CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801363

Highly Stereoselective Iodolactonization of 4,5-Allenoic Acids—An Efficient Synthesis of 5-(1′-Iodo-1′(*Z*)-alkenyl)-4,5-dihydro-2(3*H*)-furanones

Xinpeng Jiang, Chunling Fu,* and Shengming Ma*[a]

Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Abstract: In this paper, it is reported that the efficient iodolactonization of 4,5-allenoic acid with I_2 in cyclohexane in the presence or absence of K_2CO_3 afforded 5-(1′-iodo-1′(*Z*)-alkenyl)-4,5-dihydro-2(3*H*)-furanones highly stereoselectively. However, the reaction of axially optically active 4,5-allenoic acids (*R*)-(−)-**5a** and (*R*)-(−)-**5b** with I_2 afforded the corresponding products with a serious loss of chirality. This problem was solved by conducting the iodolactonization with *N*-iodosuccinimide in CH_2Cl_2 in the presence of Cs_2CO_3; however, the *Z*/*E* selectivity is somewhat lower. The pure optically active *Z* products were prepared by subsequent kinetic resolution with Sonogashira coupling. The reaction of the substrates with a substituent at the 3-position of the starting 4,5-allenoic acids afforded the *trans*-4,5-disubstituted γ-butyrolactones as the only products. The reaction of the 4,5-allenoic acids (*S*)-(+)-**1l**, (*R*)-(−)-**1l**, and (*S*)-(+)-**1m** with a center chirality at the 3-position afforded the *trans* products with very high enantiopurity and up to 98:2 *Z*/*E* selectivity regardless of the axial chirality of the allene moiety.

Keywords: acids · allenes · iodolactonization · lactones · stereoselectivity

Introduction

γ-Butyrolactones are important subunits that are present in a large variety of natural products and biologically active compounds.[1] These very attractive biological properties prompted organic chemists to develop a series of methods for the synthesis of γ-butyrolactones. The most notable methods are as follows: the intramolecular transesterification of γ-hydroxyesters;[2] the reagent-controlled stereoselective halolactonizaton[3] or manganese acetate mediated cyclization[4] of 4-pentenoic acid derivatives; lactonization of 4-pentynoic acids catalyzed by AuCl,[5] $[Pd(PPh_3)_4]$,[6] or cubane-type $MoNiS_4$ clusters;[7] lactonization of γ-allenoic acids catalyzed by $Pd(OAc)_2$ or mediated by *N*-bromosuccinimide,[8] or cationic gold(I) complexes;[9] cationic $[CpRu(NCCH_3)_3]PF_6$-[10] or $Pd(OAc)_2$-[11] promoted coupling cyclization reactions of γ-allenoic acids with α,β-unsaturated carbonyl compounds; and intramolecular cyclization of γ-(π-allylmolybdenum) carboxylic acids.[12] In addition, by using *N*-heterocyclic carbene as catalyst, the reaction of α,β-unsaturated aldehydes with 1,2-dicarbonyl compounds[13] or aldehydes[14] could also afford γ-butyrolactones. Another route toward the formation of this important skeleton is a formal [2+2+1] cycloaddition of an alkene, an aldehyde or ketone functionality, and carbon monoxide by using a catalytic amount of Ti catalyst.[15] In this paper, we wish to disclose our recent observation that 4,5-allenoic acids may be iodolactonized efficiently providing a highly stereoselective synthesis of γ-butyrolactones.[16]

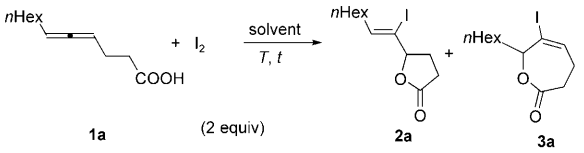
Results and Discussion

We tried the reaction of dodeca-4,5-dienoic acid (**1a**)[8] with I_2 in the first instance. In MeCN, the reaction could afford the five-membered 5-(1′-iodo-1′(*Z*)-octenyl)-4,5-dihydro-2(3*H*)-furanone (**2a**) in 92% yield. The formation of 7-membered lactone **3a** was not observed, which indicates that the iodolactonization reaction is highly regioselective; however, the stereoselectivity for the carbon–carbon double bond in **2a** is poor (*Z*/*E* 87:13; Table 1, entry 1). When the reaction was conducted at a lower temperature in the pres-

[a] X. Jiang, Prof. Dr. C. Fu, Prof. Dr. S. Ma
Laboratory of Molecular Recognition and Synthesis
Department of Chemistry, Zhejiang University
Hangzhou 310027, Zhejiang, People's Republic of China
Fax: (+86) 21-6260-9305
E-mail: masm@mail.sioc.ac.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801363. It contains full experimental details and copies of ^{1}H NMR, ^{13}C NMR, and HPLC spectra of all compounds.

Table 1. The iodolactonization of γ-allenoic acid **1a** with I_2.



Entry	Solvent	T [°C]	t	Yield of **2a** [%][a]	Z/E[a,b]
1	CH_3CN	RT	40 min	92	87:13
2	CH_3CN/H_2O[c]	−30	19 h	73	92:8
3	DMSO	RT	48 min	80	91:9
4	toluene	RT	40 min	91	97:3
5	$CHCl_3$	RT	35 min	89	96:4
6	CH_2Cl_2	RT	50 min	84	96:4
7	CH_2Cl_2	−20	2.5 h	99	97:3
8	CH_2Cl_2[d]	−20	2.5 h	100	95:5
9	$ClCH_2CH_2Cl$	RT	40 min	94	97:3
10	cyclohexane	RT	45 min	92	98:2
11	hexane	RT	30 min	70	98:2
12	cyclohexane[e]	RT	50 min	92	98:2
13	cyclohexane[f]	RT	35 min	92	97:3

[a] Determined by 400 MHz ^{1}H NMR spectroscopic analysis. [b] The alkene configuration was established by the NOE study. [c] CH_3CN/H_2O 40:1. [d] K_2CO_3 (2 equiv) was applied as an additive. [e] I_2 (1.5 equiv) was used. [f] I_2 (1.2 equiv) was used.

ence of H_2O, the stereoselectivity was higher (entry 2). In DMSO, toluene, $CHCl_3$, CH_2Cl_2, or $ClCH_2CH_2Cl$, the reaction also afforded the product (*Z*)-**2a** with better stereoselectivities (entries 3–9). The best stereoselectivity (*Z*/*E* 98:2) was observed when the reaction was conducted in cyclohexane or hexane at room temperature; however, the yield of (*Z*)-**2a** in cyclohexane is much higher than that in hexane (compare entry 10 with entry 11). After conducting the reaction with different amounts of I_2, conditions A (1.5 equiv of I_2, cyclohexane, RT) were established as the first optimized reaction conditions (entry 12). The configuration of the C=C bond in **2a** was established by a NOE study (Figure 1).

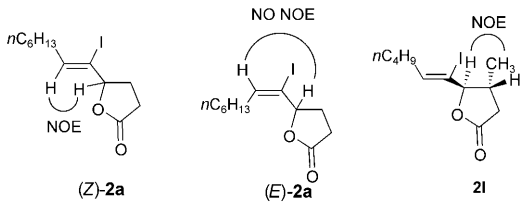
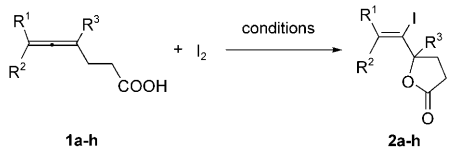


Figure 1. NOE study of (*Z*)-**2a**, (*E*)-**2a**, and **2l**.

The scope of the reaction was studied under conditions A. The results in Table 2 indicated that both 6-substituted (entries 1–4, Table 2) and 4,6-disubstituted (entry 5) 4,5-allenoic acids may be highly regio- and stereoselectively cyclized in the presence of 1.5 equivalents of I_2 affording (*Z*)-**2** in 46–85% yields. However, the corresponding reactions of 6-unsubstituted (entry 6) and 6,6-disubstituted (entry 8) 4,5-allenoic acids afforded the products in relatively low yields. To our surprise, with the addition of one equivalent of K_2CO_3 (conditions B), the reaction afforded **2f–h** in much higher yields (entries 7, 9, and 10). The structures of all the products were further established by the X-ray diffraction study of **2g** (Figure 2).[17]

Table 2. Iodolactonization of 4,5-allenoic acids **1** with I_2.



Entry	**1**			Conditions[a]	Yield of **2** [%][b]	Z/E[c]
	R^1	R^2	R^3			
1	nC_6H_{13}	H	H (**1a**)	A	83 (**2a**)	98:2
2	nC_5H_{11}	H	H (**1b**)	A	85 (**2b**)	98:2
3	nC_4H_9	H	H (**1c**)	A	85 (**2c**)	97:3
4	CH_3	H	H (**1d**)	A	79 (**2d**)	98:2
5	C_2H_5	H	nC_4H_9 (**1e**)	A	75 (**2e**)	99:1
6	H	H	nC_4H_9 (**1f**)	A	19 (**2f**)[d]	–
7	H	H	nC_4H_9 (**1f**)	B	87 (**2f**)	–
8	$-(CH_2)_5-$		H (**1g**)	A	trace (**2g**)[d]	–
9	$-(CH_2)_5-$		H (**1g**)	B	73 (**2g**)	–
10	C_2H_5	C_2H_5	H (**1h**)	B	88 (**2h**)	–

[a] Conditions A: I_2 (1.5 equiv), cyclohexane, RT, 1 h; conditions B: I_2 (1.5 equiv), K_2CO_3 (1 equiv), cyclohexane, RT, 1 h. [b] Isolated yield. [c] The *Z*/*E* ratio was determined by 400 MHz ^{1}H NMR spectroscopic analysis. [d] The yield was determined by 300 MHz ^{1}H NMR spectroscopic analysis.

