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An Efficient Synthesis of 2-Bromo-3-hydroxy Esters by Reaction of Ketones with Ethyl Dibromoacetate Promoted by Samarium Diiodide

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A simple and efficient samarium diiodide mediated synthesis of 2-bromo-3-hydroxy esters **1** by the reaction of a variety of ketones **2** with ethyl dibromoacetate (**3**) is described. The relative configuration of the major diastereoisomer obtained was established by NOESY experiments of the corresponding α,β-epoxy esters **4** prepared from **1**. Additionally, a mechanism is proposed to explain the results obtained.

Introduction

The highly functionalized 2-bromo-3-hydroxy esters **1** are interesting compounds because of their synthetic applications.[1] However, unlike the syntheses of 2-chloro-3-hydroxy esters, the preparation of 2-bromo-3-hydroxy esters is difficult to achieve by using classical methodologies. For instance, the reaction of lithium or magnesium enolates (generated with bases) derived from α-bromo esters with carbonyl compounds yields the corresponding α,β-epoxy ester as the major product instead of 2-bromo-3-hydroxy esters.[2] This result is obtained because the bromine atom is displaced by the highly nucleophilic alcoholate group even at low temperatures (–78 °C). In particular, the epoxy ester constitutes the major product when the reactant is a ketone. In addition, conventional Reformatsky conditions are generally inappropriate for the formation of α-bromo zinc ester enolates from the corresponding dibromo esters. To the best of our knowledge, the only example describing an efficient Reformatsky reaction required low temperature and a tedious process to prepare the zinc/silver-on-graphite reagent.[3] For this reason, an efficient and simple synthesis of 2-bromo-3-hydroxy esters at room temperature is very desirable.

Since its introduction into organic synthesis by Kagan in 1977,[4] samarium diiodide has become among the most important reagents to carry out transformation reactions performed under reducing conditions.[5] In particular, samarium diiodide has previously been used to promote the Reformatsky reaction starting from 2-halo esters and carbonyl compounds.[6] However, to the best of our knowledge, the SmI_2-promoted reaction of 2,2-dihalo esters with ketones to obtain 2-halo-3-hydroxy esters has not been published to date.

We have previously reported the highly diastereoselective preparation of (*E*)-α,β-unsaturated esters by treating aldehydes with ethyl dibromoacetate in the presence of SmI_2.[7] In this paper, we describe a SmI_2-mediated method to obtain 2-bromo-3-hydroxy esters by reaction between commercially available ketones and ethyl dibromoacetate.

Results and Discussion

We are interested in developing an efficient method for the synthesis of 2-bromo-3-hydroxy esters **1** so that these compounds can be used in other reactions. Initially, the method chosen to prepare compounds **1** was the reaction of the lithium enolate derived from ethyl bromo acetate with ketones at low temperature (–85 °C). The reaction with 2-pentanone or acetophenone afforded the corresponding epoxy ester as the major product and the corresponding 2-bromo-3-hydroxy esters **1** in very low yields. Higher yields of compounds **1** were not obtained by using magnesium enolates instead of lithium derivatives.

Taking into account the low nucleophilicity of the samarium alcoholates (with respect to magnesium or lithium), we demonstrated an alternative method to prepare the target products **1** by using the samarium enolate derived from ethyl bromoacetate. Thus, reaction of several ketones (1 equiv.) **2** with ethyl dibromoacetate (1.2 equiv.) (**3**) in the presence of a solution of SmI_2 (4 equiv.) in THF at room temperature afforded 2-bromo-3-hydroxy esters **1** in high yield (Scheme 1). The reaction seems to be general, as shown by the data reported in Table 1: linear, branched, and cyclic aliphatic and aromatic ketones can be used as starting materials. It is worth mentioning that these reactions can be performed on easily enolizable ketones (Table 1, entry 5), unlike other previously reported reac-

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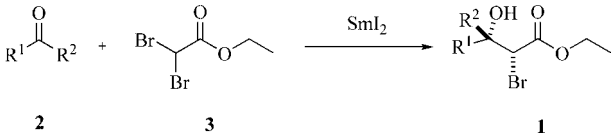
tions of anionic reagents, such as phosphorus ylides.[8] Moreover, unlike other SmI_2-promoted Reformatsky reactions previously described, byproducts such as ethyl 3-oxobutanoate or their bromo derivatives generated by a dimerization reaction of the reactant ethyl dibromoacetate were not detected.[6a]



Scheme 1.

