Synthesis of Different Deuterated Carboxylic Acids from Unsaturated Acids Promoted by Samarium Diiodide and D_2O

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

Abstract: An easy, and rapid reduction of the C=C bond of α,β-unsaturated acids by means of samarium diiodide in the presence of D_2O provides an efficient method for synthesizing 2,3-dideuterio acids. Starting from alka-2,4-dienoic acids, (*E*)-α,δ-dideuterio-$\beta\gamma$-unsaturated acids are obtained, the new C=C bond being generated with complete diastereoselectivity. When H_2O is used instead of D_2O, saturated carboxylic acids and (*E*)-β,γ-unsaturated acids are isolated. A mechanism to explain each synthesis has been proposed.

Keywords: acids · deuterium · reduction · samarium

Introduction

Relatively few general methods for the selective conjugated reduction of α,β-unsaturated carboxylic acids and their derivatives are known.[1] However, this reactivity pattern is useful for the direct reduction of unsaturated carboxylic acids because it circumvents synthetic designs requiring conjugate reduction through an ester, where efficient protection–deprotection schemes are necessitated.

Isotopically labeled compounds are very useful to establish the mechanism of organic reactions and the biosynthesis of many natural compounds.[2]

The selective conjugated reduction of α,β-unsaturated carboxylic acids and their derivatives is a useful reaction in organic chemistry and has been achieved using a number of methodologies.[1] However, the conjugated reduction of α,β-unsaturated acids using deuterium instead of hydrogen has been scarcely reported. Traditionally, such transformations were performed with special deuteration catalysts, although successful examples of selective deuteration of other types are still rare.

To the best of our knowledge, only three alternative methodologies to the catalytic addition of D_2[3] to α,β-unsaturated acids have been described:[4] by using enzymes in D_2O,[5] by diimide reductions using potassium azodicarboxylate,[6] and by using deuterated formic acid/triethylamine as the deuterium source.[7] For this reason, the development of an effective general method for the synthesis of 2,3-dideuterio acids is of significant value.

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In relation to the synthetic application of samarium diiodide in organic synthesis, only one paper describing a general conjugated reduction of α,β-unsaturated acids promoted by SmI_2 has been reported; hexamethylphosphoric triamide (HMPA) was required as an additive to facilitate the reduction.[8] In addition to this paper, only one case exists of the reduction of an α,β-unsaturated acid (cinnamic acid); this was achieved by using a solution of SmI_2/methanol/THF[9] or by using samarium metal and iodine in methanol.[10]

Despite that the presence of H_2O increases the reducing power of SmI_2,[11] to the best of our knowledge, the simpler 1,2-reduction of conjugated carboxylic acid derivatives using SmI_2 and D_2O or H_2O (without additives) has not been described.

Previously we described two practical methodologies for the synthesis of various deuterated compounds such as 2,3-dideuterioesters or amides[12] and (*E*)-α,δ-dideuterio-β,γ-unsaturated esters.[13]

In the present contribution we describe a novel and rapid method to obtain 2,3-dideuterio acids or saturated acids **2** by an efficient reduction of the C=C double bond of conjugated carboxylic acids. The reaction was promoted by SmI_2 in the presence of D_2O or H_2O, respectively.

When alka-2,4-dienoic acids were used as starting compounds, the SmI_2 promoted 1,4-reduction of the two conjugated C=C bonds provides α,δ-dideuterio-β,γ-unsaturated acids **8**, in which the new C=C bond is generated with complete diastereoselectivity. Other labeled compounds have been also obtained.

Results and Discussion

Synthesis of aromatic 2,3-dideuterio acids: Our first attempts involved the preparation of aromatic 2,3-dideuterio acids.

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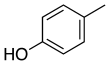
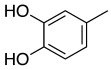
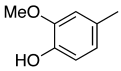
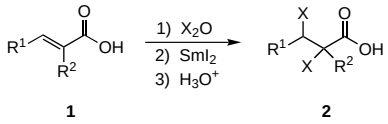
Thus, the aromatic α,β-unsaturated carboxylic acids (1 equiv) were previously stirred with a solution of D_2O (2 mL) in THF (2 mL) for 5 min at room temperature. After this treatment, a solution of SmI_2 (3 equiv) in THF (15 mL) was added, and the resulting solution was stirred for 10 min at room temperature, affording after acidification with HCl the corresponding aromatic 2,3-dideuterio acids **2** in high yield. (Scheme 1, X = D, and Table 1).

