Pergamon

Tetrahedron Vol. 50, No. 17, pp. 4957-4972, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0190-5

Ligand Exchange Reaction of Sulfoxides in Organic Synthesis: A Novel Method for Generation of Magnesium Enolates and Its Application to Synthesis of α-Halocarboxylic Acid Derivatives and α-Haloaldehydes

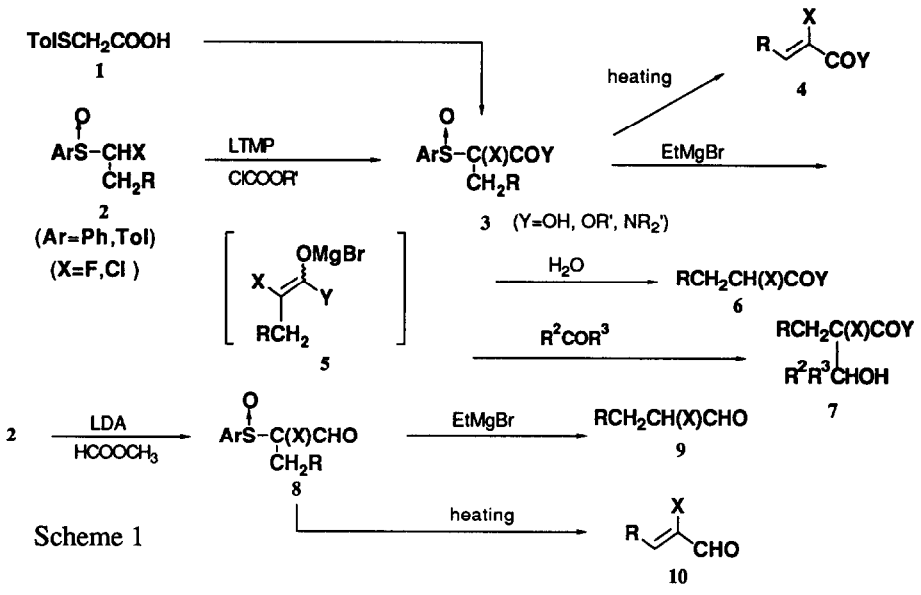
Tsuyoshi Satoh, Yasushi Kitoh, Ken-ichi Onda, Koji Takano, and Koji Yamakawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Abstract: *A new method for synthesis of α-halo(Cl, F)carboxylic acid derivatives and α-haloaldehydes is described. α-Halo-α-sulfinyl carboxylic acid, esters, and α-halo-α-sulfinyl aldehydes were easily prepared from aryl 1-haloalkyl sulfoxides and alkyl chloroformate and ethyl formate, respectively, in good yields. α-Chloro-α-sulfinyl amides were synthesized from (p-tolylthio)acetic acid. Ligand exchange reaction of the sulfinyl group of these acids, esters, amides, and aldehydes with ethylmagnesium bromide gave the magnesium enolates, which were treated with water to give α-halocarboxylic acid derivatives and α-chloroaldehydes in good yields. The magnesium enolates derived from the α-chloro-α-sulfinyl acid derivatives were trapped with carbonyl compounds to afford the adducts, which were transformed to α,β-epoxy carboxylic acid derivatives. Thermal elimination of the sulfinyl group in the α-halo-α-sulfinyl acid derivatives and the α-halo-α-sulfinyl aldehydes gave α-halo-α,β-unsaturated carboxylic acid derivatives and α-halo-α,β-unsaturated aldehydes in high yields.*

α-Halocarboxylic acids and their derivatives,[1] and α-haloaldehydes,[2] including α,β-unsaturated ones, are quite important compounds in organic synthesis. Usually, they are synthesized from the corresponding carboxylic acids and aldehydes by direct halogenation,[1,2] mainly bromination. Direct chlorination of carboxylic acids and aldehydes is less common, and direct fluorination is quite difficult. There are some other methods for preparing α-halocarboxylic acids and α-haloaldehydes; however, methods involving a carbon-carbon bond-forming reaction are limited.

In previous papers, we reported a new method for synthesizing α-haloketones from aldehydes and aryl 1-haloalkyl sulfoxides via the ligand exchange reaction of the sulfinyl group of α-halo α-sulfinylketones with alkylmetals.[3] In continuation of our studies on use of the ligand exchange reaction of sulfoxides in organic synthesis, here we report in detail a novel method for generation of magnesium enolates of α-halocarboxylic acid derivatives and α-chloroaldehydes, and its application to synthesis of several α-halocarboxylic acids and derivatives (**4**, **6**, and **7**) and α-haloaldehydes (**9** and **10**) (Scheme 1).



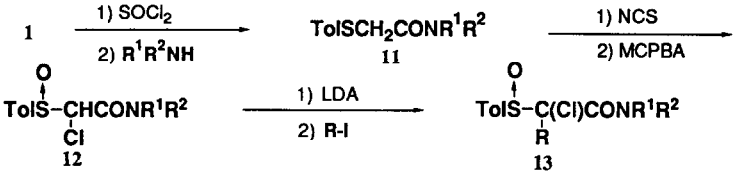
Scheme 1

RESULTS AND DISCUSSION

Synthesis of α-Halo α-Sulfinyl Carboxylic Acid Derivatives.

α-Chloro α-sulfinyl amides **13** were synthesized from (*p*-tolylthio)acetic acid **1** as follows (Table 1). The acid **1** was treated with thionyl chloride to afford the acid chloride, which was reacted with excess amines to give the desired amides **11** in over 90% yields. The amides **11** were chlorinated with NCS in CCl_4 to give α-chloro α-(*p*-tolylthio)amides. Without purification, the sulfides were oxidized to the sulfoxides **12** in moderate to good overall yields. Alkylation of **12** was carried out in the usual way with primary iodoalkanes to give the desired **13** in high yields.

Table 1. Synthesis of α-Chloro α-Sulfinylamides

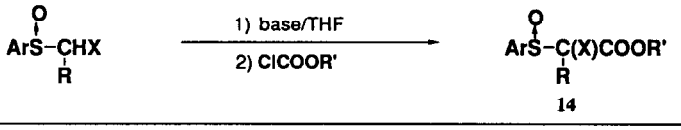


R^1R^2NH	11 (Yield/%)[a]	12 (Yield/%)[a]	R-I	13 (Yield/%)[a]
	11a (98)	12a (83)	$CH_3(CH_2)_2I$	13a (99)
$CH_3(CH_2)_5NH_2$	11b (99)	12b (53)	$CH_3(CH_2)_2I$	13b (91)
$PhCH_2NH_2$	11c (92)	12c (93)	$CH_3(CH_2)_2I$	13c (98)
NH_3[b]	11d (90)	12d (55)	$CH_3(CH_2)_9I$	13d (79)

a) Isolated yield. b) Ammonia in water (29%) was used.

Synthesis of α-chloro- and α-fluoro α-sulfinylesters is shown in Table 2. The procedure is reported for the synthesis of **14a** (entries 1 and 2) as an example. 1-Chloroundecyl *p*-tolyl sulfoxide[5] was treated with lithium diisopropylamide (LDA) in THF at -78 °C followed by ethyl chloroformate. This reaction gave the desired **14a** in 43% yield and a significant amount of *N*,*N*-diisopropylsulfinamide as a by-product. To overcome this problem, a more hindered base, lithium 2,2,6,6,-tetramethylpiperidide (LTMP), was used in this reaction. Fortunately, the reaction worked well to afford **14a** in 73% yield without the sulfinamide. Isobutyl chloroformate showed the same reactivity in the reaction (entry 3).

Table 2. Synthesis of α-Halo α-Sulfinylesters

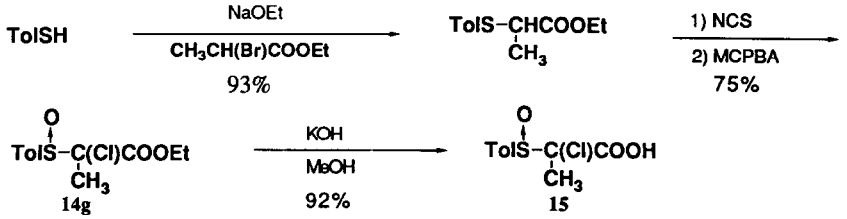


Entry	Ar	R	X	R'	base	14 (Yield/%)
1	Tol	$CH_3(CH_2)_9$	Cl	Et	LDA[a)]	14a (43)
2					LTMP[a)]	14a (73)
3	Tol	$CH_3(CH_2)_9$	Cl	^{i}Bu	LTMP[a)]	14b (72)
4	Tol	$PhCH_2$	Cl	Et	LTMP[a)]	14c (73)
5	Tol	$PhCH_2$	Cl	^{i}Bu	LTMP[a)]	14d (70)
6	Ph	$CH_3(CH_2)_9$	F	Et	LTMP[b)]	14e (62)
7	Ph	$PhCH_2$	F	Et	LTMP[b)]	14f (76)

a) The reactions were carried out in THF at -78°C. b) The reactions were carried out at -100°C

In the case of the reaction with 1-fluoroalkyl phenyl sulfoxide[6] with ethyl chloroformate, the reaction was carried out at -100 °C (entries 6 and 7). When this reaction is carried out at -78 °C, a much lower yield of **14** is obtained.