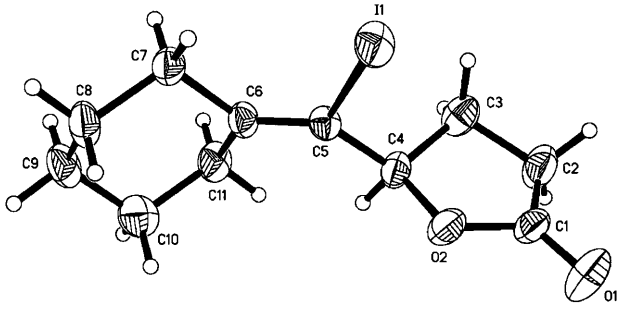
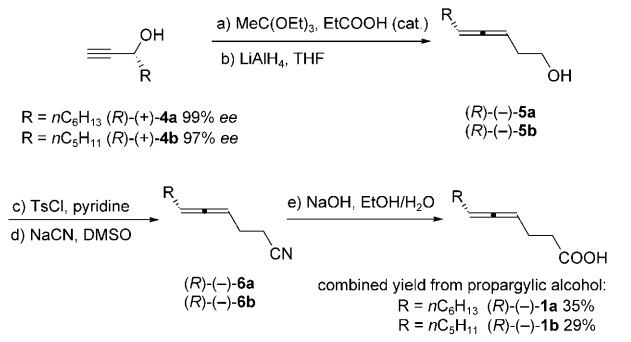


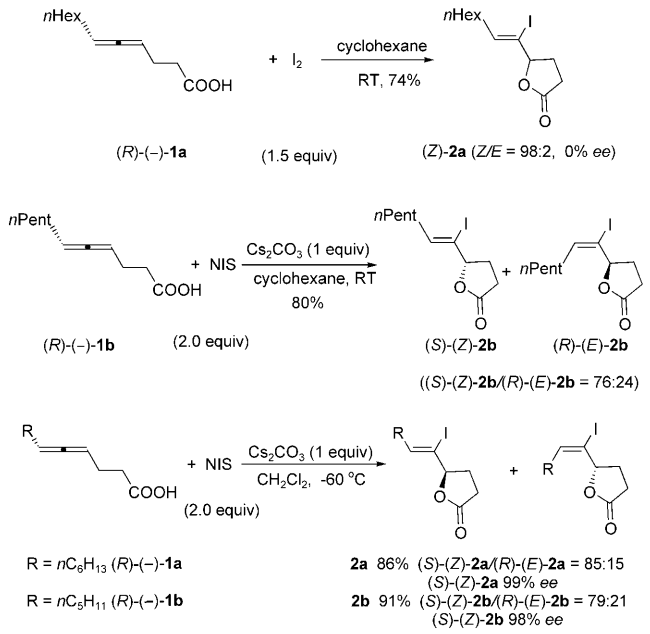
Figure 2. ORTEP drawing of **2g**.

For the synthesis of optically active 4,5-allenoic acids (*R*)-(−)-**1a** and (*R*)-(−)-**1b**, optically active propargylic alcohols (*R*)-(+)-**4a** and (*R*)-(+)-**4b**[18] were treated with excess triethyl orthoacetate in the presence of a catalytic amount of propionic acid. The resulting 3,4-allenoates were then reduced with $LiAlH_4$ to form the related alcohols (*R*)-(−)-**5a** and (*R*)-(−)-**5b**, which were tosylated and subsequently converted to nitriles (*R*)-(−)-**6a** and (*R*)-(−)-**6b**. Finally, hydrolysis with NaOH in $EtOH/H_2O$ afforded the allenoic acids (*R*)-(−)-**1a** and (*R*)-(−)-**1b** (Scheme 1).[19]

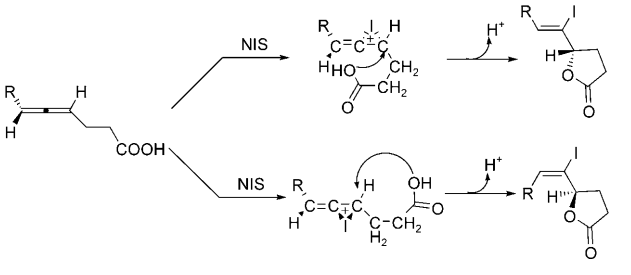
However, when optically active (*R*)-(−)-**1a** was treated with 1.5 equivalents of I_2 in cyclohexane, although the *Z*/*E* selectivity is still high (98:2), the product **2a** is racemic, which indicates that the axial chirality in (*R*)-(−)-**1a** was lost during the cyclization, probably due to the formation of the π-allylic cation intermediate. Thus, NIS was used instead of I_2 and the corresponding iodolactonization of (*R*)-(−)-**1a** and (*R*)-(−)-**1b** in CH_2Cl_2 afforded butyrolactones (*S*)-(*Z*)-**2a** (99% *ee*)/(*R*)-(*E*)-**2a** and (*S*)-(*Z*)-**2b** (98% *ee*)/(*R*)-(*E*)-**2b** (Scheme 2). The absolute configuration of the chiral



Scheme 1. Synthesis of optically active γ-allenoic acids (*R*)-(−)-**1a** and (*R*)-(−)-**1b**. Ts = tosyl.

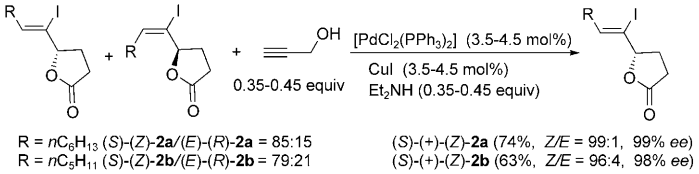


Scheme 2. Intramolecular iodolactonization of optically active 4,5-allenoic acids (*R*)-(−)-**1a** and (*R*)-(−)-**1b** with I_2 or NIS. NIS = *N*-iodosuccinimide.



Scheme 3. The *anti* iodolactonization of (*R*)-(−)-**1a** and (*R*)-(−)-**1b** with NIS.

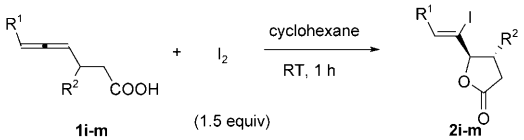
center in the above four products is tentatively assigned based on the *anti* nature of the iodolactonization reaction (Scheme 3). However, the stereoselectivity for the carbon–carbon double bond in **2a** and **2b** is poorer. To get the pure *Z* isomer, a kinetic resolution of these two products by means of the Sonogashira coupling was applied.[20] In this way, (*S*)-(+)-(*Z*)-**2b** and (*R*)-(+)-(*Z*)-**2a** were prepared in >98% *ee* and with 96:4 *Z*/*E* selectivity (Scheme 4).



Scheme 4. Kinetic resolution of *Z*/*R* and *E*/*S* mixtures of **2a** and **2b**.

Furthermore, when a substituent was introduced at the 3-position of the substrates, that is, **1i**–**m**, the reaction also afforded the products *trans*-(*Z*)-**2i**–**m** with two chiral centers highly diastereoselectively (Table 3). The relative *trans* stereochemistry of these products was established by the NOE study of **2l** (Figure 1).

Table 3. Iodolactonization of γ-allenoic acids **1i**–**m** with I_2.

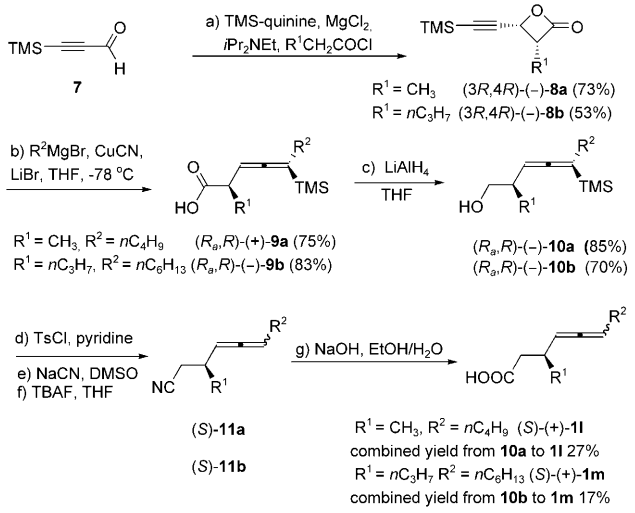


Entry	Allenoic acid R^1	R^2	d.r.[a]	Yield of **2** [%][b]	*Z*/*E*[c]	d.r.[c]
1	CH_3	CH_3 (**1i**)	2.0:1	82 (**2i**)	96:4	>99:1
2	CH_3	C_2H_5 (**1j**)	2.2:1	78 (**2j**)	97:3	>99:1
3	CH_3	nC_3H_7 (**1k**)	2.2:1	82 (**2k**)	97:3	>99:1
4	nC_4H_9	CH_3 (**1l**)	3.1:1	76 (**2l**)	97:3	>99:1
5	nC_6H_{13}	nC_3H_7 (**1m**)	2.7:1	80 (**2m**)	97:3	>99:1

[a] The d.r. value was determined by inverse gated decoupling ^{13}C NMR spectroscopic analysis.[21] [b] Isolated yield after flash chromatography. [c] The *Z*/*E* ratio and d.r. value were determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.

