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Solvent-Free Organic Reactions on Silica Gel Supports. Facile Transformation of Epoxides to β-Halohydrins with Lithium Halides

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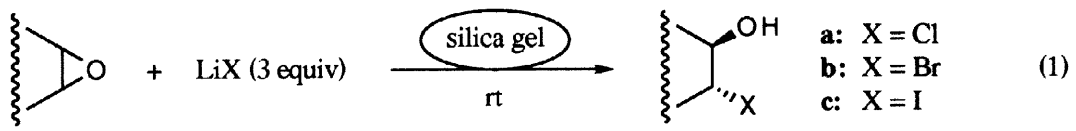
Abstract: The reaction of epoxides with lithium halides was efficiently promoted on the surface of silica gel in the absence of any solvent to give the corresponding β-halohydrins. The reactivity of lithium halides was shown to follow the order LiI > LiBr>> LiCl, and the reactivity of LiCl was dramatically increased by adding an equivalent amount of water to this system. On the other hand, a similar reaction with α,β-epoxyketones produces the α-haloenone derivatives, presumably via halohydrin intermediates. The epoxide-opening reaction of (*R*)-(+)-styrene oxide was also investigated to clarify the stereochemical features of this reaction.

Introduction

Organic reactions on supported reagents have recently received considerable attention from synthetic chemists because of their high efficiency, environmentally benign conditions, and convenient work-up procedures.[1] In particular, silica gel has been shown to be the most useful inorganic solid for effecting a variety of functional group transformations.[1, 2] The catalytic activity of silica gel is now recognized to be the results of water present in this reagent as a form of silicic acid, a so-called Brønsted acid.[1a] One of the major advantages of using silica gel as a supporting reagent is its weakly acidic character (pH 5.5-7.5).[3, 4]

In connection with our general interest in novel ring-opening reactions of epoxides with several nucleophiles, we recently found that aminolysis with amino acid esters and reactions with nitrogen heterocycles are both efficiently catalyzed by silica gel under solvent-free conditions.[5] In view of the great utility of epoxides as synthetic intermediates in organic chemistry,[6] it may be worthwhile to explore the versatility of silica gel-catalyzed epoxide-opening reactions with some other nucleophiles. In this paper, we describe results that successfully led to the development of a novel, simple method for the transformation of epoxides to β-halohydrins[7] using lithium halides supported on silica gel (eq. 1).[8, 9]



a: X = Cl
b: X = Br
c: X = I

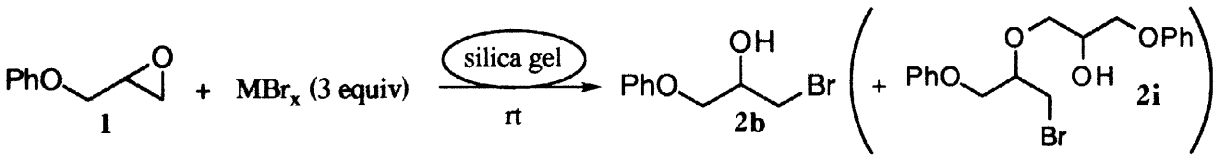
(1)

PII: S0040-4020(98)00050-7

Results and Discussion

To determine the optimum conditions, we first investigated the conversion of phenyl glycidyl ether (**1**) to the corresponding bromohydrin **2b** in the presence of a variety of metal bromides. As expected, commercial-grade chromatography silica gel (Wakogel C-300, 250 mg per mmol of epoxide)[10] and 3 equiv of metal bromide effectively triggered the desired reaction at room temperature (Table 1).

Table 1. Formation of Bromohydrin **2b** from Phenyl Glycidyl Ether (**1**) and Metal Bromides



Entry	MBr_x	Reaction Time, h	Yield, %[a]
1	LiBr • H_2O	1	100
2[b]	LiBr • H_2O	22	100
3[c]	LiBr • H_2O	48	44[d]
4	NaBr	720	24 (73)
5	KBr	168	16 (59)[e]
6	CsBr	48	No reaction
7	$MgBr_2$ • $6H_2O$	3	100
8	$CuBr_2$	240	71 (19)

[a] Isolated yield. Yields in parentheses are the corresponding diol. [b] In CH_2Cl_2 solution.
[c] Without using silica gel. [d] 25% recovery and 20% dimer (**2i**). [e] 19% recovery.

For present purposes, LiBr was the best choice from among several metal bromides, and **2b** was obtained quantitatively within 1 h (Table 1, entry 1). Comparable reactivity was also observed with $MgBr_2$ (Table 1, entry 7). Although silica gel showed a moderate catalytic activity in dichloromethane solution, the reaction was extremely slow (Table 1, entry 2). In a separate experiment, after standing for 48 h at room temperature, direct exposure of **1** to LiBr produced a rather complex mixture: **2b** was isolated from this mixture in 44% yield, along with 25% of the starting material and 20% of dimer **2i**[11] (Table 1, entry 3). Interestingly, when other salts like NaBr, KBr, and $CuBr_2$, which have no hydrate form, were used, a considerable amount of the hydrolyzed compound was obtained as a byproduct (Table 1, entries 4, 5, and 8).[12]

To clarify the effect of a wet environment, this reaction was also carried out under strictly anhydrous conditions. The use of dry LiBr and freshly dried silica gel (120 °C, 1 day) resulted in complete recovery of the starting material even after standing overnight. Since the Li^+ ion has an exceptionally high hydration energy,[13] the water molecules in LiBr could conceivably loosen the ion pairing of Li^+—Br^-, leading to an increase in the nucleophilicity of the bromide anion. In addition, a small amount of physisorbed water on the surface of silica gel also facilitates coordination of the acidic silanol groups with the dispersed LiBr through hydrogen bonding. This effectively polarizes the Li^+—Br^- bond.[4, 14] Based on these considerations, we concluded that *the use of silica gel under solvent-free conditions and the presence of water in both LiBr and silica gel played an essential role in promoting this type of epoxide ring-opening reaction.*

