JOC
The Journal of Organic Chemistry

VOLUME 66, NUMBER 13 JUNE 29, 2001

Articles

Bromolysis and Iodolysis of α,β-Epoxycarboxylic Acids in Water Catalyzed by Indium Halides

David Amantini, Francesco Fringuelli, Ferdinando Pizzo,* and Luigi Vaccaro

Dipartimento di Chimica, Università di Perugia Via Elce di Sotto 8, I-06123 Perugia, Italy

pizzo@unipg.it

Received March 7, 2001

The ring opening of α,β-epoxycarboxylic acids by bromide and iodide ions has been efficiently carried out in water in high regio- and stereoselective fashion. The iodolysis of *trans*-β-monoalkylated epoxycarboxylic acids at pH 4.0 was completely α-regioselective and *anti* diastereoselective. The $InCl_3$-catalyzed iodolysis of a variety of α,β-epoxycarboxylic acids at pH 1.5 gave the corresponding *anti* β-iodohydrins in 88−95% yields. The one-pot synthesis of the α- and β-hydroxyhexanoic acids, starting from the corresponding α,β-epoxycarboxylic acid **1a** by iodolysis followed by reduction of the resulting iodohydrins **4a** and **4b** by $NaBH_4$−$InCl_3$ in water, has been performed.

Introduction

The regio- and stereoselective ring opening of α,β-epoxycarboxylic acids and their esters by halide ions is a reaction of great interest in organic synthesis because it allows the formation of carboxyhalohydrins. These are precursors of a variety of compounds such as α-hydroxy-β-amino- and α-amino-β-hydroxycarboxylic acids and α- and β-hydroxy acids,[1] and these moieties are present in many compounds such as perstatin,[2a] taxol,[2b] KR1-1314,[2c] microgenin,[2d] echinocandin D,[3] telomycin,[4] and myrmicacin[5] that have well-known biological properties.

This topic has not been investigated very much. The only significant examples reported[1,6a−c] concern the bromolysis and iodolysis of α,β-epoxycarboxylic esters in organic solvents. High regioselective nucleophilic attack at C-β of *trans*-α,β-epoxycarboxylic esters was obtained by MgI_2[1b,6b,c] or $MgBr_2$[1a] at rt in diethyl ether, while a prevailing attack at C-α was achieved by using NaI or NaBr/Amberlyst 15 in acetone at −30 °C[6a] or NaI/TMSCl in acetonitrile at −20 °C.[6b] Neither the bromolysis and iodolysis[7] of α,β-epoxycarboxylic acids nor the effective-

* Author to whom correspondence should be addressed. Phone: +39 075 5855546; fax: +39 075 5855560.

(1) (a) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557−3560. (b) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron*: *Asymmetry* **1997**, *8*, 903−907.

(2) (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582. (b) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. (c) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707−2714. (d) Wyvratt, M. J.; Patchett, A. A. *Med. Res. Rev.* **1985**, *5*, 483−531.

(3) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151−7157.

(4) Sheehan, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462−470.

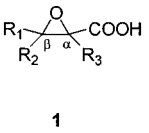
(5) Schildknecht, H.; Koob, K. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 124−125.

(6) (a) Righi, G.; Rumboldt, G.; Bonini, C. *Tetrahedron* **1995**, *51*, 13401−13408 and references therein. (b) Mawson, S. D.; Weavers, R. T. *Tetrahedron* **1995**, *51*, 11257−11270. (c) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4435−4436. (d) Sayama, S.; Inamura, Y. *Chem. Lett.* **1996**, 633−634.

(7) For the production of iodohydrins and bromohydrins from ring opening of epoxides, the terms iodination and bromination have been used.[8] We prefer the terms bromolysis and iodolysis in analogy to the term azidolysis that was used in previous papers concerning the ring opening of the epoxide ring by nucleophilic azido ion attack.[9b,c]

10.1021/jo0156215 CCC: $20.00
Published on Web 06/06/2001

Scheme 1



	a	b	c	d	e	f	g
R_1	H	H	*n*-Pr	H	H	H	H
R_2	*n*-Pr	Me	H	Et	$(CH_2)_4$	Ph	Ph
R_3	H	H	H	Me		H	Me

1

ness of Lewis acid catalysts on these reactions have been previously investigated.

