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Ketyl Radical Cyclization of β-Disubstituted Acrylates: Formal Syntheses of (+)-Secosyrin 1 and Longianone and the Total Synthesis of (+)-4-*epi*-Secosyrin 1

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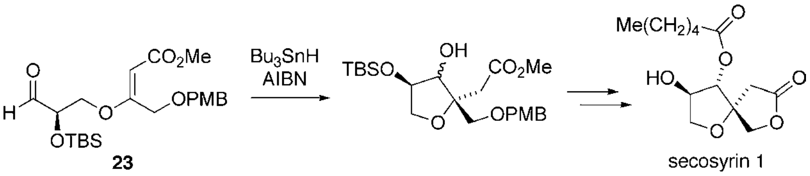
ABSTRACT



A novel approach to the synthesis of a series of 1,7-dioxaspirononanes that applies a ketyl radical cyclization strategy is described. Radical cyclization of the β-disubstituted acrylate 23, prepared in five steps from (*R*)-1,2-isopropylideneglycerol, gives both 2,3-*syn*- and 2,3-*anti*-furan products. The densely functionalized furan heterocycles are used to complete a concise formal synthesis of secosyrin 1, a metabolite of *Pseudomonas syringae*, and the total synthesis of 4-*epi*-secosyrin 1.

Naturally occurring spirocyclic ethers are widespread in nature having been isolated from a variety of sources. Most common among the dioxaspiro group are spiroketal-type ring systems[1] that can be readily prepared, at least from a conceptual standpoint, by dehydration of a keto-diol precursor. The preparation of dioxaspiro systems in which only one or neither of the oxygens is directly attached to the spiro center requires the development and application of less well-defined synthetic strategies.[2]

Of the various nonketal dioxaspiro compounds that are known to occur naturally,[3] 1,7-dioxaspiro[4.4]nonanes such as **1**–**4** and **7**–**8** (Figure 1A) represent a small group of compounds that have been isolated from bacterial and fungal sources. The syringolides 1 (**1**) and 2 (**2**), secosyrins 1 (**3**) and 2 (**4**), and syributins 1 (**5**) and 2 (**6**) were first isolated from the plant pathogen *Pseudomonas syringae*,[4] whereas sphydrofuran (**7**) was isolated from strains of Actinomycetes[5] and longianone (**8**) was isolated from the fungus *Xylaria longiana*.[6] The syringolides **1**/**2** have the most significant bioactivity of this group, being elicitors of a hypersensitive defense response in infected soy bean plants resistant to *Pseudomonas syringae*. It has been proposed that biosynthetically the secosyrins **3**/**4** are derived from syringolides **1**/**2** by a reverse Claisen reaction, with a subsequent retro-Michael reaction and 1,3-acyl migration forming the syributins **5**/**6**.[4b]

The synthesis of **3** and **4** has been the subject of some interest.[7] A number of synthetic strategies used to date for

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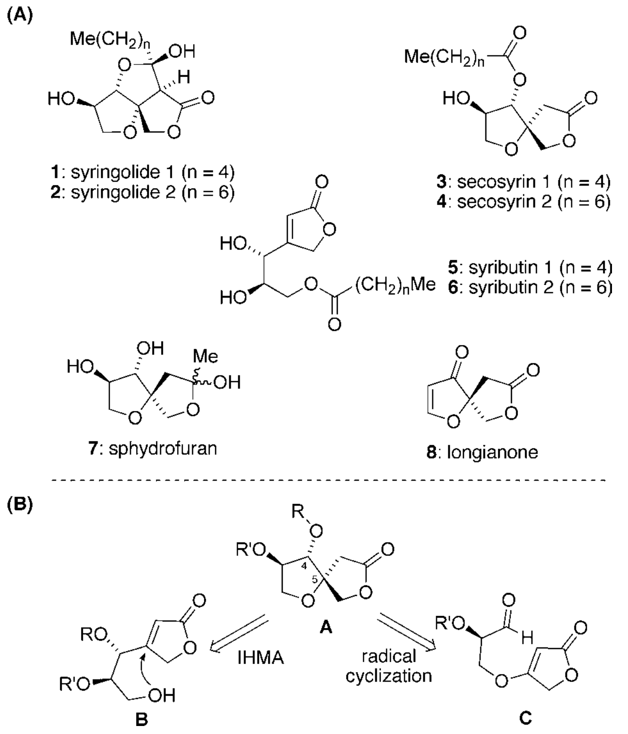

