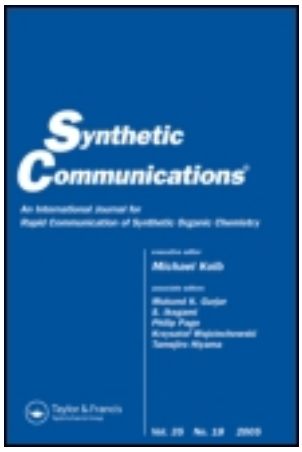

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Mang Wang [a], Lian Xun Gao [a], Wei Yue [a] & Wen Peng Mai [a]

[a] Lab 2, Changchun Institute of Applied Chemistry, Chinese Academy of Science, Changchun, 130022, P.R. China

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Reagent-Controlled Asymmetric Iodolactonization Using Cinchona Alkaloids as Chiral Sources

Mang Wang, Lian Xun Gao,* Wei Yue, and Wen Peng Mai

Lab 2, Changchun Institute of Applied Chemistry, Chinese Academy of Science, Changchun, P.R. China

ABSTRACT

A novel method for reagent-controlled asymmetric iodolactonization of 5-aryl-4-pentenoic acids is reported. This work uses carboxylate ion pairs combined with cinchona alkaloids as chiral sources of carboxylate anion for the first time leading to a mixture of two regio-isomeric iodolactones with moderate enantioselectivity (exo-18.5% ee, endo-35.0% ee) under mild reaction conditions.

Halolactonization of unsaturated acids is a powerful process in synthetic organic chemistry for regio- and stereoselective functionalization of double bonds.[1] Much recent work has centered on asymmetric halolactonization in

*Correspondence: Lian Xun Gao, Lab 2, Changchun Institute of Applied Chemistry, Chinese Academy of Science, Changchun, 130022, P.R. China; E-mail: lxgao@ciac.jl.cn.

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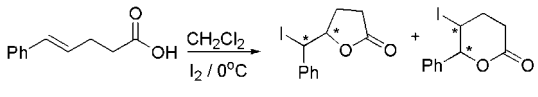
which the one or two new stereo centers are generated and a high degree of chiral induction can be achieved depending on the structure of the substrate.[2] Although this type of substrate-controlled asymmetric induction in this cyclization was well described and applied in the synthesis of natural products,[3] the investigation on reagent-controlled asymmetric halolactonization remained poorly explored. To the best of our knowledge, there are only four examples of reagent-controlled stereoselective halolactonization to date[4,5] and the stereochemistry of this lactonization reaction can be controlled by chiral carboxylate anion[4] and chiral positive halogen ion.[5] In this context, we have developed a new protocol for reagent-controlled asymmetric iodolactonization using cinchona alkaloid-carboxylate ion pairs as chiral sources of carboxylate anion. Here the new experimental results are reported.

As a probe, 5-phenyl-4-pentenoic acid **1a** was treated with iodine and saturated aqueous sodium hydrogen carbonate in CH_2Cl_2 (Sch. 1). An expected competition between the exo mode and the endo mode of cyclization for the formation of lactone was observed.[1a,1c,1d] In fact, a mixture of γ- and δ-lactone was obtained with the ratio of 20 : 80. The major product is the endo-product δ-lactone **3a** (IR 1723 cm^{-1}) due to the electronic factors from the phenyl group at the 5-position of **1a**. This product is not separable from the mixture with its isomer γ-lactone **2a** (IR 1760 cm^{-1}) by chromatography in our experiment. Interestingly, when cinchonidine **4a** was introduced as alkali instead of $NaHCO_3$, the yield ratio of the reaction products **2a** : **3a** was reversed with detectable enantioselectivity. In this case, the endo-product **3a** is not dominant product perhaps resulting from the steric repulsion between the phenyl group and the larger carboxylate ion pair combined with cinchonidine when the carbon at the 5-position is being attacked by the carboxylate anion. The above initial result prompted us to pursue the enantioselective iodolactonization using cinchona alkaloids as chiral sources.

