Sequential Elimination – Reduction Reactions Promoted by Samarium Diiodide: Synthesis of 2,3-Dideuterioesters or -amides

José M. Concellón* and Humberto Rodríguez-Solla[a]

Abstract: A facile and general sequential elimination/reduction process promoted by samarium diiodide provides an efficient method for synthesizing saturated esters or amides **3** from readily available starting materials. The reaction involves a β-elimination of the starting 2-halo-3-hydroxyesters or -amides **1** and subsequent 1,4-reduction of the obtained α,β-unsaturated esters or amides in the presence of H_2O. When D_2O is used instead of H_2O, 2,3-dideuterioesters or -amides **4** are isolated. A mechanism is proposed to account for this synthesis.

Keywords: deuterium · elimination · reduction · samarium · sequential reactions

Introduction

Sequential reactions are of enormous potential because considerably less time, effort, and material are required to obtain organic compounds with respect to more traditional multi-step procedures. One reagent that exhibits excellent properties for sequential organic reactions is samarium diiodide.[1]

We recently described the first general methodology for the promotion of β-elimination reactions using SmI_2. We reported a highly stereoselective synthesis of (*Z*)-vinyl halides from *O*-acetylated 1,1-dihaloalkan-2-ols,[2] as well as a novel preparation of α,β-unsaturated esters[3] or amides[4] with total or very high selectivity by treatment of the readily available 2-halo-3-hydroxyesters or -amides, respectively, with samarium diiodide.

On the other hand, selective conjugated reduction of α,β-unsaturated carboxylic acid derivatives is a useful reaction in organic chemistry and has been achieved by using several methodologies.[5] However, the conjugated reduction of α,β-unsaturated esters or amides with deuterium instead of hydrogen has been scarcely reported. To the best of our knowledge, only two alternative methodologies to the expensive catalytic addition of D_2 to α,β-unsaturated esters[6] have been described, specifically, the use of enzymes in D_2O,[7] and treatment with CD_3OD or D_2O in the presence of metals.[8] Similarly, in the case of deuteration of α,β-unsaturated amides, only two examples have hitherto been described,[9] both of which involved catalytic addition of D_2. For this reason, the development of an effective general method for the synthesis of 2,3-dideuterioesters or -amides would seem to be a valuable goal.

With regard to the synthetic application of samarium diiodide in organic synthesis, three papers have been published concerning its use in the conjugated reduction of α,β-unsaturated esters or amides. In two of these methodologies, additives such as *N*,*N*-dimethylacetamide (DMA)[10] or hexamethyl phosphoramide (HMPA)[11] were required to facilitate the reduction; in the third case, the reduction was carried out in the presence of methanol as a proton source.[12] However, to the best of our knowledge, the simplest 1,4-reduction of conjugated carboxylic acid derivatives by using SmI_2 and H_2O or D_2O has not been described.[13]

In the present contribution, we describe a novel means of obtaining saturated esters or amides **3** by an efficient sequential process. Thus, a β-elimination reaction of 2-halo-3-hydroxyesters or -amides **1** promoted by SmI_2, followed by a 1,4-reduction of the obtained α,β-unsaturated esters or amides with H_2O in the presence of SmI_2, has been found to afford the corresponding saturated esters or amides. In view of the utility of isotopically labeled compounds in establishing the mechanisms of organic reactions and of the biosynthesis of many natural compounds,[14] we have also applied this methodology to obtain 2,3-dideuterioesters or -amides **4** by using D_2O instead of H_2O.

Results and Discussion

Synthesis of saturated esters and amides: The 2-halo-3-hydroxyesters or -amides **1** used as starting compounds were easily prepared by reactions of the corresponding lithium enolates of α-haloesters or -amides (generated by treatment of α-haloesters or α-chloroamides **2** with LDA at $-78\,^{\circ}C$) with aldehydes at $-78\,^{\circ}C$ (Scheme 1).

[a] Dr. J. M. Concellón, H. Rodríguez-Solla
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo
33071 Oviedo (Spain)
Fax: (+34) 98-510-34-46
E-mail: jmcg@sauron.quimica.uniovi.es

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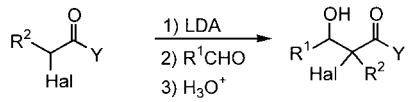
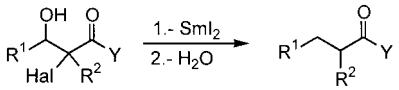


2 1

Scheme 1. Synthesis of the starting compounds **1**.

With the requisite substrates in hand, preliminary studies were performed to determine the optimum reaction conditions for preparing saturated esters. Reaction of 2-halo-3-hydroxyesters with a solution of SmI_2 (5 equivalents) in THF for 30 min at room temperature afforded the corresponding α,β-unsaturated esters, which were treated with H_2O (2 mL) at the same temperature to give, after stirring for 30 min, the corresponding saturated esters **3e–g** in high yield as a result of a conjugated reduction (Scheme 2).



1 3

Scheme 2. Synthesis of the saturated compounds **3**.

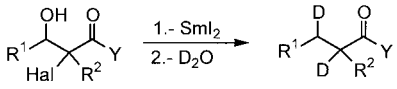
To prepare the saturated amides **3l** and **3m**, a longer reaction time (120 min) was necessary to achieve the required elimination due to the somewhat lower reactivity of the starting 2-chloro-3-hydroxyamides as compared to the esters.[4] The results obtained for the synthesis of saturated esters and amides are summarized in Table 1.

Table 1. Synthesis of saturated esters and amides **3**.

Entry	Compounds **1**		Products **3**				
	1	Hal	**3**	R^1	R^2	Y	Yield [%][a]
1	**1e**	Cl	**3e**	*p*MeO-C_6H_4	Me	OEt	84
2	**1f**	Cl	**3f**	C_7H_{15}	H	OEt	68
3	**1g**	Br	**3g**	Ph	C_4H_9	OEt	60
4	**1l**	Cl	**3l**	Ph	H	NEt_2	96
5	**1m**	Cl	**3m**	Ph	Me	NEt_2	69
6			**3n**[b]	Ph	H	NH_2	73

[a] Isolated yield after column chromatography based on compound **1** consumed. [b] See discussion of results.

