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Transformation of α,β-Epoxyesters into 2,3-Dideuterioesters Promoted by Samarium Diiodide

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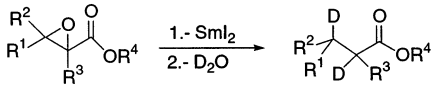
Abstract: An easy and general sequenced elimination/reduction process by means of samarium diiodide, in the presence of D_2O, provides an efficient method for synthesizing 2,3-dideuterioesters **2**. The reaction can be also carried out in the presence of H_2O instead of D_2O, yielding the corresponding saturated esters **4**. Other deuterated esters have been also obtained. A mechanism to explain this synthesis has been proposed.

Epoxides are important in organic synthesis because these compounds can be easily manipulated in variety of synthetically useful reactions. In this sense, an oxirane ring can be opened by a variety of nucleophiles affording 1,2-difunctionalized systems and can undergo rearrangement reactions such as chain-elongation or ring-expansion processes.[1] However, the reduction of epoxides to hydrocarbons has been scarcely reported,[2] and to the best of our knowledge, no general transformation of α,β-epoxyesters into saturated esters has been published.[3] In addition, the synthesis of dideuterio compounds from epoxides has not been reported either. For these reasons, and taking into account the usefulness of isotopically labeled compounds to establish the mechanism of organic reactions and the biosynthesis of many natural compounds,[4] the development of an effective general method for the synthesis of 2,3-dideuterioesters from α,β-epoxyesters is of significant value.

Previously, we reported a new synthetic application of samarium diiodide to promote β-elimination reactions with total or high diastereoselectivity from functionalized halohydrines or related compounds.[5] More recently, we have also described the deoxygenation reaction of α,β-epoxyesters promoted by samarium diiodide, obtaining (*E*)-α,β-unsaturated esters with total or high stereoselectivity.[6]

SCHEME 1. Synthesis of 2,3-Dideuterioesters



1 **2**

In addition, we also reported the transformation of 2-halo-3-hydroxyesters or amides into 2,3-dideuterioesters or amides, respectively, by using samarium diiodide and D_2O.[7]

In this paper, we describe a novel transformation of α,β-epoxyesters **1** into 1,2-dideuterioesters **2** based on the ability of samarium diiodide to produce sequential organic reactions.[8] Thus, a β-elimination reaction of α,β-epoxyesters **1** promoted by SmI_2 and a 1,4-reduction of the obtained α,β-unsaturated esters **3** with D_2O in the presence of SmI_2, afforded the corresponding 2,3-dideuterioesters **2**. This transformation can be also carried out in the presence of H_2O instead of D_2O, isolating the corresponding saturated esters. Moreover, this methodology can be also applied to prepare 2-deuterio- or 3-deuterioesters and 2-deuterio-3-hydroxyesters.

The successive treatment of epoxyesters **1** with a solution of SmI_2 (5 equiv) in THF for 2 h, at room temperature or at reflux, and further treatment with D_2O (2 mL) for 12 h (room temperature) or 30 min (reflux), afforded the corresponding 2,3-dideuterioesters **2** in high yield (Scheme 1).

This transformation was complete and took place through an efficient sequenced elimination/reduction process. No important amount of byproducts were observed on the crude reaction. The obtained results in the synthesis of 2,3-dideuterioesters **2** an their corresponding yields after column chromatography are shown in Table 1.

In the case of disubstituted α,β-epoxyesters, the reaction was carried out at room temperature. When the starting compounds were tri- or tetrasubstituted α,β-epoxyesters, the synthesis of 2,3-dideuterioesters was carried out at reflux, since the reaction was incomplete at room temperature. Moreover, when tetrasubstituted α,β-epoxyesters were used as starting compounds, an increase of the amount of samarium diiodide was necessary to obtain 2,3-dideuterioesters. The decrease of the reactivity of the starting 2,3-epoxyesters to enhance the substitution on the oxirane ring could be due to the increase of steric hindrance.

All epoxyesters **1** used as starting compounds were easily prepared by reaction[9] of the corresponding potas-

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(2) (a) Fry, J. L.; Mraz, T. J. *Tetrahedron Lett.* **1979**, *20*, 849−852. (b) Van Temelen, E. E.; Gladysz, J. A. *J. Am Chem.* Soc **1974**, *96*, 5290−5291.

