Studies on [PdH]- and [PdCl]-Catalyzed Intramolecular Cyclization: The Search for a Better Solution to Selective Enyne Coupling

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On the basis of the hydropalladation and chloropalladation of the carbon−carbon triple bond, [PdH] and [PdCl] active species were employed to catalyze the cyclization of homoallylic 2-alkynoates and ω-alken-2-ynoates. From homoallylic alkynoates, two kinds of α-alkylidene-δ-valerolactone derivatives showing different stereochemistries of the exocyclic alkylidene double bond were obtained using two catalytic systems, while from the latter, hydropalladation and chloropalladation showed opposite regioselectivity, giving bis(alkylidene)-cycloalkane and cycloalkene derivatives, respectively.

Introduction

Intramolecular enyne coupling, as an efficient strategy to construct cyclic molecules through carbon−carbon bond formation, has attracted much attention from chemists in the field of both synthetic methodology[1] and natural product synthesis.[2] In a variety of intramolecular enyne coupling reactions, transition-metal-mediated couplings are most distinguished with respect to their high efficiency, good stereoselectivity, and catalytic nature. The Trost group several years ago developed the elegant palladium hydride catalyzed enyne cycloisomerization reaction, which is stereoselective and atom economical.[3] On allylic 2-alkynoates, a special group of enynes containing electron-deficient triple bonds, we also achieved stereoselective intramolecular cyclization by $PdCl_2$−LiCl−$CuCl_2$ catalytic systems in which palladium chloride species promoted the coupling.[4] Through the manipulation of the halo functions in the resulting α-alkylidene-γ-butyrolactone derivative, we further synthesized the natural product (±)-isohinokinin.[5a] Bäckvall also used chloropalladation to realize a dienyne cyclization with a similar $Pd(OAc)_2$−LiCl−benzoquinone catalytic system.[5b]

Although palladium hydride and palladium chloride are both effective catalytic species for intramolecular enyne cyclization, a systematic study of the catalytic properties of [PdH] and [PdCl] on the same substrates has not yet been done. Furthermore, [PdH]-catalyzed cycloisomerization of more complex molecules with an enyne moiety, especially those with an electron-deficient triple bond, have still not been well studied.[3b,c] To clarify the different behaviors of [PdH] and [PdCl] catalytic species in enyne couplings and to develop an efficient route to other synthetically valuable structures, we examined both catalytic systems on two groups of enynes with electron-deficient triple bonds, namely, homoallylic 2-alkynoates (**1**) and 6- or 7-alken-2-ynoates (**9**). In this paper, we report the cyclization results of **1** and **9** with these two different catalytic systems.

Results and Discussion

Cyclization of Homoallylic 2-Alkynoates. A number of biologically active natural products containing the δ-valerolactone moiety, such as withanolides,[6] massoia lactone,[7] and psiAα and psiAβ,[8] have recently become important targets for organic synthesis owing to their exceedingly potent antitumor and insecticidal activity and many other biological activities.[6b,9] The presence of the architecturally interesting δ-valerolactone in these compounds has brought about the development of many methods for the preparation of this unit.[10,11] However, most of these methods entailed multistep preparation of the synthetic precursors, and some of them used special reagents not readily accessible. Therefore, the development of simple new methods for

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(1) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. Boyd, G. V. In *The Ene Reaction in Chemistry of Double-Bonded Functional Groups*; Patai, S. Ed.; Wiley: Chichester, U.K., 1989; part 2, p 477.

(2) Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem.* **1989**, *101*, 1559. Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390. Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087. Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160.

(3) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Trost, B. M.; Macpherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483. (c) Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735. For a review see: Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.

(4) (a) Ma, S. Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 733. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (c) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (d) Ji, J.; Lu, X. *Synlett* **1993**, 745.

(5) (a) Lu, X.; Zhu, G. *Synlett* **1993**, 68. (b) Bäckvall, J.-E.; Nilsson, Y. I. M.; Andersson, P. G.; Gatti, R. G. P.; Wu, J. *Tetrahedron Lett.* **1994**, *35*, 5713.

(6) (a) Tsubuki, M.; Kanai, K.; Keino, K.; Kakinuma, N.; Honda, T. *J. Org. Chem.* **1992**, *57*, 2930. (b) Glotter, E, *Nat. Prod. Rep.* **1991**, *8*, 415.

(7) Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335. Bomoni, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron: Asymmetry* **1992**, *3*, 29. Cavill, G. W. K.; Clark, D. V.; Whitefield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819.

(8) Mazur, P.; Nakanishi, K. *J. Org. Chem.* **1992**, *57*, 1047.

(9) Ohloff, G. *Prog. Chem. Org. Nat. Prod.* **1978**, *35*, 431. Brand, J. M.; Yuong, J.; Silverstein, R. M. *Prog. Chem. Org. Nat. Prod.* **1979**, *37*, 1. Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10*, 71.

(10) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 6, p 324. Hoffman, H. M. R.; Rabe, *J. Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157.

(11) For recent progress see: Tsubiki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281. Schink, H. E.; Bäckvall, J.-E. *J. Org. Chem.* **1992**, *57*, 1588. Pilli, R. A.; Murta, M. M. *J. Org. Chem.* **1993**, *58*, 338. Carcamo, C. Fajardo, V.; Tojo, E. *Heterocycles* **1993**, *36*, 1771.

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Scheme 1

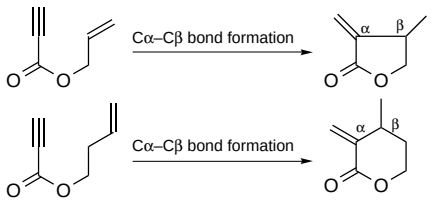


Table 1. $Pd(OAc)_2$–HOAc-Catalyzed Cycloisomerization of Homoallylic 2-Alkynoates[a]

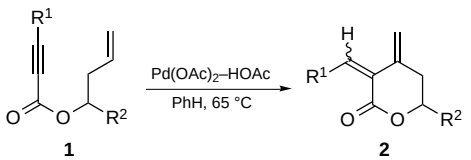
entry no.	1	R^1	R^2	2[b]	yield (%)[c]	Z:E[d]
1	**1a**	CH_3	H	**2a**	87	82:18
2	**1b**	Ph	H	**2b**	82	80:20
3	**1c**	CH_3	CH_3	**2c**	69	67:33
4	**1d**	Ph	CH_3	**2d**	75	75:25
5[e]	**1e**	C_4H_9	H			

[a] Reaction conditions: a mixture of **1** (1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), HOAc (6 mg, 0.1 mmol), and benzene (5 mL) was stirred at 65 °C under Ar. [b] The products were characterized by ^1H NMR, IR, mass spectral data, and microanalysis. [c] Isolated yield. [d] The ratio *Z*:*E* was determined by ^1H NMR spectra. [e] The reaction gave a complex mixture.

synthesizing *δ*-valerolactones from readily available starting materials is still a great challenge.

Our previous work on the stereoselective synthesis of α-alkylidene-*γ*-butyrolactone derivatives by divalent palladium-catalyzed cyclization of allylic 2-alkynoates[4] showed us that homoallylic alkynoates may lead to *δ*-valerolactones in [PdCl]-catalyzed cyclization (Scheme 1). On the other hand, the [PdH]-catalyzed cycloisomerization developed by Trost's group may be another candidate for the desired enyne coupling. Although in our early strategy of palladium-catalyzed cyclization of allylic alkynoates low-valent palladium and palladium hydride were avoided on account of the possible allylic carbon−oxygen bond cleavage in the allylic ester substrates,[12] in the present case, a homoallylic C−O linkage may completely survive the low-valent palladium or palladium hydride conditions. We thus studied the cyclization of homoallylic 2-alkynoates with [PdCl] and [PdH] catalytic systems respectively.