Synthesis of 2,3-dideuterioesters and -amides: No significant differences were observed in the reaction when D_2O was used instead of H_2O. Thus, the successive treatment of 2-halo-3-hydroxyesters or -amides **1** with a solution of SmI_2 (5 equivalents) in THF, for 30 min (esters) or 120 min (amides) at room temperature, and then with D_2O (2 mL) for 30 min, afforded the corresponding 2,3-dideuterioesters **4a–e** or amides **4i–m**, respectively, in high yields (Scheme 3). The yields obtained in the syntheses of 2,3-dideuterated compounds **4** are shown in Table 2. When the conjugated reduction was incomplete at room temperature, this step was carried out under reflux and an additional three equivalents of SmI_2 were added (Table 2).[15]



1 4

Scheme 3. Synthesis of 2,3-dideuterioesters or -amides **4**.

The position of deuteration was established by ^1H and ^{13}C NMR spectroscopy of compounds **4**, while the complete deuterium incorporation (>99%) was verified by mass spectrometry.[16] These 2,3-dideuterio compounds were isolated as mixtures of stereoisomers (roughly 1:1 by ^1H NMR spectroscopy and GC-MS).

This proposed methodology for obtaining saturated esters or amides **3** and 2,3-dideuterioesters or -amides **4** is general: R^1 and R^2 can be varied widely. Thus, aliphatic (linear, branched, or cyclic), unsaturated, or aromatic aldehydes may be used to introduce different R^1 groups; R^2 may also be varied using different α-chloroesters or -amides to prepare the starting compounds **1** (Scheme 1). The synthesis of 2,3-dideuterioesters was also found to tolerate the presence of other C=C double bonds (Table 2, entry 4), and proved to be unaffected by the presence of bulky groups R^3 on the carbonyl ester (Table 2, entry 4).

It is noteworthy that D_2O is the cheapest deuteration reagent available for obtaining organic compounds isotopically labeled with deuterium.

The synthesis of 2,3-dideuterioesters can also be carried out starting from the corresponding α,β-unsaturated esters or amides. Thus, successive treatment of methyl cinnamate with SmI_2 (2.5 equivalents) for 30 min at room temperature, and then with D_2O (2 mL) for 30 min afforded methyl 2,3-dideuterio-3-phenylpropanoate (**4h**) in 69% yield. In the case of cinnamamide, the corresponding saturated amide **3n** (73% yield) was obtained by using H_2O as a proton source under the same reaction conditions. However, when D_2O was used, a roughly 3:1 mixture of 2,3-dideuterio-3-phenylpropanamide and 3-phenylpropanamide was obtained as a consequence of competitive hydrolysis arising from H/D exchange of the NH_2 protons (see proposed mechanism). Accordingly, when the cinnamamide was pre-treated with D_2O, 2,3-dideuterio-3-phenylpropanamide (**4n**) was isolated as the sole product. In accordance with the literature,[17] no 1,4-reduction was observed[18] for α,β-unsaturated amides incorporating a tetrasubstituted C=C bond.

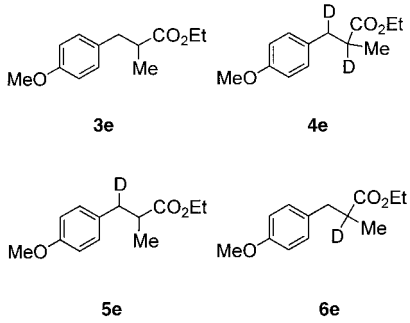
The described methodology can be used to obtain 2,3-dideuterated, 2- or 3-monodeuterated, and non-deuterated esters or amides. Thus, starting from ethyl 2-chloro-3-hydroxy-2-methyl-3-(4-methoxyphenyl)propanoate, the corresponding 2,3-dideuterated ester **4e** or saturated ester **3e**

Abstract in Spanish: *La reacción secuencial de eliminación–reducción de 2-halogeno-3-hidroxiésteres o amidas, promovida por diyoduro de samario, conduce a ésteres o amidas saturadas en presencia de H_2O. Cuando la reacción se lleva a cabo en presencia de D_2O, se aislan los correspondientes 2,3-dideuterioésteres o amidas. El método que se describe, es simple, fácil, general y los compuestos de partida son fácilmente accesibles. Se propone un mecanismo para explicar este proceso.*

Table 2. Synthesis of 2,3-dideuterioesters and -amides **4**.

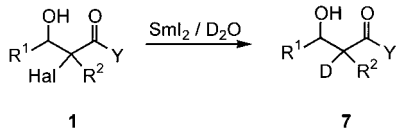
Entry	Compounds **1**		Products **4**				
	1	Hal	**4**	R^1	R^2	Y	Yield [%][a]
1	**1a**	Cl	**4a**	C_7H_{15}	Me	OEt	68
2	**1b**	Cl	**4b**	cyclohexyl[b]	Me	OEt	60
3	**1c**	Br	**4c**	PhCH(Me)	C_6H_{13}	OEt	96
4	**1d**	Cl	**4d**	$Me_2C{=}CH(CH_2)_2CH(Me)CH_2$	Ph	O*i*Pr	69
5	**1e**	Cl	**4e**	*p*MeO-C_6H_4	Me	OEt	84
6			**4h**[c]	Ph	H	OMe	69
7	**1i**	Cl	**4i**	cyclohexyl[b]	H	NEt_2	67
8	**1j**	Cl	**4j**	C_7H_{15}	H	NEt_2	77
9	**1k**	Cl	**4k**	PhCH(Me)	H	NEt_2	65
10	**1l**	Cl	**4l**	Ph	H	NEt_2	85
11	**1m**	Cl	**4m**	Ph	Me	NEt_2	57
12			**4n**[c]	Ph	H	NH_2	73

[a] Isolated yield after column chromatography based on compound **1** consumed. [b] When D_2O was added (second step), a further three equivalents of SmI_2 were also added and the reaction was allowed to proceed under reflux. [c] See discussion of results.



(without deuterium) were obtained by using D_2O or H_2O, respectively. Reaction of **4e** with LDA and further hydrolysis afforded the corresponding 3-deuterioester **5e**, while the successive treatment of **3e** with LDA and D_2O gave the 2-deuterioester **6e**.

The starting compounds **2** may be converted to 2-deuterio-3-hydroxyesters **7**[16] by a modification of the proposed methodology. Thus, treatment of **1b** and **1e** with a solution of samarium diiodide in THF/D_2O gave the corresponding monodeuterated 3-hydroxyesters **7b** and **7e** in 66 and 72% yield, respectively (Scheme 4), this transformation being difficult to achieve through other methodologies.[19] Indeed, compounds **7** are difficult to prepare by other synthetic routes.[20]



Scheme 4. Synthesis of 2-deuterio-3-hydroxyesters **7**.