α-Chloro α-sulfinylester **14** could be synthesized in another way. For example, as shown in Scheme 2, alkylation of *p*-toluenethiol with ethyl 2-bromopropionate gave ethyl 2-(*p*-tolylthio)propionate, which was chlorinated, then oxidized to give **14g** in good overall yield. α-Chloro α-sulfinylcarboxylic acid **15** was easily derived from the ester **14g** by basic hydrolysis.



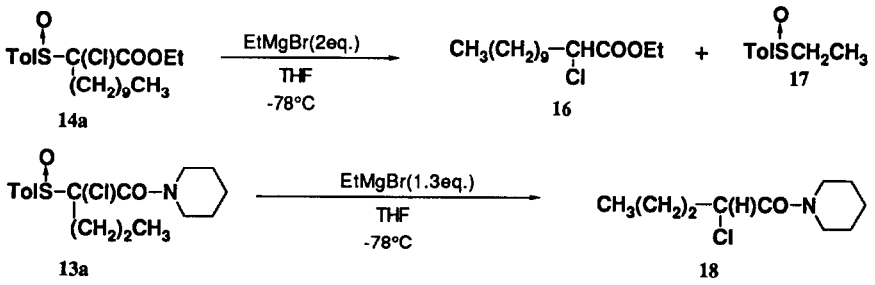
Scheme 2

Synthesis of α-Halocarboxylic Acids and Their Derivatives from α-Halo α-Sulfinyl Carboxylic Acid Derivatives by Ethylmagnesium Bromide-Promoted Desulfinylation and Trapping of the Magnesium Enolate Intermediates with Carbonyl Compounds.

Enolates are one of the most fundamental and versatile intermediates in organic synthesis with carbonyl compounds. The enolates of carbonyl compounds are now easily prepared using bases containing various metals (Li, Mg, Zn, B, Al, etc.).[7]

In our recent papers,[3] we reported a novel method for generation of magnesium enolates from α-halo α-sulfinyl ketones via the ligand exchange reaction of sulfoxides[8] with alkylmetals. We presumed that the ligand exchange reaction would be applicable to α-halo α-sulfinyl carboxylic acid derivatives. If this reaction worked, a new method for generation of magnesium enolates of α-halo carboxylic acids could be achieved.[9]

First of all, α-chloro α-sulfinylester **14a** was treated with two equivalents of EtMgBr in THF at -78 °C for 10 min (Scheme 3). Quite clean reaction took place and the desired α-chloroester **16** was obtained in 91% yield together with ethyl *p*-tolyl sulfoxide **17** (94%). Similarly, α-chloro α-sulfinyl amide **13a** gave the desulfinylated α-chloroamide **18** in slightly lower yield (78%) compared with the ester **16**.



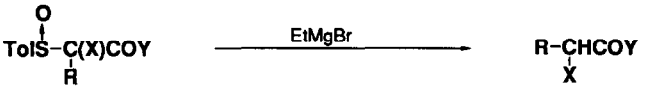
Scheme 3

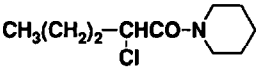
The results for EtMgBr-promoted desulfinylation of α-halo-α-sulfinyl carboxylic acid derivatives are summarized in Table 3. As shown in the table, this ligand exchange reaction takes place with both amides and esters in good yields. Even the carboxylic acid **15** reacted with EtMgBr to afford the desulfinylated product, 2-chloropropionic acid **27** in moderate yield (entry 11). In the case of α-sulfinylamides derived from primary amines and ammonia (**13b-13d**), three equivalents of EtMgBr were required to complete the reaction (entries 2-4). These results indicate that at least one equivalent of EtMgBr was consumed by the acidic hydrogen on the nitrogen.

Esters usually gave better yields than amides (entries 5 and 6); however, when a benzyl group is present on the α-carbon, the yields were lowered (entries 7 and 8). α-Fluoro α-sulfinylesters reacted with EtMgBr to give the desired α-fluoroesters **25** and **26** in moderate yields.

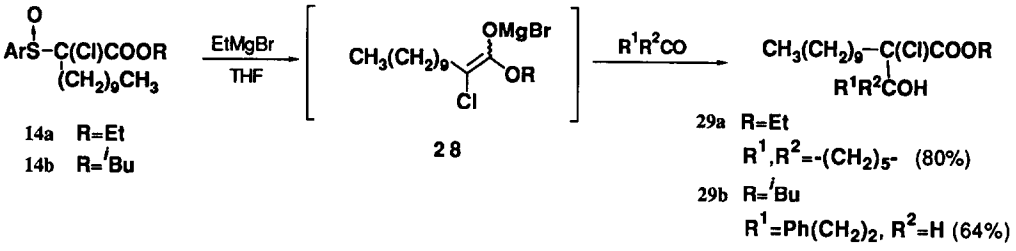
As described above, the ligand exchange reaction of the sulfinyl group of α-halo α-sulfinyl ketones afforded the magnesium enolates.[3] Similarly, the ligand exchange reaction of α-halo α-sulfinyl carboxylic acid derivatives must give the magnesium enolate **28**. Thus, after the treatment of α-chloro α-sulfinyl ester **14a** with EtMgBr, slight excess cyclohexanone was added to the reaction mixture (Scheme 4). This reaction gave the desired adduct **29a** in 80% yield. The magnesium enolate of **14b** reacted with aldehyde to give **29b** in somewhat lower yield.

Table 3. Ethylmagnesium Bromide Promoted Desulfinylation of α-Halo-α-Sulfinyl Amides, Esters, and Acids



Entry		R	X	Y	EtMgBr (equiv.)	α-Halocarboxylic Acid Derivative (Yield/%)
1	13a	$CH_3(CH_2)_2$	Cl		1.3	$CH_3(CH_2)_2$–CHCO–  Cl **18** (78)
2	13b	$CH_3(CH_2)_2$	Cl	$NH(CH_2)_5CH_3$	3.0	$CH_3(CH_2)_2$–CHCO–$NH(CH_2)_5CH_3$ Cl **19** (73)
3	13c	$CH_3(CH_2)_2$	Cl	$NHCH_2Ph$	3.0	$CH_3(CH_2)_2$–CHCO–$NHCH_2Ph$ Cl **20** (80)
4	13d	$CH_3(CH_2)_9$	Cl	NH_2	3.0	$CH_3(CH_2)_9$–CHCO–NH_2 Cl **21** (78)
5	14a	$CH_3(CH_2)_9$	Cl	OCH_2CH_3	2.0	$CH_3(CH_2)_9$–CHCOOCH_2CH_3 Cl **16** (91)
6	14b	$CH_3(CH_2)_9$	Cl	O^iBu	2.0	$CH_3(CH_2)_9$–CHCOO$CH_2CH(CH_3)_2$ Cl **22** (93)
7	14c	$PhCH_2$	Cl	OCH_2CH_3	2.0	$PhCH_2$–CHCOOCH_2CH_3 Cl **23** (72)
8	14d	$PhCH_2$	Cl	O^iBu	2.0	$PhCH_2$–CHCOO$CH_2CH(CH_3)_2$ Cl **24** (67)
9	14e	$CH_3(CH_2)_9$	F	OCH_2CH_3	1.5	$CH_3(CH_2)_9$–CHCOOCH_2CH_3 F **25** (60)
10	14f	$PhCH_2$	F	OCH_2CH_3	1.5	$PhCH_2$–CHCOOCH_2CH_3 F **26** (58)
11	15	CH_3	Cl	H	2.5	CH_3–CHCOOH Cl **27** (67)

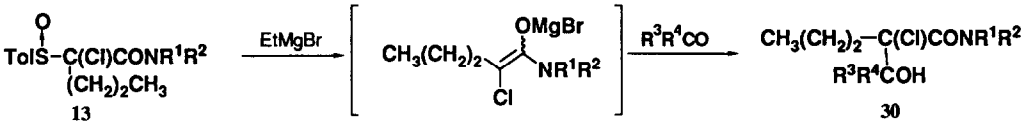
This reaction was applied to the α-fluoro α-sulfinyl ester **14e** with aldehyde. However, the magnesium enolate generated from **14e** gave not the desired adduct but only desulfinylated product **25**.



Scheme 4

Next, this reaction was applied to the α-chloro α-sulfinylamides. The results are shown in Table 4. As shown in the table, the magnesium enolates from α-chloro α-sulfinylamides **13** gave 60-80% yield of the adduct, except for two examples (entries 2 and 5); in these cases, benzophenone is a sterically hindered ketone, and benzyl ethyl ketone is very easily enolizable ketone.