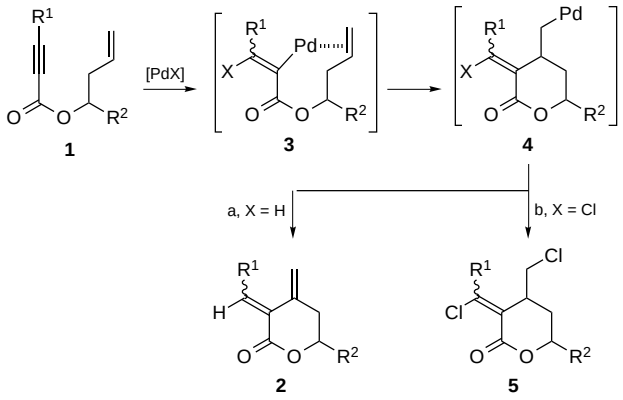
Homoallyl 2-butynoates and 3-phenyl-2-propynoates (**1a**,**b**) were first prepared, and their reactions under the catalysis of $Pd(OAc)_2$ (5 mol %) and HOAc (10 mol %) in benzene (0.2−0.5 M solution) were examined.[3] The cyclization of **1a**,**b** proceeded well, as expected, and afforded α-alkylidene-*β*-methylene-*δ*-valerolactones **2a**,**b** in good yields, respectively, with *Z*-isomers (referring to the α-exocyclic double bond) predominating (eq 1,



(1)

Table 1, entries 1 and 2). Two other 1′-substituted homoallylic alkynoates were also subjected to the cyclization conditions, and similar results were obtained (Table 1, entries 3 and 4). For homoallyl 2-heptynoate (**1e**), however, the reaction afforded no identifiable products, which might be due to the side reactions of

Scheme 2



the carbon−carbon triple bond with [PdH] species.[13] In most of Trost's reports, only one geometric isomer was obtained for the cycloisomerization of 1,6-enynes or 1,7-enynes. However, in our case, both (*Z*)-**2** and (*E*)-**2** were obtained. The stereochemistry of the α-exocyclic double bond in **2** was determined by comparing the chemical shifts of the vinylic protons, where *E*-form products showed lower field resonances in ^1H NMR spectra than the corresponding *Z*-isomers.[4,14]

The reaction path can be rationalized via a similar mechanism appearing in the literature: hydropalladation of the triple bond gave the vinylpalladium intermediate **3**, which on intramolecular olefin insertion and *β*-H elimination afforded the cyclization product **2** (Scheme 2, path a). The stereochemistry of the exocyclic carbon−carbon double bond in **2** depends upon the manner of the hydropalladation step. Transition-metal hydrides generally add to the carbon−carbon triple bond to give cis-addition complexes.[15] However, the reaction of certain metal hydrides with some acetylenes has been noted to produce trans adducts.[16] Stone[17] and Schwartz[18] proposed a reasonable explanation to account for the trans products observed. Thus, the cis vinylmetal adduct was first formed and isomerized to a trans adduct via a dipolar intermediate. In our case, the unexpected *E* isomers might also be formed by a similar cis−trans isomerization of the vinylpalladium intermediate **3** (Scheme 3, path a). However, considering the inversed polarization of an α,*β*-unsaturated ester in **6**, it is more likely that the formation of *E*,*Z* mixtures is the result of the [PdH]-mediated equilibrium of the products (Scheme 3, path b).[13a]

Chloropalladation of a carbon−carbon triple bond is another important method for the formation of vinylpal-

(12) Yamamoto, A. *Organotransition Metal Chemistry*; Wiley: New York, 1986; p 233. Hayashi, Y.; Yamamoto, T.; Yamamoto, A.; Komiya, S.; Kushi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 385.

(13) Long chain alkynoates such as **1e** may isomerize to dienes in the presence of [PdH] species, which might further induce side reactions leading to a complex mixture of products. See: (a) Ma, D.; Yu; Y.; Lu, X. *J. Org. Chem.* **1989**, *54*, 1105. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2303. (c) Guo. C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921.

(14) Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696 and references cited therein.

(15) James, B. P. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, U.K., 1982; Vol. 8, p 285. Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 8, p 417.

(16) Zargarian, D.; Alper, H. *Organometallics* **1991**, *10*, 2914. Huggin, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3002. Rice, N. C.; Oliver, J. D. *J. Organomet. Chem.* **1978**, *145*, 121. Hine, K. E.; Clark, H. C. *J. Organomet. Chem.* **1976**, *105*, C32.

(17) Blackmore, T.; Bruce, M. I.; Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1974**, 106.

(18) Hart, D. W.; Schwartz, J. *J. Organomet. Chem.* **1975**, *85*, C11.

Scheme 3

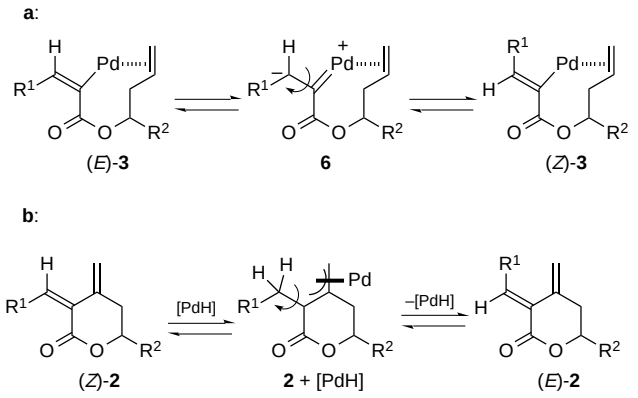


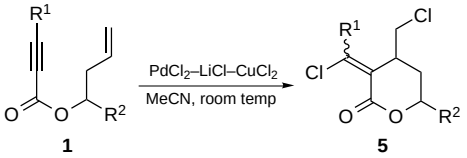
Table 2. $PdCl_2$-Catalyzed Cyclization of Homoallylic 2-Alkynoates[a]

entry no.	1	R^1	R^2	5[b]	yield (%)[c]	Z:E[d]	trans:cis[e]
1	**1a**	CH_3	H	**5b**	62	>97:3	
2	**1c**	CH_3	CH_3	**5d**	86	>97:3	>97:3
3	**1f**	CH_3	i-C_3H_7	**5f**	72	>97:3	>97:3
4	**1g**	CH_3	Ph	**5g**	77	>97:3	>97:3
5	**1h**	H	H	**5h**	67	<3:97	
6	**1i**	H	CH_3	**5i**	68	<3:97	>97:3
7	**1j**	H	i-C_3H_7	**5j**	76	<3:97	>97:3
8	**1k**	H	Ph	**5k**	77	<3:97	>97:3

[a] Reaction conditions: a mixture of **1** (1 mmol), $PdCl_2$ (9 mg, 0.05 mmol), $CuCl_2$ (405 mg, 3 mmol), LiCl (255 mg, 6 mmol), and MeCN (10 mL) was stirred at room temperature for 50 h. [b] The structure of the product was confirmed by ^{1}H NMR, IR, MS spectral data, and microanalysis. [c] Isolated yield. [d] The ratio *Z*:*E* (referring to the exocyclic carbon−carbon double bond) was determined by ^{1}H NMR spectra. [e] The ratio trans:cis (referring to the relative stereochemistry of β and δ substituents) was determined by ^{1}H NMR spectra.

ladium species.[4,19] Since the stereoselectivity of the [PdH]-catalyzed cyclization of homoallylic 2-alkynoates was only moderate, we decided to study the cyclization of **1** using [PdCl] catalytic systems.

In the presence of $PdCl_2$ (5 mol %), $CuCl_2$ (300 mol %), and LiCl (600 mol %) in MeCN, the reaction of **1** (at 0.1−0.2 M) at room temperature yielded α-(chloroalkylidene)-β-(chloromethyl)-δ-valerolactone derivatives **5** (eq 2). The results are shown in Table 2.



