Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1657-1666, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00210-3

Template Effect of Pd(II) in the Synthesis of Differently Substituted Enantiopure γ-Butyrolactones and Its Synthetic Applications

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Abstract: Under the catalysis of Pd(II) in the presence of CuX_2 and LiX, 1'-substituted allylic 2-alkynoates undergo stereoselective cyclization affording β, γ-disubstituted α-alkylidene-γ-butyrolactones with *cis* or *trans* relative configurations. A highly efficient hydrogenation reaction of the cyclization product afforded a *trans*-α, β-disubstituted-γ-butyrolactone in quantitative yield with high stereoselectivity. Isohomopilopic acid which can be converted into isopilocarpine was synthesized using this methodology by further transformation.

INTRODUCTION

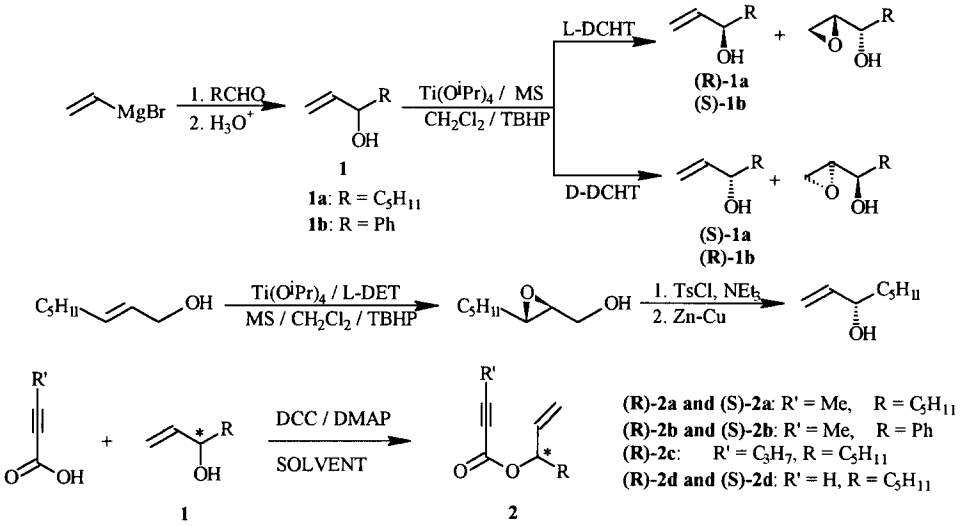
The widespread occurrence of the γ-butyrolactone unit in natural products and their important biological activities[1] have prompted considerable interest in the synthetic community. [2] The physiological activity of these γ-butyrolactones often depends on the absolute configuration.[3] Thus, the stereoselective synthesis of differently substituted enantiopure γ-butyrolactones is important and successful methodologies have been reported from a number of laboratories.[4] In a preliminary communication, we reported a palladium catalyzed construction of enantiopure β, γ-disubstituted α-alkylidene-γ-butyrolactones, in which the lactone ring was constructed by stereoselective carbon-carbon bond formation starting from homochiral allylic 2-alkynoates.[5] In this paper, we describe this reaction in detail and its application to natural products synthesis.

RESULTS AND DISCUSSION

Synthesis of the Starting Materials. The substrates for the above-mentioned cyclization reaction, homochiral 1'-substituted allylic 2-alkynoates, were synthesized according to the route shown in Scheme 1. Optically active allylic alcohols were obtained by Sharpless kinetic resolutions of racemic allylic alcohols,[6] which were prepared by vinylation of aldehydes with Grignard reagents in the usual way. Also, optically active

allylic alcohols were easily available from Sharpless asymmetric epoxidation and subsequent reduction.[7] The two different absolute configurations of the alcohols were obtained just using the tartrate with different configurations in the Sharpless reaction. The enantiomeric purities of the resulted alcohols were determined by

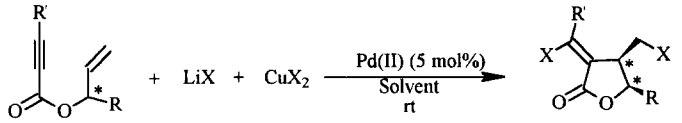
Scheme 1



300 MHz ^{1}H NMR and ^{19}F NMR spectra of their Mosher esters, no isomers were found in their NMR spectra. The esterifications between those allylic alcohols and 2-alkynoic acids were promoted by DCC in the presence of a catalytic amount of DMAP. Better results could be obtained for the esterification of propynoic acid when diethyl ether was used as the solvent, while for the synthesis of 3-substituted-2-alkynoates, the reaction should be carried out in dried CH_2Cl_2.