Continuing our research on organic synthesis in aqueous medium[9a−e] and encouraged by the fact that Lewis acid catalyzed azidolysis of α,*β*-epoxycarboxylic acids in pure water occurs with higher yields and selectivity than when it is carried out on the corresponding esters,[9f] we decided to investigate the bromolysis and iodolysis of α,*β*-epoxycarboxylic acids in pure water by using NaBr and NaI as the sources of nucleophiles and $InBr_3$ and $InCl_3$ as the catalysts, respectively.

$InCl_3$ has received much attention in recent years, and its effectiveness in many organic reactions was recently reviewed.[10] To date, $InBr_3$ has not been used much.[11] Both indium salts have been used mainly in organic solvents and rarely in pure water.[10,11]

Results and Discussion

First of all, we investigated the bromolysis of α,*β*-epoxycarboxylic acids **1** (Scheme 1). The results of the reactions to compounds **1a**,**b**,**d**,**e** with NaBr, carried out in pure water at 40 °C at pH 2.0 in the presence of $InBr_3$ (5 and 10 mol %), are illustrated in Table 1. The reactions were also carried out in the absence of $InBr_3$ at the same pH value to evaluate the importance of Brønsted acid catalysis.

$InBr_3$ efficiently catalyzed the bromolysis and promoted the production of the anti *β*-adducts **2**. However, it was difficult to develop a protocol for a wide range of α,*β*-epoxycarboxylic acids, and sometimes, it was difficult to isolate the reaction products from the reaction mixture. Thus, we turned to the iodolysis reaction.

The *trans*-α,*β*-epoxyhexanoic acid **1a** was taken as a model, and it was treated in pure water with NaI[12] (5 mol/equiv) in the presence and in the absence of $InCl_3$ (10 mol %), keeping the pH of the reaction medium constant for the entire reaction time. The control of the pH is fundamental for the success of the reaction (see Experimental Section). The results of experiments carried out at different pH values (7.0, 4.0, 1.5, and 0.0) are illustrated in Figure 1 where the regioselectivity of the reaction, expressed as percentage of *anti*-α-hydroxy-*β*-iodocarboxylic acid **4a** present at the end of the reaction, is correlated with the pH of the aqueous medium.

The $InCl_3$ catalyzed and uncatalyzed reactions did not work at pH 7.0: only 2−3% conversion was observed after 24 h. At pH 4.0, the $InCl_3$ uncatalyzed reaction was complete after 64 h, and only *anti*-*β*-hydroxy-α-iodocarboxylic acid **5a** was quantitatively isolated. At pH 4.0, the $InCl_3$ catalyzed reaction was complete in only 2.5 h and afforded 78% **4a**, 20% *anti*-α,*β*-dihydroxyhexanoic acid (diol),[13] and only 2% of **5a**. At pH 1.5, the Lewis acid uncatalyzed reaction was fast (86% conversion after 3h) but poorly regioselective (**4a**/**5a** = 36/64), while the $InCl_3$ catalyzed iodolysis afforded **4a** exclusively in 0.5 h. At pH 0.0, both $InCl_3$ catalyzed and uncatalyzed reactions occurred very rapidly (0.3 and 0.7 h, respectively) but were unregioselective (**4a**/**5a** = 65/35 and 43/57, respectively). The poor regioselectivity of $InCl_3$ catalyzed iodolysis was due to the competition with Brønsted acid catalysis. Summing up, the regioisomers **4a** and **5a** were isolated quantitatively working in water at pH 1.5 in the presence of 10 mol % $InCl_3$ and at pH 4.0 in the absence of Lewis acid catalyst, respectively.

The investigation was then extended to a variety of mono- and bisubstituited α,*β*-epoxycarboxylic acids **1**. The results are illustrated in Table 2.