(2)

The configuration of the exocyclic double bond in **5** was determined by comparing the chemical shifts of the allylic (**5b**,**d**,**f**,**g**) or vinylic (**5h**−**k**) protons with those of the analogous butyrolactone compounds.[4] In case of homoallylic 2-butynoates (**1b**,**d**,**f**,**g**), the reaction afforded only α-(*Z*)-(chloroalkylidene)-δ-valerolactones (Table 2, entries 1−4), while in the case of homoallylic propynoates (1**h**−**k**), α-(*E*)-(chloroalkylidene)-δ-valerolactones were the sole products (Table 2, entries 5−8). This result is consistent with our early reports on

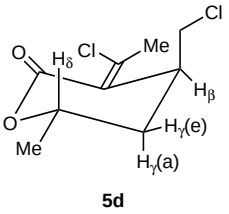
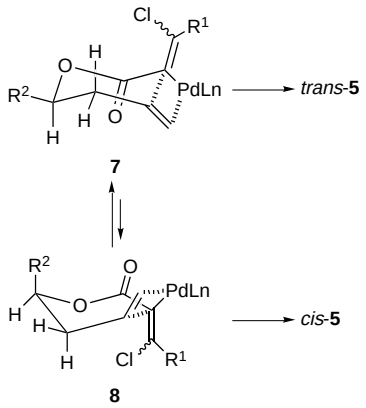


Figure 1.

Scheme 4



preparing α-(chloroalkylidene)-γ-butyrolactones from allylic alkynoates.[4c]

1,3-Stereoinduction of the present reaction was also studied through introduction of 1′-substitution in the ester group. For both 2-butynoates and 2-propynoates of 1′-substituted homoallylic alcohols, the reaction gave all one diastereomer. In contrast to our previous results on allylic alkynoate cyclization,[4c] the cis−trans selectivity was irrelevant to the substitution pattern at the triple bond; all the studied substrates gave β,δ-trans products only.

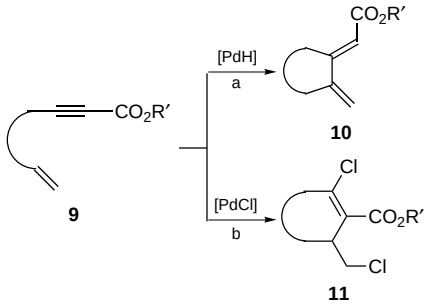
The relative stereochemistry of β,δ-substituents was determined by the related *J* values obtained from a series of irradiation experiments. Thus, for α-(*Z*)-(chloroethylidene)-β-(chloromethyl)-δ-methyl-δ-valerolactone (**5d**), irradiating H_β, H_δ, and CH_2Cl respectively showed $J(H_\beta H_\gamma{}^e) = 6.7$ Hz, $J(H_\beta H_\gamma{}^a) = 6.0$ Hz, $J(H_\delta H_\gamma{}^e) = 1.9$ Hz, and $J(H_\delta H_\gamma{}^a) = 14.1$ Hz. In the deduced favorable conformation of **5d** (Figure 1), H_β occupies the equatorial position and H_δ the axial position, indicating the trans configuration of β,δ-substituents. The reaction mechanism is proposed to resemble the cyclization of allylic 2-alkynoates[4c] (Scheme 2, path b). The high trans selectivity might be understood by the transition states shown in Scheme 4. The parallel-coplanar requirement for the C−Pd bond and the double bond obliges the transition state to adopt a chair−boat eight-membered ring conformation: compared with **8**, **7** is more favored with R^2 situated in an equatorial position, which leads to the β,δ-trans-substituted products.

Cyclization of 6- and 7-Alken-2-ynoates. Five- and six-membered carbocycles occupy an important position in the field of alicyclic natural products.[20] A great deal of effort has been spent in the development of facile and efficient methods to prepare these struc-

(19) (a) Dietl, H.; Reinheimer, H.; Moffat, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2276. Maitlis, P. M. *The Organic Chemistry of Palladium*; Academic Press: New York, 1971; Vol. 2, p 47. (b) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55. (c) Bäckvall, J.-E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242.

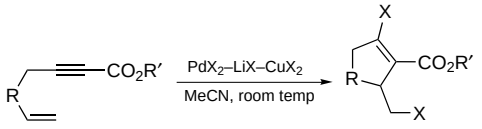
(20) Marshall, P. R. In *Aliphatic and Related Natural Product Chemistry*; Burlinton: London, 1979; Vol. 1, p 170. Green, R. H.; Lambert, P. F.; Newton, R. F.; Roberts, S. M. In *Aliphatic and Related Natural Product Chemistry*; Burlinton: London, 1979; Vol. 3, p 107. Trost, B. M. *Chem. Soc. Rev.* **1981**, *11*, 141. Ramaiah, M. *Synthesis* **1984**, 529. Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

Scheme 5



tures. Among them, alkylidene derivatives and cycloalkenes with unsaturation are especially important because they have active reaction sites and allow functional transformation. Under Trost's [PdH] conditions, the cycloisomerization of 1,6- and 1,7-enynes took place in an exo,exo manner (5-dig-exo and 5-trig-exo for the triple bond and the double bond), giving alkylidene−cyclopentane and −cyclohexane derivatives, respectively. When the substrates were substituted by an electron-withdrawing group on the triple bond, the reaction showed the same regioselectivity (Scheme 5, path a).[3]

According to our previous studies on $PdCl_2$-catalyzed reactions of alkynes, the direction of chloropalladation of triple bonds conforms to their electronic properties. Thus, nucleophilic chloride ion attacks the β-carbon of 2-alkynoates, forcing the C−Pd bond to form at the α-carbon; thus, a different regiochemistry for cyclization of ω-alken-2-ynoates would result (Scheme 5, path b). When we conducted the cyclization reaction under $PdCl_2$−$CuCl_2$−LiCl conditions using **9a**, this change was actually observed: the cyclization product **11a** was obtained in 70% yield (eq 3). Other ω-alken-2-ynoates



(3)

9 **11**

a: R = –CH(OH)–, R′ = Me
b: R = –CH(OBn)–, R′ = Me
c: R = –OCH_2– (CH_2 attaches to vinyl), R′ = Me
d: R = –OCH_2– (CH_2 attaches to vinyl), R′ = Bn

also reacted smoothly, giving cyclohexene and cyclopentene derivatives in good yield and regioselectivity. The results are listed in Table 3, together with the [PdH]-catalyzed cyclization results.

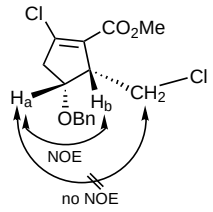
While substrates **9a**,**b** cyclized efficiently under the $PdCl_2$−LiCl−$CuCl_2$ catalytic conditions (entries 1 and 2, Table 3), the cyclization of enynes with an ether linkage between the carbon−carbon triple bond and double bond, such as in **9c**,**d**, was unsuccessful using the same catalytic system. However, using $Pd(OAc)_2$−LiBr−$CuBr_2$ in acetic acid, an analogous cyclization with bromide as the halogen source occurred, giving bromo-substituted dihydropyran derivatives **11c**,**d** in high yield (entries 3 and 4, Table 3).

Inseparable diastereomers were obtained from **9a**; the ^{1}H NMR spectra showed roughly a 1:1 mixture of the cis and trans isomers. Protecting the hydroxy group with a benzyl group increased the diastereoselectivity to 10:1 (Table 3, entry 2). After chromatographic separation, the structure of the major product was

Table 3. [PdCl]- and [PdH]-Catalyzed Cyclization of ω-En-2-ynoates 9

entry	substrate			[PdCl] cat.[a]		[PdH] cat.[b]	
no.	**9**	−R−	R′	**11**	yield (%)[c]	**10**	yield (%)[c]
1	**9a**	−CH(OH)−	Me	**11a**	70(50:50)[d]	**10a**	*e*
2	**9b**	−CH(OBn)−	Me	**11b**	75(91:9)[d]	**10b**	*e*
3	**9c**	−OCH_2−[f]	Me	**11c**	86[g]	**10c**	66
4	**9d**	−OCH_2−[f]	Bn	**11d**	88[g]	**10d**	71

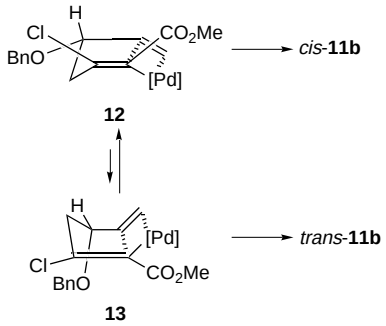
[a] Reaction conditions: same as in Table 2. [b] Reaction conditions: same as in Table 1. [c] Isolated yield. [d] The ratio in parentheses refers to the diastereomeric ratio cis:trans. [e] No identifiable products were obtained. [f] **9c** and **9d** have the structure $R'O_2CC{\equiv}CCH_2OCH_2CH{=}CH_2$. [g] Reaction conditions: **9** (1 mmol), $Pd(OAc)_2$ (0.1 mmol), $CuBr_2$ (3 mmol), and LiBr (6 mmol) in HOAc (5 mL) at room temperature. The corresponding bromo-substituted products were obtained.



cis-**11b**

Figure 2.