Table 1. Synthesis of aromatic 2,3-dideuterio acids.

Entry	2	R^1	R^2	X	Yield [%][a]
1	**2a**		H	D	77
2	**2b**		H	D	71
3	**2c**		H	D	73
4	**2d**		H	D	85
5	**2e**		Me	D	82
6	**2f**		H	H	74

[a] Isolated yield based on compound **1**.



1 **2**

Scheme 1. Synthesis of 2,3-dideuterio acids **2**.

The reaction sequence is rather crucial in this case: When the aromatic α,β-unsaturated acids were not pre-treated with D_2O and the reaction of **1** was carried out directly with SmI_2 and D_2O, a mixture of mono-, di-, and non-deuterated aromatic acid was obtained.

Aromatic α,β-unsaturated acids in which the double bond is di- or trisubstituted can be reduced and the reaction is also tolerant to aromatic rings with different functional groups, see Table 1.

The position of deuteration was established by ^1H and ^{13}C NMR spectrometry of compounds **2**, while the complete deuterium incorporation was determined by mass spectroscopy, and was found to be $>99\,\%$.[14] These 2,3-dideuterio acids were isolated as mixture of diastereoisomers (ranging between 2:1 to 1:1).

Abstract in Spanish: *Se describe una nueva metodología fácil, sencilla y general para reducir ácidos carboxílicos α,β-insaturados, promovida por SmI_2 y D_2O, obteniéndose 2,3-dideuterio ácidos. Si se utilizan como productos de partida ácidos carboxílicos alca-2,4-dienoicos, se obtienen ácidos carboxílicos (E)-α,δ-dideuterio-β,γ-insaturados en los que el nuevo enlace C=C se genera con total diastereoselección. Cuando se emplea H_2O en lugar de D_2O, se aislan ácidos carboxílicos saturados o ácidos (E)-β,γ-insaturados. Se propone un mecanismo para explicar cada proceso.*

It is noteworthy that D_2O is the cheapest deuteration reagent for obtaining isotopically labeled organic compounds, and cinnamic derivatives have been widely used in biological activities.[15]

Synthesis of labeled compounds **2** may be explained by assuming that the SmI_2-promoted 1,4-reduction of **1** is initiated by oxidative addition of SmI_2 to generate the enolate [16] **4**; this radical is then hydrolyzed by the protic medium (X = D), and afford the corresponding radical **5**. After a second electron transfer from SmI_2 the radical generated the anion **6**, this being hydrolyzed by D_2O to afford the corresponding compound **2** (Scheme 2). When the α,β-unsaturated acids were not pre-treated with D_2O, a competitive hydrolysis of **4** and **6** produced by the acid proton of the carboxylic group and D_2O afforded a mixture of mono-, di-, and non-deuterated compounds. The pretreatment of **1** with D_2O could also change the aggregation state of the substrate, avoiding intermolecular hydrogen transfers.

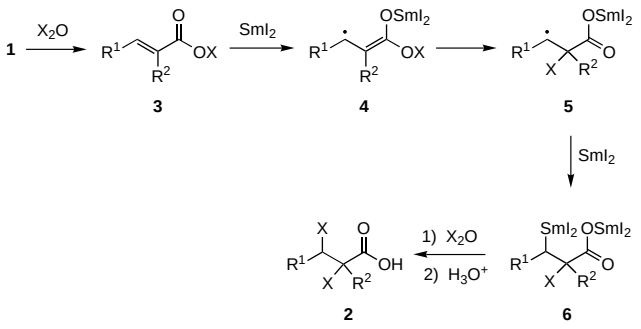
Synthesis of aliphatic 2,3-dideuterio acids: When the treatment with SmI_2 and D_2O was performed with aliphatic α-substituted-α,β-unsaturated acids or diacids, the corresponding 2,3-dideuterio acids **2g–i** were isolated in high yields (Table 2). Starting from unsaturated diacids, no differences were observed when *Z* or *E* diacids were used, and 2,3-dideuteriobutanedioic acid was obtained, for example, from maleic and fumaric acids (Table 2, entries 1 and 2).

