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Construction of α-alkylidene-γ-butyrolactones from acyclic ester precursors

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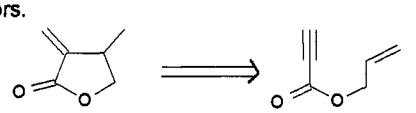
Abstract ---- Divalent palladium catalyzed cyclization of allylic alkynoates were studied. α–Alkylidene–γ–butyrolactones were produced highly regio- and stereoselectively. Controlling factors on the stereochemistry of exocyclic double bonds and β,γ–substituents were carefully studied. Bicyclic α-alkylidene-γ- lactones were also synthesized using this method. A convenient and potentially useful methodology is provided for the synthesis of natural products.

INTRODUCTION

The α-methylene-γ-butyrolactone ring is an integral building block of many natural products, especially the sesquiterpene lactones which show a broad range of biological activities, such as cytotoxicity, antitumority, etc., however, none is used clinically at present because of their high toxicity (ref. 1). Thus, new methods for the synthesis of compounds containing α–methylene-γ-butyrolactone rings for screening are needed. Generally the α-methylene lactones are synthesized by α-methylenation of preformed lactones, by oxidation of α-methylene cyclobutanone or α-methylenetetrahydrofuran, or by lactonization of functionalized acyclic precursors(ref. 2). There are reports on palladium-catalyzed cyclocarbonylation of hydroxy-substituted vinyl halides (ref. 3), cyclization of homoallylic carbonochloridates (ref. 4) and the reaction of alkynyl alcohols with nickel carbonyl (ref. 5) to construct the α-methylene-γ-butyrolactones. This lactone ring can also be built up by radical cyclization of allylic alkynoates, albeit in poor yield (ref. 6).

We are interested in the method of assembling the α-methylene-γ-butyrolactone ring by carbon-carbon bond formation which is quite different from the other methodologies reported (ref. 1,2). Should this be possible, the α-methylene-γ-butyrolactones could be constructed conveniently from the easily available unsaturated allylic ester precursors.

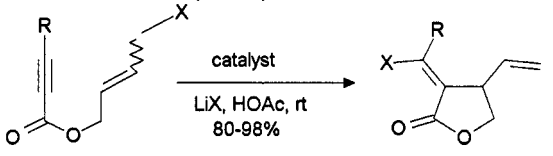


Recently, much attention has been focused on the transition metal catalyzed cyclization of dienes, enynes and diynes (ref. 7), however, the transition metal(0) or transition metal hydride catalyzed cyclization of unsaturated allylic esters that would lead to lactones has not been studied, probably due to the possibility of allylic carbon-oxygen bond cleavage by the low valent transition metal catalysts or by the transition metal hydride (ref. 8). Therefore, to find a catalyst for cyclization of allylic unsaturated esters, a low valent metal complex that would lead to the allylic carbon-oxygen bond cleavage of the allylic ester must be avoided. In the literature where a divalent palladium complex is the catalytically active species, zero valent palladium is usually formed during the reaction and is reoxidized by oxidants to complete the catalytic cycle (ref. 9). In some cases, the divalent palladium complex is used in stoichiometric amount (ref. 10). Kaneda et al. reported the bis(benzonitrile)palladium dihalide catalyzed codimerization of alkynes and allylic halides in which the divalent palladium was regenerated by dehalopalladation (ref. 11), which occurred to us that it might be possible to form α-methylene-γ-butyrolactones from molecules that contain both a carbon-carbon triple bond and an allylic halide unit.

SYNTHESIS FROM HALOALLYLIC 2-ALKYNOATES

We found that 4'-halo-2'-alkenyl 2-alkynoates (**1**) cyclize smoothly under the catalysis of bis (benzonitrile) palladium dihalide or palladium acetate and lithium halide in acetic acid at room temperature to give α-haloalkylidene–β-vinyl-γ-butyrolactones (**2**) in high yields (ref. 12).

The chloro- and bromoderivatives gave higher yields than the iododerivatives. While no clear reaction occurred for the acetoxy derivatives using palladium acetate/lithium acetate as the catalyst, the reaction of acetoxymethylallylic 2-alkynoates (**1**, X=OAc) gave same products as the haloderivatives under the catalysis of palladium acetate and lithium halide (ref. 13).

