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Note

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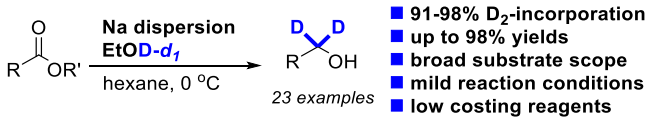
Development of a Modified Bouveault-Blanc Reduction for the Selective Synthesis of *α,α*-Dideuterio Alcohols

Minhui Han,† Xiaodong Ma,† Shangchu Yao, Yuxuan Ding, Zihan Yan, ADiLa ADiJiang, Yufei Wu, Hengzhao Li, Yuntong Zhang, Peng Lei, Yun Ling and Jie An*

College of Science, China Agricultural University, No.2 Yuanmingyuan West Road, Beijing 100193, China.

*jie_an@cau.edu.cn

†M. Han and X. Ma contributed equally.



ABSTRACT: A modified Bouveault-Blanc reduction has been developed for the synthesis of *α,α*-dideuterio alcohols from carboxylic acid esters. Sodium dispersions are used as the electron donor in this electron transfer reaction and ethanol-d_1 is employed as deuterium source. This reaction uses stable, cheap and commercially-available reagents, is operationally-simple and results in excellent deuterium incorporation across a broad range of aliphatic esters, which provides an attractive alternative to reactions mediated by expensive pyrophoric alkali metal deuterides.

Deuterium incorporation has found increasing applications in the pharmacological industry to improve metabolism and pharmacokinetic properties of drug candidates.[1] A significant number of deuterated drug candidates has been synthesized and forwarded to clinical trials.[2] The FDA is currently considering the approval of the first deuterated drug, deutetrabenazine (**A**, Figure 1).[3] The cleavage of C-D bonds requires higher activation energy than that of C-H

bonds, which is known as deuterium isotope effect.[4] Some deuterated drugs have been reported to have a longer half-life and improved toxicity profiles.[1-3] Thus, broad applications of deuterated compounds in the development of safer drugs are expected. Similarly, the metabolism rate of some deuterated pesticides is significantly slower than that of their unlabeled counterparts, which could lead to the improvement of their toxicity and insecticidal activity profiles (**B**, Figure 1).[5] In addition, deuterated compounds have been widely used as metabolic or pharmacokinetic probes in pharmaceutical studies[6], as internal standards in LC/MS analysis,[7] and as tools for studying the mechanisms of organic reactions.[8]

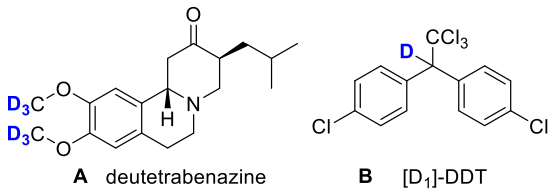
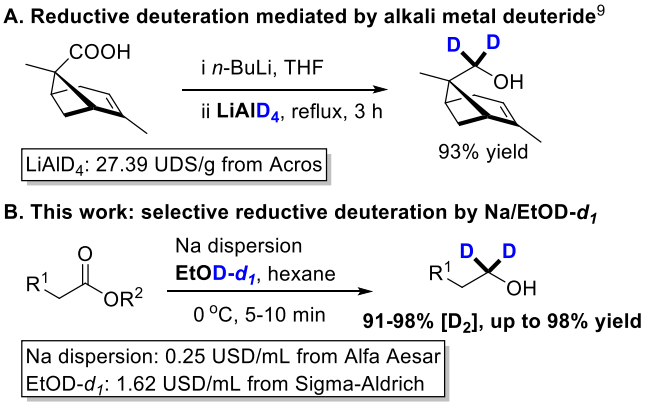


Figure 1. Deutetrabenazine: compared with tetrabenazine, **A** exhibits a significantly better toxicity profile and longer half-life; **[D_1]-DDT:** the enzyme-catalyzed dehydrochlorination process of **B** is 6 times slower than that of the unlabeled DDT.

Scheme 1. (A) Reductive deuteration using $LiAlD_4$; (B) This work: selective reductive deuteration using sodium dispersions and ethanol-d_1.