Mechanism: The synthesis of **3** and **4** may be rationalized by assuming that the metalation of the halogen of **1** with SmI_2 generates the enolate intermediate **8**. In the absence of a proton/deuteron source (H_2O or D_2O), **8** undergoes elimination to afford (*E*)-α,β-unsaturated esters or amides **9** with total or high selectivity.[3, 4] When the metalation is carried out in the presence of D_2O, the corresponding 2-deuterio-3-hydroxyester **7** is isolated. The SmI_2-promoted 1,4-reduction of the obtained α,β-unsaturated esters or amides is initiated by oxidative addition of the reagent to generate the enolate radical **10**,[21] which, after a second electron transfer from SmI_2 and hydrolysis with H_2O or D_2O, affords the corresponding compound **3** or **4** (Scheme 5).

Conclusion

The SmI_2-promoted elimination/reduction sequence (in the presence of H_2O) provides an efficient method for synthesizing saturated esters or amides. The reaction involves β-elimination from 2-chloro-3-hydroxyesters or -amides and subsequent 1,4-reduction of the obtained α,β-unsaturated esters or amides. When D_2O is used instead of H_2O, 2,3-dideuterioesters or -amides are isolated. The present method is easy, simple, and general, and the starting compounds are readily available. Moreover, the cheap deuterium source D_2O is used to obtain the isotopically labeled esters and amides. A mechanism has been proposed to account for this synthesis.

Experimental Section

General: Reactions requiring an inert atmosphere were conducted under dry nitrogen in oven-dried (120 °C) glassware. THF was distilled from sodium/benzophenone immediately prior to use. All reagents were purchased from Aldrich or Merck and were used without further purification. Samarium diiodide was prepared by the reaction of CH_2I_2 with samarium powder.[22] 2-Chloroamides **2** were prepared by reacting amines with the appropriate 2-chloro acid chlorides, which, in turn, were obtained according to a literature procedure from the corresponding carboxylic acids.[23] Silica gel for flash chromatography was purchased from Merck (230–400 mesh); compounds were visualized on analytical thin-layer chromatograms (TLC) by exposure to UV light (254 nm). All NMR spectra were recorded at room temperature. ^{1}H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR spectra were accumulated and DEPT experiments were carried out at 50 or 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which was used as an internal standard; coupling constants (*J*) are reported in hertz (Hz). GC-MS (HP 5973) and HRMS (Finnigan MAT 95) were measured at 70 eV. Only the most important IR absorptions (in cm^{-1}) and the molecular ions and/or base peaks in the mass spectra are listed.

The preparation and characterization of the following compounds are described in reference [4]: 2-chloro-*N*,*N*-diethyl-3-hydroxydecanamide (**1j**), 2-chloro-*N*,*N*-diethyl-3-hydroxy-4-phenylpentanamide (**1k**),

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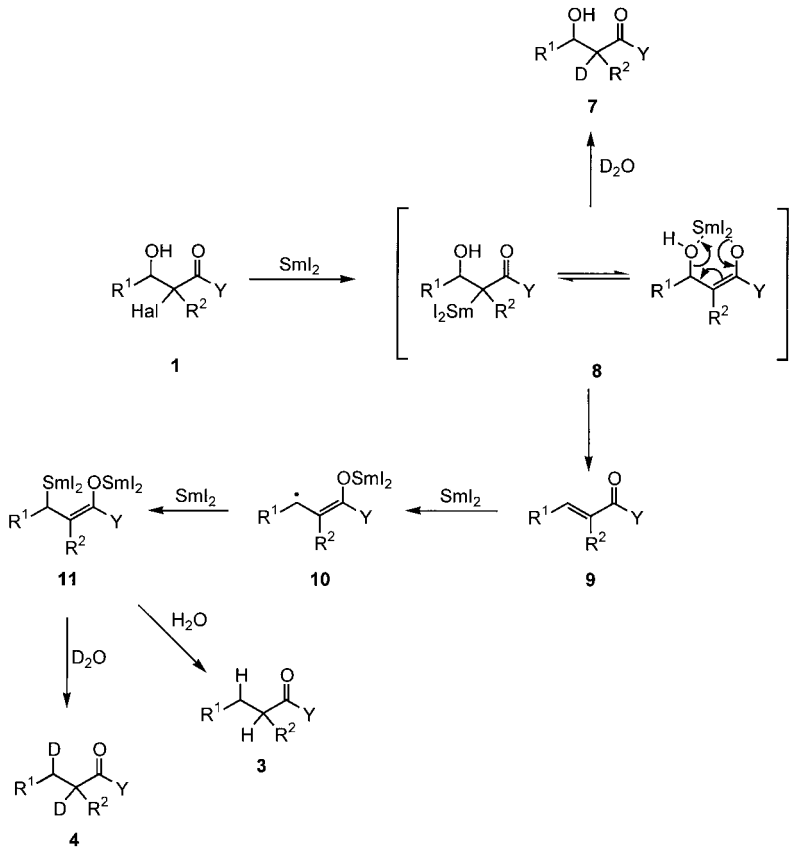

Scheme 5. Mechanism of the sequential elimination/reduction reaction.

2-chloro-*N*,*N*-diethyl-3-hydroxy-3-phenylpropanamide (**1l**), and 2-chloro-*N*,*N*-diethyl-3-hydroxy-2-methyl-3-phenylpropanamide (**1m**).

Synthesis of 2-halo-3-hydroxyesters or -amides (1):[24] Lithium diisopropylamide [prepared from MeLi (6.4 mL of a 1.5 M solution in diethyl ether, 10 mmol) and diisopropylamine (1.4 mL, 10 mmol) in THF (50 mL) at 0 °C] was added dropwise to a stirred solution of the appropriate 2-haloester **2** (9 mmol) in dry THF (4 mL) at −85 °C. After stirring for 10 min, a solution of the appropriate aldehyde (4.5 mmol) in dry THF (4.5 mL) was added dropwise at −78 °C. The reaction mixture was stirred for 1 h and then quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). Standard workup provided crude 2-halo-3-hydroxyesters **1**, which were purified by flash column chromatography on silica gel (hexane/ethyl acetate, 10:1) to provide the pure compounds.