Synthesis of Optically Active α-(*Z*)-Haloalkylidene-*cis*-β, γ-disubstituted-γ-butyrolactone (3) ---------- Cyclization of 1'-Substituted Allylic 3-Substituted 2-Alkynoates

Under the catalysis of $PdCl_2(PhCN)_2$, reaction of 1'(R)-pentyl 2'-propenyl 2-butynoate **(R)-2** with LiCl in the presence of $CuCl_2$ afforded a single cyclic product **3aA** in high yield (95%). The relative stereochemistry of the β, γ-substituents in **3aA** was determined by irradiation experiments of ^{1}H NMR and 2D NOESY spectra. Partial ^{1}H NMR spectroscopic data ($CDCl_3$, 300 MHz) are shown in Table I. Irradiation of the signal at δ 4.37 ppm (γ-position proton, H^{γ}) of the product **(4R, 5R)-3aA** led to the observation of the change of the signal at 3.46 ppm from multiple peak to pseudo-triple peak and no change at 3.75 ppm and 3.51 ppm. Thus, the signal at 3.46 ppm was assigned to the chemical shift of the proton at β-position of the lactone (H^{β}). ^{1}H 2D NOESY spectra showed a strong NOE correlation signal between H^{β} and H^{γ}, such a result strongly supported that the cyclic product was *cis* with respect to β, γ-substituents. The exocyclic carbon-carbon double bond in **(4R, 5R)-3aA** was believed to be in *Z* configuration by comparing the chemical shift of the allylic proton with its analogues, and it was also confirmed by the appearance of NOE correlation signal between H^b and H^c.

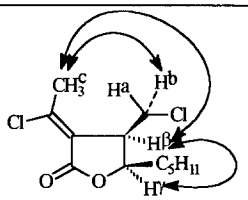


2 3

3	R'	R	X	yield (%)
(4R, 5R)-3aA	Me	C_5H_{11}	Cl	95
(4S, 5S)-3aA	Me	C_5H_{11}	Cl	94
(4R, 5S)-3bA	Me	Ph	Cl	73
(4S, 5R)-3bA	Me	Ph	Cl	70
(4R, 5R)-3cA	Pr	C_5H_{11}	Cl	80
(4R, 5R)-3aB	Me	C_5H_{11}	Br	78
(4S, 5S)-3aB	Me	C_5H_{11}	Br	75
(4R, 5S)-3aB	Me	Ph	Br	70
(4R, 5R)-3cB	Pr	C_5H_{11}	Br	71

Table 1 Partial ^{1}H NMR spectral data of **3aA**

4.37	dt	9.86Hz, 4.93Hz	1H	H^{γ}	irradiated
3.75	dd	5.59Hz, 11.39H	1H	H^{a}	no change
3.51	dd	6.70Hz, 11.10Hz	1H	H^{b}	no change
3.46	m		1H	H^{β}	t (J = 5.6 Hz)



3aA

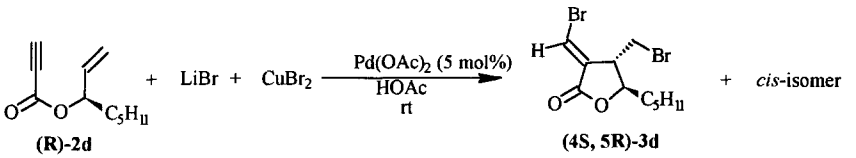
To test the generality of such a stereochemical result, a phenyl group instead of the alkyl group was introduced to the 1'-position of the substrate (**S-2b**). Under similar conditions, cyclization of **S-2b** also proceeded smoothly affording the α-(*Z*)-chloroethylidene-β, γ-*cis*-γ-butyrolactone as the single cyclic product. Similar results were also obtained for 1'-pentyl 2'-propenyl 2-hexynoate (**R-2c**).

When LiBr and $CuBr_2$ were used instead of LiCl and $CuCl_2$ respectively, none of the desired cyclic product was obtained under similar conditions in acetonitrile medium. However, when the reaction carried out in HOAc, the cyclization of 2-alkynoates occurred quickly affording the brominated β, γ-*cis*-γ-lactone as the sole cyclic product.