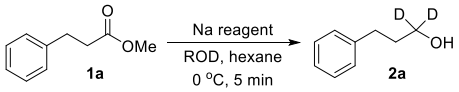
The increasing demand for deuterium labeled compounds has led to an increased interest in the development of new synthetic methodologies to introduce deuterium. Generally, three

strategies are employed in the synthesis of deuterated compounds: (a) Synthesis from deuterated precursors. The feasibility of this strategy, however, highly depends on the availability of starting materials and long synthetic routes must often be considered. (b) Post-synthetic hydrogen/deuterium exchange, including metal catalyzed and pH-dependent protocols.[9] However, a vast majority of reactions of this type requires either expensive catalysts or harsh reaction conditions, and suffers from limited scope, low levels of deuterium incorporation, and poor selectivity.[9a] (c) Reductive deuteration, including reductions mediated by alkali metal deuterides, such as sodium borodeuteride and lithium aluminum deuteride (A, Scheme 1).[10] Reductive methods of this type can selectively introduce deuterium into the targeted position and generally result in high levels of deuterium incorporation. However, the widespread application of these methods is restricted by the requirement of expensive pyrophoric alkali metal deuterides. In 2014, a SmI_2-Et_3N-D_2O mediated reductive deuteration method for the selective synthesis of *α,α*-dideuterio alcohols from carboxylic acids was reported.[11] This very selective reaction represents the first application of single electron transfer (SET) reaction in direct reductive deuteration of carboxylic acids, and shows the advantages of selective SET reagents in this field. However, despite advances in deuteration methodologies, the application of deuterium labeled compounds in industry, especially pesticide industry, is still restricted by high economic cost.[3]

Herein, we report a new and highly selective improved Bouveault-Blanc reduction for the synthesis of *α,α*-dideuterio alcohols via electron transfer reaction using low price and commercially-available reagents: sodium metal dispersion and ethanol-d_1 (B, Scheme 1). Bouveault-Blanc reduction is an important ester reduction method mediated by sodium lump and absolute ethanol (B, Scheme 1).[12] Recently, a new sodium reagent (Na-D15) has been employed for an improved Bouveault-Blanc reduction. The application of this method was, however, restricted by the limited availability of Na-D15[13]. Although various bench-stable

sodium dispersions and reagents have become commercially available, their application as mild, stable and highly chemoselective single electron donors is underdeveloped.

Table 1.Optimization of the Reductive Deuteration Mediated by Na/ROD[a]



entry	Na reagent	ROH	ROH (eq.)	yield (%)[b]	[D_2] (%)[b]
1	dispersion in oil[c]	MeOD-d_4	4.5	91	92
2	dispersion in oil[c]	MeOD-d_4	6.0	95	93
3	dispersion in oil[c]	MeOD-d_4	8.0	89	93
4	dispersion in oil[c]	EtOD-d_1	4.5	97	94
5	dispersion in oil[c]	EtOD-d_1	6.0	92	95
6	dispersion in oil[c]	EtOD-d_1	8.0	89	94
7	dispersion in oil[c]	*i*-PrOD-d_1	4.5	95	94
8	dispersion in oil[c]	*i*-PrOD-d_1	6.0	95	95
9	dispersion in oil[c]	*i*-PrOD-d_1	8.0	90	95
10	dispersion in oil[c]	*t*-BuOD-d_1	4.5	95	93
11	dispersion in oil[c]	*t*-BuOD-d_1	6.0	88	93
12	dispersion in oil[c]	*t*-BuOD-d_1	8.0	85	95
13	dispersion in paraffin[d]	EtOD-d_1	4.5	87	93
14	dispersion in toluene[e]	EtOD-d_1	4.5	64	91
15	Na-SG (I)[f]	EtOD-d_1	4.5	52	85

[a]Conditions: **1a** (0.50 mmol, 1.0 equiv), Na reagent (4.5 equiv), hexane, 0 °C, 5 min. [b]Determined by ^{1}H NMR. [c]40 wt%, particle size 5-10 μm. [d]30~35 wt%, average particle size 10 μm. [e]30 wt%, particle size <100 μm. [f]~35 wt%, sodium silica gel stage I.