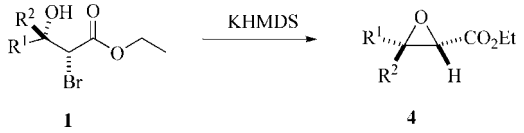
Table 1. Synthesis of 2-bromo-3-hydroxy esters **1**.

Entry	**1**[a]	R^1	R^2	*de* [%][b]	Yield [%][c]
1	**1a**	Ph	Et	34	85
2	**1b**	Me	Et	18	90
3	**1c**	Et	Et	–	93
4	**1d**	Ph	Me	22	50
5	**1e**	$PhCH_2$	Me	42	91
6	**1f**	C_5H_{11}	Me	10	87
7	**1g**	$CH_3CH(CH_3)CH_2$	Me	14	82
8	**1h**	$-(CH_2)_5-$		–	78

[a] All reactions were carried out by using 4 equiv. of SmI_2 in a reaction time of 2h. [b] Determined on crude reaction products by ^1H and ^{13}C NMR spectroscopy (300 and 75 MHz) and GC-MS. [c] Isolated yields based on starting ketone **2** after column chromatography.

The solution of SmI_2 in THF was rapidly obtained (10 min) by the reaction of diiodomethane with samarium powder in the presence of sonic waves.[9]

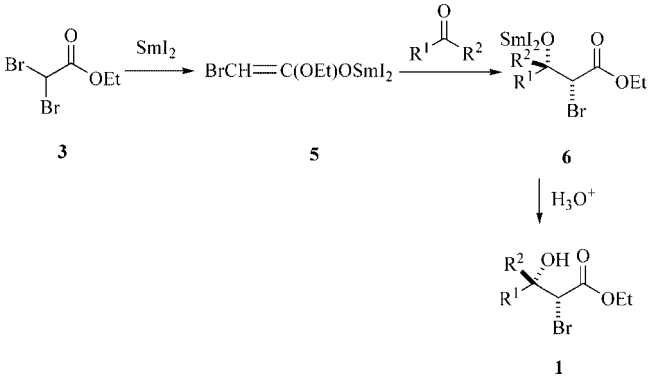
The 2-bromo-3-hydroxy esters **1** were isolated as a mixture of diastereoisomers (see Table 1), and the diastereoisomeric ratio was established by using ^1H NMR spectrometry (300 MHz). To determine the relative configuration of the major diastereoisomer, compounds **1a** and **1d** were transformed into the corresponding α,β-epoxy esters **4a** and **4d** by treatment with potassium hexamethyldisilazide at –78 °C overnight (Scheme 2). In the case of epoxide **4a**, the major diastereoisomer can be isolated in pure form by column chromatography (hexanes/EtOAc, 20:1).



Scheme 2.

The relative configuration of epoxides **4a** and **4d** was established by NOESY experiments. A *cis* relative configuration for the major diastereoisomer was determined in both cases on the basis of the observation of NOE interactions between the CH_2 (**4a**) or CH_3 (**4d**) groups and the α-hydrogen atom in the major diastereoisomer and between the Ph groups and the α-hydrogen atom in the minor diastereoisomer. Consequently, having determined the *cis* configuration of compounds **4a** and **4d**, we established the relative configuration of compounds **1a** and **1d** as 2*R**,3*S**.[10] The relative configuration of the other compounds **1** prepared was assigned by analogy.

