Palladium-Templated Regio- and Stereoselective Cyclization of 2′-Alkenyl 2-Alkynoates and Its Synthetic Applications

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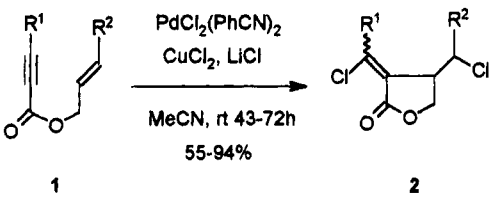
2′-Alkenyl 2-alkynoates undergo facile stereoselective cyclization to α-(haloalkylidene)-γ-butyrolactones upon treatment with a catalytic amount of palladium complex in the presence of CuX_2 and LiX. When an alkyl group is introduced to the 1′-position of the alkenyl group, unsubstituted 2-propynoates mainly give trans-β,γ-disubstituted γ-lactones, and substituted 2-propynoates afford cis-β,γ-disubstituted γ-lactones. Further elaborations of the halogen atoms and the synthesis of A-factor using this method are exemplified.

Introduction

Highly selective organic reactions have found wide applications in the synthesis of complex molecules with biological activities used in pesticides and medicines.[1] Transition metal-catalyzed reactions, especially those that directly lead to cyclic structures from easily available acyclic precursors, have received much attention owing to the template action of the transition metals.[2,3]

A number of α-methylene-γ-butyrolactones display significant biological activities, such as cytotoxity, antitumor, etc.[4] Possibile applications in immunology, virology, and cancer therapy stimulate general interest in the construction of the α-methylene-γ-butyrolactone ring structure.[5] However, few examples have been reported on the clinical uses of α-methylene-γ-butyrolactones because of their high toxicity.[4,5] The syntheses of new α-methylene-γ-butyrolactone derivatives for screening are needed.[6] We have been engaged in the development of new synthetic routes to α-alkylidene-γ-butyrolactone derivatives from acyclic 3′-(halomethyl)-2′-alkenyl 2-alkynoates.[7] Recently, our work has been centered on the preparation of α-alkylidene-γ-butyrolactone derivatives **2** from more easily available precursors, 2′-alkenyl 2-alkynoates **1**, under the catalysis of $PdCl_2(PhCN)_2$ in the presence of $CuCl_2$ and LiCl (eq 1).[8] However, many difficulties were encountered in the further elaboration of the chlorine atom in **2** to other functionalities. Considering that a carbon–bromine bond is more suitable for further transformation, a similar catalytic system using $PdBr_2(PhCN)_2$, $CuBr_2$, and LiBr was tried. Unfortunately, only an acyclic tetrabromo-substituted product (**4a**) instead of the cyclic product **3a** was obtained from allyl propynoate (**1a**) (Scheme 1).[8c]



1 2 (1)

In this paper, we report a new catalytic system to prepare **3** from acyclic 2′-alkenyl-2-alkynoates (**1**) via palladium-catalyzed intramolecular cyclization. The stereochemistry of the cyclization reaction and the further elaborations of the cyclic products will also be discussed.

Results and Discussions

Cyclization of 2′-Alkenyl 2-Alkynoates. Allyl 2-butynoate (**1b**) was used for studying the reaction conditions. The results of cyclization of **1b** using different palladium complexes as catalysts in the presence of $CuBr_2$ and LiBr in HOAc were quite different (Table 1). Palladium complexes bearing strongly coordinating ligands, which might prevent the formation of the palladium–enyne complex in the first step, were prone to give the acyclic product **4b** (entries 1 and 2, Table 1), while catalysts without ligands or with weakly coordinating ligands favored the cyclization reactions (entries 3–8, Table 1). The *Z*/*E* ratio of the exocyclic carbon–carbon double bond of **3b** can be increased by increasing the amount of LiBr (entries 4–6, Table 1), while too much amount of LiBr caused the formation of acyclic byproduct **4b** (entries 7 and 8, Table 1). Four equivalents of LiBr

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Scheme 1

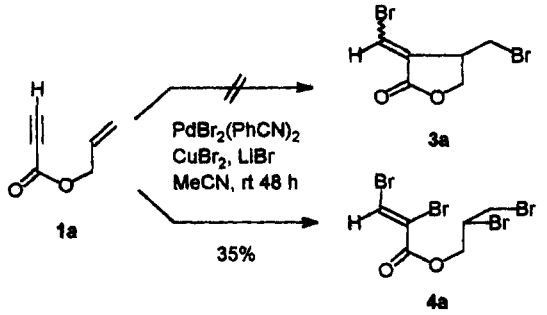
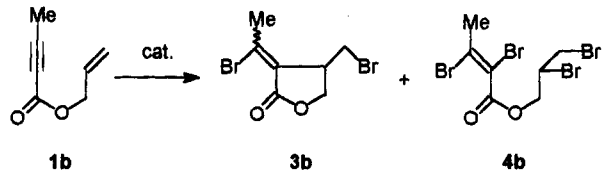


Table 1. Palladium-Catalyzed Cyclization of 2′-Propenyl 2-Butynoate (1b) in HOAc[a]



entry	cat.	LiBr (mmol)	time (h)	isolated yield (%)[b] 3b	(Z:E)[c]	4b
1	$PdBr_2(PhCN)_2$	4	5	63	>97:3	9
2	$PdCl_2(PhCN)_2$	4	5	25	88:12	45
3	$Pd(OAc)_2$	4	5	95	90:10	0
4	$Pd_2(dba)_2{\cdot}CHCl_3$	0	28	42	77:23	0
5	$Pd_2(dba)_2{\cdot}CHCl_3$	2	10	85	90:10	0
6	$Pd_2(dba)_2{\cdot}CHCl_3$	4	5	95	>97:3	0
7	$Pd_2(dba)_2{\cdot}CHCl_3$	6	5	93	>97:3	1
8	$Pd_2(dba)_2{\cdot}CHCl_3$	10	4	91	>97:3	4
9	$Pd_2(dba)_2{\cdot}CHCl_3$	4	6	0		45[d]

[a] A mixture of **1b** (124 mg, 1 mmol), cat. (0.05 mmol), $CuBr_2$ (896 mg, 4 mmol), LiBr, and HOAc (10 mL) was stirred at rt under Ar. [b] The products were confirmed by ^1H NMR, IR, mass spectral data, and microanalysis. [c] The *Z*:*E* ratio was determined by isolation. [d] Same as *a* except that $Cu(NO_3)_2$ (752 mg, 4 mmol) was used instead of $CuBr_2$.

are optimum. When $Cu(NO_3)_2$ was used as oxidant in similar conditions, only **4b** was formed, which is probably due to the addition of bromine in situ generated from oxidation of lithium bromide by $Cu(NO_3)_2$[9] (entry 9, Table 1). Therefore the cyclization reactions of **1** were carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ in HOAc as catalyst in the presence of 4 equiv of $CuBr_2$ and LiBr. The results are shown in Table 2. The configuration of the exocyclic carbon–carbon double bond in **3** was determined by comparing the chemical shifts of the vinylic proton or allylic protons in R^1.[6-8] Under similar conditions, unsubstituted propynoate (**1a**) afforded only *E*-form (referring to the exocyclic carbon–carbon double bond) product (**3a**) (entry 1, Table 2), while substituted 2-propynoates **[1b–(*E*)-1g]** mainly gave *Z*-form products **(3b–3g′)** (entries 2–9, Table 2). Compounds (*Z*)- and (*E*)-**1g** afforded single isomers **3g** and **3g′**, respectively (entries 8 and 9, Table 2). The compounds **3g** and **3g′** have the same MS molecular ion and analytical data but different ^1H NMR spectral data (shown in Table 3), indicating that **3g** and **3g′** might be a pair of diastereomers, which is consistent with our previous report.[8a]

The present reaction might occur through a mechanism similar to that proposed in our previous publication (Scheme 2).[8a] Pd^0 was first converted to Pd^{II} species in

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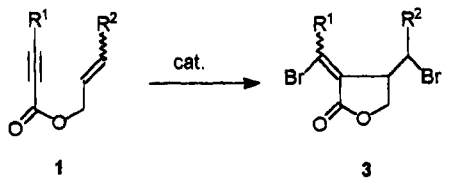
Table 2. Cyclization of 2′-Alkenyl 2-Alkylnoates[a]



entry	R^1	R^2	substrate	time (h)	product[b]	isolated yield (%)	(Z:E)[c]
1	H	H	**1a**	5	**3a**	85	<3:97
2	CH_3	H	**1b**	5	**3b**	95	>97:3
3	n-C_3H_7	H	**1c**	5	**3c**	96	>97:3
4	n-C_4H_9	H	**1d**	5	**3d**	86	>97:3
5	n-C_4H_9	H	**1d**	5	**3d**	90	78:22[d]
6	i-C_7H_{15}	H	**1e**	8	**3e**	97	>97:3
7	n-C_8H_{17}	H	**1f**	10	**3f**	81	>97:3
8	CH_3	Ph	(*Z*)[e]-**1g**	10	**3g**	91	>97:3[f]
9	CH_3	Ph	(*E*)[e]-**1g**	10	**3g′**	89	>97:3[g]

[a] A mixture of **1** (1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol), $CuBr_2$ (896 mg, 4 mmol), LiBr (348 mg, 4 mmol), and HOAc (10 mL) was stirred at rt under Ar. [b] The products were confirmed by ^1H NMR, IR, mass spectral data, and microanalysis. [c] The ratio *Z*:*E* was determined by ^1H NMR. [d] $Pd(OAc)_2$ (11 mg, 0.05 mmol) was used instead of $Pd_2(dba)_3{\cdot}CHCl_3$. [e] Referring to the allylic double bond. [f] Only pure **3g** was obtained. [g] Only pure **3g′** was obtained.

reaction system. Compound **1** coordinates with Pd and/or Cu complex to form the palladium–enyne complex **5**,[10] and the subsequent stereoselective bromopalladation of carbon–carbon triple bond[11] in the presence of $CuBr_2$ and LiBr (cis addition for R^1 = H and trans addition for R^1 = alkyl) affords the vinylpalladium intermediate **6**. The intramolecular insertion of the C=C bond into the C–Pd bond yields the cyclic intermediate **7**, which in turn gives **3** and regenerates the Pd^{II} species.