It is remarkable that this process yields diastereomerically pure γ-butyrolactones despite the low diastereomeric purity of the starting materials, which suggests that the process is diastereoconvergent. This was investigated in detail.

To show the potential for the highly diastereoselective synthesis of optically active compounds, optically active γ-allenoic acids (*S*)-(+)-**1l** and (*S*)-(+)-**1m** were prepared according to the chemistry shown in Scheme 5. 3-(Trimethylsilyl)propiolaldehyde[22] was converted to 3,4-allenoic acids following the procedures developed by Nelson et al.[23] The resulting optically active β-allenoic acids (R_a,*R*)-(+)-**9a** and (R_a,*R*)-(−)-**9b** were then reduced with $LiAlH_4$ to form the related alcohols (R_a,*R*)-(−)-**10a** and (R_a,*R*)-(−)-**10b**, which were tosylated and subsequently converted to nitriles.[24] Finally, hydrolysis with NaOH in $EtOH/H_2O$ afforded the allenoic acids (*S*)-(+)-**1l** and (*S*)-(+)-**1m**. However, epimerization of the axial chirality of the allene moiety was observed, which led to the formation of a pair of diastereoisomers. (*R*)-(−)-**1l** was prepared similarly by using TMS-qui-

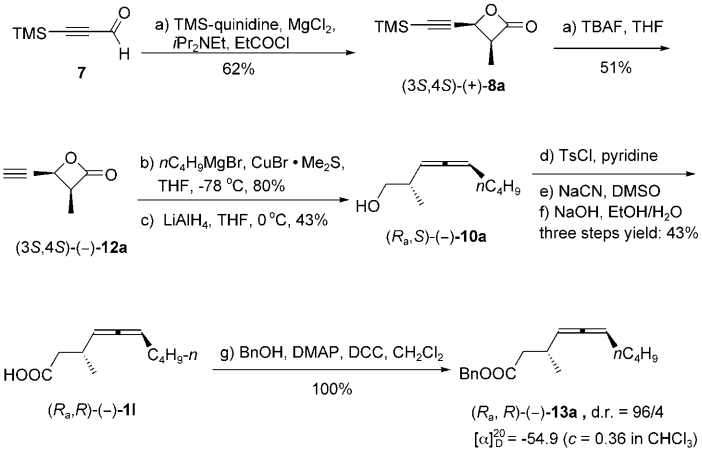


Scheme 5. Synthesis of optically active γ-allenoic acids (*S*)-(+)-**1l** and (*S*)-(+)-**1m**. TBAF = tetrabutylammonium fluoride; TMS = trimethylsilyl.

nidine in the first step converting **7** to (3*S*,4*S*)-(+)-**8a** (for the synthetic scheme with the yield information see Scheme S1 in the Supporting Information and Scheme 7).

When optically active compounds (*S*)-(+)-**1l**, (*S*)-(+)-**1m**, and (*R*)-(−)-**1l** were treated with I_2 under conditions A, (4*S*,5*S*)-(+)-(*Z*)-**2l**, (4*S*,5*S*)-(+)-(*Z*)-**2m**, and (4*R*,5*R*)-(−)-(*Z*)-**2l** were isolated in 86, 72, and 82% yields with 99% *ee*, respectively (Scheme 6). The absolute configurations of the newly formed chiral centers in the above three products were assigned based on the *trans* orientation of the two substituents and the center chirality at the 3-position of the starting acids (*S*)-(+)-**1l**, (*S*)-(+)-**1m**, and (*R*)-(−)-**1l**. Thus, consistent with the results in Scheme 2, under I_2/cyclohexane conditions, it is believed that the reaction proceeded through the common intermediacy of **14**-type π-allylic cationic species, which led to the formation of the thermodynamically more stable *trans* products by 1,2-chiral induction.

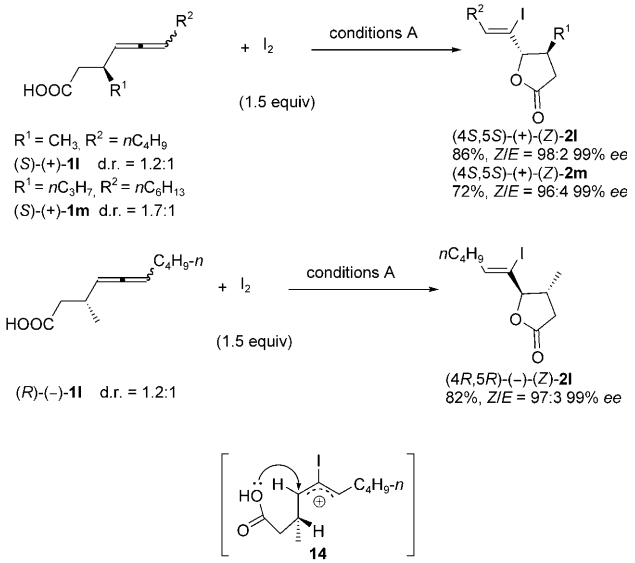
To confirm this hypothesis, (*R*$_a$,*R*)-(−)-**1l** was prepared from the known procedure (Scheme 7).[25]



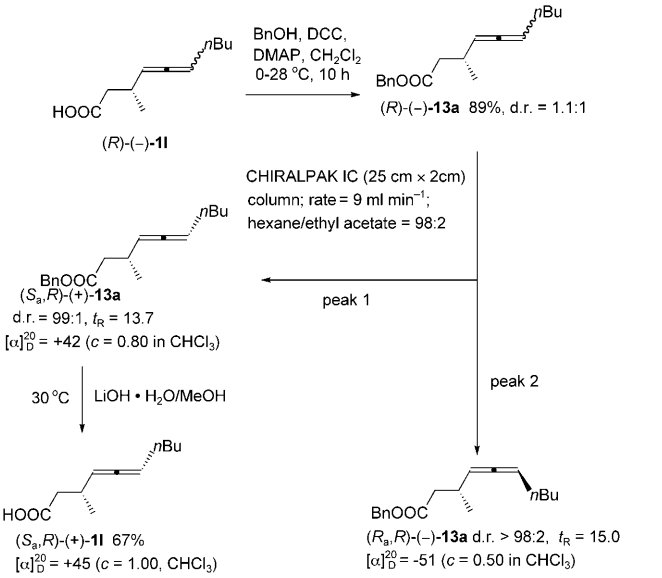
Scheme 7. Synthesis of optically active γ-allenoic acid (*R*$_a$,*R*)-(−)-**1l**. DCC = 1,3-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine.

In addition, (*S*$_a$,*R*)-(+)-**1l** was prepared by preparative HPLC separation of the benzyl ester of (*R*)-(−)-**1l**, followed by hydrolysis of (*S*$_a$,*R*)-(+)-**13a** (Scheme 8). The absolute configuration of the diastereomer related to peak 2 was determined to be *R*$_a$,*R* by comparison with the sign of the specific optical rotation of (*R*$_a$,*R*)-(−)-**13a** prepared in Scheme 7. Based on this, the absolute configuration of the diastereomer related to peak 1 was assigned as (*S*$_a$,*R*).

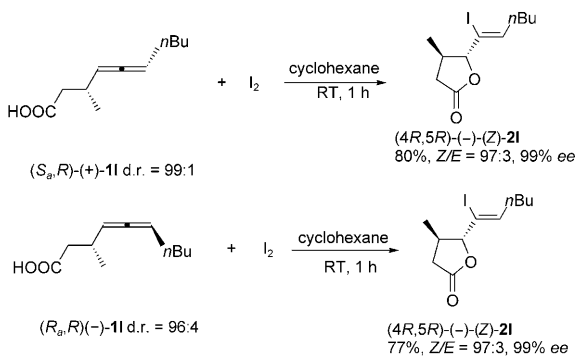
It is interesting to observe that both (*S*$_a$,*R*)-(+)-**1l** and (*R*$_a$,*R*)-(−)-**1l** indeed afforded the same product (4*R*,5*R*)-



Scheme 6. Iodolactonization of optically active 4,5-allenoic acids (*S*)-(+)-**1l**, (*S*)-(+)-**1m**, and (*R*)-(−)-**1l** with I_2.



Scheme 8. Synthesis of optically active γ-allenoic acids (*S*$_a$,*R*)-(+)-**1l**.



Scheme 9. Iodolactonization of optically active 4,5-allenoic acids (S_a,*R*)-(+)-**1l** and (R_a,*R*)-(−)-**1l** with I_2.

(*Z*)-**2l** as expected, which further supported our hypothesis (Scheme 9).

Conclusion

We have demonstrated an efficient and highly stereoselective iodolactonization reaction of 4,5-alkadienoic acids with NIS in CH_2Cl_2 or I_2 in cyclohexane. When a chiral center was installed at the 3-position of the 4,5-allenoic acids, the iodolactonization reaction with I_2 in cyclohexane at room temperature provided *trans*-5-(1′-iodo-1′(*Z*)-alkenyl)-4-substituted butyrolactones with very high diastereoselectivity. However, the axial chirality in (*R*)-(−)-**1a** and (*R*)-(−)-**1b** could not be transformed into the center chirality of the products by conducting the iodolactonization with I_2. Instead, NIS was applied to produce the optically active products (*S*)-(+)-**2a** and (*S*)-(+)-**2b** with a relatively low *Z*/*E* selectivity in CH_2Cl_2. The pure optically active *Z* isomers may be prepared by kinetic resolution through Sonogashira coupling. Compared with other reports related to the cyclization of allenoic acids, the method described here enjoys the advantage of more easily available/cheap reagents, higher *Z* stereoselectivity, referring to the formation of the C=C bond in the product, efficient axial chirality transfer, and excellent 1,2-chiral induction. Further studies in this area is being pursued in our laboratory.