Synthesis of Optically Active α-(*E*)-Halomethylene-β, γ-*trans*-γ-butyrolactones ---------- Cyclization of 1'-Substituted Propynoates

When we extended this reaction to 1'(R)-pentyl 2'-propenyl propynoate, the reaction afforded a pair of diastereomers: *trans* (referred to the β, γ-substituents)-**(4S, 5R)-3d** and the corresponding *cis* isomer **(4R, 5R)-**

3d with a ratio of 71 : 29. Based on this *trans*-selectivity in the lactone product, recently we have developed a facile route for the enantiospecific synthesis of both enantiomers of methylenolactocin.[8]



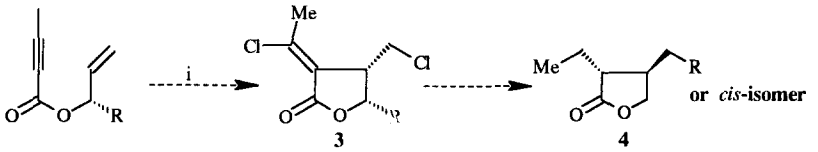
(R)-2d **(4S, 5R)-3d**

The result that the exocyclic carbon-carbon double had the *E*-configuration and the β, γ-substituents appeared to be *trans* in the cyclization product of propynoate, is quite different from the selectivity in the case of 3-substituted 2-alkynoates. Such a stereochemical result indicated that the substituent R' in the substrate **2** played an important role not only in the stereochemistry of halopalladation of carbon-carbon triple bond but also in the diastereoselectivity of the intramolecular carbon-carbon double bond insertion reaction. Thus, we can control the *Z-E* (exocyclic double bond) and *cis-trans* (β, γ-substituents) in the lactone product by using 3-substituted or unsubstituted propynoates as substrates. The stereochemical results of the cyclization reaction can be rationalized on the basis of the steric-conformational effects in the transition state for the intramolecular carbon-carbon double bond insertion, which has been proposed in our previous paper.[9]

Synthesis of Optically Active α, β-Disubstituted γ-Butyrolactone ---- Formal Synthesis of Isopilocarpine

Among the many varied structures of those natural products containing γ-butyrolactone unit, a big subgroup is comprised of β-benzyl substituted-γ-butyrolactones, such as lignan lactones,[10] pilocarpine [11] etc. We have reported a stereoselective synthesis of β-benzyl substituted-γ-butyrolactone, (±)-isohinokinin, using a palladium(II) catalyzed intramolecular carbon-carbon bond formation as the key step,[12] but in this method, only racemic α, β-disubstituted-γ-butyrolactone could be prepared.

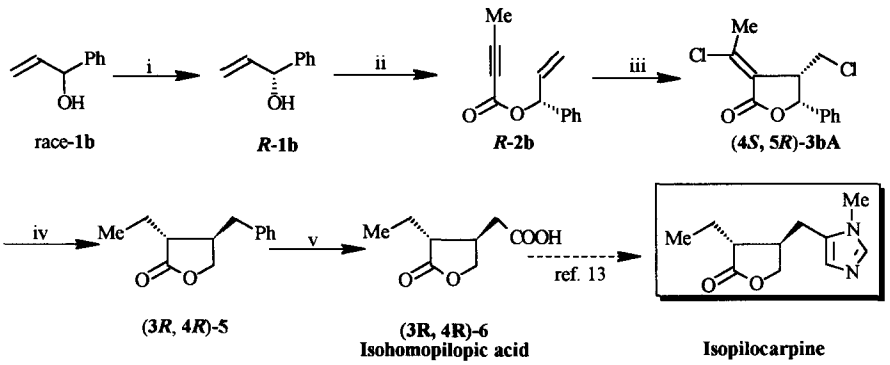
Scheme II



3 **4**

From the palladium catalyzed cyclization mentioned above, there is a chloromethyl group in the β-position of the lactone ring product **3**. Should the lactone be opened and the carboxyl group linked with the chloromethyl group, a new, α,β-disubstituted-γ-butyrolactone ring **4** could be obtained with defined configuration (Scheme II). If we started from a homochiral ester, α, β-disubstituted-γ-butyrolactone ring could be obtained in optically active form. Here, we wish to reported our recent results on the synthesis of enantiomerically pure α, β-disubstituted-γ-lactone and its application in the synthesis of homoisopilopic acid.