The solvent effect on the selectivity of this reaction was first investigated. Among the solvent tested (Table 1), it was observed that methylene chloride gave the relatively better stereoselectivity for the formation of lactone **2a** and **3a**. Another promising solvent was chloroform, leading to an ee of 8.0% for **2a** and 17.5% for **3a**. Comparatively, when ether, tetrahydrofuran, acetonitrile or



1a		2a		3a
	$NaHCO_3$ aq.	20	:	80
	Cinchonidine 4a	68 (8.0%ee)	:	32 (21.5%ee)

Scheme 1.

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Table 1. Effect of solvent on the stereoselectivity of iodolactonization of **1a** using **4a** as alkali.[a]

Solvent	Reaction time (h)	% Yields **2a** + **3a**[b]	**2a** : **3a**[c]	% ee **2a**[d]	% ee **3a**[d]	% Recovery **4a**
Et_2O	96	80	92 : 8	5.5	15.0	84
THF	45	83	83 : 17	2.5	4.5	87
CH_3CN	70	89	85 : 15	7.0	3.5	99
C_6H_6[e]	95	80	92 : 8	9.0	0	80
CH_2Cl_2	16	100	68 : 32	8.0	21.5	87
$CHCl_3$	18	90	75 : 25	8.0	17.5	86

[a]**1a** (1 mmol), **4a** (1.1 mmol), I_2 (1.5 mmol), 0°C.
[b]Isolated yield.
[c]Determined by ^{1}HNMR.
[d]Determined by ^{1}HNMR with R-(−)-2,2,2-trifloro-1-(9-anthryl) ethanol. The absolute configuration of major enantiomer was not determined.
[e]At room temperature (about 15°C).

benzene were selected as solvent, the iodolactonization need to suffer longer reaction process with lower selectivity. Further optimization of the reaction conditions was then examined by investigating temperature effects. It was found that the temperature (−78°C, −20°C, 0°C and r.t.) had only limited influence on the stereoselectivity of this cyclization. Since higher temperature, such as 30°C or higher, is disadvantageous to the stability of iodolactones, 0°C was chosen as the preferred reaction temperature for iodolactonization.

Several other commercially available cinchona alkaloids were investigated as chiral alkali (Figure 1). From the results described in Table 2, it is found that cinchonidine **4a** and quinine **4d** result in better selectivity than others. Whereas, O-substituted alkaloids **4e** and **4f** do not lead to higher selectivity. In all cases, recoveries of **4** are excellent. Compared with other cinchona alkaloids, when **4b** and **4c** as chiral alkali, the iodolactonization generated the reverse rotation in major enantiomer of products **2a** and **3a**. But the absolute configurations of major enantiomer of **2a** and **3a** were not determined.

Iodolactonization of a number of 5-substituted-4-pentenoic acids (5-substituent-4-pentenoic acids **1a**–**1e** and **1g** were prepared stereoselectively from 1-substituent-propylen-1-ol and triethyl orthoacetete via a Claisen rearrangement followed by basic cleavage of the ethyl ester. About general procedure for Claisen rearrangement, see: Ref.[6]) was then performed successfully (Sch. 2) using **4a** and **4d** as chiral alkali in CH_2Cl_2 at 0°C and the results are summarized in Table 3. Obviously, aromatic substituent at the

