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Synthesis of (±)-Secosyrin 1 and a Formal Synthesis of (−)-Secosyrin 1

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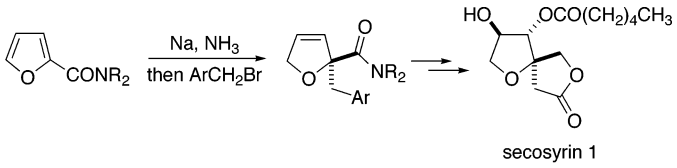
ABSTRACT



A short synthesis of (±)-secosyrin 1 is presented that starts from an electron-deficient furan; reductive alkylation under Birch conditions gives rapid access to the natural product skeleton. Two aspects of stereoselectivity are explored, the first being directed dihydroxylation of a homoallylic alcohol. Second, the facial selectivity obtained during reduction of a highly substituted cyclic ketone was examined. Finally, our synthesis was rendered enantioselective by the reduction of a furan bearing a chiral auxiliary.

Secosyrins 1 and 2 and syributins 1 and 2 were isolated by Sims and co-workers from *pseudomonas syringae* pv. *tomato* as the major coproducts with the syringolide elicitors (Figure 1).[1] The syringolides are of interest both for their unusual oxygen-rich tricyclic structure and their biological activity, which centers around their ability to elicit a hypersensitive response in resistant soybean plants. Though the secosyrins and syributins do not display the same biological activity as the syringolides, they are nonetheless of biosynthetic importance and have been the subject of a number of syntheses.[2] The secosyrins are formally related to the syringolides via an intramolecular Claisen-type reaction and to the syributins by an elimination, followed by 1,3 acyl migration.

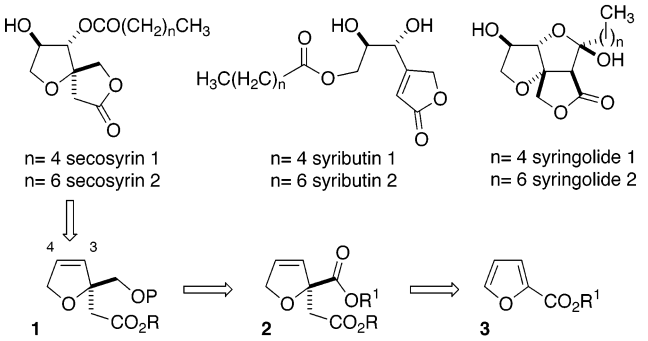


Figure 1.

In this paper, we wish to present a total synthesis of (±)-secosyrin, and a means to render this synthesis enantioselective, based on the methodologies we have developed for the Birch reduction of electron-deficient furans[3] and the directed dihydroxylation of alkenes.[4] Our approach to the secosyrins involved disconnection to dihydrofuran **1** onto which we would incorporate a *trans*-diol unit at C-3,4. Adjustment of the oxidation state of the exocyclic carbon

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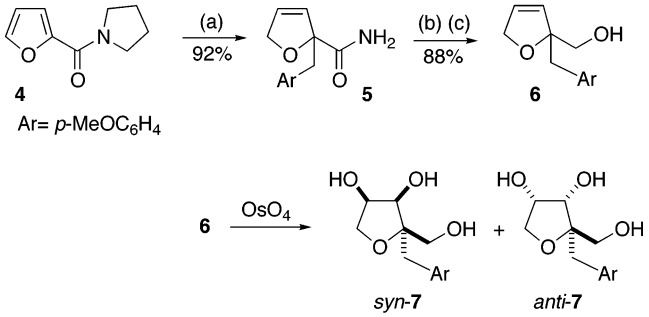
(1) Midland, S.; Keen, N. T.; Sims, J. J. *J. Org. Chem.* **1995**, *60*, 1118.
(2) Previous syntheses of secosyrin 1: (a) Mukai, C.; Moharram, S. M.; Hanaoka, M. *Tetrahedron Lett.* **1997**, *38*, 2511. (b) Yu, P.; Yang, Y.; Zhang, Z. Y.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 6359. (c) Carda, M.; Castillo, E.; Rodriguez, S.; Falomir, E.; Marco, J. A. *Tetrahedron Lett.* **1998**, *39*, 8895.
(3) For examples of the Birch reduction of furans in synthesis see: Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505. Donohoe, T. J.; Guillermin J.-B.; Walter, D. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1369.
(4) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

then revealed **2** as a likely precursor to **1** that could be prepared itself by reductive alkylation of furan **3**.