Scheme III

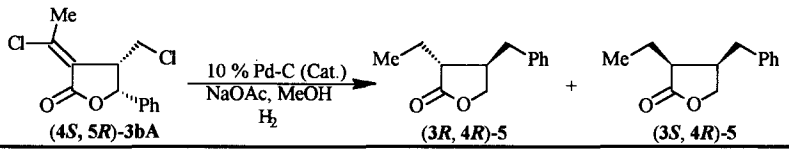


Reagents and conditions: i. TBHP, $Ti(O^iPr)_4$, (-)-DCHT, molecular sieve, CH_2Cl_2, -20°C; ii. 2-butynoic acid, DCC, DMAP, CH_2Cl_2, rt, 84%; iii. $CuCl_2$, LiCl, $Pd(OAc)_2$, HOAc, rt, 70%; iv. NaOAc, Pd-C, MeOH, H_2 (6 atm), rt, quantitative; v. $NaIO_4$, $RuCl_3 \cdot H_2O$, CCl_4-MeCN-H_2O, 0°C to rt, 79%.

Easily available 1-phenyl-2-propenol [(±)-**1b**], prepared by the reaction of benzaldehyde and vinylmagnesium bromide, was converted to ***R*-1b** by Sharpless kinetic resolution[6] with high enantioselectivity (>95 % ee).[14] The optically active allylic alcohol ***R*-1b** was directly esterified with 2-butynoic acid, in the presence of DCC and a catalytic amount of DMAP, affording acyclic 2-butynoate ***R*-2b** with the retention of the configuration of the secondary carbinol center. The palladium acetate catalyzed cyclization of ***R*-2b** proceeded smoothly at rt in HOAc and in the presence of $CuCl_2$ (5 eq.) and LiCl (2 eq.). The reaction afforded the β, γ-*cis*-disubstituted-γ-butyrolactone **(4*S*, 5*R*)-3bA** (70% yield, 100% *cis*), showed the extremely high stereoselectivity of the cyclization. Having the stereodefined β, γ-disubstituted-α-cholo-ethylidene-γ-butyrolactone, we next tried to reconstruct the new γ-butyrolactone **5**. Considering the existence of a benzylic-oxygen bond in the lactone **(4*S*, 5*R*)-3bA**, a number of reduction reactions of benzyl ester were tried. In the end, the α, β-disubstituted-γ-butyrolactone was obtained by hydrogenolysis of the lactone **(4*S*, 5*R*)-3bA**. In this hydrogenolysis reaction, the stereoselectivity of the reaction was found to be very sensitive to the pressure of the hydrogen. (The result was shown in Table 2)

From the table, it was shown that the reaction proceeded smoothly at atmospheric pressure, affording a mixture of diastereomers with a ratio of 60:40 [**(3*R*, 4*R*)-5 : (3*S*, 4*R*)-5**], and gave the best result under 6 atm of hydrogen pressure. Thus, the reduction of carbon-carbon double bond, vinyl chloride and benzyl ester of compound **5**, and the recyclization of new lactone was achieved in such a simple one-pot reaction. The newly formed stereodefined α, β-disubstituted-γ-butyrolactone was obtained in almost quantitative yield with high stereoselectivity. Compound **(3*S*, 4*S*)-5**, the other enantiomer of **(3*R*, 4*R*)-5**, could be obtained by similar way starting from allylic alcohol ***S*-1b**.

Table 2 Influence of the hydrogen pressure on the stereoselectivity in hydrogenolysis reaction [a]



(4*S*, 5*R*)-3bA (3*R*, 4*R*)-5 (3*S*, 4*R*)-5

hydrogen pressure (atm)	1	5	6	10	15
selectivity (*trans:cis*) (3*R*, 4*R*)-5 : (3*S*, 4*R*)-5[b]	60 : 40	90 : 10	94 : 6	92 : 8	92 : 8

a. The yield was nearly quantitative. b. Determined by 300 MHz NMR.

The target molecule, isohomopilopic acid **6** was obtained by $RuCl_3$ catalyzed sodium metaperiodate oxidation of lactone **5** in a mixed solvent system (CCl_4 : MeCN : H_2O =1 : 1 : 2) (79 % yield). The synthetic compound **6** has identical spectroscopic data with those in literature and a specific rotation of $[\alpha]_D^{25}$ = + 42.9 (c 0.95, H_2O); (lit:[15] $[\alpha]_D^{25}$ = + 45.6 (c 1.0, H_2O). Isohomopilopic acid has been converted into isopilocarpine reported by Preobrashenski.[13]

In summary, we have developed a new method for the synthesis of optically active β, γ-disubstituted-α-alkylidene-γ-butyrolactones with *cis* or *trans* relative configuration, and α, β-disubstituted lactone by highly efficient hydrogenolysis of the β, γ-disubstitued α-alkylidene-γ-butyrolactone resulting from the Pd(II) catalyzed cyclization. Its applications to natural product syntheses were exemplified by the total synthesis of (-)- and (+)-methylenolactocin and the formal synthesis of isopilocarpine, demonstrating the efficiency and stereoselectivity of the palladium catalyzed cyclization and hydrogenation reaction. The most important point is that this method permits the synthesis of the target molecule in either enantiomeric form, just starting from the same allylic alcohol with different absolute configuration.