The carbon–palladium bond, like most second and third row transition metal–carbon bonds, reacts very slowly in hydrolysis reaction.[12] However, the cleavage of C–Pd bond by copper(II) halides takes place in a number of palladium-catalyzed reactions.[13] The detailed mechanism of such reactions was generally speculated to proceed by reductive elimination,[14] radical,[15] or ionic mechanism.[16] Budnik and Kochi proposed a radical mechanism based on the loss of stereochemistry in the reaction of cupric bromide with nortricycle–palladium bond.[17] Bäckvall et al. studied in detail the stereochemistry of the cleavage of the C–Pd bond by cupric chloride and concluded that this reaction proceeds via an oxidative

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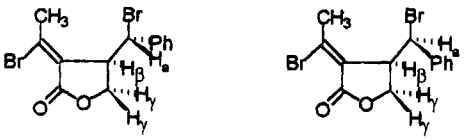
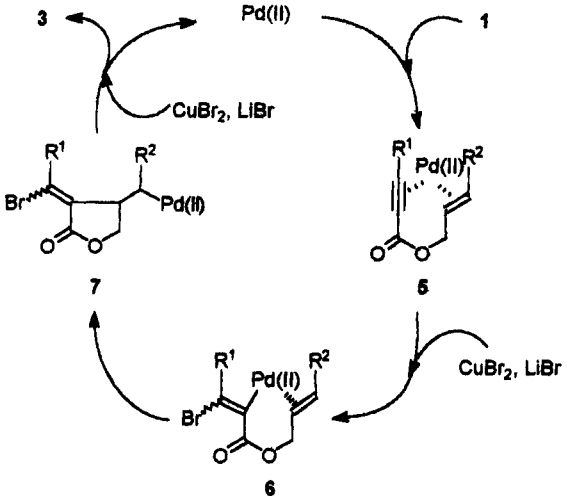
Table 3. ^{1}H NMR (300 MHz, $CDCl_3$) Spectral Data of 3g and 3g′



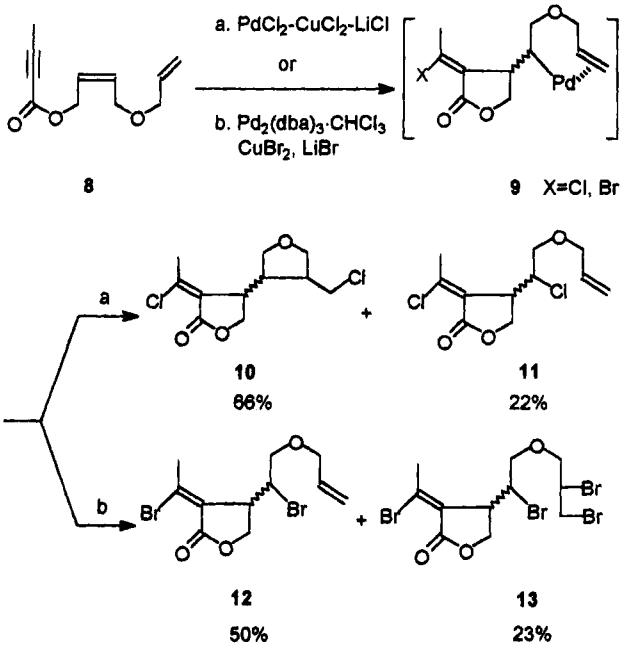
3g 3g′

3	Ph	H_a	H_γ	H_β	CH_3
3g	7.55–7.40 (m, 5H)	5.06 (d, J = 7.60 Hz, 1H)	4.27 (d, J = 9.72, 1H), 4.15 (dd, 1H, J = 9.72, 6.30 Hz)	3.90 (dd, J = 7.60, 6.30 Hz, 1H)	2.65 (s, 3H)
3g′	7.52–7.30 (m, 5H)	4.92 (d, J = 9.07 Hz, 1H)	4.72 (dd, J = 9.60, 0.72 Hz, 1H), 4.30 (dd, J = 9.60, 6.00 Hz, 1H)	3.68 (dd, J = 9.07, 6.00 Hz, 1H)	1.80 (s, 3H)

Scheme 2



Scheme 3



cleavage mechanism.[12,18] They also found that the presence of excess free nucleophiles usually resulted in the inversion of the carbon stereochemistry.[16,19] In our case, under the catalysis of $Pd_2(dba)_3$·$CHCl_3$ in the presence of HOAc, $CuBr_2$, and LiBr, even when 50 equiv of CCl_4 were used in the cyclization reaction of **1a** to trap the possible radical species, we obtained only **3a** in 90% yield. In addition, the cyclizations of (*Z*)- and (*E*)-**1g** specifically yielded single isomers **3g** and **3g′**, respectively, providing a strong evidence against the radical mechanism. The configurations of **3g** and **3g′** were tentatively assigned according to Bäckvall's mechanism. In another experiment, we found that the cyclization of compound **8** mainly yielded bicyclic γ-lactone **10** in the $PdCl_2$–$CuCl_2$–LiCl catalytic system, while in the $Pd_2(dba)_3$·$CHCl_3$–HOAc–$CuBr_2$–LiBr system, it afforded monocyclic γ-lactones **12** and **13** (Scheme 3). This result can be explained by the different nucleophilicities of the bromide and chloride ions. In both reactions, C–Pd species **9** was formed as the common intermediate. Thus, a competition between the olefin insertion and the oxidative cleavage by halide ions occurred. Bicyclic product **10** was formed due to the poorer nucleophilicity of the chloride ion, while oxidative cleavage predominated in case of more nucleophilic bromide ion.

Stereochemistry of Palladium-Catalyzed Cyclization of 1′-Substituted 2′-Alkenyl 2-Alkynoates. On the basis of the retrosynthetic analysis shown in Scheme 4, we tried to synthesize bicyclic α-methylene γ-butyrolactone derivatives **14** from easily available acyclic precursors alkadienyl 2-alkynoates **17**. However, when we carried out the cyclization of 1′-allyl-2′-propenyl propynoate (**18a**) under the catalysis of $PdCl_2$ in the presence of $CuCl_2$ and LiCl in MeCN, we mainly obtained a monocyclic product: *trans*-(referring to the relative stereochemistry of β,γ-substituents) **19a** in 59% yield (entry 1, Table 4). Model experiments showed that under similar conditions, the cyclization of unsubstituted propynoate (**18b**) mainly afforded *trans*-**19b** (entry 2, Table 4), while the cyclization of 3-substituted propynoate **18c** yielded **19c** purely in cis form (entry 3, Table 4). The dramatic results stimulated us to study the stereochemistry of $Pd_2(dba)_3$-$CHCl_3$–HOAc–$CuBr_2$–LiBr-catalyzed

Scheme 4

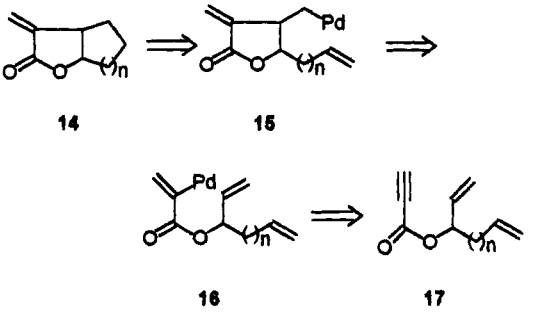


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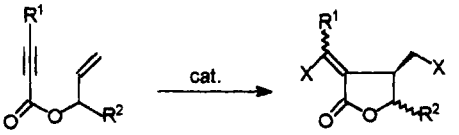
Table 4. Palladium-Templated Cyclization of 1'-Substituted-2'-alkenyl 2-Alkynoates (18)[a]



18 19

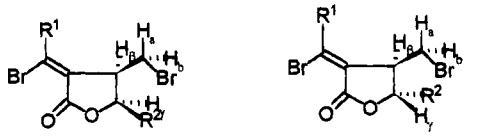
entry	R^1	R^2	X	18	cat.	time (h)	19[b]	yield (%)[c]	(cis:trans)[d]
1	H	CH_2=$CHCH_2$	Cl	**18a**	A	45	**19a**[e]	59	*f*
2	H	n-C_3H_7	Cl	**18b**	A	40	**19b**[e]	72	33:67
3	CH_3	n-C_3H_7	Cl	**18c**	A	40	**19c**[g]	80	>97:3
4	H	CH_3	Br	**18d**	B	10	**19d**[e]	92	33:67
5	H	n-C_3H_7	Br	**18b**	B	10	**19e**[e]	93	25:75
6	H	n-C_5H_{11}	Br	**18e**	B	15	**19f**[e]	82	22:78
7	H	i-C_5H_{11}	Br	**18f**	B	15	**19g**[e]	82	24:76
8	H	i-C_3H_7	Br	**18g**	B	22	**19h**[e]	85	<3:97
9	CH_3	CH_3	Br	**18h**	B	8	**19i**[g]	91	>97:3
10	CH_3	n-C_3H_7	Br	**18c**	B	10	**19j**[g]	92	>97:3
11	CH_3	n-C_4H_9	Br	**18i**	B	10	**19k**[g]	94	>97:3
12	n-C_4H_9	CH_3	Br	**18j**	B	10	**19l**[g]	82	>97:3

A: A mixture of **18** (1 mmol), $PdCl_2$ (9 mg, 0.05 mmol), $CuCl_2$ (405 mg, 3 mmol), LiCl (170 mg, 4 mmol), and MeCN (10 mL) was stirred at rt. B: A mixture of **18** (1 mmol), $Pd_2(dba)_3$ $CHCl_3$ (52 mg, 0.05 mmol), $CuBr_2$ (896 mg, 4 mmol), LiBr (348 mg, 4 mmol), and HOAc was stirred at rt under Ar. [b] The products were confirmed by ^1H NMR, IR, mass spectral data, and microanalysis. [c] Isolated yield. [d] The cis:trans ratio (referring to β,γ-substituents) was determined by ^1H NMR spectral data. [e] The exocyclic double bond in **19** exhibits *E*-configuration. [f] Only *trans*-**19a** was isolated. [g] The exocyclic double bond in **19** exhibits *Z*-configuration.

cyclization of 1'-substituted 2'-propenyl 2-alkynoates. The results are shown in Table 4 (entries 4–12). The cyclization of unsubstituted propynoates also mainly afforded trans-products (**19d–h**) (entries 4–8, Table 4) where the trans:cis ratio increased with the bulkiness of R^2 (entry 8, Table 4) and substituted propynoates gave cis-products (entries 9–12, Table 4) with high selectivity. Although the 1,2-stereoinduction leading to trans-selectivity has been reported in organolanthanide-mediated[20] and Ziegler-Natta catalysts-induced[21] cyclization of 1,5-dienes and some other transition metal-catalyzed cyclizations,[22,23] the cis-selectivity of the cyclization of substituted propynoates (entries 9–12, Table 4) under the same conditions is uncommon. Thus we can control the cis–trans stereochemistry of the β, γ-substituents by using substituted or unsubstituted propynoates as the starting materials.

