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A NEW METHOD FOR THE PREPARATION OF 3,5-DISUBSTITUTED BUTENOLIDES

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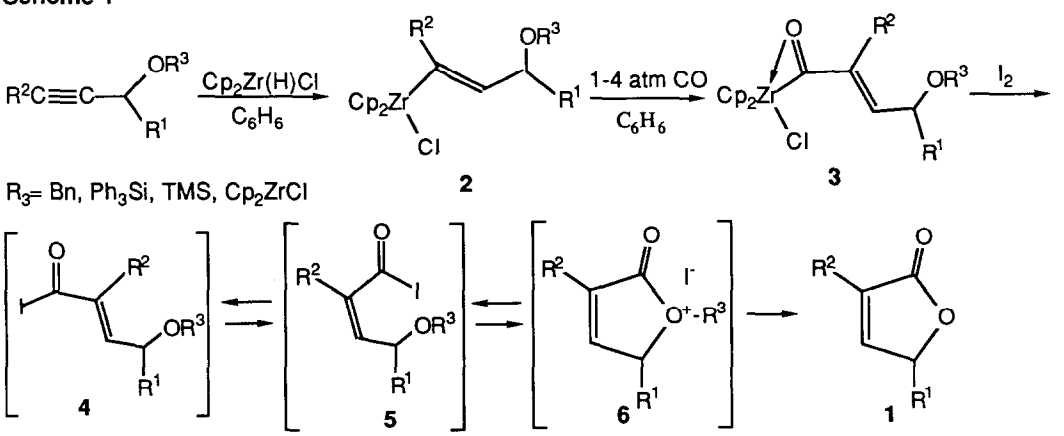
Summary: A convenient method for the transformation of suitably protected propargyl alcohols into 3,5-disubstiuted butenolides has been developed. This organozirconium-based method transforms optically active propargyl alcohols into the corresponding butenolides with no loss of optical activity.

The past few years have witnessed a flurry of activity in the area of butenolide synthesis.[2] In addition to the inherent interest in these molecules, they have been utilized as vehicles for the stereospecific construction of acyclic carbon chains bearing multiple chiral centers.[3] While many methods exist for the preparation of butenolides,[2,4] few allow for the preparation of the those versions substituted in both the 3 and 5 positions as in **1**. Of these, there are, to our knowledge, no general methods which have been demonstrated to give optically active butenolides of type **1**. We have developed a unique route to **1** from suitably protected propargyl alcohols to **1** as described below. Moreover, this methodology can be used to readily prepare optically active versions of **1**.

Shown in Scheme 1 is our method for the conversion of protected propargylic alcohols[5] into the butenolides **1**. Hydrozirconation of protected propargyl alcohol provides vinyl zirconocene **2** .[6]

Scheme 1



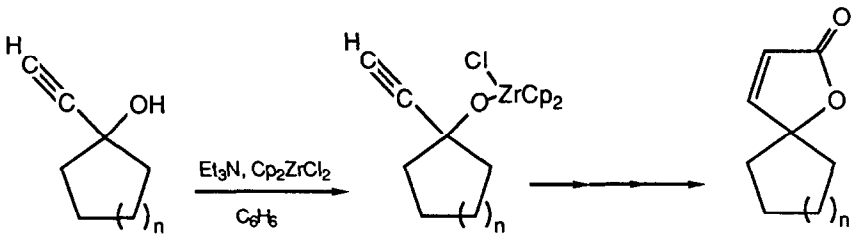
Without isolation this is carbonylated to give the corresponding acyl zirconocene complex **3**.[7] Both of these first two steps are carried out essentially as described by Schwartz in his pioneering work on hydrozirconation.[6,7] *In situ* treatment of **3** with I_2 provides the butenolides **1**, in good yield, for this one pot procedure, after standard organic workup and isolation by silica gel chromatography. We presume that the iodination of **3** produces the *E* α,β-unsaturated acyl iodide **4**. In the presence of excess I_2 **4** is in equilibrium with its *Z*-isomer **5**. The electrophilic nature of acyl iodides is well precedented and the acyl carbon in **5** is subjected to intramolecular nucleophilic attack by the adjacent ether oxygen to form the zwitterionic intermediate **6**. Loss of R^3I from **6** gives butenolide **1**. Not unexpectedly, benzyl alcohol and triphenylsilanol are produced during the aqueous workup of reactions in which R^3 is respectively,

benzyl or triphenylsilyl. A summary of our results are shown in Table 1. A wide variety of protecting groups can be utilized in this reaction sequence, the most generally useful being either the triphenylsilyl or benzyl groups.