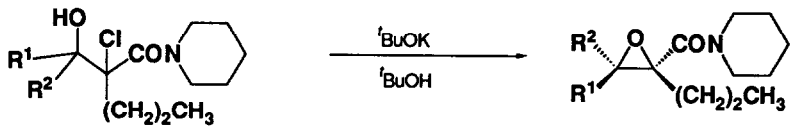
Table 4. Trapping the Magnesium Enolate Intermediate Generated by the Ligand Exchange of Amides **13** with EtMgBr with Carbonyl Compounds



Entry	13		R^3R^4CO		30
	R^1	R^2	R^3	R^4	(Yield/%)[a]
1	-$(CH_2)_5$-		-$(CH_2)_5$-		**30a** (69)
2			Ph	Ph	(0)[b]
3			m-$CH_3OC_6H_4$	H	**30b** (63)
4			Ph	H	**30c** (72)
5			$PhCH_2$	CH_3CH_2	(0)[b]
6	$PhCH_2$	H	-$(CH_2)_5$-		**30d** (72)
7			Ph	H	**30e** (68)
8			$Ph(CH_2)_2$	H	**30f** (66)
9	H	H	-$(CH_2)_5$-		**30g** (76)

a) Isolated yield. b) Desulfinylated α-chloroamide**18** was obtained as a main product after quenching the reaction with sat. aq. NH_4Cl.

As shown in Scheme 4 and Table 4, the adducts, α-chloro α-hydroxyesters and amides, are important intermediates for Darzens-type α,β-epoxy esters and amides.[10] Especially, as α,β-epoxy amide is rare, we tried to make it from the adduct **30a-30c** (Scheme 5).



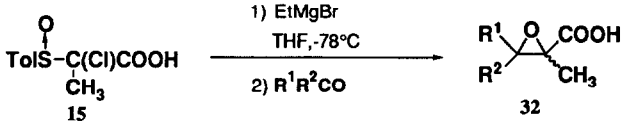
30a R^1,R^2= -$(CH_2)_5$- 31a (84%)
30b R^1=m-$CH_3OC_6H_4$, R^2=H 31b (70%)
30c R^1=Ph, R^2=H 31c (76%)

Scheme 5

Treatment of **30a** in alcohol with aqueous KOH did not give the desired **31a**. Thus, more highly basic conditions, potassium *tert*-butoxide in *tert*-butanol, was applied to **30a**, which gave the desired α,β-epoxy amide **31a** in 84% yield. The same conditions were applied to **30b** and **30c** to give **31b** and **31c** in good yields. The epoxyamides **31b** and **31c** have two chiral centers; however, both were found to be single isomers. The stereochemistry of **31b** and **31c** was determined by NOESY spectrum, as depicted in Scheme 5. This fact indicates that the reaction of the magnesium enolates with carbonyl compounds was highly stereoselective.

The trapping of the magnesium enolates derived from α-chloro α-sulfinyl acid **15** with carbonyl compounds showed somewhat different results compared with the reaction with the esters and amides (Table 5).

Table 5. Synthesis of α,β-Epoxy Carboxylic Acids from **15** and Carbonyl Compounds

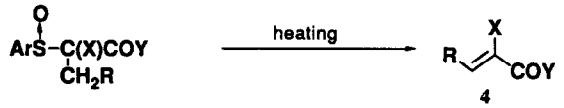


Carbonyl compound		32
R^1	R^2	(Yield/%)[a]
Ph	H	32a (68)
$PhCH_2CH_2$	H	32b (55)
Ph	CH_3	32c (73)
Ph	Ph	32d (81)

a) Isolated yield.

The acid **15** was treated with 2.2 equiv. of EtMgBr followed by benzaldehyde. The product was extracted with 10% NaOH for isolation of the acid. Acidification of the solution and extraction with ether followed by chromatographic purification gave the α,β-epoxy acid **32a** in 68% yield. Obviously, the magnesium enolate generated from **15** reacted with benzaldehyde and the adduct was epoxidized by the basic treatment. The α,β-epoxy acids were obtained from both aldehydes and ketones. Even benzophenone reacted with the magnesium enolate to afford **32d** in good yield.

Sulfoxides are of value to synthesis of olefins via thermal elimination.[11] As α-halo α,β-unsaturated carboxylic acid derivatives are quite important compounds in organic synthesis, we tried to make these compounds from the α-halo α-sulfinylamides and esters (Scheme 6).



13a	Ar=Tol, R=CH_3CH_2 X=Cl, Y= N	4a (77%)
14b	Ar=Tol, R=$CH_3(CH_2)_8$ X=Cl, Y=O^{t}Bu	4b (82%)
14c	Ar=Ph, R=$CH_3(CH_2)_8$ X=F, Y=OEt	4c (75%)
14f	Ar=Ph, R=Ph X=F, Y=OEt	4d (93%)

Scheme 6

First, α-chloro α-sulfinylamide **13a** and ester **14b** were heated in refluxing toluene. Somewhat surprisingly, the thermal elimination totally completed within 10 min to give **4a** and **4b** in good yields. Trost reported 6-14 h heating in refluxing toluene for completion of the thermal elimination of α-sulfinyl esters to α,β-unsaturated esters.[11a] From this fact, it is deduced that the elimination is greatly facilitated by the presence of α-halogen. Similarly, α-fluoro α-sulfinylesters **14e** and **14f** gave α-fluoro α,β-unsaturated esters **4c** and **4d** in good yields by heating in refluxing benzene for 25 min. All α-halo α,β-unsaturated amides and esters (**4a-4d**) have *Z*-stereochemistry, which were determined from ^{1}H NMR spectra (the chemical shift and coupling constants of the vinylic hydrogen).[12] The method described here offers a good way for a synthesis of α-halo α,β-unsaturated carboxylic acid derivatives.

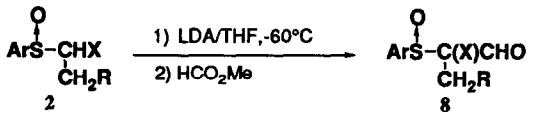
Synthesis of α-Halo α-Sulfinyl Aldehydes and Their Transformation to α-Haloaldehydes via the Ligand Exchange Reaction and Thermal Elimination of the Sulfinyl Group.

As described above, we have achieved synthesis of α-halo carboxylic esters from aryl 1-haloalkyl sulfoxides **2** and alkyl chloroformate (see Scheme 1). Accordingly, we presumed that the reaction could be extended to a new method for synthesis of α-haloaldehydes.

Similar to the synthesis of α-halo α-sulfinylesters, the carbanion of **2** was treated with methyl formate to give the desired α-halo α-sulfinyl aldehyde **8** in good yield. Four representative examples are listed in Table 6. The yields for the synthesis of **8** are usually much better compared with those for the synthesis of α-halo esters (see Table 2).

Next, the ligand exchange reaction of **8** with EtMgBr was carried out. A solution of **8** was added to a solution of EtMgBr in THF at -78 °C. This reaction worked well with α-chloro α-sulfinylaldehydes **8a** and **8b** to afford **9a** and **9b** in good yield; however, α-fluoro compound **8c** and **8d** gave only a complex mixture (Table 7).

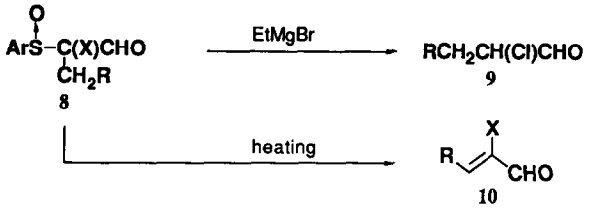
Table 6. Synthesis of α-Halo α-Sulfinyl Aldehydes **8**



2			8
Ar	R	X	Yield/%[a]
Tol	Ph	Cl	8a 73
Tol	$CH_3(CH_2)_8$	Cl	8b 91
Ph	Ph	F	8c 82
Ph	$CH_3(CH_2)_8$	F	8d 95

a) Isolated yield.

Table 7. Synthesis of α-Chloroaldehydes **9** and α,β-Unsaturated Aldehydes **10** from **8**



8			9	10
Ar	R	X	(Yield/%)[a]	(Yield/%)[a]
8a Tol	Ph	Cl	9a (89)	10a (57)[c]
8b Tol	$CH_3(CH_2)_8$	Cl	9b (66)	10b (85)[c]
8c Ph	Ph	F	--[b]	10c (78)[c]
8d Ph	$CH_3(CH_2)_8$	F	--[b]	10d (90)[c]

a) Isolated yield. b) A complex mixture c) Heating in refluxing benzene for 15 min.

The trapping of the magnesium enolate intermediate of the reaction of **8a** and **8b** with carbonyl compounds was tried, but this reaction gave not the desired adducts but the desulfinylated **9a** and **9b**.

Finally, thermal elimination of the sulfinyl group of **8** was carried out in refluxing benzene. Similar to the α-halo α-sulfinylesters and amides, the elimination proceeded quite smoothly to give the α-halo α,β-unsaturated aldehydes **10** in good yield.

In conclusion, we have developed a new method for the generation of magnesium enolates of α-halo carboxylic acid derivatives and α-chloroaldehydes via the ligand exchange reaction of α-halosulfoxides with EtMgBr. These procedures described above offer us a good way for the synthesis of various kinds of α-halo carboxylic acid derivatives and α-haloaldehydes including α,β-unsaturated ones.