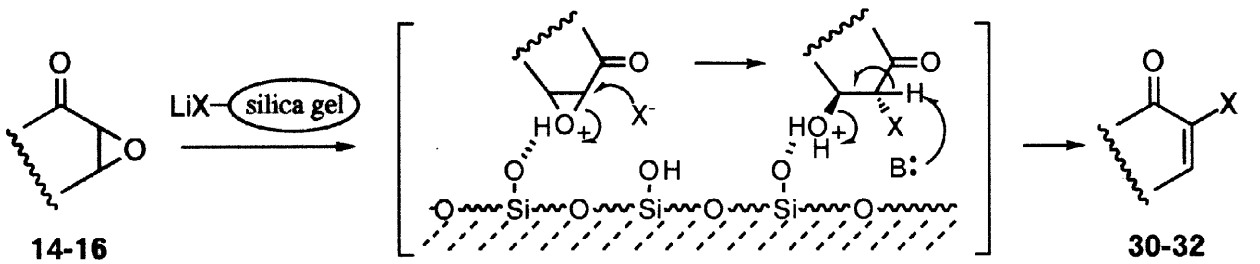
The general applicability of this procedure was clarified for a variety of epoxides, as summarized in Table 2. In most cases, the reaction proceeded smoothly to give the desired halohydrin derivatives in high yields. Due to the low reactivity of lithium chloride, concomitant hydrolysis of epoxides was observed (Table 2, entry 1). This difficulty was overcome by adding an equivalent amount of water to lithium chloride, and the reaction was complete within a shorter reaction period (Table 2, entry 2). It should be emphasized that a precise amount of water is required to produce optimal results; otherwise, the hydrolysis side-reaction is not suppressed.[15] In contrast, lithium iodide was sufficiently reactive and the desired iodohydrins were readily formed in excellent yields at room temperature. These results demonstrate that the reactivity of lithium halides definitely follows the order LiI > LiBr >> LiCl, which is in good agreement with previous observations.[8c]

A systematic survey of reactions using a series of aliphatic epoxides **3**, **4**, and **5** revealed an important aspect of this procedure (Table 2, entries 4-12). Thus, whereas 1-hexene oxide (**3**) and 1-decene oxide (**4**) showed normal reactivity, a large decrease in the reaction rate was observed for the reaction of 1-hexadecene oxide (**5**). The reaction with lithium chloride or lithium bromide took almost two weeks for completion (Table 2, entries 10 and 11). Treatment of **5** with lithium iodide gave iodohydrin **19c** in 84% yield after 4 days along with a small amount of 2-hexadecanone (8%) via an epoxide-carbonyl rearrangement (Table 2, entry 12).[16] Apparently, increasing the size of the hydrophobic side chain severely hinders the easy access of epoxides to the silica gel surface. Similar behavior was observed for cyclooctene oxide (**12**), where no product was formed even with lithium iodide (Table 2, entry 31).

For the terminal epoxides such as **1-6**, **9**, and **10**, the ring-opening reaction was highly regioselective and gave the corresponding 1-halo-2-alkanols, indicating that halide anions attacked predominantly from the less-hindered side (Table 2, entries 1-15 and 22-27). The only exception was styrene oxide (**7**), from which 2-halo-2-phenylethanols (**22**) were produced in appreciable amounts,[17] which suggests that preferential cleavage of the benzylic C-O bond provided a stabilized benzylic cation species during the reaction (Table 2, entries 16-18). For the reaction of benzoate **6** with lithium iodide, a very small amount of benzoyl migration was observed (Table 2, entry 15). The successful results for **10** and **13** demonstrate the feasibility of this method for acid-sensitive substrates with an acetonide function (Table 2, entries 25-27 and 32-34). The normal *trans*-opening stereochemistry was demonstrated for cyclic epoxides **11** and **13** (Table 2, entries 28-30 and 32-34).[6]

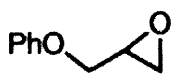
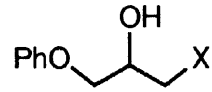
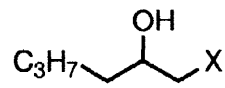
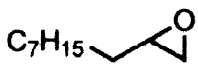
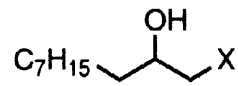
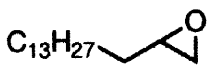
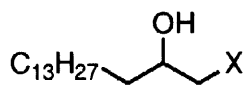
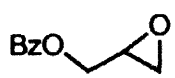
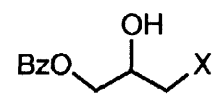
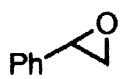
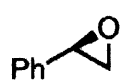
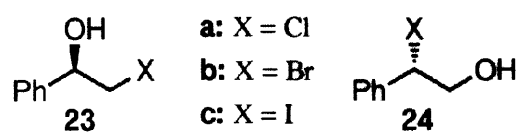
Interestingly, α,β-epoxyketones such as **14-16** produced α-haloenone derivatives in moderate yields along with unidentified minor byproducts (Table 2, entries 35-43). These results can be explained by the mechanism depicted in Scheme 1.

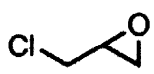
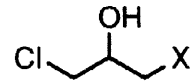
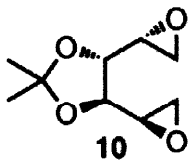
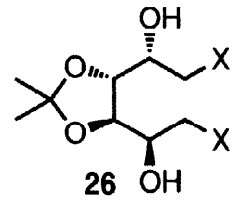
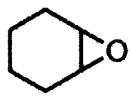
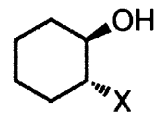
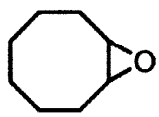
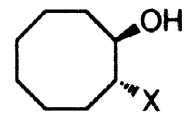
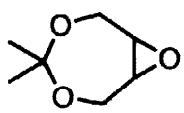
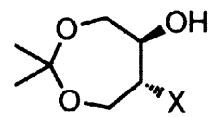
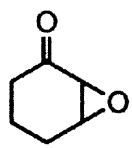
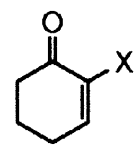
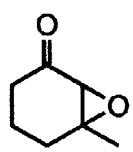
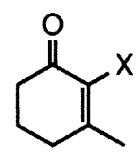
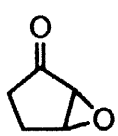
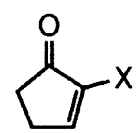
Scheme 1



On the silica gel surface, halide anions first regioselectively attack the α-carbon of the epoxide to produce the corresponding halohydrin intermediates, which are then spontaneously dehydrated to give the enone products

Table 2. Reaction of Epoxides with Silica Gel-Supported Lithium Halides[a]