Ethyl 2-chloro-3-hydroxy-2-methyldecanoate (1a): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.27$ (q, $J = 7.19$ Hz, 4H), 3.98 (d, $J = 8.21$ Hz, 2H), 2.36 (br s, 2H), 1.73 (s, 6H), 1.45–1.20 (m, 30H), 0.99–0.78 (d, $J = 7.19$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.8$ (C), 170.5 (C), 73.5 (C), 71.0 (C), 75.8 (CH), 75.5 (CH), 62.09 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 26.2 (CH_2), 22.4 (CH_2), 22.2 (CH_3), 22.0 (CH_3), 13.8 (CH_3), 13.7 (CH_3); IR (neat): $\tilde{\nu} = 3425$, 1741 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 10:1).

Ethyl 2-chloro-3-cyclohexyl-3-hydroxy-2-methylpropanoate (1b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.22$ (q, $J = 6.67$ Hz, 4H), 3.82–3.75 (m, 2H), 2.80–2.35 (m, 2H), 1.95–1.33 (m, 28H), 1.29 (t, $J = 6.67$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.8$ (C), 170.3 (C), 78.9 (CH), 78.5 (CH), 73.2 (C), 71.7 (C), 61.7 (CH_2), 61.6 (CH_2), 40.5 (CH), 40.2 (CH), 30.6 (CH_2), 30.3 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 24.6 (CH_3), 21.5 (CH_3), 13.4 (CH_3); IR (neat): $\tilde{\nu} = 3517$, 1737 cm^{-1}; $R_f = 0.3$, 0.2 (two diastereoisomers) (hexane/AcOEt, 10:1).

Ethyl 2-bromo-2-hexyl-3-hydroxy-4-phenylpentanoate (1c): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.31–7.23$ (m, 10H), 4.20–4.06 (m, 4H), 3.27–3.09 (m, 2H), 1.52–1.11 (m, 36H), 0.89–0.82 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.4$ (C), 169.9 (C), 145.1 (C), 141.6 (C), 128.3 (CH), 127.7 (CH), 127.4 (CH), 126.4 (CH), 79.2 (CH), 78.1 (C), 62.3 (CH_2), 60.2 (CH_2), 42.7 (CH), 38.0 (CH_2), 31.1 (CH_2), 28.8 (CH_2), 27.2 (CH_2), 25.8 (CH_2), 22.3 (CH_2), 22.2 (CH_2), 18.7 (CH_3), 14.0 (CH_3), 13.8 (CH_3), 13.7 (CH_3); IR (neat): $\tilde{\nu} =$ 3490, 1729 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 5:1)

Isopropyl 2-chloro-3-hydroxy-5,9-dimethyl-2-phenyldec-8-enoate (1d): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.57–7.33$ (m, 10H), 5.15–5.02 (m, 4H), 4.65–4.42 (br m, 2H), 2.2–1.0 (m, 38H), 0.96–0.76 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 169.8$ (C), 169.4 (C), 136.2 (C), 135.9 (C), 130.2 (C), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.1 (CH), 126.0 (CH), 125.9 (CH), 124.5 (CH), 124.4 (CH), 74.2 (CH), 74.0 (CH), 70.1 (CH), 70.0 (CH), 58.7 (C), 38.9 (CH_2), 38.7 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 29.0 (CH), 28.3 (CH), 25.3 (CH_3), 25.1 (CH_2), 24.9 (CH_2), 25.3 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.2 (CH_3), 20.1 (CH_3), 18.5 (CH_3), 18.4 (CH_3), 17.2 (CH_3); IR (neat): $\tilde{\nu} = 3525$, 1747 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt, 10:1).

Ethyl 2-chloro-3-hydroxy-3-(4-methoxyphenyl)-2-methyl-propanoate (1e): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37–7.28$ (m, 4H), 6.89–6.83 (m, 4H), 5.17 (s, 1H), 5.15 (s, 1H), 4.27 (q, $J =$ 7.18 Hz, 2H), 4.26 (q, $J = 7.18$ Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.29 (m, 2H), 1.64 (s, 3H), 1.57 (s, 3H), 1.30 (t, $J = 7.18$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.7$ (C), 170.3 (C), 129.6 (C), 129.2 (CH), 129.1 (CH), 128.8 (CH), 114.0 (CH), 113.0 (CH), 112.7 (CH), 76.9 (CH), 73.4 (C), 69.6 (C), 62.2 (CH_2), 62.1 (CH_2), 55.0 (CH_3), 54.9 (CH_3), 22.5 (CH_3), 21.3 (CH_3), 13.6 (CH_3); IR (neat): $\tilde{\nu} = 3490$, 1737 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt, 5:1).

Methyl 2-chloro-3-hydroxydecanoate (1f): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.29$ (d, $J =$ 3.93 Hz, 1H), 4.12 (d, $J = 6.98$ Hz, 1H), 4.02–3.81 (m, 2H), 3.74 (s, 6H), 3.11–3.01 (br s, 1H), 2.91–2.81 (br s, 1H), 1.66–1.00 (m, 24H), 0.82 (t, $J =$ 6.32 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.2$ (C), 169.0 (C), 72.4 (CH), 71.8 (CH), 61.8 (CH), 59.4 (CH), 53.0 (CH_3), 52.8 (CH_3), 33.4 (CH_2), 32.6 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 13.8 (CH_3); IR (neat): $\tilde{\nu} = 3452$, 1754 cm^{-1}; $R_f = 0.3$, 0.2 (two diastereoisomers) (hexane/AcOEt, 5:1).

Ethyl 2-bromo-2-butyl-3-hydroxy-3-phenylpropanoate (1g): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46–7.28$ (m, 10H), 5.09 (m, 2H), 4.28 (q, $J =$ 7.18 Hz, 4H), 3.19 (br s, 2H), 2.19–1.75 (m, 12H), 1.28 (t, $J = 7.18$ Hz, 6H), 0.88 (t, $J = 6.93$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.9$ (C), 169.3 (C), 138.2 (C), 137.7 (C), 128.0 (CH), 127.8 (CH), 127.6 (CH), 123.3 (CH), 78.2 (CH), 77.5 (CH), 62.2 (CH_2), 62.0 (CH_2), 37.6 (CH_2), 36.9 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 22.3 (CH_2), 22.2 (CH_2), 13.6 (CH_3), 13.5 (CH_3); IR (neat): $\tilde{\nu} = 3505$, 1725 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 5:1).