Table 2. Synthesis of aliphatic 2,3-dideuterio acids.

Entry	2	R^1	R^2	Yield [%][a]
1	**2g**	HO_2C[b]	H	61
2	**2g**	HO_2C[c]	H	65
3	**2h**	C_7H_{15}	Me	71
4	**2i**	C_6H_{11}	Me	77

[a] Isolated yield based on compound **1**. [b] From maleic acid. [c] From fumaric acid.

However, when aliphatic, non-α-alkylated acids (Scheme 1, R^2 = H) were used as starting compounds, no reduction took place and the α,β-unsaturated acids were recovered.[17] This different behaviour with respect to the aromatic or conjugated acids may be explained taking into account that the initial oxidative addition of SmI_2 is favoured in the case of aromatic acids with respect to the aliphatic non-α-substituted acids, due to the enolate radical **4** (Scheme 2) being stabilized by



3 **4** **5** **6** **2**

Scheme 2. Mechanism of the reduction reaction.

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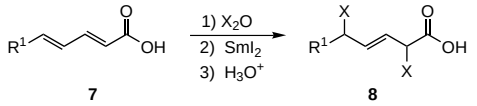
resonance. In addition, the enolate radical derived from diacids or aliphatic α-substituted-α,β-unsaturated acids is more stable than that derived from non-α-alkylated α,β-unsaturated acids due to resonance, in the first case, and to higher substitution of the C=C bond in the second.

Preparation of (*E*)-α,δ-dideuterio-β,γ-unsaturated acids: Isotopically labeled (*E*)-β,γ-unsaturated acids **8** can be prepared by using the described reaction conditions (Scheme 3) and starting, in this case, from alka-2,4-dienoic acids **7** (Table 3).



Scheme 3. Synthesis of (*E*)-α,δ-dideuterio-β,γ-unsaturated acids **8**.

Table 3. Synthesis of (*E*)-β,γ-unsaturated acids.

Entry	8	R^1	X	*ds*[a]	Yield [%][b]
1	**8a**	H	D	> 98	61
2	**8b**	Me	D	> 98	77
3	**8c**	Me	H	> 98	75

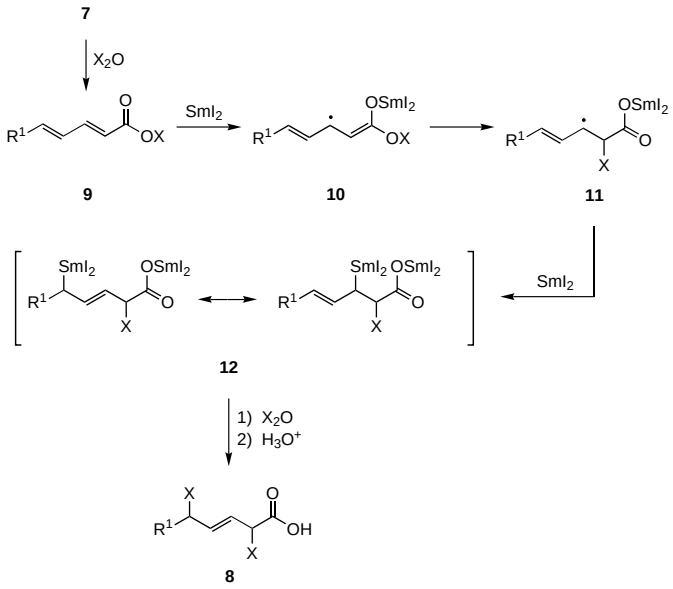
[a] Diastereoisomeric purity (*ds*) of the new C=C bond generated was determined by GC-MS and 300 MHz ^{1}H and ^{13}C NMR analysis of the crude products **8**. [b] Isolated yield based on compound **7**.