The observed results can be explained (Scheme 3) by assuming the initial metalation of the C–Br bond of dibromoacetate by two consecutive single electron transfers from SmI_2. The ketone **2** undergoes an addition reaction of the generated samarium bromoenolate intermediate **5** to afford the corresponding alcoholate **6**, which, after hydrolysis, gives the final 2-bromo-3-hydroxy esters **1**. Although we do not have direct evidence for the existence of the samarium bromoenolate intermediate **5**, a radical mechanism can be rejected considering that no differences were observed in the course or the result of the reaction when compound **1b** was synthesized either in the dark or in the presence of AIBN.



Scheme 3.

Conclusion

In conclusion, we have presented a simple and general methodology for the samarium diiodide promoted preparation of 2-bromo-3-hydroxy esters **1** by reaction of commercially available ketones **2** with ethyl dibromoacetate (**3**) at room temperature. Determination of the relative configurations of the major diastereoisomer of 2-bromo-3-hydroxy esters **1** was performed by NOESY experiments after transformation of **1** into the corresponding α,β-epoxy esters **4**. A mechanism to explain this transformation has been proposed.

Experimental Section

General Remarks: Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven-dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased in the highest quality available and were used without further purification. Samarium diiodide was prepared by reaction of CH_2I_2 with samarium powder in the presence of sonic waves.[7] Flash column chromatography was carried out on silica gel 230–400 mesh. Compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm). ^1H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane

(TMS), which is used as an internal standard, and coupling constants (*J*) are reported in Hz. The diastereomeric excesses were obtained by using ^{1}H and ^{13}C NMR spectroscopy as well as GC-MS analysis of the crude products. GC-MS and HRMS were performed at 70 eV or by using FAB conditions. When HRMS could not be measured on the basis of the molecular ion, the HRMS of a significant fragment is given. Only the most important IR absorptions (in cm^{-1}) and the molecular ions and/or base peaks in MS are given.

General Procedure for the Synthesis of Compounds 1: A THF solution (20 mL) of SmI_2 (2 mmol) was added to a stirred solution of ethyl dibromoacetate (0.6 mmol) and the corresponding ketone (0.5 mmol) in THF (2 mL) under nitrogen. The reaction was stirred at room temperature for two hours before it was quenched with aqueous HCl (1 N). The organic material was extracted with dichloromethane, the combined extracts were dried with Na_2SO_4, and the solvent was removed under reduced pressure. Purification by chromatography on silica gel (hexanes: EtOAc 5:1) provided pure compounds **1**.

Ethyl 2-Bromo-3-hydroxy-3-phenylpentanoate (1a): Yield: 85%, 128 mg. Data from a mixture of diastereoisomers in a ratio of 67:33. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 10 H), 4.70 (s, 1 H, minor isomer), 4.55 (s, 1 H, major isomer), 4.24 (q, *J* = 7.2 Hz, 2 H, major isomer), 3.98 (q, *J* = 7.1 Hz, 2 H, minor isomer), 3.80 (s, 2 H), 2.32–1.71 (m, 4 H), 1.33 (t, *J* = 7.1 Hz, 3 H, major isomer), 0.96 (t, *J* = 7.2 Hz, 3 H, minor isomer), 0.76 (t, *J* = 7.3 Hz, 3 H, major isomer), 0.70 (t, *J* = 7.3 Hz, 3 H, minor isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2 (C, major isomer), 170.0 (C, minor isomer), 141.1 (C, major isomer), 140.7 (C, minor isomer), 128.2 (2×CH, major isomer), 128.0 (2×CH, minor isomer), 127.5 (CH, minor isomer), 127.2 (CH, major isomer), 125.8 (2×CH, minor isomer), 125.4 (2×CH, major isomer), 76.7 (C, major isomer), 76.4 (C, minor isomer), 62.3 (CH_2, major isomer), 61.9 (CH_2, minor isomer), 54.3 (CH, major isomer), 53.0 (CH, minor isomer), 32.9 (CH_2, minor isomer), 31.9 (CH_2, major isomer), 13.8 (CH_3, major isomer), 13.4 (CH_3, minor isomer), 8.3 (CH_3, major isomer), 7.1 (CH_3, minor isomer) ppm. MS (70 eV, EI): *m*/*z* (%) = 271 [$M^+ - C_2H_5$, 27], 135 (100), 105 (71), 77 (12). HRMS (70 eV): calcd. for $C_{13}H_{17}BrO_3$ [$M^+ - C_2H_5$] 270.9970; found 270.9973. IR (neat): $\tilde{\nu}$ = 3491, 1713 cm^{-1}; R_f = 0.6 (hexanes/EtOAc 3:1); $C_{13}H_{17}BrO_3$ (301.18): calcd. C 51.84, H 5.69; found C 51.72, H 5.60.