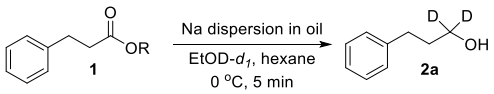
We started our investigations by studying the effect of various sodium reagents and deuterium donors on the reductive deuteration of **1a** (Table 1). Sodium dispersion in oil (particle size 5-10 μm, purchased from Alfa Aesar) was chosen as the preferred reducing reagent as it is a bench-stable commercially-available reagent which is easy to handle in an open atmosphere. The use of solid state sodium dispersions (entry 13) or dispersions with larger particle size (entry 14) led to lower yields, which may due to smaller contact surface between sodium and other reactants. Of note, sodium on silica gel (Na-SG), a stabilized sodium metal that has been demonstrated to be effective for the reduction of esters,[14] failed to achieve high D_2 incorporation in this reaction (entry 15). The presence of approximately quantitative sodium dispersion in oil[15] and MeOD-d_4 afforded the alcohol product in 91% yield with 92.0% D_2-incorporation (entry 1). Given the low solubility of MeOD-d_4 in hexane,

other proton donors were screened (entries 1-12). The use of EtOD-d_1 (4.5 equiv) led to the best yield of **2a** and 94% D_2-incorporation (entry 4). When excess of the proton donor was used, D_2-incorporations only marginally increased, while the yields were lower due to competing oxidation of sodium by alcohol (entries 5-6).

Following our optimization studies, a range of esters derived from hydrocinnamic acid was tested under the optimized conditions (Table 1, entry 4). Methyl, ethyl, *i*-propyl, *t*-butyl, *n*-butyl, allyl, benzyl and 2-methoxyethyl esters were all converted into the corresponding α,α-dideuterio alcohols in high yields and with excellent D_2-incorporation (Table 2). Even sterically-hindered ester **1d** and allyl ester **1f** were reduced in high yields (entries 3 and 5).

The substrate scope investigations demonstrate that high levels of D_2-incorporation are general across a range of aliphatic ester and lactone substrates (Table 3). Significantly, no impact on the D_2 incorporation and yield was observed with sterically-hindered substituents (entries 7 and 9), which compares favorably with reductions mediated by SmI_2/H_2O.[11a] Substrates bearing both internal and terminal olefins (entries 12, 13 and 16) were well-tolerated. Aromatic reduction was not observed in the reaction when aromatic substrates were used (entries 1-8). Sensitive functional groups such as F, OMe, and SMe (entries 2-4) were tolerated well.

Table 2.The Reductive Deuteration of Hydrocinnamic Acid Esters by Na/EtOD-d_1[a]

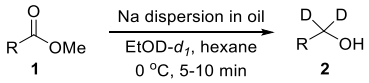


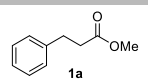
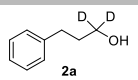
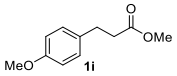
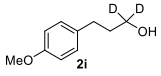
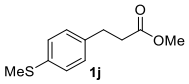
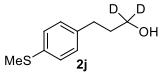
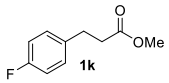
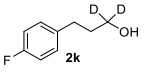
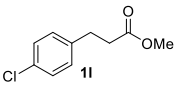
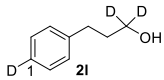
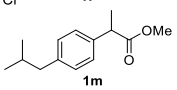
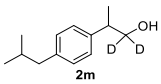
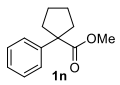
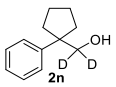
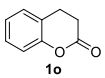
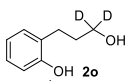
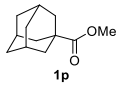
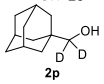
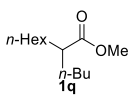
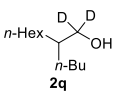
entry	ester	R	product	yield (%)[b]	[D_2] (%)[c]
1	**1b**	Et	**2a**	97	94
2	**1c**	*i*-Pr	**2a**	96	93
3	**1d**	*t*-Bu	**2a**	81	95
4	**1e**	*n*-Bu	**2a**	94	93
5	**1f**	Allyl	**2a**	77	94
6	**1g**	Bn	**2a**	88	95
7	**1h**	$(CH_2)_2OMe$	**2a**	98	93

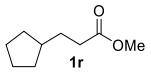
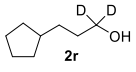
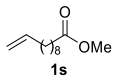
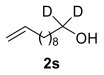
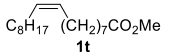
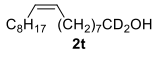
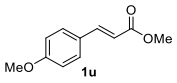
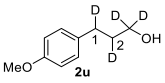
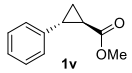
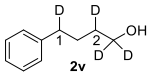
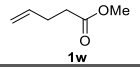
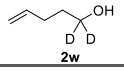
[a]Conditions: **1** (0.50 mmol, 1.0 equiv), Na (4.5 equiv), EtOD-d_1 (4.5 equiv), hexane, 0 °C, 5 min. [b]Isolated yields. [c]Determined by ^{1}H NMR.

