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Stereoselective synthesis of (*E*)- and (*Z*)-3-hydroxy-2-methyl-1-alkenyl iodides by base-promoted ring-opening of iodomethylated epoxides

Takahiro Ichige, Daisuke Matsuda and Masaya Nakata*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

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Abstract—Both (*E*)- and (*Z*)-3-hydroxy-2-methyl-1-alkenyl iodides were stereoselectively synthesized from iodomethylated epoxides by treatment with sodium hexamethyldisilazane in DMF and with LDA in THF (or lithium 2,2,6,6-tetramethylpiperidide in THF), respectively.

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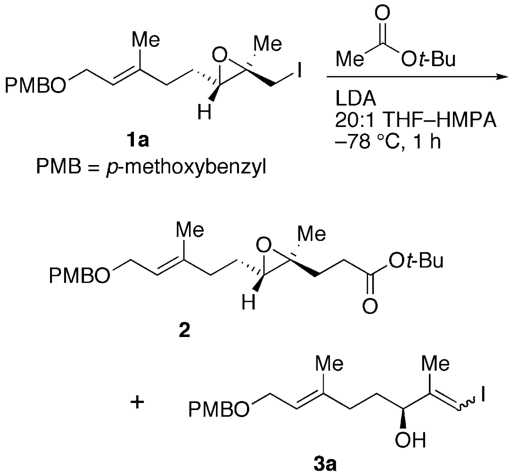
1. Introduction

During the course of our synthetic studies of biscembranoid marine natural products,[1] we encountered an interesting reaction (Scheme 1). A substitution reaction of the iodomethylated epoxide **1a** (1.0 equiv) with the anion derived from *t*-butyl acetate (4.0 equiv) and LDA (4.0 equiv) in 20:1 THF–HMPA afforded the desired product **2** in 78% yield. When this reaction was repeated using 2.0 equiv of *t*-butyl acetate and 4.0 equiv of LDA, **2** was obtained in only 37% yield accompanied by a 41% yield of vinyl iodide **3a** (*E*:*Z* = 30:70). It is reasonable to assume that the latter compound was obtained by the base-promoted ring-opening of **1a** through a β-elimination pathway. In general, vinyl iodides are versatile intermediates in natural products syntheses. Under the conceptually similar reaction conditions, vinyl chlorides[2] and, in the special cases, vinyl bromide,[3] and vinyl fluoride[4] have been prepared. However, to the best of our knowledge, there are no precedents of producing vinyl iodides under similar reaction conditions.[5] In this letter, we report the stereoselective synthesis of (*E*)- and (*Z*)-3-hydroxy-2-methyl-1-alkenyl iodides by the base-promoted ring-opening of iodomethylated epoxides.



Scheme 1. Reaction of the iodomethylated epoxide **1a** with the anion species.

2. Results and discussion

Using **1a**[6] as a model compound, we first examined the reaction conditions that afford vinyl iodide **3a** as the major product (Table 1). To a solution of **1a** (1.0 equiv) in THF was added LDA (1.5 equiv) at −78 °C, and the mixture was warmed to 0 °C during a period of 1 h. After work-up, the crude products were analyzed by ^{1}H NMR spectroscopy. It was found that besides the

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Keywords: Vinyl iodides; Epoxides; Base-promoted ring-opening; *Syn* elimination; *Anti* elimination.

* Corresponding author. Tel.: +81 45 566 1577; fax: +81 45 566 1551; e-mail: msynktxa@applc.keio.ac.jp

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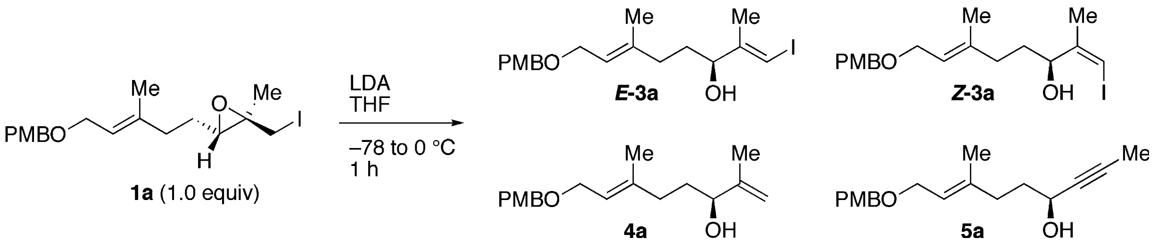
Table 1. Reaction of **1a** with LDA