Ethyl 2-Bromo-3-hydroxy-3-methylpentanoate (1b): Yield: 90%, 108 mg. Data from a mixture of diastereoisomers in a ratio of 59:41. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.28–4.21 (m, 6 H), 1.73–1.57 (m, 4 H), 1.33–1.27 (m, 12 H), 0.96 (t, *J* = 7.6 Hz, 3 H, major isomer), 0.91 (t, *J* = 7.4 Hz, 3 H, minor isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5 (C, major isomer), 169.4 (C, minor isomer), 72.7 (C, major isomer), 72.1 (C, minor isomer), 61.8 (2×CH_2), 53.9 (CH, minor isomer), 53.1 (CH, major isomer), 31.7 (CH_2, major isomer), 31.5 (CH_2, minor isomer), 22.8 (CH_3, major isomer), 22.7 (CH_3, minor isomer), 13.5 (2×CH_3), 7.8 (CH_3, major isomer), 7.5 (CH_3, minor isomer) ppm. MS (70 eV, EI): *m*/*z* (%) = 154 [$M^+ - C_2H_4$, < 1], 120 (6), 106 (52), 91 (100). HRMS (70 eV): calcd. for $C_8H_{15}BrO_3$ [$M^+ - C_2H_4$] 209.9892; found 209.9922. IR (neat): $\tilde{\nu}$ = 3511, 1726 cm^{-1}; R_f = 0.5 (hexanes/EtOAc 3:1); $C_8H_{15}BrO_3$ (239.11): calcd. C 40.19, H 6.32; found C 40.27, H 6.28.

Ethyl 2-Bromo-3-ethyl-3-hydroxypentonoate (1c): Yield: 93%, 118 mg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 (q, *J* = 7.1 Hz, 2 H), 4.31 (s, 1 H), 3.29 (s, 1 H), 1.82–1.70 (m, 2 H), 1.66–1.58 (m, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H), 0.97 (t, *J* = 7.5 Hz, 3 H), 0.87 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0 (C), 74.2 (C), 61.9 (CH_2), 52.3 (CH), 27.5 (CH_2), 27.4 (CH_2), 13.6 (CH_3), 7.8 (CH_3), 7.2 (CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 252 [M^+, <1], 223 (66), 87 (100), 57 (97). IR (neat): $\tilde{\nu}$ = 3516, 1722, 1156 cm^{-1}; R_f = 0.6 (hexanes/EtOAc 3:1); $C_9H_{17}BrO_3$ (253.13): calcd. C 42.70, H 6.77; found C 42.75, H 6.90.