Scheme 6



established by ^{1}H NMR methods. Thus, $J(H_a-H_b)$ was determined to be 7.1 Hz, suggesting a cis configuration;[21] the NOESY spectra unambiguously confirmed this assignment (Figure 2).

The preferential formation of a thermodynamically unfavorable cis isomer is obviously of synthetic merit, and it can be rationalized by the transition state model (Scheme 6). First, the double bond resulting from trans chloropalladation confines the related atoms in a boat-form seven-membered ring; though both **12** and **13** have the parallel-coplanar arrangement for the C−Pd bond and carbon−carbon double bond, **13** is unfavorable with a pseudo-axial benzyloxy group, and thus the cyclization tended to occur through **12** and gave mainly the cis-substituted isomer. For **9a**, the low selectivity may be ascribed to the small size of the hydroxy group, which makes little energy difference between two transition states.

Remarks

From the results of the cyclization of **1** and **9** mediated by two catalytic systems, some conclusions with respect to regioselectivity, stereoselectivity, and substrate limitations could be drawn.

(21) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057.

Although both hydropalladation and chloro(halo)-palladation of a carbon−carbon triple bond can give vinylpalladium intermediates, their regioselectivities are different: in contrast to the hydridopalladium species whose addition direction is irrelevant to the polarization of the triple bond,[22] halopalladation strictly conforms to the electronic requirements. Thus, [PdH]-catalyzed cyclization of **9** afforded an exo, exo product which stems from the ring strain requirement; [PdCl] on the other hand, only performs Michael-type addition to electron-deficient triple bonds, leading to endo, exo cyclization products in spite of the unfavorable strain factors (Scheme 5).

In the cyclization of some homoallylic alkynoates, [PdH] and [PdCl] catalytic systems both gave δ-valerolactone derivatives in good yields, but propynoates or alkynoates with longer alkyl chains are not suitable substrates in the [PdH]-catalyzed cyclization: with the former, oxidative coupling products between two substrate molecules formed quickly with precipitated metallic palladium,[23] and with the latter, the reaction only afforded a complex mixture.

Furthermore, in the reaction preparing bis(alkylidene)cycloalkane or δ-valerolactone derivatives under [PdH] conditions, the yield decreased evidently on elongation of the reaction time. The [PdH]-induced side reactions of the polyunsaturated products may explain these results.[24] This, compared with the clean reactions with the [PdCl] catalytic system, also indicated that chloropalladation is more selective in discriminating different types of carbon−carbon multiple bonds in the substrates and products than hydropalladation.

Besides yield and generality, stereoselectivity is another major concern in developing an efficient synthetic method. In contrast to the cycloisomerization of simple enynes, poor *Z*/*E* selectivity was encountered for homoallylic alkynoate substrates; when the [PdCl] catalytic system was used, the reaction gave a single geometric isomer for each substrate (*Z* for 3-substituted propynoates and *E* for unsubstituted propynoates). This may also be rationalized on basis of the chemical selectivity of chloropalladation: unlike [PdH] species, palladium chloride does not react with the α-alkylidene-δ-valerolactone products to induce isomerization (see Scheme 3, path b). When isomerization was prohibited, the stereochemistry was solely determined by the step of alkyne chloropalladation: stereospecific chloropalladation (cis addition for propynoates and trans addition for 3-substituted propynoates) leads to a stereodefined carbon−carbon double bond in high selectivity.

Conclusions

As part of a systematic study concerning the properties of hydridopalladium species and palladium chloride, we examined the [PdH] and [PdCl] catalytic systems on homoallylic 2-alkynoates and ω-alken-2-ynoates. With homoallylic alkynoates, better stereoselectivity of the cyclized α-alkylidene-δ-valerolactone product was obtained in the chloropalladation system; and with ω-alken-2-ynoates, exo,exo and endo,exo cyclization were observed for [PdH] and [PdCl] systems, respectively, showing different regiochemistries. These results implied that the chloropalladation process of electron-deficient alkynes is much more selective than the corresponding hydropalladation with regard to regioselectivity and stereoselectivity.

In the comparison of these catalytic systems, we also developed two facile synthetic methods to α-alkylidene-δ-valerolactone and cycloalkene derivatives, which provided highly diastereoselective construction of β,δ-trans-substituted δ-lactones and cis-disubstituted cyclopentene derivatives, respectively. The high yield, simple procedure and good stereoselectivity should make them the methods of choice in the synthesis of functionalized lactones and carbocycles. The application of these reactions in natural product synthesis is the subject of our current interest.

Experimental Section

The catalyst $Pd(OAc)_2$ was prepared by the literature method.[25] LiCl and $CuCl_2$ were dried at 120 °C under reduced pressure for 4 h. MeCN was distilled from P_2O_5 under nitrogen. HOAc was refluxed with $KMnO_4$ for 6 h and then distilled from P_2O_5. The analytical samples were further purified by Kugelrohr distillation at the given oven temperature (ot).

Typical Procedure for the Synthesis of Homoallylic 2-Alkynoates 1. Synthesis of Homoallyl 2-Butynoate (1a). To a solution of 2-butynoic acid (1.68 g, 20 mmol) and 3-buten-1-ol (1.80 g, 25 mmol) in anhydrous ether (10 mL) was added at −20 °C dropwise a solution of DCC (4.53 g, 22 mmol) and DMAP (4-(dimethylamino)pyridine; 244 mg, 2 mmol) in anhydrous ether (40 mL) with stirring. Then the reaction mixture was stirred at 20 °C for 20 h. After the reaction was complete, the white solid was filtered off and the solvent was removed at reduced pressure. The crude product was then submitted to column chromatography on silica gel (eluent petroleum ether/ethyl acetate, 15/1), affording pure **1a**: yield 86%; ot (oven temperature) 70 °C/20 mmHg; ^{1}H NMR (300 MHz/CCl_4) δ 6.1−5.5 (m, 1H), 5.2−4.9 (m, 2H), 4.1 (t, J = 6.0 Hz, 2H), 2.3 (q, J = 6.0 Hz, 2H), 1.9 (s, 3H) ppm; IR (neat) 3060, 2200, 1710, 1640, 1250, 990, 920, 750 cm^{-1}; MS m/z 139 ($M^+ + 1$), 97, 68, 54. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.46; H, 7.65.

3-Buten-1-yl 3-phenyl-2-propynoate (1b): yield 72%; ot 70 °C/5 mmHg; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.60 (d, J = 7.0 Hz, 2H), 7.50−7.33 (m, 3H), 5.90−5.75 (m, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 9.9 Hz, 1H), 4.30 (t, J = 6.8 Hz, 2H), 2.48 (q, J = 6.8 Hz, 2H) ppm; IR (neat) 3050, 2200, 1710, 1640, 1280, 920, 760, 690 cm^{-1}; MS m/z 201($M^+ + 1$), 159, 146, 129, 102, 91, 69, 55, 43. HRMS calcd for $C_{13}H_{12}O_2$ 200.0838, found 200.0805.

1-Methyl-3-buten-1-yl 2-butynoate (1c): yield 83%; ot 82−85 °C/10 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.1−5.5 (m, 1H), 5.2−4.8 (m, 3H), 2.2 (t, J = 6.0 Hz, 2H), 1.9 (s, 3H), 1.2 (d, J = 7.0 Hz, 3H) ppm; IR (neat) 3080, 2220, 1710, 1640, 1260, 1170, 990, 750 cm-1; MS m/z 152 (M^+), 123, 82, 67, 58, 43. Anal. Calcd for $C_9H_{12}O_2$: C, 71.63; H, 7.95. Found: C, 71.87; H, 8.06.