Our synthesis began with amide **4** (prepared in 98% yield from furoyl chloride and pyrrolidine) and subjected it to reductive alkylation in ammonia, quenching with *p*-methoxybenzyl bromide (Scheme 1). In this reaction, we obtained

Scheme 1[a]



(i) OsO_4 (cat.) NMO, quinuclidine, acetone/ H_2O	68:32 (76%)
(ii) OsO_4 (cat.) $Me_3NO.H_2O$, CH_2Cl_2	87:13 (80%)
(iii) OsO_4 (cat.) $Me_3NO.H_2O$, 8, CH_2Cl_2	**88:12 (84%)**
(iv) OsO_4 (1 eq.) TMEDA, CH_2Cl_2, then MeOH, HCl	**99:1 (82%)**

[a] Reagents and conditions: (a) Na, NH_3 then $ArCH_2Br$; (b) (aq) HCl; (c) $LiAlH_4$.

a mixture of amides derived from both pyrrolidine and ammonia and therefore modified the conditions (by warming) to allow efficient conversion into **5**. After hydrolysis and reduction to yield alcohol **6**, we investigated oxidation of the alkene in order to prepare the *trans*-1,2-diol unit. The first approach that we adopted involved epoxidation of **6** with both mcpba and $VO(acac)_2$/*t*-BuOOH. Unfortunately, formation of the epoxide was not observed under either of these reaction conditions.

Therefore, we turned to tactics that involved dihydroxylation of the alkene, which would clearly have to be followed by an inversion sequence. The dihydroxylation of **6** was examined under a variety of different conditions. The results in Scheme 1 show that Upjohn-type conditions[5] (i) were only moderately selective for formation of *syn*-**7**. However, this bias could be increased by utilizing hydrogen bonding control during the oxidation sequence. Conditions (ii) and (iii) were capable of exhibiting a higher degree of hydrogen bonding during oxidation with *catalytic* OsO_4.[6] Interestingly, we found that these catalytic hydrogen bonding conditions were cleaner if they were run in the presence of a polymer-bound DABCO (**8**).[7]

Finally, we also showed that complete selectivity for *syn*-**7** could be obtained using stoichiometric OsO_4 with TMEDA at low temperatures.[4]

(5) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. Quinuclidine was added because it increases the rate of reaction.

(6) For example, see: Blades, K.; Donohoe, T J.; Winter, J. J. G.; Stemp, G. *Tetrahedron Lett.* **2000**, *41*, 4701.

(7) Compound **8** is 1,4-diazabicyclo[2.2.2]octane hydrochloride, polymer bound, 1% DVB, 100−200 mesh. Prior to the reaction, the polymer was added to a solution of OsO_4 in cyclohexane; the solvent was then evaporated, and the solid so obtained was added to the dihydroxylation mixture. See: Cainelli, G.; Contento, M.; Manescalchi, Plessi, L. *Synthesis* **1989**, 45.

The syn and anti isomers of **7** were separable by chromatography, and the stereochemical identity of *syn*-**7** was proven by X-ray crystallography (Figure 2).

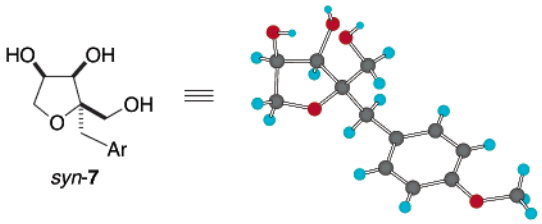
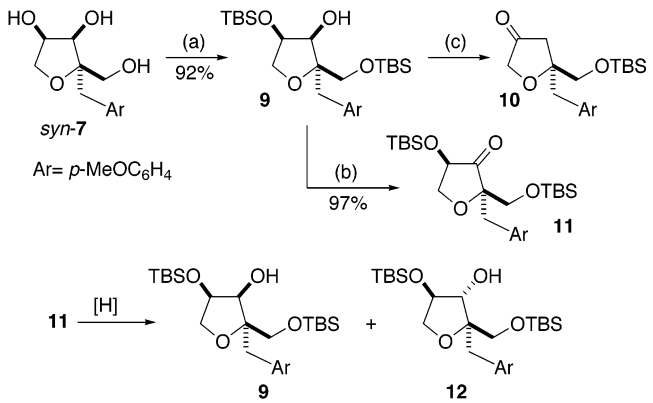


Figure 2.