(3) Transformation of 2,3-epoxy-3-phenylpropionic acid ethyl ester into 3-phenylpropionic acid ethyl ester by using a borohydride exchange resin has been described: Sim, T. B.; Yoon, N. M. *Bull. Chem Soc. Jpn.* **1997**, *70*, 1101−1107.

(4) Mann, J. *Secondary Metabolism*; Oxford University Press: Oxford, 1986; p 23.

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(6) Concellón, J. M.; Bardales, E. *Org. Lett.* **2002**, *4*, 189−191.

(7) Concellón, J. M.; Rodríguez-Solla, H. *Chem. Eur. J.* **2001**, *7*, 4266−4271.

(8) For recent reviews on sequenced reactions promoted by samarium diiodide: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354.

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TABLE 1. Synthesis of 2,3-Dideuterioesters 2

2[a]	R^1	R^2	R^3	R^4	yield[b] (%)
2a[c]	*p*-(MeO)Ph	H	H	Me	81
2b[c]	MeCH(Ph)	H	H	Me	49
2c	*n*-Bu	H	Ph	*i*-Pr	61
2d	C_7H_{15}	H	Me	Et	70
2e	cyclohexyl	H	Me	Et	81
2f	Ph	H	Bu	Et	64
2g	*p*-(MeO)Ph	H	Me	Et	68
2h	MeCH(Ph)	H	C_6H_{13}	Et	62
2i	C_9H_{17}[d]	H	Me	Et	67
2j	Ph	Me	Me	Et	85
2k	Ph	Et	Me	Et	71

[a] Unless otherwise noted, reactions were carried out under reflux in THF. [b] Isolated yield after column chromatography based on compound **1**. [c] The reaction was carried out at room temperature. [d] $C_9H_{17}/Me_2C{=}CH(CH_2)_2CH(Me)CH_2$.

sium enolates of α-chloroesters[10] (generated by treatment of α-chloroesters with potassium hexamethyldisilazide at −78 °C) with aldehydes or ketones, at −78 °C and further heating to room temperature.[11]

The position of deuteration was established by ^1H and ^{13}C NMR spectrometry of the compounds **2**, while complete deuterium incorporation (>99%) was determined by mass spectroscopy.[12] The obtained 2,3-dideuterioesters **2** were isolated as mixture of diastereoisomers (ranging between 1:1 and 2:1) due to the fact that incorporation of deuterium generates two new stereogenic centers.

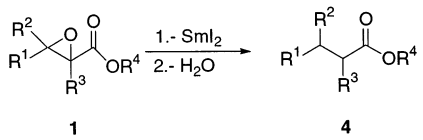
It can be seen from Table 1 that this methodology to obtain 2,3-dideuterioesters **2** is general. The oxirane ring of the starting epoxyesters can be di-, tri-, or tetrasubstituted, and R^1, R^2, R^3, and R^4 can be varied widely. Thus, R^1 can be aliphatic (linear, branched, or cyclic), unsaturated, or aromatic; R^3 could also be changed using different α-haloesters to prepare the starting epoxyesters, and the reaction was unaffected by the presence of bulky groups R^4 on the carbonyl ester (Table 1, compound **2c**). The synthesis of 2,3-dideuterioesters also showed tolerance to the presence of other C=C (Table 1, compound **2i**) and methoxy groups (Table 1, compounds **2a** and **2g**).

It is noteworthy that D_2O is the cheapest deuteration reagent to obtain organic compounds isotopically labeled with deuterium. Only a few examples of the synthesis of 1,2-dideuterioesters have been reported.[7]

The synthesis of nondeuterated saturated esters **4** can be also carried out starting from the same epoxyesters **1** by treatment with H_2O instead of D_2O and no important differences were observed (Scheme 2 and Table 2).