1-Methyl-3-buten-1-yl 3-phenyl-2-propynoate (1d): yield 84%; ot 75 °C/7 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 7.4−7.3 (m, 5H), 6.1−5.5 (m, 1H), 5.1−4.8 (m, 3H), 2.3 (t, J = 6.0 Hz, 2H), 1.2 (d, J = 7.0 Hz, 3H) ppm; IR (neat) 3060, 2200, 1710, 1640,

(22) Elimination and inverse readdition of metal hydride species to carbon−carbon multiple bonds were substantially documented: Wilkinson, G.; Stone, F. G. A.; Abel, W. *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, U.K., 1982. Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301. Ma, D.; Yu, Y.; Lu, X. *J. Org. Chem.* **1989**, *54*, 1105.

(23) Ma, S.; Lu, X. Unpublished results.

(24) Maitlis, P. M. *The Organic Chemistry of Palladium*; Academic Press: New York, 1971; Vol. 2, p 137.

(25) Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G. *J. Chem. Soc.* **1965**, 3632.

1490, 1280, 1190, 760 cm-1; MS *m*/*z* 214 (M^+), 199, 173, 137, 109, 84, 68, 55, 43. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.78; H, 6.69.

3-Buten-1-yl 2-heptynoate (1e): yield 85%; ot 75 °C/5mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.1−5.5 (m, 1H), 5.2−4.9 (m, 2H), 4.2 (t, J = 6.0 Hz, 2H), 2.5 (q, J = 6.0 Hz, 2H), 2.1 (t, J = 6.0 Hz, 2H), 1.7−1.3 (m, 2H), 0.9 (t, J = 6.5 Hz, 3H) ppm; IR (neat) 3050, 2200, 1710, 1640, 1260, 990, 920, 750 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.48; H, 9.10.

1-Isopropyl-3-buten-1-yl 2-butynoate (1f): yield 78%; ot 80 °C/6 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.1−5.5 (m, 1H), 5.2−4.7 (m, 3H), 2.3 (t, J = 6.0 Hz, 2H), 2.0 (s, 3H), 1.8 (m, 1H), 0.9 (d, J = 6.0 Hz, 6H) ppm; IR (neat) 3080, 2100, 1710, 1640, 1390, 1230, 980, 920, 750 cm^{-1}; MS *m*/*z* 179 ($M^+ - 1$), 165, 151, 137, 109, 99, 79, 67, 55, 43. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.16; H, 8.56.

1-Phenyl-3-buten-1-yl 2-butynoate (1g): yield 75%; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.40−7.20 (m, 5H), 5.82 (t, J = 6.3 Hz, 2H), 5.75−5.60 (m, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.05 (d, J = 10.0 Hz, 1H), 2.75−2.50 (m, 2H), 1.95 (s, 3H) ppm; IR (neat) 3060, 3020, 2200, 1720, 1640, 1250, 760, 700 cm^{-1}; MS *m*/*z* 214 (M^+), 200, 135, 127, 121, 93, 67, 55, 43. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.92; H, 6.25.

3-Buten-1-yl propynoate (1 h): yield 57%; bp 166−170 °C; ^{1}H NMR (60 MHz/CCl_4) δ 6.0−5.5 (m, 1H), 5.2−4.9 (m, 2H), 4.1 (t, J = 6.0 Hz, 2H), 2.7 (s, 1H), 2.4 (m, 2H) ppm; IR (neat) 3300, 3060, 2100, 1720, 1640, 1220, 980, 920 cm^{-1}; MS *m*/*z* 123 ($M^+ - 1$), 96, 82, 68, 42. Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.40; H, 6.08.

1-Methyl-3-buten-1-yl propynoate (1i): yield 51%; ot 71 °C/15 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.0−5.5 (m, 1H), 5.2−4.9 (m, 3H), 2.7 (s, 1H), 2.3 (t, J = 7.0 Hz, 2H), 1.2 (d, J = 6.0 Hz, 6H) ppm; IR (neat) 3300, 2180, 1720, 1630, 1240, 1190, 990, 910 cm^{-1}; MS *m*/*z* 137($M^+ - 1$), 123, 109, 97, 67, 43. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.91; H, 7.52.

1-Isopropyl-3-buten-1-yl propynoate (1j): yield 56%; ot 80 °C/6 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.1−5.5 (m, 1H), 5.2−4.7 (m, 3H), 2.8 (s, 1H), 2.3 (t, J = 6.0 Hz, 2H), 1.9 (m, 1H), 0.9 (d, J = 6.0 Hz, 6H) ppm; IR (neat) 3300, 3080, 2200, 1710, 1640, 1370, 1230, 980, 920, 750 cm^{-1}; MS *m*/*z* 165 ($M^+ - 1$), 123, 109, 96, 84, 67, 53, 43. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.27.

1-Phenyl-3-buten-1-yl propynoate (1k): yield 45%; ot 90 °C/2 mmHg; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.40−7.25 (m, 5H), 5.87 (t, J = 7.5 Hz, 1H), 5.77−5.60 (m, 1H), 5.17−5.03 (m, 2H), 2.86 (s, 1H), 2.78−2.52 (m, 2H) ppm; IR (neat) 3300, 3080, 2100, 1720, 1640, 1220, 750, 700 cm^{-1}; MS *m*/*z* 200(M^+), 159, 131, 115, 91, 77, 65, 53. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.40; H, 5.58.

[PdH]-Catalyzed Cycloisomerization of Homoallylic 2-Alkynoates 1. General Procedure. A mixture of **1** (1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), HOAc (6 mg, 0.1 mmol), and benzene (5 mL) was stirred at 65 °C under argon. The reaction was monitored by TLC on silica gel (eluent petroleum ether/ethyl acetate, 10/1). After the reaction was completed, the solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was submitted to column chromatography on silica gel for purification. The results are shown in Table 1. The spectroscopic and analytical data of **2** are given below.

α-Ethylidene-*β*-methylene-*δ*-valerolactone (2a): yield 87%; ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.90−5.82 [m, 0.18H (*E* isomer, C_α=CH−)], 5.80−5.66 [m, 0.82H (*Z* isomer, C_α=CH−)], 5.18−5.02 (m, 2H), 4.18 (t, J = 7.0 Hz, 2H), 2.46−2.36 (m, 2H), 2.34 [d, J = 6.0 Hz, 2.46H (*Z* isomer, =CCH_3)], 2.20 [d, J = 6.0 Hz, 0.54H (*E* isomer, =CCH_3)] ppm; IR (neat) 3060, 1770, 1640, 1200, 1050, 890, 860 cm^{-1}; MS *m*/*z* 139 ($M^+ + 1$), 123, 110, 99, 85, 69. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.66; H, 7.17.

α-Benzylidene-*β*-methylene-*δ*-valerolactone (2b): yield 82%; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.68−7.30 (m, 5H), 6.30 [s, 0.20H (*E* isomer, C_α=CH−)], 5.90 [s, 0.80H (*Z* isomer, C_α=CH−)], 5.80−5.60 [m, 0.40H (*E* isomer, C_β=CH_2)], 5.20−5.00 [m, 1.60H (*Z* isomer, C_β=CH_2)], 4.22 [t, J = 8.0 Hz, 0.40H (*E* isomer, OCH_2)], 4.10 [t, J = 8.0 Hz, 1.60H (*E* isomer, OCH_2)], 2.40−2.20 (m, 2H) ppm; IR (neat) 3050, 1770, 1640, 1600, 1190, 1150, 900, 760, 690 cm^{-1}; MS *m*/*z* 200 (M^+), 147, 105, 77, 69, 55, 43. Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.48; H, 6.59. Found: C, 78.62: H, 6.64.