Experimental Section

Typical procedure for the preparation of γ-allenoic acids[8] 1a–m

Preparation of dodeca-4,5-dienoic acid (1a)

*Synthesis of undeca-3,4-dien-1-ol (**5a**)*: A mixture of nonyn-3-ol (**4a**) (7.0010 g, 0.05 mol), EtCOOH (1 mL, $d=0.99\,g\,mL^{-1}$, 0.99 g, 0.013 mol), and $MeC(OEt)_3$ (30 mL, $d=0.876\,g\,mL^{-1}$, 26.28 g, 0.16 mol) was heated at 130 °C for 5 h with a Dean–Stark apparatus to remove the in situ formed EtOH and the excess $MeC(OEt)_3$. After removing most of the compounds with low boiling points, the mixture was cooled to RT and then purified by chromatography on silica gel to afford ethyl undeca-3,4-dienoate (9.8926 g, crude yield: 94%). The product was used in the next step without further characterization. A solution of the above prepared ethyl undeca-3,4-dienoate (5.6457 g, 26.9 mmol) in THF (25 mL) was added dropwise to an ice-cold suspension of $LiAlH_4$ (1.3310 g, 34.9 mmol) in anhydrous THF (25 mL) under N_2. After 1.2 h, the reaction was complete, as determined by TLC analysis, and it was quenched by slow addition of H_2O, extracted with 60 mL of ethyl ether, and then filtered to remove the solid. The resulting mixture was extracted with ether and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, evaporated, and purified by chromatography on silica gel to afford **5a** (3.8973 g, 86%). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.19$–5.12 (m, 1H), 5.12–5.04 (m, 1H), 3.70 (t, $J=6.2$ Hz, 2H), 2.28–2.21 (m, 2H), 2.02–1.95 (m, 2H), 1.64 (s, 1H), 1.43–1.21 (m, 8H), 0.88 ppm (t, $J=6.8$ Hz, 3H); this compound was used in the next step without further characterization.

*Synthesis of dodeca-4,5-dienenitrile (**6a**)*: *p*TsCl (22.2 g, 0.12 mol) was added in several portions to an ice-cooled solution of **5a** (6.5161 g, 0.039 mol) in dry pyridine (50 mL) at 0–4 °C with an ice/water bath. After 4 h, the mixture was poured into ice/water and the resulting mixture was extracted with ether (50 mL×3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and then concentrated in vacuum. The product was then used in the next step without further purification. NaCN (2.0526 g, 0.042 mol) was added to a mixture of the tosylate prepared above and anhydrous DMSO (30 mL) at 20 °C. The reaction mixture was stirred for 25 h at this temperature, quenched with H_2O (30 mL), and extracted with ether (30 mL×3). The organic layers were washed with water and brine, dried over Na_2SO_4, filtered, evaporated, and purified by chromatography on silica gel to afford **6a** (5.0199 g, the combined yield from **5a** to **6a** is 73%). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.31$–5.20 (m, 1H), 5.20–5.10 (m, 1H), 2.42 (t, $J=7.0$ Hz, 2H), 2.35–2.28 (m, 2H), 2.06–1.97 (m, 2H), 1.45–1.20 (m, 8H), 0.88 ppm (t, $J=6.6$ Hz, 3H); this compound was used in the next step without further characterization.

*Synthesis of dodeca-4,5-dienoic acid (**1a**)*: A mixture of dodeca-4,5-dienenitrile (2.0040 g, 11.3 mmol), ethanol (15 mL), and NaOH solution (4.0 g in 5.2 mL of H_2O, 100 mmol) was stirred at 80 °C for 5 h. The mixture was concentrated in vacuum and the residue was quenched with water (20 mL). The aqueous solution was extracted with ether to remove neutral impurities. The aqueous layer was then acidified with 5% HCl (aq.) to pH 1 and extracted with ether (30 mL×3). The ether extraction was washed with water and brine, dried over Na_2SO_4, filtered, and then concentrated in vacuum. Chromatography on silica gel (petroleum ether/ethyl acetate 5:1) of the crude product afforded **1a** (2.1065 g, 95%). Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.82$ (br s, COOH, 1H), 5.21–5.09 (m, 2H), 2.48 (t, $J=7.1$ Hz, 2H), 2.36–2.23 (m, 2H), 2.03–1.90 (m, 2H), 1.46–1.16 (m, 8H), 0.88 ppm (t, $J=6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=203.6$, 179.6, 92.9, 89.2, 33.1, 31.7, 29.1, 28.84, 28.82, 23.5, 22.6, 14.1 ppm; IR (neat): $\tilde{\nu}=3030$, 2957, 2927, 2856, 1964, 1712, 1435, 1336, 1278, 1211, 1173 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 196 (0.46) $[M]^+$, 126 (100); HRMS: *m*/*z*: calcd for $C_{12}H_{20}O_2Na$: 219.1356 [M^++Na]; found: 219.1351.

Procedures for the preparation of optically active γ-allenoic acids[26] (*R*)-(−)-1a, (*R*)-(−)-1b, (*S*)-(+)-1l, (*S*)-(+)-1m, and (R_a,*R*)-(−)-1l

Preparation of optically active γ-allenoic acid[19a] (*R*)-(−)-1a

Synthesis of (R)*-(−)-dodeca-4,5-dienenitrile (*(R)*-(−)-**6a**)*: Following the procedure for the preparation of **5a**, the reaction of (*R*)-(+)-nonyn-3-ol ((*R*)-(+)-**4a**) (4.0693 g, 29 mmol, 99% *ee*, $[\alpha]_D^{20}=+4.6$ ($c=1.92$ in $CHCl_3$)), EtCOOH (1.5 mL, $d=0.99\,g\,mL^{-1}$, 1.49 g, 0.020 mol), and $MeC(OEt)_3$ (14.3 g, 86 mmol) afforded ethyl (*R*)-(−)-undeca-3,4-dienoate (4.1724 g). The product was used in the next step without further characterization. A solution of this ester (4.1724 g, 19.9 mmol) in THF (30 mL) was treated with $LiAlH_4$ (0.7990 g, 21 mmol) in anhydrous THF (30 mL) to afford (*R*)-(−)-**5a** (2.4345 g, the crude combined yield from (*R*)-(+)-**4a** to (*R*)-(−)-**5a** is 50%). The product was used in the next step without further characterization. Following the procedure for the preparation of **6a**, the reaction of (*R*)-(−)-**5a** (1.6055 g, 10 mmol), *p*TsCl (5.7 g, 30 mmol), and dry pyridine (20 mL) afforded the tosylate, which was used in the next step without further purification. The reaction of the tosylate prepared above and NaCN (0.5584 g, 11.4 mmol) in anhydrous DMSO (20 mL) afforded (*R*)-(−)-**6a** (1.3584 g, the combined yield from

(*R*)-(−)-**5a** to (*R*)-(−)-**6a** is 66%). Oil; $[\alpha]_D^{20}=-69.2$ ($c=0.99$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.32$–5.20 (m, 1H), 5.20–5.08 (m, 1H), 2.42 (t, $J=6.8$ Hz, 2H), 2.35–2.24 (m, 2H), 2.06–1.95 (m, 2H), 1.47–1.16 (m, 8H), 0.87 ppm (t, $J=6.3$ Hz, 3H); this compound was used in the next step without further characterization.

Synthesis of (R)*-(−)-dodeca-4,5-dienoic acid* ((R)*-(−)-**11a**)*: Following the procedure for the preparation of **1a**, the reaction of (*R*)-(−)-**6a** (0.7106 g, 4.0 mmol), ethanol (10 mL), and NaOH solution (3.0 g in 4 mL of H_2O, 75 mmol) afforded (*R*)-(−)-**1a** (0.5703 g, 72%). Oil; $[\alpha]_D^{20}=-71.4$ ($c=1.06$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.45$ (brs, 1H; COOH), 5.21–5.08 (m, 2H), 2.53–2.41 (m, 2H), 2.38–2.22 (m, 2H), 2.01–1.87 (m, 2H), 1.44–1.16 (m, 8H), 0.88 ppm (t, $J=6.8$ Hz, 3H).