These labeled unsaturated compounds were synthesized through an SmI_2 promoted 1,4-reduction of the two conjugated C=C bonds (see mechanism), generating the new C=C bond with total diastereoselectivity. The incorporation of deuterium generated a new stereogenic centre and consequently the deuterated compounds **8** were isolated as a roughly 1:1 mixture of diastereoisomers.[18]

The diastereoisomeric purity of **8** was determined on the crude reaction products by ^{1}H NMR spectroscopy (300 MHz). The positions of the newly generated double bond and the deuterium atoms were established by ^{1}H and ^{13}C NMR spectroscopy of compounds **8**. Analysis of the multiplicity of the signals of the alkene protons allowed us to establish the proposed structure (Scheme 3) and to verify that the product was not a result of a possible 1,2-reduction of the two conjugated C=C bonds (α,β-dideuterated-γ,δ-unsaturated acids). The *E*-stereochemistry in the C=C bond was established on the basis of the value of the ^{1}H NMR coupling constant between the olefinic protons of compounds **8**. Complete deuterium incorporation (> 99 %) was confirmed by mass spectrometry.[14]

Synthesis of **8** may be explained by assuming that the SmI_2-promoted 1,4-reduction of the two conjugated double bonds C=C, is initiated by oxidative addition of SmI_2 generating enolate radical **10**,[16] which is hydrolyzed by the acid medium (X = D). The resulting radical **11** suffers a second electron transfer from SmI_2 affording an allylic anion **12**, and the hydrolysis of **12** with D_2O produces the corresponding compound **8** (Scheme 4).

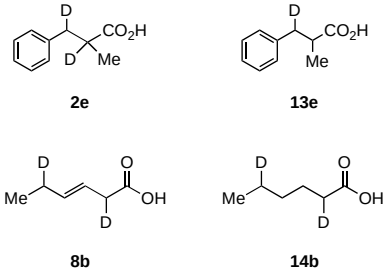
The C5 deuteration instead of C3 deuteration of the allyl anion **12** (1,4-reduction versus 1,2-reduction) may be explained by taking into account that the carboxylate C-5 anion structure is more stable than the carboxylate C-3 anion structure; this as a result of the charge repulsions and the steric hindrance produced by the two samarium atoms.



Scheme 4. Proposed mechanism for the conversion of **7** into **8**.

Synthesis of saturated or β,γ-unsaturated acids: No differences were observed in the reaction when D_2O or H_2O was used as proton source, and consequently saturated acids (Table 1, entry 6) and β,γ-unsaturated carboxylic acids (Table 3, entry 3) can be obtained by reaction of SmI_2 in the presence of H_2O with **1** or **7**, respectively. In these cases no pre-treating of the α,β-unsaturated acids with H_2O was necessary.

Synthesis of other deuterated carboxylic acids: The described methodology can be applied to obtain 3-deuterated carboxylic acids as depicted below. Thus, the treatment of the 2,3-dideuterio acid **2e** with LDA and further hydrolysis with H_2O afforded the corresponding 3-deuterio acid **13e** in 75 % yield.



Taking into account that the C=C bond of α,δ-dideuterio-β,γ-unsaturated acids can be easily hydrogenated, the proposed methodology can be used to prepare saturated α,δ-dideuterio acids. In this respect, 2,5-dideuteriohexanoic acid **14b** was prepared by hydrogenation of **8b** by using Rh/Al_2O_3 as catalyst[19] in 82 % yield (Figure 1).

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It is noteworthy that synthesis of deuterated carboxylic acids in a carbon atom different to the α-position is very difficult to achieve.

Conclusion

SmI_2-promoted reduction in the presence of D_2O provides a rapid and efficient method for synthesizing aromatic or aliphatic α-alkylated 2,3-dideuterio acids. Starting from alka-2,4-dienoic acids, α,δ-dideuterio-β,γ-unsaturated acids were prepared, their new C=C being generated with total diastereoselectivity. When H_2O was used instead of D_2O, saturated or β,γ-unsaturated carboxylic acids were isolated. The present method is easy, simple and rapid. In addition, cheap D_2O is used to obtain isotopically labeled compounds. Mechanisms to explain these syntheses have been proposed. Other isotopically labeled acids were also obtained.

Experimental Section

General: Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF and diethyl ether were 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 reaction of CH_2I_2 with samarium powder.[20] Deuterium oxide minimun isotopic purity 99.95 atom % D was used. Silica gel for flash chromatography was purchased from Merck (200–450 mesh), and compounds were visualized by thin-layer chromatography on analytical silica gel coated aluminium plates using UV light (254 nm). ^{1}H NMR spectra were recorded at 200, 300, or 400 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 or using FAB conditions. When HRMS could not be measured on molecular ion the HRMS of a significant fragment is given. Only the most important IR absortions (in cm^{-1}) and the molecular ions and/or base peaks in MS are given.

