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Molecular oxygen promoted oxidative cleavage of carbon–palladium bonds — catalytic cyclization of allylic 2-alkynoates to α-alkylidene-γ-butyrolactones by a Pd^{II} complex

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Abstract

Molecular oxygen was used as the oxidant to promote the Pd^{II} and Cu^{II} catalyzed cyclization of acyclic allylic 2-alkynoates, yielding α-haloalkylidene-γ-butyrolactones with high stereoselectivity. The stereochemistry of halopalladation of the carbon–carbon triple bond, 1,2-induction in the intramolecular carbon–carbon double insertion and oxidative cleavage of carbon–palladium bonds in the cyclization reaction were studied in detail.

Keywords: Palladium(II); Molecular oxygen; Oxidative cleavage; Butyrolactone; Cyclization; Stereoselectivity

1. Introduction

The stereoselective process has played a central role in the synthesis of compounds possessing medicinal or theoretical significance [1]. Recently, transition metal-catalyzed reactions, especially those that construct cyclic structures from easily available acyclic precursors, have received much attention owing to the template action of the transition metals [2].

The α-methylene-γ-butyrolactone ring is an integral building block of many important naturally occurring compounds which exhibit many interesting biological activities such as cytotoxicity, antitumority, etc. [3]. Also, γ-butyrolactones are versatile intermediates in organic synthesis and are widely used in natural product synthesis [4]. Thus, it is of common interest to study the construction of γ-butyrolactones. We have been engaged in the development of new synthetic methods for α-alkylidene-γ-butyrolactone derivatives from readily available acyclic allylic 2-alkynoates [5]. In our reaction, the lactone ring is constructed by carbon–carbon bond formation, which is quite different from the other methodologies reported. Based on this strategy, the carbon–carbon triple bond was first halopalladated to generate a vinylpalladium species, followed by intramolecular carbon–carbon double-bond insertion to form a new carbon–palladium bond which was quenched using different methods, such as dehalopalladation [5b], deacetoxypalladation [5c], dehydroxypalladation [5d], carbonylation [5e] and oxidative cleavage by CuX_2 [5f], etc., to complete the catalytic cycle. Thus, a series of α-methylene-γ-butyrolactone derivatives were synthesized stereoselectively (Scheme 1).

Recently, considerable attention has been devoted to the development of aerobic oxidation catalysts for economical and environmental reasons [6]. The $CuCl_2$ assisted cleavage of the carbon–palladium bond by molecular oxygen in a Waker-type oxidation reaction has been extensively studied [7]. We wondered if oxidative cleavage of the carbon–palladium bond by molecular oxygen in the presence of a nucleophile would take place in our cyclization reaction. Should this be possible, the α-alkylidene-γ-butyrolactone derivatives could be synthesized from acyclic precursors in a very simple manner. In this paper, we wish to report our recent results on the molecular oxygen promoted palladium(II) and cupric salt catalyzed cyclization of 2′-alkenyl 2-alkynoates in the presence of lithium halide.

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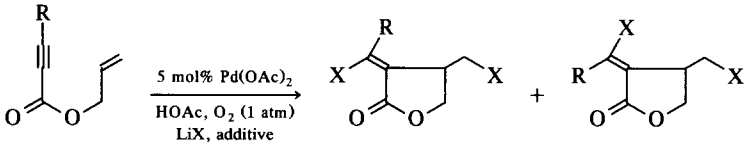
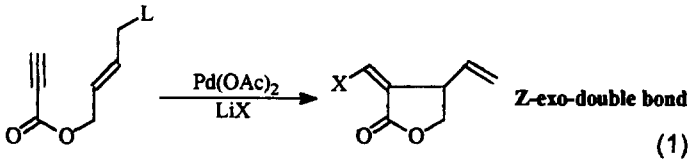
Table 1
Cyclization of allyl 2-alkynoates (**1**) under oxygen



(**1**) (*Z*-**2**) (*E*-**2**)

Entry no.	**1**; R	LiX (equiv.)	Additive (equiv.)	Isolated yield (%)	
				Z-**2**	*E*-**2**
1 [a]	Me (**1a**)	LiCl(3)	–	40.5 (*Z*-**2a**)	–
2	Me (**1a**)	LiCl(5)	CuCl(0.4)	64.0 (*Z*-**2a**)	3 (*E*-**2a**)
3 [b]	Me (**1a**)	LiCl(5)	CuCl(0.4)	38.0 (*Z*-**2a**)	3 (*E*-**2a**)
4	Me (**1a**)	LiCl(5)	$CuCl_2$(0.4)	73.0 (*Z*-**2a**)	6 (*E*-**2a**)
5	Me (**1a**)	LiCl(5)	$Cu(OAc)_2$(0.4)	83.0 (*Z*-**2a**)	8 (*E*-**2a**)
6	i-C_7H_{15}(**1b**)	LiCl(6)	$Cu(OAc)_2$(0.4)	68.0 (*Z*-**2b**)	14.5 (*E*-**2b**)
7	i-C_7H_{15}(**1b**)	LiCl(6)	$CuCl_2$(0.4)	61.0 (*Z*-**2b**)	12.5 (*E*-**2b**)
8	^{n}Pr (**1c**)	LiCl(6)	$Cu(OAc)_2$(0.4)	68.0 (*Z*-**2c**)	12.0 (*E*-**2c**)
9	^{n}Pr (**1c**)	LiCl(10)	$Cu(OAc)_2$(0.4)	71.5 (*Z*-**2c**)	7.0 (*E*-**2c**)
10	^{n}Pr (**1c**)	LiBr(8)	$Cu(OAc)_2$(0.4)	80.5 (*Z*-**2′c**)	14.5 (*E*-**2′c**)
11	Me (**1a**)	LiBr(8)	$Cu(OAc)_2$(0.4)	70.0 (*Z*-**2′a**)	6.5 (*E*-**2′a**)

[a] $PdCl_2(PhCN)_2$ as the catalyst.
[b] Reaction using ultrasonic means (100 W).