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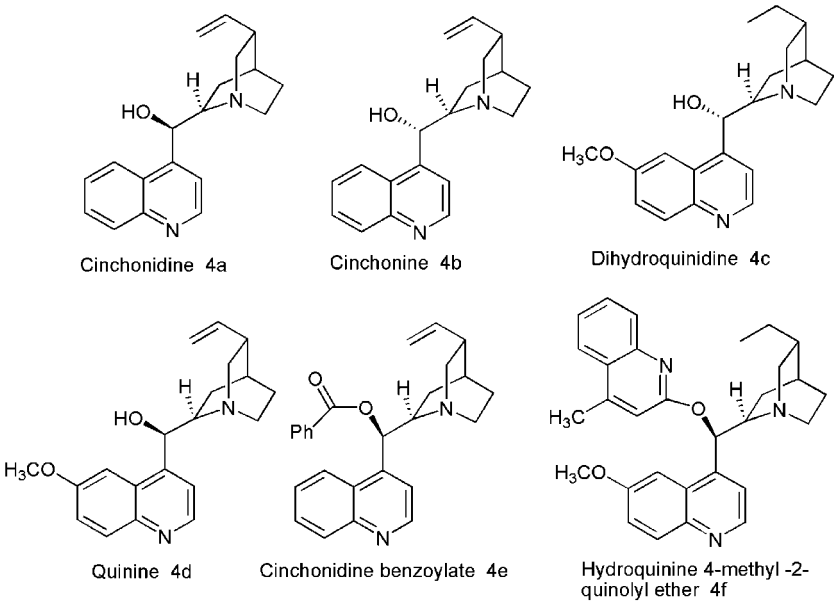

Figure 1.

Table 2. Results of the steroselective iodolactonization of **1a** using different **4** as alkali.[a]

Alkali **4**	Reaction time (h)	% Yields **2a** + **3a**[b]	**2a** : **3a**[c]	% ee **2a**[d]	% ee **3a**[d]	% Recovery **4**
4a	16	100	68 : 32	8.0	21.5	87
4b	18	93	75 : 25	6.0	16.0	90
4c	22	96	84 : 16	2.5	16.0	82
4d	22	100	76 : 24	9.5	28.0	82
4e	36	83	66 : 34	8.5	3.0	98
4f	24	80	82 : 18	7.0	3.5	93

[a]**1a** (1 mmol), **4** (1.1 mmol), CH_2Cl_2, I_2 (1.5 mmol), 0°C.
[b]Isolated yield.
[c]Determined by ^{1}HNMR.
[d]Determined by ^{1}HNMR with R-(−)-2,2,2-trifloro-1-(9-anthryl) ethanol. The absolute configuration of major enantiomer was not determined.

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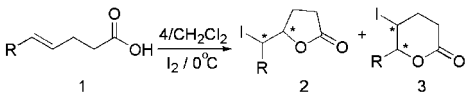

1a, 2a, 3a: R= phenyl; 1b, 2b, 3b: R= *p*-tolyl;
1c, 2c, 3c: R= *o*-tolyl; 1d, 3d: R= anthracen-9-yl;
1e, 2e, 3e: R= *p*-chlorophenyl; 1f, 2f: R=H;
1g, 2g: R= n-propyl

Scheme 2.

5-position of the acids **1** (**1a**–**1e**) is necessary to have the proper selectivity. Unsaturated carboxylic acids (**1f** and **1g**) with hydrogen or an aliphatic substituent at the 5-position only lead to racemic γ-lactones. Table 3 shows that the substrate with strong electron-donating aryl at the 5-position leads to an increase in the ratio of the endo-product to the exo-product during cyclization (entries 4 and 11). Unfortunately, when an aryl with strong electron-withdrawing substituent was introduced to form 5-aryl-4-pentenoic acid, such as pyridinyl, no lactone was detected after five days under the similar reaction conditions. Besides the recovery of the substrate, the reaction

Table 3. Substituted carboxylic acids **1** in iodolactonization reaction.[a]

Entry	Acid **1**	Alkali **4**	Reaction time (h)	% Yields **2** + **3**[b]	**2** : **3**[c]	% ee **2**[d]	% ee **3**[d]	% Recovery **4**
1	**1a**	**4a**	12	100	68 : 32	8.0	21.5	87
2	**1b**	**4a**	8	95	38 : 62	8.5	32.0	95
3	**1c**	**4a**	12	100	65 : 35	18.5	25.5	93
4	**1d**	**4a**	24	33	0 : 100	–	35.0	93
5	**1e**	**4a**	23	89	86 : 14	5.5	25.0	90
6	**1f**	**4a**	7	88	100 : 0	0	–	96
7	**1g**	**4a**	8	86	100 : 0	0	–	98
8	**1a**	**4d**	22	100	76 : 24	9.5	28.0	82
9	**1b**	**4d**	14	93	57 : 43	10.0	32.0	84
10	**1c**	**4d**	16	95	74 : 26	15.0	31.5	90
11	**1d**	**4d**	47	25	0 : 100	–	32.0	92
12	**1e**	**4d**	30	86	83 : 17	11.5	34.0	91
13	**1f**	**4d**	10	90	100 : 0	0	–	94
14	**1g**	**4d**	12	89	100 : 0	0	–	90