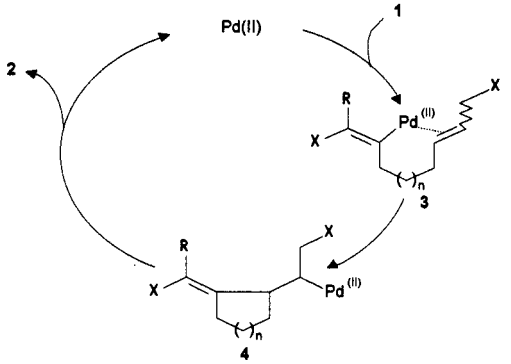


1(Z or E) X=Cl, Br, I, OAc **2** (1)

Mechanism

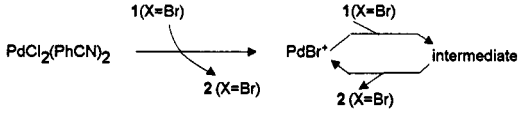
The present reaction might occur through a mechanism similar to that of the codimerization of acetylene and allylic halide proposed by Kaneda et al. (ref. 11). This would involve an intramolecular insertion of the allylic carbon-carbon double bond into the carbon-palladium bond in the vinyl palladium intermediate formed by the halopalladation of the carbon-carbon triple bond, followed by dehalopalladation to yield **2** and the catalytically active divalent palladium species.

Scheme 1



The halogen atom in **2** comes from the allylic halogen atom in **1** was illustrated by the fact that the bromolactone (**2**, X=Br) was isolated in 70% yield from the reaction of the bromo derivatives (**1**, X=Br) even 5 mol % of $PdCl_2(PhCN)_2$ was used as the catalyst. As soon as the reaction is initiated, the palladium bromide species formed by dehalopalladation during the reaction plays the main role and enters the catalytic cycle together with the minute amount of the originally added palladium dichloride to complete the catalytic process.

Scheme 2



Selectivity

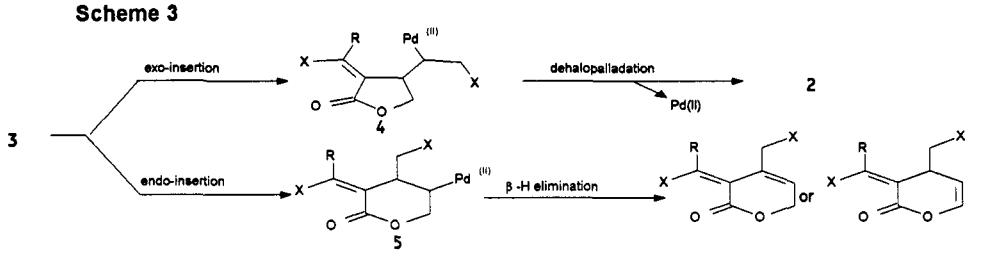
The exocyclic double bonds were formed highly stereoselectively in Z-configuration for the unsubstituted 2-alkynoates, while for alkynoates with substitutents on the carbon-carbon triple bond, the reaction afforded products with low (Z)-stereoselectivity. The stereoselectivity of Z-configuration can be improved when more lithium halide was added. The addition of lithium halide and use of polar solvents in halopalladation of unsaturated carbon-carbon bonds usually favor *trans* halopalladation (ref. 11, 14), which is in accordance with our previous work of electron-deficient alkynes (ref. 15). But in this case, even the sluggish reaction in benzene afforded the trans halopalladation product implying that the high stereoselectivity might also be attributed to another factor. Thus, coordination of palladium with the carbon-carbon multiple bonds in **1** to form a palladium-enyne complex is suggested. The formation of a palladium-enyne complex favors the attack of halide ion from outside of the coordination sphere which would be expected to give *trans* halopalladation (ref. 14, 16). The fact that bis(triphenylphosphine)palladium dichloride failed to catalyze this cyclization is probably due to the stronger coordination ability of triphenylphosphine compared to that of benzonitrile.

The stereochemistry of the exocyclic carbon-carbon double bond and the formation of the five membered ring **2** as the sole product show that the halopalladation step is not only highly stereoselective (*trans*), but

also highly regioselective. Being an electron-withdrawing group, the ester group directs the palladium to the α-carbon atom of the alkynoates, which leads to the five-membered ring instead of a six-membered ring.