2-Chloro-3-cyclohexyl-*N*,*N*-diethyl-3-hydroxypropanamide (1i): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.97$ (s, 1H), 4.30 (s, 1H), 3.51–3.01 (m, 5H), 1.95 (d, $J = 13.05$ Hz, 1H), 1.55–1.46 (m, 6H), 1.21–0.65 (m, 4H), 1.07 (t, $J =$ 7.18 Hz, 3H), 0.96 (t, $J = 7.18$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 178.7 (C), 74.8 (CH), 52.3 (CH), 41.9 (CH_2), 40.2 (CH_2), 38.9 (CH), 28.3 (CH_2), 28.0 (CH_2), 25.7 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 14.0 (CH_3), 11.9 (CH_3); IR (neat): $\tilde{\nu} = 3368$, 1629 cm^{-1}; $R_f = 0.4$ (hexane/AcOEt, 3:1).

Synthesis of saturated esters and amides (3 and 4): Under nitrogen, a solution of SmI_2 (2.3 mmol) in THF (24 mL) was added dropwise to a stirred solution of the appropriate 2-halo-3-hydroxyester or -amide **1** (0.4 mmol) in THF (4 mL) at room temperature. After stirring for 30 min (esters) or 120 min (amides) at the same temperature, H_2O or D_2O (2 mL) was added to the solution. The resulting mixture was stirred for 30 min at this temperature, and then quenched by the addition of 0.1 M aqueous HCl (5 mL). Standard workup afforded the crude saturated esters and amides **3**, which were purified by flash column chromatography on silica gel (eluent: hexane/AcOEt, 5:1).

Ethyl 3-(4-methoxyphenyl)-2-methylpropanoate (3e): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 8.72$ Hz, 4H), 6.81 (d, $J = 8.72$ Hz, 4H), 4.05 (q, $J =$ 7.18 Hz, 4H), 3.77 (s, 6H), 3.00–2.88 (m, 2H), 2.76–2.56 (m, 4H), 1.19 (t,

$J = 7.18$ Hz, 6H), 1.14 (d, $J = 6.67$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.0$ (C), 157.9 (C), 131.3 (C), 129.7 (CH), 113.5 (CH), 60.0 (CH_2), 55.0 (CH_3), 41.5 (CH), 38.7 (CH_2), 16.5 (CH_3), 14.0 (CH_3); MS (70 eV): *m/z* (%): 222 (80) $[M]^+$, 177 (12), 149 (18), 121 (100); HRMS calcd for $C_{13}H_{18}O_3$: 222.1251; found: 222.1256; IR (neat): $\tilde{\nu} = 3026, 2977, 2836, 1730, 1584, 1462, 1349\ cm^{-1}$; $R_f = 0.3$ (hexane/AcOEt, 10:1).

Ethyl decanoate (3f): The ^{1}H and ^{13}C NMR spectra of the product obtained were identical to those of a commercial sample.

Ethyl 2-butyl-3-phenylpropanoate (3g): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.23 – 7.15 (m, 5H), 4.08 (q, $J = 7.18$ Hz, 2H), 3.00 – 2.51 (m, 3H), 1.73 – 1.28 (m, 4H), 1.19 (t, $J = 7.18$ Hz, 3H), 0.94 – 0.86 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.5$ (C), 139.4 (C), 128.7 (CH), 128.1 (CH), 126.1 (CH), 59.9 (CH_2), 47.5 (CH), 38.5 (CH_2), 31.7 (CH_2), 29.3 (CH_2), 22.4 (CH_2), 14.0 (CH_3), 13.8 (CH_3); MS (70 eV): *m/z* (%): 234 (11) $[M]^+$, 189 (4), 161 (12), 91 (100); HRMS calcd for $C_{15}H_{22}O_2$: 234.1619; found: 234.1617; IR (neat): $\tilde{\nu} = 3028, 2930, 2859, 1732\ cm^{-1}$; $R_f = 0.5$ (hexane/AcOEt, 5:1).

***N,N*-Diethyl-3-phenylpropanamide (3l)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.32 – 7.15 (m, 5H), 3.38 (q, $J = 7.18$ Hz, 2H), 3.21 (q, $J = 7.18$ Hz, 2H), 3.17 – 2.94 (m, 2H), 2.65 – 2.54 (m, 2H), 1.11 (t, $J = 7.18$ Hz, 3H), 1.09 (t, $J =$ 7.18 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.0$ (C), 141.4 (C), 128.2 (CH), 125.8 (CH), 41.7 (CH_2), 40.0 (CH_2), 34.9 (CH_2), 31.5 (CH_2), 14.1 (CH_3), 12.9 (CH_3); MS (70 eV): *m/z* (%): 205 (100) $[M]^+$, 176 (12), 133 (4), 105 (28), 91 (44), 77 (16); HRMS calcd for $C_{12}H_{19}NO$: 205.1466; found: 205.1468; IR (neat): $\tilde{\nu} = 3083, 3059, 3028, 2975, 1640\ cm^{-1}$; $R_f = 0.2$ (hexane/AcOEt, 5:1).

***N,N*-Diethyl-2-methyl-3-phenylpropanamide (3m)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26 – 7.12$ (m, 5H), 3.43 – 3.34 (m, 1H), 3.22 – 3.14 (m, 1H), 3.13 – 2.93 (m, 3H), 2.89 – 2.78 (m, 1H), 2.64 – 2.56 (m, 1H), 1.13 (d, $J =$ 6.55 Hz, 3H), 0.99 (t, $J = 7.12$ Hz, 3H), 0.92 (t, $J = 7.12$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.9$ (C), 140.1 (C), 128.9 (CH), 128.0 (CH), 125.9 (CH), 41.5 (CH_2), 40.6 (CH_2), 40.2 (CH_2), 38.0 (CH), 18.1 (CH_3), 14.5 (CH_3), 12.8 (CH_3); MS (70 eV): *m/z* (%): 219 (100) $[M]^+$, 204 (55), 119 (24), 91 (99); IR (neat): $\tilde{\nu} = 3062, 3026, 2971, 1636, 1379\ cm^{-1}$; $R_f = 0.3$ (hexane/AcOEt, 3:1).

3-Phenylpropanamide (3n): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35 – 7.18$ (m, 5H), 6.30 (br s, 1H), 5.83 (br s, 1H), 2.94 (t, $J = 7.63$ Hz, 2H), 2.50 (t, $J =$ 7.63 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.1$ (C), 140.4 (C), 128.4 (CH), 128.1 (CH), 126.1 (CH), 37.2 (CH_2), 31.1 (CH_2); IR (neat): $\tilde{\nu} = 3401$, 3015, 2941, 1864, 1644, 1458, 1375 cm^{-1}; elemental analysis calcd (%) for $C_9H_{11}NO$: C 72.46, H 7.43, N 9.39; found: C 72.40, H 7.49, N 9.31; $R_f = 0.2$ (hexane/AcOEt, 1:1).