(**1**)

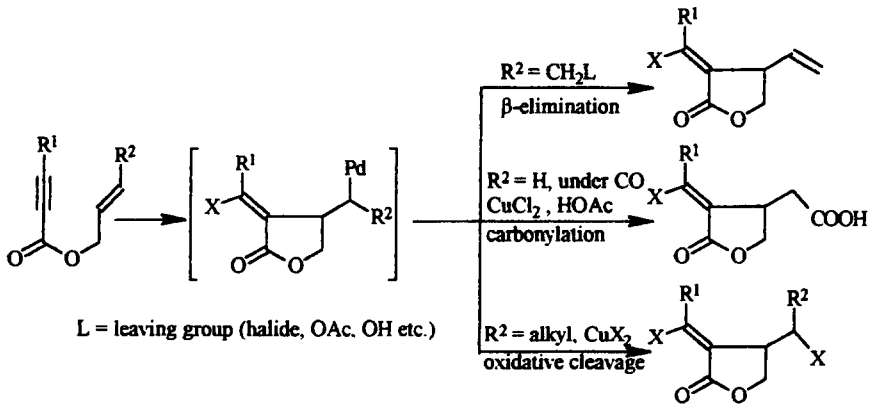
2. Results and discussion

2.1. Cyclization of allyl 2-alkynoates (1) promoted by molecular oxygen

We first tried the $PdCl_2(PhCN)_2$-catalyzed reaction of allyl 2-butynoate (**1a**) under O_2 in HOAc. The reaction afforded α-chloromethylene-β-chloromethyl-γ-butyrolactone (**2a**) with *Z*-selectivity in the exocyclic double bond, which was similar to the result found in the reaction of allyl 2-butynoate with a stoichiometric amount of $CuCl_2$ [5f]. When a catalytic amount of co-oxidant, e.g. CuCl, $CuCl_2$, etc. was added, the cyclization reaction occurred with improved yield. Finally, the cyclization reaction in HOAc catalyzed by $Pd(OAc)_2$ (0.05 equiv.) and $Cu(OAc)_2$ (0.4 equiv.) in the presence of LiCl (5 equiv.) gave the best results (Table 1).

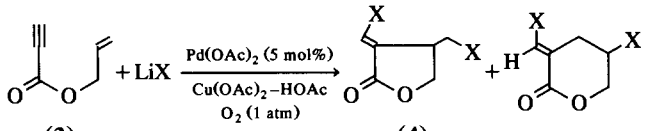
Using the similar catalytic system, the cyclization of other allyl 3-substituted 2-alkynoates also proceeded smoothly under oxygen at room temperature (entries 6–9, Table 1).

When lithium bromide was used as the nucleophile



Scheme 1.

Table 2
Oxygen-mediated cyclization of allyl propynoate (3) [a]



(3) (4) (5)

Entry no.	LiX (equiv.)	$Cu(OAc)_2$ (equiv.)	Isolated yield (%)		
			4	5	(4/5) [b]
1	LiCl(6)	0	8.5	14	38:62
2	LiCl(6)	0.4	33	16.5	67:33
3	LiCl(2)	[c]	58	0	–
4	LiBr(6)	0.4	42.5 [d]	37 [e]	53.5:46.5

[a] All reaction were carried out at 40°C. [b] Isolated ratio.
[c] $CuCl_2$ (5 equiv.) was used in the reaction. [d] Brominated γ-butyrolactone product **4'**.
[e] Brominated δ-valerolactone product **5'**.

instead of lithium chloride, the oxygen-promoted cyclization also took place with the same catalytic system affording brominated α-alkylidene-γ-butyrolactone derivatives (entries 10, 11, Table 1).

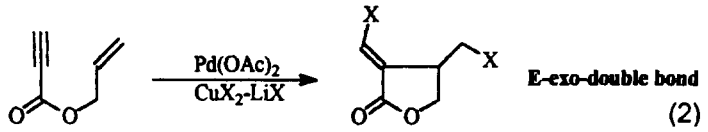
2.2. Cyclization of allyl propynoate (3) — stereochemistry of halopalladation of terminal carbon–carbon triple bonds

We found that halopalladation of the carbon–carbon triple bond of propynoates exhibited a different stereochemical behaviour in the two catalytic systems {Eq. (1) [5b] and Eq. (2) [5f]}.

In the first reaction, *trans*-halopalladation of the carbon–carbon triple bond occurred to afford a *Z*-exocyclic double bond in the lactone product [5b], while *cis*-halopalladation of the carbon–carbon triple bond affording an *E*-exocyclic double bond was found in the second reaction [5f]. The only difference is that in the second reaction, $CuCl_2$ was used as the oxidant in the oxidative cleavage of the carbon–palladium bond [Eq. (2)]. It is suggested that the cupric salt may play an important role in the halopalladation step in the second reaction. To demonstrate the role of the Cu^{II} salt, the palladium acetate-catalyzed reaction of allyl propynoate (**3**) with LiCl in HOAc under oxygen was carried out in the absence of $CuCl_2$ (entry 1, Table 2). We found that the exocyclic double bond of the isolated γ-butyrolactone product was still in the *E* form, implying that halopalladation still occurred in a *cis* manner under the oxygen even in the absence of a cupric salt. It is possible that the oxidant caused the halopalladation to occur in a different way. In this reaction, besides the five-membered γ-butyrolactone product **4**, a six-membered δ-valerolactone (**5**) was also obtained in 14% yield; this was not found in the reaction using 5 equiv. of $CuCl_2$ (entry 3, Table 2). Also, the cyclization of allyl 2-propynoate could be improved by a catalytic amount of $Cu(OAc)_2$ (entry 2, Table 2).