Ethyl 2-Bromo-3-hydroxy-3-phenylbutanoate (1d): Yield: 50%, 72 mg. Data from a mixture of diastereoisomers in a ratio of 61:39. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.28 (m, 10 H), 4.67 (s, 1 H, minor isomer), 4.55 (s, 1 H, major isomer), 4.40 (q, *J* = 7.1 Hz, 2 H, major isomer), 3.98 (q, *J* = 7.1 Hz, 2 H, minor isomer), 2.63 (s, 2 H), 1.78 (s, 3 H, major isomer), 1.67 (s, 3 H, minor isomer), 1.27 (t, *J* = 7.1 Hz, 3 H, major isomer), 0.98 (t, *J* = 7.1 Hz, 3 H, minor isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C, major isomer), 169.4 (C, minor isomer), 142.9 (C, major isomer), 142.7 (C, minor isomer), 132.9 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (2×CH), 127.5 (CH), 127.4 (CH), 124.9 (2×CH), 74.1 (C, minor isomer), 73.8 (C, major isomer), 62.1 (CH_2, major isomer), 61.8 (CH_2, minor isomer), 55.0 (CH, major isomer), 53.0 (CH, minor isomer), 28.2 (CH_3, minor isomer), 26.6 (CH_3, major isomer), 13.6 (CH_3, major isomer), 13.3 (CH_3, minor isomer) ppm. MS (70 eV, EI): *m*/*z* (%) = 286 [M^+, <1], 271 (5), 121 (100), 105 (62), 91 (7). HRMS (70 eV): calcd. for $C_{12}H_{15}BrO_3$ [M^+] 286.0205, found 286.0192. IR (neat): $\tilde{\nu}$ = 3500, 1720, 763.5 cm^{-1}; R_f = 0.6 (hexanes/EtOAc 3:1); $C_{12}H_{15}BrO_3$ (287.15): calcd. C 50.19, H 5.27; found C 50.15, H 5.19.

Ethyl 2-Bromo-3-hydroxy-3-methyl-4-phenylbutanoate (1e): Yield: 91%, 137 mg. Data from a mixture of diastereoisomers in a ratio of 71:29. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (s, 10 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 4.18 (s, 1 H, major isomer), 4.17 (s, 1 H, minor isomer), 3.34 (s, 1 H, major isomer), 3.20 (s, 1 H, minor isomer), 3.10–2.90 (m, 4 H), 1.42 (s, 3 H, minor isomer), 1.32 (s, 3 H, major isomer), 1.29 (t, *J* = 7.0 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6 (2×C), 136.0 (C), 135.8 (C), 130.3 (4×CH), 128.2 (4×CH), 126.8 (2×CH), 73.3 (C, minor isomer), 72.4 (C, major isomer), 62.1 (2×CH_2), 53.6 (CH, major isomer), 51.2 (CH, minor isomer), 45.3 (CH_2, minor isomer), 44.8 (CH_2, major isomer), 24.1 (CH_3, minor isomer), 23.8 (CH_3, major isomer), 13.7 (2×CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 300 [M^+, <1], 209 (69), 91 (100), 65(19), 43 (53). IR (neat): $\tilde{\nu}$ = 3516, 1724 cm^{-1}; R_f = 0.6 (hexanes/EtOAc 3:1). $C_{13}H_{17}BrO_3$ (301.18): calcd. C 51.84, H 5.69; found C 51.95, H 5.72.

Ethyl 2-Bromo-3-hydroxy-3-methyloctanate (1f): Yield: 87%, 122 mg. Data from a mixture of diastereoisomers in a ratio of 45:55. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.22 (q, *J* = 7.1 Hz, 2 H, major isomer), 4.21 (q, *J* = 7.2 Hz, 2 H, minor isomer), 4.21 (s, 1 H, minor isomer), 4.20 (s, 1 H, major isomer), 3.08 (s, 2 H), 1.62–1.53 (m, 16 H), 1.31 (s, 3 H, minor isomer), 1.30 (s, 3 H, major isomer), 1.27 (t, *J* = 7.1 Hz, 6 H), 0.84 (t, *J* = 6.8 Hz, 3 H, minor isomer), 0.82 (t, *J* = 6.9 Hz, 3 H, major isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (C, major isomer), 169.6 (C, minor isomer), 72.7 (C, major isomer), 72.2 (C, minor isomer), 62.0 (2×CH_2), 54.4 (CH, minor isomer), 53.5 (CH, major isomer), 39.3 (CH_2, major isomer), 39.1 (CH_2, minor isomer), 32.0 (CH_2, major isomer), 31.9 (CH_2, minor isomer), 23.7 (CH_2, major isomer), 23.6 (CH_2, minor isomer), 23.4 (CH_2, minor isomer), 22.4 (CH_2, major isomer), 13.8 (2×CH_3), 13.7 (4×CH_3) ppm. MS (70 eV, EI): *m*/*z* (%) = 280 [M^+, <1], 209 (81), 115 (100), 55 (80), 43 (97). IR (neat): $\tilde{\nu}$ = 3517, 1725, 1146 cm^{-1}; R_f = 0.5 (hexanes/EtOAc 3:1); $C_{11}H_{12}BrO_3$ (281.19): calcd. C 46.99, H 7.53; found C 47.08, H 7.47.