Preparation of (*S*)-3-methyldeca-4,5-dienoic acid ((*S*)-(+)-11)

*Synthesis of (3*R*,4*R*)-(−)-3-methyl-4-(trimethylsilyl)ethynyloxetan-2-one ((3*R*,4*R*)-(−)-**8a**)*:[23a] A solution of *N,N*-diisopropylethylamine (2.49 g, 20 mmol) and *O*-trimethylsilylquinine (0.3402 g, 0.8 mmol) in anhydrous CH_2Cl_2 (25 mL) was added to a suspension of $MgCl_2$ (0.7614 g, 8 mmol) in anhydrous diethyl ether (12 mL). Then a solution of **7**[6] (1.0107 g, 8 mmol) in anhydrous CH_2Cl_2 (5 mL) was added at −80 °C. After being stirred at −80 °C for 40 min, a solution of propionyl chloride (1.5348 g, 17 mmol) in anhydrous CH_2Cl_2 (5 mL) was then added over 3 h by a syringe pump at this temperature. The reaction mixture was stirred for 14.5 h at −80 °C and then quenched by adding a saturated aqueous NH_4Cl solution (25 mL). The resulting mixture was extracted with diethyl ether (200 mL×3) and the combined organic extracts were washed successively with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether (30–60 °C)/ethyl ether 10:1) to afford (3*R*,4*R*)-(−)-**8a** (1.0794 g, 73%). Colorless oil; $[\alpha]_D^{20}=-12.9$ ($c=1.26$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.12$ (d, $J=6.4$ Hz, 1H), 3.92–3.81 (m, 1H), 1.42 (d, $J=7.6$ Hz, 3H), 0.21 ppm (s, 9H).

Synthesis of (R$_a$,R)*-(−)-2-methyl-5-(trimethylsilyl)nona-3,4-dienoic acid* ((R$_a$,R)*-**9a**)*: 1,2-Dibromoethane (60 μL, 0.7 mmol) was added to a mixture of magnesium turnings (0.8477 g, 35 mmol) in anhydrous THF (10 mL) under nitrogen. Upon the initiation of the Grignard reaction, a solution of *n*BuBr (2.057 g, 15 mmol) in THF (25 mL) was then added dropwise over 15 min at RT. After being stirred for 30 min, the resulting Grignard reagent solution (14 mL, 6.02 mmol) was added dropwise to a mixture of (3*R*,4*R*)-(−)-**8a** (365.2 mg, 2.0 mmol), CuCN (18.8 mg, 0.2 mmol), and anhydrous lithium bromide (40.5 mg, 0.46 mmol) in anhydrous THF (20 mL) at −78 °C within 20 min. After being stirred at −78 °C for additional 20 min, the reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL). The resulting mixture was extracted with ethyl acetate (200 mL×2) and the combined organic extracts were successively washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 40:1 to 5:1) to afford (*R*$_a$,*R*)-(+)-**9a** as a colorless oil (397.6 mg, 83%). Oil; $[\alpha]_D^{20}=+22.3$ ($c=1.53$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=11.30$ (brs, 1H), 5.13–4.90 (m, 1H), 3.20–2.97 (m, 1H), 1.96 (td, $J_1=7.4$, $J_2=3.0$ Hz, 2H), 1.46–1.27 (m, 4H), 1.24 (d, $J=6.9$ Hz, 3H), 0.89 (t, $J=7.1$ Hz, 3H), 0.08 ppm (s, 9H); this compound was used in the next step without further characterization.

Synthesis of (R$_a$,R)*-(−)-2-methyl-5-(trimethylsilyl)nona-3,4-dien-1-ol* ((R$_a$,R)*-(−)-**10a**)*: K_2CO_3 (1.1472 g, 8.3 mmol) and MeI (0.42 mL, 6.8 mmol) were added sequentially to a solution of (*R*$_a$,*R*)-(+)-**9a** (1.0191 g, 4.2 mmol) in DMF (10 mL). The resulting mixture was then stirred for 105 min at 10 °C. After being stirred at this temperature, the mixture was quenched with H_2O (5 mL) and extracted with ethyl ether (50 mL×3). The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent, chromatography on silica gel afforded (*R*$_a$,*R*)-methyl 2-methyl-5-(trimethylsilyl)nona-3,4-dienoate (0.9813 g, crude yield: 91%). It was used in the next step without further purification. Following the procedure for the preparation of (*R*)-**5a**, a solution of ester (0.9484 g, 3.7 mmol) in anhydrous THF (15 mL) was added to a suspension of $LiAlH_4$ (0.1819 g, 4.8 mmol) in anhydrous THF (20 mL) to afford (*R*$_a$,*R*)-(−)-**10a** (0.7875 g, 93%). Oil; $[\alpha]_D^{20}=-0.6$ ($c=0.81$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.68$ (dt, $J_1=6.6$, $J_2=3.2$ Hz, 1H), 3.55–3.37 (m, 2H), 2.40–2.24 (m, 1H), 1.99–1.90 (m, 2H), 1.57 (brs, 1H), 1.48–1.24 (m, 4H), 1.00 (d, $J=6.9$ Hz, 3H), 0.90 (t, $J=7.1$ Hz, 3H), 0.08 ppm (s, 9H); this compound was used in the next step without further characterization.

Synthesis of (S)*-(−)-3-methyldeca-4,5-dienenitrile* ((S)*-(−)-**11a**)*: Following the procedure for the preparation of (*R*)-**6b**, a mixture of (*R*$_a$,*R*)-(−)-**10a** (0.7625 g, 3.4 mmol) and anhydrous pyridine (15 mL) was treated with *p*TsCl (in two portions: 1.9899+0.9936 g, 15.7 mmol) to afford the tosylate, which was used in the next step without further purification. The reaction of the tosylate prepared above and NaCN (0.1701 g, 3.9 mmol) in anhydrous DMSO (10 mL) afforded (*R*$_a$,*S*)-3-methyl-6-trimethylsilyldeca-4,5-dienenitrile, which was used in the next step without further purification. A solution of tetrabutylammonium fluoride in THF (3.0 mL, 1 M) was added to a solution of this nitrile in of anhydrous THF (10 mL). The mixture was stirred at 30 °C for 40 min, diluted with ether, and washed with a saturated aqueous solution of ammonium chloride. The organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to afford (*S*)-(−)-**11a**[24] (195.1 mg, the combined yield from (*R*$_a$,*R*)-**10a** to (*S*)-(−)-**11a** is 35%). Oil; $[\alpha]_D^{20}=-9.1$ ($c=0.51$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.32$–5.23 (m, 1H), 5.17–5.10 (m, 1H), 2.60–2.49 (m, 1H), 2.41 (dd, $J_1=16.5$, $J_2=6.2$ Hz, 1H), 2.32 (dd, $J_1=16.5$, $J_2=6.8$ Hz, 1H), 2.07–1.98 (m, 2H), 1.44–1.29 (m, 4H), 1.20–1.15 (m, 3H), 0.90 ppm (t, $J=7.2$ Hz, 3H); this compound was used in the next step without further characterization.

Synthesis of (S)*-(+)-3-methyldeca-4,5-dienoic acid* ((S)*-(+)-**11**)*: Following the procedure of **6a**, the reaction of (*S*)-(−)-**11a** (0.1951 g, 1.2 mmol), ethanol (8 mL), and NaOH solution (2.0 g in 2.6 mL of H_2O, 50 mmol) afforded (*S*)-(+)-**11** (0.1688 g, 77%). Oil; $[\alpha]_D^{20}=+19.0$ ($c=0.93$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.94$ (brs, 1H; COOH), 5.23–5.09 (m, 2H), 2.73–2.60 (m, 1H), 2.55–2.39 (m, 1H), 2.37–2.21 (m, 1H), 2.05–1.90 (m, 2H), 1.46–1.24 (m, 4H), 1.08 (d, $J=6.3$ Hz, 3H), 0.89 ppm (t, $J=6.9$ Hz, 3H).

The d.r. value of (*S*)-**11** was determined after its conversion to the corresponding benzyl ester.

Synthesis of benzyl (S)*-(+)-3-methyldeca-4,5-dienoate* ((S)*-(+)-**13a**)*: Following the procedure for the benzylation of (*R*$_a$,*R*)-**11**, the reaction of (*S*)-**11** (9.8 mg, 0.05 mmol), BnOH (17.8 mg, 0.16 mmol), DMAP (5.1 mg, 0.04 mmol), and DCC (14.4 mg, 0.07 mmol) in CH_2Cl_2 (1 mL) afforded (*S*)-(+)-**13a** (12.0 mg, 82%), d.r.=1.2:1; the d.r. value was determined by HPLC (Chiralcel AS-H column, rate=0.5 mL min^{-1}, eluent=hexane/*i*PrOH 100:0, $\lambda=214$ nm, t_R(minor)=27.1, (major)=32.4). $[\alpha]_D^{20}=+12.1$ ($c=0.475$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.42$–7.29 (m, 5H), 5.20–5.06 (m, 4H), 2.76–2.63 (m, 1H), 2.50–2.40 (m, 1H), 2.36–2.24 (m, 1H), 2.01–1.89 (m, 2H), 1.41–1.27 (m, 4H), 1.05 (d, $J=6.9$ Hz, 3H), 0.93–0.84 ppm (m, 3H); IR (neat): $\tilde{\nu}=1961$, 1738, 1499, 1455, 1378, 1159 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 272 (0.57) [M^+], 69 (100); HRMS: *m*/*z*: calcd for $C_{18}H_{24}O_2Na$: 295.1669 [M^++Na]; found: 295.1666.