Entry	Epoxide	LiX	Time	Product(s)		Yield, %[b]
1		LiCl	22 days		**a:** X = Cl	50 (33)
2		LiCl + H_2O	6 days		**a:** X = Cl	91
3	**1**	LiI	15 min	**2**	**c:** X = I	96
4		LiCl + H_2O	17 h		**a:** X = Cl	76
5		LiBr•H_2O	6 h		**b:** X = Br	75
6	**3**	LiI	15 min	**17**	**c:** X = I	74
7		LiCl + H_2O	12 days		**a:** X = Cl	97
8		LiBr•H_2O	19 h		**b:** X = Br	97
9	**4**	LiI	15 min	**18**	**c:** X = I	97
10		LiCl + H_2O	15 days		**a:** X = Cl	91
11		LiBr•H_2O	14 days		**b:** X = Br	88
12	**5**	LiI	4 days	**19**	**c:** X = I	84[c]
13		LiCl + H_2O	34 h		**a:** X = Cl	95
14		LiBr•H_2O	3 h		**b:** X = Br	90
15	**6**	LiI	15 min	**20**	**c:** X = I	81[d]
						
	7			**21** **22**		
16		LiCl + H_2O	5 days	**a:** X = Cl (21 : 79)		80 (1)[e]
17		LiBr•H_2O	3 h	**b:** X = Br (36 : 64)		91[e]
18		LiI	3 h	**c:** X = I (47 : 53)		96[e]
						
	8			**23** **a:** X = Cl **b:** X = Br **c:** X = I **24**		
19		LiCl + H_2O	7 days	(100% ee)[f]	23 : 77 (18% ee)[f]	76 (5)[e]
20		LiBr•H_2O	5 h	(100% ee)[f]	47 : 53 (76% ee)[f]	81[e]
21		LiI	2 h	(84% ee)[f]	59 : 41 (0% ee)[f]	79[e]

22		$LiCl + H_2O$	4 days		**a:** X = Cl	95
23		$LiBr{\bullet}H_2O$	1 h		**b:** X = Br	73
24	**9**	LiI	15 min	**25**	**c:** X = I	99
25		$LiCl + H_2O$	5 days		**a:** X = Cl	75
26		$LiBr{\bullet}H_2O$	4 days		**b:** X = Br	60
27	**10**	LiI	15 min	**26**	**c:** X = I	75
28		$LiCl + H_2O$	11 days		**a:** X = Cl	73
29		$LiBr{\bullet}H_2O$	30 min		**b:** X = Br	75
30	**11**	LiI	15 min	**27**	**c:** X = I	94
31		LiI	7 days		**c:** X = I	0
	12			**28**		
32		$LiCl + H_2O$	4 days		**a:** X = Cl	76
33		$LiBr{\bullet}H_2O$	8 h		**b:** X = Br	80
34	**13**	LiI	15 min	**29**	**c:** X = I	90
35		$LiCl + H_2O$	36 h		**a:** X = Cl	61
36		$LiBr{\bullet}H_2O$	1 h		**b:** X = Br	61
37	**14**	LiI	15 min	**30**	**c:** X = I	61
38		$LiCl + H_2O$	3.5 days		**a:** X = Cl	42
39		$LiBr{\bullet}H_2O$	3 h		**b:** X = Br	52
40	**15**	LiI	30 min	**31**	**c:** X = I	43
41		$LiCl + H_2O$	1 days		**a:** X = Cl	60
42		$LiBr{\bullet}H_2O$	12 h		**b:** X = Br	63
43	**16**	LiI	15 min	**32**	**c:** X = I	65

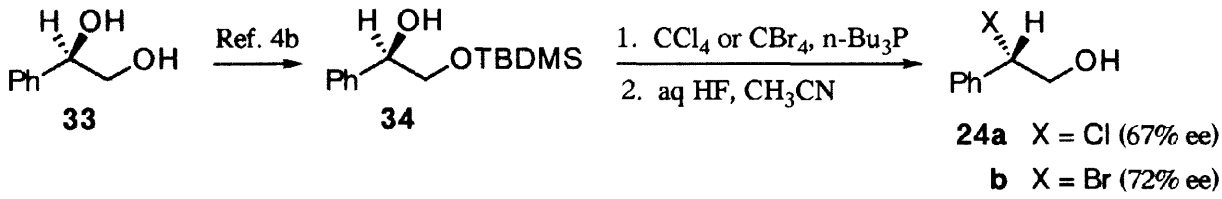
[a]All reactions were performed using 3 equiv of LiX and silica gel (250 mg / mmol). [b]Isolated yield. Yields in parentheses are the corresponding diol. [c]2-Hexadecanone (8%) was also obtained as a major byproduct. [d]The regioisomer through benzoyl migration was also obtained in 5% yield. [e]A very small amount of (*E*)-2,4-diphenyl-2-butenal was also detected. See ref. 17. [f]Opical purity was determined by HPLC analysis. See Experimental Section.

30-32.[18] Unfortunately, all of our efforts to isolate the halohydrin intermediates were unsuccessful and no other products caused by reverse regioselective opening were detected. Due to the synthetic importance of α-haloenone derivatives as α-acylvinyl anion equivalents,[19] several methods are available for deriving these molecules.[20] Accordingly, the present method can serve as an alternative pathway to α-haloenones, since the starting epoxides are readily available by simple epoxidation of conjugated enone precursors.[21]

Due to our general interest in understanding the stereochemical outcome of epoxide ring-opening, (*R*)-(+)-styrene oxide (**8**) was subjected to the above transformations (Table 2, entries 19-21). The optical purity of each product was determined by chiral HPLC analyses. Unlike **23c**, the primary halides **23** retained the asymmetric character present in **8**. The specific rotations for **23a**, $[\alpha]_D^{25}$ -39.1 (*c* 1.2, $CHCl_3$) {lit.[22] $[\alpha]_D$ -47.8 (*c* 2.8, cyclohexane)}, and **23b**, $[\alpha]_D^{26}$ -39.6 (*c* 1.1, $CHCl_3$) {lit.[23] $[\alpha]_D^{20}$ -39.0 (*c* 8.0, $CHCl_3$)}, established their correct stereochemistry. On the other hand, the optical purities of **24** showed quite confusing results: **24a**, **b**, and **c** exhibited 18, 76, and 0% ee, respectively.[24]

