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Palladium-catalyzed epimerization of γ-alkenyl-γ-butyrolactone derivatives

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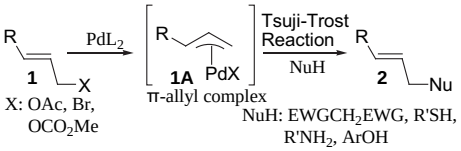
ABSTRACT

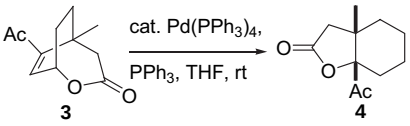
γ-Alkenyl-α,β,γ-trisubstituted-γ-butyrolactones (**12**–**16**) and γ-alkenyl-furofurandione derivatives (**21**-**Z**-**24**-**Z**; **21**-**E**-**24**-**E**; **25**-**Z**-**28**-**Z**; and **25**-**E**-**28**-**E**) were successfully epimerized in high yield by a palladium catalyst.

1. Introduction

The Tsuji–Trost reaction is the palladium-catalyzed allylation of nucleophiles, such as active methylenes, enolates, amines, and phenols with allylic compounds, such as allyl acetates, allyl carbonates, and allyl bromides. The reaction occurs via intermediate allylpalladium complexes, typically with overall retention of stereochemistry (Eq. 1).[1–5] In the absence of a nucleophile, Pd-catalyzed allylic isomerization is possible. For example, substituted bicyclo [2.2.2]oct-5-en-2-one (**3**) can be converted to *cis*-fused hydrobenzofuran derivative (**4**) when catalyzed by Pd(0) (Eq. 2).[6]



(1)



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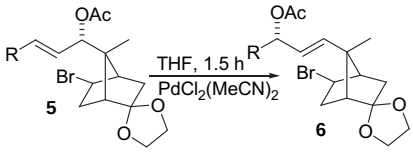

(3)

Complete transfer of chirality in the [3,3]-sigmatropic rearrangement of allylic acetates **5** can be catalyzed by Pd^{2+} (Eq. 3). The reaction has been applied to stereocontrolled synthesis of prostaglandins that possess either the C-l5(*S*) or C-15(*R*) configuration.[7,8]

We have completed the total syntheses of furofurandione natural products by using 4-*endo*-hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one (**7**)[9] as a building block. In this process, the key step is palladium-catalyzed epimerization of the γ-alkenyl substituted of bislactones.[10] To the best of our knowledge, studies of the recombination of the η^3 π-allyl complex to give epimerized allylic esters are rare in the literature. Herein, we describe palladium-catalyzed epimerization of γ-alkenyl-γ-butyrolactone derivatives.

2. Results and discussions

2.1. Synthesis of γ-alkenyl-α,β,γ-trisubstituted-γ-butyrolactones and their Pd-catalyzed epimerization

The *endo*-hydroxylactone **7** was treated with sodium hydride and benzyl bromide to give the corresponding benzyl ether **8** and *exo*-benzyloxylactone **9**. Due to the α-acidity of the benzyl ether **8**, it was epimerized in situ to give **9** as the major product. Ozonolysis

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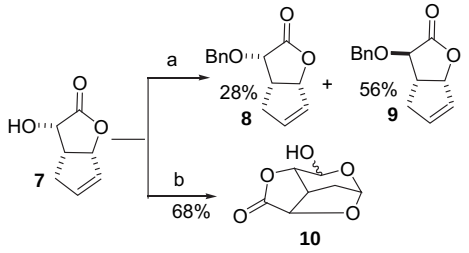
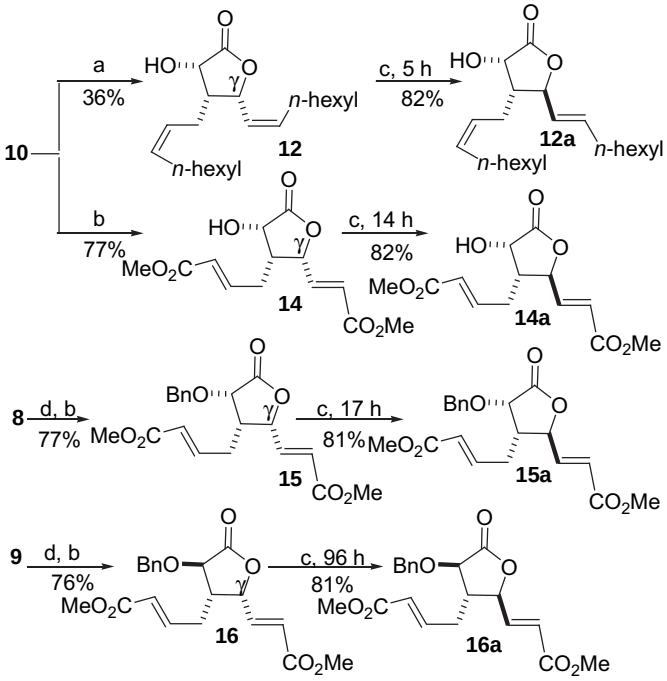
of lactone **7** in CH_2Cl_2 at −78 °C followed by reduction with Me_2S gave tricyclic hemiacetal **10** as a 10:1 mixture of two diastereomers in 68% yield. The axial anomer was the major isomer, as confirmed by its 2D-NOESY spectrum (Scheme 1).



Scheme 1. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to rt; 8 h. (b) (1) O_3, CH_2Cl_2, −78 °C; (2) Me_2S, CH_2Cl_2, 0 °C, 6 h.