Figure 1. (A) Naturally occurring 1,7-dioxaspiro[4.4]nonanes and cometabolites. (B) Retrosynthesis of dioxaspirononanes using a "conventional" intramolecular hetero-Michael addition strategy and ketyl radical cyclization strategy.

the synthesis of dioxaspirononanes take advantage of the nucleophilic behavior of a tethered primary alcohol such as **B** (Figure 1B) that can undergo an intramolecular hetero-Michael addition (IHMA) to form the C–O bond of the spiro center in spirocycle **A**,[7b,f–h,8] in a reverse manner to that which is proposed to occur biosynthetically. We identified a less intuitive disconnection of the secosyrin dioxaspiro framework **A** that would involve a ketyl radical cyclization of substrate **C** to form the C4–C5 bond. This strategy would allow formation of the adjacent C4 (secondary alcohol) and C5 (spiro) stereocenters in a single step. With the existing C3 asymmetric center expected to impart favorable diastereocontrol during formation of the C5 center,[9] the ability to control the relative stereochemistry between the C4 and C5 centers is of importance. Samarium(II) iodide has become the reagent of choice for the formation of ketyl radicals;[10] however, use of SmI$_2$ commonly leads to a preference for the formation of *anti*-products upon cyclization with acrylate acceptors. This reagent may therefore not enable us to directly access the required *syn*-arrangement of alcohol and acetate substituents flanking the C4–C5 bond in **A**. Use of tributyltin hydride to generate ketyl radicals typically results in the formation of mixtures of diastereomers,[11] with the addition of Lewis acids also allowing *anti*-selectivity to be achieved.[12] However, we have demonstrated cases in which the use of tributyltin hydride can lead to preferential formation of *syn*-isomers from β-alkoxyacrylate systems.[13]

Despite the extensive use of ketyl radical cyclizations with acrylate acceptors,[10,14] the use of hindered β-disubstituted acrylate systems as ketyl radical acceptors appears to have been used on limited occasions.[15] To explore the proposed cyclization we first prepared the aldehyde substrate **13** (Scheme 1), anticipating that this model system would also give us access to longianone (**8**). Aldehyde **13** was obtained in three steps (64% yield) from alcohol **9** and acetylene **10**, the (*E*)-configuration being formed exclusively upon conjugate addition of **9** with **10** in the presence of PMe$_3$.[16] Heating a solution of **13** with tributyltin hydride (1.3 equiv) and AIBN (0.2 equiv) led to the formation of two products that were identified as the *syn*-**14** and *anti*-**15** substituted furans that were isolated in 34% and 38% yields, respectively, the less polar *syn*-product having undergone lactonization in situ.[17] Organotin byproducts from the reaction mixture were removed efficiently by filtration through a short column of 10% KF-silica prior to further chromatographic purification.[18] The *anti*-product **15** was then converted to dihydrolongianone (**17**)[6,19] by oxidation of the secondary alcohol using Swern conditions to form ketone **16** followed by deprotection of the primary alcohol using DDQ and acid-catalyzed lactonization (56% yield, three steps).[20] Dihydrolongianone has previously been converted to **8** by oxidation using

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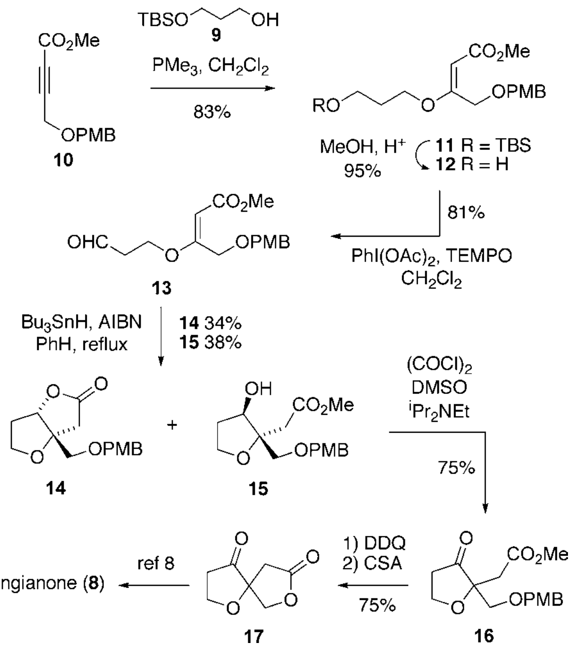
(20) The spectroscopic data for **17** were identical to material we had prepared previously via an acyl radical cyclization (ref 19) and also to the data reported for dihydrolongianone **17** formed by reduction of the natural product longianone **8** (ref 6).