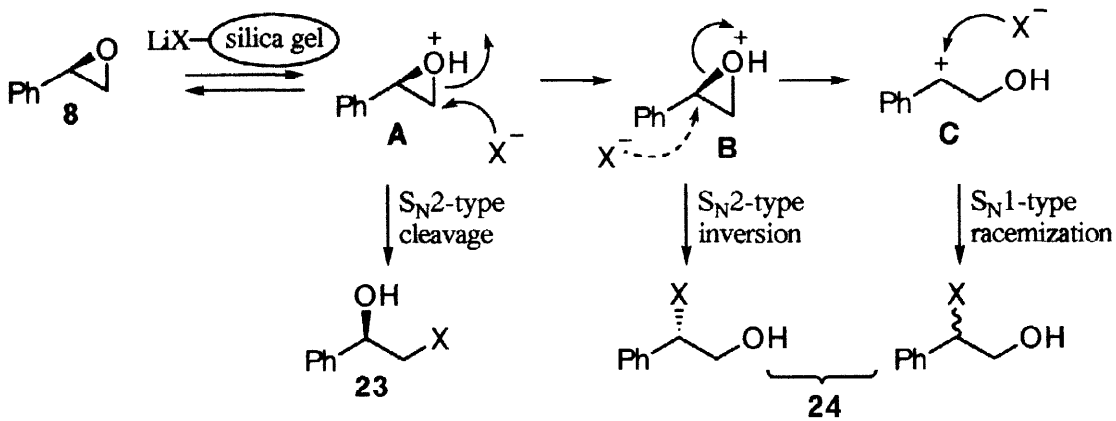
To confirm the absolute configuration of **24a** and **b**, the independent synthesis of these compounds was achieved starting from commercially available (*R*)-(-)-styrenediol (**33**) by analogy with our previous investigation (Scheme 2).[5b] Careful exposure of **34**[5b] to CCl_4 or CBr_4 with n-Bu_3P in toluene at room temperature followed by desilylation gave **24a** and **b** in overall yields of 11 and 23% and in 67 and 72% ee, respectively.[25] Although the S_N2 inversion at halogenation onto **34** was incomplete, the retention time for each of the major isomers was consistent with those of the samples obtained by epoxide ring-opening (*vide supra*).

Scheme 2



The complete retention of the stereochemistry in **23** can be rationalized by considering that the reaction proceeded by cleavage at the methylene carbon via a protonated intermediate **A** (Scheme 3).

Scheme 3



At present, we cannot clearly account for the loss of optical purity in **23c**. The unusual fluctuation of optical purity in **24** may reflect a competitive S_N1- and S_N2-type epoxide ring fission (path **B** and **C**), similar to that suggested by Umezawa et al. for hydrofluorination of epoxides.[26] These results can be explained simply by considering the difference in nucleophilicity and the size of the halide anion. The nearly racemic mixture of **24c** indicates that the S_N1-type process via a benzylic carbenium ion **C** predominated because of the unfavorable approach by the bulky iodide anion. The relatively high enantioselectivity of **24b** implies the borderline nucleophilicity and steric bulkiness of the bromide anion.

Conclusion

Although several methods are available for transforming epoxides into the corresponding β-halohydrins,[7] we believe that the present method offers considerable advantages in terms of simplicity, high efficiency, and very mild conditions. The relative reactivity of the lithium halides was rigorously established to be LiI > LiBr >> LiCl, and the reactivity of LiCl was dramatically increased by the addition of an equivalent amount of water to this system. The similar treatment of α,β-epoxyketones provided α-haloenone derivatives, presumably via halohydrin intermediates. Finally, it should be emphasized that these solvent-free conditions could be valuable given the increasing demand for environmentally benign technology.[27]

Experimental Section

General Procedure.

All melting points and boiling points are uncorrected. NMR spectra were recorded on a Hitachi R-90H (90 MHz for ^1H NMR analysis and 22.6 MHz for ^{13}C NMR analysis) spectrometer in $CDCl_3$ solution and are reported in parts per million (δ) downfield from TMS (δ = 0) or $CDCl_3$ (δ = 77.0) as an internal standard. The FT-IR spectra were measured with a JASCO Model FT/IR-5300 Fourier transform infrared spectrometer and are reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained with a JEOL HX-100 spectrometer. Optical rotations were recorded on a JASCO DIP-370 polarimeter. HPLC analyses were carried out using a Hitachi L-6200 HPLC system. Thin-layer chromatography (TLC) was performed using Merck Kiesegel 60F-254 plates (0.25 mm). Column chromatography was done on Wakogel C-300.

Commercially available reagents were used without further purification.

Typical Procedure for the Reaction of Epoxides on Silica Gel Supports. With LiBr or LiI: To a mixture of epoxide (1.0 mmol) and LiBr or LiI (3.0 mmol) in a few mL of CH_2Cl_2 was added silica gel (250 mg).[10] The suspension was shaken at rt for a while and evaporated to dryness. After allowing to stand at rt for the lengths of time shown in Tables 1 and 2, silica gel was removed by filtration and the crude product was purified by preparative TLC or by silica gel column chromatography.

With LiCl: To a mixture of epoxide (1.0 mmol), LiCl (3.0 mmol), and water (3.0 mmol) in a few mL of CH_2Cl_2 was added silica gel (250 mg),[10] and the mixture was treated as described above.

1-Chloro-3-phenoxy-2-propanol (2a):[8c, 28] Colorless oil; IR (neat) ν 3407, 1599, 1497; ^1H NMR δ 2.59 (1H, d, J = 5.5 Hz), 3.74 (2H, m), 4.10 (3H, m), 6.8-7.1 (3H, m), 7.1-7.4 (2H, m); ^{13}C NMR δ 45.90, 68.52, 69.83, 114.50 (× 2), 121.30, 129.41 (× 2), 158.07.

1-Bromo-3-phenoxy-2-propanol (2b):[8c, 28] Colorless oil; IR (neat) ν 3409, 1599, 1495; ^{1}H NMR δ 2.71 (1H, d, *J* = 4.6 Hz), 3.60 (2H, m), 4.09 (3H, m), 6.8-7.1 (3H, m), 7.1-7.4 (2H, m); ^{13}C NMR δ 34.74, 69.07, 69.23, 114.35 (× 2), 121.06, 129.20 (× 2), 157.83.

1-Iodo-3-phenoxy-2-propanol (2c):[8c, 28] Colorless oil; IR (neat) ν 3409, 1599, 1495; ^{1}H NMR δ 2.52 (1H, m), 3.43 (2H, m), 4.05 (3H, m), 6.8-7.1 (3H, m), 7.1-7.4 (2H, m); ^{13}C NMR δ 9.16, 69.44, 70.38, 114.53 (× 2), 121.30, 129.41 (× 2), 157.98.

1-Chloro-2-hexanol (17a):[29] Colorless oil; IR (neat) ν 3380, 1466, 1046; ^{1}H NMR δ 0.92 (3H, m), 1.1-1.8 (6H, m), 2.26 (1H, d, *J* = 4.4 Hz), 3.47 (1H, dd, *J* = 10.9, 6.4 Hz), 3.62 (1H, dd, *J* = 10.9, 3.2 Hz), 3.80 (1H, m); ^{13}C NMR δ 13.95, 22.61, 27.70, 33.98, 50.50, 71.45.