EXPERIMENTAL SECTION

Infrared spectra were obtained with a Shimadzu IR-440 instrument. Proton magnetic resonance spectra were recorded with a Varian EM-390 or Bruker AM-300 spectrometer and were reported in ppm downfield of internal tetramethylsilane (δ units); ^{19}F magnetic resonance spectra were recorded with a JEOL FX-90Q spectrometer. Mass spectral data were taken on a Finnigan 4021 spectrometer and HRMS data were obtained on an Finnigan MAT 8430 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC instrument. The analytical samples were further purified by Kugelrohr distillation at the specified oven temperatures (ot).

Optically active allylic alcohols were obtained by Sharpless kinetic resolution of racemic allylic alcohols[6]

or by Sharpless asymmetric epoxidation and subsequent reduction.[7] The enantiomeric purity of the allylic alcohols were determined from 300 MHz ^{1}H NMR and ^{19}F NMR spectra of their Mosher esters, no enantiomer was found in the NMR spectra respectively.

Synthesis of Allylic 2-Alkynoates: Typical Procedure: (1'R)-Pentyl 2'-propenyl 2-Butynoate ((R)-2a). To a solution of 2-butynoic acid (0.34 g, 4 mmol), 1-octen-(3R)-ol (0.77 g, 6 mmol) in CH_2Cl_2 (6 mL) was added dropwise a solution of DCC (0.91 g, 4.4 mmol) and DMAP (4-N,N-dimethylaminopyridine) (50 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) at -20°C. After stirred at rt for 24h, the mixture was filtered and the filter cake was washed with small portions of CH_2Cl_2. The organic layer was washed by 10% HCl and saturated brine respectively, and dried. The solvent was removed under vacuum, and the residue was submitted to column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15/1). Pure product **(R)-2a** was obtained (0.68 g, 87 %). Oil, $[\alpha]_D^{25}$ = -9.00 (c, 1.32; $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.00-5.60 (m, 1H), 5.36-5.08 (m, 3H), 2.00 (s, 3H), 1.76-1.50 (m, 2H), 1.44-1.10 (m, 6H), 1.00-0.75 (m, 3H); MS m/e: 194 (M^+, 1.42), 183 (10.20), 173 (21.2), 151 (M^+-Pr, 5.40), 137 (M^+-Bu, 3.23), 123 (M^+-C_5H_{11}, 5.67), 111 (5.29), 99 (82.35), 83 (17.44), 55 (100.00); IR (neat): 2940, 2860, 2250, 1715, 1650, 1470, 1260, 1170 cm^{-1}; HRMS: Calcd for $C_9H_{11}O_2$ (M^+-Pr): 151.0759; found: 151.0732. **(S)-2a:** $[\alpha]_D^{25}$ = + 8.73 (c, 1.33; $CHCl_3$).

(1'R)-Phenyl 2'-Propenyl 2-Butynoate ((R)-2b): oil; $[\alpha]_D^{25}$ = -1.11 (c, 1.57; $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.32-7.08 (m, 5H), 6.28-6.10 (m, 1H), 6.10-5.70 (m, 1H), 5.32-5.04 (m, 2H), 1.80 (s, 3H); MS m/e: 200 (M^+, 0.36), 199 (1.51), 116 (100.00), 105 (27.78), 91 (15.08), 77 (10.65), 67 (66.90); IR (neat): 2900, 2200, 1710, 1640, 1240, 1060 cm^{-1}; Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.73; H, 6.60. **(S)-2b:** $[\alpha]_D^{25}$ = + 1.21 (c, 1.65; $CHCl_3$).