α-Ethylidene-*β*-methylene-*δ*-methyl-*δ*-valerolactone (2c): yield 69%; ^{1}H NMR (300 MHz/$CDCl_3$) δ 6.14−6.04 [m, 0.33H (*E* isomer, C_α=CH−)], 5.92−5.78 [m, 0.67H (Z-isomer, C_α=CH−)], 5.60−5.40 [m, 0.66H (*E* isomer, C_β=CH_2)], 5.20−5.05 [m, 1.34H (*Z* isomer, C_β=CH_2)], 5.05−4.95 (m, 1H), 2.48−2.32 (m, 1H), 2.38 [d, J = 4.0 Hz, 2H (*Z* isomer, =CCH_3)], 2.28 [d, J = 4.0 Hz, 1H (*Z* isomer, =CCH_3)], 2.25−2.15 (m, 2H), 1.28 [d, J = 6.0 Hz, 2H (*Z* isomer, $OCCH_3$)], 1.20 [d, J = 6.0 Hz, 1H (*E* isomer, $OCCH_3$)] ppm; IR (neat) 3050, 1770, 1640, 1200, 1050, 890, 850 cm^{-1}; MS *m*/*z* 153 ($M^+ + 1$), 137, 107, 85, 69, 43. Anal. Calcd for $C_9H_{12}O_2$: C, 71.63; H, 7.95. Found: C, 71.26; H, 8.02.

α-Benzylidene-*β*-methylene-*δ*-methyl-*δ*-valerolactone (2d): yield 75%; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.52−7.22 (m, 5H), 6.27 [s, 0.25H (*E* isomer, C_α=CH−)], 5.92 [s, 0.75H (*Z* isomer, C_α=CH−)], 5.70−5.50 [m, 0.50H (*E* isomer, C_β=CH_2)], 5.10−5.00 [m, 1.50H (*Z* isomer, C_β=CH_2)], 4.98−4.90 (m, 1H), 2.40−2.00 (m, 2H), 1.64 [d, J = 7.0 Hz, 0.75H (*E* isomer, $OCCH_3$)], 1.20 [d, J = 7.0 Hz, 2.25H (*Z* isomer, $OCCH_3$)] ppm; IR (neat) 3080, 1760, 1640, 1600, 1500, 1190, 760, 700 cm^{-1}; MS *m*/*z* 214 (M^+), 171, 147, 131, 105, 77, 69, 43. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.52; H, 6.99.

$PdCl_2$-Catalyzed Cyclization of Homoallylic 2-Alkynoates (1) in the Presence of $CuCl_2$ and LiCl. General Procedure. A mixture of **1** (1 mmol), $PdCl_2$ (9 mg, 0.05 mmol), $CuCl_2$ (405 mg, 3 mmol), LiCl (255 mg, 6 mmol) and MeCN (10 mL) was stirred at room temperature for 50 h. The reaction was monitored by TLC on silica gel (eluent petroleum ether/ethyl acetate, 10/1). After the reaction was completed, ether (80 mL) was added. The mixture was then washed with water (10 mL × 3) and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was submitted to column chromatography on silica gel to give **5**.

α-(*Z*)-(1-Chloroethylidene)-*β*-(chloromethyl)-*δ*-valerolactone (5a): yield 62%; mp 67−70 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.30 (dt, J = 11.0, 2.0 Hz, 1H), 4.04 (dt, J = 11.0, 2.0 Hz, 1H), 3.55−3.35 (m, 3H), 2.36 (s, 3H), 2.32−2.24 (m, 1H), 2.04−1.80 (m, 1H) ppm; IR (Nujol) 1740, 1620, 1460, 1380, 1140, 780, 760, 660 cm^{-1}; MS *m*/*z* 213 [M^+(^{37}Cl) + 1], 211 [M^+(^{37}Cl,^{35}Cl) + 1], 209 [M^+(^{35}Cl) + 1], 175, 173, 161, 159, 129, 77, 65. Anal. Calcd for $C_8H_{10}Cl_2O_2$: C, 45.96; H, 4.82. Found: C, 46.14; H, 5.10.

***trans*-α-(*Z*)-(1-Chloroethylidene)-*β*-(chloromethyl)-*δ*-methyl-*δ*-valerolactone (5c):** yield 86%; mp 85−87 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.25 (dqd, J = 12.4, 6.3, 1.9 Hz, 1H), 3.55 (m, 1H), 3.36 (d, J = 6.9 Hz, 2H), 2.36 (ddd, J = 14.2, 6.7, 1.8 Hz, 1H), 2.30 (s, 3H), 1.65 (ddd, J = 14.2, 12.4, 6.7 Hz, 1H), 1.40 (d, J = 6.3 Hz, 3H) ppm; IR (Nujol) 1730, 1630, 1380, 1260, 1200, 940, 790, 700 cm^{-1}; MS *m*/*z* 227 [M^+(^{37}Cl) + 1], 225 [M^+(^{37}Cl,^{35}Cl) + 1], 223 [M^+(^{35}Cl) + 1], 175, 173, 131, 129, 109, 67, 65. Anal. Calcd for $C_9H_{12}Cl_2O_2$: C, 48.45; H, 5.42. Found: C, 48.29; H, 5.37.

***trans*-α-(*Z*)-(1-Chloroethylidene)-*β*-(chloromethyl)-*δ*-isopropyl-*δ*-valerolactone (5f):** yield 72%; mp 53−55 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 3.80 (ddd, J = 12.3, 6.8, 1.6 Hz, 1H), 3.56−3.48 (m, 1H), 3.45 (d, J = 7.0 Hz, 2H), 2.40 (ddd, J = 14.6, 7.1, 1.5 Hz, 1H), 2.30 (s, 3H), 1.90 (ddd, J = 14.6, 12.3, 6.8 Hz, 1H), 1.68−1.55 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H) ppm; IR (Nujol) 1740, 1630, 1360, 1160, 720, 660 cm^{-1}; MS *m*/*z* 255 [M^+(^{37}Cl) + 1], 253 [M^+(^{37}Cl,^{35}Cl) + 1], 251 [M^+(^{35}Cl) + 1], 211, 209, 207, 162, 160, 129, 79, 43.

Anal. Calcd for $C_{11}H_{16}Cl_2O_2$: C, 52.61; H, 6.42. Found: C, 52.83; H, 6.40.

***trans*-α-(*Z*)-(1-Chloroethylidene)-*β*-(chloromethyl)-*δ*-phenyl-*δ*-valerolactone (5g):** yield 77%; mp 114−116 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.45−7.30 (m, 5H), 5.05 (dd, J = 12.0, 1.8 Hz, 1H), 3.62−3.40 (m, 3H), 2.55 (ddd, J = 15.0, 6.9, 1.7 Hz, 1H), 2.40 (s, 3H), 2.00 (ddd, J = 15.0, 12.0, 6.9 Hz, 1H) ppm; IR (Nujol) 3030, 1730, 1630, 1370, 1160, 790, 760, 700, 670 cm^{-1}; MS m/z 289 [M$^+$(^{37}Cl) + 1], 287 [M$^+$(^{37}Cl,^{35}Cl) + 1], 285 [M$^+$(^{35}Cl) + 1], 223, 221, 145, 143, 105, 91, 77, 65. Anal. Calcd for $C_{14}H_{14}Cl_2O_2$: C, 58.97; H, 4.95. Found: C, 58.98; H, 4.90.

α-(*E*)-(1-Chloromethylene)-*β*-(chloromethyl)-*δ*-valerolactone (5h): yield 67%; mp 72-75 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 6.92 (d, J = 1.2 Hz, 1H), 4.36 (dt, J = 11.5, 4.6 Hz, 1H), 4.17 (dt, J = 11.5, 4.3 Hz, 1H), 3.54 (d, J = 6.8 Hz, 2H), 3.24−3.08 (m, 1H), 2.36−2.18 (m, 1H), 2.08−1.86 (m, 1H) ppm; IR (Nujol) 3060, 1760, 1640, 1180, 780, 690, 660, 540 cm^{-1}; MS m/z 197 [M$^+$(^{37}Cl) − 1], 195 [M$^+$(^{37}Cl,^{35}Cl) − 1], 193 [M$^+$(^{35}Cl) − 1], 161, 159, 109, 107, 93, 65, 49. Anal. Calcd for $C_7H_8Cl_2O_2$: C, 43.11; H, 4.13. Found: C, 43.32; H, 3.76.

