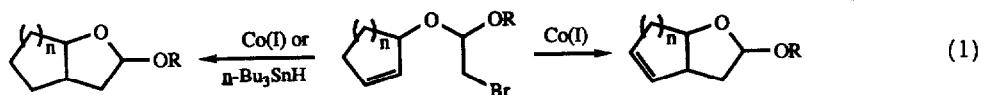


SYNTHESIS OF UNSATURATED BICYCLIC LACTONES AND ACETALS VIA PALLADIUM-PROMOTED
 CYCLIZATION OF CYCLIC ALLYLIC ALCOHOLS

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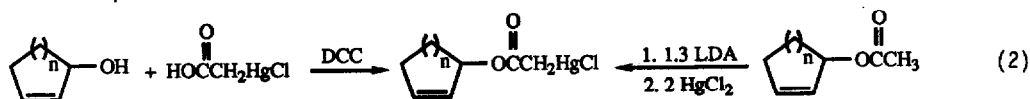
Summary: Unsaturated bicyclic lactones are readily prepared by converting cyclic allylic alcohols to the corresponding α -chloromercurio acetate esters and reacting them with Li_2PdCl_4 . The corresponding acetals can be synthesized directly by reaction of the allylic alcohols with ethyl vinyl ether and $\text{Pd}(\text{OAc})_2$.

Bicyclic lactones or acetals are evident in many natural products and have proven extraordinarily valuable as intermediates in many total syntheses. Considerable interest has been exhibited in free radical¹⁻³ and cobalt⁴⁻⁷ approaches to bicyclic acetals (eq. 1), but only



recently has the free radical approach, through atom transfer cyclization, been extended to the preparation of related lactones.⁸ It occurred to us that organopalladium chemistry might provide a direct entry into both the unsaturated acetals and lactones. We wish to report at this time the success of those endeavors.

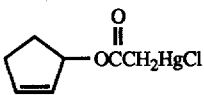
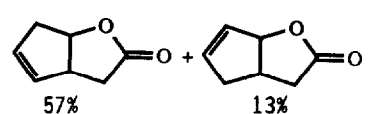
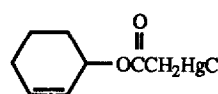
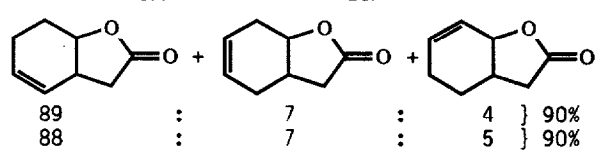
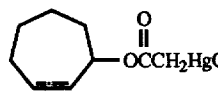
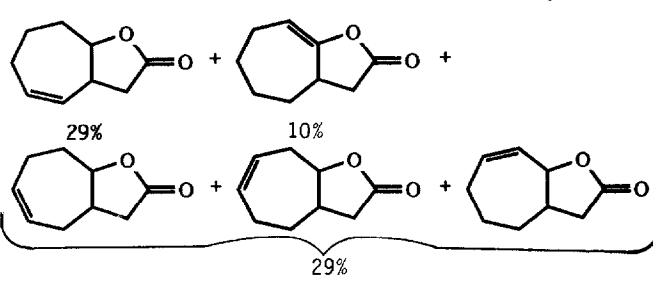
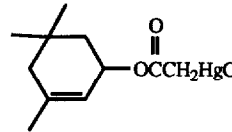
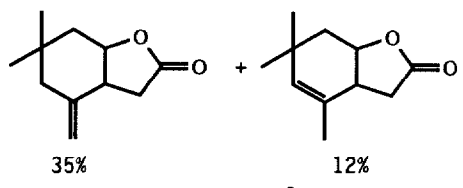
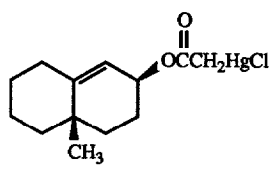
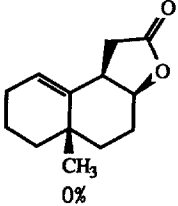
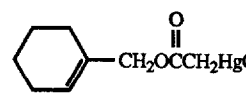
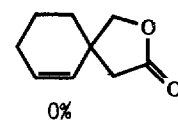
We first examined the preparation of the unsaturated lactones. α -Chloromercurio acetate esters, readily prepared by either dicyclohexylcarbodiimide (DCC)⁹ condensation of cyclic allylic alcohols and α -(chloromercurio)acetic acid¹⁰ or mercuriation of the corresponding acetate ester enolates (eq. 2), appeared to be ideal precursors to the desired organopalladium intermediates. While substrate dependent, the yields of organomercurials are generally high using one of these procedures.