The relative stereochemistry of β,γ-substituents in **19b** and **19d–h** was determined by $^3J(H_\beta$-$H_\gamma)$ values and the chemical shifts of H_γ shown in Table 5. It has been reported[24] that H_γ in a cis-β,γ-disubstituted α-methylene-γ-butyrolactone was at a lower field than that in the corresponding trans-β,γ-disubstituted isomers. In the cases when both trans- and cis-isomers were formed, H_γ in the minor isomers of **19b** and **19d–g** were found to be at a lower field than that in the corresponding major isomers. In addition, the $^3J(H_\beta$-$H_\gamma)$ values of major isomers of **19b** and **19d**–g were 3.8–4.2 Hz, while $^3J(H_\beta$–$H_\gamma)$ of minor isomers were 5.8–6.1 Hz. These ^1H NMR spectral data indicated that the major isomers of **19b** and **19d–g** have β,γ-trans configurations. The chemical shifts of H_γ and the $^3J(H_\beta$–$H_\gamma)$ values of **19a** and **19h** are in good agreement with those in the major isomers of **19b** and **19d–g**, showing that **19a** and **19h** were also in trans configuration. This assignment is consistent with our other reports.[7c]

Table 5. Significant ^1H NMR Data of α-(Haloalkylidene)-β,γ-disubstituted-γ-butyrolactones 19



	cis		trans	
γ-butyrolactone	δ H_γ (ppm)	^3J (H_β–H_γ) (Hz)	δ H_γ (ppm)	$^3J(H_\beta$–$H_\gamma)$ (Hz)
19a			4.50	4.0
19b	4.55	6.2	4.40	4.2
19c	4.50	6.2		
19d	4.66	6.0	4.32	4.0
19e	4.56	6.0	4.40	4.0
19f	4.58	5.8	4.40	4.2
19g	4.56	6.1	4.40	4.1
19h			4.35	3.8
19i	4.60	6.0		
19j	4.52	6.2		
19k	4.56	6.0		
19l	4.60	6.0		

In the cases where only one isomer was isolated, the comparison of $^3J(H_\beta$–$H_\gamma)$ values and the chemical shifts of H_γ of different isomers is impossible. However, the chemical shift of H_γ and the coupling constant $^3J(H_\beta$–$H_\gamma)$ of **19i** are in agreement with that of the minor isomers of **19b** and **19d–g**, suggesting a cis configuration (Table 5). The configuration of **19i** was finally solved by the appearance of strong NOE between H_β and H_γ, which indicated that **19i** was in cis form. **19c** and **19j–l** were also assigned to be in cis form on the basis that in ^1H NMR spectra they have similar $^3J(H_\beta$-$H_\gamma)$ values and chemical shifts of H_γ as **19i** (Table 5).

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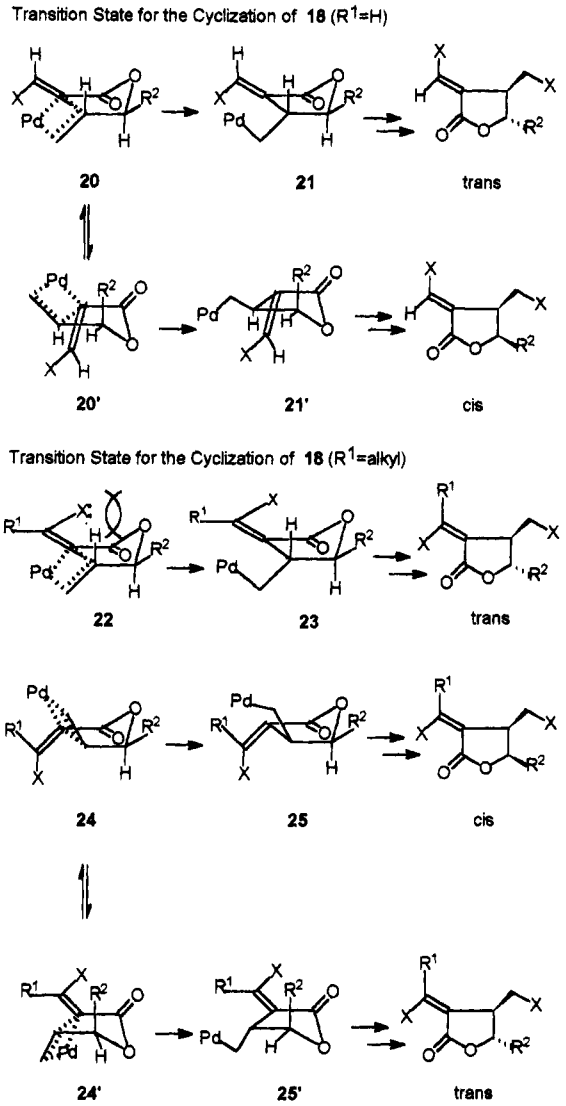
Scheme 5

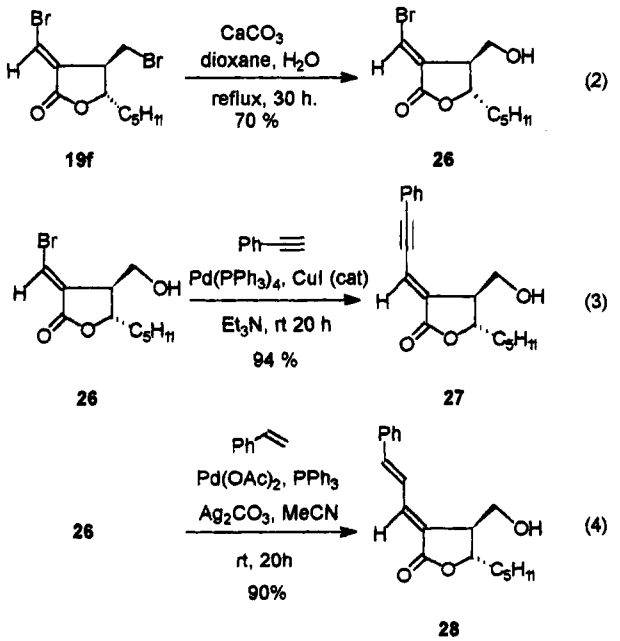


These results indicated that R^1 in **18** plays an important role in the stereochemistry of the present reaction, implying that the reaction might proceed via different transition states when R^1 is H or alkyl. The stereochemical results of the cyclization of **18** could be rationalized on the basis of steric/conformational effects in a seven-membered ring transition state for olefin insertion (Scheme 5).[20,21] From unsubstituted propynoates (R^1 = H), the transition state can adopt seven-membered cyclic pseudo chair forms **20** or **20'**, in which the palladium and the halogen atom are in cis position. In order to insert the C=C double bond into the C−Pd bond, these two bonds should be parallel and coplanar to each other. Thus, the nonbonded interactions should destabilize the sterically unfavorable conformation **20'**, in which R^2 is in axial position, and favor the conformation **20** to preferentially give trans products. Additionally, the influence of R^2 will be more important as R^2 becomes bulkier, which is also observed in our study.

While from 3-substituted propynoates, the palladium and the halogen atom in the vinyl palladium moiety are trans to each other, the stereoelectronic effect[25] between the vinylic bromine atom and the lactone oxygen atom may destabilize the seven-membered cyclic chair transition state **22**. It has been reported that there exists small energy difference between chair and boat conformations in seven-membered carbocyclic compounds.[26] In the study of a palladium-catalyzed polyene cyclization of dienylaryl iodides, Overman et al. proposed a seven-membered pseudoboat transition state to provide a rational for the observed stereoselectivity.[27] Thus, a transition state of seven-membered pseudoboat conformation such as **24** or **24'** might also work in our case. In **24'**, the R^2 group is in pseudoaxial position; consequently, the steric interaction between the vinylic bromine atom and R^2 makes this transition state unfavorable. Thus, the transition state **24** in which R^2 is in the favorable pseudoequatorial position predominates, and this gives a reasonable explanation for the observed stereoselectivity of the cyclization.

Based on the mechanism and stereochemical outcome of the cyclization, a facile route to bicyclic lactone from acyclic precursors was developed, which was published as a communication.[28]

Further Elaborations. There are two bromine atoms in the synthesized lactone molecule. We then studied some transformations of the bromine atoms into other functional groups. According to Dibble's method,[29] refluxing **19f** with $CaCO_3$ in dioxane/water (1:1) for 30 h, we obtained α-(bromomethylene)-β-(hydroxymethyl)-γ-butyrolactone (**26**) in good yield (eq 2). If $CaCO_3$ was replaced by $NaHCO_3$, the lactone ring would be perfectly opened. Using Heck's[30] and Overman's[27] methods, we succeeded in the further elaboration of the vinyl bromide function in **26** under the catalysis of palladium to obtain **27** (eq 3) and **28** (eq 4), respectively.



Synthesis of (±)-A-factor. A-factor (**29**) is an inducer of the biosynthesis of Streptomycin in inactive mutants

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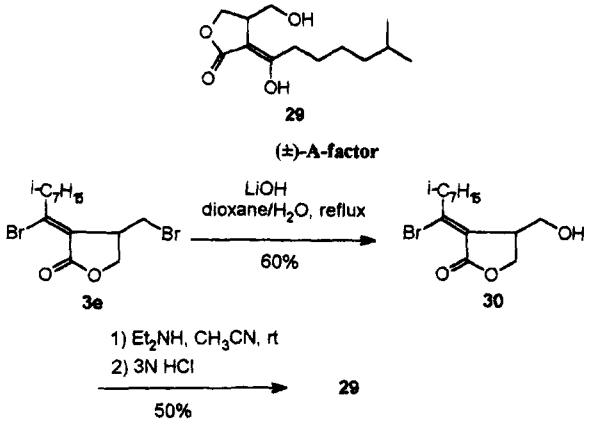
Scheme 6



of *Streopmyces griseus*.[31] Khokhlov et al. proposed the gross structure of A-factor to be **29**,[32] which was later confirmed by a synthesis of its racemic form.[33] Recently, the synthesis of optically active A-factor had also been reported.[34] On considering the fact that the lactone molecule **3** possesses two bromine atoms, A-factor was conveniently synthesized from the cyclization product **3e** by two simple transformations: alkaline hydrolysis of the bromomethyl unit gave β-(hydroxymethyl) γ-lactone **30**, and then treatment of **30** with diethylamine[35] transformed the vinyl bromide to ketone function to afford (±)-A-factor (Scheme 6). This concise synthesis, compared to the reported ones, furthermore illustrated the effectiveness of the transition metal-catalyzed ring construction method.

In summary, we developed a catalytic system to prepare bromo-functionalized α-alkylidene-γ-butyrolactone derivatives from 2'-alkenyl 2-alkynoates which are suitable for further elaboration in synthesis. In studying the stereochemistry of the cyclization of 1'-substituted 2'-alkenyl 2-alkynoates, we found that the stereoselectivity was highly dependent on the acetylenic substituent in the substrate: thus, unsubstituted propynoates gave trans-selectivity for the β,γ-substituents in the cyclic product while substituted propynoates gave cis-selectivity. We also studied the transformation of the bromine atoms in the cyclization products, and as an illustration, (±)-A-factor was synthesized efficiently from easily available acyclic precursor. Further study of the application of this cyclization reaction is now under way.