***trans*-α-(*Z*)-(1-Chloromethylene)-*β*-(chloromethyl)-*δ*-methyl-*δ*-valerolactone (5i):** yield 68%; mp 77−78 °C. ^{1}H NMR (300 MHz/$CDCl_3$) δ 6.65 (s, 1H), 4.30 (dqd, J = 12.5, 6.0, 1.7 Hz, 1H), 3.50 (d, J = 6.7 Hz, 2H), 3.20 (quint, J = 8.0 Hz, 1H), 2.25 (ddd, J = 14.3, 8.3, 1.6 Hz, 1H), 1.65 (ddd, J = 14.3, 12.5, 8.1 Hz, 1H), 1.45 (d, J = 6.0 Hz, 3H) ppm; IR (Nujol) 3030, 1740, 1590, 1230, 1130, 960, 870, 700, 640 cm^{-1}; MS m/z 213 [M$^+$(^{37}Cl) + 1], 211 [M$^+$(^{37}Cl,^{35}Cl) + 1], 209 [M$^+$(^{35}Cl) + 1], 175, 173, 131, 129, 89, 87, 65. Anal. Calcd for $C_8H_{10}Cl_2O_2$: C, 45.96; H, 4.82. Found: C, 45.95; H, 4.54.

***trans*-α-(*Z*)-(1-Chloromethylene)-*β*-(chloromethyl)-*δ*-isopropyl-*δ*-valerolactone (5j):** yield 76%; mp 52−56 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 6.65 (s, 1H), 3.88 (ddd, J = 12.0, 6.0, 1.7 Hz, 1H), 3.52 (d, J = 6.6 Hz, 2H), 3.15 (quint, J = 7.0 Hz, 1H), 2.25 (ddd, J = 14.1, 7.4, 1.7 Hz, 1H), 1.92 (ddd, J = 14.1, 12.0, 7.4 Hz, 1H), 1.65−1.50 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H) ppm; IR (Nujol) 3060, 1730, 1610, 1210, 1120, 980, 920, 850, 700, 580 cm^{-1}; MS m/z 241 [M$^+$(^{37}Cl) + 1], 239 [M$^+$(^{37}Cl,^{35}Cl) + 1], 237 [M$^+$(^{35}Cl) + 1], 195, 193, 167, 165, 131, 129, 65. Anal. Calcd for $C_{10}H_{14}Cl_2O_2$: C, 50.65; H, 5.95. Found: C, 50.38; H, 5.66.

***trans*-α-(*Z*)-(1-Chloromethylene)-*β*-(chloromethyl)-*δ*-phenyl-*δ*-valerolactone (5k):** yield 78%; mp 125−127 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.45−7.30 (m, 5H), 6.35 (s, 1H), 5.15 (dd, J = 11.9, 2.0 Hz, 1H), 3.55 (d, J = 6.7 Hz, 2H), 3.28 (quint, J = 7.2 Hz, 1H), 2.46 (ddd, J = 14.4, 7.3, 2.1 Hz, 1H), 1.95 (ddd, J = 14.4, 11.9, 7.1 Hz, 1H) ppm; IR (Nujol) 3050, 1730, 1590, 1200, 1130, 870, 770, 710, 580 cm^{-1}; MS m/z 275 [M$^+$(^{37}Cl) + 1], 273 [M$^+$(^{37}Cl,^{35}Cl) + 1], 271 [M$^+$(^{35}Cl) + 1], 209, 207, 130, 105, 91, 77, 65. Anal. Calcd for $C_{13}H_{12}Cl_2O_2$: C, 57.59; H, 4.40. Found: C, 57.87; H, 4.67.

Preparation of Methyl 5-Hydroxy-6-hepten-2-ynoate (9a). The corresponding acid[26] (1.40 g, 10 mmol), Na_2CO_3 (1.06 g, 10 mmol), and MeI (2.84 g, 20 mmol) were mixed in anhydrous DMF (20 mL). Stirring was continued for 24 h at room temperature. Ethyl ether (80 mL) was added, and the mixture was washed by brine (5 mL × 5). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (eluent petroleum ether/ethyl acetate, 10/2) on silica gel gave the product **9a** (1.50 g, 98%): ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.95 (ddd, J = 17.1, 10.4, 6.1 Hz, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 4.68−4.55 (m, 1H), 3.90 (s, 3H), 3.05 (dd, J = 14.0, 8.2 Hz, 1H), 2.71 (dd, J = 14.0, 5.3 Hz, 1H) ppm; IR (neat) 3400, 2950, 2250, 1720, 1440, 1260, 1120, 1080, 990, 930, 820, 755 cm^{-1}; MS m/z (%) 154 (M$^+$) (0.12), 136 (18.11), 115 (25.18), 105 (100.00), 87 (79.77), 65 (21.34), 51 (17.18). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.71; H, 6.33.

(26) The acid was prepared from lithium acetylide of hex-1-en-5-yn-3-ol and CO_2 (Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 100).

Methyl 5-(Benzyloxy)-6-hepten-2-ynoate (9b). 9b was prepared from **9a** and benzyl bromide in the presence of NaH using the literature method:[27] ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.45−7.30 (m, 5H), 5.80 (ddd, J = 16.5, 10.8, 7.6 Hz, 1H), 5.37 (d, J = 10.8 Hz, 1H), 5.32 (d, J = 16.5 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.04 (dt, J = 7.6, 6.0 Hz, 1H), 3.90 (s, 3H), 2.78 (dd, J = 17.0, 6.0 Hz, 1H), 2.64 (dd, J = 17.0, 6.0 Hz, 1H) ppm; IR (neat) 3050, 2950, 2220, 1720, 1420, 1260, 1180, 1070, 980, 750, 695 cm^{-1}; MS m/z (%) 243 (M$^+$ − 1) (1.77), 213 (17.81), 185 (10.03), 147 (10.71), 129 (3.80), 91 (100.00), 77 (71.12), 65 (50.99). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.55; H, 6.98.

Methyl 4-(Allyloxy)-2-butynoate (9c). To a solution of allyl propargyl ether (4.80 g, 50 mmol) in anhydrous THF (40 mL) was added BuLi in hexane (2.5 M, 22 mL) at 0 °C. The solution was stirred for another 15 min at room temperature. To a cooled solution of ClCOOMe (7.08 g, 75 mmol) in THF (20 mL) was slowly added the prepared acetylide solution. The temperature was kept at −30 to −20 °C and stirring continued for 30 min. After removal of solvent and excess ClCOOMe by evaporation, distillation under reduced pressure afforded **9c** (5.65 g, 73%): bp 108 °C/10 mmHg; ^{1}H NMR (300 MHz/$CDCl_3$) δ 5.88-5.72 (m, 1H), 5.25 (d, J = 17.2 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.21 (s, 2H), 4.00 (d, J = 5.7 Hz, 2H), 3.70 (s, 3H) ppm; IR (neat) 2950, 2240, 1725, 1440, 1260, 1040, 750 cm^{-1}; MS m/z (%) 153 (M$^+$ − 1) (23.80), 125 (31.51), 111 (33.92), 93 (46.84), 81 (52.01), 73 (93.35), 69 (72.66), 55 (100.00). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.08; H, 6.77.

Benzyl 4-(Allyloxy)-2-butynoate (9d). 9d was prepared from allyl propargyl ether and ClCOOBn similarly: yield 75%; bp 85 °C/2 mmHg; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.45−7.30 (m, 5H), 5.94−5.80 (m, 1H), 5.33 (dt, J = 17.4, 1.6 Hz, 1H), 5.15 (dt, J = 10.4, 1.2 Hz, 1H), 5.10 (s, 2H), 4.28 (s, 2H), 4.12−4.02 (m, 2H) ppm; IR (neat) 3050, 2900, 2250, 1720, 1500, 1460, 1380, 1250, 1100, 1060, 940, 750 cm^{-1}; MS m/z (%) 229 (M$^+$ − 1) (0.16), 201 (0.15), 183 (1.60), 172 (12.12), 155 (12.40), 115 (19.91), 91 (100.00), 79 (14.35), 66 (18.84). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.87; H, 6.11.