EXPERIMENTAL SECTION

All melting points are uncorrected. ^1H NMR spectra were measured in a $CDCl_3$ solution with a JEOL FX-100 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel BW-127 ZH (Fuji-Devison) containing 2% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent, THF was distilled from diphenylketyl, diisopropylamine, 2,2,6,6-tetramethylpiperidine, benzene, and toluene were dried over CaH_2 and distilled.

***N*-[2-(*p*-Tolylthio)ethanoyl]piperidine (11a).** In a dry flask, thioacetic acid **1** (1.63 g; 9.1 mmol) was reacted with thionyl chloride (4 ml; 45.4 mmol) at 80 °C for 1.5 h. The excess thionyl chloride was evaporated under vacuum, and the residue was diluted with dry benzene (10 ml). The solution was cooled to 0 °C and piperidine (2.7 ml; 27.2 mmol) was added dropwise with stirring. After 5 min, the reaction mixture was diluted with AcOEt and the solution was washed with water, dried, and concentrated. The residue was purified by silica gel column chromatography to afford **11a** (2.22 g; 98%) as a colorless oil. IR (neat) 1640 (CO) cm^{-1}; ^1H NMR δ 1.3-1.7 (6H, m), 2.30 (3H, s), 3.3-3.6 (4H, m), 3.68 (2H, s), 7.0-7.4 (4H, m); MS *m/z* (%) 249 (M^+, 57), 216 (4), 126 (32), 112 (100). Found: *m/z* 249.1188. Calcd for $C_{14}H_{19}NOS$: M, 249.1186.

Amides (11b-11d). These amides were synthesized as described for **11a**. **11b**: Colorless oil; IR (neat) 3300 (NH), 1645 (CO) cm^{-1}; ^1H NMR δ 0.85 (3H, t, *J*=7 Hz), 1.0-1.6 (8H, m), 2.30 (3H, s), 3.22 (2H, q, *J*=6 Hz), 3.58 (2H, s), 6.78 (1H, bs), 7.0-7.3 (4H, m); MS *m/z* (%) 265 (M^+, 64), 138 (100). Found: *m/z* 265.1491. Calcd for $C_{15}H_{23}NOS$: M, 256.1499. **11c**: Colorless crystals; mp 80.5-81.5 °C (AcOEt-hexane); IR (KBr) 3340, 3300 (NH), 1645 (CO) cm^{-1}; ^1H NMR δ 2.30 (3H, s), 3.62 (2H, s), 4.39 (2H, d, *J*=6 Hz), 6.9-7.3 (5H, m); MS *m/z* (%) 271 (M^+, 45), 148 (100). Found: C, 70.67; H, 6.24; N, 5.03; S, 11.67%. Calcd for $C_{16}H_{17}NOS$: C, 70.82; H, 6.31; N, 5.61; S, 11.81%. **11d**: Colorless crystals; mp 119-121 °C (AcOEt-hexane); IR (KBr) 3375, 3200 (NH), 1675 (CO) cm^{-1}; ^1H NMR δ 2.30 (3H, s), 3.54 (2H, s) 6.32, 6.64 (each 1H, bs), 7.0-7.3 (4H, m); MS *m/z* (%) 181 (M^+, 100), 137 (95). Found: C, 59.58; H, 6.07; N, 7.65; S, 17.51%. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73; S, 17.69%.

***N*-[2-Chloro-2-(*p*-tolylsulfinyl)ethanoyl]piperidine (12a).** *N*-Chlorosuccinimide (NCS; 660 mg; 4.9 mmol) was added to a solution of **11a** (1.12 g; 4.5 mmol) in 15 ml of CCl_4. The suspension was stirred at room temperature for 1 h. The suspension was filtered and the filtrate was evaporated to give a residue. The residue was dissolved in 15 ml of CH_2Cl_2 and cooled to -60 °C. 3-Chloroperbenzoic acid (5.8 mmol) was added to the solution and the reaction mixture was stirred at -60 to -50 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 and the solution was washed successively with 10% NaOH, H_2O, and sat. aq. NH_4Cl. The product was purified by silica gel column chromatography to afford 1.12 g (83%) of **12a** as colorless amorphous (about 1:1 diastereomeric mixture). IR (KBr) 1650 (CO), 1090, 1065 (SO) cm^{-1}; ^1H NMR δ 1.0-1.8 (6H, m), 2.41, 2.43 (each 1.5H, s), 3.1-3.8 (4H, m), 4.98, 5.09 (each 0.5H, s), 7.2-7.8 (4H, m); MS *m/z* (%) 299 (M^+, 20), 160 (54), 132 (88), 84 (100). Found: *m/z* 299.0753. Calcd for $C_{14}H_{18}ClNO_2S$: M, 299.0746.

α-Chloro α-Sulfinyl Amides (12b-12d). These amides were synthesized as described for **12a**. **12b:** Colorless oil (about 1:1 diastereomeric mixture), IR (neat) 3320 (NH), 1670 (CO), 1090, 1055 (SO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.0-1.8 (8H, m), 2.42 (3H, s), 3.0-3.4 (4H, m), 4.89, 5.23 (each 0.5H, s), 6.42, 6.60 (each 0.5H, bs), 7.1-7.6 (4H, m). **12c**: Colorless amorphous (about 3:1 diastereomeric mixture); IR (KBr) 3300 (NH), 1665 (CO), 1090, 1070 (SO) cm^{-1}; ^1H NMR δ 2.38 (2.3H, s), 2.40 (0.7H, s), 4.30 (1.4H, d, *J*=6 Hz), 4.45 (0.6H, dd, *J*=1, 6 Hz), 4.96 (0.3H, s), 5.25 (0.7H, s), 6.86 (1H, bs), 7.0-7.6 (9H, m); MS *m/z* (%) 321 (M^+, 19), 139 (100). Found: *m/z* 321.0574. Calcd for $C_{16}H_{16}ClNO_2S$: M, 321.0588. **12d**: Colorless amorphous (about 1:1 diastereomeric mixture); IR (KBr) 3400, 3250 (NH), 1670 (CO), 1090, 1055 (SO) cm^{-1}; ^1H NMR (CD_3OD-$CDCl_3$) δ 2.43 (3H, s), 5.01 (0.5H, s), 5.27 (0.5H, s), 7.2-7.7 (4H, m); MS *m/z* (%) 231 (M^+, 7), 155 (5), 139 (100). Found: *m/z* 231.0130. Calcd for $C_9H_{10}ClNO_2S$: M, 231.1290.

***N*-[2-Chloro-2-(*p*-tolylsulfinyl)pentanoyl]piperidine (13a).** A solution of **12a** (600 mg; 2 mmol) in 5 ml of THF was added dropwise with stirring to a solution of LDA (2.4 mmol) at -60 °C. After 10 min, iodopropane (4 mmol) and HMPA (4 mmol) were added. The temperature of the reaction mixture was allowed to warm to 0 °C for 3 h. The reaction was quenched with sat. aq. NH_4Cl and the whole was extracted with AcOEt. The product was purified by silica gel column chromatography to give 660 mg (99%) of **13a** as a colorless oil; IR (neat) 1630 (CO), 1085, 1060 (SO) cm^{-1}; ^1H NMR δ 1.03 (3H, t, *J*=7 Hz), 1.2-2.8 (10H, m),

2.38 (3H, s), 3.1-3.9 (4H, m), 7.1-7.8 (4H, m); MS *m/z* (%) 341 (M^+, 0.6), 289 (1.5), 202 (88), 172 (85), 139 (100). Found: *m/z* 341.1234. Calcd for $C_{17}H_{24}ClNO_2S$: M, 341.1215.

α-Chloro α-Sulfinylamides (13b-13d). These amides were synthesized as described for **13a**. **13b**: Colorless oil; IR (neat) 3360 (NH), 1670 (CO), 1095, 1070 (SO) cm^{-1}; ^1H NMR δ 0.7-1.1 (6H, m), 1.1-1.7 (12H, m), 2.41 (3H, s), 3.21 (2H, t, *J*=7 Hz), 7.1-7.8 (4H, m); MS *m/z* (%) 357 (M^+, 0.8), 337 (4), 218 (63), 43 (100). Found: m/z 357.1524. Calcd for $C_{18}H_{28}ClNO_2S$: M, 357.1527. **13c**: Colorless amorphous; IR (KBr) 3370 (NH), 1675 (CO), 1095, 1070 (SO) cm^{-1}; ^1H NMR δ 0.96 (3H, t, *J*=7 Hz), 1.2-2.0 (4H, m), 2.40 (3H, s), 4.35 (2H, m), 6.8-7.6 (9H, m); MS *m/z* (%) 363 (M^+, 0.6), 278 (0.5), 224 (16), 140 (53), 91 (100). Found: *m/z* 363.1064. Calcd for $C_{19}H_{22}ClNO_2S$: M, 363.1059. **13d:** Colorless oil; IR (neat) 3320 (NH), 1690 (CO), 1095, 1065 (SO) cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.0-1.8 (18H, m), 2.40 (3H, s), 5.95, 6.33 (each 1H, bs), 7.1-7.7 (4H, m); MS *m/z* (%) 371 (M^+, 0.1), 271 (0.1), 196 (28), 139 (68), 106 (100). Found: *m/z* 371.1663. Calcd for $C_{19}H_{30}ClNO_2S$: M, 371.1683.