In exclusively aqueous medium at pH 1.5 and in the presence of $InCl_3$ (10 mol %), the iodolysis was fast, and in every case, the *β*-iodo derivatives **4** were the sole reaction products and were isolated with 88−95% yields. At pH 1.5, in the absence of $InCl_3$, the reaction is much slower and generally unregioselective, indicating that the competition of Brønsted acid catalysis in the course of Lewis acid catalyzed reaction is modest.

At pH 4.0, in the absence of $InCl_3$, the reactions were generally slow with little conversion. A sole α-regioselectivity was observed for the iodolysis of *trans*-monoalkylated epoxyacids **1a**,**b** (entries 3 and 6), which gave exclusively the *anti*-*β*-hydroxy-α-iodocarboxylic acids **5a**,**b**, respectively. The *cis*-α,*β*-epoxycarboxylic acid **1c** gave a prevalence of α-iodo derivative (entry 9), and the α,*β*-epoxycyclohexane carboxylic acid (**1e)** did not give a reverse regioselectivity with respect to that observed at pH 1.5, either in the absence or in the presence of $InCl_3$ (entries 14−17). The epoxyacids **1d**,**f**,**g** at pH 4.0 gave a complex mixture of products, and a similar behavior was observed for the iodolysis of *β*-methyl-α,*β*-epoxybutyric acid and 2-methyl-1-oxaspiro[5.2]octane-2-carboxylic acid, as already found in the iodolysis of analogous carboxylic esters.[6c]

The behavior of diastereoisomeric *trans*- and *cis*-α,*β*-epoxyhexanoic acids **1a**,**c** gives some indications about the reactive species that regulate the stereochemistry of iodolysis. In the absence of $InCl_3$, on going from pH 4.0 to pH 1.5, the percentage of nucleophilic attack on the *β*-carbon of the oxirane ring increases for both diastereoisomers (Table 2, entries 1,3 and 7,9), while in the presence of $InCl_3$ at pH 1.5, only *β*-selectivity was observed. This means that when the hydrogenionic concentration increases, the Brønsted acid catalysis tends to give the same regioselectivity as Lewis acid catalyzed reactions. The same thing occurred for **1b**. The reason

(8) Sharghi, H.; Naeimi, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1525−1531.

(9) (a) Fringuelli, F.; Piermatti, O.; Pizzo, F. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998; pp 223−249 and 250−261. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **1999**, *64*, 6094−6096. (c) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synlett* **2000**, 311−314. (d) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646−650. (e) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439−455. (f) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 3544−3548.

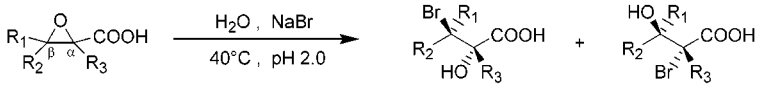
(10) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16−22.

(11) (a) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214−8219. (b) Ceschi, M. A.; de Araujo Felix, L.; Peppe, C. *Tetrahedron Lett.* **2000**, 41, 9695−9699.

(12) The use of LiI, KI, and MgI_2 was also investigated. NaI is the salt that, when the reaction is carried out in the absence of catalyst at pH 1.5 and 40 °C, gives the lowest reaction conversion. All salts investigated, when used in the absence of Lewis acid catalyst, gave mixtures of *β*- and α-iodohydrins (30−70%).

(13) The formation of diol is not the result of hydrolysis of iodohydrin **4a**. It comes from the hydrolysis of epoxyacid **1a**. Indeed, by submitting **4a** to the same reaction conditions used for the iodolysis of **1a**, no diol was detected.