Ethyl 2,3-dideuterio-2-methyldecanoate (4a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.13$ (q, $J = 7.18$ Hz, 2H), 1.30 – 1.21 (m, 16H), 1.13 (s, 3H), 0.88 (t, $J =$ 6.15 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.9$ (C), 59.9 (CH_2), 39.0 (t, $J = 19.2$ Hz, CD), 33.3 (t, $J = 19.2$ Hz, CHD), 31.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 16.9 (CH_3), 14.2 (CH_3), 14.0 (CH_3); MS (70 eV): *m/z* (%): 216 (21) $[M]^+$, 187 (4), 171 (46), 143 (3), 117 (4); HRMS calcd for $C_{13}H_{24}D_2O_2$: 216.1932; found: 216.2054; IR (neat): $\tilde{\nu} = 2957, 2926, 2856, 1734, 1375\ cm^{-1}$; $R_f = 0.5$ (hexane/AcOEt, 10:1).

Ethyl 2,3-dideuterio-3-cyclohexyl-2-methylpropanoate (4b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.10$ (q, $J = 7.12$ Hz, 2H), 4.09 (q, $J = 7.12$ Hz, 2H), 2.00 – 1.50 (m, 12H), 1.23 (t, $J = 7.12$ Hz, 6H), 1.22 – 1.00 (m, 8H), 1.09 (s, 6H), 0.90 – 0.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.2$ (C), 59.9 (CH_2), 40.9 (t, $J = 18.9$ Hz, CHD), 36.3 (t, $J = 20.4$ Hz, CD), 35.2 (CH), 33.1 (CH_2), 33.0 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 17.3 (CH_3), 14.2 (CH_3); MS (70 eV): *m/z* (%): 200 (5) $[M]^+$, 155 (33), 127 (11), 103 (100); HRMS calcd for $C_{12}H_{20}D_2O_2$: 200.1773; found: 200.1745; IR (neat): $\tilde{\nu} = 2975, 2923, 2852, 1733, 1448, 1376\ cm^{-1}$; $R_f = 0.5$ (hexane/AcOEt, 10:1).

Ethyl 2,3-dideuterio-2-hexyl-4-phenylpentanoate (4c): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.33 – 7.16$ (m, 10H), 4.22 – 3.99 (m, 4H), 2.76 – 2.64 (m, 2H), 2.00 – 1.90 (m, 2H), 1.71 – 1.20 (m, 32H), 0.93 – 0.84 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 176.4$ (C), 176.0 (C), 146.7 (C), 146.4 (C), 128.5 (CH), 128.2 (CH), 126.9 (CH), 126.8 (CH), 125.9 (CH), 59.8 (CH_2), 43.2 (t, $J = 19.2$ Hz, CD), 40.4 (t, $J = 20.9$ Hz, CHD), 38.0 (CH), 37.7 (CH), 32.9 (CH_2), 32.3 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 27.0 (CH_2), 22.8 (CH_3), 22.4 (CH_2), 21.7 (CH_3), 14.2 (CH_3), 14.1 (CH_3), 14.0 (CH_3); MS (70 eV): *m/z* (%): 292 (12) $[M]^+$, 247 (12), 215 (4), 173 (100), 120 (59), 105 (95), 101 (89); HRMS calcd for $C_{19}H_{28}D_2O_2$: 292.2245; found: 292.2369; IR (neat): $\tilde{\nu} = 3084, 3062, 3027, 2928, 2857, 1729\ cm^{-1}$; $R_f = 0.4$ (hexane/AcOEt, 5:1).

Isopropyl 2,3-dideuterio-5,9-dimethyl-2-phenyldec-8-enoate (4d): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34 – 7.22$ (m, 10H), 5.62 – 5.58 (m, 2H), 5.12 – 4.95 (m, 2H), 2.12 – 1.90 (m, 8H), 1.68 (s, 6H), 1.59 (s, 6H), 1.35 – 1.05 (m, 8H), 1.23 (d, $J = 6.10$ Hz, 3H), 1.14 (d, $J = 6.11$ Hz, 3H), 0.90 – 0.84 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.5$ (C), 173.4 (C), 139.5 (C), 139.4 (C), 130.9 (C), 128.3 (CH), 127.7 (CH), 126.9 (CH), 124.7 (CH), 67.6 (CH), 51.7 (t, $J = 19.7$ Hz, CD), 36.7 (CH_2), 34.5 (CH_2), 34.4 (CH_2), 32.1 (CH), 30.6 (t, $J = 19.2$ Hz, CHD), 25.6 (CH_3), 25.4 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 19.3 (CH_3), 17.5 (CH_3); MS (70 eV): *m/z* (%): 318 (38) $[M]^+$, 193 (3), 178 (14), 137 (100); HRMS calcd for $C_{21}H_{30}D_2O_2$: 318.2402; found 318.2522; IR (neat): $\tilde{\nu} = 3084, 3060, 2927, 2860, 1727, 1375\ cm^{-1}$; $R_f = 0.5$ (hexane/AcOEt, 5:1).

Ethyl 2,3-dideuterio-3-(4-methoxyphenyl)-2-methylpropanoate (4e): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 8.48$ Hz, 4H), 6.81 (d, $J =$ 8.48 Hz, 4H), 4.08 (q, $J = 6.97$ Hz, 4H), 3.75 (s, 6H), 2.92 (s, 1H), 2.59 (s, 1H), 1.19 (t, $J = 6.97$ Hz, 6H), 1.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.1$ (C), 157.9 (C), 131.2 (C), 129.7 (CH), 113.5 (CH), 60.1 (CH_2), 55.0 (CH_3), 41.1 (t, $J = 20.0$ Hz, CD), 38.3 (t, $J = 19.2$ Hz, CHD), 16.5 (CH_3), 14.0 (CH_3); MS (70 eV): *m/z* (%): 224 (72) $[M]^+$, 179 (12), 122 (100), 92 (35); IR (neat): $\tilde{\nu} = 3026, 2977, 2836, 1730, 1584, 1462, 1349\ cm^{-1}$; $R_f = 0.3$ (hexane/AcOEt, 10:1).