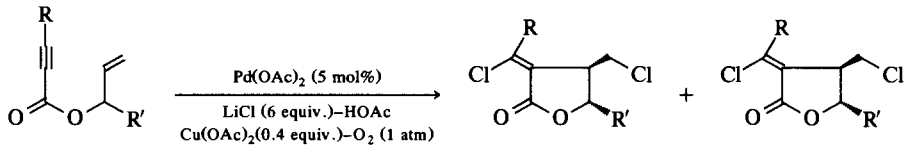
The reaction of **3** with LiBr under oxygen in the absence of $CuCl_2$ yielded a brominated acyclic product **6** rather than the expected cyclic product [Eq. (3)]. It is possible that the bromide ion is easily oxidized in the reaction system to give molecular bromine, which added readily to the carbon–carbon triple bond.

In the presence of a catalytic amount of $Cu(OAc)_2$, the palladium-catalyzed cyclization reaction of **3** with



(2)

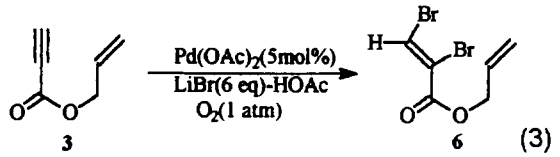
Table 3
Oxygen-mediated cyclization of 1'-substituted allylic 2-alkynoates



(7) (*cis*-8) (*trans*-8)

Entry No.	7	R	R'	Yield (%)	*cis*-8/*trans*-8 [a]	
1	*rac*-**7a**	CH_3	C_5H_{11}	53	(>97:3)	*cis*-**8a**/*trans*-**8a** [b]
2	(*S*)-**7a**	CH_3	C_5H_{11}	58	(>97:3)	(4*S*,5*S*)-**8a**/(4*R*,5*S*)-**8a** [b]
3	*rac*-**7b**	H	^iPr	42	(<3:97)	*cis*-**8b**/*trans*-**8b** [c]

[a] Determined by 300 MHz ^1H NMR spectroscopy. [b] *Z*-Exocyclic double bond.
[c] *E*-Exocyclic double bond.



(3)

LiBr under oxygen also occurred smoothly, affording two cyclic products **4'** and **5'** in reasonable yield with good stereoselectivity (entry 4, Table 2).

2.3. 1,2-Stereoinduction of intramolecular carbon–carbon double-bond insertion in the oxygen-mediated cyclization reaction

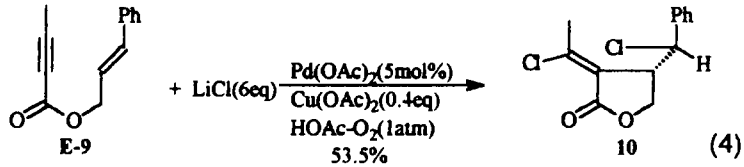
Our recent research has revealed that the Pd^{II}-catalyzed reaction of 1'-alkyl 3-unsubstituted 2-propynoates with $CuCl_2/LiCl$ gave *trans* selectivity for the β,γ-substituents in the lactones, while 1'-alkyl 3-substituted 2-alkynoates afforded *cis* selectivity for the β,γ-substituents in the lactones [5f,8].

The reaction under oxygen showed a similar stereochemistry. For the allylic 3-substituted 2-alkynoate, only *cis*-β,γ-disubstituted-α-(*Z*)-alkylidene-γ-butyrolactone was obtained (entry 1, Table 3). Starting from a homochiral substrate, an enantiomerically pure β,γ-substituted-α-alkylidene-γ-butyrolactone could be obtained (entry 2, Table 3). However, cyclization of 1'-isopropyl-allyl propynoate only gave the *trans* product (relative to the β,γ-substituents) with an *E*-exocyclic double bond (entry 3, Table 3). Such stereochemistry indicates that the substituent R in substrate **7** plays an important role, not only in the stereochemistry of halopalladation of the carbon–carbon triple bond but also in the diastereoselectivity of the intramolecular carbon–carbon double-bond insertion reaction. The stereochemical results arising from the cyclization reaction may be rationalized on the basis of steric/conformational effects in the transition state for intramolecular carbon–carbon double-bond insertion, as proposed in our previous paper [5f].

2.4. Stereochemistry of oxidative cleavage of the carbon–palladium bond under oxygen

Oxidative cleavage of the carbon–palladium σ-bond takes place in a number of palladium-catalyzed oxidation reactions in the presence of nucleophiles [9]. The oxidizing agent usually weakens the palladium–carbon bonds, so that the palladium is converted into a good leaving group [10]. Although oxidative cleavage of carbon–palladium bonds has been studied extensively, the detailed mechanisms of these reactions are still unclear. Recently, we established the cleavage of carbon–palladium bonds by cupric chloride with predominant retention of configuration at the carbon atom [11], which is different from results reported in the literature [9,12].