[a]**1** (1 mmol), **4** (1.1 mmol), CH_2Cl_2, I_2 (1.5 mmol), 0°C.
[b]Isolated yield.
[c]Determined by ^{1}HNMR.
[d]Determined by ^{1}HNMR with R-(−)-2,2,2-trifloro-1-(9-anthryl) ethanol. The absolute configuration of major enantiomer was not determined.

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resulted in complex mixtures which could not identified by ^{1}H NMR. From the results described in Table 3, it is clear that the ee values of **3** are higher than those of their isomer **2** in all cases. It can be rationally explained that the aryl substituent located at the 5-position can maximize the asymmetric face of the endo-mode cyclization by the steric repulsion with the chiral carboxylate ion pair formed with cinchona.

In conclusion, we have developed a new protocol for reagent-controlled asymmetric iodolactonization. This method uses carboxylate ion pair combined with commercially available cinchona alkaloids as chiral sources of carboxylate anion for the first time leading to a mixture of iodolactonized products with moderate enantioselectivity. Further studies to optimize this reaction are in progress.

EXPERIMENTAL SECTION

IR spectra (KBr) were measured using a Bio-Rad FTS135 spectrometer. The ^{1}H NMR spectra were determined on Bruker spectrometer (300, 400 or 600 MHz) in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on LCQ spectrometer. Elemental analyses were obtained on a VarioEL analyser. Unless otherwise noted materials were obtained from commercially available sources and used without further purification.

General Procedure for Iodolactonization of Acids 1

To a solution of acid **1a**–**1g** (1 mmol) in CH_2Cl_2 (10 mL) was added **4a**–**4f** (1.1 mmol). After stirring for 10 min, iodine (1.5 mmol) was added to this rapidly stirred reaction mixture at 0°C. The flask was protected from light and stirred for 7–47 h at 0°C. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and then quenched with saturated aqueous $Na_2S_2O_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2×60 mL), 2N HCl (2×60 mL) and brine (1×60 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to afford a mixture of two regio-isomeric products (25–100%). The reaction products need to be stored at −20°C protected from light. The ratio of two isomers was determined by ^{1}HNMR. The enantiomeric excess was also confirmed by ^{1}HNMR (600 MHz) spectrum of a mixture of endo- and exo-lactones with R-(−)-2,2,2-trifloro-1-(9-anthryl)ethanol.

The aqueous acidic washes were made basic with NaOH and extracted with CH_2Cl_2.The organic layer was dried over $MgSO_4$, filtered, and evaporated to give recovered 4 (82–98%) as a white solid.

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5-(Iodo-phenyl-methyl)-dihydrofuran-2-one 2a. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.12–2.20$ (m, 1H), 2.53–2.65 (m, 3H), 4.86–4.92 (m, 1H, C*H*O), 5.12 (d, $J = 8.0$ Hz, 1H, C*H*I), 7.27–7.34 (m, 3H), 7.41 (d, $J = 7.6$ Hz, 2H). IR (KBr): 3029, 2940, 1760, 1188 cm^{-1}. MS (EI, 30 eV): m/z (%) 302 (4) [M$^+$], 175 (100), 129 (20), 91 (75). Anal. Calcd. for $C_{11}H_{11}IO_2$: C 43.73 H 3.67, Found: C 43.47 H 3.56. Elemental analyses was obtained with a mixture of two structural isomers **2a** and **3a**.