Entry	Equiv of LDA	Additive (equiv)	Ratio of the products[a]		Yield (%) of **3a**[b]
			E*-3a**:Z*-3a**:**4a**:**5a**	***E*-3a**:***Z*-3a**	
1	1.5	—	2:86:12:0	2:98	80
2	3.0	—	0:0:14:86	—	54[c]
3	1.5	HMPA (3.0)	40:40:11:9	50:50	50
4	1.5	HMPA (6.0)	41:26:10:23	61:39	55
5	1.5	HMPA (12)	46:24:10:20	66:34	48
6	1.5	HMPA (24)	52:20:11:17	72:28	52

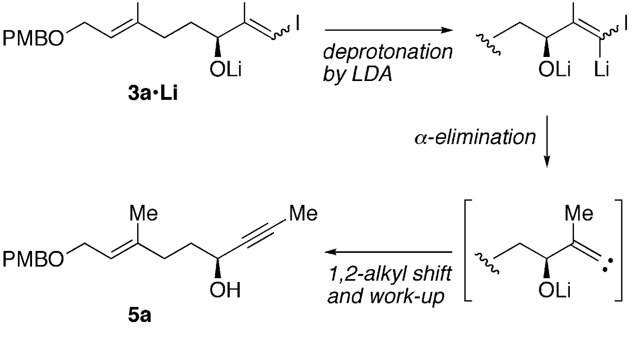
[a] The ratio of the products was based on ^{1}H NMR analysis of the crude products.

[b] Isolated yield of the mixture of ***E*-3a** and ***Z*-3a** after silica-gel column chromatography.

[c] Isolated yield of **5a**.

desired vinyl iodides, ***E*-3a** and ***Z*-3a**,[7] the deiodinated allylic alcohol **4a**[7] was obtained and the ratio of ***E*-3a**:***Z*-3a**:**4a** was 2:86:12 (entry 1). The *E*:*Z* ratio of **3a** was 2:98 and the isolated yield of the mixture of ***E*-3a** and ***Z*-3a** was 80%.[8] These are the best conditions to date producing ***Z*-3a** as the major product.[9] Compound **4a** was derived via the base-promoted dehalogenative ring-opening of **1a**. When 3.0 equiv of LDA was used, the major product was alkyne **5a**[7] (54%, entry 2). Alkyne **5a** would be derived from vinyl iodides, ***E*-3a** and ***Z*-3a**, via deprotonation, α-elimination (alkylidenecarbene formation), and the 1,2-alkyl shift mechanism (Scheme 2).[10,11] The amount of HMPA as an additive affected the *E*:*Z* ratio; the larger the amount of HMPA, the larger the *E*:*Z* ratio (up to 72:28, entries 3–6).

We next examined the hexamethyldisilazane bases (Table 2). Lithium, sodium, and potassium hexamethyldisilazanes (LHMDS in THF, NHMDS in THF, and KHMDS in toluene, respectively) had no effect in THF (entries 1–3). In contrast, gratifyingly, in the presence of HMPA, both LHMDS and NHMDS were effective for the synthesis of *E*-vinyl iodide; the ratio of ***E*-3a**:***Z*-3a** reached 95:5 albeit in moderate isolated yields (entries 4 and 5). When the solvent was changed to DMF, the isolated yields increased to 64% (LHMDS) and 73% (NHMDS) (entries 7 and 8). The bis(trimethylsilyl)amino-substituted byproduct **6a**[7] was also produced. KHMDS was ineffective in all cases (entries 6 and 9). Alternatively, when 3.0 equiv of NHMDS was used in DMF at −60 °C for 12 h, a 77% yield of a 96:4 mixture of ***E*-3a** and ***Z*-3a** was obtained (entry 10). In all cases using the HMDS bases, no alkyne **5a** was observed.