The palladium-catalyzed cyclization of the 2-butynoate *E*-**9** with LiCl under oxygen in the presence of 0.4 equiv. of $Cu(OAc)_2$ afforded the cyclic product **10** selectively [Eq. (4)]; for the *Z*-substrate *Z*-**9**, the cyclization reaction afforded **10'** as the major product



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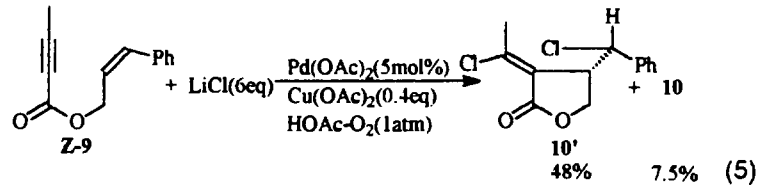
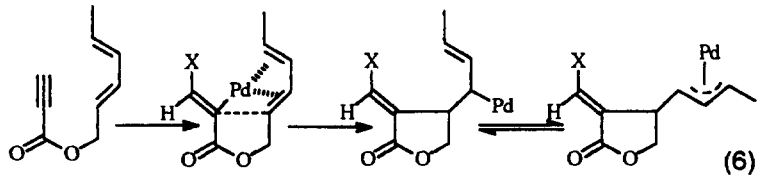
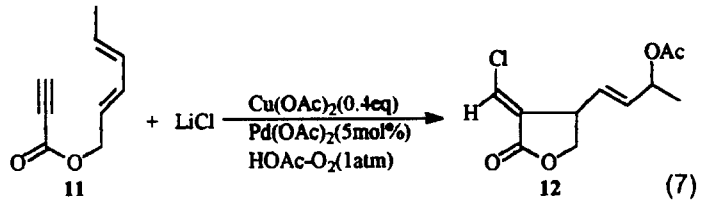
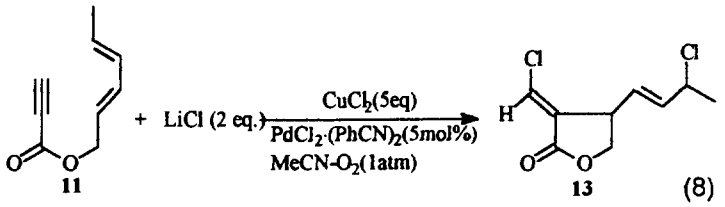


(5)



(6)





[Eq. (5)]. The structure of the products was determined by comparing the spectral data with those for the authentic compounds. This result indicates that oxidative cleavage of the carbon–palladium bond under oxygen also occurs with predominant retention of the configuration at the carbon atom [11].

2.5. Cyclization of 2,4-hexadienyl propynoate

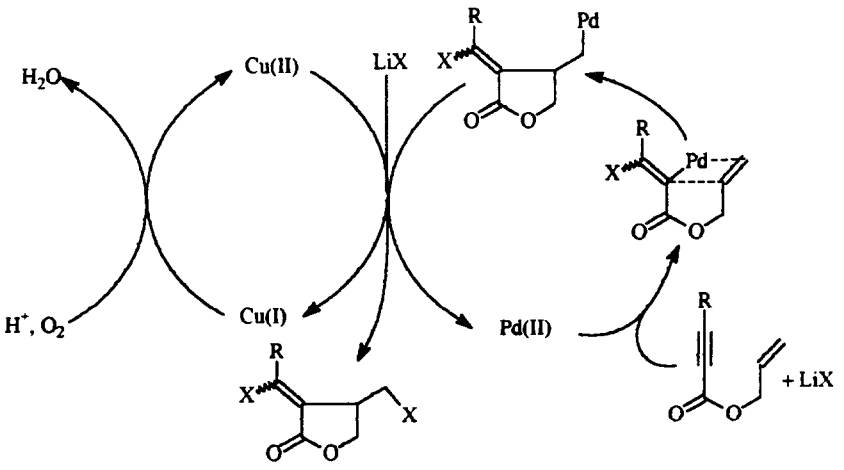
In the cyclization reactions discussed so far, a σ-carbon–palladium bond is formed through intramolecular carbon–carbon double-bond insertion into the vinyl–palladium bond. If a conjugated dienyl propynoate is used, a π-allyl palladium intermediate could be formed which could also be quenched by a nucleophile in the presence of an oxidant [Eq. (6)].

We first tried the palladium-catalyzed reaction of 2,4-hexadienyl propynoate with LiCl under oxygen in HOAc. Reaction occurred to afford a mixture of cyclic diasteromers. With product **12**, we found the allyl–palladium species could be quenched by OAc^-, possibly derived from the solvent [Eq. (7)]. When the reaction was carried out in MeCN, the chlorinated cyclization product **13** was obtained [Eq. (8)]. However, the stereoselectivity of this reaction was poor with a mixture of isomers being obtained.

Reaction of 2,3-butadienyl propynoate with LiCl catalyzed by palladium(II) and the cupric salt under oxygen led to no cyclic product being isolated.

2.6. Mechanism

A possible mechanism for this palladium-catalyzed cyclization is given in Scheme 2. Halopalladation of the carbon–carbon triple bond in the presence of the oxidant and LiCl (*cis* addition for R = H and *trans* addition for R = alkyl) would produce a vinyl–palladium species which can be inserted intramolecularly by a



Scheme 2.

carbon–carbon double bond. The latter reaction would yield a cyclic intermediate containing a σ-carbon–palladium bond which may then be further oxidatively cleaved directly by oxygen in the presence of a catalytic amount of cupric salt to generate Pd^{II} catalytic species and afford the cyclic product. Here, the role of the oxidant is not limited to re-oxidation of the low-valent palladium species, but it may also labilize the palladium–carbon bond in such a way that palladium is converted into a good leaving group. As a result, nucleophilic substitution of the metal may take place readily. The second catalytic circle involving oxidation of Cu^{I} to Cu^{II} by oxygen then takes place to complete the cycle.