IBX;[8] thus, preparation of **17** constitutes a formal synthesis of **8**.

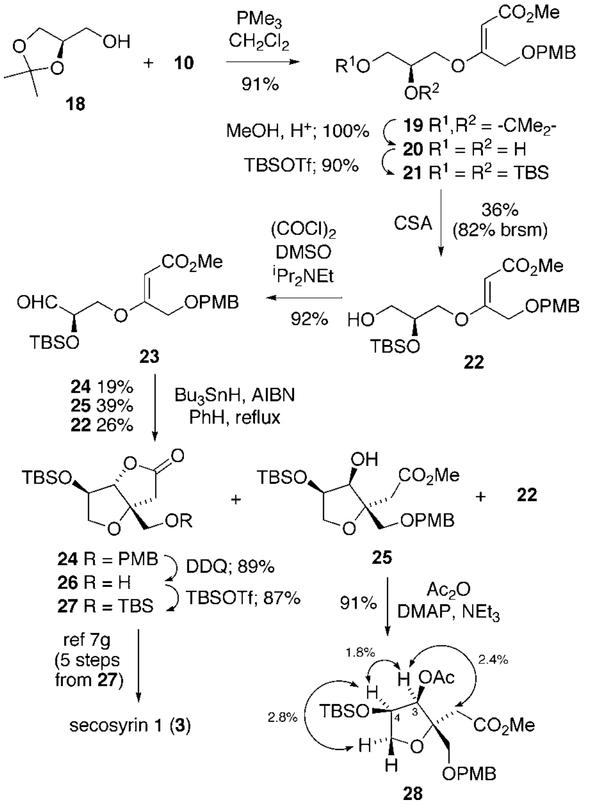
Scheme 1. Formal Synthesis of Longianone (**8**)



Having established the viability of using a ketyl radical cyclization approach for the synthesis of dioxaspiro systems, albeit without apparent diastereoselectivity, we continued with our plans for the synthesis of secosyrin 1 (**3**) using a similar strategy. Toward this end, the asymmetric protected triol **18** underwent addition to acetylene **10** to deliver the β-disubstituted acrylate **19** in 91% yield, exclusively as the *E*-isomer (Scheme 2). Protecting group interconversion involving first the removal of the acetonide (HCl/MeOH) to give the 1,2-diol **20**, bis-silylation using TBSOTf, and finally selective silyl group removal (CSA/CH_2Cl_2/MeOH) gave the primary alcohol **22** in 74% yield over the three steps. Oxidation of **22** using Swern conditions then delivered the (*R*)-configured aldehyde substrate **23** in preparation for cyclization.

Subjecting aldehyde **23** to *O*-stannyl ketyl radical forming conditions (Bu_3SnH/AIBN) led to the isolation of the *syn*- and *anti*-cyclized products **24** and **25**, respectively, having a combined yield of 58%. The stereochemical assignment for the *anti*-product **25** could be made confidently by acetylation of the secondary alcohol to give **28**, the product showing clear NOE correlations between the C3 methine proton and both the C4 methine proton and α-methylene protons (Scheme 2). The stereochemistry of the *syn*-product **24** was also confirmed by NOE analysis. Stereochemical control during formation of the quaternary centers in **24** and **25** may be explained by invoking a chairlike transition state for the radical cyclization.[9,21]

Scheme 2. Formal Synthesis of Secosyrin 1 (**3**)



The bis-silyl ether **27** has previously been converted over five steps to secosyrin 1 (**3**);[7g] thus, a straightforward exchange of the PMB protecting group in **24** for a TBS group delivers **27** (77%, two steps) and completes a concise formal synthesis of **3**. The spectroscopic data for the bis-silyl ether **27** obtained in this manner,[21] including specific rotation, are in complete agreement with the material prepared by Rao over 12 steps from D-mannitol.[7g,22]

In addition to the formation of cyclized products **24** and **25** from the ketyl radical cyclization reaction of aldehyde **23**, reduction of aldehyde **23** also took place to form alcohol **22**. Isolation of the alcohol **22** was unexpected given the simpler aldehyde **13** described above (Scheme 1) showed no evidence of competitive reduction taking place under similar conditions. With the expectation that formation of the alcohol **22** results from H-atom transfer from Bu_3SnH to the intermediate ketyl radical, with the rate of such a process being competitive with cyclization, the effect of tin hydride concentration was examined. However, little change in the product ratio was observed across a 10-fold concentration range.[21]