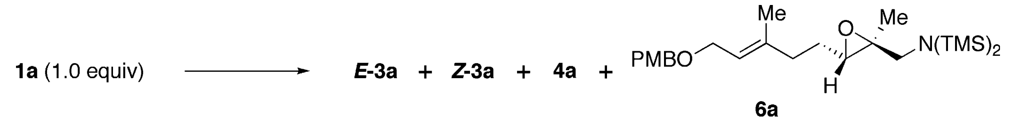


Scheme 2. Probable mechanism for formation of **5a** from **3a**.

In addition, other reagents were surveyed. As anticipated, only the deiodinated allylic alcohol **4a** was quantitatively obtained by the treatment of **1a** with 1.2 equiv of *n*-BuLi (THF, −78 to 0 °C, 1 h). Organoaluminum amides,[12] such as diethylaluminum diisopropylamide and diethylaluminum 2,2,6,6-tetramethylpiperidide (benzene, 0 °C, 0.5 h), also gave **4a** as the major product. In contrast, lithium 2,2,6,6-tetramethylpiperidide (LTMP) proved to be an alternative for LDA (THF, −20 °C, 15 min, 81%, ***E*-3a**:***Z*-3a**:**4a**:**5a** = 2:83:10:5, ***E*-3a**:***Z*-3a** = 2:98).

The formation of allylic alcohols from the reaction of epoxides with amide bases in a relatively nonpolar solvent (such as THF) appears to proceed by a β-elimination pathway and also *syn* elimination is operative during this transformation (Fig. 1).[13] An amide base would preferentially coordinate to the epoxide on the hydrogen substituent side (R^1 = Me, R^2 = alkyl, R^3 = H), as depicted in Figure 1, due to steric factors.[13] Among the two transition state models, **TS-A** would be preferable to **TS-B**; because **TS-B** experiences a substantial nonbonded interaction between the methyl (R^1) and iodine substituents. In contrast, the use of an additive (such as HMPA) or a more polar solvent (such as DMF) precludes a significant association with weakly basic epoxides; therefore, the typical E2 reaction

Table 2. Reaction of **1a** with hexamethyldisilazane bases



Entry	Base (equiv)	Additive (equiv)	Solvent	Temperature (°C)	Time (h)	Ratio of the products[a]		Yield (%)of **3a**[b]
						E*-3a**:Z*-3a**:**4a**:**6a**	***E*-3a**:***Z*-3a**	
1	LHMDS (1.5)	—	THF	−78 to 0	1	—:—:—:—	—	—[c]
2	NHMDS (1.5)	—	THF	−78 to 0	1	—:—:—:—	—	—[c]
3	KHMDS (1.5)	—	THF	−78 to 0	1	—:—:—:—	—	—[c]
4	LHMDS (1.5)	HMPA (6.0)	THF	−78 to 0	1	59:3:13:25	95:5	42
5	NHMDS (1.5)	HMPA (6.0)	THF	−78 to 0	1	60:3:11:26	95:5	59
6	KHMDS (1.5)	HMPA (6.0)	THF	−78 to 0	1	—:—:—:—	—	—[d]
7	LHMDS (1.5)	—	DMF	−60 to 0	1	78:4:9:9	95:5	64
8	NHMDS (1.5)	—	DMF	−60 to 0	1	79:4:0:17	95:5	73
9	KHMDS (1.5)	—	DMF	−60 to 0	1	—:—:—:—	—	Decomp.
10	NHMDS (3.0)	—	DMF	−60	12	82:3:2:13	96:4	77

[a] The ratio of the products was based on ^{1}H NMR analysis of the crude products.

[b] Isolated yield of the mixture of ***E*-3a** and ***Z*-3a** after silica-gel column chromatography.

[c] Almost no reaction.

[d] An as-yet-unidentified byproduct was obtained.

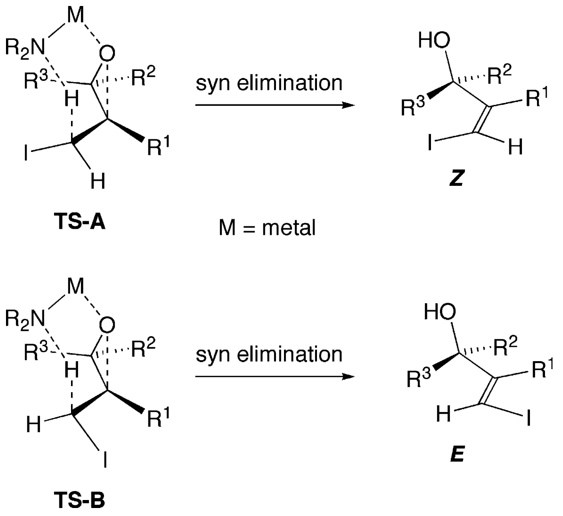


Figure 1. Proposed transition state models for *syn* elimination.