In summary, we have studied the chemical behavior of the molecular oxygen mediated oxidative cleavage of the carbon–palladium bond and the stereochemistry of the reaction in detail. The present method provides a facile catalytic system capable of synthesizing functionalized α-alkylidene-γ-butyrolactone derivatives from readily available acyclic allylic 2-alkynoates, thus avoiding the use of a large excess of cupric salt. Due to its simplicity, both in terms of the starting materials and the reaction conditions, the present reaction could be of utility in organic synthesis, especially in large-scale reactions.

3. Experimental details

The starting allylic 2-alkynoates were synthesized according to the reported procedure [5,13]. Analytical samples were further purified by Kugelrohr distillation using the stated oven temperatures (ot).

3.1. General procedure for oxygen-mediated palladium-catalyzed cyclization of allylic 2-alkynoates

Under an oxygen atmosphere, $Pd(OAc)_2$ (11 mg, 0.05 mmol) was added to a solution of allylic 2-alkynoate (1 mmol), $Cu(OAc)_2$ (75 mg, 0.4 mmol) and lithium halide (6 mmol) in HOAc (5 ml), and the reaction was monitored by TLC (eluent: petroleum ether/ethyl acetate = 10:3). After reaction was complete, ethyl acetate (60 ml) was added and the mixture washed with water (3 × 5 ml) and dried ($MgSO_4$). Preparative TLC on silica gel (eluent: petroleum ether/ethyl acetate = 10:2) afforded the pure cyclic product. The results obtained are described in the text. The spectral and analytical data for compounds *Z*-**2a**, *E*-**2a**, *Z*-**2′a**, *E* − **2′a**, **4** and **4′** have been reported previously [5,10].

α-(*E*)-(1′-Chloro-6′-methylheptylidene)-β-chloromethyl-γ-butyrolactone (*E*-**2b**): Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.43–4.33 (m, 2H); 3.82–3.77 (m, 1H); 3.66–3.60 (m, 2H); 3.19–3.12 (m, 1H); 3.09–3.02 (m, 1H); 1.64–1.51 (m, 3H); 1.39–1.18 (m, 4H); 0.89 ~ 0.85 (m, 6H) ppm. MS *m/e*: 282 (7.22); 281 (48.90); 280 (13.07); 279 (79.69); 277 (5.38); 245 (33.82, M − ^{35}Cl); 243 (100.00, M − ^{37}Cl); 209 (30.96); 207 (52.36); 193 (37.85); 175 (12.48); 173 (19.68); 160 (28.39); 151 (12.62); 149 (11.58); 147 (25.25); 145 (31.02); 99 (7.93). IR (neat)(cm^{-1}): 2950; 1765; 1680; 1470; 1380; 1230; 1080; 800; 740; 690. HRMS for $C_{13}H_{20}O_2Cl_2$: calc: 278.0840; found: 278.0851.

α-(*Z*)-(1′-Chloro-6′-methylheptylidene)-β-chloromethyl-γ-butyrolactone (*Z*-**2b**): Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.93 (dd, $J = 0.69$ Hz, $J = 9.73$ Hz, 1H); 4.27 (m, 1H); 3.54 (m, 3H); 2.53 (m, 2H); 1.75–1.54 (m, 3H); 1.40–1.26 (m, 2H); 1.24–1.18 (m, 2H); 0.90–0.87 (m, 6H) ppm. MS *m/e*: 281 (0.47); 209 (1.91); 207 (2.64); 1.75 (1.96); 173 (1.05); 151 (1.16); 149 (1.05); 121 (1.21) 119 (1.11); 58 (27.26); 43 (100.00). IR (neat)(cm^{-1}): 2960; 2765; 1645; 1470; 1380; 1230; 1140; 1000; 750. Analysis: Calc. for $C_{13}H_{20}O_2Cl_2$:C, 55.92; H, 7.22%. Found: C, 55.90; H, 7.04%.

α-(*E*)-(1′-Chlorobutylidene)-β-chloromethyl-γ-butyrolactone (*E*-**2c**): Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.44–4.36 (m, 2H); 3.82–3.80 (m, 1H); 3.66–3.62 (m, 2H); 3.18–3.11 (m, 1H); 3.07–3.00 (m, 1H); 1.72–1.64 (m, 2H); 0.96 (t, $J = 7.37$ Hz, 3H) ppm. MS *m/e*: 227 (10.32); 226 [M$^+$(2 × ^{37}Cl), 8.13]; 225 (61.92); 224 [M$^+$(^{37}Cl, ^{35}Cl), 21.72]; 223 (100.00); 222 [M$^+$(2 × ^{35}Cl), 19.36); 189 [M$^+$(^{37}Cl) − Cl, 5.77]; 187 [M$^+$(^{37}Cl) − Cf, 16.20]; 175 [M$^+$(^{37}Cl) − CH_2Cl, 17.86]; 173 [M$^+$(^{35}Cl) − CH_2Cl, 53.52]; 147 (1.72); 145 (4.63); 137 (18.13); 109 (17.54); 93 (21.49); 91 (36.08). IR (neat)(cm^{-1}): 2980; 1760; 1660; 1440; 1380; 1230; 1070; 800; 740. HRMS: Calc. for $C_9H_{12}O_2Cl_2$: 224.01849 (^{37}Cl, ^{35}Cl); 222.0214 (2 × ^{35}Cl). Found: 224.0153 (^{37}Cl, ^{35}Cl); 222.0177 (2 × ^{35}Cl).