Other deuterated esters, such as 2- or 3-deuterioesters and 2-deuterio-3-hydroxyesters, can be prepared with the described methodology (Figure 1). Thus, starting from isopropyl 2,3-epoxy-2-phenylheptanoate, the corresponding 2,3-dideuterated ester **2c** or saturated ester **4c** (without deuterium) were obtained by using D_2O or H_2O,

SCHEME 2. Synthesis of Saturated Esters

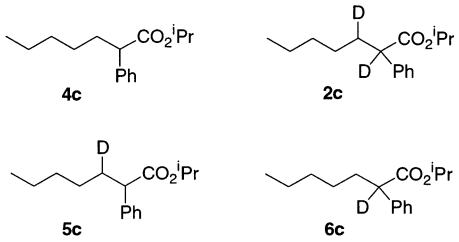


1 **4**

TABLE 2. Synthesis of Saturated Esters 4

4	R^1	R^2	R^3	R^4	yield[a] (%)
4c	*n*-Bu	H	Ph	*i*-Pr	71
4e	cyclohexyl	H	Me	Et	82
4g	*p*-(MeO)Ph	H	Me	Et	70

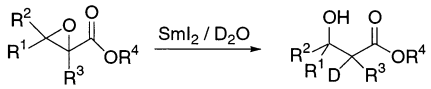
[a] Isolated yield after column chromatography based on compound **1**.



4c **2c** **5c** **6c**

FIGURE 1. Synthesis of 3- or 2-deuterioesters.

SCHEME 3. Synthesis of 2-Deuterio-3-hydroxyesters



1 **7**

respectively. The reaction of **2c** with LDA and further hydrolysis afforded the corresponding 3-deuterioester **5c** (90% yield) and the successive treatment of **4c** with LDA and D_2O gave the 2-deuterioester **6c** (89% yield).

The transformation of starting compounds **1** into 2-deuterio-3-hydroxyesters **7** can be achieved by modifying the proposed methodology. In this respect, treatment of **1c** and **1k** with a solution of samarium diodide in THF and D_2O at reflux gave the corresponding monodeuterated 3-hydroxyesters **7c** and **7k** in 60 and 68% yield, respectively (Scheme 3).[13]

Mechanism. Synthesis of **2**, **4**, and **7** may be explained by assuming that the metalation of **1** with SmI_2 generates the enolate intermediate **8**, which (in the absence of D_2O or H_2O) eliminates affording (*E*)-α,β-unsaturated esters **3** with total or high diastereoselection.[6] When the reaction of **1** with SmI_2 is carried out in the presence of D_2O, the corresponding 2-deuterio-3-hydroxyester **7** is isolated. The 1,4-reduction promoted by SmI_2 of the obtained α,β-unsaturated esters **3** is initiated by oxidative addition of SmI_2 to generate the enolate radical **9**,[14] which, after a second electron transfer from SmI_2 and hydrolysis with D_2O or H_2O, affords the corresponding compound **2** or **4** (Scheme 4).

(9) Rosen, T. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2; p 409.

(10) Compounds **1f** and **1h** were obtained from the corresponding α-bromoesters.

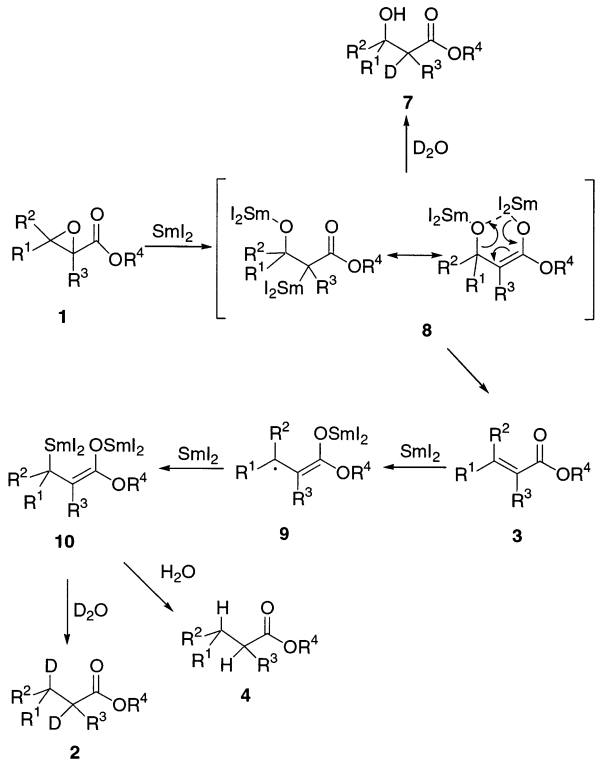
(11) Preparation of α,β-epoxyesters can be also accomplished by epoxidation of α,β-unsaturated esters: Meth-Cohn, O.; Moore, C.; Taljaard, H. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663−2674.