[PdH]-Catalyzed Cyclization of 9. The procedure was similar to that for **1**.

3-Methylene-4-((methoxycarbonyl)methylene)tetrahydrofuran (10c): ^{1}H NMR (300 MHz/$CDCl_3$) δ 6.12 (t, J = 2.2 Hz, 1H), 5.70 (t, J = 2.2 Hz, 1H), 5.23−5.20 (m, 1H), 4.90 (d, J = 2.2 Hz, 2H), 4.45 (s, 2H), 3.72 (s, 3H) ppm; IR (neat) 3010, 2950, 1720, 1660, 1500, 1380, 1350, 1170, 1070 cm^{-1}; MS m/z (%) 153 (M$^+$ − 1)(41.18), 125 (32.78), 111 (51.10), 94 (34.81), 81 (52.40), 73 (93.16), 69 (100.00), 55 (59.18). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.08; H, 6.71.

3-Methylene-4-(((benzyloxy)carbonyl)methylene)tetrahydrofuran (10d): mp 67−69 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.45−7.25 (m, 5H), 6.11 (t, J = 2.6 Hz, 1H), 5.61 (t, J = 2.6 Hz, 1H), 5.26−5.20 (m ,1H), 5.20 (s, 2H), 4.95 (d, J = 2.6 Hz, 2H), 4.49 (t, J = 2.6 Hz, 2H) ppm; IR (KBr) 3050, 2950, 2820, 1720, 1660, 1500, 1450, 1380, 1350, 1260, 1070, 750, 695 cm^{-1}; MS m/z (%) 230 (2.71), 201 (1.54), 183 (17.26), 172 (21.67), 155 (12.44), 116 (19.01), 91 (100.00), 79 (42.16), 65 (28.81). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.41; H, 6.18.

[PdCl]-Catalyzed Cyclization of 9. The procedure was similar to that for **1**.

4-Chloro-3-(methoxycarbonyl)-2-(chloromethyl)-3-cyclopenten-1-ol (11a): ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.75−4.55 (m, 1H), 4.20−3.95 (m, 2H), 3.85 [s, 1.50H (cis isomer)], 3.80 [s, 1.50H (trans isomer)], 3.50−3.30 (m, 1H), 3.00−2.70 (m, 2H) ppm; IR (neat) 3500, 2950, 2870, 1720, 1630, 1470, 1380, 1250, 1150, 1040, 980, 690 cm^{-1}; MS m/z (%) 228 [M$^+$(^{37}Cl)] (0.15), 226 [M$^+$(^{37}Cl,^{35}Cl)] (0.56), 224 [M$^+$(^{35}Cl)] (1.47), 208 (10.19), 206 (30.44), 195 (4.69), 193 (13.18), 160 (7.99), 158

(27) Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529.

(19.78), 117 (25.11), 105 (17.49), 95 (100.00), 43 (15.96). Anal. Calcd for $C_8H_{10}Cl_2O_3$: C, 42.69; H, 4.48. Found: C, 42.50; H, 4.77.

4-(Benzyloxy)-1-Chloro-3-(chloromethyl)-2-(methoxycarbonyl)-1-cyclopentene (11b). Cis isomer: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.42−7.33 (m, 5H), 4.59 (s, 2H), 4.35 (q, J = 7.1 Hz, 1H), 4.00 (dd, J = 10.8, 3.4 Hz, 1H), 3.91 (dd, J = 10.8, 6.1 Hz, 1H), 3.80 (s, 3H), 3.55−3.45 (m,1H), 3.01 (dd, J = 17.3, 6.5 Hz, 1H), 2.82 (dd, J = 17.3, 7.4 Hz, 1H) ppm; IR (neat) 2900, 1720, 1620, 1440, 1350, 1230, 1085, 1020, 750, 700 cm^{-1}; MS m/z (%) 318 [M^+(^{37}Cl)] (0.10), 316 [M^+(^{37}Cl,^{35}Cl)] (0.48), 314 [M^+(^{35}Cl)] (0.66), 285 (0.95), 283 (1.39), 243 (1.60), 208 (4.79), 160 (6.76), 125 (6.72), 91 (100.00), 65 (9.18). Anal. Calcd for $C_{15}H_{16}Cl_2O_3$: C, 57.16; H, 5.12. Found: C, 57.00; H, 5.42. Trans isomer: ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.42−7.30 (m, 5H), 4.50 (s, 2H), 4.17−4.10 (m, 1H), 3.95−3.82 (m, 1H), 3.77 (s, 3H), 3.75−3.60 (m, 1H), 3.50−3.42 (m, 1H), 2.94 (dd, J = 17.2, 6.6 Hz, 1H), 2.75 (dd, J = 17.2, 4.0 Hz, 1H) ppm; IR (neat) 2950, 1725, 1625, 1440, 1350, 1240, 1085, 1020, 750, 700 cm^{-1}; MS m/z (%) 318 [M^+(^{37}Cl)] (0.10), 316 [M^+(^{37}Cl,^{35}Cl)] (0.44), 314 [M^+(^{35}Cl)] (0.78), 285 (1.25), 283 (3.55), 243 (4.16), 208 (5.80), 174 (7.11), 125 (7.62), 91 (100.00), 65 (10.98). Anal. Calcd for $C_{15}H_{16}Cl_2O_3$: C, 57.16; H, 5.12. Found: C, 56.97; H, 5.00.

3-Bromo-5-(bromomethyl)-4-(methoxycarbonyl)dihydropyran (11c): ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.38−4.25 (m, 2H), 4.20 (dd, J = 17.8, 2.3 Hz, 1H), 3.88 (s, 3H), 3.67 (dd, J = 11.8, 2.7 Hz, 1H), 3.55 (dd, J = 9.9, 4.0 Hz, 1H), 3.47 (d, J = 9.9 Hz, 1H), 3.06−2.98 (m, 1H) ppm; IR (neat) 2950, 2850, 1730, 1620, 1440, 1275, 1240, 1140, 1110, 895, 790 cm^{-1}; MS m/z (%) 316 [M^+(^{81}Br)] (5.26), 314 [M^+(^{81}Br,^{79}Br)] (9.42), 312 [M^+(^{79}Br)] (4.91), 285 (6.29), 283 (11.67), 281 (6.12), 257 (18.45), 255 (34.06), 253 (17.46), 235 (100.00), 233 (95.03), 203 (52.08), 95 (38.86), 65 (59.96). Anal. Calcd for $C_8H_{10}Br_2O_3$: C, 30.60; H, 3.21. Found: C, 30.39; H, 2.86.

3-Bromo-4-((benzyloxy)carbonyl)-5-(bromomethyl)dihydropyran (11d): ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.45−7.30 (m, 5H), 5.10 (s, 2H), 4.38−4.25 (m, 2H), 4.20 (dd, J = 17.6, 2.1 Hz, 1H), 3.67 (dd, J = 12.0, 2.1 Hz, 1H), 3.56 (dd, J = 10.1, 5.0 Hz, 1H), 3.49 (d, J = 10.1 Hz, 1H), 3.10−3.00 (m, 1H) ppm; IR (neat) 3030, 2950, 1725, 1620, 1440, 1270, 1250, 1140, 1110, 890, 750, 700 cm^{-1}; MS m/z (%) 392 [M^+(^{81}Br)] (5.12), 390 [M^+(^{81}Br,^{79}Br)] (10.48), 388 [M^+(^{79}Br)] (6.01), 299 (10.78), 297 (6.15), 285 (12.10), 283 (26.78), 281 (13.17), 255 (6.19), 253 (10.71), 107 (45.45), 91 (100.00), 77 (43.66), 65 (10.44). Anal. Calcd for $C_{14}H_{14}Br_2O_3$: C, 43.11; H, 3.62. Found: C, 43.41; H, 3.91.

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Supporting Information Available: Figures giving ^{1}H NMR spectra for **1b**,**g**,**k** (3 pages). Ordering information is given on any current masthead page.

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