α-(*Z*)-(1′-Chlorobutylidene)-β-chloromethyl-γ-butyrolactone (*Z* − **2c**): Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.39 (dd, $J_1 = 0.72$ Hz, $J_2 = 9.83$ Hz, 2H); 4.31–4.26 (m, 1H); 3.60–3.52 (m, 3H); 2.52 (dt, $J_1 = 1.92$ Hz, $J_2 = 7.67$ Hz, 2H); 1.78 (hexa, $J = 7.64$ Hz, 2H); 1.01 (t, $J = 7.41$ Hz, 3H) ppm. MS *m/e*: 227 (5.10); 226 [M$^+$(2 × ^{37}Cl), 4.74]; 225 (31.51); 224 [M$^+$(^{37}Cl, ^{35}Cl), 15.07]; 223 (49.75); 222 [M$^+$(2 × ^{35}Cl), 16.03]; 209 (4.58); 207 (7.61); 189 [M$^+$(^{37}Cl) − Cl, 4.55]; 187 [M$^+$(^{37}Cl) − Cl, 13.37]; 175 [M$^+$(^{37}Cl) − CH_2Cl, 33.41]; 173 [M$^+$(^{35}Cl) − CH_2Cl, 100.00]; 147 (2.70); 145 (75.7); 137 (24.30); 109 (33.97); 93 (44.56); 91 (63.91). IR (neat)(cm^{-1}): 2980; 2880; 1765; 1645; 1460; 1380; 1240; 1215; 1140; 910; 750. HRMS: Calc. for $C_9H_{12}O_2Cl_2$: 226.01553 (2 × ^{37}Cl); 224.01849 (^{37}Cl, ^{35}Cl); 222.02143 (2 × ^{35}Cl). Found: 226.0131 (2 × ^{37}Cl); 224.0186 (^{37}Cl, ^{35}Cl); 222.0257 (2 × ^{35}Cl).

α-(*E*)-(1′-Bromobutylidene)-β-bromomethyl-γ-butyrolactone (*E* − **2′c**): Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.44 (m, 2H); 3.71–3.59 (m, 1H); 3.48 (t,

J = 9.61 Hz, 1H); 3.33–3.26 (m, 1H); 3.19–3.13 (m, 1H); 1.66 (hexa, J = 7.37 Hz, 2H); 0.96 (t, J = 7.28 Hz, 3H) ppm. MS m/e: 315 [$M^+(2\times{}^{80}Br)+1$, 32.73]; 314 [$M^+(2\times{}^{80}Br)$, 7.83); 313 [$M^+({}^{80}Br,\ {}^{79}Br)+1$, 68.33]; 312 [$M^+(2\times{}^{79}Br)$, 6.14]; 311 [$M^+(2\times{}^{79}Br)+1$, 36.37]; 310 [$M^+(2\times{}^{79}Br)$, 1.64]; 233 [$M^+({}^{80}Br)-Br$, 97.91]; 231 [$M^+({}^{79}Br)-Br$, 100.00]; 219 [$M^+({}^{80}Br)-CH_2Br$, 5.29]; 217 [$M^+({}^{79}Br)-CH_2Br$, 2.08]; 203 (4.75); 201 (8.04); 199 (4.65); 177 (9.51); 175 (12.38); 137 (13.64); 135 (13.24); 107 (16.34); 105 (13.19); 79 (21.63). IR (neat)(cm^{-1}): 2960; 2880; 1760; 1645; 1460; 1435; 1380; 1220; 1140; 1060; 780. HRMS: Calc. for $C_9H_{11}O_2Br_2$: 311.9183 [$M^+({}^{79}Br,\ {}^{80}Br)-1$]; 309.9204 [$M^+({}^{79}Br,\ {}^{79}Br)-1$]. Found: 311.9136 [$M^+({}^{79}Br,\ {}^{80}Br)-1$]; 309.9271 [$M^+({}^{79}Br,\ {}^{80}Br)-1$].

α-(Z)-(1′-Bromobutylidene)-β-bromomethyl-γ-butyrolactone ($Z-$**2′c**): Oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.35 (dd, J_1 = 1.11 Hz, J_2 = 9.96 Hz, 1H); 4.26 (dd, J_1 = 6.24 Hz, J_2 = 9.40 Hz, 1H); 3.60–3.55 (m, 1H); 3.44–3.31 (m, 2H); 2.63 (dt, J_1 = 1.85 Hz, J_2 = 7.77 Hz, 2H); 1.84–1.69 (m, 2H); 0.99 (t, J = 7.42 Hz, 3H) ppm. MS m/e: 315 [$M^+(2\times{}^{80}Br)+1$, 17.20]; 314 [$M^+(2\times{}^{80}Br)$; 4.21]; 313 [$M^+({}^{80}Br,\ {}^{79}Br)+1$, 35.85]; 312 [$M^+(2\times{}^{79}Br)$, 3.20]; 311 [$M^+(2\times{}^{79}Br)+1$, 18.25]; 233 [$M^+({}^{80}Br)-Br$, 94.55]; 231 [$M^+({}^{79}Br)-Br$, 100.00]; 219 [$M^+({}^{80}Br)-CH_2Br$, 3.14]; 217 [$M^+({}^{79}Br)-CH_2Br$, 3.40]; 203 (3.39); 201 (3.19); 175 (2.40); 173 (6.03); 137 (6.05); 135 (1.74); 109 (14.28); 107 (22.66); 105 (19.82). IR (neat)(cm^{-1}): 2960; 2880; 1760; 1640; 1460; 1430; 1375; 1235; 1210; 1130; 770; 740. Analysis: Calc. for $C_9H_{12}O_2Br_2$: C, 34.64; H, 3.88%. Found: C, 34.68; H, 3.84%.

