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Stereoselective Synthesis of *cis*-2,5-Disubstituted Tetrahydrofuran-3-ones *via* an Acyl Radical Cyclization

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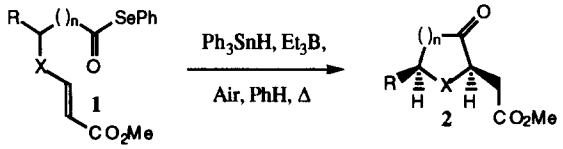
Abstract: *Treatment of the acyl selenide 7 with triphenyltin hydride and triethylborane generates the acyl radical which undergoes 5-exo trigonal cyclization to afford the 2,5-disubstituted tetrahydrofuran-3-ones* ***10a/b*** *in 97% yield as a 94 : 6 mixture of diastereoisomers.*

Tetrahydrofuran containing marine natural products continue to attract attention as biologically important synthetic targets, particularly with respect to polyether natural products.[1] Despite the emergence of a number of novel approaches to these structures,[2,3] the development of new methodology with increased skeletal and stereochemical flexibility continues. Recent reports in the literature on radical based approaches[4] have prompted us to report our results on an acyl radical[5] based strategy. We have initiated a program aimed at preparing a variety of oxygen, sulfur and nitrogen containing heterocycles. Our strategy involves a novel intramolecular addition of an acyl radical to an enol ether, enol thioether and enamine (**Scheme 1**).

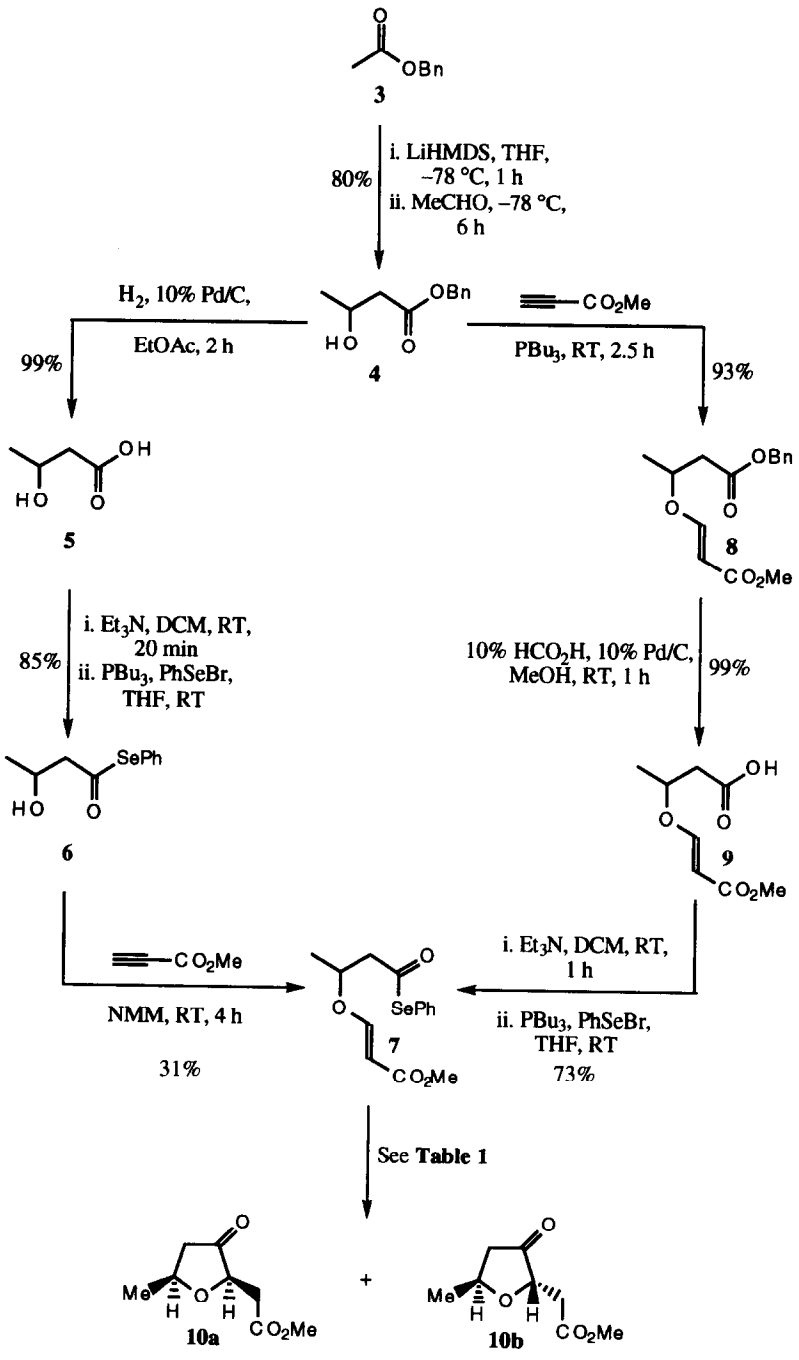
Scheme 1



X = O, S and NR
n = 1,2,3 etc.