Ethyl 2-Chloro-2-(*p*-tolylsulfinyl)dodecanoate (14a). A solution of *n*-BuLi (0.38 mmol) in hexane was added to a solution of 2,2,6,6-tetramethylpiperidine (0.38 mmol) in 4 ml of THF at 0 °C under Ar atmosphere. The solution was stirred at 0 °C for 15 min and then cooled to -78 °C. To the solution was added a solution of 1-chloroundecyl *p*-tolyl sulfoxide (113 mg; 0.34 mmol) in 1 ml of THF. After 15 min, ethyl chloroformate (0.48 mmol) was added through a syringe. The reaction mixture was stirred at -78 °C for 15 min and then quenched with sat. aq. NH_4Cl. The whole was extracted with AcOEt and the organic layer was washed successively with 5% HCl, sat. $NaHCO_3$, and sat. NH_4Cl. The product was purified by silica gel column chromatography to give **14a** (107 mg; 73%) as a colorless oil. IR (neat) 1750, 1730 (CO), 1095, 1070 (SO) cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.13 (3H, t, *J*=7 Hz), 1.0-2.1 (18H, m), 2.41 (3H, s), 3.98 (2H, q, *J*=7 Hz), 6.9-7.7 (4H, m); MS *m/z* (%) 400 (M^+, 0.1), 364 (1.5), 309 (1), 140 (100). Found: *m/z* 400.1840. Calcd for $C_{21}H_{33}ClO_3S$: M, 400.1843.

Esters (14b-14f). These esters were synthesized in a similar way as described for **14a**. **14b**: Colorless oil (about 1:1 diastereomeric mixture); IR (neat) 1755, 1735 (CO), 1100, 1075 (SO) cm^{-1}; ^1H NMR δ 0.7-1.0 (9H, m), 1.0-2.2 (19H, m), 2.40 (3H, s), 3.5-4.0 (2H, m), 7.1-7.7 (4H, m); MS *m/z* (%) 428 (M^+, 0.1), 289 (1.5), 57 (100). Found: *m/z* 428.2155. Calcd for $C_{23}H_{37}ClO_3S$: M, 428.2149. **14c**: Colorless oil; IR (neat) 1750, 1725 (CO), 1090, 1070 (SO) cm^{-1}; ^1H NMR δ 1.05 (3H, t, *J*=7 Hz), 2.41 (3H, s), 3.36 (1H, d, *J*=13 Hz), 3.86 (1H, d, *J*=13 Hz), 3.8-4.0 (2H, m), 7.1-7.7 (9H, m); MS *m/z* (%) 350 (M^+, 3), 278 (4), 140 (100). Found: *m/z* 350.0746. Calcd for $C_{18}H_{19}ClO_3S$: M, 350.0742. **14d**: Colorless oil; IR (neat) 1750, 1730 (CO), 1100, 1070 (SO) cm^{-1}; ^1H NMR δ 0.74, 0.77 (each 3H, d, *J*=6 Hz), 1.71 (1H, septet, *J*=6 Hz), 2.39 (3H, s), 3.3-4.1 (4H, m), 7.1-7.7 (9H, m); MS *m/z* (%) 378 (M^+, 4), 238 (44), 182 (100). Found: *m/z* 378.1051. Calcd for $C_{20}H_{23}ClO_3S$: M, 378.1054. **14e**: Colorless oil; IR (neat) 1760, 1725 (CO), 1090, 1060 (SO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.13 (3H, t, *J*=7 Hz), 1.1-2.6 (18H, m), 4.08 (2H, q, *J*=7 Hz), 7.2-7.7 (5H, m); MS *m/z* (%) 370 (M^+, 0.1), 298 (2), 126 (100). Found: *m/z* 370.1976. Calcd for $C_{20}H_{31}FO_3S$: M, 370.1976. **14f**: Colorless oil (about 1:1 diastereomeric mixture); IR (neat) 1765, 1730 (CO), 1090, 1060 (SO) cm^{-1}; ^1H NMR δ 0.93 (2H, t, *J*=7 Hz), 1.05 (1H, t, *J*=7 Hz), 3.3-4.3 (4H, m), 7.1-7.8 (10H, m); MS *m/z* (%) 320 (M^+, 25), 194 (100). Found: *m/z* 320.0873. Calcd for $C_{17}H_{17}FO_3S$: M, 320.0880.

2-Chloro-2-(*p*-tolylsulfinyl)propionic Acid (15). Ethyl ester **14g** was synthesized from ethyl 2-bromopropionate and *p*-toluenethiol in a similar way as described for **12**. **14g**: Colorless oil; IR (neat) 1755 (CO), 1100, 1065 (SO) cm^{-1}. To a solution of **14g** (907 mg; 3.3 mmol) in 12 ml of methanol was added Claisen's alkali[13] (1.6 ml) and the reaction mixture was stirred and heated at 70 °C for 1 h. After cooling, 30 ml of water was added to the reaction mixture and acidified with 10% HCl. The whole mixture was extracted with AcOEt-benzene. The organic layer was washed with water, dried and evaporated to give crystals, which were purified by recrystallization to give 749 mg (92%) of **15** as colorless crystals. Mp 143.5-145 °C; IR (KBr) 1750 (CO), 1085, 1030, 1015 (SO) cm^{-1}; ^1H NMR δ 1.76 (3H, s), 2.42 (3H, s), 7.2-7.7 (4H, m).

Ethyl 2-Chlorododecanoate (16). A solution of **14a** (124 mg; 0.31 mmol) in THF was added dropwise with stirring to a solution of EtMgBr (0.62 mmol) in THF at -78 °C under Ar atmosphere. The reaction mixture was stirred at -78 °C for 10 min and then quenched with sat. aq. NH_4Cl. The whole was extracted with AcOEt and the organic layer was washed once with sat. aq. NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give **16** (74 mg; 91%) as a colorless oil. IR (neat) 1750 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.1-1.6 (16H, m), 1.30 (3H, t, *J*=7 Hz), 1.93 (2H, m), 4.22 (2H, q, *J*=7 Hz), 4.24 (1H, t, *J*=7 Hz); MS *m/z* (%) 262 (M^+, 5), 227 (6), 122 (100). Found: *m/z* 262.1703. Calcd for $C_{14}H_{27}ClO_2$: M, 262.1698.

***N*-(2-Chloropentanoyl)piperidine (18).** Colorless oil; IR (neat) 1655 (CO) cm^{-1}; ^1H NMR δ 0.95 (3H, t, *J*=7 Hz), 1.2-1.8 (8H, m), 1.8-2.2 (2H, m), 3.2-3.8 (4H, m), 4.44 (1H, t, *J*=7 Hz); MS *m/z* (%) 203 (M^+, 7), 168 (68), 161 (70), 126 (63), 112 (100). Found: *m/z* 203.1069. Calcd for $C_{10}H_{18}ClNO$: M, 203.1075.

***N*-Hexyl-2-chloropentanamide (19).** Colorless oil; IR (neat) 3310 (NH), 1655 (CO) cm^{-1}; ^1H NMR δ 0.89, 0.95 (each 3H, t, *J*=7 Hz), 1.1-1.7 (10H, m), 1.8-2.2 (2H, m), 3.26 (2H, q, *J*=7 Hz), 4.34 (1H, dd, *J*=8, 4 Hz), 6.58 (1H, bs); MS *m/z* (%) 219 (M^+, 8), 177 (53), 128 (51), 43 (100). Found: *m/z* 219.1373. Calcd for $C_{11}H_{22}ClNO$: M, 219.1388.

***N*-Benzyl-2-chloropentanamide (20).** Colorless oil; IR (neat) 3310 (NH), 1660 (CO) cm^{-1}; ^1H NMR δ 0.94 (3H, t, *J*=7 Hz), 1.2-1.7 (2H, m), 1.8-2.3 (2H, m), 4.38 (1H, dd, *J*=7, 4 Hz), 4.44 (2H, d, *J*=6 Hz), 6.86 (1H, bs), 7.28 (5H, m); MS *m/z* (%) 225 (M^+, 18), 190 (62), 91 (100). Found: *m/z* 225.0911. Calcd for $C_{12}H_{16}ClNO$: M, 225.0918.

2-Chlorododecanamide (21). Colorless crystals; mp 77.5-78 °C (AcOEt-hexane); IR (KBr) 3420, 3200 (NH), 1655 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.1-1.6 (12H, m), 1.8-2.2 (2H, m), 4.30 (1H, dd, *J*=8, 4 Hz), 6.08, 6.28 (each 1H, bs); MS *m/z* (%) 233 (M^+, 1), 198 (20), 93 (100). Found: C, 61.42; H, 10.41; N, 6.12%. Calcd. for $C_{12}H_{24}ClNO$: C, 61.65; H, 10.35; N, 5.99%.

Isobutyl 2-Chlorododecanoate (22). Colorless oil; IR (neat) 1750 (CO) cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 0.94 (6H, d, *J*=7 Hz), 1.1-1.5 (17H, m), 1.7-2.2 (2H, m), 3.94 (2H, d, *J*=7 Hz), 4.15 (1H, t, *J*=6 Hz); MS *m/z* (%) 290 (M^+, 0.3), 262 (0.3), 246 (1), 57 (100). Found: *m/z* 290.1999. Calcd for $C_{16}H_{31}ClO_2$: M, 290.2010.