1-Bromo-2-hexanol (17b):[30] Colorless oil; IR (neat) ν 3378, 1466, 1036; ^{1}H NMR δ 0.92 (3H, m), 1.2-1.8 (6H, m), 2.18 (1H, d, *J* = 4.8 Hz), 3.37 (1H, dd, *J* = 10.2, 7.0 Hz), 3.53 (1H, dd, *J* = 10.2, 3.4 Hz), 3.74 (1H, m); ^{13}C NMR δ 13.89, 22.51, 27.70, 34.77, 40.29, 70.99.

1-Iodo-2-hexanol (17c):[31] Colorless oil; IR (neat) ν 3383, 1464, 1009; ^{1}H NMR δ 0.91 (3H, m), 1.1-1.8 (6H, m), 2.13 (1H, br), 3.23 (1H, dd, *J* = 9.5, 6.2 Hz), 3.38 (1H, dd, *J* = 9.5, 3.5 Hz), 3.4-3.7 (1H, m); ^{13}C NMR δ 13.92, 16.33, 22.45, 27.73, 36.20, 70.81.

1-Chloro-2-decanol (18a):[8e, 32] Colorless oil; IR (neat) ν 3374, 1464, 1059; ^{1}H NMR δ 0.88 (3H, m), 1.28 (14H, m), 2.19 (1H, br d, *J* = 4.4 Hz), 3.46 (1H, dd, *J* = 11.0, 7.0 Hz), 3.62 (1H, dd, *J* = 11.0, 3.3 Hz), 3.80 (1H, br); ^{13}C NMR δ 13.98, 22.58, 25.47, 29.16, 29.44 (× 2), 31.78, 34.19, 50.14, 71.36.

1-Bromo-2-decanol (18b):[8e, 32] Colorless oil; IR (neat) ν 3380, 1464, 1028; ^{1}H NMR δ 0.88 (3H, m), 1.28 (14H, m), 2.12 (1H, d, *J* = 5.4 Hz), 3.37 (1H, dd, *J* = 10.3, 7.0 Hz), 3.53 (1H, dd, *J* = 10.3, 3.3), 3.77 (1H, br); ^{13}C NMR δ 13.95, 22.51, 25.47, 29.10, 29.37 (× 2), 31.72, 35.02, 39.95, 70.90.

1-Iodo-2-decanol (18c):[8e, 32] Colorless oil; IR (neat) ν 3380, 1464, 1013; ^{1}H NMR δ 0.88 (3H, m), 1.28 (14H, m), 1.98 (1H, d, *J* = 4.6 Hz), 3.22 (1H, dd, *J* = 10.1, 6.8 Hz), 3.38 (1H, dd, *J* = 10.1, 3.3 Hz), 3.4-3.7 (1H, m); ^{13}C NMR δ 14.07, 15.99, 22.61, 25.62, 29.19, 29.44 (× 2), 31.81, 36.60, 71.05.

1-Chloro-2-hexadecanol (19a): Mp 42.5-43.0 °C (from pentane); IR (KBr) ν 3380, 1468, 1074; ^{1}H NMR δ 0.88 (3H, m), 1.25 (26H, m), 2.12 (1H, d, *J* = 4.8 Hz), 3.4-3.9 (3H, m); ^{13}C NMR ($CDCl_3$) δ 14.16, 22.76, 25.59, 29.41, 29.59 (× 3), 29.71 (× 5), 32.00, 34.31, 50.53, 71.48. Anal. Calcd for $C_{16}H_{33}ClO$: C, 69.41; H, 12.01. Found: C, 69.20; H, 11.87.

1-Bromo-2-hexadecanol (19b): Mp 46.5-47.0 °C (from pentane) (lit.[33] 48-49 °C); IR (KBr) ν 3383, 1468, 1046; ^{1}H NMR δ 0.88 (3H, m), 1.26 (26H, m), 2.11 (1H, d, *J* = 5.1 Hz), 3.3-3.9 (3H, m); ^{13}C NMR δ 14.13, 22.73, 25.66, 29.41, 29.56 (× 3), 29.71 (× 5), 31.97, 35.17, 40.47, 71.08.

1-Iodo-2-hexadecanol (19c): Mp 50.5-51.5 °C (from pentane); IR (KBr) ν 3389, 1466, 1074; ^{1}H NMR δ 0.88 (3H, m), 1.26 (26H, m), 1.91 (1H, d, *J* = 5.3 Hz), 3.2-3.6 (3H, m); ^{13}C NMR δ 14.19, 16.75, 22.76, 25.75, 29.41, 29.56 (× 2), 29.62 (× 2), 29.71 (× 4), 32.00, 36.69, 71.05. Anal. Calcd for $C_{16}H_{33}IO$: C, 52.17; H, 9.03. Found: C, 52.52; H, 8.89.

3-Chloro-2-hydroxypropyl benzoate (20a):[34] Colorless oil; IR (neat) ν 3459, 1723, 1277; ^{1}H NMR δ 2.89 (1H, d, *J* = 5.5 Hz), 3.69 (2H, m), 4.23 (1H, sextet, *J* = 5.3 Hz), 4.46 (2H, m), 7.3-7.7 (3H, m), 7.9-8.2 (2H, m); ^{13}C NMR δ 45.93, 65.63, 69.59, 128.28 (× 2), 129.32, 129.53 (× 2), 133.16, 166.43.

3-Bromo-2-hydroxypropyl benzoate (20b):[35] Colorless oil; IR (neat) ν 3459, 1721, 1275; ^{1}H NMR δ 2.89 (1H, d, *J* = 5.7 Hz), 3.56 (2H, m), 4.24 (1H, m), 4.47 (2H, m), 7.3-7.7 (3H, m), 7.9-8.2 (2H, m); ^{13}C NMR δ 34.68, 66.21, 69.07, 128.19 (× 2), 129.26, 129.44 (× 2), 133.04, 166.24.

2-Hydroxy-3-iodopropyl benzoate (20c):[36] Colorless oil; IR (neat) ν 3445, 1719, 1275; ^{1}H NMR δ 2.86 (1H, d, *J* = 5.5 Hz), 3.33 (1H, dd, *J* = 10.5, 6.2 Hz), 3.41 (1H, dd, *J* = 10.5, 5.0 Hz), 3.99 (1H, sextet, *J* = 5.5 Hz), 4.44 (2H, m), 7.3-7.7 (3H, m), 7.9-8.1 (2H, m); ^{13}C NMR δ 8.76, 67.21, 68.98, 128.16 (× 2), 129.14, 129.38 (× 2), 133.01, 166.21.