Synthesis of benzyl (R)*-(−)-3-methyldeca-4,5-dienoate* ((R)*-(−)-**13a**)*: Following the procedure for the preparation of (*R*$_a$,*R*)-(−)-**13a**, the reaction of (*R*)-(−)-**11** (52.8 mg, 0.29 mmol), BnOH (92.5 mg, 0.86 mmol), DMAP (27.5 mg, 0.23 mmol), and DCC (65.1 mg, 0.32 mmol) in CH_2Cl_2 (1.8 mL) afforded (*R*)-(−)-**13a** (69.9 mg, 89%, d.r.=1.2:1; HPLC (Chiralcel OJ-H column, rate=0.7 mL min^{-1}, eluent=hexane/*i*PrOH 99:1, $\lambda=214$ nm, t_R(minor)=9.4, (major)=9.9)). Oil; $[\alpha]_D^{20}=-5.6$ ($c=0.33$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.40$–7.29 (m, 5H), 5.20–5.06 (m, 4H), 2.74–2.61 (m, 1H), 2.52–2.39 (m, 1H), 2.36–2.22 (m, 1H), 2.01–1.88 (m, 2H), 1.42–1.26 (m, 4H), 1.08–1.02 (m, 3H), 0.92–0.84 ppm (m, 3H); IR (neat): $\tilde{\nu}=1961$, 1740, 1498, 1456, 1377, 1261, 1155 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 272 (0.57) [M^+], 139 (100); HRMS: *m*/*z*: calcd for $C_{18}H_{24}O_2Na$: 295.1669 [M^++Na]; found: 295.1666.

Preparation of (*S*$_a$,*R*)-(+)-3-methyldeca-4,5-dienoic acid ((*S*$_a$,*R*)-(+)-11): The two isomers (*S*$_a$,*R*)-(+)-**13a** and (*R*$_a$, *R*)-(−)-**13a** were separated by using a CHIRALPAK IC column (25 cm×2 cm), rate=9 mL min^{-1}, eluent=hexane/ethyl acetate 98:2, $\lambda=214$ nm, injection=2 mL (C=1 mg mL^{-1}): peak 1, $t_R=13.7$; peak 2, $t_R=15.0$. The two portions collected were kept over dry ice. After evaporation of the solvent, pure isomers were obtained.

(S_a,R*)-(+)-**13a***: Oil; $[\alpha]_D^{20}=+42$ ($c=0.80$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.42$–7.29 (m, 5H), 5.20–5.06 (m, 4H), 2.76–2.63 (m, 1H), 2.46 (dd, $J_1=15.2$, $J_2=6.8$ Hz, 1H), 2.30 (dd, $J_1=15.2$, $J_2=7.4$ Hz, 1H), 2.01–1.89 (m, 2H), 1.41–1.27 (m, 4H), 1.05 (d, $J=6.9$ Hz, 3H), 0.89 ppm (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=202.4$, 172.4, 136.0, 128.5, 128.17, 128.15, 95.7, 93.2, 66.1, 41.4, 31.3, 30.0, 28.6, 22.2, 20.2, 13.9 ppm; IR (neat): $\tilde{\nu}=1962$, 1737, 1499, 1456, 1161 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 272 (0.58) [M^+], 91 (100); HRMS: *m*/*z*: calcd for $C_{18}H_{24}O_2$: 272.1776 [M^+]; found: 272.1778; HPLC: (Chiralcel OJ-H column, rate = 0.7 mL min^{-1}, eluent = hexane/*i*PrOH 99:1, $\lambda=214$ nm, t_R-(major) = 9.377 (((*S*$_a$,*R*)-(+)-**13a**), t_R(minor) = 9.930, (*R*$_a$,*R*)-(−)-**13a**)): peak 1: d.r. > 99:1.

(R_a,R*)-(−)-**13a***: Oil; $[\alpha]_D^{20}=-50$ ($c=0.50$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.42$–7.28 (m, 5H), 5.20–5.06 (m, 4H), 2.76–2.63 (m, 1H), 2.46 (dd, $J_1=15.3$, $J_2=6.9$ Hz, 1H), 2.29 (dd, $J_1=15.2$, $J_2=7.7$ Hz, 1H), 2.01–1.89 (m, 2H), 1.41–1.27 (m, 4H), 1.05 (d, $J=6.9$ Hz, 3H), 0.88 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=202.4$, 172.5, 136.0, 128.5, 128.2, 128.16, 95.7, 93.3, 66.1, 41.3, 31.3, 30.0, 28.6, 22.2, 20.3, 13.9 ppm; IR (neat): $\tilde{\nu}=1961$, 1737, 1498, 1456, 1379, 1351, 1263, 1161 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 272 (0.54) [M^+], 141 (100); HRMS: *m*/*z*: calcd for $C_{18}H_{24}O_2$: 272.1776 [M^+]; found: 272.1775; HPLC (Chiralcel OJ-H column, rate = 0.7 mL min^{-1}, eluent = hexane/*i*PrOH 99:1, $\lambda=214$ nm, t_R(minor) = 9.377 (((*S*$_a$,*R*)-(+)-**13a**), t_R(major) = 9.930 (((*R*$_a$,*R*)-(−)-**13a**)): peak 2: d.r. > 98:2.

The absolute configuration of the isomer related to peak 2 was determined as (*R*$_a$,*R*) by comparison with the specific optical rotation of (*R*$_a$,*R*)-(−)-**13a** prepared on p. S47 in the Supporting Information. The absolute configuration of the isomer related to peak 1 was then assigned as *S*$_a$,*R*.

Synthesis of (S_a,R*)-(+)-3-methyldeca-4,5-dienoic acid ((*S_a,R*)-(+)-**11l**)*: LiOH·H_2O (8 mg, 0.18 mmol) was added to a solution of (*S*$_a$,*R*)-(+)-**13a** (16 mg, 0.06 mmol) prepared above in H_2O (0.3 mL) and MeOH (0.6 mL). After being stirred for 12 h at 30 °C, the reaction was complete as detected by TLC analysis (eluent = petroleum ether/ethyl acetate 5:1). The mixture was then adjusted with 5% HCl (aq.) to pH 1 and extracted with ether (30 mL × 3). The ether layer was subsequently washed with water and brine, dried over Na_2SO_4, filtered, and then concentrated under vacuum. Chromatography on silica gel (petroleum ether/ethyl acetate 20:1) of the crude product afforded (*S*$_a$,*R*)-(+)-**11** (7.1 mg, 66%). Oil; $[\alpha]_D^{20}=+45$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 5.21–5.09 (m, 2H), 2.73–2.58 (m, 1H), 2.45 (dd, $J_1=15.6$, $J_2=6.9$ Hz, 1H), 2.29 (dd, $J_1=15.6$, $J_2=7.2$ Hz, 1H), 2.05–1.90 (m, 2H), 1.46–1.24 (m, 4H), 1.08 (d, $J=6.9$ Hz, 3H), 0.89 ppm (t, $J=7.1$ Hz, 3H), the acidic proton is missing here in this spectrum; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 202.4, 178.7, 95.6, 93.5, 41.0, 31.3, 29.7, 28.6, 22.2, 20.2, 13.9 ppm; IR (neat): $\tilde{\nu}=1962$, 1710, 1458, 1410, 1378, 1293 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 182 (3.54) [M^+], 81 (100); HRMS: *m*/*z*: calcd for $C_{11}H_{18}O_2$: 182.1307 [M^+]; found: 182.1308.

Preparation of (*R_a,*R*)-(−)-3-methyldeca-4,5-dienoic acid ((*R_a,*R*)-(−)-11l)

*Synthesis of (3*S*,4*S*)-(−)-3-methyl-4-ethynyloxetan-2-one ((3*S*,4*S*)-(−)-**12a**)*:[25] A solution of tetrabutylammonium fluoride in THF (14.0 mL, 1 M, 14 mmol) was added to a solution of (3*S*,4*S*)-(+)-**8a** (2.3543 g, 13 mmol) in 20 mL of anhydrous THF. The mixture was stirred at 0 °C for 25 min, and then the resulting mixture was filtered through a 1.5 cm plug of silica gel, eluting with CH_2Cl_2. The filtrate was concentrated and purified by flash chromatography on silica gel (petroleum ether (30–60 °C)/ether 5:1) to afford (3*S*,4*S*)-(−)-**12a** (0.7234 g, 51%). Oil; $[\alpha]_D^{20}=$ −5.4 ($c=0.70$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.13$ (dd, $J_1=$ 6.6, $J_2=2.1$ Hz, 1H), 3.95–3.85 (m, 1H), 2.84 (d, $J=2.1$ Hz, 1H), 2.44 ppm (d, $J=7.8$ Hz, 3H).

Synthesis of (R_a,S*)-(−)-2-methylnona-3,4-dien-1-ol ((*R_a,S*)-(−)-**10a**)*: (3*S*,4*S*)-(−)-**12a** (34.1 g, 0.3 mmol) was added to a solution of CuBr·SMe_2 (6.8 mg, 0.03 mmol) and dimethylsulfide (0.2 mL) in anhydrous THF (3.5 mL). Then the Grignard reagent solution (0.65 mL, 1 M in THF, 0.65 mmol) was added dropwise to the mixture at −78 °C within 5 min. After being stirred at −78 °C for additional 20 min, the reaction was quenched with a saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was extracted with ether (30 mL × 3) and the combined organic extracts were successively washed with H_2O and brine, dried over Na_2SO_4, filtered, and then concentrated. The residue was purified by flash chromatography on silica gel to afford (*R*$_a$,*S*)-2-methylnona-3,4-dienoic acid (0.0415 g, 80%). Colorless oil; $[\alpha]_D^{20}=-110.9$ ($c=1.21$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.78$ (brs, 1H), 5.35–5.20 (m, 2H), 3.21–3.04 (m, 1H), 2.09–1.90 (m, 2H), 1.44–1.31 (m, 4H), 1.27 (d, $J=7.2$ Hz, 3H), 0.89 ppm (t, $J=7.1$ Hz, 3H); it was used in the next step without further purification. Following the procedure for the preparation of (*R*)-(−)-**5a**, a solution of the dienoic acid prepared above (0.3229 g, 1.9 mmol) in anhydrous ether (3 mL) was added to a suspension of $LiAlH_4$ (0.1441 g, 3.8 mmol) in anhydrous ether (15 mL) to afford (*R*$_a$,*S*)-(−)-**10a** (0.1284 g, 43%). Oil; $[\alpha]_D^{20}=-82.3$ ($c=0.39$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.21$–5.11 (m, 1H), 5.10–5.01 (m, 1H), 3.48 (d, $J=$ 6.3 Hz, 2H), 2.39–2.28 (m, 1H), 2.03–1.92 (m, 2H), 1.91 (brs, 1H), 1.43–1.24 (m, 4H), 0.95 (d, $J=6.9$ Hz, 3H), 0.88 ppm (t, $J=7.1$ Hz, 3H); this compound was used in the next step without further characterization.