Synthesis of 2,3-dideuterated or saturated carboxylic acids 2 and preparation of (*E*)-2,5-dideuterio-β,γ-unsaturated or (*E*)-β,γ-unsaturated acids 8: Under nitrogen, a solution of SmI_2 (1.2 mmol) in THF (15 mL) was added dropwise to a stirred solution of the appropriate acid **1** or **7** in D_2O (2 mL) and THF (2 mL) at room temperature. The reaction mixture was stirred for 30 min and then treated with 0.1M aqueous HCl (5 mL). Standard workup afforded the crude dideuterio acids **2** or **8**, which were purified by flash column chromatography on silica gel (hexane/ethyl acetate 5:1).

If H_2O was used instead of D_2O, saturated acids or (*E*)-β,γ-unsaturated acids were obtained.

2,3-Dideuterio-3-phenylpropionic acid (2a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.91$ (br s, 1H), 7.40–7.23 (m, 5H), 3.00 (br d, $J = 7.69$ Hz, 1H), 2.71 (br d, $J = 7.69$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 179.2$ (C), 140.0 (C), 128.4 (CH), 128.1 (CH), 126.2 (CH), 35.2 (t, $J = 19.5$ Hz, CHD), 30.1 (t, $J = 19.8$ Hz, CHD); MS (70 eV): m/z (%): 152 (43) $[M]^+$, 106 (49), 92 (100); IR (neat): $\tilde{\nu} = 3427$, 3056, 2687, 1708 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt 3:1).

2,3-Dideuterio-3-(4-hydroxyphenyl)propionic acid (2b): ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 7.09$ (d, $J = 8.47$ Hz, 2H), 6.76 (d, $J = 8.47$ Hz, 2H), 2.76 (d, $J = 7.18$ Hz, 1H), 2.53 (d, $J = 7.18$ Hz, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 176.1$ (C), 156.1 (C), 132.4 (C), 130.4 (CH), 116.3 (CH), 35.5 (t, $J = 18.7$ Hz, CHD), 30.2 (t, $J = 17.0$ Hz, CHD); MS (70 eV): m/z (%): 168 (23) $[M]^+$, 108 (100), 78 (10); HRMS calcd for $C_9H_8D_2O_2$: 168.0753; found: 168.0759; IR (neat): $\tilde{\nu} = 3423$, 3092, 2995, 1652 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt 1:1).

2,3-Dideuterio-3-(3,4-dihydroxyphenyl)propionic acid (2c): ^{1}H NMR (300 MHz, D_2O): $\delta = 6.78$ (d, $J = 8.26$ Hz, 1H), 6.71 (d, $J = 1.99$ Hz, 1H), 6.58 (dd, $J = 8.26$, 1.99 Hz, 1H), 2.66 (d, $J = 7.40$ Hz, 1H), 2.50 (d, $J = 7.40$ Hz, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 177.9$ (C), 143.7 (C), 142.1 (C), 133.3 (C), 120.4 (CH), 116.1 (CH), 116.0 (CH), 35.1 (t, $J = 19.5$ Hz, CHD), 29.1 (t, $J = 19.8$ Hz, CHD); MS (70 eV): m/z (%): 184 (26) $[M]^+$, 124 (100), 108 (18), 78 (13); HRMS: calcd for $C_9H_8D_2O_4$: 184.0703; found: 184.0705; IR (neat): $\tilde{\nu} = 3399$, 3052, 2994, 1660 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt 1:1).

2,3-Dideuterio-3-(4-hydroxy-3-methoxyphenyl)propionic acid (2d): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.85$ (d, $J = 8.46$ Hz, 1H), 6.74–6.68 (m, 2H), 3.85 (s, 3H), 2.88 (d, $J = 7.70$ Hz, 1H), 2.64 (d, $J = 7.70$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 179.0$ (C), 146.3 (C), 143.8 (C), 131.9 (C), 120.6 (CH), 114.3 (CH), 110.8 (CH), 55.7 (CH_3), 35.5 (t, $J = 19.9$ Hz, CHD), 29.8 (t, $J = 19.9$ Hz, CHD); MS (70 eV): m/z (%): 198 (34) $[M]^+$, 138 (100); HRMS: calcd for $C_{10}H_{10}D_2O_4$: 198.0859; found: 198.0875; IR (neat): $\tilde{\nu} =$ 3421, 3055, 2939, 1706 cm^{-1}; $R_f = 0.2$ (hexane/AcOEt 1:1).