Experimental Section

Materials. The catalysts $Pd_2(dba)_3{\cdot}CHCl_3$,[36] $PdBr_2(PhCN)_2$,[37] $PdCl_2(PPh_3)_2$,[38] and $Pd(OAc)_2$ were prepared by literature methods. $CuCl_2$, LiCl, $CuBr_2$, and LiBr were dried at 120 °C under reduced pressure for 4 h. MeCN was distilled from P_2O_5 under N_2. HOAc was refluxed with $KMnO_4$ for 2–6 h and then distilled from P_2O_5. HMPA was distilled from CaH_2 under reduced pressure (99 °C/6mmHg). Allyl 2-propynoate (**1a**), 2-butynoate (**1b**), and 2-heptynoate (**1d**), (*E*)- and (*Z*)-3'-phenyl-2'-propenyl 2-butynoates ((*E*)-1g, (*Z*)−1g) were also prepared by reported methods.[8a] The analytical samples were further purified by Kugelrohr distillation with the given oven temperature (ot).

Synthesis of 8-Methyl-2-nonynoic Acid (31). 8-Methyl-2-nonyoic acid was prepared[39] from lithium 7-methyl-1-octynylide and carbon dioxide in 63% yield: bp 140–2°C/20 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 11.50 (s, 1H), 2.35 (t, J = 7.0 Hz, 2H), 1.7–1.3 (m, 7H), 0.95 (d, J = 7.0 Hz, 6H) ppm; IR (neat): 3200–2500 (band), 2215, 1700, 1470, 1380, 1280 cm^{-1}; MS *m/e* (%): 169 (M^+ + 1) (47), 168 (M^+) (2.5), 126 (17), 109 (23), 77 (8.6), 57 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 70.81; H, 9.81. HRMS: Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1119.

Synthesis of Allyl 2-Hexynoate (1c). To a solution of 2-hexynoic acid (1.12 g, 10 mmol) in HMPA (10 mL) was added in portions powdered anhydrous Na_2CO_3 (1.17 g, 11 mmol). After an additional stirring at rt for 1 h, allyl bromide (1.45 g, 12 mmol) was added. The reaction was stirred at rt for 20 h. Water (10 mL) was then added, and the mixture was extracted with ether (3 × 25 mL). The extracts were dried over $MgSO_4$, and the product **1c** was purified by chromatography on silica gel using petroleum ether/ethyl acetate (15:1) as the eluent: yield 1.40 g (92%); ot 80 °C/10 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.0–5.6 (m, 1H), 5.3–5.0 (m, 2H), 4.6 (d, J = 6Hz, 2H), 2.3 (t, J = 6 Hz, 2H), 1.4 (m, 2H), 0.9 (t, J = 6Hz, 3H) ppm; IR (neat) 3100, 2250, 1720, 1650, 1250 cm^{-1}; MS *m/e* 153 (M^+ + 1), 137, 108, 96, 67, 57, 43, 41. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.76; H, 8.22. The following compounds were prepared similarly.

Allyl 8-methyl-2-nonynoate (1e): yield 98%; ot 75 °C/1 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.0–5.6 (m, 1H), 5.3–5.0 (m, 2H), 4.5 (d, J = 6Hz, 2H), 2.3 (d, J = 6 Hz, 2H), 1.7–1.2 (m, 7H), 0.9 (d, J = 7Hz, 6H) ppm; IR (neat) 2250, 1720, 1650, 1470, 1240, 1070, 740 cm^{-1}; MS *m/e* 209 (M^+ + 1), 151, 137, 123, 107, 67, 55. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.78; H, 9.98.

Allyl 2-undecynoate (1f): yield 95%; ot 80 °C/1 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.0–5.6 (m, 1H), 5.3–4.9 (m, 2H), 4.4 (d, J = 5 Hz, 2H), 2.1 (t, J = 6 Hz, 2H), 1.4–1.0 (m, 12 H), 0.8 (t, J = 6 Hz, 3H) ppm; IR (neat) 3080, 2220, 1720, 1640, 1200, 760 cm^{-1}; MS *m/e* 222 (M^+), 180, 165, 149, 137, 57, 55, 43, 41. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 76.02; H, 10.32.

Tetrabromination of Allyl 2-Propynoate (1a). To a solution of **1a** (110 mg, 1 mmol), $CuBr_2$ (896 mg, 4 mmol), and LiBr (348 mg, 4 mmol) in MeCN (10 mL) was added $PdBr_2(PhCN)_2$ (23.6 mg, 0.05 mmol), and the reaction was monitored by TLC (eluent: petroleum ether/ethyl acetate = 10/1). After the reaction was complete, ether (80 mL) was added, and the mixture was washed with water (3 × 5 mL) and dried ($MgSO_4$). Preparative TLC on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) afforded the product **4a**: yield 150 mg (35%), oil; ^{1}H NMR (90 MHz/$CDCl_3$) δ 7.22 (s, 1H), 4.63 (d, J = 5Hz, 2H), 4.35 (m, 1H), 3.80 (d, J = 6Hz, 2H) ppm; IR (neat) 1730, 1280, 1200, 1100, 830, 710 cm^{-1}; MS *m/e* (%) 432 [M^+(^{81}Br, ^{79}Br)] (0.91), 430 [M^+(^{81}Br, ^{79}Br)] (1.39), 428 [M^+(^{81}Br, ^{79}Br)] (0.86), 426 [M^+(^{79}Br)] (0.51), 351 (100). Anal. Calcd for $C_6H_6Br_4O_2$: C, 16.77; H, 1.41. Found: C, 17.15; H, 1.28.

Effect of Catalyst. General Procedure. To a solution of **1b** (124 mg, 1 mmol), $CuBr_2$ (896 mg, 4 mmol), and LiBr (348 mg, 4 mmol) in HOAc (10 mL) was added the catalyst (0.05 mmol) under argon. The mixture was stirred at rt with monitoring by TLC on silica gel. After the reaction was over, ether (80 mL) was added. The mixture was washed with water (3 × 5 mL) and dried over $MgSO_4$. Finally, the ether solution was concentrated and the residue was submitted to prepara-

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(33) Kleiner, E. M.; Onoprienko, V. V.; Pliner, S. A.; Soifer, V. S.; Khokhlov, A. S. *Bioorg. Khim.* **1977**, *3*, 424.
(34) (a) Mori, K.; Yamane, K. *Tetrahedron* **1982**, *38*, 2919. (b) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1990**, 30.
(35) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
(36) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253.
(37) Smith, E. F.; Wallace, D. L. *J. Am. Chem. Soc.* **1894**, *16*, 465.
(38) Chatt, J.; Mann, F. G. *J. Chem. Soc.* **1939**, 1622.
(39) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Oxford, 1988; p 100.

tive TLC on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to give the products **3b** and **4b** (Table 1).

Effect of LiBr. General Procedure. To a stirred solution of **1b** (124 mg, 1 mmol), $CuBr_2$ (896 mg, 4 mmol), and $Pd_2(dba)_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol) in HOAc (10 mL) was added LiBr at rt under argon. The reaction was monitored by TLC on silica gel. After the reaction was over, it was similarly worked up to give the products.

α-(*Z*)-(1′-Bromoethylidene)-β-(bromomethyl)-γ-butyrolactone ((*Z*)-3b): mp 52−54 °C; ^{1}H NMR (200 MHz/$CDCl_3$) δ 4.36 (m, 2H), 3.66 (m, 1H), 3.48 (d, *J* = 7Hz, 2H), 2.60 (s, 3H) ppm; IR (Nujol) 1760, 1650, 1470, 1380, 1240, 770, 680, 640 cm^{-1}; MS *m/e* (%) 287 [M$^+$(^{2}^{81}Br) + 1] (61), 285 [M$^+$(^{81}Br, ^{79}Br) + 1] (100), 283 [M$^+$(^{2}^{79}Br) + 1] (58), 205 (63), 203 (59), 191 (7.9), 189 (8.3), 163, 161, 147, 145, 95, 93, 77; Anal. Calcd for $C_7H_8Br_2O_2$: C, 29.61; H, 2.84. Found: C, 29.48; H, 2.71.

α-(*E*)-(1′-Bromoethylidene)-β-(bromomethyl)-γ-butyrolactone ((*E*)-3b): ot 120 °C/2 mmHg; ^{1}H NMR (200 MHz/$CDCl_3$) δ 4.40 (m, 2 H), 3.70−3.50 (m, 3H), 2.90 (s, 3H) ppm; IR (neat) 1760, 1650, 1480, 1370, 1220, 800, 770, 740, 640, 560 cm^{-1}; MS *m/e* (%): 287 [M$^+$(^{2}^{81}Br) + 1] (22), 285 [M$^+$(^{81}Br, ^{79}Br) + 1] (51), 283 [M$^+$(^{2}^{79}Br) + 1] (33), 205 (100), 203 (98), 191 (25), 189 (28), 164 (34), 161 (39), 147, 145, 109, 95, 77. Anal. Calcd for $C_7H_8Br_2O_2$: C, 29.61; H, 2.84. Found: C, 29.59; H, 2.48.

2′,3′-Dibromopropyl 2,3-dibromo-2(*E*)-butenoate (4b): oil; ^{1}H NMR (90 MHz/$CDCl_3$) δ 4.6 (d, *J* = 5 Hz, 2H), 4.3 (m, 1H), 3.8 (d, *J* = 7Hz, 2H), 2.5 (s, 3H) ppm; IR (neat) 1760, 1650, 1380, 1230, 690 cm^{-1}; MS *m/e* (%) 448 [M$^+$(^{4}^{81}Br)] (4.2), 446 [M$^+$(^{3}^{81}Br, ^{79}Br)] (16), 444 [M$^+$(^{2}^{81}Br, ^{2}^{79}Br)] (20), 442 [M$^+$(^{81}Br, ^{3}^{79}Br)] (2.1), 440 [M$^+$(^{4}^{79}Br)] (2.4), 367 (3.9), 365 (12), 363 (12), 361 (3.6), 229 (48), 227 (100). Anal. Calcd for $C_7H_8Br_4O_2$: C, 18.95; H, 1.82. Found: C, 18.92; H, 1.81.