We then proceeded to doubly protect the triol *syn*-**7** intending to then invert the hydroxyl at C-3 (Scheme 2).[8] Formation of **9** proceeded smoothly with 2 equiv of TBSOTf. Initial attempts at forming and displacing a triflate derived from **9** were unsuccessful (displacement at a neopentyl center) and only yielded the ketone **10** (Scheme 2). Instead, we oxidized the C-3 hydroxyl group to form ketone **11** with Dess−Martin periodinane (DMP) and then attempted diastereoselective reduction. Our first attempt at reduction of **11** used sodium borohydride (in THF),[9] which gave a 1:1 mixture of **9** and **12**. Further screening showed that two other reducing agents ($LiAlH_4$ and $LiBH_4$) both gave more of the desired configuration during the reduction process. Finally, reduction with $LiAlH_4$ at −78 °C gave a useful level of anti selectivity (93:7). Interestingly, the bulky hydride source lithium superhydride ($LiEt_3BH$) yielded the undesired diastereoisomer selectively.

If we attempt to rationalize the reduction reactions, then arguments based on steric interaction between the substrate and hydride source would appear to favor the formation of

Scheme 2[a]



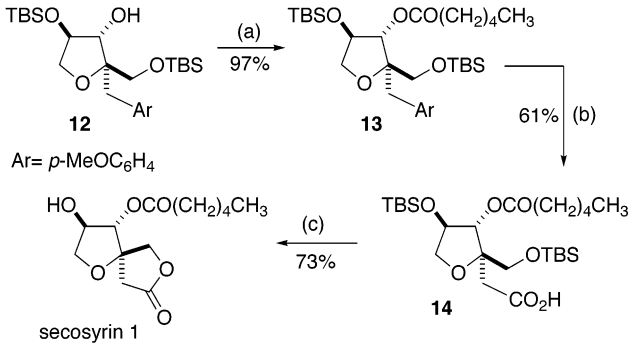
(i) $NaBH_4$ THF, RT	50:50
(ii) $LiBH_4$, THF, RT	33:66
(iii) $LiAlH_4$, THF, -78°C	**7:93 (62%)**
(iv) $LiEt_3BH$, THF, -78°C	≥85:15

[a] Reagents and conditions: (a) TBSOTf, −78 °C; (b) DMP, CH_2Cl_2; (c) Tf_2O then KOAc, 18-C-6.

9. This is consistent with the result using bulky $LiEt_3BH$. As far as the contrasteric selectivity observed with the less bulky reducing agents (to give **12**) is concerned, we suggest two possible reasons why sterics can be overturned. First, the *p*-methoxy aryl group may be involved in an electronic (π-stacking) interaction with the carbonyl, thus effectively shielding the lower face of the carbonyl compound.[10] Second, the role of stereoelectronic effects in this system (such as approach by a nucleophile so as to minimize torsional strain[11]) may also be an important factor in determining the observed stereoselectivity.

To complete the synthesis, the hexanoic ester side-chain was attached at C-3 (**12**→**13**) and then the electron-rich aryl ring was oxidized to carboxylic acid **14** using catalytic ruthenium tetroxide[12] (Scheme 3). Lactonization ensued after

Scheme 3[a]