In this letter, we report the first example of the intramolecular addition of an acyl radical to an enol ether to afford the corresponding *cis*-2,5-disubstituted tetrahydrofuran-3-one **10a** (**Scheme 2**). This methodology provides a stereoselective and efficient entry into this important class of molecules. Our strategy begins with the treatment of benzyl acetate **3** with lithium hexamethyldisilylazide to form the enolate, followed by the aldol condensation with acetaldehyde to afford the β-hydroxy ester **4** in 80% yield. Catalytic hydrogenation of the benzyl ester **4** with 10% palladium on charcoal afforded the carboxylic acid **5** in a quantitative yield. The carboxylic acid **5** was then converted to the acyl selenide **6**[6] in 85% yield *via* the Crich protocol.[7] However, attempted formation of the enol ether with the acyl selenide present proved rather problematic. Treatment of the alcohol **6** with methylpropiolate and *N*-methyl morpholine gave the enol ether **7**[6] in 31% yield.[8] Attempted optimization of the poor yield under a variety of reaction conditions proved futile.

Scheme 2


3
80%
i. LiHMDS, THF, −78 °C, 1 h
ii. MeCHO, −78 °C, 6 h
4
H2, 10% Pd/C, EtOAc, 2 h
99%
5
PBu3, RT, 2.5 h
93%
8
CO2Me
i. Et3N, DCM, RT, 20 min
ii. PBu3, PhSeBr, THF, RT
85%
6
10% HCO2H, 10% Pd/C, MeOH, RT, 1 h
99%
9
CO2Me
NMM, RT, 4 h
31%
i. Et3N, DCM, RT, 1 h
ii. PBu3, PhSeBr, THF, RT
73%
7
CO2Me
See Table 1
10a
10b
CO2Me

Therefore, an alternative strategy was devised in order to circumvent this problem. Treatment of the alcohol **4** with methylpropiolate and tributyl phosphine furnished the enol ether **8**[6] in 93% yield.[9] Transfer hydrogenation of the benzyl ester **8** with 10% palladium on charcoal and formic acid furnished the carboxylic acid **9**[6] in a quantitative yield.[10] The carboxylic acid **9** was then converted to the acyl selenide **7**[6] under analogous conditions in 73% yield.[7]

Table 1: Acyl Radical Cyclization Study for the Acyl Selenide **7**

Entry	*Reaction Conditions*[a]	*Ratio of* **10a/10b**[b]	*Yield (%)*[c]
1	Ph_3SnH, AIBN, Δ, 3 h	88 : 12	82
2	Bu_3SnH, AIBN, Δ, 2.5 h	85 : 15	94
3	Ph_3SnH, Et_3B, Air, RT, 96 h	≥ 95 : 5	63
4	Ph_3SnH, Et_3B, Air, Δ, 4 h	94 : 6	97

[a] All the reactions were carried out in benzene at a concentration of 0.011 M. [b] Ratios determined by ^1H NMR. [c] Isolated yields.

Table 1 summarizes the results from the cyclization of the acyl selenide **7** to the oxacycles **10a/b**.[6] Treatment of the acyl selenide **7** with triphenyltin hydride, delivered *via* a syringe pump, in the presence of AIBN afforded **10a/b** in 82% as a 88 : 12 ratio of diastereoisomers (Entry 1). The major diastereoisomer was assigned as the *cis*-2,5-disubstituted tetrahydrofuran-3-one **10a** from NOE studies. The yield was further increased at the expense of the diastereoselectivity when tributyltin hydride was employed (Entry 2). However, the major problem with the protocol was the practicality of employing a syringe pump, which would be particularly problematic for large scale preparative work. Clive and coworkers[11] have developed a very mild method for the formation of alkyl and acyl radicals which avoids syringe pump additions. Treatment of the acyl selenide **7** with triphenyltin hydride and triethylborane at room temperature in the presence of air, gave **10a/b** in 63% yield after several days as a ≥95 : 5 mixture of diastereoisomers (Entry 3). However, when the reaction mixture was heated at reflux the reaction was complete within 4 hours affording the oxacycles **10a/b** in a 97% yield as a 94 : 6 ratio of diastereoisomers (Entry 4).[12]

In conclusion, we have developed a highly efficient and stereoselective route to *cis*-2,5-disubstituted tetrahydrofuran-3-ones. Several methods are available for the preparation of enantiomerically pure β-hydroxy esters,[13] which should allow access to enantiomerically pure substrates. We are currently applying this methodology to other ring sizes and to the nitrogen and sulfur containing heterocycles.

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12. In a typical procedure the acyl selenide **7** (0.609 g, 1.86 mmol) was dissolved in anhydrous benzene (156 ml), protected from moisture by a drying tube packed with Drierite. Triphenyltin hydride (0.783 g, 2.23 mmol, 1.2 eq) was added in anhydrous benzene (20 ml) followed by triethylborane (2 ml, 2.0 mmol, 1.05 eq of a 1M solution in hexanes) and the mixture heated at reflux for 2 hours. The reaction mixture was cooled to ambient temperature and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with 1 : 4, 1 : 1, 7 : 3 Ethyl Acetate/ Hexane) furnished the *2,5-disubstituted tetrahydrofuran-3-one* **10a/b** (0.31 g, 97%) as a colorless oil in a 92 : 8 mixture of diastereoisomers.

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