Methyl 2,3-dideuterio-3-phenylpropanoate (4h): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33 – 7.19$ (m, 5H), 3.68 (s, 3H), 2.94 (d, $J = 8.28$ Hz, 1H), 2.63 (d, $J = 8.28$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.3$ (C), 140.3 (C), 128.4 (CH), 128.2 (CH), 126.2 (CH), 51.5 (CH_3), 35.2 (t, $J = 19.8$ Hz, CHD), 30.5 (t, $J = 19.8$ Hz, CHD); MS (70 eV): *m/z* (%): 166 (40) $[M]^+$, 135 (12), 107 (37), 106 (100), 92 (65); IR (neat): $\tilde{\nu} = 3085, 3027, 2958, 1738, 1496, 1435\ cm^{-1}$; $R_f = 0.3$ (hexane/AcOEt, 10:1).

3-Cyclohexyl-2,3-dideuterio-*N,N*-diethylpropanamide (4i): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.29$ (q, $J = 7.11$ Hz, 2H), 3.23 (q, $J = 7.11$ Hz, 2H), 2.20 (m, 1H), 1.66 – 0.80 (m, 12H), 1.10 (t, $J = 7.11$ Hz, 3H), 1.03 (t, $J = 7.11$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.4$ (C), 41.8 (CH_2), 39.8 (CH_2), 37.2 (CH), 32.9 (CH), 32.3 (t, $J = 19.2$ Hz, CHD), 30.1 (t, $J =$ 19.2 Hz, CHD), 26.4 (CH_2), 26.1 (CH_2), 14.2 (CH_3), 12.9 (CH_3); MS (70 eV): *m/z* (%): 213 (< 1) $[M]^+$, 141 (< 1), 130 (25), 116 (100); IR (neat): $\tilde{\nu} = 2970$, 2922, 2845, 1640, 1450, 1426 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt, 3:1).

2,3-Dideuterio-*N,N*-diethyldecanamide (4j): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.42 – 3.24$ (m, 4H), 2.25 – 2.23 (m, 1H), 1.61 (m, 1H), 1.35 – 1.22 (m, 12H), 1.17 (t, $J = 7.18$ Hz, 3H), 1.10 (t, $J = 7.18$ Hz, 3H), 0.87 (t, $J = 6.46$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.2$ (C), 41.8 (CH_2), 39.8 (CH_2), 32.6 (t, $J = 19.2$ Hz, CHD), 31.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 24.9 (t, $J = 19.2$ Hz, CHD), 22.5 (CH_2), 14.2 (CH_3), 14.0 (CH_3), 13.0 (CH_3); MS (70 eV): *m/z* (%): 229 (7) $[M]^+$, 200 (< 1), 130 (12), 129 (14), 116 (100); HRMS calcd for $C_{14}H_{27}D_2NO$: 229.2249; found: 229.2369; IR (neat): $\tilde{\nu} =$ 2957, 2925, 2854, 1642 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 1:1).

2,3-Dideuterio-*N,N*-diethyl-4-phenylpentanamide (4k): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38 – 7.10$ (m, 5H), 3.32 (q, $J = 7.12$ Hz, 2H), 3.10 (q, $J = 7.12$ Hz, 2H), 2.77 – 2.70 (m, 1H), 2.15 – 1.83 (m, 2H), 1.28 (d, $J =$ 6.97 Hz, 3H), 1.07 (t, $J = 7.12$ Hz, 3H), 1.01 (t, $J = 7.12$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.9$ (C), 146.6 (C), 128.2 (CH), 126.9 (CH), 125.9 (CH), 41.7 (CH_2), 39.9 (CH_2), 39.3 (CH), 33.0 (t, $J = 19.0$ Hz, CHD), 30.5 (t, $J = 19.5$ Hz, CHD), 22.4 (CH_3), 14.0 (CH_3), 12.9 (CH_3); MS (70 eV): *m/z* (%): 235 (3) $[M]^+$, 163 (3), 130 (8), 116 (100); IR (neat): $\tilde{\nu} = 1066$, 3028, 2970, 2922, 2874, 1639, 1450, 1379 cm^{-1} ; $R_f = 0.2$ (hexane/AcOEt, 3:1).

2,3-Dideuterio-*N,N*-diethyl-3-phenylpropanamide (4l): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34 – 7.19$ (m, 5H), 3.38 (q, $J = 7.18$ Hz, 2H), 3.23 (q, $J = 7.18$ Hz, 2H), 3.00 – 2.94 (m, 1H), 2.61 – 2.55 (m, 1H), 1.12 (t, $J =$ 7.18 Hz, 3H), 1.11 (t, $J = 7.18$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 171.0 (C), 141.2 (CH), 128.2 (CH), 125.8 (CH), 41.6 (CH_2), 39.9 (CH_2), 34.4 (t, $J = 19.7$ Hz, CHD), 31.0 (t, $J = 19.7$ Hz, CHD), 14.0 (CH_3), 12.8 (CH_3); MS (70 eV): *m/z* (%): 207 (42) $[M]^+$, 178 (7), 149 (10), 135 (4), 107 (18), 92 (53), 77 (50); HRMS calcd for $C_{12}H_{17}D_2NO$: 207.1466; found: 207.1589; IR (neat): $\tilde{\nu} = 3083$, 3060, 3025, 2973, 2932, 1638 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 5:1).

2,3-Dideuterio-*N,N*-diethyl-2-methyl-3-phenylpropanamide (4m): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30 – 7.15$ (m, 10H), 3.48 – 3.36 (m, 2H), 3.25 – 3.13 (m, 2H), 3.05 (q, $J = 7.18$ Hz, 4H), 2.62 (s, 2H), 1.26 (s, 3H), 1.16 (s, 3H), 1.02 (t, $J = 7.18$ Hz, 6H), 0.93 (t, $J = 7.18$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.0$ (C), 140.6 (C), 140.1 (C), 129.0 (CH), 128.9

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(CH), 128.1 (CH), 126.0 (CH), 125.7 (CH), 41.6 (CH_2), 40.3 (CH_2), 40.3 (t, $J = 19.8$ Hz, CHD), 37.6 (t, $J = 19.8$ Hz, CD), 18.0 (CH_3), 14.5 (CH_3), 12.9 (CH_3); MS (70 eV): *m/z* (%): 221 (36) $[M]^+$, 206 (22), 121 (19), 92 (100); HRMS calcd for $C_{14}H_{19}D_2NO$: 221.1735; found: 221.1749; IR (neat): $\tilde{\nu} =$ 3062, 3026, 2971, 1636, 1379 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt, 3:1).