5-Iodo-6-phenyl-tetrahydro-pyran-2-one 3a. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.30–2.49$ (m, 2H), 2.68–2.76 (m, 1H), 2.82–2.90 (m, 1H), 4.40–4.45 (m, 1H, C*H*I), 5.60 (d, $J = 8.0$ Hz, 1H, C*H*O), 7.32–7.34 (m, 2H), 7.39–7.41 (m, 3H). IR (KBr): 3036, 2950, 1723, 1205 cm^{-1}. MS (EI, 30 eV): m/z (%) 302 (6) [M$^+$], 254 (17), 175 (100), 129 (30), 91 (95). Anal. Calcd. for $C_{11}H_{11}IO_2$: C 43.73 H 3.67, Found: C 43.47 H 3.56. Elemental analyses was obtained with a mixture of two structural isomers **2a** and **3a**.

5-(Iodo-*p*-tolyl-methyl)-dihydro-furan-2-one 2b. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.11–2.18$ (m, 1H), 2.33 (s, 3H, CH_3), 2.52–2.63 (m, 3H), 4.84–4.91 (m, 1H, C*H*O), 5.12 (d, $J = 8.0$ Hz, 1H, C*H*I), 7.12 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H). IR (KBr): 3050, 2989, 1759, 1185, 822 cm^{-1}. MS (EI, 30 eV): m/z (%) 316 (2) [M$^+$], 254 (38), 189 (98), 127 (20), 105 (100). Anal. Calcd. for $C_{12}H_{13}IO_2$: C 45.59 H 4.14, Found: C 45.53 H 3.93. Elemental analyses was obtained with a mixture of two structural isomers **2b** and **3b**.

5-Iodo-6-*p*-tolyl-tetrahydro-pyran-2-one 3b. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.35–2.50$ (m, 2H), 2.39 (s, 3H, CH_3), 2.67–2.77 (m, 1H), 2.81–2.90 (m, 1H), 4.40–4.47 (m, 1H, C*H*I), 5.56 (d, $J = 8.0$ Hz, 1H, C*H*O), 7.23 (s, 4H). IR (KBr): 3031, 2951, 1727, 1201, 1016 cm^{-1}. MS (EI, 30 eV): m/z (%) 316 (2) [M$^+$], 254 (39), 189 (100), 143 (34), 131 (38), 119 (53), 105 (75), 91 (18), 69 (35). Anal. Calcd. for $C_{12}H_{13}IO_2$: C 45.59 H 4.14, Found: C 45.53 H 3.93. Elemental analyses was obtained with a mixture of two structural isomers **2b** and **3b**.

5-(Iodo-*o*-tolyl-methyl)-dihydrofuran-2-one 2c. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.17–2.27$ (m, 1H), 2.35 (s, 3H, CH_3), 2.61–2.67 (m, 2H), 2.71–2.79 (m, 1H), 5.01–5.09 (m, 1H, C*H*O), 5.30 (d, $J = 7.5$ Hz, 1H, C*H*I), 7.12 (d, $J = 7.5$ Hz, 1H), 7.15–7.24 (m, 2H), 7.51 (d, $J = 7.5$ Hz, 1H). IR (KBr): 3050, 2967, 1763, 1199 cm^{-1}. MS (EI, 30 eV): m/z (%) 316 (5) [M$^+$], 189 (70), 105 (100), 91 (18), 55 (30). Anal. Calcd. for $C_{12}H_{13}IO_2$: C 45.59 H 4.14, Found: C 45.75 H 3.94. Elemental analyses was obtained with a mixture of two structural isomers **2c** and **3c**.