We next examined the palladium-promoted cyclization of these organomercurials. A variety of reaction conditions were examined, but best results were obtained using 0.5 mmol of organomercurial, 0.5 mmol PdCl_2 , 1.0 mmol LiCl , and 1.0 mmol Et_3N in 10 ml of THF and 2 ml of either HMPA or DMF at room temperature. The results are summarized in Table I.

While a variety of ring systems undergo the desired lactonization, generally in reasonable yield, virtually every possible regioisomeric unsaturated lactone was obtained. Endocyclic and exocyclic double bond formation was also observed in a purely statistical ratio (Table I, entry 5; 3 hydrogens on the methyl versus 1 methylene hydrogen syn to palladium)

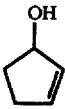
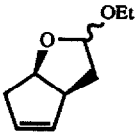
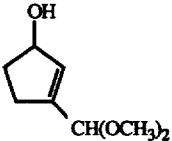
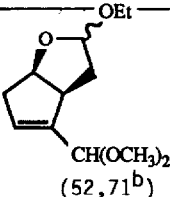
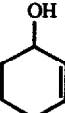
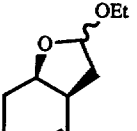
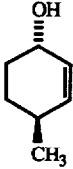
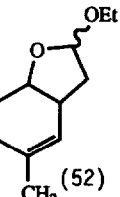
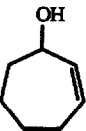
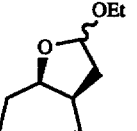
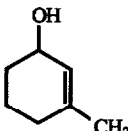
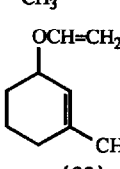
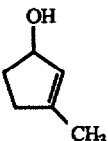
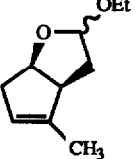
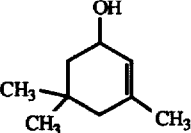
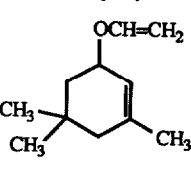
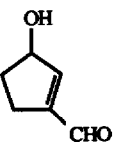
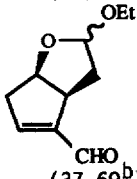
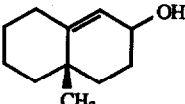
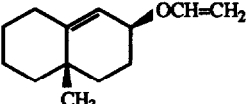
Table I. Synthesis of Bicyclic Lactones

Entry	Organomercurial	Solvents	Time	Products (isolated yield)
1		THF/HMPA	4 d	
2		THF/HMPA	4 d	
3		THF/DMF	4 d	
4		THF/HMPA	4 d	
5		THF/DMF	30 h	
6		THF/DMF	7 d	
7		THF/DMF or THF/HMPA	1 d	

Increasing the steric hindrance about the carbon-carbon double bond (entry 6) or substitution on the double bond (entry 7) completely inhibited cyclization. It appears that this approach to bicyclic lactones is limited synthetically to those systems where double bond isomerization is either acceptable or impossible.