Synthesis of (R_a,R*)-(−)-3-methyldeca-4,5-dienoic acid ((*R_a,R*)-(−)-**11l**)*: Following the procedure for the preparation of (*R*)-(−)-**6a**, a mixture of (*R*$_a$,*S*)-(−)-**10a** (0.1284 g, 0.8 mmol) and anhydrous pyridine (1 mL) was treated with *p*TsCl (0.4785 g, 2.5 mmol) to afford the tosylate, which was used in the next step without further purification. The reaction of the tosylate prepared above and NaCN (0.0482 g, 0.96 mmol) in anhydrous DMSO (2 mL) afforded (*R*$_a$,*S*)-3-methyldeca-4,5-dienenitrile, which was used in the next step without further purification. Following the procedure for the preparation of **6a**, the reaction of (*R*$_a$,*S*)-3-methyldeca-4,5-dienenitrile (0.0814 g, 0.5 mmol), ethanol (2 mL), and NaOH solution (0.4 g in 0.6 mL of H_2O, 10 mmol) afforded (*R*$_a$, *R*)-(−)-**11l** (0.0660 g, the combined yield from (*R*$_a$,*S*)-(−)-**10a** to (*R*$_a$,*R*)-(−)-**11l** is 43%). Oil; $[\alpha]_D^{20}=-74.9$ ($c=1.34$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.65$ (brs, 1H; COOH), 5.21–5.09 (m, 2H), 2.73–2.60 (m, 1H), 2.44 (dd, $J_1=$ 15.6, $J_2=7.0$ Hz, 1H), 2.23 (dd, $J_1=15.6$, $J_2=7.3$ Hz, 1H), 2.05–1.90 (m, 2H), 1.46–1.24 (m, 4H), 1.08 (d, $J=6.6$ Hz, 3H), 0.89 ppm (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=202.4$, 179.3, 95.5, 93.4, 41.2, 31.3, 29.8, 28.6, 22.2, 20.3, 13.9 ppm; IR (neat): $\tilde{\nu}=1962$, 1710, 1458, 1410, 1378, 1294 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 182 (1.90) [M^+], 140 (100); HRMS: *m*/*z*: calcd for $C_{11}H_{18}O_2$: 182.1307 [M^+]; found: 182.1307.

Synthesis of benzyl (R_a,R*)-(−)-3-methyldeca-4,5-dienoate ((*R_a,R*)-(−)-**13a**)*: BnOH (16.9 mg, 0.165 mmol) and DMAP (5.4 mg, 0.044 mmol) were added sequentially to a solution of (*R*$_a$,*R*)-(−)-**11** (8.9 mg, 0.055 mmol) in CH_2Cl_2 (1 mL). Then DCC (13.6 mg, 0.06 mmol) was added at 0 °C. After being stirred for 23.5 h at RT, the reaction was over as determined by TLC analysis and the resulting mixture was diluted with ether (10 mL) and transferred to a round-bottomed flask and evaporated. The residue was purified by chromatography on silica gel to afford (*R*$_a$,*R*)-(−)-**13a** (13.3 mg, 100%, d.r. = 96/4; HPLC (Chiralcel OJ-H column, rate = 0.5 mL min^{-1}, eluent = hexane/*i*PrOH 99:1, $\lambda=214$ nm, t_R-(minor) = 12.1, (major) = 12.5)). Oil; $[\alpha]_D^{20}=-54.9$ ($c=0.36$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.42$–7.29 (m, 5H), 5.20–5.06 (m, 4H), 2.76–2.62 (m, 1H), 2.47 (dd, $J_1=15.4$, $J_2=6.9$ Hz, 1H), 2.30 (dd, $J_1=15.4$, $J_2=7.7$ Hz, 1H), 2.02–1.89 (m, 2H), 1.40–1.29 (m, 4H), 1.06 (d, $J=$ 6.9 Hz, 3H), 0.89 ppm (t, $J=7.2$ Hz, 3H).

Typical procedure for the preparation of 4,5-dihydro-2(3*H*)-furanones ((*Z*)-2a–m)

5-(1′-Iodo-1′(*Z*)-octenyl)-4,5-dihydro-2(3*H*)-furanone (*Z*-2a): I_2 (114.3 mg, 0.45 mmol, solid) was added to a solution of **1a** (59.3 mg, 0.3 mmol) in cyclohexane (4 mL) with stirring at RT. After the reaction was complete as determined by TLC (eluent: petroleum ether/ethyl acetate 5:1), it was quenched with H_2O (6 mL), which was followed by the addition of sat. aqueous $Na_2S_2O_3$ (4 mL). The resulting mixture was extracted with ether (20 mL × 3), washed with brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent, the *Z*/*E* ratio of the products was determined to be 98:2 by 400 MHz ^{1}H NMR spectroscopic analysis. Chromatography on silica gel (petroleum ether/ethyl acetate 5:1) of the crude product afforded (*Z*)-**2a** (81 mg, 83%, *Z*/*E* 98:2). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.02$ (td, $J_1=6.6$, $J_2=1$ Hz, 1H), 4.76 (t, $J=7.0$ Hz, 1H), 2.70–2.58 (m, 1H), 2.58–2.45 (m, 1H), 2.45–2.33 (m, 1H), 2.21–2.08 (m, 3H), 1.45–1.34 (m, 2H), 1.34–1.16 (m, 6H), 0.86 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=176.4$, 138.5, 106.9,

84.3, 35.5, 31.5, 28.8, 28.6, 28.0, 27.9, 22.5, 14.0 ppm; IR (neat): $\tilde{\nu}$ = 2955, 2926, 2855, 1785, 1640, 1457, 1316, 1180, 1024 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 322 (30.18) [M^+], 111 (100); elemental analysis calcd (%) for $C_{12}H_{19}IO_2$: C 44.74, H 5.94; found: C 44.74, H 6.01.

Typical procedure for the iodocyclization of 1f–h in the presence of I_2 and K_2CO_3

5-Butyl-5-(1′-iodo-1′-vinyl)-4,5-dihydro-2(3*H*)-furanone (2f): K_2CO_3 (43.7 mg, 0.3 mmol) was added to a solution of **1f** (50.5 mg, 0.3 mmol) in cyclohexane (4 mL). After stirring for 20 min, I_2 (116.0 mg, 0.45 mmol, solid) was added, and the mixture was stirred for a further 1 h. The resulting mixture was quenched sequentially with H_2O (6 mL) and sat. aqueous $Na_2S_2O_3$ (4 mL), extracted with ether (25 mL × 3), washed with brine, dried over Na_2SO_4, and then filtered. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to afford **2f** (76.9 mg, 87%). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (d, *J* = 2.2 Hz, 1H), 5.91 (d, *J* = 2.2 Hz, 1H), 2.55–2.43 (m, 3H), 2.14–2.01 (m, 2H), 1.73–1.64 (m, 1H), 1.42–1.20 (m, 4H), 0.90 ppm (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 126.9, 111.4, 90.2, 38.6, 33.2, 28.1, 25.5, 22.5, 13.8 ppm; IR (neat): $\tilde{\nu}$ = 2956, 2930, 2871, 1784, 1611, 1456, 1183, 1090, 1024 cm^{-1}; MS (70 ev, EI): *m*/*z* (%): 294 (0.36) [M^+], 237 (100) [$M^+ - C_4H_9$]; HRMS: *m*/*z*: calcd for $C_{10}H_{15}IO_2$: 294.0111 [M^+]; found: 294.0130.