Table 1. Bromolysis of α,β-Epoxycarboxylic Acids 1 in Water with NaBr in the Presence and in the Absence of $InBr_3$



1 (β) **2** (α) **3**

entry	1	cat	time (h)	conv (%)[a]	product	β:α [b]	yield (%)[c]
1	**1a**[d]		1.3	15	**2a** + **3a**	50:50	
2	**1a**[d]		8	94	**2a** + **3a**	50:50	23[e]
3	**1a**[d]	$InBr_3$[f]	1.3	99	**2a**	99:1	78
4	**1b**[d]		0.7	18	**2b** + **3b**	55:45	
5	**1b**[d]		8	98	**2b** + **3b**	55:45	22[g]
6	**1b**[d]	$InBr_3$[f]	0.7	99	**2b**	99:1	80
7	**1d**[h]		0.5	46	**2d**	99:1	
8	**1d**[h]	$InBr_3$[i]	0.5	99	**2d**	99:1	62
9	**1e**[h]		0.3	47	**2e**	95:5	
10	**1e**[h]	$InBr_3$[i]	0.3	99	**2e**[j]	99:1	32

[a] Reaction conversion based on GC analysis of methyl esters. [b] **2**:**3** ratio determined by GC analysis of methyl esters. [c] Yield of isolated main reaction product. The structure of products **2** and **3** was proven by spectroscopic data (see Experimental Section) and by comparison with authentic methyl esters.[1a,6a] [d] NaBr 5 mol/equiv. [e] Yield of **3a**. [f] 10 mol %. [g] Yield of **3b**. [h] NaBr 20 mol/equiv. [i] 5 mol %. [j] 20% diol is present.

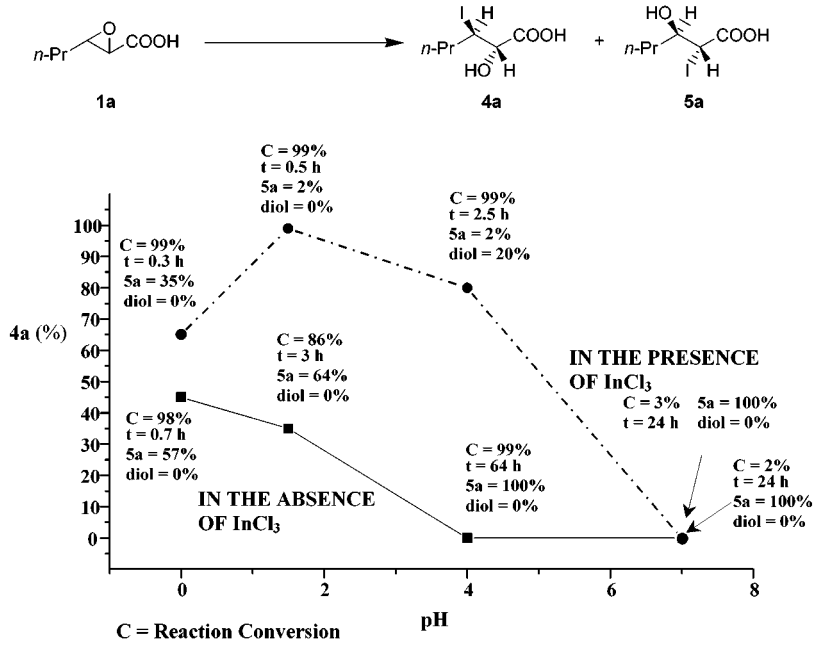


Figure 1. pH dependence of the iodolysis of *trans*-α,β-epoxyhexanoic acid **1a** in the presence and in the absence of $InCl_3$.

of this tendency must await future study. However, a possible explanation could be that in the absence of $InCl_3$ at pH 4.0 and pH 1.5 the reactive species are the unprotonated and the protonated epoxyacid, respectively. In the protonated epoxides, the proton coordinates one oxygen of the carboxylic group and one oxygen of the oxirane ring. In the absence of any coordination (the sodium ion of the nucleophile reagent is a poor Lewis acid), the C-α position of the epoxyacid is preferred for the iodide ion because of electronic effects of the carboxylic functionality.[6a,14] At pH 1.5, electronic effects favor the attack of iodide at the C-β of the proton-complexed oxirane ring.[6c] When the reaction is carried out in the presence of $InCl_3$, the active species is the metal-coordinated epoxyacid. The indium works as an aqua ion,[15] and we retain that it coordinates either the oxygen atoms of the epoxyacid or the iodide ions. The highly regioselective nucleophilic attack at C-β then occurs via direct delivery of iodide from the metal center.[14,16] The iodolysis, therefore, is strongly accelerated and highly β-regioselective. The better results obtained with iodolysis as compared to bromolysis can be justified by considering that iodide is a better nucleophile than bromide for S_N2 reactions in protic solvents.[17] Finally, we have developed a new procedure for the reductive deiodination of carboxyiodohydrins.