Cyclization of 2′-Alkenyl 2-Alkynoate (1). Typical Procedure. To a solution of **1a** (110 mg, 1 mmol), $CuBr_2$ (896 mg, 4 mmol), and LiBr (348 mg, 4 mmol) in HOAc (10 mL) was added $Pd_2(dba)_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol). The reaction was then stirred at rt under Ar and monitored by TLC (eluent: petroleum ether/ethyl acetate = 10/1). After the reaction was complete, ether (80 mL) was added and then the mixture was washed with water (3 × 5 mL). The ether layer was dried ($MgSO_4$) and concentrated. The yellow residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) giving (*E*)-3a (230 mg, 85%): mp 86−88 °C; ^{1}H NMR (200 MHz/$CDCl_3$) δ 7.18 (s, 1H), 4.50 (dd, *J* = 10, 7Hz, 1H), 4.20 (dd, *J* = 10, 3Hz, 1H), 3.52 (m, 3H) ppm; IR (Nujol) 3080, 1760, 1650, 1460, 1240, 1220, 1140, 770, 660, 620 cm^{-1}; MS *m/e* (%) 272 [M$^+$(^{2}^{81}Br)] (16), 270 [M$^+$(^{81}Br, ^{79}Br)] (33), 268 [M$^+$(^{2}^{79}Br)] (16), 191 (23), 189 (24), 177 (21), 175 (20), 161 (100), 159 (84), 147 (34), 65, 51. Anal. Calcd for $C_6H_6Br_2O_2$: C, 26.70; H, 2.24. Found: C, 26.75; H, 2.05. The following compounds were prepared similarly.

α-(*Z*)-(1′-Bromobutylidene)-β-(bromomethyl)-γ-butyrolactone ((*Z*)-3c): yield 96%; ot 120−125 °C/1 mmHg; ^{1}H NMR (200 MHz/$CDCl_3$) δ 4.38 (d, *J* = 10 Hz, 1H), 4.28 (dd, *J* = 10, 6Hz, 1H), 3.60 (m, 1H), 3.40 (d, *J* = 4 Hz, 2H), 2.64 (t, *J* = 7Hz, 2H), 1.78 (m, 2H), 1.00 (t, *J* = 7 Hz, 3H) ppm; IR (neat) 1760, 1640, 1380, 1220, 910, 810, 780, 760, 670 cm^{-1}; MS *m/e* (%): 315 [M$^+$(^{2}^{81}Br) + 1] (56), 313 [M$^+$(^{81}Br, ^{79}Br) + 1] (100), 311 [M$^+$(^{2}^{79}Br) + 1] (43), 233, 231, 219, 217, 121, 119, 93, 91. Anal. Calcd for $C_9H_{12}Br_2O_2$: C, 34.64; H, 3.88. Found: C, 34.52; H, 3.66.

α-(*Z*)-(1′-Bromopentylidene)-β-(bromomethyl)-γ-butyrolactone ((*Z*)-3d): yield 86%; oil; ^{1}H NMR (200 MHz/$CDCl_3$) δ 4.36 (d, *J* = 10Hz, 1H), 4.16 (dd, *J* = 10, 5Hz, 1H), 3.60 (m, 1H), 3.40 (d, *J* = 4.0 Hz, 2H), 2.65 (t, *J* = 6Hz, 2H), 1.70 (m, 2H), 1.40 (m, 2H), 0.90 (t, *J* = 7Hz, 3H) ppm; IR (neat) 1760, 1640, 1470, 1380, 1200, 940, 740, 680, 640, 540 cm^{-1}; MS *m/e* (%) 329 [M$^+$(^{2}^{81}Br) + 1] (66), 327 [M$^+$(^{81}Br, ^{79}Br) + 1] (100), 325 [M$^+$(^{2}^{79}Br) + 1] (65), 247 (63), 245 (45), 93, 65, 51. Anal. Calcd for $C_{10}H_{14}Br_2O_2$: C, 36.84; H, 4.33. Found: C, 37.19; H, 4.42.

α-(*E*)-(1′-Bromopentylidene)-β-(bromomethyl)-γ-butyrolactone ((*E*)-3d): yield 20% (Table 2, entry 5); oil; ^{1}H NMR (200 MHz/$CDCl_3$) δ 4.34 (m, 2H), 3.50 (m, 3H), 3.18 (m, 2H), 1.56 (m, 2H), 1.30 (m, 2H), 0.90 (t, *J* = 6Hz, 3H) ppm; IR (neat) 1760, 1640, 1460, 1220, 900, 730, 690, 630, 540 cm^{-1}; MS *m/e* (%) 329 (58), 327 [M$^+$(^{81}Br, ^{79}Br) + 1] (100), 325 [M$^+$(^{2}^{79}Br) + 1] (52), 247 (63), 245 (45), 204, 202, 63, 51, 42. Anal. Calcd for $C_{10}H_{14}Br_2O_2$: C, 36.84; H, 4.33. Found: C, 37.19; H, 4.42.

α-(*Z*)-(1′-Bromo-6′-methylheptylidene)-β-(bromomethyl)-γ-butyrolactone: (*Z*)-3e: yield 97%; oil; ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.35 (dd, *J* = 9.5, 1.5 Hz, 1H), 4.26 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.70−3.40 (m, 3H), 2.7 (m, 2H), 1.8−1.2 (m, 7H), 0.95 (d, *J* = 6.0 Hz, 6H) ppm; IR (neat) 1765, 1640, 1220, 1130, 640 cm^{-1}; MS *m/e* (%) 371 [M$^+$(^{2}^{81}Br) + 1] (2.8), 369 [M$^+$(^{81}Br, ^{79}Br) + 1] (5.7), 367 [M$^+$(^{2}^{79}Br) + 1] (3.0), 287 (100), 193 (85), 191 (43), 109 (47); Anal. Calcd for $C_{13}H_{20}Br_2O_2$: C, 42.42; H, 5.48. Found: C, 42.41; H, 5.48.

α-(*Z*)-(1′-Bromononylidene)-β-(bromomethyl)-γ-butyrolactone ((*Z*)-3f): yield 81%; oil; ^{1}H NMR (200 MHz/$CDCl_3$) δ 4.40 (dd, *J* = 10, 1Hz, 1H), 4.30 (dd, *J* = 10, 6Hz, 1H), 3.60 (m, 1H), 3.42 (d, *J* = 3Hz, 2H), 2.66 (t, *J* = 6Hz, 2H), 1.70 (m, 10H), 1.30 (m, 2H), 0.92 (t, *J* = 7Hz, 3H) ppm; IR (neat) 1770, 1640, 1220, 900, 770, 700, 680, 650, 540 cm^{-1}; MS *m/e* (%) 385 [M$^+$(^{2}^{81}Br) + 1] (48), 383 [M$^+$(^{81}Br, ^{79}Br) + 1] (100), 381 [M$^+$(^{2}^{79}Br) + 1] (39), 303 (63), 301 (54), 285, 283, 219, 191, 109, 107, 81. Anal. Calcd for $C_{14}H_{22}Br_2O_2$: C, 44.00; H, 5.80. Found: C, 44.28; H, 5.86.

α-(*Z*)-(1′-Bromoethylidene)-β-(phenylbromomethyl)-γ-butyrolactone ((*Z*)-3g): yield 91%; mp 100−2 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.55−7.40 (m, 5 H), 5.06 (d, *J* = 7.60 Hz, 1H), 4.27 (d, *J* = 9.72 Hz, 1H), 4.15 (dd, *J* = 9.72, 6.30 Hz, 1H), 3.90 (dd, *J* = 7.60, 6.30 Hz, 1H), 2.65 (s, 3H) ppm; IR (Nujol) 1760, 1650, 1220, 760, 700, 680, 540 cm^{-1}; MS *m/e* (%) 363 [M$^+$(^{2}^{81}Br) + 1] (23), 361 [M$^+$(^{81}Br, ^{79}Br) + 1] (44), 359 [M$^+$(^{2}^{79}Br) + 1] (21), 281 (14), 279 (13), 171 (92), 169 (100), 142 (19), 141 (24), 115, 91, 77. Anal. Calcd for $C_{13}H_{12}Br_2O_2$: C, 43.37; H, 3.36. Found: C, 43.08; H, 3.76.

α-(*Z*)-(1′-Bromoethylidene)-β-(phenylbromomethyl)-γ-butyrolactone ((*Z*)-3g′): yield 89%; mp 119−20 °C; ^{1}H NMR (300 MHz/$CDCl_3$) δ 7.52−7.30 (m, 5H), 4.92 (d, *J* = 9.07 Hz, 1H), 4.72 (dd, *J* = 9.60, 0.72 Hz, 1H), 4.30 (dd, *J* = 9.60, 6.00 Hz, 1H), 3.68 (dd, *J* = 9.07, 6.00 Hz, 1H), 1.80 (s, 3H) ppm; IR (Nujol) 1760, 1640, 1200, 750, 690, 660, 550, 480 cm^{-1}; MS *m/e* (%) 363 [M$^+$(^{2}^{81}Br) + 1] (2.4), 361 [M$^+$(^{81}Br, ^{79}Br) + 1] (4.4), 359 [M$^+$(^{2}^{79}Br) + 1] (2.1), 281 (18), 279 (7.3), 171 (94), 169 (100), 142 (14), 141 (17), 115, 91, 77. Anal. Calcd for $C_{13}H_{12}Br_2O_2$: C, 43.37; H, 3.36. Found: C, 43.05; H, 3.32.

Cyclization of 1a in the Presence of CCl_4. To a solution of **1a** (110 mg, 1 mmol), $CuBr_2$ (896 mg, 4 mmol), LiBr (348 mg, 4 mmol), and CCl_4 (7.1 g, 50 mmol) in HOAc (10 mL) was added $Pd_2(dba)_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol). The reaction was then stirred at rt under Ar and monitored by TLC. When the reaction was complete, ether (80 mL) was added and then the mixture was washed with water (3 × 5 mL). The ether layer was dried ($MgSO_4$), concentrated and submitted to preparative TLC on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) to give the product **2a** (240 mg, 90%).

Preparation of 4′-(Allyloxy)-2′(*Z*)-butenyl 2-Butynoate (8).[40] To a solution of 2-butynoic acid (0.84 g, 10 mmol) and 4-(allyloxy)-2-buten-1-ol (1.54 g, 12 mmol) in ether (10 mL) was dropwise added the solution of DCC (2.47 g, 12 mmol) in ether (20 mL) at 0 °C. DMAP (4-(*N,N*-dimethylamino)-pyridine) (186 mg, 1 mmol) dissolved in ether (10 mL) was subsequently added at 0 °C. After the addition, the mixture was stirred at rt for 20 h. The mixture was filtered and the filter cake was washed with small portions of ether. The ether solution was concentrated, and the crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15/1). The product **8** was obtained (1.60 g, 82%): ot 90 °C/2 mmHg; ^{1}H NMR (60 MHz/CCl_4) δ 6.1−5.5 (m, 3H), 5.3−4.9 (m, 2H), 4.6 (d, *J* = 6Hz, 2H), 4.0 (d, *J* = 5Hz, 2H), 3.9 (d, *J* = 6Hz, 2H), 1.9 (s, 3H) ppm; IR (neat) 3050, 2200, 1720, 1630, 1250, 990, 910 cm^{-1}; MS *m/e* 194 (M$^+$), 179, 153, 122, 110, 73, 67, 57, 42. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.40; H, 7.38.