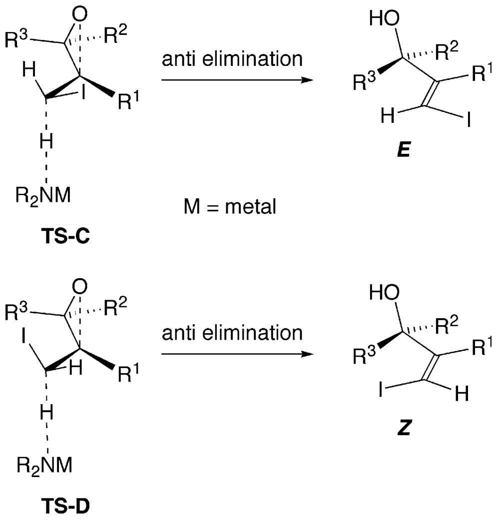


Figure 2. Proposed transition state models for *anti* elimination.

(*anti* elimination) would occur as depicted in Figure 2.[13] Among the two transition state models, **TS-C** would be preferable to **TS-D**; because **TS-D** suffers from a substantial nonbonded interaction between the lone pairs of the oxygen and iodine substituents.

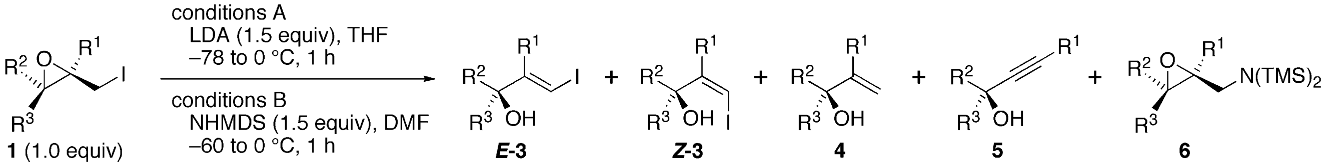
With the reaction conditions suitable for the stereoselective synthesis of *E*- and *Z*-vinyl iodides in hand, the scope of this reaction was investigated with various substrates **1b**–**h**[6] (Table 3). For the structurally similar trisubstituted epoxides **1b**–**f**, good yields and stereoselectivities were obtained (entries 1–10). The 2,2-disubstituted epoxide, which was derived in situ from **1g** by treatment with LiI in THF (rt, 0.5 h) due to the volatility of the corresponding vinyl iodide (entries 11 and 12), and **1h**, having the trityloxymethyl group instead of the methyl group (entries 13 and 14),[14] were also suitable for this reaction.

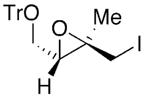
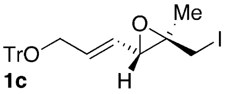
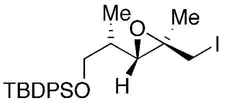
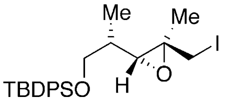
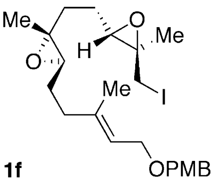
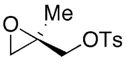
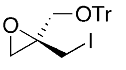
Epoxides having the cis substituent to the iodomethyl group showed a dismissive reactivity under the LDA–THF conditions (Table 4). When the compounds **1i**–**k**[6] were subjected to LDA in THF, *E*-vinyl iodides were preferred over *Z*-vinyl iodides albeit in low isolated yields (entries 1, 3, and 5). This *E*-selectivity would be explained by considering that **TS-B** is sterically preferable to **TS-A** when R^3 is not a hydrogen substituent (Fig. 1). In contrast, under the NHMDS–DMF conditions, the same compounds **1i**–**k** showed an excellent *E*-selectivity with good isolated yields (entries 2, 4, and 6).