(12) MS and HRMS spectra of compounds **2**, **5**, **6**, and **7** show a lack of a peak or a very weak peak of the $[M]^+$ of the corresponding nondeuterated compound, indicating a presence of the nondeuterated compound <1%.

(13) The transformation of α,β-epoxyesters into 3-hydroxyesters, by using SmI_2 in the presence of HMPA and *N*,*N*-dimethylaminoethanol, has been previously described: Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437−4440.

(14) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2121−2124.

SCHEME 4. Proposed Mechanism



In conclusion, the SmI_2-promoted elimination/reduction sequence (in the presence of D_2O or H_2O) provides an efficient method for synthesizing 2,3-dideuterioesters or nondeuterated saturated esters. Others deuterated esters such as 2-deuterio- or 3-deuterioesters and 2-deuterio-3-hydroxyesters can be also obtained. The present method is easy, simple, general and the starting compounds are easily available. In addition, cheap D_2O is used to obtain the isotopically labeled products. A mechanism to explain this synthesis has been proposed.

Experimental Section

General Methods. 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 higher quality available and were used without further purification. Isopropyl 2-chloro-2-phenylpropanoate was prepared by treatment of 2-chlorophenylacetyl chloride with isopropyl alcohol, and in turn, 2-chlorophenylacetyl chloride was obtained according to literature from the corresponding carboxylic acids.[15] Samarium diiodide was prepared by reaction of CH_2I_2 with samarium powder.[16] Compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm). All NMR spectra were registered at room temperature. ^1H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 or 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. GC−MS and HRMS were measured at 70 eV. Only the most important IR absorptions (in cm^{-1}) and the molecular ions and/or base peaks in MS are given.

(15) Harpp, D. N.; Bao, L Q.; Black, C. J.; Gleason, J. G.; Smith, R A. *J. Org. Chem.* **1975**, *40*, 3420−3426.

(16) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chem.* **1981**, *5*, 479−484.

General Procedure for the Synthesis of Epoxyesters 1. To a −78 °C stirred solution of the corresponding 2-haloester (2.5 mmol) in dry THF (4 mL) was added dropwise potassium hexamethyldisilazide (6.5 mL of 0.5 m solution in toluene, 3.25 mmol). After the mixture was stirred for 10 min, a solution of the corresponding aldehyde or ketone (2.5 mmol) in dry THF (4 mL) was added dropwise at −78 °C, and the resulting mixture was allowed to warm to room temperature. The resulting solution was quenched with aqueous saturated solution of NH_4Cl (20 mL). Usual workup provided crude 2,3-epoxyesters **1**, which were purified by column flash chromatography over silica gel (hexane/ethyl acetate) provided pure compound.

General Procedure for the Synthesis of 2,3-Dideuterioesters 2 and Saturated Esters 4. A solution of SmI_2 (2.3 mmol) in THF (24 mL) was added dropwise, under nitrogen atmosphere, to a stirred solution of the corresponding α,β-epoxyester **1** (0.4 mmol) in THF (4 mL) at room temperature or at reflux (see Table 1). After the mixture was stirred for 2 h, D_2O or H_2O (2 mL) was added to the solution. The mixture was stirred for 12 h (room temperature) or 30 min (reflux). Then the reaction was quenched with aqueous HCl (0.1 M, 10 mL). Usual workup afforded crude 2,3-dideuterioesters **2** or saturated esters **4**, which were purified by column flash chromatography over silica gel (hexane/ethyl acetate).