In an attempt to obtain evidence that directly identifies the source of hydrogen that leads to formation of alcohol **22** we resorted to deuterium-labeling experiments. Reaction of **23** with Bu_3SnD/AIBN led to the isolation of three products (Scheme 3). Analysis by both ^1H and ^{13}C NMR spectroscopy showed that the *syn*-product ***24-d*** contained

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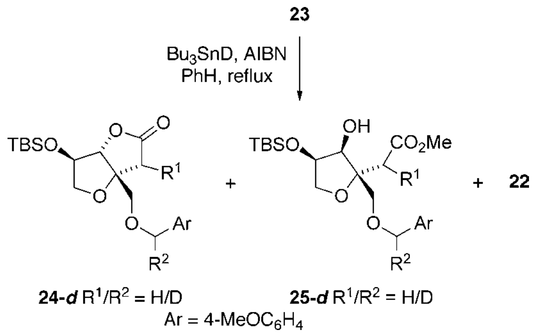
(21) See Supporting Information.

(22) Dr. B. V. Rao, Indian Institute of Chemical Technology, is thanked for providing the complete spectroscopic data for compound **27**, including specific rotation, not reported in the original publication (ref 7g).

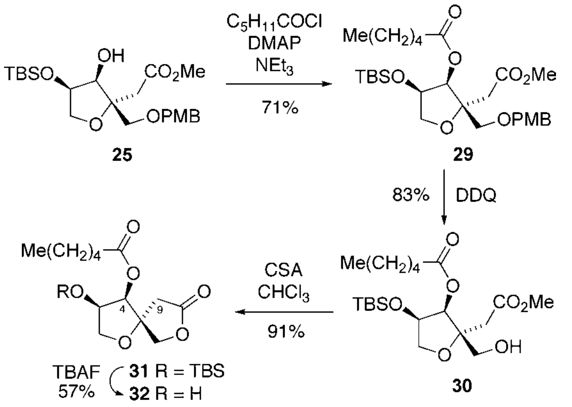
Scheme 3. Deuterium Incorporation into **24** and **25**



deuterium at the α-methylene or benzylic ether position in near equal amounts, while the *anti*-product **25-*d*** was deuterated almost exclusively at the benzylic ether position. Incorporation of deuterium at the benzylic position is likely to occur after initial cyclization, and a subsequent 1,5-hydrogen atom transfer takes place. Such a process closely resembles reported tandem radical reactions that have been used to prepare all-carbon spirocycles from similar β-disubstituted acrylate systems.[15b] However, the product of most interest from the radical cyclization, alcohol **22**, showed no incorporation of deuterium as determined by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass measurement. While not entirely efficient, it should be recognized that the alcohol **22** that results from this competing side reaction can simply be oxidized to regenerate aldehyde **23**, a notable advantage in the use of aldehydes as radical precursors, in comparison to alkyl halides, when competitive reduction of the substrate occurs.

The isolation of *anti*-furan **25** from the cyclization of aldehyde **23** gave us the opportunity to prepare a novel analogue of the secosyrins. Thus, acylation of **25** with hexanoyl chloride provided **29** in 71% yield (Scheme 4). Deprotection of the primary alcohol in **29** using DDQ gave **30**, which upon exposure to acid formed the dioxaspiro system **31** in 76% yield over the two steps. Finally, desilylation of **31** using TBAF gave alcohol **32** having $[\alpha]_D^{26}$ +27.3 (c 0.14, $CHCl_3$). NOE analysis of **32** showed a clear correlation between the deshielded C4 methine proton and the C9 methylene protons, confirming both the location of the acyl group and absolute configuration of the final product, 4-*epi*-secosyrin 1 (**32**).

Scheme 4. Completion of the Synthesis of 4-*epi*-Secosyrin 1 (**32**)



In summary, the formal syntheses of both (+)-secosyrin 1 (**3**) and longianone (**8**) have been achieved by applying a ketyl radical cyclization of β-disubstituted acrylate precursors. While the diastereoselectivity exhibited upon cyclization of model aldehyde **13** was not significant, the further functionalized substrate **23** exhibited a preference for the formation of the 2,3-*anti*-substituted furan **25**. Additionally, we have recognized this as an opportunity to access analogues of the naturally occurring compounds and thus completed a synthesis of (+)-4-*epi*-secosyrin 1 (**32**).

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **9**−**17** and **19**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.