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Enyne cyclization methodology for the synthesis of bioactive lactones

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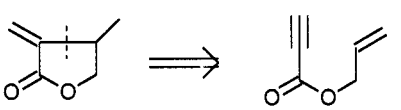
Abstract: A new methodology for the synthesis of enantiopure natural bioactive lactones from the enyne cyclization of allylic alkynoates under the catalysis of PdX_2 was developed. For α,β,γ-trisubstituted butyrolactones, the β,γ relative stereochemistry can be controlled by the substituent on the triple bond of the alkynoates and a chiral center is easily introduced from the optically active allylic alcohols. For α,β-disubstituted lactones, the key intermediate, lactonic aldehyde, is successfully resolved to both enantiomers *via* its tartrate acetal derivative.

INTRODUCTION

The challenge of synthesizing optically active α-methylene-γ-butyrolactone derivatives has stimulated much activity because the α-methylene-γ-butyrolactone is found to be a basic structural unit in a wide range of important naturally occurring compounds (ref. 1). Also, γ-butyrolactones are versatile intermediates in organic synthesis and are widely used in the synthesis of various natural products (ref. 2). Much effort has been focused on the enantioselective entry to functionalized γ-butyrolactones, and several such methods have been developed (ref. 1-3).

We are interested in the method of assembling the γ-lactone ring by carbon-carbon bond formation which is quite different from the other reported methodologies (ref. 1). 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. 4), however, the zero valent transition metal 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 (ref. 5) or isomerization of the triple bond in the starting materials (ref. 6). Therefore, to find a catalyst for cyclization of an allylic unsaturated acid ester, low valent metal complexes or transition metal hydrides that would lead to the side reactions must be avoided. In the literature where a divalent palladium complex is the catalytic active species, zero valent palladium is usually formed during the reaction and is reoxidized by oxidants to complete the catalytic cycle (ref. 7). In some cases, the divalent palladium complex is used in stoichiometric amount (ref. 8). Kaneda et al. reported the bis(benzonitrile)palladium dihalide catalyzed codimerization of alkynes and allylic halides in which the divalent palladium

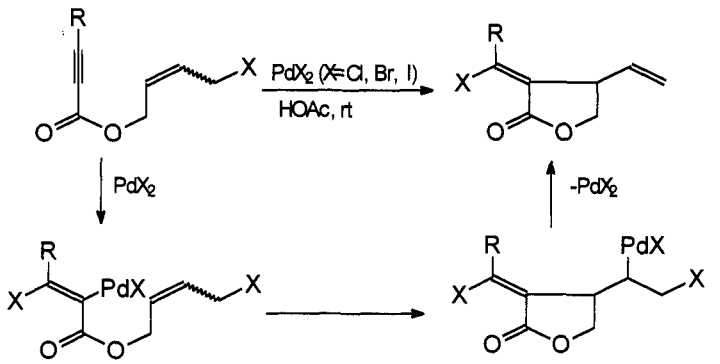
was regenerated by dehalopalladation (ref. 9), which suggested to us that it might be possible to develop divalent palladium catalyzed reactions without the participation of the zero valent palladium species.

CYCLIZATION OF ALLYLIC ALKYNOATES AND THE STEREOCHEMISTRY OF CYCLIZATION

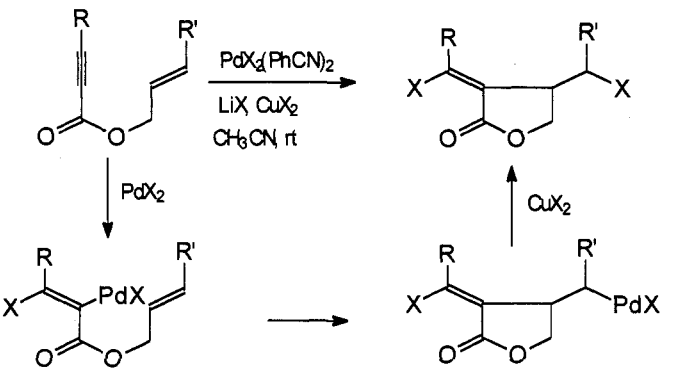
We applied this methodology to the synthesis of lactones and developed two methods for the synthesis of α-alkylidene-γ-butyrolactone derivatives from 4'-halo-2'-alkenyl 2-alkynoates (Method 1) (ref. 10, 12) and 2'-alkenyl 2-alkynoates (Method 2) (ref. 11, 12) under the catalysis by palladium(II) halide. In these reactions, first, halopalladation of the alkyne moiety generates alkenylpalladiums, followed by subsequent carbopalladation to form the lactone ring. The carbon-palladium bond is finally quenched by dehalopalladation (Method 1) (ref. 10) or oxidative cleavage by CuX_2 (Method 2) (ref. 11), respectively, to regenerate the palladium(II) halide species as the catalysts (**Scheme 1**).