(40) (a) Balas, L.; Jousseaume, B.; Langwost, B. *Tetrahedron Lett.* **1989**, *30*, 4525. (b) Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350.

$PdCl_2$–$CuCl_2$–LiCl-Catalyzed Cyclization of 8. The procedure was similar to the general method.

10: yield 66%; oil; ^1H NMR (200 MHz/$CDCl_3$) δ 4.38 (m, 2H), 4.16 (m, 1H), 4.00 (m, 1H), 3.80–3.50 (m, 5H), 2.84 (m, 2H), 2.50 (s, 3H), 1.90 (m, 1H) ppm; IR (neat) 1760, 1650, 1380, 1140, 780, 690 cm^{-1}; MS *m/e* (%): 269 [$M^+(^{37}Cl)$ + 1] (2.4), 267 [$M^+(^{37}Cl, ^{35}Cl)$ + 1] (13), 265 [$M^+(^{35}Cl)$ + 1] (23), 231 (6.2), 229 (20), 191 (6.4), 189 (18), 173 (3.3), 171 (11), 147 (16), 145 (34), 81 (100). Anal. Calcd for $C_{11}H_{14}Cl_2O_3$: C, 49.83; H, 5.32. Found: C, 50.19; H, 4.97.

11: yield 22%; oil; ^1H NMR (200 MHz/$CDCl_3$) δ 6.10–5.60 (m, 1H), 5.20–4.90 (m, 2H), 4.40–3.90 (m, 7H), 3.60 (m, 1H), 2.40 (s, 3H) ppm; IR (neat) 3060, 1760, 1640, 1470, 1210, 990, 920, 810, 760 cm^{-1}; MS *m/e* (%): 269 [$M^+(^{37}Cl)$ + 1] (1.3), 267 [$M^+(^{37}Cl, ^{35}Cl)$ + 1] (7.6), 265 [$M^+(^{35}Cl)$ + 1] (11), 231 (3.2), 229 (10), 210 (3.5), 208 (16), 206 (26), 147 (9.9), 145 (23), 95 (100). Anal. Calcd for $C_{11}H_{14}Cl_2O_3$: C, 49.83; H, 5.32. Found: C, 49.95; H, 5.20.

$Pd_2(dba)_3CHCl_3$–HOAC–$CuBr_2$–LiBr-Catalyzed Cyclization of 8. The procedure was the same as the general method.

12: yield 50%; oil; ^1H NMR (200 MHz/$CDCl_3$) δ 6.2–5.6 (m, 1H), 5.4–5.0 (m, 2H), 4.3–3.9 (m, 5H), 3.5 (m, 3H), 2.6 (s, 3H) ppm; IR (neat) 3050, 1770, 1640, 1380, 1230, 920, 690 cm^{-1}; MS *m/e* (%) 357 [$M^+(^{2}{}^{81}Br)$ + 1] (7.0), 355 [$M^+(^{81}Br, ^{79}Br)$ + 1] (11), 353 [$M^+(^{2}{}^{79}Br)$ + 1] (7.1), 191 (5.6), 189 (6.0), 163 (100). Anal. Calcd for $C_{11}H_{14}Br_2O_3$: C, 37.32; H, 3.99; Found: C, 37.22; H, 4.14.

13: yield 23%; oil; ^1H NMR (200 MHz/$CDCl_3$) δ 4.24 (m, 2H), 3.92–3.74 (m, 8H), 3.50 (m, 1H), 2.54 (s, 3H) ppm; IR (neat) 1770, 1640, 1380, 1210, 770, 690, 510 cm^{-1}; MS *m/e* (%) 519 [$M^+(^{4}{}^{81}Br)$ + 1] (6.6), 517 [$M^+(^{3}{}^{81}Br, ^{79}Br)$ + 1] (27), 515 [$M^+(^{2}{}^{81}Br, ^{2}{}^{79}Br)$ + 1] (46), 513 [$M^+(^{81}Br, ^{3}{}^{79}Br)$ + 1] (30), 511 [$M^+(^{4}{}^{79}Br)$ + 1] (8.4), 437 (0.8), 435 (2.4), 433 (2.3), 431 (0.8), 357 (1.5), 355 (3.6), 353 (3.0), 299 (4.1), 297 (8.8), 295 (4.4), 217 (12), 215 (12), 192 (57), 190 (61), 163 (98), 161 (100). Anal. Calcd for $C_{11}H_{14}Br_4O_3$: C, 25.71; H, 2.75. Found: C, 25.80; H, 2.80.

Preparation of 1'-Substituted 2'-Alkenyl 2-Alkynoates (18). The procedure was similar to the preparation of compound **8**.

1'-Allyl-2'-propenyl 2-propynoate (18a): yield 45%; ot 66 °C/10 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.0–4.9 (m, 7H), 2.7 (s, 1H), 2.3 (t, J = 7Hz, 2H) ppm; IR (neat) 3250, 3050, 2100, 1710, 1640, 1220, 990, 920, 760 cm^{-1}; MS *m/e* 151 (M^+ + 1), 109, 82, 54, 42. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.99; H, 7.07.

1'-Propyl-2'-propenyl 2-propynoate (18b): yield 52%; ot 70 °C/6 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.0–5.5 (m, 1H), 5.3–5.0 (m, 3H), 2.7 (s, 1H), 1.5–1.2 (m, 4H), 0.9 (t, J = 6 Hz, 3H) ppm; IR (neat) 3300, 2100, 1710, 1640, 1230, 990, 760 cm^{-1}; MS *m/e* 152 (M^+), 109, 82, 68, 55, 43. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.15; H, 7.56.

1'-Propyl-2'-propenyl 2-butynoate (18c): yield 88%; ot 80–6 °C/10 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.0–5.5 (m, 1H), 5.3–5.0 (m, 3H), 1.9 (s, 3H), 1.6–1.2 (m, 4H), 0.9 (t, J = 6Hz, 3H) ppm; IR (neat): 3080, 2200, 1710, 1250, 990, 930, 750 cm^{-1}; MS *m/e* 165 (M^+ – 1), 151, 122, 95, 68, 55, 43. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.64; H, 8.89.

1'-Methyl-2'-propenyl 2-propynoate (18d): yield 56%; ot 70–80 °C/10 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.1–5.6 (m, 1H), 5.3–5.0 (m, 3H), 2.7 (s, 1H), 1.3 (d, J = 6Hz, 3H) ppm; IR (neat) 3350, 3080, 2220, 1710, 1640, 1260, 990, 930, 750 cm^{-1}; MS *m/e* 125 (M^+ + 1), 97, 82, 69, 55, 42. Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.57; H, 6.80.

1'-Pentyl-2'-propenyl 2-propynoate (18e): yield 52%; ot 75 °C/5 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.1–5.5 (m, 1H), 5.35–5.05 (m, 3H), 2.8 (s, 1H), 1.6–1.1 (m, 8H), 0.9 (t, J = 6Hz, 3H) ppm; IR (neat) 3300, 2200, 1720, 1230, 990, 910, 760 cm^{-1}; MS *m/e* 181 (M^+ + 1), 151, 137, 111, 95, 71, 69, 57, 53, 43. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.25; H, 9.02.

1'-(3''-Methylbutyl)-2'-propenyl 2-propynoate (18f): yield 42%; ot 75–80 °C/5 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.1–5.5 (m, 1H), 5.3–4.9 (m, 3H), 2.7 (s, 1H), 1.5–1.0 (m, 5H), 0.85 (d, J = 6 Hz, 6H) ppm; IR (neat) 3250, 3080, 2100, 1720, 1640, 1230, 990, 930, 760 cm^{-1}; MS *m/e* 181 (M^+ + 1), 111, 95, 71, 69, 57, 53, 43. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.16; H, 8.90.

1'-Isopropyl-2'-propenyl 2-propynoate (18g): yield 55%; ot 70 °C/8 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.0–5.0 (m, 3H), 4.0 (t, J = 7 Hz, 1H), 2.8 (s, 1H), 1.8 (m, 1H), 0.9 (d, J = 6 Hz, 6H) ppm; IR (neat) 3250, 2100, 1710, 1220 cm^{-1}; MS *m/e* 153 (M^+ + 1), 109, 83, 69, 55, 43. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.28; H, 7.64.

1'-Methyl-2'-propenyl 2-butynoate (18h): yield 76%; bp 168–70 °C; ^1H NMR (60 MHz/CCl_4) δ 6.2–5.6 (m, 1H), 5.3–5.0 (m, 2H), 4.5 (t, J = 7 Hz, 1H), 2.0 (s, 3H), 1.3 (d, J = 7 Hz, 3H) ppm; IR (neat) 3080, 2250, 1720, 1640, 1470, 1260, 990, 930, 760 cm^{-1}; MS *m/e* 138 (M^+), 123, 95, 72, 67, 55, 43. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.82; H, 6.90.

1'-Butyl-2'-propenyl 2-butynoate (18i): yield 89%; ot 90 °C/8 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.1–5.7 (m, 1H), 5.4–5.1 (m, 2H), 4.1 (t, J = 6 Hz, 1H), 2.0 (s, 3H), 1.7–1.2 (m, 6H), 0.9 (t, J = 6 Hz, 3H) ppm; IR (neat) 3080, 2200, 1710, 1640, 1250, 990, 920, 750 cm^{-1}; MS *m/e* 179 (M^+ – 1), 165, 151, 137, 123, 113, 97, 68, 55. Anal. Calcd for $C_{11}H_{16}O_2$: C, 38.85; H, 4.74. Found: C, 38.96; H, 4.64.

1'-Methyl-2'-propenyl 2-heptynoate (18j): yield 76%; ot 75 °C/5 mmHg; ^1H NMR (60 MHz/CCl_4) δ 6.1–5.6 (m, 1H), 5.4–5.0 (m, 3H), 2.4 (t, J = 6 Hz, 2H), 1.7–1.5 (m, 4H), 1.3 (d, J = 6 Hz, 3H), 0.9 (t, J = 6 Hz, 3H) ppm; IR (neat) 3090, 2220, 1720, 1250, 990, 930, 760 cm^{-1}; MS *m/e* 181 (M^+ + 1), 151, 135, 127, 109, 81, 55. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.96; H, 8.92.

$PdCl_2$–$CuCl_2$–LiCl-Catalyzed Cyclization of Compound 18. The procedure was similar to the cyclization of compound **1a**.