Methyl 2,3-dideuterio-3-[(4-methoxy)phenyl]propanoate (2a): R_f = 0.4 (hexane/AcOEt 5/1); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.13 (2 H, d, J = 8.7 Hz), 6.84 (2 H, d, J = 8.7 Hz), 3.80 (3 H, s), 3.68 (3 H, s), 2.97−2.84 (1 H, m), 2.67−2.54 (1 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (C), 157.9 (C), 133.0 (C), 129.1 (CH), 113.8 (CH), 55.1 (CH_3), 51.4 (CH_3), 35.5 (CHD, t, J = 20.0 Hz), 29.6 (CHD, t, J = 22.0 Hz); MS (70 eV) m/z 196 (14) $[M]^+$, 37 (6), 122 (98), 59 (97); IR (neat) 2958, 1738, 1614, 1513, 1464. Anal. Calcd for $C_{11}H_{12}D_2O_3$: C, 67.32; H, 8.22. Found: C, 67.41; H, 8.18.

Methyl 2,3-dideuterio-4-phenylpentanoate (2b): R_f = 0.4 (hexane/AcOEt 5/1); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.29−7.16 (10 H, m), 3.62 (6 H, s), 2.73−2.70 (2 H, m), 2.20−2.17 (2 H, m), 1.90−1.83 (2 H, m), 1.28 (3 H, s), 1.26 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0 (C), 172.8 (C), 146.1 (C), 145.6 (C), 128.4 (CH), 128.3 (CH), 126.9 (CH), 126.6 (CH), 126.3 (CH), 126.1 (CH), 51.4 (CH_3), 42.2 (CHD, t, J = 19.8 Hz), 39.2 (CH), 35.9 (CHD, t, J = 19.8 Hz), 32.7 (CHD, t, J = 19.8 Hz), 31.9 (CHD, t, J = 19.8 Hz), 22.1 (CH_3), 21.5 (CH_3); MS (70 eV) m/z 194 (6) $[M]^+$, 120 (42), 105 (100), 77 (33), 59 (20); IR (neat) 2967, 1744, 1615, 1459, 1210. Anal. Calcd for $C_{12}H_{14}D_2O_2$: C, 74.19; H, 9.34. Found: C, 74.01; H, 9.28.

Isopropyl 2,3-dideuterio-2-phenylheptanoate (2c): R_f = 0.3 (hexane/ethyl acetate 20/1); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.32−7.23 (10 H, m), 5.04−4.96 (2 H, m), 2.08−1.981 (m, 1 H), 1.77−1.62 (m, 1 H), 1.48−1.18 (12 H, m), 1.23 (6 H, d, J = 6.2), 1.14 (6 H, d, J = 6.2), 0.87 (6 H, t, J = 6.8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (C), 139.4 (C), 128.3 (CH), 127.7 (CH), 126.9 (CH), 67.7 (CH), 51.5 (CD, t, J = 19.2 Hz), 33.1 (CHD, t, J = 19.8 Hz), 31.5 (CH_2), 27.0 (CH_2), 22.4 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 13.9 (CH_3); MS (70 eV) m/z 250 (1) $[M]^+$, 163 (36), 92 (100), 77 (3), 43 (63); IR (neat) 2969, 1743, 1615, 1473, 1262. Anal. Calcd for $C_{16}H_{22}D_2O_2$: C, 76.75; H, 10.47. Found: C, 76.84; H, 10.50.

Ethyl 2,3-Dideuterio-2-methyldecanoate (2d).[7]

Ethyl 3-Cyclohexyl-2,3-dideuterio-2-methylpropanoate (2e).[7]

Ethyl 2-butyl-2,3-dideuterio-3-phenylpropanoate (2f): R_f = 0.5 (hexane/ethyl acetate 5/1); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.28−7.14 (10 H, m), 4.16 (2 H, q, J = 7.1), 4.04 (2 H, q, J = 7.1), 2.89 (1 H, s), 2.72 (1 H, s), 1.81−1.02 (15 H, m), 1.13 (3 H, t, J = 7.1), 0.89−0.84 (6 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6 (C), 174.3 (C), 139.3 (C), 128.7 (CH), 128.1 (CH), 126.1 (CH), 60.2 (CH_2), 59.9 (CH_2), 47.1 (CD, t, J = 19.7 Hz), 59.9 (CHD, t, J = 19.8 Hz), 31.6 (CH_2), 30.1 (CH_2), 29.3 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 14.2 (CH_3), 14.1 (CH_3), 13.8 (CH_3), 13.7 (CH_3); MS (70 eV) m/z 236 (15) $[M]^+$, 179 (21), 163 (12), 92 (100), 77 (3); IR (neat) 1728, 1452, 1367, 1249. Anal. Calcd for $C_{15}H_{20}D_2O_2$: C, 76.23; H, 10.23. Found: C, 76.18; H, 10.26.