Scheme 1

Method 1

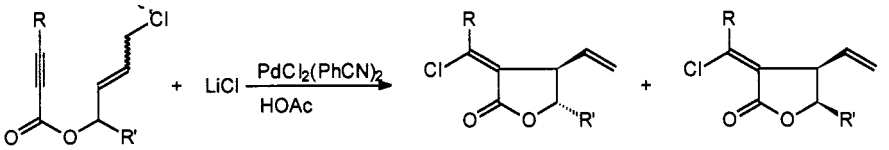


Method 2



In the above two reactions, when a substituent is introduced into the 1'-position of the 2'-alkenyl group of the starting alkynoates, significant results were found in the stereochemistry of the cyclization of different alkynoates. The cyclization of unsubstituted propynoates mainly afforded β,γ-*trans*-disubstituted lactones, while the cyclization of 3-substituted propynoates yielded β,γ-*cis*-disubstituted products as shown in the Table (ref. 12-14).

Table. The Stereochemistry of Cyclization



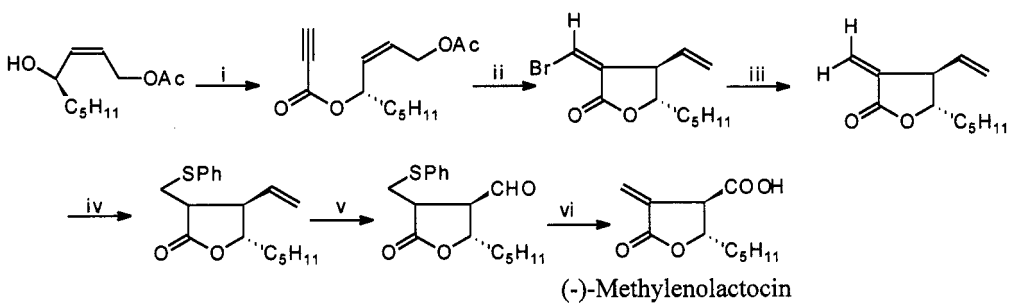
R	exocyclic double bond	β,γ–stereochemistry	influence of allylic double bond	influence of R'
H	Z	trans	Z>E	i-Pr>Me
alkyl	Z	cis	E>Z	

These reactions constitute a highly efficient route for constructing a stereodefined lactone in a single operation. In addition, due to the well documented methods to prepare optically pure allylic alcohols (ref. 15), it is easy to prepare the optically pure starting esters which is the key point in synthesizing the enantiopure lactones.

SYNTHESIS OF BOTH ENANTIOMERS OF METHYLENOLACTOCIN

(-)-Methylenolactocin is a β,γ-*trans*-substituted α-methylene-γ-butyrolactone. The total synthesis of (-)-methylenolactocin from a functionalized optically active allylic alcohol is shown in **Scheme 2** (ref. 16). It is worth noting that this method permits the synthesis of the target molecule in either enantiomeric form by simply starting with one or the other enantiomer of the same allylic alcohol.

Scheme 2



Reagents and conditions: (i) propynoic acid, DEAD, PPh_3, THF, rt; (ii) LiBr, $Pd(OAc)_2$, HOAc, rt; (iii) Zn-Ag, MeOH; (iv) Et_3N, PhSH, THF, rt; (v) O_3, MeOH-CH_2Cl_2, -78°C; (vi) (a) PDC, DMF, 0°C to rt; (b) $NaIO_4$, MeOH-benzene-H_2O, rt; (c) toluene, reflux.