3. Conclusion

In summary, we have developed the stereoselective synthesis of both (*E*)- and (*Z*)-3-hydroxy-2-methyl-1-alkenyl

Table 3. Reactions of the substrates **1b–h** under the optimized conditions



Entry	Substrate **1**	Conditions	Ratio of the products[a]		Yield (%) of **3**[b]
			E*-3**:Z*-3**:**4**:**5**:**6**	***E*-3**:***Z*-3**	
1[c]	 **1b**	A	3:79:9:0:—	4:96	80
2		B	92:7:1:—:0	93:7	98
3	 **1c**	A	1:86:6:7:—	1:99	83
4		B	80:6:1:—:13	93:7	62
5	 **1d**	A	2:79:15:4:—	3:97	74
6		B	96:1:3:—:0	99:1	74
7	 **1e**	A	2:83:11:4:—	2:98	76
8		B	96:4:0:—:0	96:4	77
9[d]	 **1f**	A	2:77:11:0:—	3:97	77
10[e]		B	82:4:0:—:14	95:5	83
11[f]	 **1g**	A	2:98:0:0:—	2:98	76
12[f]		B	93:7:0:—:0	93:7	72
13[g,h]	 **1h**	A	2:89:4:0:—	2:98	89
14[h]		B	90:9:1:—:0	91:9	74

[a] The ratio of the products was based on ^{1}H NMR analysis of the crude products.

[b] Isolated yield of the mixture of ***E*-3a** and ***Z*-3a** after silica-gel column chromatography.

[c] The ratio of ***E*-3b**:***Z*-3b**:**4b**:**5b**:**1b** = 3:79:9:0:9.

[d] The ratio of ***E*-3f**:***Z*-3f**:**4f**:**5f**:**1f** = 2:77:11:0:10.

[e] NHMDS (3.0 equiv), DMF, −60 °C, 12 h.

[f] **1g** was in situ converted into iodide (LiI, THF, rt, 0.5 h) before subjecting it to the reaction conditions (2.0 equiv of the base was used).

[g] The ratio of ***E*-3h**:***Z*-3h**:**4h**:**5h**:**1h** = 2:89:4:0:5.

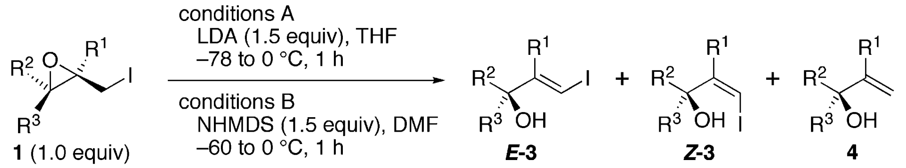
[h] See Ref. 14.

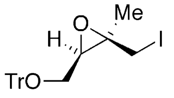
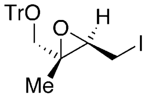
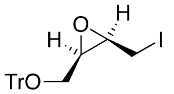
iodides from the same iodomethylated epoxides by using the different bases: NHMDS in DMF for *E*-vinyl iodides and LDA in THF (or LTMP in THF) for *Z*-vinyl iodides. This method will be applicable to natural products syntheses.

4. General procedure

(Table 1, entry 1) To a solution of the iodomethylated epoxide **1a** (100 mg, 0.240 mmol) in dry THF (2.4 mL) was added LDA (1.49 M in heptane/THF/ethylbenzene,

Table 4. Reactions of the substrates **1i–k** under the optimized conditions



Entry	Substrate **1**	Conditions	Ratio of the products[a]		Yield (%) of **3**[b]
			E*-3**:Z*-3**:**4**	***E*-3**:***Z*-3**	
1[c]	 **1i**	A	13:4:62	76:24	17
2		B	94:3:3	97:3	86
3[d]	 **1j**	A	45:0:18	>99:1	35
4		B	>99:0:0	>99:1	96
5[e]	 **1k**	A	26:0:59	>99:1	21
6		B	>99:0:0	>99:1	94

[a] The ratio of the products was based on ^1H NMR analysis of the crude products.

[b] Isolated yield of the mixture of ***E*-3a** and ***Z*-3a** after silica-gel column chromatography.