Ethyl 2-Bromo-3-hydroxy-3,5-dimethylhexanoate (1g): Yield: 82%, 110 mg. Data from a mixture of diastereoisomers in a ratio of

57:43. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.23 (q, J = 7.1 Hz, 2 H, minor isomer), 4.24 (q, J = 7.1 Hz, 2 H, major isomer), 4.24 (s, 1 H, major isomer), 4.19 (s, 1 H, minor isomer), 2.95 (s, 2 H), 1.87–1.76 (m, 2 H), 1.59–1.48 (m, 4 H), 1.38 (s, 3 H, major isomer), 1.32 (s, 3 H, minor isomer), 1.27 (t, J = 7.1 Hz, 6 H), 0.98 (d, J = 6.6 Hz, 6 H), 0.95 (d, J = 6.7 Hz, 3 H, major isomer), 0.92 (d, J = 6.7 Hz, 3 H, minor isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C, minor isomer), 169.5 (C, major isomer), 73.2 (C, minor isomer), 72.7 (C, major isomer), 62.0 (2×CH_2), 55.7 (CH, major isomer), 54.1 (CH, minor isomer), 47.2 (CH_2, minor isomer), 46.9 (CH_2, major isomer), 24.7 (CH_3, minor isomer), 24.6 (CH_3, major isomer), 24.4 (2×CH), 23.9 (CH_3, major isomer), 23.8 (CH_3, minor isomer), 13.8 (4×CH_3) ppm. MS (70 eV, EI): m/z (%) = 252 [M^+, <1], 209 (48), 101 (99), 43 (100). IR (neat): $\tilde{\nu}$ = 3518, 1724, 1144 cm^{-1}; R_f = 0.5 (hexanes/EtOAc 3:1); $C_{10}H_{19}BrO_3$ (267.16): calcd. C 44.96, H 7.17; found C 45.02, H 7.26.

Ethyl 2-Bromo-2-(1-hydroxycyclohexyl)acetate (1h): Yield: 78%, 103 mg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (q, J = 7.1 Hz, 2 H), 4.21 (s, 1 H), 3.15 (s, 1 H), 1.66–1.48 (m, 10 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5 (C), 70.7 (C), 61.7 (CH_2), 54.5 (CH), 34.5 (CH_2), 34.2 (CH_2), 25.0 (CH_2), 21.5 (CH_2), 21.0 (CH_2), 13.6 (CH_3) ppm. MS (70 eV, EI): m/z (%) = 264 [M^+, 1], 131 (37), 97 (89), 69 (100). HRMS (70 eV): calcd. for $C_{10}H_{17}BrO_3$ [M^+] 264.0361; found 264.0296. IR (neat): $\tilde{\nu}$ = 3516, 1723, 118 cm^{-1}; R_f = 0.5 (hexanes/EtOAc 3:1). $C_{10}H_{17}BrO_3$ (265.14): calcd. C 45.30, H 6.46;. found C 45.40, H 6.51.