SYNTHESIS OF PHASEOLINIC ACID

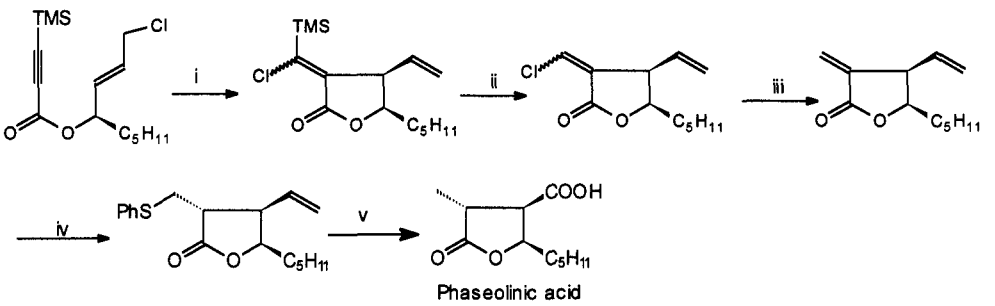
In phaseolinic acid, the β,γ-substituents are in *cis* form. The cyclization of allylic trimethylsilyl-propynoate was applied to obtain the β,γ-*cis*-disubstituted lactone. Desilylation and further elaboration completed the total synthesis (**Scheme 3**) (ref. 17).

SYNTHESIS OF LACTONES WITH α,β-SUBSTITUENTS

For those γ-butyrolactones which only have α,β-substituents, the optically active lactones can be synthesized through the elaboration of a β,γ-disubstituted optically active lactone, e.g., isohomopilopic acid was synthesized in this way as shown in **Scheme 4** (ref. 18). Thus, we

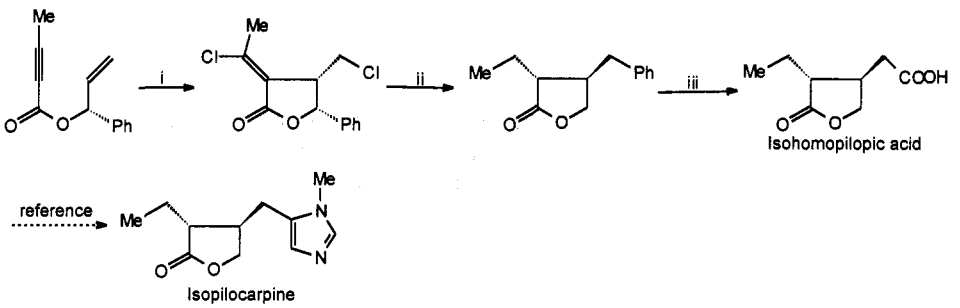
finished the formal synthesis of isopilocarpine. In this case, only α,β-*trans*-disubstituted lactone can be synthesized.

Scheme 3



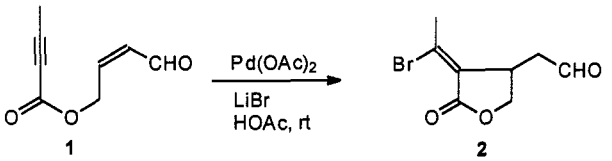
Reagents and conditions: (I) $Pd(OAc)_2$, LiCl, HOAc, rt; (ii) TBAF, HOAc, rt; (iii) Zn-Ag / MeOH; (iv) PhSH, Et_3N, rt; (v) (a) $NaIO_4$, $RuCl_3 \cdot H_2O$, CCl_4-MeCN-H_2O; (b) Na-Hg, NaH_2PO_4, MeOH, -20°C.

Scheme 4

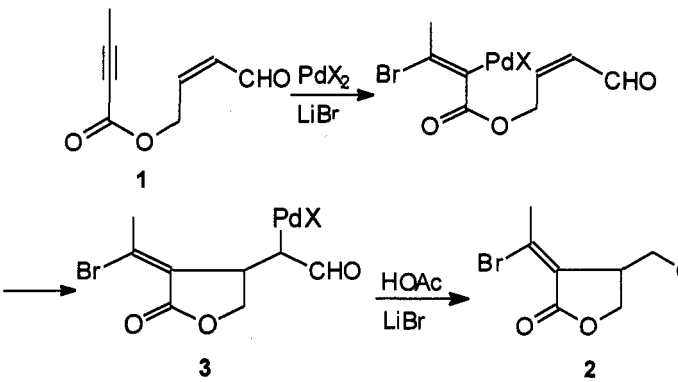


Reagents and conditions: (i) $CuCl_2$, LiCl, $Pd(OAc)_2$, HOAc, rt; (ii) NaOAc, Pd-C, MeOH, H_2 (6 atm), rt; (iii) $NaIO_4$, $RuCl_3 \cdot H_2O$, CCl_4-MeCN-H_2O, 0°C to rt.