It is noteworthy that we are able to form the intermediate acyl iodides **3** and **4** under essentially neutral conditions. These highly reactive species are usually formed under highly acidic conditions or by treatment of carboxylic acids with powerful Lewis Acids.[8] We are continuing to investigate the synthetic utility of acyl iodides generated under these mild conditions.

In entries 9 and 10, the free alcohol, in benzene, is treated with Cp_2ZrCl_2 in the presence of triethylamine (1 eq) to form the zirconium alkoxide **7** as shown in Scheme 2. Without isolation **7** is subjected to the hydrozirconation, carbonylation, iodination sequence to give the spirobutenolide

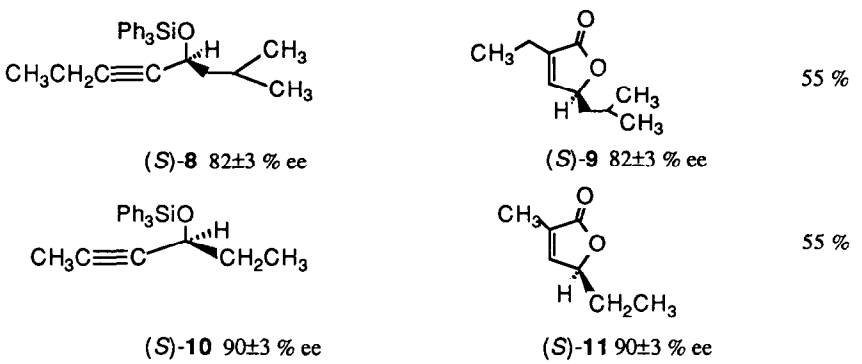
Scheme 2



products in 60% isolated yield.

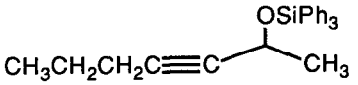
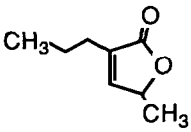
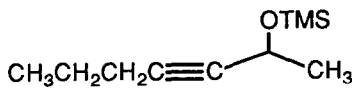
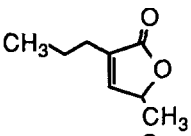
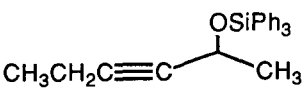
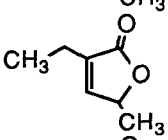
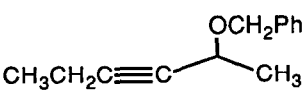
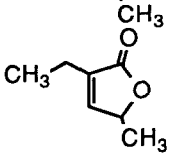
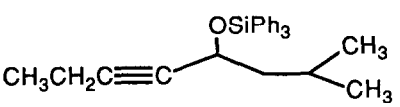
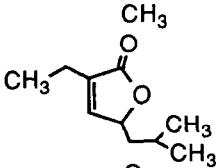
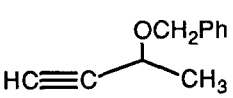
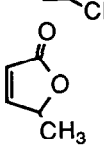
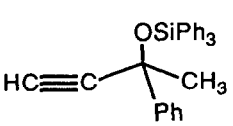
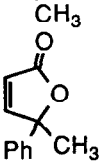
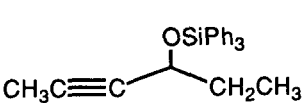
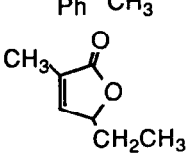
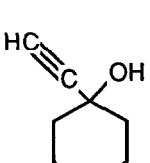
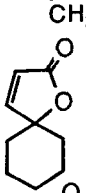
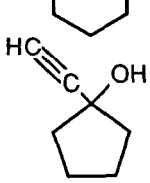
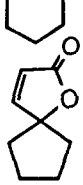
Of great practical importance was the determination that, starting with an optically active substrate, no loss of optical purity was experienced in going to the product **1**,[9] as is shown in scheme 3.