Ethyl 2,3-Dideuterio-2-methyl-3-[4-(methoxy)phenyl]propanoate (2g).[7]

Ethyl 2,3-Dideuterio-2-hexyl-4-phenylpentanoate (2h).[7]

Ethyl 2,3-dideuterio-2,5,9-trimethyldec-8-enoate (2i): R_f = 0.3 (hexane/AcOEt 20/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.14−5.06 (1H, m), 4.13 (2 H, q, J = 7.2 Hz), 2.18−1.02 (8 H, m), 1.69 (3 H, s), 1.60 (3 H, s), 1.26 (3 H, t, J = 7.2 Hz), 1.14 (3 H, s), 0.87 (3 H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.9 (C), 131.0 (C), 124.8 (CH), 60.0 (CH_2), 39.3 (CD, t, J = 20.4 Hz), 36.9 (CH_2), 34.1 (CH_2), 32.3 (CH), 30.4 (CHD, t, J = 20.4 Hz), 25.6 (CH_3), 25.4 (CH_2), 19.4 (CH_3), 17.5 (CH_3), 14.2 (CH_3); MS (70 eV) m/z 242 (11) $[M]^+$, 140 (10), 111 (7), 103 (100), 69 (83); IR (neat) 2965, 2860, 1736, 1674, 1462. Anal. Calcd for $C_{15}H_{26}D_2O_2$: C, 74.33; H, 12.47. Found: C, 74.45; H, 12.54.

Ethyl 2,3-dideuterio-2-methyl-3-phenylbutanoate (2j): R_f = 0.4 (hexane/ethyl acetate 10/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36−7.16 (10 H, m), 4.20 (2 H, q, J = 7.2), 3.93 (2 H, q, J = 7.2), 1.31 (3 H, t, J = 7.2), 1.27 (3 H, s), 1.26 (3 H, s), 1.19 (3 H, s), 1.03 (3 H, t, J = 7.2), 0.94 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.3 (C), 175.6 (C), 144.9 (C), 144.3 (C), 128.3 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 126.3 (CH), 126.2 (CH), 60.1 (CH_2), 59.8 (CH_2), 46.2 (CD, t, J = 20.1 Hz), 46.1 (CD, t, J = 20.7 Hz), 42.8 (CD, t, J = 20.1 Hz), 41.9 (CD, t, J = 19.8 Hz), 20.4 (CH_3), 17.6 (CH_3), 16.0 (CH_3), 14.2 (CH_3), 14.1 (CH_3), 13.8 (CH_3); MS (70 eV) m/z 208 (5) $[M]^+$, 135 (4), 106 (100), 77 (17); IR (neat) 2980, 1732, 1653, 1507, 1277. Anal. Calcd for $C_{13}H_{16}D_2O_2$: C, 74.96; H, 9.68. Found: C, 74.80; H, 9.63.

Ethyl 2,3-dideuterio-2-methyl-3-phenylpentanoate (2k): R_f = 0.3 (hexane/ethyl acetate 10/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41−7.12 (10 H, m), 4.19 (2 H, q, J = 7.2), 3.88 (2 H, q, J = 7.2), 1.30 (6 H, t, J = 7.2), 1.23 (3 H, s), 0.98 (6 H, t, J = 7.2), 0.90 (3 H, s), 0.72 (4 H, q, J = 7.2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.5 (C), 175.6 (C), 142.6 (C), 142.0 (C), 128.2 (CH), 127.9 (CH), 126.3 (CH), 126.2 (CH), 60.1 (CH_2), 59.7 (CH_2), 50.3 (CD, t, J = 21.2 Hz), 49.9 (CD, t, J = 19.8 Hz), 45.3 (CD, t, J = 20.4 Hz), 27.2 (CH_2), 24.5 (CH_2), 15.9 (CH_3), 14.8 (CH_3), 14.2 (CH_3), 13.8 (CH_3), 12.0 (CH_3), 11.8 (CH_3); MS (70 eV) m/z 222 (4) $[M]^+$, 149 (3), 120 (65), 91 (100), 77 (20); IR (neat) 2972, 1731, 1507, 1461, 1270. Anal. Calcd for $C_{14}H_{18}D_2O_2$: C, 75.63; H, 9.97. Found: C, 75.74; H, 9.89.