Interestingly, when 6.5 equiv of sodium was used, 4-chlorophenyl group was sequentially reduced with 95% D_1-Ar-incorporation (Table 3, entry 5). Conjugated alkenyl (**1u**) and cyclopropane (**1v**) groups were also fully reduced to give alcohols **2u** and **2v** with high deuterium incorporations (entries 14-15). These results suggest the potential application of this protocol for the selective introduction of deuterium in tandem sequences via electron transfer. It is noteworthy that a 20-fold scale up of this reaction (0.50 mmol to 10 mmol) resulted in excellent yield and D_2 incorporation (entry 1). High D_2 incorporation (90%) was also obtained in the reaction carried out in open flask conditions, which demonstrated that this reaction was relatively insensitive to moisture and atmospheric oxygen.

Table 3.Reductive Deuteration of Esters by Na/EtOD-d_1[a]

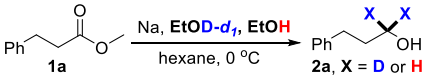


entry	substrate	product	yield (%)[b]	[D_2] (%)[c]
1[d]			93	96
2			91	93
3			81	92
4			87	94
5[e]			81	94[f]
6			92	95
7			95	96
8			77	91
9			95	97
10			75	95

11	 1r	 2r	80	97
12	 1s	 2s	95	94
13	 1t	 2t	95	91
14[e]	 1u	 2u	78	91[g]
15[e]	 1v	 2v	66	94[h]
16	 1w	 2w	85	>98%

[a]Conditions: **1** (0.50 mmol, 1.0 equiv), Na (4.5 equiv), EtOD-d_1 (4.5 equiv), hexane, 0 °C, 5 min. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Conditions: **1** (10.0 mmol). [e]Conditions: Na dispersion in oil (6.5 equiv), EtOD-d_1 (6.5 equiv). [f]95% [D_1] at C_1. [g] 94% [D_1] at C_1, 74% [D_1] at C_2. [h]93% [D_1] at C_1, 89% [D_1] at C_2.

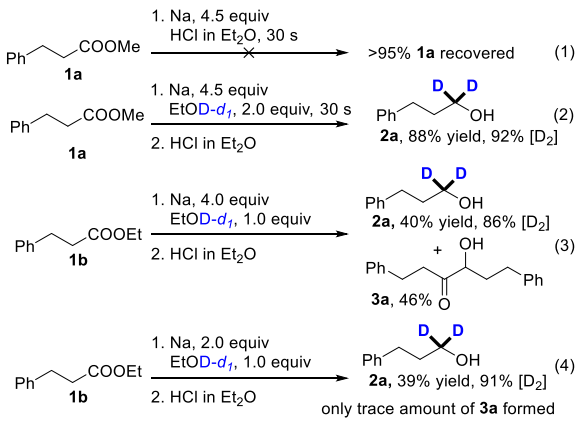
Table 4. The Effect of the Amount and Addition Order of EtOD-d_1 and EtOH on the Deuterium Incorporation[a]



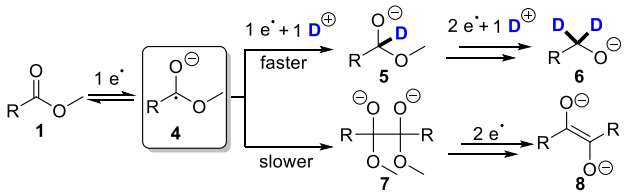
entry	EtOD/H (equiv)	EtOD/H (ratio)	addition method[b]	yield (%)[c]	[D_2] (%)[c]
1	4.5	1:1	A	94	82
2	4.5	1:1	B	95	50
3	4.5	1:1	C	93	11
4	4.5	2:1	A	96	88
5	4.5	8:1	A	95	91

[a]Conditions: **1a** (0.50 mmol, 1.0 equiv), Na (4.5 equiv), hexane, 0 °C. [b] A: EtOD-d_1 was added followed by EtOH after 10 s; B: EtOD-d_1 and EtOH were added together; C: EtOH was added followed by EtOD-d_1 after 10 s. [c]Determined by ^{1}H NMR.