General Procedure for the Synthesis of Compounds 4: To a –78 °C stirred solution of the corresponding compound **1** (1 mmol) in dry THF (2 mL) was added dropwise potassium hexamethyldisilazide (6.5 mL of 0.5 M solution in toluene, 2 mmol). After stirring overnight, the resulting solution was quenched with aqueous saturated solution of NH_4Cl (10 mL). The organic material was extracted with dichloromethane, the combined extracts were dried with Na_2SO_4, and the solvent was removed under reduced pressure. Purification by chromatography on silica gel (hexanes/EtOAc 20:1) provided pure compounds **4**.

(2*S,3*S**)-Ethyl 3-Phenyl-1,2-epoxypentanoate (2*S**,3*S**-4a):** Yield: 57%, 125 mg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.17 (m, 5 H), 3.85–3.74 (m, 2 H), 3.59 (s, 1 H), 2.13–2.01 (m, 1 H), 1.87–1.64 (m, 1 H), 0.85 (t, J = 7.5 Hz, 3 H), 0.83 (t, J = 7.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (C), 135.9 (C), 127.8 (2×CH), 127.7 (CH), 126.8 (2×CH), 67.1 (C), 60.8 (CH_2), 59.2 (CH), 30.5 (CH_2), 13.5 (CH_3), 8.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2978, 1750, 1729, 1200 cm^{-1}; R_f = 0.6 (hexanes/EtOAc 3:1); $C_{13}H_{16}O_3$ (220.26): calcd. C 70.89, H 7.32; found C 71.02, H 7.23.

(2*R,3*S**)-Ethyl 3-Phenyl-1,2-epoxypentanoate (2*R**,3*S**-4a):** Yield: 28%, 62 mg. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.17 (m, 5 H), 4.20 (c, J = 7.0 Hz), 3.37 (s, 1 H), 2.13–2.01 (m, 1 H), 1.87–1.64 (m, 1 H), 1.21 (t, J = 5.8 Hz, 3 H), 0.76 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 (C), 138.3 (C), 128.3 (2×CH), 127.7 (CH), 126.0 (2×CH), 66.4 (C), 61.4 (CH), 61.2 (CH), 23.8 (CH_2), 14.1 (CH_3), 9.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2976, 1756, 1728, 1199 cm^{-1}; R_f = 0.5 (hexanes/EtOAc 3:1); $C_{13}H_{16}O_3$ (220.26): calcd. C 70.89, H 7.32; found C 71.02, H 7.23.

Ethyl 3-Pheny-2,3-epoxybutanoate (4d): Yield: 90%, 186 mg. Data from a mixture of diastereoisomers in a ratio of 61:39. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.23 (m, 10 H), 4.32–4.22 (m, 2 H, minor isomer), 3.94–3.82 (m, 2 H, major isomer), 3.64 (s, 1 H, major isomer), 3.43 (s, 1 H, minor isomer), 1.75 (s, 3 H, minor isomer), 1.71 (s, 3 H, major isomer), 1.30 (t, J = 7.1 Hz, 3 H, minor isomer), 0.87 (t, J = 7.1 Hz, 3 H, major isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4 (C, minor isomer), 166.9 (C, major isomer), 139.9 (C, minor isomer), 137.0 (C, major isomer), 128.3 (2×CH, minor isomer), 127.9 (CH, minor isomer), 127.8 (2×CH, major isomer), 126.7 (CH, major isomer), 126.1 (2×CH, major isomer), 125.0 (2×CH, minor isomer), 63.4 (CH, major isomer), 61.3 (CH, minor isomer), 60.7 (CH_2, major isomer), 60.4 (CH_2, minor isomer), 26.4 (CH_3, minor isomer), 24.4 (CH_3, major isomer), 14.0 (CH_3, minor isomer), 13.5 (CH_3, major isomer) ppm. IR (neat): $\tilde{\nu}$ = 2983, 1752, 1729, 1201 cm^{-1}; R_f = 0.5 (hexanes/EtOAc 3:1); $C_{12}H_{14}O_3$ (206.24): calcd. C 69.88, H 6.84; found C 70.01, H 6.76.

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