2,3-Dideuterio-2-methyl-3-phenylpropionic acid (2e): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 11.40$ (br s, 2H), 7.49–7.11 (m, 10H), 3.00 (br s, 1H), 2.71 (br s, 1H), 1.22 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 182.6$ (C), 138.9 (C), 128.9 (CH), 128.3 (CH), 126.3 (CH), 40.7 (t, $J = 19.2$ Hz, CD), 38.6 (t, $J =$ 19.4 Hz, CHD), 16.2 (CH_3); MS (70 eV): m/z (%): 166 (21) $[M]^+$, 92 (100), 73 (14); IR (neat): $\tilde{\nu} = 3424$, 3028, 2931, 1704 cm^{-1}; $R_f = 0.4$ (hexane/AcOEt 3:1).

3-Phenylpropionic acid (2f): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 10.92$ (br s, 1H), 7.40–7.23 (m, 5H), 3.01 (t, $J = 7.72$ Hz, 2H), 2.72 (t, $J = 7.72$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 179.2$ (C), 140.0 (C), 128.4 (CH), 128.1 (CH), 126.2 (CH), 35.5 (CH_2), 30.4 (CH_2); MS (70 eV): m/z (%): 150 (41) $[M]^+$, 104 (57), 90 (100); IR (neat): $\tilde{\nu} = 3427$, 3056, 2687, 1708 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt 3:1).

2,3-Dideuteriosuccinic acid (2g): ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta =$ 12.20 (br s, 4H), 2.51 (br s, 2H), 2.40 (br s, 2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 173.9$ (C), 28.7 (t, $J = 19.7$ Hz, CHD); HRMS: calcd for $C_4H_4D_2O_4$: 120.0390; found: 120.0394; IR (neat): $\tilde{\nu} = 3424$, 1652 cm^{-1}; $R_f =$ 0.1 (hexane/AcOEt 1:1).

2,3-Dideuterio-2-methyldecanoic acid (2h): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01-1.01$ (m, 16H), 1.00–0.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 182.8$ (C), 38.8 (t, $J = 22.1$ Hz, CD), 33.0 (t, $J = 18.9$ Hz, CHD), 31.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 16.6 (CH_3), 14.0 (CH_3); MS (70 eV): m/z (%): 188 (3) $[M]^+$, 88 (29), 75 (100); IR (neat): $\tilde{\nu} = 3432$, 2924, 2855, 1705 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt 5:1).

3-Cyclohexyl-2,3-dideuterio-2-methylpropionic acid (2i): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.05-0.84$ (m, 12H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 183.6$ (C), 40.7 (t, $J = 19.2$ Hz, CHD), 36.1 (t, $J =$ 20.4 Hz, CD), 35.0 (CH), 33.1 (CH_2), 32.9 (CH_2), 29.6 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 17.2 (CH_3); MS (70 eV): m/z (%): 172 (2) $[M]^+$, 127 (35), 98 (100), 75 (61), 55 (48); HRMS: calcd for $C_{10}H_{16}D_2O_2$: 172.1430; found: 172.1438; IR (neat): $\tilde{\nu} = 3408$, 2923, 2852, 1704 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt 5:1).

(*E*)-2,5-Dideuteriopent-3-enoic acid (8a): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.65$ (br s, 1H), 5.64 (dd, $J = 15.65$, 5.09 Hz, 1H), 5.57–5.44 (m, 1H), 3.11–3.00 (br m, 1H), 1.82–1.60 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.7$ (C), 130.0 (CH), 121.8 (CH), 37.4 (t, $J = 19.7$ Hz, CHD), 17.5 (t, $J = 19.5$ Hz, CH_2D); MS (70 eV): m/z (%): 102 (55) $[M]^+$, 84 (10), 57 (100); IR (neat): $\tilde{\nu} = 3418$, 3013, 2922, 1707 cm^{-1}; $R_f = 0.4$ (hexane/AcOEt 3:1).