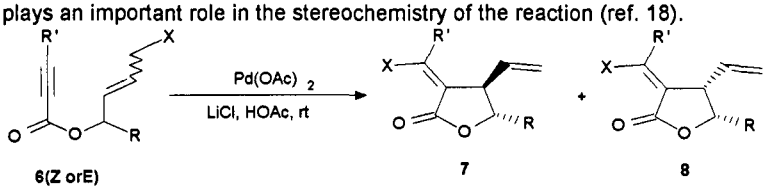
Regioselective exo-intramolecular insertion of the allylic carbon-cabon double bond to the carbon-palladium bond in **3**, forms a new palladium intermediate **4**, which affords **2** through dehalopalladation. The possibility of dehalopalladation might also be one of the factors controlling the direction of insertion. The endo-insertion would form a six-membered intermediate **5**, including a carbon-palladium bond incapable of dehalopalladation (**Scheme 3**), thus, a catalytic cycle could not be formed. This result is in accordance with the fact that dehalopalladation, deacetoxypalladation and dehydroxypalladation are faster than the β-hydride elimination (ref. 12, 13, 17).

Scheme 3



Stereochemistry of cyclization

Next, we wonder which kind of stereoinduction would occur on the relative configuration of the carbon atom at β-position of the lactone ring, if a substituent is introduced into the 1'-position of the 2-alkenyl group of **1**. We began our research with 1'-methyl-4'-chloro-2'(E)-butenyl 2-propynoate (**(E)-6a**) under the catalysis of 5 mol % of palladium acetate in acetic acid. The reaction did afford a pair of diastereoisomers **7a** (*trans*) and **8a**(*cis*) with an isolated ratio of 70:30. But, occasionally, it was found that **(Z)-6a** afforded 7a highly stereoselectively (**7a:8a**>96:4). This result implies that the configuration of allylic carbon-carbon double bond in **6** plays an important role in the stereochemistry of the reaction (ref. 18).



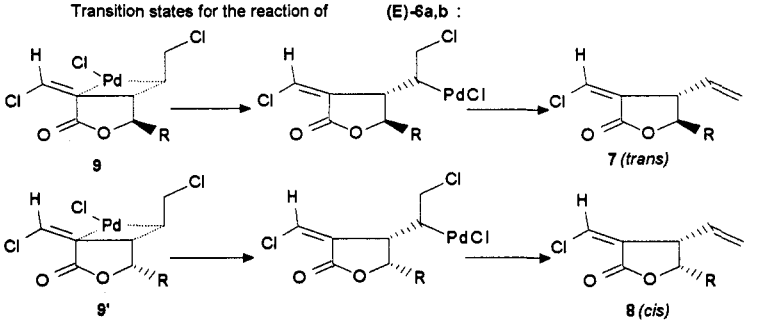
6(Z orE)

X=Cl, OAc **7** **8**

a: R'=H, R=Me b: R'=H, R=i-Pr (2)

Scheme 4

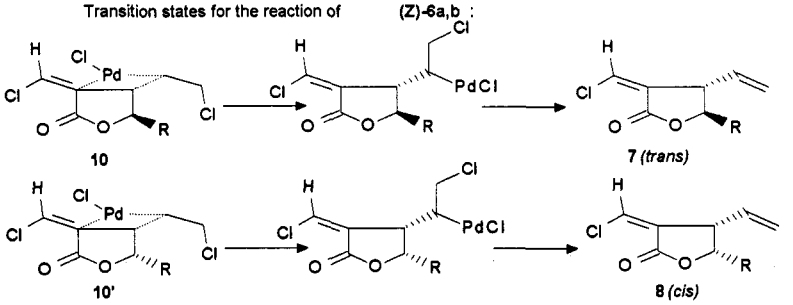
Transition states for the reaction of (E)-6a,b :



9 **7** *(trans)*

9' **8** *(cis)*

Transition states for the reaction of (Z)-6a,b :

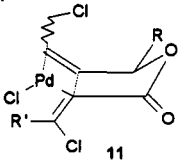


10 **7** *(trans)*

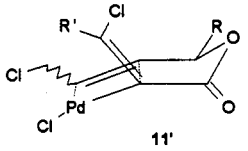
10' **8** *(cis)*

The stability of the transition states for the insertion reaction might be responsible for the unique stereochemical behavior. In a seven-membered metallocyclic transition state (**Scheme 4**), in order to insert the carbon-carbon double bond into the carbon-palladium bond, these two bonds should be as close as possible and in a position favoring the intramolecular insertion reaction. In the transition states of the reaction of **(E)-6a,b**, the energy difference between **9** and **9'** is not very large, while in that of **(Z)-6a,b**, **10** is obviously more favorable than **10'** due to the steric hindrance present in **10'**. Thus, **(Z)-6a,b** afforded the *trans* products **7a,b** highly diastereoselectively via the transition state **10**.

