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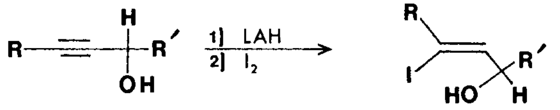
PALLADIUM CATALYZED SYNTHESIS OF BUTENOLIDES

A. Cowell and J.K. Stille*
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

A variety of $\Delta^{\alpha,\beta}$- butenolides occur naturally, and many have been shown to possess varied physiological properties.[1-3] We have developed a new synthetic route to these compounds starting from readily available acetylenic alcohols (Eq. 1 and 2).



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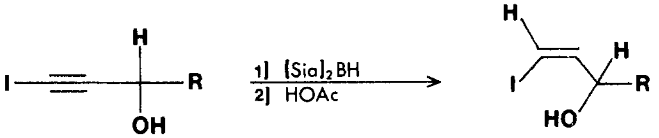

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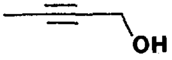
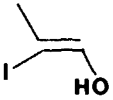
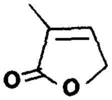
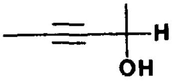
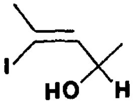
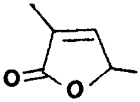
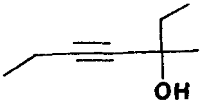
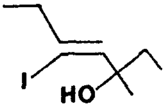
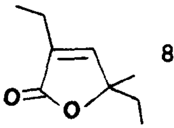
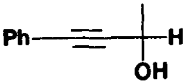
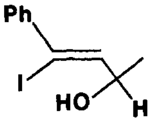
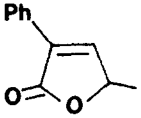
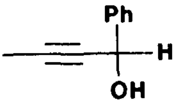
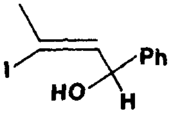
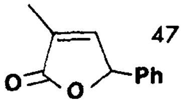
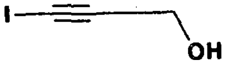
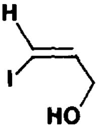
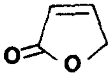
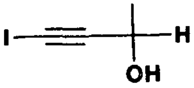
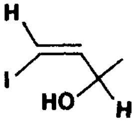
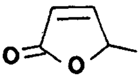
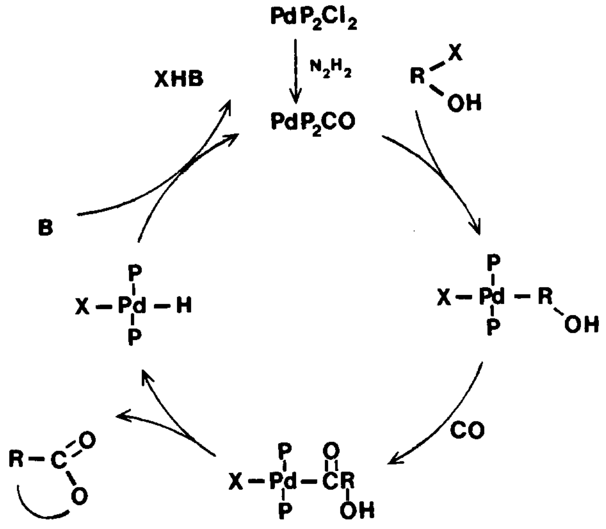
The addition of LAH to the acetylenic alcohol followed by iodination has been used for the synthesis of an iodoalcohol which is a precusor to farnesol.[4] This general procedure was carried out with a variety of acetylenic alcohols (Eq. 1) to afford the Z-vinyl iodides in good yield (Table 1). Unfortunately this method could not be used with terminal acetylenic alcohols so an alternate method (Eq. 2) involving the addition of an organoborane to an iodoacetylenic alcohol was employed.[5]

Vinyl halides undergo oxidative addition to palladium (0), yielding sigma bonded complexes with retention of configuration at carbon.[6] Carbon monoxide inserts into the palladium-carbon sigma bond, once again with retention of configuration at carbon.[7] The stereochemical integrity of this sequence is necessary for facile intramolecular attack by -OH.

TABLE 1

ACETYLENE	IODIDE	%	BUTENOLIDE	%
		71		100
		80		99
		49		85
		80		68
		66		47
		63		76
		80		95

This sequence of events, oxidative addition, insertion of carbon monoxide, and cleavage by R-OH, is known to occur when an organic halide is allowed to react with carbon monoxide in an alcohol solvent with a catalytic amount of palladium(0) (Scheme 1). The mild reaction conditions (25°C,1-3 atm CO) allow the presence of a wide variety of other functional groups on the organic halide.



Scheme 1

The $\Delta^{\alpha,\beta}$- butenolides prepared *via* this method are listed in Table 1. The palladium(0) is generated *in situ* by reduction of a palladium(II) complex with hydrazine. In addition a base is needed in order to remove the acid generated in the reaction so that the palladium(0) complex will survive the reaction and give a high turnover.

The following procedure illustrates the general method for converting the iodoalkenol to the corresponding butenolide.

Into a carbonylation flask were placed 0.0230g(0.0328 mmol) of $PdCl_2(PPh_3)_2$ and 0.552g of potassium carbonate. The flask was evacuated, filled with argon, and then connected to a carbon monoxide line. After the flask was pressurized several times with carbon monoxide, 10ml of deoxygenated THF was added via a syringe. To this slurry was added 0.848g(4.00 mmol) of 4-iodo-pent-3-ene-2-ol (prepared as described in ref. 4) followed by one drop of hydrazine, both added by means of a syringe. The mixture was then stirred at 35° under 2 atm. carbon monoxide. After 2 days, 30ml of ether was added and the mixture was filtered. The solvents were removed *in vacuo* and the residue was distilled in a Kugelrohr apparatus to afford 0.442g (3.95 mmol, 99%) of 2(5H)-3,5-Dimethylfuranone (^{1}H nmr 1.4 d 3H, 1.8 t 3H, 5.0 q/t 1H, 7.05 p 1H δ; ^{13}C nmr 10.4 g, 19.0 g, 77.5 d, 128.6 s, 150.8 d, 173.8 s ppm; ir $\nu_{C=O}$ 1770 cm^{-1}).

The butenolides formed by this method may be further functionalized by reaction of their lithium salts with aldehydes, organic halides, and Michael acceptors.[9] By using these methods, a large number of highly substituted butenolides may be synthesized in just a few steps. In addition, butenolides may be readily reduced providing a route to a variety of substituted furans.[10]

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References and Notes

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