Isopropyl 2-phenylheptanoate (4c): R_f = 0.2 (hexane/ethyl acetate 20/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35−7.25 (5 H, m), 5.08−4.96 (1 H, m), 3.51 (1 H, t, J = 7.7), 2.13−1.30 (8 H, m), 1.25 (3 H, d, J = 6.2), 1.16 (3 H, d, J = 6.2), 0.89 (3 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (C), 139.5 (C), 128.3 (CH), 127.7 (CH), 126.8 (CH), 67.6 (CH), 51.9 (CH), 33.5 (CH_2), 31.4 (CH_2), 27.1 (CH_2), 22.3 (CH_2), 21.6 (CH_3), 21.4 (CH_3), 13.8 (CH_3); MS (70 eV) m/z 248 (1) $[M]^+$, 161 (27), 105 (37), 91 (100), 77 (7); IR (neat) 3030, 2931, 1729, 1602, 1455. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.29; H, 9.80.

Ethyl 3-cyclohexyl-2-methylpropanoate (4e): R_f = 0.4 (hexane/AcOEt 10/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.19−4.04 (4 H, m), 2.58−2.46 (2 H, m), 1.83−0.75 (26 H, m), 1.25 (6 H, t, J = 6.9 Hz), 1.12 (6 H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2 (C), 59.9 (CH_2), 41.5 (CH_2), 36.8 (CH), 35.3 (CH), 33.2 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 17.5 (CH_3), 14.2 (CH_3); MS (70 eV) m/z 198 (1) $[M]^+$, 115 (35), 102 (100), 83 (14), 73 (11); IR (neat) 2924, 1736, 1450, 1378, 1257. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.52; H, 11.12.

Ethyl 2-Methyl-3-[4-(methoxy)phenyl]propanoate (4g).[7]

Isopropyl 3-Dideuterio-2-phenylheptanoate 5c. To a stirred solution of lithium diisopropylamide (0.48 mmol) in THF (5 mL) was added a solution of the compound **2c** (0.4 mmol) in THF (4 mL), under nitrogen atmosphere, dropwise at −78 °C. After being stirred for 30 min, the reaction mixture was quenched with H_2O (2 mL). Usual workup provided 3-deuterio-esters **5c**. Compound **5c** was >98% pure and further purification was not necessary: R_f = 0.3 (hexane/ethyl acetate 20/1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.34−7.25 (10 H, m), 5.07−4.92 (2 H, m), 3.50 (2 H, d, J = 7.9), 2.12−1.98 (1 H, m), 1.86−1.62 (1 H, m), 1.45−1.09 (12 H, m), 1.24 (6 H, d, J = 6.4), 1.15 (6 H, d, J = 6.4), 1.01−0.77 (6 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (C), 139.5 (C), 128.4 (CH), 127.8 (CH), 126.9 (CH), 67.7 (CH), 51.9 (CH), 33.1 (CHD, t, J = 19.6 Hz), 33.5 (CH_2), 27.1 (CH_2), 22.4 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 13.9 (CH_3); IR (neat) 2969, 1743, 1615, 1473, 1262. Anal. Calcd for $C_{16}H_{23}DO_2$: C, 77.06; H, 10.10. Found: C, 77.21; H, 10.06.