(1'R)-Pentyl 2'-Propenyl 2-Hexynoate ((R)-2c): oil, $[\alpha]_D^{25}$ = -12.9 (c, 1.18; $CHCl_3$) ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.00-5.60 (m, 1H), 5.40-5.08 (m, 3H), 2.32 (t, J = 7.2 Hz, 2H), 1.95-0.80 (m, 16H); MS m/e: 222 (M^+, 0.51), 193 (M^+-Et, 2.99), 179 (M^+-Pr, 6.90), 165 (5.33), 151 (6.52), 123 (14.63), 95 (100.00), 81 (23.35), 54 (95.96); IR (Nujol film): 2900, 2850, 2200, 1710, 1460, 1240 cm^{-1}; HRMS: Calcd for $C_{10}H_{15}O_2$ (M^+-C_4H_9): 167.1072; found: 167.1111.

(1'R)-Pentyl 2'-Propenyl 2-Propynoate ((R)-2d) and (S)-2d: The spectral data were reported in reference 8.

Palladium Catalyzed Cyclization of Allylic 2-Alkynoates in the Presence of $CuCl_2$ and LiCl: General Procedure : To a solution of allylic 2-alkynoate (1 mmol), $CuCl_2$ (400 mg, 3 mmol) and LiCl (260 mg, 6 mmol) in MeCN (10 mL) was added $PdCl_2(PhCN)_2$ (20 mg, 0.05 mmol), the reaction was monitored by TLC (eluent: petroleum ether / ethyl acetate=10 / 3). After the reaction was complete, ethyl acetate (60 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 / 2) afforded the product.

3-(*E*)-Chloroethylidene-4R-chloromethyl-5R-pentyl-γ-butyrolactone ((4R, 5R)-3aA): oil; $[\alpha]_D^{25}$ = + 26.8 (c, 1.33; $CHCl_3$); ^{1}H 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); MS m/e: 268 [M^+ (2 x ^{37}Cl), 1.02], 266 [M^+ (^{35}Cl, ^{37}Cl), 4.75], 264 [M^+ (2 x ^{35}Cl), 6.19], 231 (2.14), 229 (2.77), 219 [M^+ (2 x ^{37}Cl)-CO_2-1, 0.01], 217 [M^+ (^{37}Cl, ^{35}Cl)-CO_2-1, 3.37], 215 [M^+(2 x ^{35}Cl)-CO_2-1, 8.83], 197 [M^+ (2 x ^{37}Cl)-C_5H_{11}, 3.48], 195 [M^+ (^{37}Cl, ^{35}Cl)-C_5H_{11}, 15.22], 193 [M^+(2 x ^{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): 2900, 2840, 1740, 1660, 1470, 1160 cm^{-1}; Anal. Calcd for $C_{12}H_{18}Cl_2O_2$: C, 54.30; H, 6.84. Found: C, 54.32; H, 7.09. **(4S, 5S)-3aA:** oil; $[\alpha]_D^{25}$= -26.0 (c, 1.33; $CHCl_3$).

3-(*E*)-Chloroethylidene-4R-chloromethyl-5R-phenyl-γ-butyrolactone ((4S, 5R)-3bA): mp 136~137 °C, $[\alpha]_D^{25}$ = + 92.8(c, 1.08; $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.35 (m, 5H), 5.56 (d, J = 5.85 Hz, 1H), 3.71 (dt, J_1 = 8.45 Hz, J_2 = 5.51 Hz, 1H), 3.22 (m, 2H), 2.47 (s, 3H); MS m/e: 274 [M^+ (2 x ^{37}Cl), 0.72], 272 [M^+ (^{35}Cl, ^{37}Cl), 7.06], 270 [M^+ (2 x ^{35}Cl), 9.30], 166 (28.88), 164 (45.13), 131 [M^+ (^{37}Cl)-PhCHO-Cl, 33.15], 129 [M^+ (^{35}Cl)-PhCHO-Cl, 100.00], 103 (4.67), 101 (15.54), 77 (13.06), 65 (29.98), 51 (16.22); IR (Nujol film): 2950, 2860, 1760, 1650, 1470, 1160, 1030 cm^{-1}; Anal. Calcd for $C_{13}H_{12}Cl_2O_2$: C, 57.58; H, 4.46. Found: C, 57.78; H, 4.32. **(4*R*, 5*S*)-3bA:** mp 147-148 °C; $[\alpha]_D^{25}$ = - 92.2 (c, 1.08; $CHCl_3$).