Scheme 3



In summary we have developed an efficient, one pot method for the conversion of protected propargyl acohols into the corresponding butenolides. This procedure allows the utilization of several different common protecting groups and in some instances the free alcohols can be utilized. We have shown that, if optically active substrates are employed, the product butenolides are produced with no loss of optical activity. Since these butenolides can serve as progenitors for a variety of stereospecifically substituted acyclic structures, this method should be a useful addition to the repertoire of synthetic organic chemists.

Table 1

Entry	Substrate	Product	Isolated Yield
1			72
2			55
3			70
4			53
5			55
6			50
7			62
8			55
9			60
10			60

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References and Notes

1. Dreyfus Grantee for Newly Appointed Faculty in Chemistry, 1984-89; American Cancer Society Junior Faculty Research Awardee 1987-89; Eli Lilly Grantee 1988-9; Alfred P. Sloan Research Fellow, 1988-90, Union Carbide Innovation Recognition Program Awardee, 1988.

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8. For a description of other methods used to prepare acyl iodides Cf. (a) Haase, K.; Hoffman, H.M.R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 83. (b) Hoffmann, H.M.R., Haase, K. *Synthesis*, **1981**, 715 and references therein.

9. **Representative procedure for the preparation of the butenolides of protected propargyl alcohols:** (R)-3-triphenylsiloxy-hex-4-yne (0.995 g, 2.79 mmol) **10** (90±3 % ee, see below) and $Cp_2Zr(H)Cl$ (0.791 g, 3.070 mmol) were weighed into a flame-dried Schlenk flask under argon. Benzene (30 mL.) was added and the pale yellow suspension was allowed to stir at room temperature for 16 h. During this time the solution became homogeneous and yellow-orange in color. The resulting solution was freeze-pump-thaw degassed and was allowed to stir under a carbon monoxide atmosphere at room temperature for 6 h. A solution of iodine (0.708g, 2.79 mmol) in benzene (20 mL) was added via cannula and stirring was continued at room temperature for 1 h. The reaction mixture was diluted with diethyl ether, the organic layer was washed with aqueous sodium sulfite,water and brine, dried over magnesium sulfate, filtered, and the solvent was evaporated at reduced pressure (160 mm Hg) to yield a yellow-brown oil admixed with white crystals of triphenylsilanol. The oil was diluted with pentane:diethyl ether (4:1) , and the white crystals were removed by filtration through a small plug of glass wool. The resulting product was the purified by radial plate chromatography using a Chromatotron 4mm silica gel plate, using a gradient of pentane:diethyl ether (9:1 to 7:3). The solvent was removed at reduced pressure to yield **11** as a pale yellow oil (1.93 g, 1.53 mmol, 55% yield, $\geq$98 % pure as determined by capillary GC and ^1H and ^{13}C NMR. Studies using NMR chiral shift reagents showed the product to have an enantiomeric excess of 90±3 %.^1H NMR ($CDCl_3$, 500 MHz) δ 1.00 (t, J= 7.5 Hz, 3H), 1.69 (m, 1H), 1.78, m, 1H), 1.92, t, J=1.5 Hz, 3H), 4.85, m, 1H), 7.04, m, 1H); ^{13}C NMR ($CDCl_3$, 125.4 MHz) δ 9.00, 10.52, 26.49, 82.05, 130.00, 148.41, 174.33; IR (NaCl, neat) 1662 cm^{-1}, 1755 cm^{-1}; M^+= 126.

The optical purity of both the starting material and product were determined by ^1H NMR using the commercially available chiral shift reagent tris[3-(heptafluoropropylhydroxymethyene)-(+)-tricamphanato], europium (III) derivative ($Eu(hfc)_3$) in dry benzene (1mL). The determination of the optimal ratio of substrate to shift reagent was made using racemic substrate. It should be noted that the optically active butenolides slowly racemize in the presence of the shift reagent.

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