Interestingly, in contrast to the unsubstituted propynoates, in the cyclization of substituted 2-alkynoates, *cis*-product **8** were obtained stereoselectively. Thus, the substituents at the 3-position of **6** might play an important role in the unique stereochemical behavior. As revealed by molecular models, in a similar cyclic seven-membered transition state as in **Scheme 4**, or in other representation as in the chair-like conformation **11'**, in addition to the possible interaction between the halogen atom and the ring oxygen atom, the substituent R' and the chloromethyl group might make the transition states (similar to **9, 10** and **11'**) more crowded when the exocyclic double bond is in Z configuration. Thus, for 3-substituted 2-alkynoates, a cyclic seven-membered transition state **11**, which places more of the substituents in favorable pseudoequatorial position, might provide a rationale for the observed diastereoselectivity.



11



11'

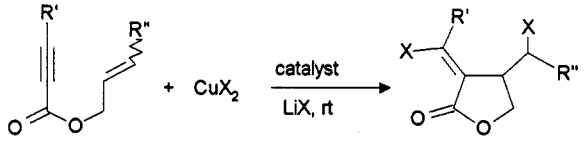
The stereochemistry of the cyclization can be summarized as follows (ref. 13, 18):

Starting materials **(6)**	Configuration	
R'	exo C=C	β,γ
H	Z	*trans*
alkyl	Z (excess LiCl)	*cis*

Thus, we can control the stereochemistry of β,γ-substituents on the lactone ring. The unsubstituted 2-alkynoates afford *trans* form **7** while the substituted 2-alkynoates give the *cis*-form **8** diastereoselectively.

SYNTHESIS FROM ALLYLIC 2-ALKYNOATES

In the above mentioned reaction, in order to regenerate the catalytic divalent palladium species by dehalopalladation, a halomethyl group or acetoxymethyl group is necessary in the starting material **1**. We found that by the addition of cupric halide, the palladium intermediate can be trapped by another pathway to yield the α-alkylidene-γ-butyrolactone derivatives. Thus, a procedure for the synthesis of the title compound from very easily available acyclic ester precursors, 2'-alkenyl 2-alkynoates, was developed.



12(Z or E) R'=H, alkyl; R"=H, alkyl; X=Cl, Br **13** **(3)**

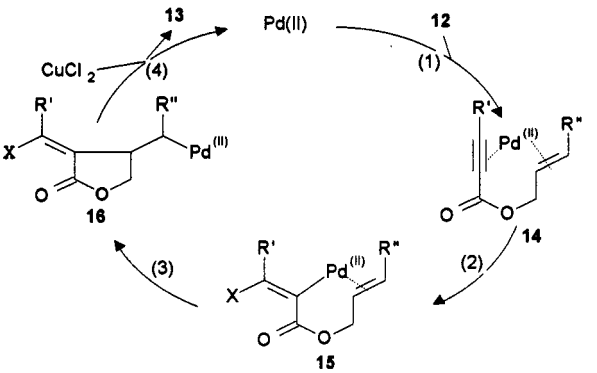
The cyclization occurred smoothly at room temperature by the Pd catalyst in the presence of cupric halide and lithium halide. For reaction of cupric chloride $PdCl_2(PhCN)_2$ in acetonitrile was used as the catalyst while $Pd_2(dba)_3{\cdot}CHCl_3$ in acetic acid was used as catalyst for the reaction of cupric bromide. Both reactions gave the analogous product **13** in moderate (R'=H) to high (R'=alkyl) yields (ref. 19).