3-(*E*)-Chlorobutylidene-4R-chloromethyl-5R-phenyl-γ-butyrolactone: (4R, 5R)-3cA: oil; $[\alpha]_D^{25}$ = + 38.8 (c, 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (dt, J_1 = 9.64 Hz, J_2 = 4.82 Hz, 1H), 3.64 (m, 1H), 3.45-3.33 (m, 2H), 2.48 (t, J = 8.13 Hz, 2H), 1.68 (m, 2H), 1.32 (m, 6H), 0.91 (t, J = 7.36 Hz, 3H), 0.83 (t, J = 6.78 Hz, 3H); MS m/e: 296 [M^+ (2 x ^{37}Cl), 0.05], 294 [M^+ (^{35}Cl, ^{37}Cl), 7.46], 292 [M^+ (2 x ^{35}Cl), 11.64], 259 [M^+ (^{37}Cl)-Cl, 0.44], 257 [M^+ (^{35}Cl)-Cl, 3.36], 225 [M^+(2 x ^{37}Cl)-C_5H_{11}, 0.29], 223 [M^+(^{37}Cl, ^{35}Cl)-C_5H_{11}, 1.82], 221 [M^+(2 x ^{35}Cl)-C_5H_{11}, 8.61], 159 (37.20), 157 (100.00), 151 (2.10), 149 (11.64), 129 (10.97), 115 (20.82), 105 (12.22); IR (Nujol film): 2950, 2850, 1760, 1650, 1470, 1150 cm^{-1}; Anal. Calcd for $C_{14}H_{22}Cl_2O_2$: C, 57.34; H, 7.56. Found: C, 57.57; H, 7.77.

Palladium Catalyzed Cyclization of Allylic 2-Alkynoates in the Presence of $CuBr_2$ and LiBr: General Procedure : To a solution of $CuBr_2$ (896 mg, 4 mmol), LiBr (350 mg, 4 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol) in HOAc (10 mL) was added allylic 2-alkynoate (1 mmol), the reaction was monitored by TLC. After the reaction was over, it was similarly worked up to give the products.

3-(*E*)-Bromoethylidene-4R-bromomethyl-5R-pentyl-γ-butyrolactone ((4R, 5R)-3aB): oil; $[\alpha]_D^{25}$ = - 7.28 (c, 1.25; $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.35 (q, J = 4.90 Hz, 1H), 3.60-3.50 (m, 2H), 3.33 (m, 1H), 2.61 (s, 3H), 1.88-1.62 (m, 4H), 1.40-1.34 (m, 4H), 0.91 (t, J = 6.79 Hz, 3H); MS m/e: 356 [M^+ (2 x ^{81}Br), 0.69], 354 [M^+ (^{79}Br, ^{81}Br), 1.73], 352 [M^+ (2 x ^{79}Br), 1.26], 275 [M^+ ^{81}Br)-Br, 16.26], 273 [M^+ (^{79}Br)-Br, 15.21], 203 [M^+(^{81}Br)-Br-C_5H_{11}, 2.64], 201 [M^+(^{79}Br)-Br-C_5H_{11}, 2.17], 175 (100.00), 173 (96.39), 147 (15.57), 145 (12.85), 71 (6.52), 57 (13.35); IR (Nujol film): 2950, 2850, 1740, 1650, 1460, 1150 cm^{-1}; Anal. Calcd for $C_{12}H_{18}Br_2O_2$: C, 40.70; H, 5.12. Found: C, 40.83; H, 5.14. **(4S, 5S)-3aB:** oil; $[\alpha]_D^{25}$= + 7.20 (c, 1.20; $CHCl_3$).

3-(*E*)-Bromoethylidene-4R-bromomethyl-5R-phenyl-γ-butyrolactone(4R, 5S)-3bB: mp, 88-90°C; $[\alpha]_D^{25}$ = + 93.58 (c, 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.36 (m, 5H), 5.54 (d, J = 5.73 Hz, 1H), 3.82 (m,

1H), 3.13-2,99 (m, 2H), 2.69 (s, 3H); MS m/e: 362 [M^+(2 x ^{81}Br), 0.67], 360 [M^+(^{81}Br, ^{79}Br), 1.04], 358 [M^+(2 x ^{79}Br), 0.39], 281 [M^+ (^{81}Br)+1-Br, 25.92], 279 [M^+ (^{79}Br)+1-Br, 23.66], 175 [M^+ (^{81}Br)-PhCHO-Br, 98.56], 173 [M^+ (^{79}Br)-PhCHO-Br, 100.00]], 147 (15.07), 145 (15.99), 107 (17.29), 105 (16.87), 77 (22.97), 65 (48.30); IR (Nujol film): 2900, 2840, 1750, 1640, 1460, 1150, 1020 cm^{-1}; Anal. Calcd for $C_{13}H_{12}Br_2O_2$: C, 43.37; H, 3.36. Found: C, 43.58; H, 3.32.