2-Chloro-1-phenylethanol (21a):[8b, 37] Colorless oil; IR (neat) ν 3407, 1454, 1065; ^{1}H NMR δ 2.69 (1H, br), 3.67 (1H, dd, *J* = 11.2, 7.9 Hz), 3.72 (1H, dd, *J* = 11.2, 4.4 Hz), 4.88 (1H, dd, *J* = 7.9, 4.4 Hz), 7.35 (5H, s); ^{13}C NMR δ 50.84, 74.07, 126.00 (× 2), 128.38, 128.59 (× 2), 139.93.

2-Bromo-1-phenylethanol (21b):[8d] Colorless oil; IR (neat) ν 3395, 1454, 1061; ^{1}H NMR δ 2.64 (1H, d, *J* = 3.1 Hz), 3.53 (1H, dd, *J* = 10.8, 8.4 Hz), 3.63 (1H, dd, *J* = 10.8, 4.3 Hz), 4.91 (1H, m), 7.36 (5H, s); ^{13}C NMR δ 40.20, 73.86, 125.94 (× 2), 128.41, 128.65 (× 2), 140.30.

2-Iodo-1-phenylethanol (21c):[8c] Colorless oil; IR (neat) ν 3407, 1453, 1175, 1055; ^{1}H NMR δ 2.49 (1H, br), 3.39 (1H, dd, *J* = 10.3, 7.9 Hz), 3.48 (1H, dd, *J* = 10.3, 4.6 Hz), 4.81 (1H, m), 7.34 (5H, s); ^{13}C NMR δ 15.26, 74.01, 125.69 (× 2), 128.25, 128.59 (× 2), 141.09.

2-Chloro-2-phenylethanol (22a):[8b, 37] Colorless oil; IR (neat) ν 3383, 1453, 1067; ^{1}H NMR δ 2.22 (1H, m), 3.91 (1H, br t, *J* = 6.6 Hz), 4.96 (1H, t, *J* = 6.6 Hz), 7.36 (5H, s); ^{13}C NMR δ 64.68, 67.82, 127.40 (× 2), 128.68 (× 2), 128.74, 137.89.

2-Bromo-2-phenylethanol (22b): Mp 35.0-36.5 °C (from Et_2O-pentane) (lit.[38] 38 °C); IR (KBr) ν 3401, 1454, 1022; ^{1}H NMR δ 2.22 (1H, br s), 3.93 (1H, dd, *J* = 12.5, 6.5 Hz), 4.04 (1H, dd, *J* = 12.5, 7.2 Hz), 5.04 (1H, dd, *J* = 7.2, 6.5 Hz), 7.36 (5H, m); ^{13}C NMR δ 56.88, 67.55, 127.86 (× 2), 128.47, 128.80 (× 2), 138.22.

2-Iodo-2-phenylethanol (22c):[8c] Mp 75.0-76.0 °C (from Et_2O-hexane) (lit.[39] 77-78 °C); IR (KBr) ν 3252, 1453, 1011; ^{1}H NMR δ 2.10 (1H, br), 4.02 (2H, m), 5.19 (1H, t, *J* = 7.2 Hz), 7.2-7.5 (5H, m); ^{13}C NMR δ 35.63, 68.58, 127.89 (× 2), 128.47, 128.86 (× 2), 139.99.

(*R*)-2-Chloro-1-phenylethanol (23a): $[\alpha]_D^{25}$ -39.1 (*c* 1.2, $CHCl_3$) (lit.[22] $[\alpha]_D$ -47.8 (*c* 2.8, cyclohexane)) (100% ee by HPLC analysis).

(*R*)-2-Bromo-1-phenylethanol (23b): $[\alpha]_D^{26}$ -39.6 (*c* 1.1, $CHCl_3$) (lit.[23] $[\alpha]_D^{20}$ -39.0 (*c* 8, $CHCl_3$)) (100% ee by HPLC analysis).

(*R*)-2-Iodo-1-phenylethanol (23c): $[\alpha]_D^{26}$ -15.8 (*c* 1.2, $CHCl_3$) (82% ee by HPLC analysis).

(*S*)-2-Chloro-2-phenylethanol (24a): $[\alpha]_D^{27}$ +30.7 (*c* 1.1, $CHCl_3$) (18% ee by HPLC analysis).

(*S*)-2-Bromo-2-phenylethanol (24b): $[\alpha]_D^{27}$ +102.1 (*c* 1.0, $CHCl_3$) (76% ee by HPLC analysis).

Enantiomeric Analyses of 23 and 24: The absolute configurations of **23** and **24** were determined by the sign of the specific rotation or by independent synthesis (*vide infra*). The enantiomeric excess (ee) values of **23** and **24** were determined by HPLC analysis (254 nm, flow rate: 0.5 mL/min). This analysis was carried out with CHIRALCEL OB for **23a** (eluent: hexane/2-propanol 88:12, t_R 15.3 min for *S* isomer and t_R 20.2 min for *R* isomer), **23b** (eluent: hexane/2-propanol 90:10, t_R 15.7 min for *R* isomer and t_R 19.3 min for *S* isomer), and **23c** (eluent: hexane/2-propanol 88:12, t_R 14.1 min for *R* isomer and t_R 15.8 min for *S* isomer), with CHIRALCEL OJ for **24a** (eluent: hexane/2-propanol 88:12, t_R 21.0 min for *R* isomer and t_R 25.4 min for *S* isomer) and **24b** (eluent: hexane/2-propanol 90:10, t_R 35.5 min for *S* isomer and t_R 41.8 min for *R* isomer), and with CHIRALCEL OD for **24c** (eluent: hexane/2-propanol 99:1, t_R 29.5 and 33.9 min).

1,3-Dichloro-2-propanol (25a):[40] Colorless liquid; IR (neat) ν 3387, 1431, 1053; ^{1}H NMR δ 2.73 (1H, br), 3.69 (4H, d, *J* = 5.1 Hz), 4.07 (1H, m); ^{13}C NMR δ 45.69 (× 2), 70.81.

1-Bromo-3-chloro-2-propanol (25b):[8d, 41] Colorless liquid; IR (neat) ν 3407, 1427, 1042; ^{1}H NMR δ 2.51 (1H, d, J = 6.8 Hz), 3.56 (2H, d, J = 5.0 Hz), 3.70 (2H, d, J = 4.8 Hz), 4.02 (1H, m); ^{13}C NMR δ 34.71, 46.45, 70.41.