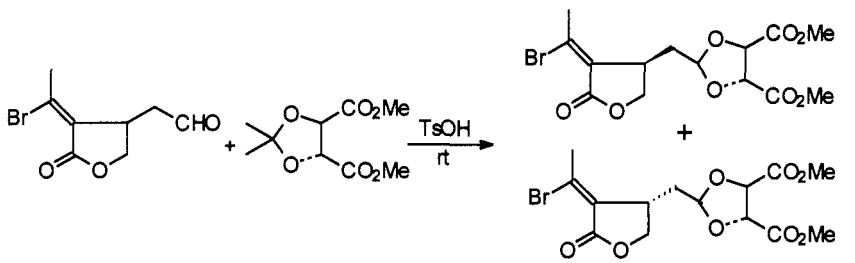
Recently, we found that 4'-oxo-2'-butenyl butynoate (**1**) could be cyclized under the catalysis by $Pd(OAc)_2$ in the presence of LiBr and HOAc at rt to yield the lactonic aldehyde **2** (ref. 19).



This cyclization reaction can be regarded as an intramolecular version of the nucleophile-alkyne-α,β-unsaturated carbonyl coupling reaction (ref. 20). The mechanism of this reaction can be speculated as follows: halopalladation of the triple bond gives the vinyl palladium intermediate followed by double bond insertion to form the 2-oxoalkylpalladium intermediate **3**. The key step to form the product **2** and regenerate the Pd(II) catalytic species is the protonolysis of the carbon-palladium bond in **3**. The ease of this process in this case might be due to the large excess of halide ion which may suppress the β-H elimination and enhance the mesomeric palladium enolate structure in **3** which may subsequently readily undergo a heterolytic Pd-O fission under the reaction conditions.

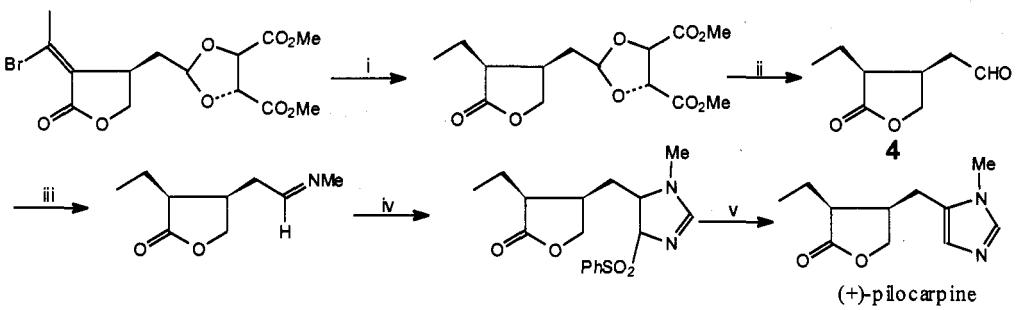


Compound **2** forms diastereomeric acetals with dimethyl tartrate which could be easily separated by column chromatography.



After further transformation, both enantiomers of aldehyde **4** were obtained, from which the two enantiomers of pilocarpine could be prepared in optically pure form (**Scheme 5**) (ref. 19).

Scheme 5



Reagents and conditions: (I) H_2, Pd/C, EtOAc, NaOAc; (ii) HOAc, H_2O; (iii) $MeNH_2$, benzene; (iv) $PhSO_2CH_2NC$, K_2CO_3; (v) -$PhSO_2H$.

In summary, the new enyne cyclization methodology for the synthesis of bioactive lactones has the advantages of facile control of the stereochemistry of β,γ-substituents, the simplicity of introducing a chiral center into the starting materials and the successful resolution of the lactonic aldehyde through their tartrate acetals. The application of this method to the synthesis of more of the bioactive lactones is anticipated.

Acknowledgements:
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