advantage of alkyne-cobalt chemistry.[5] Upon treatment with $Co_2(CO)_8$, **9** afforded the cobalt complex, which was subsequently exposed to $BF_3 \cdot OEt_2$ in CH_2Cl_2 at room temperature producing, after decomplexation, **10** with the desired stereochemistry in 74% yield from **9** together with the 2-epimer (15%)(**10** : 2-epimer = 83 : 17).



Reaction Conditions : (a) 1) Swern oxid. 2) phenylacetylene, ^{n}BuLi, THF, -78°C, 80%; (b) Swern oxid., 90%; (c) LHMDS, MeCOSBu^{t}, THF, -78°C, 94%; (d) TBAF-HF, 95%; (e) $Co_2(CO)_8$, Et_2O, 98%; (f) 1) BF_3•OEt_2 , CH_2Cl_2, rt, 2) CAN, MeOH, 89% [10 (74%) and 2-epimer (15%)]; (g) Lindlar, H_2, 78%; (h) 1) O_3, pyridine, CH_2Cl_2, 2) $NaBH_4$, MeOH, 3) DBU, CH_2Cl_2, 75%; (i) Pd-C, H_2, 10% HCl, MeOH, 90%; (j) hexanoic anhydride, THF, DMAP, 95% [1 (70%) and 12 (25%)]

With **10** possessing proper stereochemistry in hand, the next stage of our synthesis was faced to efficient construction of the spiro γ-lactone moiety. Half-reduction of **10** with Lindlar catalyst furnished the *cis*-olefin, ozonolysis of which was followed by successive treatment with $NaBH_4$ and DBU to provide the spiro derivative **11**. Finally **11** underwent debenzylation to give the diol, which was acylated with hexanoic anhydride to give (+)-secosyrin 1 (**1**)[$[\alpha]_D^{26}$ +48.2° (*c* 0.12, $CHCl_3$)][6] along with the diacylated derivative **12**. ^{1}H-NMR spectrum of synthetic (+)-secosyrin 1 was in agreement with that of natural one.[1b] Thus, we have completed the first total synthesis of (+)-secosyrin 1.[7] This synthesis discloses that (+)-secosyrin 1 should be depicted as (3*R*,4*S*,5*R*)-4-hexanoyloxy-3-hydroxy-1,7-dioxaspiro[4.4]nonan-8-one, while (-)-secosyrin 1 should have its mirror form.

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(4) Compound **9** was efficiently converted into the 5-epimer of **11** by conventional means. X-Ray crystallographic analysis of the latter unambiguously established its stereochemistry, thereby the stereochemistry of **9** was confirmed. Details of X-ray analysis will be reported in somewhere else.

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(6) No information on specific rotation of natural secosyrin 1 is available.[1b]

(7) Treatment of (+)-**1** with lithium hexamethyldisilazide afforded (+)-syributin 1 (**5**)[$[\alpha]_D^{20}$ +7.8° (*c* 0.33, $CHCl_3$)][lit.[2e] $[\alpha]_D^{26}$ +6.8° (*c* 0.5, $CHCl_3$)]. This transformation combined with the details of this text will appear as a full paper in due course.

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