***trans*-α-(*E*)-(Chloromethylene)-β-(chloromethyl)-γ-allyl-γ-butyrolactone (19a):** yield 59%; oil; ^1H NMR (200 MHz/$CDCl_3$) δ 6.90 (d, J = 6 Hz, 1H), 5.80 (m, 1H), 5.24 (m, 2H), 4.50 (td, J = 7.0, 4.0 Hz, 1H), 3.62 (dd, J = 7.0, 2.0 Hz, 2H), 3.20 (m, 1H), 2.50 (m, 2H) ppm; IR (neat) 3080, 1760, 1640, 1180, 920, 790, 720, 670 cm^{-1}; MS *m/e* (%) 225 [$M^+(^{2}{}^{37}Cl)$ + 1] (2.5), 223 [$M^+(^{37}Cl, ^{35}Cl)$ + 1] (11), 221 [$M^+(^{2}{}^{35}Cl)$ + 1] (20), 183 (75), 181 (75), 179 (100), 155 (3.6), 153 (18), 151 (27), 145 (23), 143 (60), 117 (11), 115 (39), 89, 87, 41. Anal. Calcd for $C_9H_{10}Cl_2O_2$: C, 48.90; H, 4.56. Found: C, 48.87; H, 4.71.

α-(*E*)-(Chloromethylene)-β-(chloromethyl)-γ-propyl-γ-butyrolactone (19b): yield 72%; ot 140 °C/2 mmHg; ^1H NMR (300 MHz/$CDCl_3$) δ 6.88 [d, J = 1.5 Hz, 0.67 H (trans isomer)], 6.80 [d, J = 1.5 Hz, 0.33 H (cis isomer)], 4.55 [q, J = 6.2 Hz, 0.33 H (cis isomer)], 4.40 [td, J = 5.2, 4.2 Hz, 0.67 H (trans isomer)], 3.72 [dd, J = 11.1, 6.0 Hz, 0.67 H (trans isomer)], 3.60 [m, 0.66 H (cis isomer)], 3.54 [dd, J = 11.1, 8.0 Hz, 0.67 H (trans isomer)], 3.38 [dddd, J = 7.9, 6.2, 6.0, 1.5 Hz, 0.33 H (cis isomer)], 3.10 [ddd, J = 7.6, 4.2, 1.6 Hz, 0.67 H (trans isomer)], 1.7–1.4 (m, 4H), 0.95 (t, J = 6.5 Hz, 3H) ppm; IR (neat) 3080, 1770, 1640, 1190, 970, 760, 670 cm^{-1}; MS *m/e* (%) 227 [$M^+(^{2}{}^{37}Cl)$ + 1] (10), 225 [$M^+(^{37}Cl, ^{35}Cl)$ + 1] (70), 223 [$M^+(^{2}{}^{35}Cl)$ + 1] (86), 183 (2.2), 181 (16), 179 (23), 145 (19), 143 (56), 117 (40), 115 (100), 89, 87, 43. Anal. Calcd for $C_9H_{12}Cl_2O_2$: C, 48.45; H, 5.42. Found: C, 48.35; H, 5.18.

cis-α-(*E*)-(1'-Chloroethylidene)-β-(chloromethyl)-γ-propyl-γ-butyrolactone (19c): yield 80%; ot 145 °C/2 mmHg; ^1H NMR (300 MHz/$CDCl_3$) δ 4.50 (q, J = 6.2 Hz, 1H), 3.75 (dd, J = 11.1, 5.2 Hz, 1H), 3.55 (dd, J = 11.1, 6.8 Hz, 1H), 3.45 (m, 1H), 2.40 (s, 3H), 1.70 (m, 2H), 1.50 (m, 2H), 1.05 (t, J = 6.4 Hz, 3H) ppm; IR (neat) 1770, 1660, 1430, 1380, 1220, 960, 870, 760, 700, 660 cm^{-1}; MS *m/e* (%) 240 [$M^+(^{2}{}^{37}Cl)$] (1.1), 238 [$M^+(^{37}Cl, ^{35}Cl)$] (5.6), 236 [$M^+(^{2}{}^{35}Cl)$] (8.5), 197 (2.2), 195 (12), 193 (17), 166 (11), 131 (49), 129 (100), 71, 65, 43. Anal. Calcd for $C_{10}H_{14}Cl_2O_2$: C, 50.65; H, 5.95. Found: C, 50.55; H, 6.03.

$Pd_2(dba)_3$-$CHCl_3$–$CuBr_2$–LiBr-Catalyzed Cyclization of Compounds 18b–j. The procedure was similar to the cyclization of compound **1a**.

α-(*E*)-(Bromomethylene)-β-(bromomethyl)-γ-methyl-γ-butyrolactone (19d): yield 92%; ot 150 °C/2 mmHg; ^1H NMR (200 MHz/$CDCl_3$) δ 7.14 [d, J = 2.0 Hz, 0.67 H (trans isomer)], 7.08 [d, J = 2.0 Hz, 0.33 H (cis isomer)], 4.66 [quint, J = 6.0

Hz, 0.33 H (cis isomer)], 4.32 [qd, J = 6.2, 4.0 Hz, 0.67 H (trans isomer)], 3.70 [d, J = 6.8 Hz, 1.34 H (trans isomer)], 3.60 [m, 0.66 H (cis isomer)], 3.10 (m, 1H), 1.48 [d, J = 6.2 Hz, 2.01 H (trans isomer)], 1.42 [d, J = 6.0 Hz, 0.99 H (cis isomer)] ppm; IR (neat) 3030, 1750, 1730, 1620, 1460, 1380, 940, 920, 870, 520 cm^{-1}; MS *m/e* (%) 287 [$M^+(^{81}Br)$ + 1] (17), 285 [$M^+(^{81}Br, ^{79}Br)$ + 1] (34), 283 [$M^+(^{79}Br)$ + 1] (18), 205 (92), 203 (100), 191 (21), 189 (22), 175 (11), 173 (12), 147 (14), 145 (15), 81, 65, 53. Anal. Calcd for $C_7H_8Br_2O_2$: C, 29.61; H, 2.84. Found: C, 30.05; H, 2.48.

α-(*E*)-(Bromomethylene)-β-(bromomethyl)-γ-propyl-γ-butyrolactone (19e): yield 93% ot 160 °C/1 mmHg; ^1H NMR (200 MHz/$CDCl_3$) δ 7.18 [d, J = 2.0 Hz, 0.75 H (trans isomer)], 7.12 [d, J = 2.0 Hz, 0.25 H (cis isomer)], 4.56 [quint, J = 6.0 Hz, 0.25 H (cis isomer)], 4.40 [td, J = 6.0, 4.0 Hz, 0.75 H (trans isomer)], 3.50 [d, J = 6.0 Hz, 1.50 H (trans isomer)], 3.40 [m, 0.50 H (cis isomer)], 3.16 (m, 1H), 1.74−1.42 (m, 4H), 1.00 (t, J = 6.0 Hz, 3H) ppm; IR (neat) 3050, 1770, 1640, 1180, 970, 840, 750, 700, 630 cm^{-1}; MS *m/e* (%) 315 [$M^+(^{81}Br)$ + 1] (12), 313 [$M^+(^{81}Br, ^{79}Br)$ + 1] (23), 311 [$M^+(^{79}Br)$ + 1] (12), 271 (5.9), 269 (13), 267 (7.2), 189 (12), 187 (12), 161 (100), 159 (98), 133 (19), 95, 80. Anal. Calcd for $C_9H_{12}Br_2O_2$: C, 35.80; H, 4.00. Found: C, 35.40; H, 4.13.

α-(*E*)-(Bromomethylene)-β-(bromomethyl)-γ-pentyl-γ-butyrolactone (19f): yield 82%; ot 160 °C/1 mmHg; ^1H NMR (200 MHz/$CDCl_3$) δ 7.18 [d, J = 1.5 Hz, 0.78 H (trans isomer)], 7.10 [d, J = 1.5 Hz, 0.22 H (cis isomer)], 4.58 [quint, J = 5.8 Hz, 0.22 H (cis isomer)], 4.40 [td, J = 6.0, 4.2 Hz, 0.78 H (trans isomer)], 3.60 [d, J = 6.0 Hz, 1.56 H (trans isomer)], 3.52 [m, 0.44 H (cis isomer)], 3.16 (m, 1H), 1.70 (t, J = 7.0 Hz, 2H), 1.40 (m, 6H), 0.96 (t, J = 6.0 Hz, 3H) ppm; IR (neat) 3050, 1770, 1630, 1180, 840, 770, 700, 620, 550 cm^{-1}; MS *m/e* (%) 343 [$M^+(^{81}Br)$ + 1] (10), 341 [$M^+(^{81}Br, ^{79}Br)$ + 1] (25), 339 [$M^+(^{79}Br)$ + 1] (11), 261 (3.9), 259 (4.5), 161 (100), 159 (91), 139 (16), 137 (12), 95, 93, 43. Anal. Calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74. Found: C, 38.87; H, 4.53.

α-(*E*)-(Bromomethylene)-β-(bromomethyl)-γ-isopentyl-γ-butyrolactone (19g): yield 82%; ot 162 °C/1 mmHg; ^1H NMR (300 MHz/$CDCl_3$) δ 7.15 [d, J = 1.7 Hz, 0.76 H (trans isomer)], 7.10 [d, J = 1.7 Hz, 0.24 H (cis isomer)], 4.56 [quint, J = 6.1 Hz, 0.24 H (cis isomer)], 4.40 [td, J = 6.5, 4.1 Hz, 0.76 H (trans isomer)], 3.45 [d, J = 7.6 Hz, 1.52 H (trans isomer)], 3.35 [m, 0.48 H (cis isomer)], 3.30 (m, 1H), 1.7−1.2 (m, 5H), 0.95 (d, J = 7.2 Hz, 6H) ppm; IR (neat) 3070, 1770, 1640, 1470, 1180, 920, 840, 760, 700, 620, 550 cm^{-1}; MS *m/e* (%) 343 [$M^+(^{81}Br)$ + 1] (17), 341 [$M^+(^{81}Br, ^{79}Br)$ + 1] (35), 339 [$M^+(^{79}Br)$ + 1] (18), 270 (42), 268 (100), 266 (43), 261, 259, 159, 109, 66. Anal. Calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74. Found: C, 38.99; H, 4.68.

***trans*-α-(*E*)-(Bromomethylene)-β-(bromomethyl)-γ-isopropyl-γ-butyrolactone (19h):** yield 85%; ot 160 °C/2 mmHg; ^1H NMR (300 MHz/$CDCl_3$) δ 7.15 (d, J = 1.7 Hz, 1H), 4.35 (dd, J = 6.0, 3.8 Hz, 1H), 3.45 (d, J = 6.0 Hz, 2H), 3.25 (m, 1H), 1.90 (m, 1H), 1.05 (d, J = 8.0 Hz, 6H) ppm; IR (neat) 3080, 1770, 1630, 1170, 840, 740, 630 cm^{-1}; MS *m/e* (%) 315 [$M^+(^{81}Br)$ + 1] (2.1), 313 [$M^+(^{81}Br, ^{79}Br)$ + 1] (3.7), 311 [$M^+(^{79}Br)$ + 1] (2.1), 271 (28), 269 (29), 243 (12), 241 (26), 239 (14), 189 (25), 187 (28), 106 (91), 104 (100). Anal. Calcd for $C_9H_{12}Br_2O_2$: C, 35.80; H, 4.00. Found: C, 35.78; H, 4.01.