α-(E)-(1′-Chloromethylene)-γ-chloro-δ-valerolactone (**5**): Oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32 (t, J = 3.19 Hz, 1H); 4.87 (m, 1H); 3.73 (d, J = 4.5 Hz, 2H); 3.15 (ddd, J_1 = 3.20 Hz, J_2 = 8.23 Hz, J_3 = 18.45 Hz, 1H); 2.94 (ddd, J_1 = 3.09 Hz, J_2 = 4.81 Hz, J_3 = 18.32 Hz, 1H) ppm; radiating at δ 4.87 ppm: 3.73 (s); 3.15 (dd, J_1 = 3.10 Hz, J_2 = 18.8 Hz); 2.94 (dd, J_1 = 3.13 Hz, J_2 = 18.5 Hz) ppm. MS m/e: 184 [$M^+(2\times{}^{37}Cl)$, 0.70]; 182 [$M^+({}^{37}Cl,\ {}^{35}Cl)$, 3.71]; 180 [$M^+(2\times{}^{35}Cl)$, 5.53]; 147 [$M^+({}^{37}Cl)-Cl$, 0.85]; 145 [$M^+({}^{35}Cl)-Cl$, 2.27]; 133 [$M^+({}^{37}Cl)-CH_2Cl$, 32.36]; 131 [$M^+({}^{35}Cl)-CH_2Cl$, 100.00]; 105 (11.27); 103 (34.23); 87 (2.42); 75 (19.0); 63 (2.49). IR (neat)(cm^{-1}): 3050; 2920; 1760; 1600; 1425; 1340; 1300; 1190; 840. HRMS: Calc. for $C_6H_6O_2Cl_2$: 181.9715 ($^{35}Cl,\ ^{37}Cl$); 179.9714 ($2\times{}^{35}Cl$). Found: 181.9713 ($^{35}Cl,\ ^{37}Cl$); 179.9714 ($2\times{}^{35}Cl$).

α-(E)-(1′-Bromomethylene)-γ-bromo-δ-valerolactone (**5′**): Oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.56 (t, J = 3.17 Hz, 1H); 4.85 (m, 1H); 3.58 (m, 2H); 3.08 (ddd, J_1 = 3.15 Hz, J_2 = 8.24 Hz, J_3 = 18.5 Hz, 1H); 2.81 (ddd, J_1 = 3.20 Hz, J_2 = 4.88 Hz, J_3 = 18.51 Hz, 1H) ppm. MS m/e: 272 [$M^+(2\times{}^{80}Br)$, 7.05]; 270 [$M^+({}^{80}Br,\ {}^{79}Br)$, 14.17]; 268 [$M^+(2\times{}^{79}Br)$, 7.35]; 191 [$M^+({}^{80}Br)-Br$, 12.14]; 189 [$M^+({}^{79}Br)-Br$, 12.80]; 177 [$M^+({}^{80}Br)-CH_2Br$, 97.87]; 175 [$M^+({}^{79}Br)-CH_2Br$, 100.00]; 149 (24.94); 147 (27.14); 121 (14.51); 119 (15.43); 109 (4.58). IR (neat)(cm^{-1}): 3080; 2940; 1765; 1650; 1430; 1285; 1185; 1020; 710. HRMS: Calc. for $C_6H_6O_2Br_2$: 269.8697 [$M^+({}^{79}Br,\ {}^{80}Br)-1$]; 267.8735 [$M^+({}^{79}Br,\ {}^{79}Br)-1$]. Found: 269.8738 [$M^+({}^{79}Br,\ {}^{80}Br)-1$]; 267.8721 [$M^+({}^{79}Br,\ {}^{80}Br)-1$].

cis-β-Chloromethyl-γ-pentyl-α-(Z)-(1′-chloroethylidene)-γ-butyrolactone (*cis*-**8a**): M.p. 57–58°C. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.37 (dt, J_1 = 9.86 Hz, J_2 = 4.93 Hz, 1H); 3.75 (dd, J_1 = 5.59 Hz, J_2 = 11.39 Hz, 1H); 3.54–3.43 (m, 2H); 2.40 (s, 3H); 1.85–1.59 (m, 4H); 1.43–1.34 (m, 4H); 0.91 (t, J = 6.64 Hz, 3H) ppm; radiating at δ 4.37 ppm: 3.50 (dd, J_1 = 6.60 Hz, J_2 = 11.10 Hz); 3.46 (t, J = 5.60 Hz) ppm. MS m/e: 268 [$M^+(2\times{}^{37}Cl)$, 1.02]; 266 [$M^+({}^{35}Cl,\ {}^{37}Cl)$, 4.75]; 264 [$M^+(2\times{}^{35}Cl)$, 6.19]; 231 (2.14); 229 (2.77); 219 [$M^+(2\times{}^{37}Cl)-CO_2-1$, 0.01]; 217 [$M^+\ ({}^{37}Cl,\ {}^{35}Cl)-CO_2-1$, 3.37]; 215 [$M^+(2\times{}^{35}Cl)-CO_2-1$, 8.83]; 197 [$M^+(2\times{}^{37}Cl)-C_5H_{11}$, 3.48]; 195 [$M^+({}^{37}Cl,\ {}^{35}Cl)-C_5H_{11}$, 15.22]; 193 [$M^+(2\times{}^{35}Cl)-C_5H_{11}$, 25.59]; 167 (5.59); 165 (56.11); 163 (32.12); 133 (2.66); 131 (51.26); 129 (100.00); 65 (41.67). IR (Nujol film) (cm^{-1}) 2900; 2840; 1740; 1660; 1470; 1160. Analysis: Calc. for $C_{12}H_{18}Cl_2O_2$: C, 54.30; H, 6.84%. Found: C, 54.32; H, 7.09%.