Isopropyl 2-Dideuterio-2-phenylheptanoate 6c. To a stirred solution of lithium diisopropylamide (0.48 mmol) in THF (5 mL) was added a solution of the compound **4c** (0.4 mmol) in THF (4 mL), under nitrogen atmosphere, dropwise at −78 °C. After being stirred for 30 min, the reaction mixture was quenched with D_2O (2 mL). Usual workup provided 3-deuterio-esters **6c**. Compound **6c** was >98% pure, and further purification was not necessary: R_f = 0.3 (hexane/ethyl acetate 20/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32−7.24 (10 H, m), 5.04−4.96 (2 H, m), 2.17−1.20 (16 H, m), 1.23 (6 H, d, J = 6.6), 1.14 (6 H, d, J = 6.6), 0.90−0.82 (6 H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6 (C), 139.4 (C), 128.3 (CH), 127.7 (CH), 126.9 (CH), 67.7 (CH), 51.5 (CD, t, J = 20.8. Hz), 33.4 (CH_2), 31.4 (CH_2), 27.1 (CH_2), 22.3 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 13.9 (CH_3); IR (neat) 2969, 1743, 1615, 1473, 1262. Anal. Calcd for $C_{16}H_{23}DO_2$: C, 77.06; H, 10.10. Found: C, 77.00; H, 10.15.

General Procedure for the Synthesis of 2-Deuterio-3-hydroxyesters 7. A solution of SmI_2 (1.6 mmol) in THF (19 mL) and D_2O (2 mL) was added dropwise, under nitrogen atmosphere, to a stirred solution of the corresponding 2,3-epoxyester **1** (0.4 mmol) in THF (4 mL) at room temperature. After being stirred for 30 min under reflux, the reaction was quenched with aqueous HCl (0.1 M, 20 mL). Usual workup afforded crude 2-deuterio-3-hydroxyesters **7**, which were purified by column flash chromatography over silica gel (10:1 hexane ethyl acetate).

Isopropyl 2-deuterio-3-hydroxy-2-phenylheptanoate (7c): R_f = 0.3 (hexane/ethyl acetate 5/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.39−7.31 (5 H, m), 5.10−4.97 (1 H, m), 4.20−4.17 (1 H, m), 2.37−2.18 (1 H, s, br), 1.58−1.20 (6 H, m), 1.26 (3 H, d, J = 6.2), 1.15 (3 H, d, J = 6.2), 0.91 (3 H, t, J = 7.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7 (C), 135.2 (C), 129.0 (CH), 128.5 (CH), 127.5 (CH), 72.1 (CH), 68.2 (CH), 57.3 (CD, t, J = 19.5 Hz), 33.9 (CH_2), 27.7 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 21.3 (CH_3), 13.9 (CH_3); IR (neat) 2956, 1725, 1449, 1262, 1107. Anal. Calcd for $C_{16}H_{23}DO_3$: C, 72.42; H, 9.50. Found: C, 72.56; H, 9.44.

Ethyl 2-deuterio-3-hydroxy-2-methyl-3-phenylpentanoate (7k): R_f = 0.2, 0.4 (hexane/ethyl acetate 5/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.42−7.21 (10 H, m), 4.24 (2 H, q, J = 7.2), 4.07 (1 H, s), 3.87 (2 H, q, J = 7.2), 3.75 (1 H, s), 1.96−169 (4 H, m), 1.32 (6 H, m), 0.94 (3 H, s), 0.92 (3 H, t, J = 7.2), 0.68 (3 H, t, J = 7.1), 0.66 (3 H, t, J = 7.2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.5 (C), 176.9 (C), 145.2 (C), 142.4 (C), 127.9 (CH), 127.7 (CH), 126.3 (CH), 125.4 (CH), 77.1 (C), 76.9 (C), 60.7 (CH_2), 60.3 (CH_2), 48.4 (CD, t, J = 19.8 Hz), 47.0 (CD, t, J = 20.1 Hz), 34.4 (CH_2), 31.4 (CH_2), 14.1 (CH_3), 13.6 (CH_3), 12.5 (CH_3), 11.8 (CH_3), 7.7 (CH_3), 7.4 (CH_3); MS (70 eV) m/z 237 (1) $[M]^+$, 208 (5), 135 (75), 77 (45), 100 (57); IR (neat) 2979, 1706, 1461, 1280, 1080. Anal. Calcd for $C_{14}H_{19}DO_3$: C, 70.86; H, 8.92. Found: C, 70.71; H, 8.99.

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Supporting Information Available: Experimental data for compounds **1a**−**k** and ^{13}C NMR spectra of **2**, **4**, **5c**, **6c**, and **7c**,**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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