Ethyl 2-Chloro-3-phenylpropionate (23). Colorless oil; IR (neat) 1750 (CO) cm^{-1}; ^1H NMR δ 1.20 (3H, t, *J*=7 Hz), 3.25 (2H, m), 4.15 (2H, q, *J*=7 Hz), 4.41 (1H, t, *J*=6 Hz), 7.22 (5H, m); MS *m/z* (%) 210 ($[M-2]^+$, 2), 177 (56), 176 (58), 131 (100).

Isobutyl 2-Chloro-3-phenylpropionate (24). Colorless oil; IR (neat) 1755 (CO) cm^{-1}; ^1H NMR δ 0.86 (6H, d, *J*=7 Hz), 1.89 (1H, m), 3.26 (2H, m), 3.88 (2H, d, *J*=7 Hz), 4.43 (1H, t, *J*=6 Hz), 7.22 (5H, m); MS *m/z* (%) 240 (M^+, 0.7), 238 (2), 149 (100).

Ethyl 2-Fluorododecanoate (25). Colorless oil; IR (neat) 1765, 1740 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.0-2.1 (18H, m), 1.31 (3H, t, *J*=7 Hz), 4.26 (2H, q, *J*=7 Hz), 4.87 (1H, dt, *J*=50, 6 Hz); MS *m/z* (%) 246 (M^+, 52), 175 (48), 106 (100). Found: *m/z* 246.1998. Calcd for $C_{14}H_{27}FO_2$: M, 246.1994.

Ethyl 2-Fluoro-3-phenylpropionate (26). Colorless oil; IR (neat) 1760, 1745 (CO) cm^{-1}; ^1H NMR δ 1.22 (3H, dt, *J*=7, 4 Hz), 3.32 (2H, m), 4.20 (2H, dq, *J*=7, 2 Hz), 5.07 (1H, ddd, *J*=50, 7, 4 Hz), 7.24 (5H, m); MS *m/z* (%) 196 (M^+, 5), 176 (96), 148 (37), 131 (100). Found: *m/z* 196.0883. Calcd for $C_{11}H_{13}FO_2$: M, 196.0898.

Ethyl 2-Chloro-2-(1-hydroxycyclohexyl)dodecanoate (29a). A solution of **14a** (76 mg; 0.19 mmol) in 2 ml of THF was added dropwise with stirring to a solution of EtMgBr (0.23 mmol) in 2 ml of THF at -78 °C under Ar atmosphere. The reaction mixture was stirred for 10 min, then cyclohexanone (0.28 mmol) was added to the mixture. The reaction mixture was stirred for 20 min and quenched with sat. aq. NH_4Cl. The whole was extracted with AcOEt and the organic layer was washed with sat. aq. NH_4Cl. The product was purified by silica gel column chromatography to afford **29a** (55 mg; 80%) as a colorless oil. IR (neat) 3530 (OH), 1755, 1735 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, *t*, J=7 Hz), 1.0-2.8 (28H, m), 1.32 (3H, t, *J*=7 Hz), 4.25 (2H, q, *J*=7 Hz); MS *m/z* (%) 360 (M^+, 0.3), 325 (24), 262 (100). Found: *m/z* 360.2421. Calcd for $C_{20}H_{37}ClO_3$: M, 360.2428.

Isobutyl 2-Chloro-2-(1-hydroxy-3-phenylpropyl)dodecanoate (29b). Colorless oil; IR (neat) 3510 (OH), 1765, 1730 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 0.91 (6H, d, *J*=7 Hz), 1.1-2.2 (23H, m), 2.5-3.1 (2H, m), 3.8-4.0 (2H, m), 7.28 (5H, m); MS *m/z* (%) 424 (M^+, 0.7), 406 (0.7), 371 (10), 91 (100). Found: *m/z* 424.2744. Calcd for $C_{25}H_{41}ClO_3$: M, 424.2742.

***N*-[2-Chloro-2-(1-hydroxycyclohexyl)pentanoyl]piperidine (30a).** Colorless amorphous; IR (KBr) 3480 (OH), 1615 (CO) cm^{-1}; ^1H NMR δ 0.92 (3H, t, *J*=7 Hz), 1.1-2.6 (20H, m), 3.71 (4H, m); MS *m/z*

(%) 301 (M^+, 0.4), 266 (81), 248 (32), 203 (88) 174 (86), 168 (100). Found: m/z 301.1808. Calcd for $C_{16}H_{28}ClNO_2$: M, 301.1807.

***N*-[2-Chloro-2-(hydroxy-3-methoxyphenylmethyl)pentanoyl]piperidine (30b).** Colorless oil; IR (neat) 3450 (OH), 1615 (CO) cm^{-1}; ^1H NMR δ 0.86 (3H, t, *J*=7 Hz), 1.3-2.3 (10H, m), 3.64 (4H, m), 3.79 (3H, s), 5.20 (1H, s), 6.7-7.3 (4H, m); MS *m/z* (%) 339 (M^+, 0.5), 304 (30), 274 (19), 203 (48), 174 (65), 168 (100). Found: *m/z* 339.1603. Calcd for $C_{18}H_{26}ClNO_3$: M, 339.1600.

***N*-[2-Chloro-2-(hydroxybenzyl)pentanoyl]piperidine (30c).** Colorless oil; IR (neat) 3450 (OH), 1615 (CO) cm^{-1}; ^1H NMR δ 0.90 (3H, t, *J*=7 Hz), 1.1-2.4 (10H, m), 3.3-3.8 (4H, m), 5.37 (1H, s), 7.0-7.6 (5H, m); MS *m/z* (%) 301 (M^+, trace), 274 (13), 244 (11), 203 (57), 174 (97), 168 (100). Found: *m/z* 309.1490. Calcd for $C_{17}H_{24}ClNO_2$: M, 309.1494.

***N*-Benzyl-2-chloro-2-(1-hydroxycyclohexyl)pentanamide (30d).** Colorless oil; IR (neat) 3320 (OH), 1665 (CO) cm^{-1}; ^1H NMR δ 0.94 (3H, t, *J*=7 Hz), 1.1-2.5 (14H, m), 4.44 (2H, d, *J*=6 Hz), 7.28 (5H, m); MS *m/z* (%) 225 ($[M-C_6H_{10}O]^+$, 11), 190 (45), 91 (100).

***N*-Benzyl-2-chloro-2-(hydroxybenzyl)pentanamide (30e).** Colorless oil; IR (neat) 3320 (OH), 1640 (CO) cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.0-2.4 (4H, m), 4.39 (1H, s), 4.50 (1H, d, *J*=8 Hz), 4.62 (1H, d, *J*=14 Hz), 7.0-7.8 (10H, m).

***N*-Benzyl-2-chloro-2-(1-hydroxy-3-phenylpropyl)pentanamide (30f).** Colorless oil; IR (neat) 3300 (OH), 1630 (CO) cm^{-1}; ^1H NMR δ 1.05 (3H, t, *J*=7 Hz), 1.5-1.9 (4H, m), 2.0-2.4 (2H, m), 2.5-3.0 (2H, m), 4.44 (2H, t, *J*=6 Hz), 7.0-7.4 (10H, m).

2-Chloro-2-(1-hydroxycyclohexyl)pentanamide (30g). Colorless oil; IR (neat) 3350 (OH), 1660 (CO) cm^{-1}; ^1H NMR δ 0.95 (3H, t, *J*=7 Hz), 1.1-2.7 (14H, m), 6.25, 6.96 (each 1H, bs); MS *m/z* (%) 233 (M^+, 0.1), 198 (70), 135 (96), 106 (100). Found: *m/z* 233.1197. Calcd for $C_{11}H_{20}ClNO_2$: M, 233.1181.

Epoxy Amide (31a). Potassium *tert*-butoxide (33 mg; 0.29 mmol) was added to a solution of **30a** (60 mg; 0.2 mmol) in 2.6 ml of *t*-BuOH and the reaction mixture was stirred at room temperature for 1.2 h. The reaction was quenched by adding powdered NH_4Cl, then the solution was filtered. The filtrate was diluted with AcOEt and the solution was washed with sat. aq. NH_4Cl, dried and evaporated. The product was purified by silica gel column chromatography to afford 44 mg (84%) of **31a** as a colorless oil. IR (neat) 1640 (CO) cm^{-1}; ^1H NMR δ 0.94 (3H, t, *J*=6 Hz), 1.1-2.3 (20H, m), 3.0-4.0 (4H, m); MS *m/z* (%) 265 (M^+, 63), 236 (75), 222 (18), 111 (77), 84 (100). Found: *m/z* 265.2034. Calcd for $C_{16}H_{27}NO_2$: M, 265.2039.