While a few selective−reductive debrominations of α-bromocarbonyl and α-bromoacyl compounds are known,[6a,d] to our knowledge, there is only one example of reductive deiodination of α-hydroxy-β-iodocarboxylic

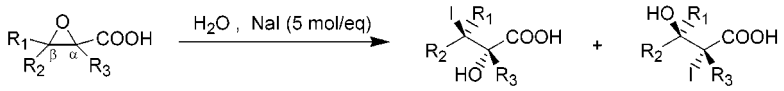
(14) (a) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560−1563. (b) Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645−4650.

(15) (a) Baes, C. F., Jr.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley: New York, 1976. (b) Richens, D. T. *The Chemistry of Aqua Ions*; Wiley: New York, 1997.

(16) (a) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898. (b) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557−1560.

(17) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions Mechanisms and Structures*, 5th ed.; Wiley: New York, 2001.

Table 2. Iodolysis of α,β-Epoxycarboxylic Acids 1 in Water with NaI in the Presence and in the Absence of $InCl_3$

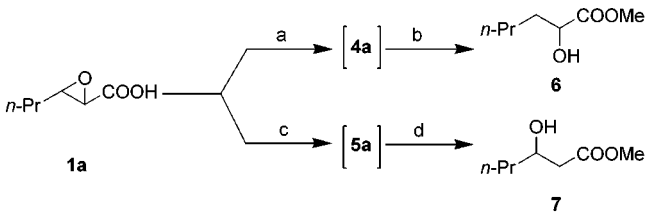


1 (β) 4 (α) 5

entry	1	cat[a]	pH	temp (°C)	time (h)	conv (%)[b]	product	β:α[c]	yield (%)[d]
1	**1a**		1.5	40	0.5	18	**4a** + **5a**	36:64	
2	**1a**	$InCl_3$	1.5	40	0.5	100	**4a**	98:2	93
3	**1a**		4.0	40	64	99	**5a**	1:99	91
4	**1b**		1.5	0	2	18	**4b** +**5b**	31:69	
5	**1b**	$InCl_3$	1.5	0	2	100	**4b**	98:2	94
6	**1b**		4.0	40	8	100	**5b**	1:99	93
7	**1c**		1.5	40	0.5	20	**4c**	99:1	
8	**1c**	$InCl_3$	1.5	40	0.5	100	**4c**	99:1	88
9	**1c**		4.0	40	70	15	**4c** + **5c**	35:65	
10	**1d**		1.5	20	0.5	8	**4d** + **5d**	61:39	
11	**1d**		1.5	20	24	94	**4d** + **5d**	61:39	25[e]
12	**1d**	$InCl_3$	1.5	20	0.5	100	**4d**	99:1	94
13	**1d**		4.0	20	16	*f*	*f*	*f*	
14	**1e**		1.5	0	0.5	12	**4e** + **5e**	87:13	
15	**1e**		1.5	0	9	97	**4e** + **5e**	87:13	7[g]
16	**1e**	$InCl_3$	1.5	0	0.5	100	**4e**	99:1	95
17	**1e**		4.0	0	0.5	8	**4e** + **5e**	80:20	
18	**1f**		1.5	0	0.5	12	**4f**	99:1	
19	**1f**	$InCl_3$	1.5	0	0.5	100	**4f**	99:1	91
20	**1f**		4.0	0	0.5	*f*	*f*	*f*	
21	**1g**		1.5	0	9	5	**4g**	99:1	
22	**1g**	$InCl_3$	1.5	0	9	100	**4g**	99:1	90
23	**1g**		4.0	30	100	*f*	*f*	*f*	

[a] $InCl_3$ 10 mol %. [b] Reaction conversion based on GC analysis of methyl esters. [c] **4**:**5** ratio determined by GC analysis of methyl esters. [d] Yield of isolated main reaction product. The structure of products **4** and **5** was proven by spectroscopic data (see Experimental Section) and by comparison with authentic methyl esters.[1a,6a] [e] Yield of **5d** methyl ester derivative isolated by column chromatography. [f] Mixture of products. [g] Yield of **5e** methyl ester derivative isolated by column chromatography.