***cis*-α-(*E*)-(1-Bromoethylidene)-β-(bromomethyl)-γ-methyl-γ-butyrolactone (19i):** yield 91%; ot 140 °C/1 mmHg; ^1H NMR (300 MHz/$CDCl_3$) δ 4.60 (quint, J = 6.0 Hz, 1H), 3.56 (m, 2H), 3.38 (dd, J = 13.3, 8.1 Hz, 1H), 2.64 (s, 3H), 1.56 (d, J = 7.0 Hz, 3H) ppm; IR (neat) 1760, 1650, 1470, 1390, 1220, 910, 750, 650, 570 cm^{-1}; MS *m/e* (%) 301 [$M^+(^{81}Br)$ + 1] (1.6), 299 [$M^+(^{81}Br, ^{79}Br)$ + 1] (3.3), 297 [$M^+(^{79}Br)$ + 1] (2.1), 219 (56), 217 (64), 175 (76), 173 (81), 147 (25), 145 (26), 43 (100). Anal. Calcd for $C_8H_{10}Br_2O_2$: C, 32.25; H, 3.38. Found: C, 32.53; H, 3.37.

***cis*-α-(*E*)-(1-Bromoethylidene)-β-(bromomethyl)-γ-propyl-γ-butyrolactone (19j):** yield 87%; ot 150 °C/1 mmHg; ^1H NMR (200 MHz/$CDCl_3$) δ 4.52 (quint, J = 6.2 Hz, 1H), 3.64 (m, 2H), 3.40 (dd, J = 13.3, 8.4 Hz, 1H), 2.66 (s, 3H), 1.96−1.24 (m, 4H), 1.04 (t, J = 7.0 Hz, 3H) ppm; IR (neat) 1750, 1640, 1460, 1380, 940, 870, 740, 640, 570 cm^{-1}; MS *m/e* (%): 329 [$M^+(^{81}Br)$ + 1] (49), 327 [$M^+(^{81}Br, ^{79}Br)$ + 1] (87), 325 [$M^+(^{79}Br)$ + 1] (46), 247 (22), 245 (20), 175 (92), 173 (100), 147 (28), 145 (25), 121, 66. Anal. Calcd for $C_{10}H_{14}Br_2O_2$: C, 36.84; H, 4.33. Found: C, 37.12; H, 4.35.

***cis*-α-(*E*)-(1-Bromoethylidene)-β-(bromomethyl)-γ-butyl-γ-butyrolactone (19k):** yield 94% ot 156 °C/1 mmHg. ^1H NMR (200 MHz/$CDCl_3$) δ 4.56 (quint, J = 6.0 Hz, 1H), 3.56 (m, 2H), 3.26 (dd, J = 13.6, 8.4 Hz, 1H), 2.62 (s, 3H), 1.80−1.30 (m, 6H), 0.92 (t, J = 6.0 Hz, 3H) ppm; IR (neat) 1760, 1650, 1460, 1380, 1220, 970, 740, 650, 570 cm^{-1}; MS *m/e* (%) 343 [$M^+(^{81}Br)$ + 1] (47), 341 [$M^+(^{81}Br, ^{79}Br)$ + 1] (89), 339 [$M^+(^{79}Br)$ + 1] (42), 261 (12), 259 (11), 175 (100), 173 (91), 147, 145, 109, 107. Anal. Calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74. Found: C, 38.96; H, 4.64.

***cis*-α-(*E*)-(1-Bromoethylidene)-β-(bromomethyl)-γ-methyl-γ-butyrolactone (191):** yield 82%; ot 162 °C/1 mmHg; ^1H NMR (200 MHz/$CDCl_3$) δ 4.60 (quint, J = 6.0 Hz, 1H), 3.75 (m, 2H), 3.55 (dd, J = 14.0, 8.4 Hz, 1H), 2.70 (t, J = 7.0 Hz, 2H), 1.74 (m, 2H), 1.58 (d, J = 6.0 Hz, 3H), 1.42 (m, 2H), 0.97 (t, J = 6.0 Hz, 3H) ppm; IR (neat) 1750, 1640, 1470, 1380, 1230, 920, 840, 750, 560 cm^{-1}; MS *m/e* (%) 343 [$M^+(^{81}Br)$ + 1] (49), 341 [$M^+(^{81}Br, ^{79}Br)$ + 1] (100), 339 [$M^+(^{79}Br)$ + 1] (50), 261 (7.0), 259 (6.2), 133, 107, 65, 43. Anal. Calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74. Found: C, 38.89; H, 4.71.

The Hydrolysis of Dibromosubstituted Derivatives of α-Methylene-γ-butyrolactone. Preparation of α-(Bromoalkylidene)-β-(hydroxymethyl)-γ-butyrolactones. α-(*E*)-(Bromomethylene)-β-(hydroxymethyl)-γ-pentyl-γ-butyrolactone (26). To a solution of **19f** (340 mg, 1.0 mmol) in dioxane−water (1:1) (10 mL) was added $CaCO_3$ (500 mg, 5.0 mmol). After refluxing for 30 h, the reaction mixture was cooled to room temperature, acidified with 10% HCl, and extracted with ether (10 mL × 3). The combined organic solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed on silica gel (eluent: petroleum ether:ethyl acetate = 7:3) to yield *trans*-**26** (138 mg, 50.0%) and *cis*-**26** (35 mg, 12.5%): oil; ^1H NMR (200 MHz/$CDCl_3$) δ trans isomer 7.06 (d, J = 2Hz, 1H), 4.36−4.24 (q, J = 6 Hz, 1H), 3.74 (d, J = 6 Hz, 2H), 3.30 (brs, 1H), 3.0−2.9 (m, 1H), 1.6−1.1 (m, 8H), 0.90 (t, J = 7 Hz, 3H) ppm; cis isomer 7.08 (d, J = 2.0 Hz, 1H), 4.66 (td, J = 7, 3 Hz, 1H), 3.90−3.72 (m, 2H), 3.08−2.94 (m, 1H), 2.62 (brs, 1H), 1.6−1.1 (m, 8H), 0.90 (t, J = 6 Hz, 3H) ppm; IR (neat) 3400, 2950, 1760, 1630, 1170, 770, 700 cm^{-1}; MS *m/e* (%) 279 (18), 277 (17), 248 (8.4), 246 (8.9), 207 (13), 205 (13), 167 (46), 97 (100). Anal. Calcd for $C_{11}H_{17}BrO_3$: C, 47.67; H, 6.18. Found: C, 47.81; H, 6.50.

Further Transformation of 26. Compound **27** and **28** were prepared from *trans*-**26** according to refs 30 and 27, respectively.

27: yield 94%; oil; ^1H NMR (300 MHz/$CDCl_3$) δ 7.45−7.30 (m, 5H), 6.35 (d, J = 2.2 Hz, 1H), 4.40−4.25 (m, 1H), 3.77 (d, J = 6.6 Hz, 1H), 3.70 (dd, J = 6.6, 5.0 Hz, 1H), 2.98−2.88 (m, 1H), 2.60 (brs, 1H), 1.6−1.1 (m, 8H), 0.95 (t, J = 6.0 Hz, 3H) ppm; IR (neat) 3400, 3030, 1750, 1630, 1600, 1490, 1460, 760, 700 cm^{-1}; MS *m/e* (%): 298 (M^+) (2.4), 297 ($M^+ - 1$) (11), 227 (2.1), 211 (100), 197 (2.5), 165 (4.7), 123 (10), 83 (35). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.82; H, 7.50.

28: yield 90%; oil; ^1H NMR (300 MHz/$CDCl_3$) δ 7.4−6.5 (m, 8H), 4.35−4.25 (m, 1H), 3.80 (d, J = 8.6 Hz, 1H), 3.70 (dd, J = 8.6, 4.0 Hz, 1H), 2.98−2.88 (m, 1H), 2.60 (brs, 1H), 1.6−1.1 (m, 8H), 0.95 (t, J = 6.0 Hz, 3H) ppm; IR (neat) 3400, 3060, 1770, 1670, 1600, 1180, 800, 700 cm^{-1}; MS *m/e* (%) 301 (M^+ + 1), 300 (M^+), 269 (14), 199 (9.3), 167 (6.5), 99 (36), 43 (100). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.88; H, 7.83.

Synthesis of (±)-A-factor. α-(*Z*)-(1′-Bromo-6′-methylheptylidene)-β-(hydroxymethyl)-γ-butyrolactone (30). To a solution of **3e** (368 mg, 1.0 mmol) in dioxane−water (1:1) (10 mL) was added lithium hydroxide (120 mg, 5.0 mmol). After refluxing for 10 h, the reaction mixture was cooled to room temperature, acidified with 10% HCl, and extracted with ether (10 mL × 3). The combined organic solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed on silica gel (eluent: petroleum ether:ethyl acetate = 7:3) to yield

30 (183 mg, 60%) as a colorless oil: ^{1}H NMR (300 MHz/$CDCl_3$) δ 4.33 (dd, J = 9.2, 1.4 Hz, 1H), 4.22 (dd, J = 9.2, 6.5 Hz, 1H), 3.75–3.65 (m, 2H), 3.4 (m, 1H), 2.7–2.5 (m, 3H), 1.7–1.1 (m, 7H), 0.85 (d, J = 6.5 Hz, 6H) ppm; IR (neat) 3400, 2950, 1725, 1640, 1480, 1370, 1210, 1130, 1020, 670 cm^{-1}; MS *m/e* 307 [$M^+(^{81}Br)$ + 1] (97), 305 [$M^+(^{79}Br)$ + 1] (100), 225 (49), 129 (11), 109 (27). Anal. Calcd for $C_{13}H_{21}BrO_3$: C, 51.16; H, 6.93. Found: C, 51.67; H, 7.10. HRMS calcd for $C_{13}H_{21}O_3$ 225.1540, found 225.1491.

α-(6'-Methylheptanoyl)-β-(hydroxymethyl)-γ-butyrolactone [(±)-A-factor] (29). A mixture of compound **30** (305 mg, 1.0 mmol), and diethylamine (365 mg, 5.0 mmol) in acetonitrile (4 mL) was stirred at room temperature for 3 days. 3 N HCl (5 mL) was then added. The reaction mixture was stirred for an additional 10 h. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (10 mL × 3). The CH_2Cl_2 solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (eluent: petroleum ether:ethyl acetate = 7:3) to afford (±)-A-factor (**29**) (125 mg, 51%) as a waxy solid. It showed the same IR, ^{1}H NMR, and MS data as those for the natural product.[34a]

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Supplementary Material Available: ^{1}H NMR spectra for compounds **19d**, **30**, and **31** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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