Epoxy Amide (31b). Colorless oil; IR (neat) 1640 (CO) cm^{-1}; ^1H NMR δ 0.81 (3H, t, *J*=7 Hz), 1.2-1.8 (10H, m), 3.4-3.7 (4H, m), 3.80 (4H, s), 4.13 (1H, s), 6.7-7.4 (4H, m); MS *m/z* (%) 303 (M^+, 75), 274 (16), 201 (71), 111 (100). Found: *m/z* 303.1824. Calcd for $C_{18}H_{25}NO_3$: M, 303.1832.

Epoxy Amide (31c). Colorless oil; IR (neat) 1640 (CO) cm^{-1}; ^1H NMR δ 0.80 (3H, t, *J*=7 Hz), 1.2-1.8 (10H, m), 3.4-3.7 (4H, m), 4.16 (1H, s), 7.31 (5H, s); MS *m/z* (%) 273 (M^+, 78), 244 (20), 174 (60), 111 (100). Found: *m/z* 273.1734. Calcd for $C_{17}H_{23}NO_2$: M, 273.1728.

Epoxy Carboxylic Acid (32a). A solution of **15** (134 mg; 0.54 mmol) in 2 ml of THF was added dropwise with stirring to a solution of EtMgBr (1.19 mmol) in 2 ml of THF at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for 10 min, then benzaldehyde (1.36 mmol) was added. The reaction was quenched with sat. aq. NH_4Cl and excess 10% NaOH was added. The water layer was separated and acidified with 10% HCl. The solution was extracted with ether and the organic layer was dried and evaporated. The product was purified by silica gel column chromatography to afford 66 mg (68%) of **32a** as light yellow oil. IR (neat) 1730 (CO) cm^{-1}; ^1H NMR δ 1.34 (3H, s), 4.35 (1H, s). Further characterization was carried out with its methyl ester (by diazomethane). Colorless oil; IR (neat) 1745 (CO) cm^{-1}; ^1H NMR δ 1.31 (3H, s), 3.81 (3H, s), 4.31 (1H, s), 7.30 (5H, m); MS *m/z* (%) 192 (M^+, 0.3), 121 (100). Found: *m/z* 192.0782. Calcd for $C_{11}H_{12}O_3$: M, 192.0785.

Epoxy Carboxylic Acid (32b). Colorless oil (about 1:1 diastereomeric mixture); IR (neat) 1720 (CO) cm^{-1}; ^1H NMR δ 1.42, 1.56 (each 1.5H, s, CH_3). Methyl ester: Colorless oil; IR (neat) 1750 (CO) cm^{-1}; ^1H NMR δ 1.41, 1.52 (each 1.5H, s), 1.7-2.0 (2H, m), 2.6-2.9 (2H, m), 2.94, 3.22 (each 0.5H, t, *J*=6 Hz), 3.68,

3.72 (each 1.5H, s), 7.0-7.4 (5H, m); MS *m/z* (%) 220 (M^+, 0.2), 202 (3), 161 (14), 117 (85), 91 (100). Found: *m/z* 220.1105. Calcd for $C_{13}H_{16}O_3$: M, 220.1099.

Epoxy Carboxylic Acid (32c). Colorless oil; IR (neat) 1740 (CO) cm^{-1}; ^1H NMR δ 1.24, 1.70 (each 3H, s). Methyl ester: Colorless oil; IR (neat) 1755, 1735 (CO) cm^{-1}; ^1H NMR δ 1.19, 1.61, 3.82 (each 3H, s), 7.30 (5H, m); MS *m/z* (%) 206 (M^+, 1), 205 (3), 174 (5), 146 (67), 135 (100). Found: *m/z* 206.0936. Calcd for $C_{12}H_{14}O_3$: M, 206.0942.

Epoxy Carboxylic Acid (32d). Colorless oil; IR (neat) 1730 (CO) cm^{-1}; ^1H NMR δ 1.43 (3H, s), 7.1-7.5 (10H, m); MS *m/z* (%) 254 (M^+, 0.9), 253 (1.5), 210 (55), 167 (100).

(Z)-*N*-(2-Chloro-2-pentenoyl)piperidine (4a). A solution of **13a** (82 mg; 0.24 mmol) in 5 ml of toluene was refluxed for 10 min. The toluene was evaporated and the residue was chromatographed on silica gel to afford 37 mg (77%) of **4a** as a colorless oil. IR (neat) 1640 (CO) cm^{-1}; ^1H NMR δ 1.05 (3H, t, *J*=7 Hz), 1.4-1.8 (6H, m), 2.28 (2H, quintet, *J*=7 Hz), 3.3-3.6 (4H, m), 5.94 (1H, t, *J*=7 Hz); MS *m/z* (%) 201 (M^+, 25), 174 (32), 172 (100). Found: *m/z* 201.0921. Calcd for $C_{10}H_{16}ClNO$: M, 201.0920.

(Z)-Isobutyl 2-Chloro-2-dodecenoate (4b). Colorless oil; IR (neat) 1725 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 0.96 (6H, d, *J*=7 Hz), 1.1-1.6 (14H, m), 2.01 (1H, m), 2.35 (2H, q, *J*=7 Hz), 3.97 (2H, d, *J*=7 Hz), 7.04 (1H, t, *J*=7 Hz); MS *m/z* (%) 288 (M^+, 1), 273 (0.5), 232 (8), 215 (6), 57 (100). Found: *m/z* 288.1856. Calcd for $C_{16}H_{29}ClO_2$: M, 288.1855.

(Z)-Ethyl 2-Fluoro-3-phenylpropenoate (4c). Colorless oil; IR (neat) 1740 (CO) cm^{-1}; ^1H NMR δ 1.38 (3H, t, *J*=7 Hz), 4.34 (2H, q, *J*=7 Hz), 6.90 (1H, d, *J*=35 Hz), 7.2-7.7 (5H, m); MS *m/z* (%) 194 (M^+, 100), 165 (38), 149 (40). Found: *m/z* 194.0735. Calcd for $C_{11}H_{11}FO_2$: M, 194.0742.

(Z)-Ethyl 2-Fluoro-2-dodecenoate (4d). Colorless oil; IR (neat) 1735 (CO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.1-1.6 (14H, m), 1.32 (3H, t, *J*=7 Hz), 2.0-2.4 (2H, m), 4.27 (2H, q, *J*=7 Hz), 6.09 (1H, dt, *J*=34, 7 Hz); MS *m/z* (%) 244 (M^+, 1), 224 (1), 199 (3), 43 (100). Found: *m/z* 244.1837. Calcd for $C_{14}H_{25}FO_2$: M, 244.1837.

2-Chloro-3-phenyl-2-(*p*-tolylsulfinyl)propanal (8a). A solution of 1-chloro-2-phenylethyl *p*-tolyl sulfoxide (578 mg; 2.07 mmol) in 5 ml of dry THF was added to a solution of LDA (3.11 mmol) in 10 ml of THF at -60 °C with stirring. The reaction mixture was stirred at -60 °C for 20 min. Methyl formate (0.39 ml; 6.22 mmol) was added to the solution and the reaction mixture was stirred at -60 °C for 20 min. The reaction was quenched with sat. aq. NH_4Cl and the whole was extracted with AcOEt. The organic layer was washed with sat. aq. NH_4Cl, dried over $MgSO_4$, and evaporated. The product was purified by silica gel column chromatography to give **8a** (462 mg; 73%) as a colorless oil (about 4:1 diastereomeric mixture). IR (neat) 1730 (CO), 1090, 1075 (SO) cm^{-1}; ^1H NMR δ 2.40 (3H, s), 3.60, 3.72 (each 1H, d, *J*=14 Hz), 7.1-8.0 (9H, m), 8.92 (0.8H, s), 9.47 (0.2H, s); MS *m/z* (%) 306 (M^+, 2), 278 (4), 262 (8), 246 (10), 214 (22), 139 (100). Found: *m/z* 306.0477. Calcd for $C_{16}H_{15}ClO_2S$: M, 306.0480.

2-Chloro-2-(*p*-tolylsulfinyl)dodecanal (8b). Colorless oil (about 3:1 diastereomeric mixture); IR (neat) 1730 (CO), 1095, 1070 (SO) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.0-1.8 (18H, m), 2.42 (3H, s), 7.2-7.7 (4H, m), 8.97 (0.75H, s), 9.34 (0.25H, s); MS *m/z* (%) 326 ($[M-HCHO]^+$, 0.07), 278 (4), 246 (53), 123 (100).

2-Fluoro-3-phenyl-2-(phenylsulfinyl)propanal (8c). Colorless oil; IR (neat) 1740 (CO), 1090, 1055 (SO) cm^{-1}; ^1H NMR δ 3.59 (2H, d, *J*=30 Hz), 7.1-7.8 (10H, m), 9.08 (1H, d, *J*=6 Hz); MS *m/z* (%) 276 (M^+, 20), 234 (3), 150 (95), 149 (100). Found: *m/z* 276.0613. Calcd for $C_{15}H_{13}FO_2S$: M, 276.0619.

2-Fluoro-2-(phenylsulfinyl)dodecanal (8d). Colorless oil (about 1:1 diastereomeric mixture); IR (neat) 1730 (CO), 1090, 1070 (SO) cm^{-1}; ^1H NMR δ 0.87 (3H, t, *J*=7 Hz), 1.0-2.5 (18H, m), 7.2-7.7 (5H, m), 9.11 (0.5H, d, *J*=4 Hz), 9.23 (0.5H, d, *J*=7 Hz); MS *m/z* (%) 326 (M^+, 4), 234 (24), 186 (40), 126 (97), 125 (100). Found: *m/z* 326.1718. Calcd for $C_{18}H_{27}FO_2S$: M, 326.1714.