Next, the effect of proton donors on the reaction was explored by using limiting deuterium donor (Table 4). The sequential addition of EtOD-d_1 (2.25 equiv) and EtOH (2.25 equiv) led to the formation of **2a** in 94% yield and 82% D_2-incorporation (entry 1). However, the reverse addition resulted in the formation of non-deuterium labeled product as the major product (entry 3). These results indicate that only 2 equiv of the proton donor are involved in the Bouveault-Blanc reduction under these conditions, while ruling out the four proton transfer process.[16] In addition, the use of pre-mixed EtOD-d_1/EtOH (1:1) led to the formation of **2a** in 50% D_2 incorporation. The kinetic isotope effect (k_H/k_D=1.0) determined by this experiment indicates that the proton transfer is not involved in the rate determine step.[8a]



Scheme 2. The Proposed Mechanism for the Reductive Deuteration of Esters Using Na/EtOD-*d*$_1$



Control reactions (eq. 1 and 2) demonstrated that: (a) ester reduction by Na/HCl is not observed (eq. 1); (b) in the reaction with 2.0 equiv of EtOD-*d*$_1$, Na was all consumed within 30 sec (eq. 2). Moreover, in the presence of 4.0 equiv of Na and 1.0 equiv of EtOD-*d*$_1$, **2a** was formed in 40% yield and 88% D_2-incorporation, while 46% of acyloin **3a** was also formed (eq. 3). Interestingly, in the presence of 2.0 equiv of Na and 1.0 equiv of EtOD-*d*$_1$, only **2a** was observed (eq. 4). These observations together with the opening of the cyclopropyl radical clock (Table 3, entry 15) indicate that: (a) the first electron transfer (**1**→**4**) may be reversible and occurs even without a proton donor[17]; (b) the second electron transfer step (**4**→**5**) occurs only in the presence of a proton donor and this process is faster than the condensation process (**4**→**7**) (Scheme 2); (c) The high levels of deuterium incorporation (eq. 2, 3 and 4) indicate that anions are selectively protonated by the proton donor (cf. intramolecular proton transfer), which may lead to the development of new selective SET synthetic protocols using Na dispersion and EtOH.[18]

In summary, *α,α*-dideuterio alcohols can be synthesized from carboxylic acid esters by using Na dispersion in oil and ethanol-d_1. High levels of deuterium incorporation and excellent yields have been achieved across a broad range of substrates. This study also provides new insights into the mechanism of the Bouveault-Blanc reduction. Compared with the reductive deuteration mediated by alkali metal deuterides or SmI_2, this protocol is safer, lower costing and with higher atom economy. The potential for the reductive deuteration of halides, alkenes and cyclopropanes by tandem sequences has also been demonstrated and will be the subject of our further studies.

Experimental Section

Glassware was dried in an oven overnight before use. Thin layer chromatography was carried out on SIL G/UV254 silica-aluminum plates and plates were visualized using ultra-violet light (254 nm) and $KMnO_4$ solution. For flash column chromatography, silica gel 60, 35-70 μ was used. NMR data was collected at 300, 400, or 500 MHz. Data was manipulated directly from the spectrometer or *via* a networked PC with appropriate software. All samples were analyzed in $CDCl_3$ unless otherwise stated. Reference values for residual solvent were taken as δ = 7.27 ($CDCl_3$) for ^{1}H-NMR; δ = 77.1 ($CDCl_3$) for ^{13}C-NMR. Multiplicities for coupled signals were designated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad signal, and are given in Hz.

All compounds used in this study have been described in the literature or are commercially available. All solvents and reagents were used as supplied. Esters were purchased from commercial suppliers or prepared by standard methods.[11c, 13, 14b]

Optimization Studies (Table 1)

To a solution of ester (0.500 mmol) in anhydrous hexane (2.5 mL), was added anhydrous ROD (2.25 mmol-4.00 mmol), followed by Na reagent (2.25 mmol) under N_2 at 0 ºC and the resulted solution was stirred vigorously. After 5 min the reaction was quenched by an aqueous solution of HCl (1.0 mL, 3.0 M) and the reaction mixture was diluted with Et_2O (10 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Then the sample was analyzed by ^1H NMR ($CDCl_3$, 400/500 MHz) to obtain the deuterium incorporation and yield using internal standard ($MeNO_2$) and comparison with corresponding samples.