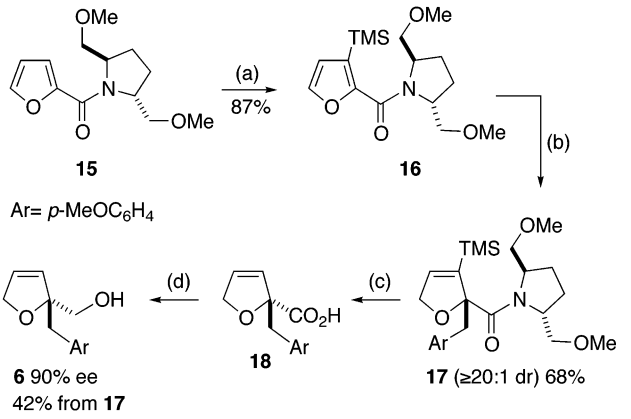


[a] Reagents and conditions: (a) hexanoic anhydride; (b) $NaIO_4$, (cat.) $RuCl_3 \cdot 2H_2O$, H_2O, CCl_4, MeCN; (c) $(CF_3CO)_2O/CF_3CO_2H$, TBAF.

reaction of **14** with trifluoroacetic anhydride/trifluoroacetic acid, and finally deprotection of the more robust secondary OTBS group was achieved, in one-pot, with the addition of TBAF. Secosyrin 1 produced in this way exhibited spectroscopic data that matched that of the natural product.[13]

Finally, we completed a formal synthesis of (−)-secosyrin by performing a Birch reduction on the auxiliary laden furan **16** (Scheme 4). Previous work had shown that the presence of a substituent at C-3 was essential to the success of the asymmetric methodology.[14] We believe that the requirement for a substituent ortho to the acyl group has its origins in

Scheme 4[a]



[a] Reagents and conditions: (a) BuLi then TMSCl; (b) Na, NH_3 then $pMeOC_6H_4CH_2Br$; (c) (aq) HCl, Δ; (d) $LiAH_4$.

setting the correct enolate geometry during the reduction reaction. So, compound **16** was prepared by ortholithiation of **15**, followed by trapping with TMSCl. Compound **16** was then reductively alkylated with *p*-methoxybenzyl bromide to an inseparable mixture of diastereoisomers **17** (≥20:1). The sense of diastereoselectivity for this reaction is assumed to be consistent with our previously described model for the reductive alkylation of **16**.[14]

Finally, acid hydrolysis of the amide auxiliary was performed with 10 M HCl so as to promote concomitant protodesilylation of the vinyl silane. After reduction of acid **18**, the alcohol **6** was shown to be ≥90% ee by HPLC on a chiral column (measured against a racemic standard).

Clearly, if we so desired, this material could be converted into (−)-secosyrin 1 (≥90% ee) by the sequence shown above,[15] and therefore this represents a formal synthesis of (−)-secosyrin 1.

To conclude, we have demonstrated the effectiveness of partial reduction reactions in total synthesis by completing an 11-step synthesis of secosyrin 1 from readily available starting materials. We have also further showcased the utility of our directed dihydroxylation method for setting the alcohol stereochemistry in this system. Finally, we have also been able to apply our recently developed chiral auxiliary methodology to develop a formal total synthesis of (−)-secosyrin 1.

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Supporting Information Available: Copies of ^1H NMR spectra and detailed spectroscopic data for all new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See: Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999.

(9) See: *Reductions by the Alumino- and Borohyrides in Organic Synthesis*; Seyden-Penne, J.; Wiley VCH: New York, 1997.

(10) Teixeira, L. H. P.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Commun.* **1997**, *27*, 3241; for a review see: Jones, G. B. *Tetrahedron* **2001**, *57*, 7999.

(11) See: Larsen, C. H.; Ridagway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208.

(12) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(13) See Supporting Information. Secosyrin 1: δ_C ($CDCl_3$) 174.1, 173.7, 86.53, 81.99, 75.88, 75.62, 72.59, 35.37, 34.00, 31.16, 24.46, 22.21, 13.84; lit.[2b], δ_C ($CDCl_3$) 174.4, 173.6, 86.61, 81.67, 76.40, 75.85, 72.83, 35.47, 34.01, 31.15, 24.46, 22.19, 13.75 ppm.

(14) Donohoe, T. J.; Calabrese, A. A.; Guillermin, J.-B.; Walter, D. S. *Tetrahedron Lett.* **2001**, *42*, 5841. Donohoe, T. J.; Calabrese, A. A.; Guillermin, J.-B.; Frampton C. S.; Walter, D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1748.

(15) This argument assumes that compound (−)-**6** does not racemize under the dihydroxylation conditions, which seems unlikely.