The tricyclic hemiacetal **10** reacted with 2 equiv of $Ph_3P{=}CHC_6H_{13}$-*n* (**11**) or 2 equiv of $Ph_3P{=}CHCO_2Me$ (**13**) to give the corresponding *Z,Z*-Wittig product **12** in 36% yield[11] and *E,E*-Wittig product **14** in 77% yield, respectively. Compound **8** was cleaved by ozone followed by reduction with Me_2S. The resulting product was reacted with 2 equiv of $Ph_3P{=}CHCO_2Me$ (**13**) to give the corresponding *E,E*-Wittig product **15** in 77% yield. Similarly, compound **9** was converted to the corresponding *E,E*-Wittig product **16** in 76% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) 2 equiv $Ph_3P{=}CHC_6H_{13}$ (**11**), THF; (b) 2 equiv $Ph_3P{=}CHCO_2Me$ (**13**), THF; (c) 0.1 equiv $Pd(OAc)_2$, 1 equiv Ph_3P, THF, rt; (d) (1) O_3, CH_2Cl_2, −78 °C; (2) Me_2S, CH_2Cl_2, 0 °C, 6 h.

All of the substituents of γ-alkenyl-γ-butyrolactones **12**, **14**, and **15** were *syn* to each other. When they were treated with palladium catalyst, their γ-chiral centers were epimerized to give the corresponding **12a**–**15a**. In the case of compound **12**, γ-chiral center epimerization was concomitant with γ-(*Z*)-octenyl group isomerization. Interestingly, the geometry of its β-(*Z*)-octenyl group was unchanged. The relative stereochemistries of compound **16** at the α, β, and γ positions were *anti-syn* to each other. Its γ-chiral center was also epimerized by the palladium catalyst to give the corresponding *anti–anti* diastereomer **16a** (Scheme 2).

A plausible mechanism for the palladium-catalyzed epimerization is illustrated using the example of conversion of compound **12** to **12a** in Figure 1. The coordination of the Pd(0)-catalyst to the double bond forms an η^2 π-allyl complex. An oxidative addition, during which the leaving group is expelled, gives the η^3 π-allyl complex **A**. The isomerization from **A** to **B** occurs to relieve $A^{1,3}$-strain.[11] The interconversion of intermediate **B** to **C** is ascribed to electrostatic attraction of the ion pair. Recombination of the C–O bond of **C** causes γ-stereogenic center epimerization and γ-octenyl group isomerization. The torsional strain from β and γ substituents is relieved. The double bond geometry of the β-substituent is retained (Fig. 1).

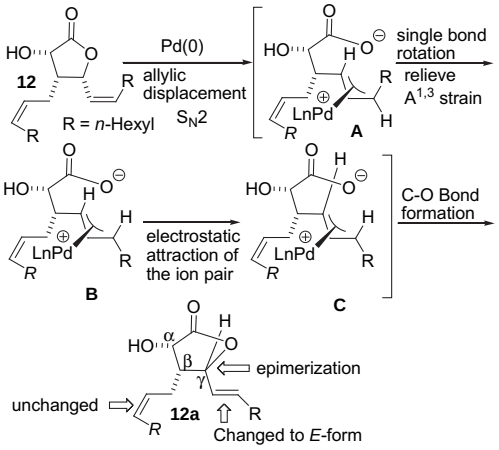


Figure 1. Plausible mechanism of the Pd-catalyzed epimerization of compound **12**.

2.2. Synthesis of γ-alkenyl-furofurandione derivatives and their Pd-catalyzed epimerization

Tricyclic hemiacetal **10** reacted with semistable phosphonium ylide **17** to give separable lactols **21Z** (52%) and **21E** (14%). Compound **10** reacted with semistable phosphonium ylide **18** to give lactol **22Z** in 78% yield stereoselectively. The hemiacetal **10** reacted with semistable phosphonium ylides **19**–**20** to give Wittig products **23Z**–**24Z** and **23E**–**24E**, respectively. The cis-isomer is the major one in each case. In this study, there were two pathways for epimerization starting from lactols **22Z**–**24Z** and **22E**–**24E**. The oxidation of lactol to lactone followed by epimerization is pathway A in Scheme 3, and the epimerization of lactol followed by oxidation is pathway B in Scheme 3.

By way of pathway A, lactols **21Z**–**24Z** were oxidized by Jones reagent to give the corresponding bislactones **25Z**–**28Z**, respectively, in high yields. The *trans*-analogues **21E**–**24E** were oxidized by Jones reagent to give the corresponding bislactones **25E**–**28E**, respectively, in high yields. Both bislactones **25Z** and **25E** were treated with Pd catalyst to give the same epimerized product **25a**, in which the γ-stereogenic center was epimerized and the *Z*-olefinic side chain of **25Z** was converted to a more stable *E*-form. Similarly, both **26Z**–**28Z** and **26E**–**28E** were converted to **26a**–**28a**, respectively (Scheme 3).

By way of pathway B, the lactol **21Z** was epimerized with Pd catalyst first. The crude product was then oxidized by Jones reagent to give furofurandione **25a**, in which the γ-stereogenic center was epimerized and the *Z*-olefinic side chain was isomerized to a more stable *E*-form. Similarly, both **26Z**–**28Z** and **26E**–**28E** were converted to **26a**–**28a**, respectively (Scheme 3).

Interestingly, under Sonogashira coupling reaction conditions,[13] vinyl bromide **26Z** reacted with 1-hexyne to give the crossed coupling product **29** in 71% yield. The crossed coupling epimerization at the C-4 chiral center and the isomerization of the *Z*-double