General Procedure for the Reduction of Esters by Na/EtOD-*d_1*

To a solution of ester (0.500 mmol) in anhydrous hexane (2.5 mL), was added EtOD (2.25 mmol), followed by Na dispersion in oil (40 wt%, 2.25 mmol) under N_2 at 0 ºC and the resulted solution was stirred vigorously. After 5 min at 0 ºC, the temperature was raised to rt. After the specified time (typically 0-10 min), the reaction was quenched by an aqueous solution of HCl (1.0 mL, 3.0 M) and the reaction mixture was diluted with Et_2O (10 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica, 0-30% EtOAc/hexane).

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] **(**Table 1, entry 4). According to the general procedure, the reaction of methyl 3-phenylpropanoate (0.50 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, after chromatography (hexanes-10% EtOAc/hexane), afforded **2a** 67 mg in 97% yield as a colorless oil. D_2 incorporation = 94%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.25-7.17 (m, 3H), 2.72 (t, J = 7.8, 2H), 1.91 (t, J = 7.8, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 128.5, 128.5, 126.0, 61.7 (m), 34.1, 32.1.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] **(**Table 2, entry 1**)**. According to the general procedure, the reaction of ethyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, afforded **2a** 67 mg in 97% yield as a colorless oil. D_2 incorporation = 94%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] (Table 2, entry 2). According to the general procedure, the reaction of isopropyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 10 min at rt, afforded **2a** 66 mg in 96% yield as a colorless oil. D_2 incorporation = 93%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] **(**Table 2, entry 3). According to the general procedure, the reaction of *tert*butyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 10 min at rt, afforded **2a** 56 mg in 81% yield as a colorless oil. D_2 incorporation = 95%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] (Table 2, entry 4). According to the general procedure, the reaction of *n*-butyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, afforded **2a** 65 mg in 94% yield as a colorless oil. D_2 incorporation = 93%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] (Table 2, entry 5). According to the general procedure, the reaction of allyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, afforded **2a** 53 mg in 77% yield as a colorless oil. D_2 incorporation = 94%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] **(**Table 2, entry 6). According to the general procedure, the reaction of benzyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, afforded **2a** 61 mg in 88% yield as a colorless oil. D_2 incorporation = 95%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] **(**Table 2, entry 7). According to the general procedure, the reaction of 2-methoxyethyl 3-phenylpropanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, afforded **2a** 68 mg in 98% yield as a colorless oil. D_2 incorporation = 93%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] (Table 3, entry 1). According to the general procedure, the reaction of methyl 3-phenylpropanoate (10.0 mmol), EtOD (45.0 mmol) and Na dispersion in oil (45.0 mmol) for 5 min at 0 ºC, after chromatography (hexanes-10% EtOAc/hexane), afforded **2a** 1.28 g in 93% yield as a colorless oil. D_2 incorporation = 96%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-phenylpropan-1-ol 2a[11a] (*reaction under open flask conditions*). To a solution of methyl 3-phenylpropanoate (1.00 mmol) in anhydrous hexane (5.0 mL), was added EtOD (4.5. mmol), followed by Na dispersion in oil (4.50 mmol) in an open flask at 0 ºC and the resulted solution was stirred vigorously. After 5 min at 0 ºC, the temperature was raised to rt. The reaction was quenched by an aqueous solution of HCl (2.0 mL, 3.0 M) and the reaction mixture was diluted with Et_2O (10 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica, 0-

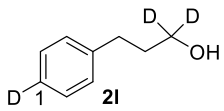
10% EtOAc/hexane), afforded **2a** 127 mg in 92% yield as a colorless oil. D_2 incorporation = 90%. Spectroscopic properties matched those previously described.

1,1-Dideuterio-3-(4-methoxyphenyl)propan-1-ol 2i[11a] **(**Table 3, entry 2). According to the general procedure, the reaction of methyl 3-(4-methoxyphenyl)propanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2i** 76 mg in 91% yield as a colorless oil. D_2 incorporation = 93%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.10 (m, 2H), 6.88-6.82 (m, 2H), 3.80 (s, 3H), 2.66 (t, J = 7.7, 2H), 1.86 (t, J = 7.7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 133.9, 129.4, 113.9, 61.6 (m), 55.4, 34.3, 31.2.

3-(4-(Methylthio)phenyl)propan-1,1-*d*$_2$-1-ol 2j[11a] **(**Table 3, entry 3). According to the general procedure, the reaction of methyl 3-(4-(methylthio)phenyl)propanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2j** 75 mg in 81% yield as a colorless oil. D_2[2] incorporation = 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 7.17 – 7.11 (m, 2H), 2.68 (t, J = 7.7, 2H), 2.48 (s, 3H), 1.86 (t, J = 7.7, 2H), 1.48 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 135.4, 129.0, 127.1, 61.5 (m), 34.0, 31.5, 16.3.