5-Iodo-6-*o*-tolyl-tetrahydro-pyran-2-one 3c. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.34–2.46$ (m, 2H), 2.43 (s, 3H, CH_3), 2.74–2.94 (m, 2H), 4.43–4.50 (m, 1H, C*H*I), 5.81 (d, $J = 7.5$ Hz, 1H, C*H*O), 7.20–7.29 (m, 4H). IR (KBr): 3024, 2966, 1719, 1219 cm^{-1}. MS (EI, 30 eV): m/z (%) 316 (4)

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[M^+], 254 (100), 189 (50), 127 (70), 105 (78), 55 (22). Anal. Calcd. for $C_{12}H_{13}IO_2$: C 45.59 H 4.14, Found: C 45.75 H 3.94. Elemental analyses was obtained with a mixture of two structural isomers **2c** and **3c**.

6-Anthracen-9-yl-5-iodo-tetrahydro-pyran-2-one 3d. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.86–3.09$ (m, 4H), 5.33–5.39 (m, 1H, C*H*I), 7.04 (d, $J = 10.5$ Hz, 1H, C*H*O), 7.49 (dd, $J = 6.8$ Hz, $J = 8.5$ Hz, 2H), 7.57 (dd, $J = 6.8$ Hz, $J = 8.5$ Hz, 2H), 8.08 (d, $J = 8.5$ Hz, 2H), 8.30 (d, $J = 8.5$ Hz, 2H), 8.57 (s, 1H). IR (KBr): 3049, 2922, 1728, 1207, 1007, 729 cm^{-1}. MS (EI, 70 eV): m/z (%) 402 (2) [M^+], 191 (100), 178 (32), 127 (38). Anal. Calcd. for $C_{19}H_{15}IO_2$: C 56.74 H 3.76, Found: C 56.56 H 3.69.

5-(*p*-Chloro-phenyl-iodo-methyl)-dihydrofuran-2-one 2e. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.10–2.13$ (m, 1H), 2.56–2.60 (m, 2H), 2.63–2.66 (m, 1H), 4.87–4.91 (m, 1H, C*H*O), 5.05 (d, $J = 8.4$ Hz, 1H, C*H*I), 7.30 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H). IR (KBr): 3040, 2982, 1766, 1494, 1191, 833 cm^{-1}. MS (EI, 30 eV): m/z (%) 337 (2) [M^+], 254 (26), 211 (30), 209 (100), 127 (56), 125 (70), 55 (32). Anal. Calcd. for $C_{11}H_{10}ClIO_2$: C 39.26 H 2.99 Cl 10.66, Found: C 39.68 H 2.82 Cl 11.32. Elemental analyses was obtained with a mixture of two structural isomers **2e** and **3e**.

6-(*P*-Chloro-phenyl)-5-iodo-tetrahydro-pyran-2-one 3e. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.46–2.56$ (m, 2H, CH_2), 2.73–2.84 (m, 2H, CH_2), 4.30–4.38 (m, 1H, C*H*I), 5.50 (d, $J = 8.4$ Hz, 1H, C*H*O), 7.31 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H). IR (KBr): 3063, 2983, 1731, 1201, 1011 cm^{-1}. MS (EI, 30 eV): m/z (%) 339 (8) [$M^+ + 2$], 337 (23) [M^+], 211 (15), 209 (70), 163 (30), 69 (100), 55 (42). Anal. Calcd. for $C_{11}H_{10}ClIO_2$: C 39.26 H 2.99 Cl 10.66, Found: C 39.68 H 2.82 Cl 11.32. Elemental analyses was obtained with a mixture of two structural isomers **2e** and **3e**.

5-(1-Iodo-butyl)-dihydro-furan-2-one 2g. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.4$ Hz, 3H, CH_3), 1.36–1.48 (m, 1H), 1.50–1.86 (m, 3H), 1.95–2.10 (m, 1H), 2.48-2.64 (m, 3H), 4.10–4.16 (m, 1H, C*H*O), 4.34–4.41 (m, 1H, C*H*I). IR (KBr): 2959, 1775, 1457, 1166, 1016 cm^{-1}. MS (EI, 70 eV): m/z (%) 268 (5) (M^+), 141 (89), 85 (100). Anal. Calcd. for $C_8H_{13}IO_2$: C 35.84 H 4.89, Found: C 36.24 H 4.98.

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