2-Chloro-3-phenylpropanal (9a). Colorless oil; IR (neat) 1740 (CO) cm^{-1}; ^1H NMR δ 3.07 (1H, dd, *J*=16, 8 Hz), 3.35 (1H, dd, *J*=15, 6 Hz), 4.37 (1H, m), 7.1-7.7 (5H, m), 9.50 (1H, d, *J*=3 Hz); MS *m/z* (%) 168 (M^+, 10), 133 (100), 91 (76). Found: *m/z* 168.0341. Calcd for C_9H_9ClO: M, 168.0341.

2-Chlorododecanal (9b). Colorless oil; IR (neat) 1740 (CO) cm^{-1}; ^1H NMR δ 0.97 (3H, t, *J*=7 Hz), 1.0-1.7 (16H, m), 1.7-2.1 (2H, m), 4.14 (1H, m), 9.45 (1H, d, *J*=2 Hz); MS *m/z* (%) 218 (M^+, 6), 165 (8), 140 (38), 41 (100). Found: *m/z* 218.1441. Calcd for $C_{12}H_{23}ClO$: M, 218.1436.

(Z)-2-Chloro-3-phenylpropenal (10a). Colorless oil; IR (neat) 1700 (CO), 1620 (C=C) cm^{-1}; ^1H NMR δ 7.4-7.6 (3H, m), 7.53 (1H, s), 7.8-8.1 (2H, m), 9.48 (1H, s); MS *m/z* (%) 166 (M^+, 100), 138 (13), 103 (55). Found: m/z 166.0182. Calcd for C_9H_7ClO: M, 166.0184.

(Z)-2-Chloro-2-dodecenal (10b). Colorless oil; IR (neat) 1705 (CO), 1630 (C=C) cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J*=7 Hz), 1.0-1.7 (14H, m), 2.52 (2H, q, *J*=7 Hz), 6.87 (1H, t, *J*=7 Hz), 9.33 (1H, s); MS *m/z* (%) 216 (M^+, 2), 181 (6), 172 (12), 129 (26), 41 (100). Found: *m/z* 216.1270. Calcd for $C_{12}H_{21}ClO$: M, 216.1279.

(Z)-2-Fluoro-3-phenylpropenal (10c). Colorless oil; IR (neat) 1695 (CO), 1645 (C=C) cm^{-1}; ^1H NMR δ 6.61 (1H, d, *J*=34 Hz), 7.2-7.8 (5H, m), 9.33 (1H, d, *J*=17 Hz); MS *m/z* (%) 150 (M^+, 100), 149 (98), 122 (25). Found: *m/z* 150.0471. Calcd for C_9H_7FO: M, 150.0480.

(Z)-2-Fluoro-2-dodecenal (10d). Colorless oil; IR (neat) 1710 (CO), 1670 (C=C) cm^{-1}; ^1H NMR δ 0.89 (3H, t, *J*=7 Hz), 1.1-1.8 (14H, m), 2.1-2.5 (2H, m), 5.94 (1H, dt, *J*=32, 8 Hz), 9.19 (1H, d, *J*=18 Hz); MS *m/z* (%) 200 (M^+, 1.6), 169 (3), 95 (45), 88 (100). Found: *m/z* 200.1566. Calcd for $C_{12}H_{21}FO$: M, 200.1575.

Acknowledgments. This study was supported by a Grant-in-Aid for Scientific Research No. 05671771 from the Ministry of Education, Science and Culture, which is gratefully acknowledged. We are grateful to Noriko Sawabe and Fukiko Hasegawa of this laboratory for NMR and MS measurements.

REFERENCES AND NOTES

1. A. Cox, "Comprehensive Organic Chemistry" I. O. Sutherland Ed., Vol 2, pp 719-737, Pergamon Press, Oxford (1979).
2. N. D. Kimpe and R. Verhe, "The Chemistry of α-Haloketone, α-Haloaldehydrs and α-Haloimines" S. Patai and Z. Rappoport Ed., John Wiley and Sons, Chichester (1988).
3. T. Satoh, K. Onda, N. Itoh, and K. Yamakawa, *Tetrahedron Lett.*, **32**, 5599 (1991); T. Satoh, N. Itoh, K. Onda, Y. Kitoh, and K. Yamakawa, *Bull. Chem. Soc. Jpn.*, **68**, 2800 (1992).
4. A part of this study was reported as a communication: T. Satoh, Y. Kitoh, K. Onda, and K. Yamakawa, *Tetrahedron Lett.*, **34**, 2331 (1993).
5. T. Satoh, T. Oohara, Y. Ueda, and K. Yamakawa, *J. Org. Chem.*, **54**, 3130 (1989).
6. S. F. Wnuk and M. J. Robins, *J. Org. Chem.*, **55**, 4757 (1990); M. J. Robins and S. F. Wnuk, *J. Org. Chem.*, **58**, 3800 (1993).
7. T. Mukaiyama, *Org. Reacct.*, **28**, 203 (1982); C. H. Heathcock, "Comprehensive Carbanion Chemistry" Ed. by E. Buncel and T. Durst, Elsevir, Amsterdam: Part B, p. 177 (1984); T. Ishihara, *J. Syn. Org. Chem. Jpn.*, **50**, 347 (1992).
8. T. Satoh, Y. Kaneko, and K. Yamakawa, *Tetrahedron Lett.*, **27**, 2379 (1986); N. Furukawa, T. Shibutani, K. Matsumura, H. Fujihara, and S. Oae, *Tetrahedron Lett.*, **27**, 3899 (1986); T. Satoh, Y. Kaneko, and K. Yamakawa, *Bull. Chem. Soc. Jpn.*, **59**, 2463 (1986); N. Furukawa, T. Shibutani, and H. Fujihara, *Tetrahedron Lett.*, **28**, 2727 (1987); T. Satoh, T. Oohara, Y. Ueda, and K. Yamakawa, *Tetrahedron Lett.*,

29, 313 (1988); T. Satoh, T. Oohara, and K. Yamakawa, *Tetrahedron Lett.*, **29**, 2851 (1988); T. Satoh, T. Oohara, and K. Yamakawa, *Tetrahedron Lett.*, **29**, 4093 (1988); T. Satoh, T. Oohara, Y. Ueda, and K. Yamakawa, *J. Org. Chem.*, **54**, 3130 (1989); T. Satoh, T. Sato, T. Oohara, and K. Yamakawa, *J. Org. Chem.*, **54**, 3973 (1989); P. G. Theobald and W. H. Okamura, *J. Org. Chem.*, **55**, 741 (1990); S. Ogawa and N. Furukawa, *J. Org. Chem.*, **56**, 5723 (1991); N. Furukawa, S. Ogawa, K. Matsumura, and H. Fujihara, *J. Org. Chem.*, **56**, 6341 (1991); S. Oae, "Reviews on Heteroatom Chemistry" Ed. by S. Oae, Vol. 4, p 194, MYU, Tokyo (1991); H. Uno, K. Sakamoto, F. Semba, and H. Suzuki, *Bull. Chem. Soc. Jpn.*, **65**, 210 (1992); H. Uno, K. Sakamoto, and H. Suzuki, *Bull. Chem. Soc. Jpn.*, **65**, 218 (1992); C. Cardellicchio, V. Fiandanse, and F. Naso, *J. Org. Chem.*, **57**, 1718 (1992); C. Cardellicchio, V. Fiandanse, F. Naso, and A. Scilimati *Tetrahedron Lett.*, **33**, 5121 (1992); T. Satoh, Y. Hayashi, and K. Yamakawa, *Bull. Chem. Soc. Jpn.*, **66**, 1866 (1993).

9. Some papers concerning the enolates of carboxylic acid derivatives have been published: M. W. Rathke, *Org. React.*, **22**, 423 (1975); N. Kunieda, J. Nokami, and M. Kinoshita, *Tetrahedron Lett.*, **1974**, 3997; J. Nokami, N. Kunieda, and M. Kinoshita, *Tetrahedron Lett.*, **1975**, 2179; J. Nokami, H. Ohtsuki, Y. Sakamoto, M. Mitsuoka, and N. Kunieda, *Chem. Lett.*, **1992**, 1647.
10. M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 413 (1949); T. Rosen "Comprehensive Organic Synthesis" B. M. Trost, Ed., Vol. 2, pp 409-439, Pergamon Press, Oxford (1991).
11. a) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976); b) B. M. Trost, *Chem. Rev.*, **78**, 363 (1978).
12. R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectroscopic Identification of Organic Compounds" 4th Ed., p 227 and 236, John Wiley and Sons, New York (1981).
13. D. S. Tarbell, J. W. Wilson, and P. E. Fanta, *Org. Syn., Coll. Vol.* **3**, 267 (1955).

(*Received in Japan* 26 *January* 1994; *accepted* 23 *February* 1994)