Scheme 2[a]



[a] Key: (a) NaI, $InCl_3$, pH 1.5, 40 °C, H_2O; (b) $NaBH_4$, pH 4.5−5.5, rt, CH_2N_2; (c) NaI, pH 4.0, 40 °C, H_2O; (d) $NaBH_4$−$InCl_3$, pH 4.5−5.5, rt, CH_2N_2.

esters that employed tributyltin hydride (TBTH) in hexane.[6c] We have found that the combination of $InCl_3$ with $NaBH_4$ is a reducing system. Therefore, by treating the regioisomers **4a** and **5a**, obtained from the same precursor **1a**, with the $InCl_3$−$NaBH_4$ system, the α-hydroxy- and β-hydroxyhexanoic acids were isolated as methyl esters **6** and **7** with 60 and 79% yield, respectively. Since both the iodolysis and the deiodination reaction were carried out in water, a one-pot procedure for preparing α- and β-hydroxyacids via iodolysis of α,β-epoxyacids was developed. Starting from *trans*-α,β-epoxyhexanoic acid **1a**, the esters **6** and **7** were prepared one-pot with 57 and 74% total yield, respectively (Scheme 2).

In conclusion, *anti*-α-hydroxy-β-iodocarboxylic acids can be easily prepared regio- and stereoselectively with high yields by iodolysis of α,β-epoxycarboxylic acids with NaI performed solely in water at pH 1.5 and catalyzed by 10 mol % $InCl_3$. Iodolysis of trans-β-monoalkyl substituted α,β-epoxycarboxylic acids carried out in pure water at pH 4.0 in the absence of Lewis acids gave a reversed regioselectivity, and *anti*-β-hydroxy-α-iodocarboxylic acids can be isolated quantitatively.

Reductive deiodination of α- and β-hydroxyiodocarboxylic acids can be conveniently carried out by the $InCl_3$−$NaBH_4$ system in pure water, and this allows a one-pot procedure for synthesizing α- and β-hydroxycarboxylic acids via iodolysis of α,β-epoxycarboxylic acids to be performed.

Experimental Section

General Procedures. All chemicals were purchased and used without any further purification. GC analyses were performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter), an "on column" injector system, an FID detector, and hydrogen as the carrier gas. GC/MS analyses were carried out with 70 eV electron energy. The reaction products from the halogenolysis of α,β-epoxycarboxylic acids were analyzed by GC as methyl ester derivatives obtained by treating them with an ether solution of CH_2N_2. ^1H and ^{13}C NMR spectra were recorded at 400, 200, 100.6, and 50.3 MHz, respectively, in CD_3COCD_3 or CD_3OD. IR spectra were recorded with a FTIR instrument using CCl_4 or $CHCl_3$ as solvents. Reactions were carried out at a controlled pH value using a pH-stat apparatus with a combined refillable pH electrode. Column chromatography was performed on silica gel (32−62 μm). All the bromohydrins and iodohydrins herein reported are new compounds and are described in the Supporting Information. Some of these compounds are described as carboxylic esters.[1a,6a] Typical procedure only is reported; more detailed procedures are described in the Supporting Information.