1,1-Dideuterio-3-(4-fluorophenyl)propan-1-ol 2k[11a] **(**Table 3, entry 4). According to the general procedure, the reaction of methyl 3-(4-fluorophenyl)propanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2k** 68 mg in 87% yield as a colorless oil. D_2 incorporation = 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 7.01 – 6.94 (m, 2H), 2.69 (t, J = 7.8 Hz, 2H), 1.87 (t, J = 7.8, 2H), 1.42 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, $J_{(C-F)}$ = 243.4), 137.5 (d, $J_{(C-F)}$ = 3.2), 129.8 (d, $J_{(C-F)}$ = 7.8), 115.2 (d, $J_{(C-F)}$ = 21.1), 61.4 (m), 34.2, 32.3.

3-(Phenyl-4-*d*)propan-1,1-d_2-1-ol 2l[11a] (Table 3, entry 5).



2l

According to the general procedure, the reaction of methyl 3-(4-chlorophenyl)propanoate (0.500 mmol), EtOD (3.25 mmol) and Na dispersion in oil (3.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2l** 56 mg in 81% yield as a colorless oil. D_2 incorporation = 94% and D_1 incorporation = 95% at C_1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.19 (m, 2H), 2.73 (t, *J* = 7.7, 2H), 1.90 (t, *J* = 7.7, 2H), 1.48 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 128.5, 128.4, 125.6 (t, $J_{(C\text{-}D)}$ = 24.4), 61.6 (m), 34.1, 32.1.

2-(4-*Iso*butylphenyl)propan-1,1-d2-1-ol 2m[11a] **(**Table 3, entry 6**).** According to the general procedure, the reaction of methyl 2-(4-*iso*butylphenyl)propanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2m** 89 mg in 92% yield as a colorless oil. D_2 incorporation = 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.09 (m, 4H), 2.92 (q, *J* = 7.0, 1H), 2.46 (d, *J* = 7.2, 2H), 1.85 (m, 1H), 1.28 (d, *J* = 7.0, 3H), 0.92 (d, *J* = 6.6, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 140.2, 129.5, 127.2, 68.1 (m), 45.1, 41.9, 30.3, 22.5, 17.7.

(1-Phenylcyclopentyl)methan-d_2-ol 2n[13] **(**Table 3, entry 7**).** According to the general procedure, the reaction of methyl 1-phenylcyclopentanecarboxylate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2n** 85 mg in 95% yield as a colorless oil. D_2 incorporation = 96%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.23 (m, 4H),

7.19-7.15 (m, 1H), 2.02 – 1.92 (m, 2H), 1.87 – 1.77 (m, 2H), 1.75 – 1.61 (m, 4H), 1.19 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 128.4, 127.4, 126.3, 69.6 (m), 53.2, 34.3, 23.9.

2-(3-Hydroxypropyl-3,3-*d*$_2$)phenol 2o[13] **(**Table 3, entry 8). According to the general procedure, the reaction of methyl chroman-2-one (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-30% EtOAc/hexane), afforded **2o** 59 mg in 77% yield as a colorless oil. D_2 incorporation = 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.07 (m, 2H), 6.92-6.82 (m, 2H), 2.79 (t, *J* = 6.8, 2H), 1.88 (t, *J* = 6.8, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 130.7, 127.7, 127.2, 120.9, 116.3, 60.4 (m), 32.1, 25.2.

1-Dideuterio-adamantanemethanol 2p[13] **(**Table 3, entry 9)**.** According to the general procedure, the reaction of methyl adamantane-1-carboxylate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC, after chromatography (hexanes-10% EtOAc/hexane), afforded **2p** 80 mg in 95% yield as a white solid. D_2 incorporation = 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (m, 3H), 1.74 (m, 3H), 1.65 (m, 3H), 1.51 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.2 (m), 39.1, 37.3, 34.6, 28.3.

2-Butyloctan-1,1-*d*$_2$-1-ol 2q[13] **(**Table 3, entry 10). According to the general procedure, the reaction of methyl 2-butyloctanoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2q** 71 mg in 75% yield as a colorless oil. D_2 incorporation = 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.40 (s, 1H), 1.38 – 1.22 (m, 16H), 0.97-0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.1 (m), 40.4, 32.0, 31.0, 30.7, 29.8, 29.2, 27.0, 23.2, 22.8, 14.2×2.