1-Chloro-3-iodo-2-propanol (25c):[42] Colorless liquid; IR (neat) ν 3387, 1424, 1034; ^{1}H NMR δ 2.6 (1H, br), 3.38 (2H, d, J = 5.1 Hz), 3.71 (3H, m); ^{13}C NMR δ 9.10, 47.85, 70.48.

1,6-Dideoxy-1,6-dichloro-3,4-*O*-isopropylidene-D-mannitol (26a): Colorless oil; $[\alpha]_D^{21}$ +12.8 (*c* 1.4, $CHCl_3$); IR (neat) ν 3364, 1375, 1074; ^{1}H NMR δ 1.38 (6H, s), 3.5-4.0 (10H, m); ^{13}C NMR δ 26.91 (× 2), 47.73 (× 2), 72.70 (× 2), 79.99 (× 2), 110.14; MS *m/z* (rel intensity) 261 (48), 259 (M^+ + 1, 74), 245 (26), 243 (40), 201 (18), 179 (100), 165 (16), 147 (15), 59 (95); HRMS calcd for $C_9H_{16}Cl_2O_4$ + H 259.0504, found 259.0507.

1,6-Dideoxy-1,6-dibromo-3,4-*O*-isopropylidene-D-mannitol (26b): Colorless oil; $[\alpha]_D^{27}$ +15.9 (*c* 1.1, $CHCl_3$); IR (neat) ν 3364, 1375, 1078; ^{1}H NMR δ 1.38 (6H, s), 3.4-4.0 (10H, m); ^{13}C NMR δ 26.87 (× 2), 37.33 (× 2), 72.24 (× 2), 80.72 (× 2), 110.08; MS *m/z* (rel intensity) 351 (41), 349 (80), 347 (M^+ + 1, 44), 333 (21), 273 (26), 225 (30), 223 (30), 129 (100), 59 (30); HRMS calcd for $C_9H_{16}Br_2O_4$ + H 346.9494, found 346.9473.

1,6-Dideoxy-1,6-diiodo-3,4-*O*-isopropylidene-D-mannitol (26c): Colorless oil; $[\alpha]_D^{21}$ +17.7 (*c* 1.0, $CHCl_3$); IR (neat) ν 3362, 1375, 1078; ^{1}H NMR δ 1.37 (6H, s), 3.3-3.9 (10H, m); ^{13}C NMR δ 12.45 (× 2), 26.94 (× 2), 72.30 (× 2), 81.97 (× 2), 110.02; MS *m/z* (rel intensity) 442 (M^+ + 1, 1), 427 (24), 297 (5), 271 (96), 257 (3), 239 (4), 213 (31), 169 (13), 101 (9), 86 (19), 59 (100); HRMS calcd for $C_9H_{16}I_2O_4$ 441.9138, found 441.9119.

***trans*-2-Chlorocyclohexanol (27a):**[43] Colorless oil; IR (neat) ν 3385, 1451, 1074; ^{1}H NMR δ 1.0-2.4 (8H, m), 2.59 (1H, s), 3.3-4.0 (2H, m); ^{13}C NMR δ 23.95, 25.62, 33.16, 35.14, 67.30, 75.20.

***trans*-2-Bromocyclohexanol (27b):**[43b] Colorless oil; IR (neat) ν 3387, 1451, 1073; ^{1}H NMR δ 1.1-2.5 (8H, m), 2.53 (1H, d, J = 2.2 Hz), 3.61 (1H, m), 3.91 (1H, ddd, J = 9.5, 9.3, 4.4 Hz); ^{13}C NMR δ 24.07, 26.60, 33.55, 36.17, 61.57, 75.17.

***trans*-2-Iodocyclohexanol (27c):** Mp 38.0-38.5 °C (from pentane) (lit.[43b] 40.0-41.7 °C); IR (KBr) ν 3206, 1449, 1071; ^{1}H NMR δ 1.2-2.6 (8H, m), 2.38 (1H, br), 3.67 (1H, m), 4.05 (1H, ddd, J = 11.7, 9.7, 4.4 Hz); ^{13}C NMR δ 24.25, 27.76, 33.67, 38.40, 42.79, 75.60.

***trans*-6-Chloro-2,2-dimethyl-1,3-dioxepan-5-ol (29a):** Colorless oil; IR (neat) ν 3443, 1379, 1221; ^{1}H NMR δ 1.35 (6H, s), 3.21 (1H, br), 3.4-4.1 (6H, m); ^{13}C NMR δ 24.34, 24.56, 61.02, 61.15, 62.30, 73.59, 101.67; MS *m/z* (rel intensity) 183 (20), 181 (M^+ + 1, 67), 165 (30), 163 (46), 145 (37), 105 (20), 87 (28), 59 (100); HRMS calcd for $C_7H_{13}ClO_3$ + H 181.0631, found 181.0603.

***trans*-6-Bromo-2,2-dimethyl-1,3-dioxepan-5-ol (29b):**[8d] Colorless oil; IR (neat) ν 3430, 1377, 1219; ^{1}H NMR δ 1.36 (6H, s), 2.79 (1H, d, J = 5.3 Hz), 3.4-4.1 (6H, m); ^{13}C NMR δ 24.53, 24.59, 55.60, 61.27, 61.66, 73.95, 101.73; MS *m/z* (rel intensity) 227 (97), 225 (M^+ + 1, 100), 209 (35), 207 (26), 145 (38), 115 (28), 87 (14), 59 (54); HRMS calcd for $C_7H_{13}BrO_3$ + H 225.0126, found 225.0118.

***trans*-2,2-Dimethyl-6-iodo-1,3-dioxepan-5-ol (29c):** Colorless oil; IR (neat) ν 3428, 1217, 1080; ^{1}H NMR δ 1.37 (6H, s), 2.75 (1H, d, J = 5.7 Hz), 3.5-4.2 (6H, m); ^{13}C NMR δ 24.68, 24.83, 37.82, 62.27, 62.58, 75.23, 101.79; MS *m/z* (rel intensity) 273 (M^+ + 1, 63), 255 (38), 215 (31), 197 (96), 169 (16), 145 (63), 115 (42), 87 (21), 59 (100); HRMS calcd for $C_7H_{13}IO_3$ + H 272.9988, found 272.9961.