3-(*E*)-Bromobutylidene-4R-bromomethyl-5R-pentyl-γ-butyrolactone(4R, 5R)-3cB: $[\alpha]_D^{25}$= + 10.8 (c, 1.52; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (quint, J = 4.72 Hz, 1H), 3.55-3.51 (m, 2H), 3.33 (dd, J_1 = 7.77 Hz, J_2 = 10.55 Hz, 1H), 2.74-2.61 (m, 2H), 1.90-1.59 (m, 6H),1.44-1.31 (m, 4H), 0.97 (t, J = 10.0 Hz, 3H), 0.91 (t, J = 7.14 Hz, 3H); MS m/e: 385 [M^+ (2 x ^{81}Br)+1, 2.50], 383 [M^+ (^{79}Br, ^{81}Br)+1, 5.00], 381 [M^+ (2 x ^{79}Br)+1, 2.50], 303 (59.10), 301 (59.50), 257 (6.20), 255 (6.20), 203 (100.00), 201(100.00), 175 (13.60), 151 (8.30), 149 (8.30), 93 (47.90), 79 (27.30); IR (neat): 2950, 2850, 1750, 1640, 1460, 1010 cm^{-1}; Anal. Calcd for $C_{14}H_{22}Br_2O_2$: C, 44.00; H, 5.80. Found: C, 44.40; H, 5.69.

Hydrogenolysis of Compound (4*S*, 5*R*)-3bA: A suspension of **(4*S*, 5*R*)-3bA** (60 mg, 0.22 mmol), NaOAc (61 mg, 0.66 mmol), and 10% Pd-C (60 mg) in methanol (2 mL) was hydrogenated under 6 atm pressure for 24 h at rt. The reaction mixture was filtered and condensed. The residue was diluted with ethyl acetate, washed with water and saturated sodium chloride, dried ($MgSO_4$) and evaporated. Preparative TLC (eluent: petroleum ether / ethyl acetate = 20:1) gave the pure **(3*R*, 4*R*)-5** (45 mg), yield: 100%; oil; the spectroscopic data were identical with those in literature.[16] $[\alpha]_D^{25}$ = + 15.0 (c,1.3; $CHCl_3$); **(3*S*, 4*S*)-5:** $[\alpha]_D^{25}$ = -15.3 (c,1.3; $CHCl_3$).

Oxidation of Compound (3*R*, 4*R*)-5: To a biphasic solution of lactone **(3*R*, 4*R*)-5** in CCl_4 (4 mL), MeCN (4 mL) and H_2O (8.1 mL) was added $NaIO_4$ (3.85 g, 18.1 mmol) and $RuCl_3{\cdot}H_2O$ (4.5 mg, 0.10 mmol) at 0 °C under stirring. The mixture was stirred vigorously at room temperature and monitored by TLC. After the reaction was complete, CH_2Cl_2 (20 mL) was added and the solution was filtered through a pad of celite. The filtrate was evaporated and the residue was dissolved in ether (5 mL). After usual workup, the pure product **6** was obtained (0.12 g, 68%). oil, $[\alpha]_D^{25}$= + 42.9 (c, 0.95; H_2O); (lit: $[\alpha]_D^{25}$ = + 45.6 (c 1.0, H_2O).[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.71 (br, 1H), 4.52 (dd, J_1 = 7.55 Hz, J_2 = 9.37 Hz, 1H), 3.91 (dd, J_1 = 7.58 Hz, J_2 = 9.45 Hz, 1H), {4.38 (dd, 6.7%), 4.15 (dd, 6.7%) for *cis* isomer}, 2.73-2.64 (m, 2H), 2.49 (dd, J_1 = 10.33 Hz, J_2= 17.75 Hz, 1H), 2.25 (dt, J_1 = 8.36 Hz, J_2 = 6.10 Hz, 1H), 1.78-1.68 (m, 2H), 1.01 (t, J = 7.53 Hz, 3H); IR(neat): 3500-2500(br), 2920, 2850, 1760, 1690, 1410, 1250, 1170, 1020, 940 cm^{-1}.

Acknowledgment: We thank the National Natural Science Foundation of China and Chinese Academy of Sciences for financial support.

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(*Received in Japan* 2 *May* 1995)