The mechanism of the reaction might be similar to that described in **Scheme 1**. Compound **12** first coordinates with Pd and/or Cu to form a metal-enyne complex **14**, and subsequent stereoselective halopalladation in the presence of CuX_2 affords the intermediate **15**, followed by intramolecular insertion of the C=C bond into the C-Pd bond to afford **16**, which through formation of a C-X bond (ref.20) yields product **13** and regenerate the Pd(II) species **(Scheme 5)**.

Stereoselectivity

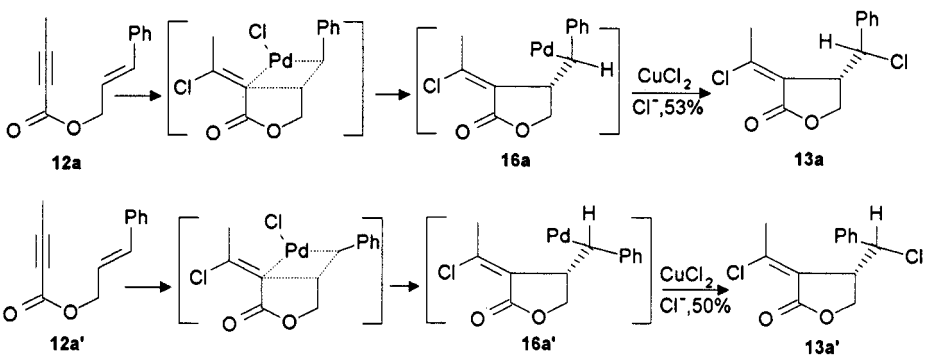
Sterechemistry of the exocyclic C=C bond. Surprisingly, the cyclization of unsubstituted propynoates shows E-selectivity, which is different from the reaction of **1** to **2**, while cyclization of substituted 2-alkynoates shows Z-selectivity. The difference in stereochemistry of the exo C=C bond implies that cupric chloride might participate in the halopalladation step. The different stereochemical results of unsubstituted propynoates and substituted 2-alkynoates might be due to their different reaction behavior to cupric halide or CuX_2-$PdCl_2$ complex.

Scheme 5



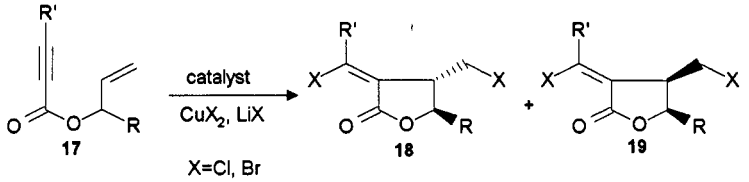
Stereochemistry of oxidative cleavage. The mechanism of cleavage of a C-Pd bond by $CuCl_2$ has been extensively studied (ref. 21), but is still unclear. We have used tert-butyl nitroxide to try to capture the possible radical intermediate. No radical signal was detected by an ESR study. As to the stereochemistry of step 4 of **Scheme 5**, we chose 3'-phenyl-2'(Z)- (or 2'(E))-propenyl 2-butynoate (E isomer, **12a**; Z isomer, **12a'**) as model compounds. Under the same conditions, **12a** and **12a'** afforded different products **13a** and **13a'**, respectively. Compounds 13a and 13a' showed not only the same MS molecular ion but also the same analytical data, indicating that **13a** and **13a'** might be a pair of diastereoisomers of the γ-butyrolactone products. The stereochemistry of the insertion of a C=C bond into a C-Pd bond is believed to be *cis* (ref. 22); thus the relative configuration of intermediates **16a** and **16a'** are as shown in **Scheme 6**. Unfortunately, the configurations of **13a** and **13a'** could not be exactly assigned from their ^1H NMR and ^1H 2D NOESY spectra. Anyhow, the fact that isolation of a pair of diastereoisomers **13a** and **13a'** from the E,Z isomers **12a** and **12a'**, respectively, are inconsistent with those expected for a radical cyclization (ref. 23). From Bäckvall's results (ref. 24), the oxidative cleavage of the C-Pd bond by cupric chloride occurs with inversion in the presence of excess chloride ion. Another possible pathway is the attack of chloride ion on the metal, followed by reductive elimination to give **13** and Pd(0) which is oxidized by $CuCl_2$ to regenerate the divalent palladium catalytic species (ref. 20). Configurations of **13a** and **13a'** are tentatively assigned according to Bäckvall's results as shown in **Scheme 6**. This might be the reason why substituted allylic esters **12** ($R^"$=alkyl or phenyl) always give the product **13** as a single diastereoisomer. Thus, the relative stereochemistry of the diastereoisomers can be controlled by changing the configuration of the allylic double bond. The bromo analogs behave similarly.