(*E*)-2,5-Dideuteriohex-3-enoic acid (8b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 10.46 (br s, 1H), 6.65 (dd, $J = 15.15$, 5.28 Hz, 1H), 5.50 (dd, $J = 15.15$, 5.87 Hz, 1H), 3.08–3.03 (m, 1H), 2.09–1.99 (m, 1H), 0.99 (d, $J = 7.44$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.7$ (C), 136.8 (CH), 119.7 (CH), 37.5 (t, $J = 19.5$ Hz, CHD), 25.1 (t, $J = 19.4$ Hz, CHD), 13.2 (CH_3); MS (70 eV): m/z (%): 116 (63) $[M]^+$, 70 (63), 56 (100), 42 (85); HRMS: calcd for $C_6H_8D_2O_2$: 116.0804; found: 116.0810; IR (neat): $\tilde{\nu} = 3325$, 2964, 1713 cm^{-1}; $R_f = 0.5$ (hexane/AcOEt 3:1).

(*E*)-Hex-3-enoic acid (8c): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 11.04$ (br s, 1H), 5.80–5.41 (m, 2H), 3.07 (d, $J = 6.26$ Hz, 2H), 2.13–1.98 (m, 2H), 0.99 (t, $J = 7.44$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 178.8$ (C), 136.8 (CH), 119.7 (CH), 37.7 (CH_2), 25.4 (CH_2), 13.3 (CH_3); MS (70 eV): m/z (%): 114 (43) $[M]^+$, 68 (55), 55 (86), 41 (100); IR (neat): $\tilde{\nu} = 3325$, 2964, 1713 cm^{-1}; $R_f = 0.5$ (hexane/AcOEt 3:1).

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Synthesis of 3-deuterio acid 13e: Under nitrogen, a solution of compound **2e** (0.4 mmol) in THF (4 mL) was added dropwise to a stirred solution of lithium diisopropylamide (1.6 mmol) in THF (18 mL) at room temperature and the reaction was allowed to proceed under reflux. After stirring for 30 min, the reaction mixture was quenched by the addition of H_2O (5 mL). Standard workup provided the 3-deuterio acid **13e** which was purified by flash column chromatography on silica gel (hexane/AcOEt 5:1).

3-Deuterio-2-methyl-3-phenylpropionic acid (13e): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 10.07$ (br s, 2H), 7.38–7.02 (m, 10H), 3.17–3.07 (m, 1H), 2.84–2.66 (m, 3H), 1.21 (d, $J = 6.65$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 182.6 (C), 138.9 (C), 128.9 (CH), 128.3 (CH), 126.3 (CH), 40.7 (t, $J =$ 19.2 Hz, CD), 38.6 (t, $J = 19.4$ Hz, CHD), 16.2 (CH_3); MS (70 eV): m/z (%): 165 (50) $[M]^+$, 118 (14), 92 (100), 66 (17); HRMS: calcd for $C_{10}H_{11}DO_2$: 165.0899; found: 165.0901; IR (neat): $\tilde{\nu} = 3424$, 3028, 2931, 1704 cm^{-1}; $R_f = 0.4$ (hexane/AcOEt 3:1)

Synthesis of 2,5-dideuteriohexanoic acid (14b): 5% Rh/alumina (50 mg) was added to a solution of compound **8b** (0.4 mmol) in MeOH (25 mL). The solution was stirred under H_2 atmosphere for 12 h. The mixture was filtered through Celite and washed with 0.1M HCl. Standard workup provided the 2,5-dideuterio acid **14b** which was purified by flash column chromatography on silica gel (hexane/AcOEt 5:1).

2,5-Dideuteriohexanoic acid (14b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.13$ (br s, 1H), 2.31–2.24 (m, 1H), 1.60–0.70 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.5$ (C), 33.7 (t, $J = 19.7$ Hz, CHD), 31.0 (CH_2), 24.2 (CH_2), 21.8 (t, $J = 19.0$ Hz, CHD), 13.6 (CH_3); MS (70 eV): m/z (%): 118 (<1) $[M]^+$, 88 (18), 74 (50), 61 (100), 42 (30); IR (neat): $\tilde{\nu} = 3425$,2993, 2822, 1705 cm^{-1}; $R_f = 0.3$ (hexane/AcOEt 5:1).

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