Bromo- and Iodolysis of α,β-Epoxycarboxylic Acids. Typical Procedure. In a flask thermostated at 40 °C and equipped with a magnetic stirrer and pH-stat apparatus, *trans*-α,β-epoxyhexanoic acid **1a** (130 mg, 1.0 mmol) was dissolved in water (2 mL), and while being stirred, powdered NaI (750 mg, 5.0 mmol) was added. In the case of the bromolysis, powdered NaBr (515 mg, 5.0 mmol) was added. The resulting pH value was 1.5, and it was adjusted by adding some drops of a 50% H_2SO_4 aqueous solution or some drops of a 5 M NaOH

aqueous solution until the pH reached the desired value. When the reaction was carried out under catalytic conditions, 200 μL of an aqueous solution of 0.5 M $InBr_3$ or $InCl_3$ (10 mol %) was immediately added. During the reaction, the pH was kept constant at its fixed value by means of a pH-stat by adding a 50% H_2SO_4 aqueous solution. After the end of the reaction, the mixture was cooled to 0 °C and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give the results illustrated in Tables 1 and 2.

One-Pot Synthesis of α-Hydroxyhexanoic Acid Methyl Ester (6). In a flask thermostated at 40 °C and equipped with a magnetic stirrer and pH-stat apparatus, *trans*-α,*β*-epoxyhexanoic acid **1a** (130 mg, 1.0 mmol) was dissolved in water (1.8 mL), and while being stirred, powdered NaI (750 mg, 5.0 mmol) was added. The resulting pH value was about 1.5 and was adjusted to pH 1.8 with 10 μL of 5 M NaOH aqueous solution. A total of 200 μL of an aqueous solution of 0.5 M $InCl_3$ (10 mol %) was added, and the resulting pH value was 1.5. During the reaction, the pH was kept constant at 1.5 by means of a pH-stat by adding a 50% H_2SO_4 aqueous solution. After 30 min, 6 mL of distilled water was added to the reaction mixture. At rt, powdered $NaBH_4$ (190 mg, 5 mmol) was added portionwise in 10 min while the mixture was being stirred. The pH value of the reaction mixture was kept between 4.5 and 5.5. The pH value was adjusted with a 50% H_2SO_4 aqueous solution. After the additions, the reaction mixture was acidified to pH 2.0 by adding a 50% H_2SO_4 aqueous solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product that was treated with an ethereal diazomethane solution. The ethereal solution was evaporated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/Et_2O = 95/5). Pure methyl α-hydroxyhexanoate[18] was obtained with 57% overall yield.

One-Pot Synthesis of *β*-Hydroxyhexanoic Acid Methyl Ester (7). In a flask thermostated at 40 °C and equipped with a magnetic stirrer and pH-stat apparatus, *trans*-α,*β*-epoxyhexanoic acid **1a** (130 mg, 1.0 mmol) was dissolved in water (2 mL). The pH was adjusted to 4.5 by adding some drops of a 5 M NaOH aqueous solution. While the mixture was being stirred, powdered NaI (5.0 mmol) was added, and during the reaction, the pH was kept constant at 4.0 by means of a pH-stat by adding a 50% H_2SO_4 aqueous solution. After 64 h, 4 mL of distilled water and 2 mL of an aqueous solution of 0.5 M $InCl_3$ (1 mol/equiv) were added to the reaction mixture. At rt, powdered $NaBH_4$ (570 mg, 15 mmol) was added portionwise in 10 min while the mixture was being stirred. The pH value of the reaction mixture was kept between 4.5 and 5.5 by adding a 50% H_2SO_4 aqueous solution. At the end of the additions, the reaction mixture was acidified to pH 2.0 by adding a 50% H_2SO_4 aqueous solution, and the reaction mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give a mixture of products that were treated with an ethereal diazomethane solution. The ethereal solution was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O = 95/5). Pure methyl *β*-hydroxyhexanoate[19] was obtained with 74% overall yield.

Acknowledgment. The Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), the Consiglio Nazionale delle Ricerche (CNR), and the Università degli Studi di Perugia are thanked for financial support.

Supporting Information Available: Detailed procedures and descriptions of all bromohydrins and iodohydrins. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0156215

(18) Orito, K.; Seki, Y.; Suginome, H.; Iwadare, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2013−2017.

(19) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *53*, 12469−12486.