Scheme 6



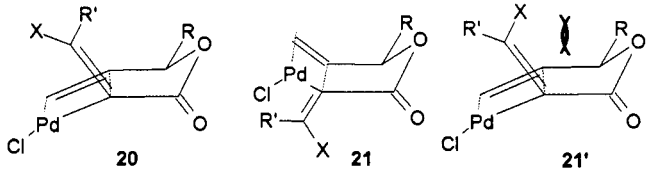
Stereochemistry of cyclization. The stereochemistry of the cyclization is the same as that described in the cyclization of **6**. The unsubstituted allylic propynoates **17a** gave *trans*-β,γ-disubstituted lactones **18a**, while the substituted allylic 2-alkynoates **17b** gave *cis*-β,γ-disubstituted lactones **19b**.

It should be noted that the configuration of the exocyclic C=C bond here may influence the β,γ-configuration of the products. For (E) exocyclic double bond, it is easy to realize from the seven-membered transition states (**20**) that the product is favorable in *trans* configuration. While for (Z) exocyclic double bond, there might exist an interaction between the halogen atom and the ring oxygen atom in the chair-like transition state **21'**, thus a boat-like transition state **21** (similar to **11**) which places more of the substituents in pseudoequatorial position may be responsible for the reaction.



(4)

	R'	Configuration	
		exo C=C	β, γ
a:	H	E	*trans*
b:	alkyl	Z	*cis*

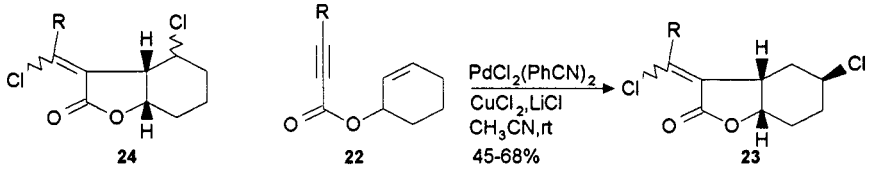


Thus, we can also control the stereochemistry at β,γ-position by use of different starting materials (ref. 19).

SYNTHESIS OF BICYCLIC LACTONES

From 2'-cyclohexenyl 2-alkynoates

The cyclization of 2'-cyclohexenyl 2-alkynoates **22** proceeds similarly to give the bicyclic lactones **23** (ref. 25).

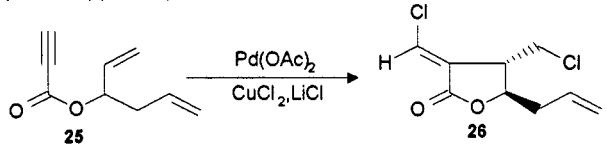


(5)

The stereochemistry of the exocyclic double bond is similar to that described in the monocyclic lactones. The cyclohexane ring is found to be *cis*-fused to the lactone ring. It is worth noting that instead of the expected product **24**, compound 23 was isolated as the main product. There are preceding examples that the chlorine atom can migrate on the cyclohexane ring through the addition-elimination of palladium hydride species (ref. 26).

From cascade reaction of 1',5'-hexadien-3'-yl 2-alkynoates

First, 1,5-hexadien-3-yl propynoate (**25**) was tried in the presence of $PdCl_2$, $CuCl_2$ and LiCl, a monocyclic product, *trans*-β,γ-disubstituted α-(E)-chloromethylene-γ-butyrolactone (**26**) was obtained as the main product (equation 6)(ref. 27).