[c] The ratio of ***E*-3i**:***Z*-3i**:**4i**:**1i** = 13:4:62:21.

[d] The ratio of ***E*-3j**:***Z*-3j**:**4j**:**5j**:**1j** = 45:0:18:15:22.

[e] The ratio of ***E*-3k**:***Z*-3k**:**4k**:**1k** = 26:0:59:15.

0.242 mL, 0.360 mmol) at −78 °C and the mixture was gradually warmed to 0 °C during a period of 1 h. The reaction was quenched by adding satd aq NH_4Cl solution (1.2 mL) at 0 °C and the resulting mixture was extracted with EtOAc (2.4 mL × 3). The extracts were washed with satd aq NaCl solution (2.4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (10 g of silica gel, 3:1 hexane/EtOAc) to afford vinyl iodide **3a** (80.2 mg, 80%) as a 2:98 mixture of *E*- and *Z*-isomers (a pale yellow syrup). ***Z*-3a**, $R_f = 0.34$ (2:1 hexane/ethyl acetate); $[\alpha]_D^{23}$ −28.0 (*c* 2.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.50–1.83 (2H, m), 1.68 (3H, s), 1.87 (3H, d, $J = 1.5$ Hz), 1.98–2.28 (2H, m), 3.80 (3H, s), 4.01 (2H, d, $J = 7.0$ Hz), 4.44 (2H, s), 4.52–4.63 (1H, m), 5.45 (1H, tq, $J = 7.0$, 1.0 Hz), 5.93 (1H, q, $J = 1.5$ Hz), 6.87 (2H, d, $J = 8.6$ Hz), 7.27 (2H, d, $J = 8.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.68, 18.83, 32.27, 35.49, 55.35, 66.34, 71.83, 74.48, 75.54, 113.81, 121.52, 129.51, 130.58, 139.69, 148.57, 159.16; MS (EI) *m/z* 416 (M^+); HRMS (EI) *m/z* calcd for $C_{18}H_{25}O_3I$ (M^+) 416.0849, found 416.0819.

(Table 2, entry 8) To a solution of the iodomethylated epoxide **1a** (105 mg, 0.252 mmol) in dry DMF (2.52 mL) was added NHMDS (1.0 M in THF, 0.378 mL, 0.378 mmol) at −60 °C and the mixture was gradually warmed to 0 °C during a period of 1 h. The reaction was quenched by adding satd aq NH_4Cl solution (1.3 mL) at 0 °C and the resulting mixture was extracted with 1:1 hexane–EtOAc (2.5 mL × 3). The extracts were washed with satd aq NaCl solution (2.5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (10.5 g of silica gel, 3:1 hexane/ethyl acetate) to afford **3a** (76.3 mg, 73%) as a 95:5 mixture of *E*- and *Z*-isomers (a pale yellow syrup). ***E*-3a**, $R_f = 0.34$ (2:1 hexane/ethyl acetate); $[\alpha]_D^{27}$ +4.85 (*c* 2.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.54–1.76 (2H, m), 1.64 (3H, s), 1.79 (3H, d, $J = 1.0$ Hz), 1.92–2.26 (2H, m), 3.80 (3H, s), 3.98 (2H, d, $J = 7.0$ Hz), 4.11 (1H, br t, $J = 6.0$ Hz), 4.43 (2H, s), 5.39 (1H, tq, $J = 7.0$, 1.5 Hz), 6.24 (1H, s), 6.87 (2H, d, $J = 8.6$ Hz), 7.27 (2H, d, $J = 8.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.60, 19.80, 32.82, 35.45, 55.37, 66.29, 71.88, 76.23, 78.55, 113.83, 121.53, 129.52, 130.53, 139.58, 150.04, 159.19; MS (EI) *m/z* 416 (M^+); HRMS (EI) *m/z* calcd for $C_{18}H_{25}O_3I$ (M^+) 416.0849, found 416.0824.

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6. The substrates used in this letter were generally prepared from the corresponding allylic alcohols by epoxidation followed by iodination. Compounds **1a**, **1d**, **1e**, and **1f** are the optically active compounds and the others are racemates.
7. All products were characterized by NMR (^{1}H and ^{13}C) and MS spectra.
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