(4S)-Chloromethyl-(5S)-pentyl-(2Z)-(1′-chloroethylidene)-γ-butyrolactone (4S, 5S)-**8a**: Oil. $[\alpha]_D^{25} = -26.0°$ (c, 1.33; $CHCl_3$).

trans-β-Chloromethyl-γ-isopropyl-α-(E)-(1′-chloromethylene)-γ-butyrolactone (*trans*-**8b**): Oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.88 (d, J = 1.65 Hz, 1H); 4.16 (dd, J_1 = 2.83 Hz, J_2 = 5.99 Hz, 1H); 3.59 (m, 2H); 3.19 (m, 1H); 1.87 (m, 1H); 0.99 (d, J = 6.73 Hz, 6H) ppm. MS m/e: 227 [$M^+(2\times{}^{37}Cl)+1$, 4.29]; 225 [$M^+({}^{37}Cl,\ {}^{35}Cl)+1$, 25.19]; 223 [$M^+(2\times{}^{35}Cl)$, 39.62]; 189 [$M^+({}^{37}Cl)-Cl$, 4.73]; 187 [$M^+({}^{37}Cl)-Cl$, 14.37]; 183 (10.61); 181 (62.62); 179 (100.00); 153 (19.11); 151 (34.24); 145 (33.89); 143 (99.76); 117 (20.54); 115 (63.63); 109 (1.97); 107 (4.62); 89 (16.66); 87 (50.44). IR (neat)(cm^{-1}): 3050; 2960; 2880; 1760; 1640; 1465; 1440; 1180; 1090; 1000; 860. HRMS: Calc. for $C_9H_{12}O_2Cl_2$: 224.01849 ($^{37}Cl,\ ^{35}Cl$); 222.02143 ($2\times{}^{35}Cl$). Found: 224.0153 ($^{37}Cl,\ ^{35}Cl$); 222.0237 ($2\times{}^{35}Cl$).

α-(Z)-(1′-Chloroethylidene)-β(S^*)-[1″(R^*)-chlorobenzyl]-γ-butyrolactone (**10**) [5f]: M.p. 119 ~ 121°C. ^1H NMR (600 MHz, $CDCl_3$) δ: 7.45 ~ 7.20 (m, 5H); 5.00 (d, J = 7.10 Hz, 1H); 4.23 (d, J = 9.70 Hz, 1H); 4.15 (dd, J_1 = 7.10 Hz, J_2 = 9.70 Hz, 1H); 3.75 (t, J = 7.10 Hz, 1H); 2.31 (s, 3H) ppm. IR (Nujol film)(cm^{-1}): 1760; 1650; 1240; 1140. MS m/e: 275 [$M^+(2\times{}^{37}Cl)+1$, 0.12]; 273 [$M^+({}^{35}Cl,\ {}^{37}Cl)+1$, 0.25]; 271 [$M^+(2\times{}^{35}Cl$, 0.31].

α-(Z)-(1′-Chloroethylidene)-β(S^*)-[1″(S^*)-chloro-

benzyl]-γ-butyrolactone (**10'**) [5f]: M.p. 134 ~ 136°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.42 ~ 7.32 (m, 5H); 4.88 (d, J = 8.76 Hz, 1H); 4.68 (d, J = 9.54 Hz, 1H); 4.25 (dd, J_1 = 6.12 Hz, J_2 = 9.54 Hz, 1H); 3.56 (dd, J_1 = 6.12 Hz, J_2 = 8.76 Hz, 1H); 1.60 (s, 3H) ppm. IR (neat)(cm^{-1}): 2950; 1740; 1630; 1460; 1370. MS *m/e*: 273 [$M^+(^{35}Cl, ^{37}Cl) + 1$, 0.45]; 271 [$M^+(2 \times ^{35}Cl) + 1$, 0.87]; 127 ($^{37}ClPhCH^+$, 30.23); 125 ($^{35}ClPhCH^+$, 100.00).

α-(*E*)-(1'-Chloromethylene)-β-(3'-chloro-1'-butenyl)-γ-butyrolactone (**13**) [14]: Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.59 (d, J = 2.71 Hz); 6.56 (d, J = 2.69 Hz, 1H); 5.90–5.83 (m, 1H); 5.66–5.40 (m, 1H); 4.58–4.30 (m, 2H); 4.04–3.97 (m, 1H); 3.90–3.81 (m, 1H); 1.64–1.61 (m, 3H) ppm. MS *m/e*: 225 [$M^+(2 \times ^{37}Cl) + 1$, 2.29]; 224 [$M^+(2 \times ^{37}Cl)$, 1.56]; 223 (12.62); 222 (3.22); 221 (18.01); 220 (2.53); 194 (3.15); 192 (17.91); 190 (29.00); 187 [$M^+(^{37}Cl) - Cl$, 4.26]; 185 [$M^+(^{35}Cl) - Cl$, 6.74]; 178 (1.74); 176 (1.92); 157 [$M^+(^{37}Cl) - CHClCH_3$, 16.59]; 155 [$M^+(^{35}Cl) - CHClCH_3$, 40.55]; 141 (12.61); 132 (27.70); 130 (5.11); 119 (22.43); 105 (2.22); 91 ($CH=CHCHClCH_3$, 100.00). IR (neat)(cm^{-1}) : 3050; 2980; 2900; 1770; 1640; 1480; 1450; 1380; 1320; 1180; 1020; 970.

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