2,3-Dideuterio-3-phenylpropanamide (4n): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.32-7.18$ (m, 5H), 5.85 (br s, 1H), 5.51 (br s, 1H), 2.93 (d, $J = 6.26$ Hz, 1H), 2.49 (d, $J = 6.26$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.7$ (C), 149.5 (C), 128.4 (CH), 128.2 (CH), 126.2 (CH), 37.0 (t, $J = 19.5$ Hz, CHD), 30.9 (t, $J = 19.8$ Hz, CHD); IR (neat): $\tilde{\nu} = 3395$, 3009, 2941, 1864, 1643, 1450, 1373 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 1:1).

Synthesis of 2-deuterioesters and 3-deuterioesters (5e and 6e): Under nitrogen, a solution of compound **3** or **4** (0.4 mmol) in THF (4 mL) was added dropwise to a stirred solution of diisopropylamide (0.48 mmol) in THF (5 mL) at $-78\,^\circ C$. After stirring for 30 min, the reaction mixture was quenched by the addition of D_2O or H_2O (2 mL). Standard workup provided the 3- or 2-deuterioesters **5e** or **6e**, respectively, which were purified by flash column chromatography on silica gel (hexane/AcOEt, 5:1).

Ethyl 3-deuterio-3-(4-methoxyphenyl)-2-methylpropanoate (5e): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 8.71$ Hz, 4H), 6.81 (d, $J = 8.71$ Hz, 4H), 4.09 (q, $J = 7.19$ Hz, 4H), 3.78 (s, 6H), 2.94–2.92 (m, 1H), 2.71–2.58 (m, 3H), 1.20 (t, $J = 7.19$ Hz, 6H), 1.13 (d, $J = 6.98$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.1$ (C), 158.0 (C), 131.4 (C), 129.8 (CH), 113.6 (CH), 60.1 (CH_2), 55.1 (CH_3), 41.5 (CH), 38.4 (t, $J = 19.8$ Hz, CHD), 16.6 (CH_3), 14.1 (CH_3); MS (70 eV): *m/z* (%): 223 (45) $[M]^+$, 178 (9), 150 (15), 122 (100); HRMS calcd for $C_{13}H_{17}DO_3$: 223.1318; found: 223.1319; IR (neat): $\tilde{\nu} =$ 3026, 2977, 2836, 1730, 1584, 1462, 1349 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt, 10:1)

Ethyl 2-deuterio-3-(4-methoxyphenyl)-2-methylpropanoate (6e): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.07$ (d, $J = 8.72$ Hz, 4H), 6.83 (d, $J = 8.72$ Hz, 4H), 4.10 (q, $J = 7.18$ Hz, 4H), 3.80 (s, 6H), 2.95 (d, $J = 13.72$ Hz, 2H), 2.61 (d, $J = 13.72$ Hz, 2H), 1.21 (t, $J = 7.18$ Hz, 6H), 1.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.1$ (C), 157.9 (C), 131.3 (C), 129.7 (CH), 113.5 (CH), 60.1 (CH_2), 55.0 (CH_3), 41.1 (t, $J = 20.3$ Hz, CD), 38.6 (CH_2), 16.5 (CH_3), 14.0 (CH_3); MS (70 eV): *m/z* (%): 223 (39) $[M]^+$, 178 (8), 150 (10), 121 (100); IR (neat): $\tilde{\nu} = 3026$, 2977, 2836, 1730, 1584, 1462, 1349 cm^{-1}; $R_f =$ 0.3 (hexane/AcOEt, 10:1).

Synthesis of 2-deuterio-3-hydroxyesters (7b and 7e): Under nitrogen, a solution of SmI_2 (1.3 mmol) in THF/D_2O (2 mL) was added dropwise to a stirred solution of the appropriate 2-halo-3-hydroxyester **1** (0.4 mmol) in THF (4 mL) at room temperature. After stirring for 30 min at the same temperature, the reaction was quenched by the addition of 0.1M aqueous HCl (5 mL). Standard workup afforded the crude 2-deuterio-3-hydroxyesters **7**, which were purified by flash column chromatography on silica gel (hexane/AcOEt, 5:1).

Ethyl 3-cyclohexyl-2-deuterio-3-hydroxy-2-methylpropanoate (7b): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.14$ (q, $J = 7.01$ Hz, 4H), 3.59 (d, $J =$ 7.95 Hz, 1H), 3.34 (d, $J = 5.65$ Hz, 1H), 2.64 (br s, 2H), 2.08–0.79 (m, 22H), 1.25 (t, $J = 7.01$ Hz, 6H), 1.19 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.6$ (C), 176.4 (C), 77.6 (CH), 75.5 (CH), 60.4 (CH_2), 60.3 (CH_2), 41.3 (t, $J = 19.8$ Hz, CD), 41.0 (CH), 39.9 (CH), 29.8 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 14.6 (CH_3), 14.0 (CH_3), 9.8 (CH_3); MS (70 eV): *m/z* (%): 215 (<1) $[M]^+$, 200 (25), 170 (8), 132 (98); IR (neat): $\tilde{\nu} = 3495$, 2970, 2922, 2864, 1728, 1450, 1376 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 10:1).

Ethyl 2-deuterio-3-hydroxy-3-(4-methoxyphenyl)-2-methylpropanoate (7e): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.27-7.20$ (m, 4H), 6.87–6.82 (m, 4H), 4.94 (s, 1H), 4.70 (s, 1H), 4.16 (q, $J = 7.12$ Hz, 2H), 4.06 (q, $J = 7.12$ Hz, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.06 (br s, 2H), 1.24 (t, $J = 7.12$ Hz, 3H), 1.16 (t, $J = 7.12$ Hz, 3H), 1.12 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.8$ (C), 175.5 (C), 159.1 (C), 158.7 (C), 133.6 (C), 127.7 (CH), 127.1 (CH), 113.6 (CH), 113.4 (CH), 75.7 (CH), 73.4 (CH), 60.5 (CH_2), 60.4 (CH_2), 55.0 (CH_3), 46.7 (t, $J = 20.1$ Hz, CD), 14.2 (CH_3), 14.0 (CH_3), 13.9 (CH_3), 11.1 (CH_3); MS (70 eV): *m/z* (%): 239 (33) $[M]^+$, 220 (3), 194 (37), 137 (100); IR (neat): $\tilde{\nu} = 3491$, 3028, 3018, 2978, 1936, 1727, 1612, 1513, 1461, 1374 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt, 10:1).

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