2-Chloro-2-cyclohexenone (30a): Mp 73.0-73.5 °C (from Et_2O-hexane) (lit.[44] 67-68 °C); IR (KBr) ν 1686, 1607; ^1H NMR δ 1.8-2.3 (2H, m), 2.4-2.7 (4H, m), 7.15 (1H, t, J = 4.4 Hz); ^{13}C NMR δ 22.61, 27.03, 38.46, 132.00, 146.39, 191.09.

2-Bromo-2-cyclohexenone (30b): Mp 74.5-76.0 °C (from Et_2O-hexane) (lit.[18] 74-76 °C); IR (KBr) ν 1682, 1597; ^1H NMR δ 1.9-2.8 (6H, m), 7.42 (1H, t, J = 4.4 Hz); ^{13}C NMR δ 22.61, 28.28, 38.22, 123.59, 150.91, 190.70.

2-Iodo-2-cyclohexenone (30c): Mp 46.0-47.0 °C (from Et_2O-hexane) (lit.[20a] 48-48.5 °C); IR (KBr) ν 1676, 1586; ^1H NMR δ 1.9-2.9 (6H, m), 7.77 (1H, t, J = 4.3 Hz); ^{13}C NMR δ 22.79, 29.86, 37.18, 103.65, 159.20, 191.70.

2-Chloro-3-methyl-2-cyclohexenone (31a):[45] Colorless oil; IR (neat) ν 1686, 1611, 1279; ^1H NMR δ 1.9-2.2 (2H, m), 2.13 (3H, s), 2.4-2.7 (4H, m); ^{13}C NMR δ 21.54, 22.30, 33.25, 37.73, 128.65, 156.64, 190.54; MS *m/z* (rel intensity) 147 (33), 145 (M^+ + 1, 100), 116 (7), 81 (4); HRMS calcd for C_7H_9ClO + H 145.0420, found 145.0414.

2-Bromo-3-methyl-2-cyclohexenone (31b):[18] Colorless oil; IR (neat) ν 1680, 1605, 1271; ^1H NMR δ 1.9-2.2 (2H, m), 2.17 (3H, s), 2.3-2.7 (4H, m); ^{13}C NMR δ 21.72, 25.75, 34.04, 37.52, 122.46, 160.18, 190.54.

2-Iodo-3-methyl-2-cyclohexenone (31c):[20a] Colorless oil; IR (neat) ν 1676, 1593, 1263; ^1H NMR δ 1.97 (2H, quintet, J = 5.9 Hz), 2.25 (3H, s), 2.54 (2H, t, J = 5.9 Hz), 2.60 (2H, t, J = 5.9 Hz); ^{13}C NMR δ 22.18, 31.91, 34.25, 36.36, 106.85, 166.27, 191.79.

2-Chloro-2-cyclopentenone (32a):[44] Colorless oil; IR (neat) ν 1723, 1599, 1294; ^1H NMR δ 2.5-2.8 (4H, m), 7.58 (1H, t, J = 2.9 Hz); ^{13}C NMR δ 25.81, 32.97, 136.15, 156.94, 200.73.

2-Bromo-2-cyclopentenone (32b): Mp 35.0-36.0 °C (from Et_2O-pentane) (lit.[19a, 44] 36-37 °C); IR (KBr) ν 1709, 1586, 1302; ^1H NMR δ 2.4-2.8 (4H, m), 7.78 (1H, t, J = 2.9 Hz); ^{13}C NMR δ 27.97, 32.36, 126.06, 161.58, 201.31.

2-Iodo-2-cyclopentenone (32c): Mp 74.0-74.5 °C (from Et_2O-hexane) (lit.[20a] 71 °C); IR (KBr) ν 1707, 1564, 1281; ^1H NMR δ 2.4-2.9 (4H, m), 8.01 (1H, t, J = 2.9 Hz); ^{13}C NMR δ 30.93, 31.23, 102.82, 169.26, 203.59.

Preparation of 24a and 24b: To a solution of **34**[5b] (0.98 mmol) and CX_4 (X = Cl or Br; 1.5 mmol) in toluene (8 mL) at rt was added dropwise n-Bu_3P via a microsyringe, and the mixture was stirred for 2 days. Conventional workup (AcOEt extraction) gave the crude product, which was roughly separated by silica gel column chromatography (hexane/AcOEt, 19:1 to 9:1). This sample was dissolved in CH_3CN (5 mL) and treated dropwise with 48% aqueous HF (ca. 3 mL). After being stirred for 4 h at rt, the mixture was quenched with pyridine[46] to around pH 3 and then diluted with AcOEt. Conventional workup followed by purification by silica gel column chromatography (hexane/AcOEt, 4:1 to 2:1) gave the desired compound as a colorless oil (23% yield for **24a**, 11% yield for **24b**).[25] **24a**: $[\alpha]_D^{25}$ +113.9 (*c* 1.6, $CHCl_3$) (67% ee by HPLC analysis, *vide supra*). **24b**: $[\alpha]_D^{25}$ +97.5 (*c* 1.0, $CHCl_3$) (72% ee by HPLC analysis, *vide supra*).

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12. The addition of an equivalent amount of water to the salts gave somewhat better results. For example, KBr (72 h): **2b** (36%), the hydrolyzed diol (3%), and 61% recovery; NaBr (72 h): **2b** (45%), the hydrolyzed diol (4%), and 51% recovery; CsBr (72 h): **2b** (45%), the hydrolyzed diol (4%), and 51% recovery.
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17. In this case, a very small amount of (*E*)-2,4-diphenyl-2-butenal was also detected: IR (neat) ν 1692, 1634, 1601, 1495, 702; ^{1}H NMR (400 MHz) δ 3.70 (2H, d, J = 7.6 Hz), 6.87 (1H, t, J = 7.6 Hz), 7.15-7.49 (10H, m), 9.66 (1H, s); ^{13}C NMR (100 MHz) δ 35.82, 126.81, 128.21, 128.39 (× 2), 128.47 (× 2), 128.87 (× 2), 129.46 (× 2), 132.19, 138.06, 144.15, 153.38, 193.48; MS *m/z* (rel intensity) 222 (M^+, 100), 205 (90), 193 (16), 145 (39), 131 (15), 117 (22), 105 (39), 91 (36), 77 (4), 65 (4), 51 (4). Probably this compound was formed by spontaneous self-condensation of phenylacetaldehyde after epoxide-carbonyl rearrangement[16] of **7** or **8**. See also: Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1988**, *29*, 2575-2576; Axelsson, O.; Becker, H. D.; Skelton, B. W.; Sørenson, H.; White, A. H. *Aust. J. Chem.* **1988**, *41*, 727-733.
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