Typical procedure for the preparation of optically active 5-(1′-iodo-1′-alkenyl)-4,5-dihydro-2(3*H*)-furanones (*R*)-2a and (*R*)-2b

Optically active 5-(1′-iodo-1′-octenyl)-4,5-dihydro-2(3*H*)-furanone (mixture of (*S*)-(*Z*)-2a and (*R*)-(*E*)-2a): Cs_2CO_3 (667.8 mg, 2 mmol) was added to a solution of (*R*)-(−)-**1a** (396.0 mg, 2 mmol) in CH_2Cl_2 (24 mL) with stirring at RT. NIS (677.2 mg, 3 mmol) was then added to the mixture at −60 °C. After 10 h, another 0.5 equivalents of NIS (0.2251 g, 1 mmol) was added at −60 °C. After the reaction was complete, as determined by TLC (eluent = petroleum ether/ethyl acetate 5:1), the resulting mixture was warmed up to RT and quenched sequentially with H_2O (10 mL) and a sat. aqueous solution of $Na_2S_2O_3$ (6 mL). The mixture was then extracted with ether (25 mL × 3), washed with brine, and then dried over Na_2SO_4. After filtration, evaporation of the solvent and chromatography on silica gel (petroleum ether/ethyl acetate/CH_2Cl_2 6:1:1) afforded **2a** (575.8 mg, 89%, (*S*)-(*Z*)-**2a**/(*R*)-(*E*)-**2a** 85:15, (*S*)-(*Z*)-**2a**: 99% *ee*; HPLC (Chiralcel OJ-H column, rate = 0.5 mL min^{-1}, eluent = hexane/*i*PrOH 90:10, λ = 254 nm, t_R(minor) = 14.8, (major) = 15.8)). Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (t, *J* = 7.6 Hz, 0.15H), 6.04 (td, J_1 = 7.0, J_2 = 0.9 Hz, 0.85H), 4.89 (t, *J* = 7.0 Hz, 0.15H), 4.79 (t, *J* = 7.0 Hz, 0.85H), 2.78–2.61 (m, 1H), 2.61–2.48 (m, 1H), 2.48–2.33 (m, 1H), 2.25–2.08 (m, 3H), 1.48–1.36 (m, 2H), 1.36–1.20 (m, 6H), 0.88 ppm (t, *J* = 6.8 Hz, 3H); this *Z*/*E* mixture was submitted to the kinetic resolution without further characterization.

Typical procedure for the kinetic resolution of (*R*)-(*Z*)- and (*S*)-(*E*)-isomers of optically active products 2a and 2b

(*S*)-(+)-5-(1′-Iodo-1′(*Z*)-octenyl)-4,5-dihydro-2(3*H*)-furanone ((*S*)-(+)-(*Z*)-2a): A solution of Et_2NH (8.3 mg, 0.11 mmol), prop-2-yn-1-ol (5.4 mg, 0.096 mmol), and a mixture of (*S*)-(*Z*)-**2a** and (*R*)-(*E*)-**2a** (95.8 mg, 0.3 mmol) in CH_3CN (1 mL) were added to a mixture of CuI (2.1 mg, 0.011 mmol, 3.5 mol%) and $[PdCl_2(PPh_3)_2]$ (7.4 mg, 0.011 mmol, 3.5 mol%). The mixture was stirred at 3 °C with an ice/water bath for 1 h under nitrogen. After the reaction was complete, as determined by GC analysis, the resulting mixture was quenched with H_2O (10 mL), diluted with ether (10 mL), separated, extracted with ether (3 × 30 mL), washed with brine, and then dried over Na_2SO_4. Filtration, evaporation, and purification by chromatography on silica gel (petroleum ether/ethyl acetate 6:1) afforded (*S*)-(+)-(*Z*)-**2a** (70.9 mg, 74%, *Z*/*E* 98:2, 99% *ee*; HPLC (Chiralcel OJ-H column, rate = 0.5 mL min^{-1}, eluent = hexane/*i*PrOH 90:10, λ = 254 nm, t_R(minor) = 17.2, (major) = 18.3)). $[\alpha]_D^{20}$ = +16.4 (*c* = 0.95 in $CHCl_3$); the ^{1}H NMR spectroscopic data are the same as those for racemic (*Z*)-**2a**.

Acknowledgements

Financial support from the National Natural Science Foundation of China (no. 20572093) and the Zhejiang Provincial Natural Science Foundation of China (Y 404262) is greatly appreciated. S. Ma is a Qiu Shi adjunct professor at Zhejiang University. We thank Mr. Y. Deng for reproducing the results presented in entry 2 of Table 2, entry 5 of Table 3, and the formation of (4*S*,5*S*)-(*Z*)-**2m** from (*S*)-**1m** in Scheme 6.

[1] a) M. S. Maier, D. I. G. Marimon, C. A. Stortz, M. T. Adler, *J. Nat. Prod.* **1999**, *62*, 1565; b) S.-C. Lee, G. D. Brown, *J. Nat. Prod.* **1998**, *61*, 29; c) J. D. Connolly, R. A. Hill, *Dictionary of Terpenoids, Vol. 1*, Chapman and Hall, London, **1991**, p. 476.

[2] P. M. Donate, D. Frederico, R. Da Silva, M. G. Constantino, G. D. Ponte, P. S. Bonatto, *Tetrahedron: Asymmetry* **2003**, *14*, 3253.

[3] a) J. Haas, S. Piguel, T. Wirth, *Org. Lett.* **2002**, *4*, 297; b) M. Wang, L. X. Gao, W. P. Mai, A. X. Xia, F. Wang, S. B. Zhang, *J. Org. Chem.* **2004**, *69*, 2874; c) M. Pattarozzi, C. Zonta, Q. B. Broxterman, B. Kaptein, R. D. Zorzi, L. Randaccio, P. Scrimin, G. Licini, *Org. Lett.* **2007**, *9*, 2365.

[4] D. G. Hulcoop, J. W. Burton, *Chem. Commun.* **2005**, 4687.

[5] E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genêt. , V. Michelet, *J. Am. Chem. Soc.* **2006**, *128*, 3112.

[6] Z. Huo, N. T. Patil, T. Jin, N. K. Pahadi, Y. Yamamoto, *Adv. Synth. Catal.* **2007**, *349*, 680.

[7] I. Takei, Y. Wakebe, K. Suzuki, Y. Enta, T. Suzuki, Y. Mizobe, M. Hidai, *Organometallics* **2003**, *22*, 4639.

[8] C. Jonasson, A. Horváth, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2000**, *122*, 9600.

[9] G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496.

[10] B. M. Trost, A. McClory, *Org. Lett.* **2006**, *8*, 3627.

[11] G. Liu, X. Lu, *Tetrahedron Lett.* **2003**, *44*, 127.

[12] A. J. Pearson, E. F. Mesaros, *Org. Lett.* **2001**, *3*, 2665.

[13] V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507.

[14] a) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370; b) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; c) W. Ye, G. Cai, Z. Zhuang, X. Jia, H. Zhai, *Org. Lett.* **2005**, *7*, 3769.

[15] a) S. K. Mandal, S. R. Amin, W. E. Crowe, *J. Am. Chem. Soc.* **2001**, *123*, 6457; b) W. E. Crowe, A. T. Vu, *J. Am. Chem. Soc.* **1996**, *118*, 1557.

[16] For our recent results on the halolactonization of allenoic acid see: a) C. Fu, S. Ma, *Eur. J. Org. Chem.* **2005**, 3942; b) S. Ma, S. Wu, *Chem. Commun.* **2001**, 441; c) S. Ma, S. Wu, *Tetrahedron Lett.* **2001**, *42*, 4075; d) S. Ma, Z. Shi, Z. Yu, *Tetrahedron Lett.* **1999**, *40*, 2393; e) S. Ma, Z. Shi, Z. Yu, *Tetrahedron* **1999**, *55*, 12137; f) S. Ma, S. Wu, *J. Org. Chem.* **1999**, *64*, 9314; g) S. Ma, Z. Shi, *J. Org. Chem.* **1998**, *63*, 6387.

[17] Crystal data for compound **2g**: $C_{11}H_{15}IO_2$; M_W = 306.13; monoclinic; space group = *P*2(1)/*c*; final *R* indices = [$I > 2\sigma(I)$], R_1 = 0.0576, wR_2 = 0.1303; *a* = 28.562(16), *b* = 5.262(3), *c* = 7.779(4) Å; α = 90, β = 90, γ = 90°; *V* = 1169.1.0(11) Å^3; *Z* = 4; ρ_{calcd} = 1.739 g cm^{-3}; reflections collected/unique: 6317/2274 (R_{int} = 0.1153); parameters: 131. CCDC-663501 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] D. Xu, Z. Li, S. Ma, *Tetrahedron Lett.* **2003**, *44*, 6343.

[19] For the synthesis of optically active γ-allenoic acid from optically active propargylic alcohol, see: a) K. Mori, T. Nukada, T. Ebata, *Tetrahedron* **1981**, *37*, 1343; b) R. A. Brawn, J. S. panek, *Org. Lett.* **2007**, *9*, 2689.

[20] For kinetic resolution by using Sonogashira coupling, see: a) S. Ma, Z. Ma, *Synlett* **2006**, *8*, 1263; b) B. P. Añdreini, A. Carpita, R. Rossi, *Tetrahedron Lett.* **1986**, *27*, 5533; for recent reviews of Sonogashira reactions, see: c) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*,

874; d) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850; *Angew. Chem. Int. Ed.* **2007**, *46*, 834; for a seminal paper on the Sonogashira reaction, see: K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.
[21] J. N. Shooiery, *Prog. NMR Spectrosc.* **1977**, *11*, 79.
[22] N. J. Harris, J. J. Gajewski, *J. Am. Chem. Soc.* **1994**, *116*, 6121.
[23] a) C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352; b) Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352.
[24] When we removed the TMS group by treatment with TBAF in THF, this desilylation led to serious loss of axial chirality. For a similar example, see: C. Rameshkumar, R. P. Hsung, *Angew. Chem.* **2004**, *116*, 625; *Angew. Chem. Int. Ed.* **2004**, *43*, 615.
[25] Z. Wan, S. G. Nelson, *J. Am. Chem. Soc.* **2000**, *122*, 10470.
[26] S. Arseniyadis, J. Gore, M. L. Roumestant, *Tetrahedron* **1979**, *35*, 353.

Received: July 5, 2008
Published online: September 9, 2008