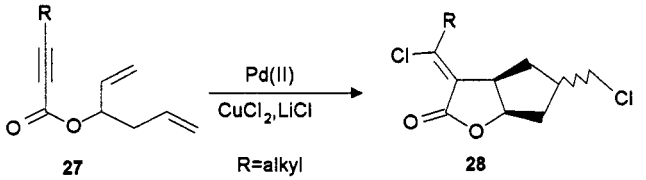


(6)

The failure of the second cyclization might be due to the *trans*-configuration of the β,γ-substituents. From the results discussed above, the stereochemistry of the cyclization can be controlled by the substituent (R') on the triple bond of the alkynoates. Thus, the cyclization of 1',5'-hexadien-3'-yl 2-alkynoates (**27**) were studied. The bicyclization reactions of **27** proceeded smoothly under the above mentioned conditions. cis-Fused

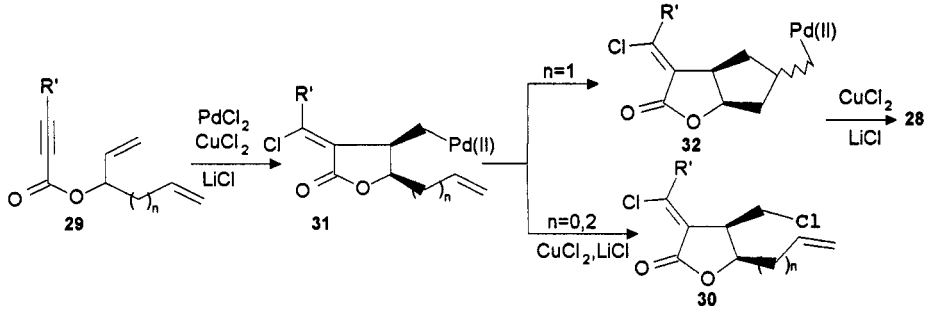
bicyclic α-(Z)-chloroalkylidene-γ-butyrolactone derivatives (**28**) were stereoselectively obtained in good yields (equation 7). Thus, the first cyclization is crucial to the second cyclization.

While the reaction of **27** gave **28** smoothly, 1',4'-pentadien-3'-yl 2-heptynoate (**29**, n=0) and 1,6-heptadien-3-yl butynoate (**29**, n=2) afforded monocyclic lactone **30** (n=0 and n=2, respectively) implying that besides the first cyclization, the length of olefinic chains at γ-position is also crucial to the second ring formation. The reaction path is speculated in **Scheme 7**.



27 **28** (7)

Scheme 7



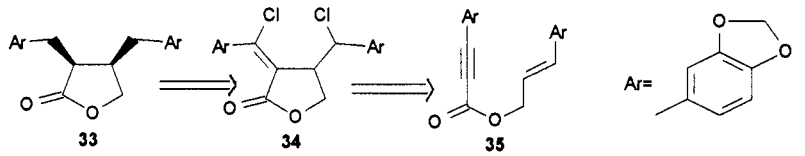
The cyclic intermediate **31** would first be formed via stereoselective chloropalladation and intramolecular olefin insertion (ref. 19). Then the oxidative cleavage of C-Pd bond (ref. 21, 24) of **31** to yield the monocyclic product **30** is in competition with the intramolecular olefin insertion to give the bicyclic intermediate **32** in the presence of $CuCl_2$ and LiCl. The second insertion of C=C bond into C-Pd bond is favorable only when n=1. Finally, the oxidative cleavage of C-Pd bond in **32** would occur to yield the bicyclic products **28** and regenerate the catalytic species.

APPLICATION TO THE SYNTHESIS OF (+)-ISOHINOKININ

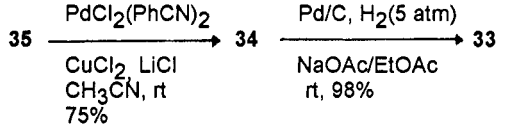
Lignans are distributed widely in the plant kingdom and show many important biological activities (ref. 25). Isohinokinin (**33**) belongs to a major subgroup which is comprised of 3,4-disubstituted γ-butyrolactones. For the synthesis of this type of compound, the construction of a γ-butyrolactone is the first task. Lee reported a radical cyclization of allylic propynoates to synthesize α-methylene-γ-butyrolactones (ref. 6a), but the selectivity of this radical cyclization was low.

A retrosynthetic analysis is shown in Scheme 8, in which (+)-Isohinokinin (**33**) can be synthesized by reduction of **34** which can be obtained from the cyclization reaction of **35** using the present reaction.

Scheme 8



The cyclization of **35** was achieved in 75% yield to give the lactone **34**. Hydrogenation of **34** gave (+)-Isohinokinin (**33**) in one step in nearly quantitative yield (ref. 29). The stereochemistry of **33** can be deduced from Crombie's result (ref. 30) as well as from the mechanism of hydrogenation.



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