The desired isomer undoubtedly arises by organopalladium formation, syn organopalladation of the double bond, followed by syn beta hydride elimination, while isomers arise by palladium hydride readdition and elimination (Scheme I). So far we have been unsuccessful in preventing such isomerization. Isomerization is clearly due to the presence of mercury in a way we do

Table II. Synthesis of Bicyclic Acetals^a

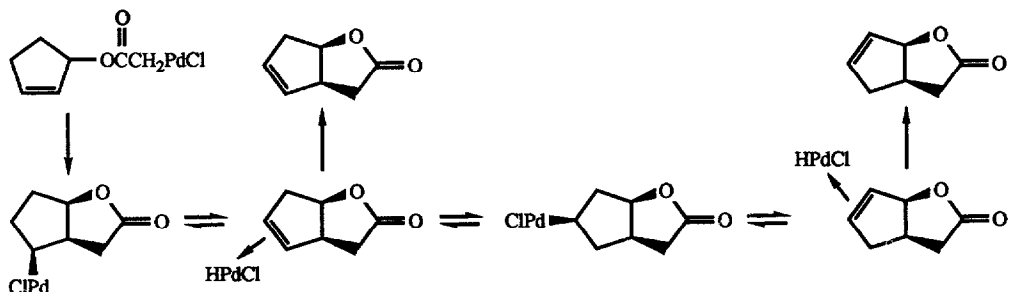
Entry	Allylic Alcohol	Product (% Isolated Yield)	Entry	Allylic Alcohol	Product (% Isolated Yield)
1		 (56)	6		 (52, 71 ^b)
2		 (70)	7		 (52)
3		 (60)	8		 (39)
4		 (27)	9		 (40)
5		 (37, 69 ^b)	10		 (47)

^aPd(OAc)₂ (1.0 mmol) was added to the allylic alcohol (1.0 mmol) dissolved in 1 ml of ethyl vinyl ether at 0°C. The ice bath was removed and the reaction stirred at room temperature for 2 h. Hexanes (20 ml) and pyridine (0.2 ml) were added, the solution filtered and concentrated, and the oil was purified by column chromatography.

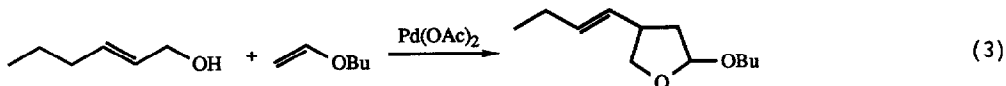
^bReactions run on a 3.17 mmol scale using 31 mmol EtOCH=CH₂, 1.27 mmol Pd(OAc)₂, 7.93 mmol Cu(OAc)₂ and 7 ml CH₃CN.

not fully understand at present. Efforts to make the reaction catalytic in palladium by adding CuCl₂ as a reoxidant for palladium have also met with limited success, as catalytic turnovers of only 3 were achieved.

Scheme I



Our limited success with the organomercurial approach to bicyclic lactones has encouraged us to examine palladium approaches to the corresponding acetals. During the course of our organomercurial work, Utimoto and co-workers reported that the reaction of acyclic allylic alcohols, vinyl ethers and $\text{Pd}(\text{OAc})_2$ afforded good yields of 2-alkoxy-4-alkenyltetrahydrofurans (eq. 3).¹¹ This chemistry looked extremely promising for the preparation of the desired



bicyclic acetals. Indeed, cyclic allylic alcohols undergo facile coupling with ethyl vinyl ether and $\text{Pd}(\text{OAc})_2$ to afford the corresponding acetals in reasonable yield (Table II).

In general, the vinyl ether approach affords bicyclic acetals in good yields from a variety of cyclic allylic alcohols. No double bond isomerization is observed. Allylic alcohols with more hindered double bonds tend to give vinyl ethers as the major product of the reaction (Table II, entries 8-10). It is important to point out that these reactions can be carried out in good yield using only catalytic amounts of $\text{Pd}(\text{OAc})_2$, if $\text{Cu}(\text{OAc})_2$ is added as a reoxidant for palladium (see Table II, entries 5 and 6). This chemistry has recently proven valuable in the total synthesis of the iridoid hydroxysemperoside deglucoside,¹² and in our own work on the synthesis of prostaglandins.¹³ We believe it should prove useful in the synthesis of a wide variety of naturally-occurring substrates.

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