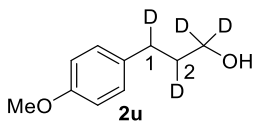
3-Cyclopentylpropan-1,1-*d*$_2$-1-ol 2r[19] **(**Table 3, entry 11). According to the general procedure, the reaction of methyl 3-cyclopentylpropanoate (0.500 mmol), EtOD (2.25 mmol)

and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2r** 52 mg in 80% yield as a colorless oil. D_2 incorporation = 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 – 1.69 (m, 3H), 1.65 – 1.30 (m, 9H), 1.15 – 1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.7 (m), 40.0, 32.8, 32.2, 31.9, 25.2.

1,1-Dideuterioundec-10-en-1-ol 2s[13] **(**Table 3, entry 12)**.** According to the general procedure, the reaction of methyl undec-10-enoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2s** 82 mg in 95% yield as a colorless oil. D_2 incorporation = 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.04 - 4.89 (m, 2H), 2.04 (m, 2H), 1.56 (m, 2H), 1.44 - 1.20 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 114.2, 62.4 (m), 33.9, 32.7, 29.6, 29.5, 29.5, 29.2, 29.0, 25.7.

(*Z*)-Octadec-9-en-1,1-*d*$_2$-1-ol 2t[13] **(**Table 3, entry 13). According to the general procedure, the reaction of methyl oleate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2t** 128 mg in 95% yield as a colorless oil. D_2 incorporation = 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (m, 2H), 2.02 (m, 4H), 1.56 (t, *J* = 7.4, 2H), 1.41-1.19 (m, 22H), 0.89 (t, *J* = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.1, 129.9, 62.6 (m), 32.7, 32.0, 29.9, 29.8, 29.6, 29.6, 29.5, 29.4×2, 29.3, 27.3, 27.3, 25.8, 22.8, 14.2.

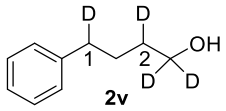
3-(4-Methoxyphenyl)propan-1,1,2,3-*d*$_4$-1-ol 2u[13] (Table 3, entry 14).



2u

According to the general procedure (but a mixture of hexane (2.5 mL) an Et_2O (2.0 mL) was used as the solvent), the reaction of methyl (*E*)-3-(4-methoxyphenyl)acrylate (0.500 mmol), EtOD (3.25 mmol) and Na dispersion in oil (3.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2u** 66 mg in 78% yield as a colorless oil. D_2 incorporation = 91%; D_1 incorporation = 94% at C_1; and D_1 incorporation = 74% at C_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 2H), 6.87 – 6.81 (m, 2H), 3.80 (s, 3H), 2.69 – 2.60 (m, 1H), 1.89 – 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 133.9, 129.4, 113.8, 61.7 (m), 55.3, 33.8 (m), 30.7 (m).

4-phenylbutan-1,1,2,4-*d*$_4$-1-ol 2v[11d] (Table 3, entry 15).



2v

According to the general procedure, the reaction of methyl 2-phenylcyclopropane-1-carboxylate (0.500 mmol), EtOD (3.25 mmol) and Na dispersion in oil (3.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2v** 51 mg in 66% yield as a colorless oil. D_2 incorporation = 94%; D_1 incorporation =93% at C_1; and D_1 incorporation = 89% at C_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.23 – 7.15 (m, 3H), 2.69 – 2.59 (m, 1H), 1.74 – 1.64 (m, 2H), 1.64 – 1.55 (m, 1H), 1.42 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 128.5, 128.4, 125.8, 62.1 (m), 35.3 (t, $J_{(C\text{-}D)}$ = 19.4), 31.8 (t, $J_{(C\text{-}D)}$ = 19.0), 27.4.

Pent-4-en-1,1-d2-1-ol 2w[20] **(**Table 3, entry 16). According to the general procedure, the reaction of methyl pent-4-enoate (0.500 mmol), EtOD (2.25 mmol) and Na dispersion in oil (2.25 mmol) for 5 min at 0 ºC and 5 min at rt, after chromatography (hexanes-Et_2O), afforded **2w** 37 mg in 85% yield as a colorless oil. D_2 incorporation >98%. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 5.79 (m, 1H), 5.06 – 4.87 (m, 2H), 2.88 (br, 1H), 2.08 (m, 2H), 1.60 (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 114.7, 61.2 (m), 31.5, 29.9.

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Supporting Information

^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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