JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

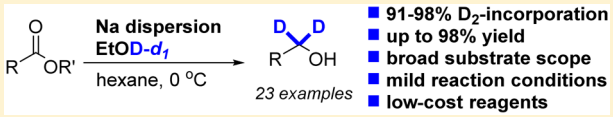
Development of a Modified Bouveault−Blanc Reduction for the Selective Synthesis of α,α-Dideuterio Alcohols

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

Supporting Information

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 the 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 for improving metabolism and pharmacokinetic properties of drug candidates.[1] A significant number of deuterated drug candidates have 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 the 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 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]

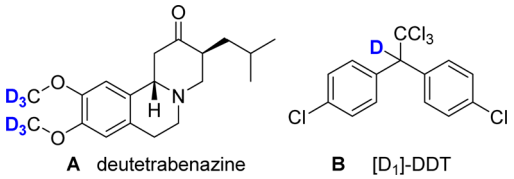
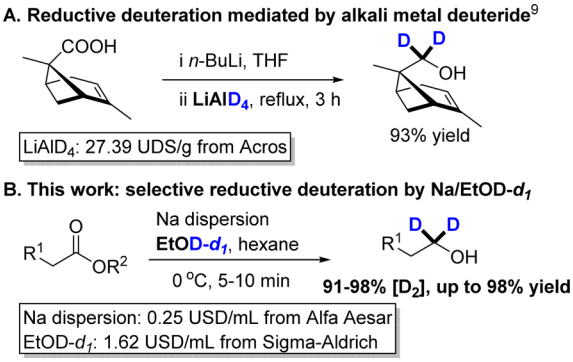


Figure 1. Deutetrabenazine: compared with tetrabenazine, **A** exhibits a significantly better toxicity profile and longer half-life. [D_1]-DDT: the enzyme-catalyzed dehydrochlorination process of **B** is 6 times slower than that of the unlabeled DDT.

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) postsynthetic hydrogen/deuterium exchange, including metal-catalyzed and pH-dependent protocols;[9] however, a vast majority of reactions of this type require either expensive catalysts or harsh reaction conditions and suffer from limited scope, low levels of deuterium incorporation, and poor selectivity;[9a] and (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

Scheme 1. (A) Reductive Deuteration Using $LiAlD_4$ and (B, this work) Selective Reductive Deuteration Using Sodium Dispersions and Ethanol-d_1



Received: December 8, 2016
Published: December 28, 2016

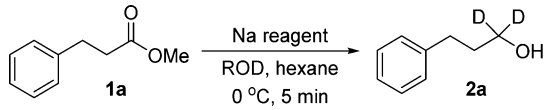
DOI: 10.1021/acs.joc.6b02950
J. Org. Chem. 2017, 82, 1285−1290

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 the 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 the electron transfer reaction using the low cost 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.[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.[3] 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.

We started our investigations by studying the effects of various sodium reagents and deuterium donors on the reductive deuteration of **1a** (Table 1). Sodium dispersion in oil

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



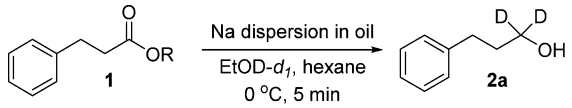
entry	Na reagent	ROH	ROH (equiv)	yield (%)[b]	$[D_2]$ (%)[b]
1	dispersion in oil[c]	MeOD-d_4	4.5	91	92
2	dispersion in oil[c]	MeOD-d_4	6.0	95	93
3	dispersion in oil[c]	MeOD-d_4	8.0	89	93
4	dispersion in oil[c]	EtOD-d_1	4.5	97	94
5	dispersion in oil[c]	EtOD-d_1	6.0	92	95
6	dispersion in oil[c]	EtOD-d_1	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]In 40 wt % with particle sizes of 5–10 μm. [d]In 30–35 wt % with average particle size of 10 μm. [e]In 30 wt % with particle sizes of <100 μm. [f]~35 wt % sodium silica gel stage I.

(5–10 μm particle size; purchased from Alfa Aesar) was chosen as the preferred reducing reagent as it is a bench-stable commercially available reagent that is easy to handle in an open atmosphere. The use of solid-state sodium dispersions (entry 13) or dispersions with larger particle sizes (entry 14) led to lower yields, which may due to a smaller contact surface between the 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, whereas the yields were lower due to competing oxidation of sodium by alcohol (entries 5 and 6).

Following our optimization studies, a range of esters derived from hydrocinnamic acid were 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

Table 2. 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.

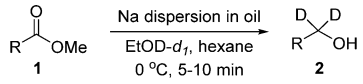
hindered ester **1d** and allyl ester **1f** were reduced in high yields (entries 3 and 5).

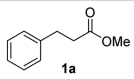
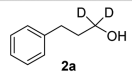
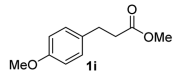
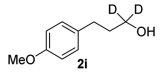
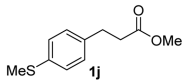
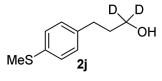
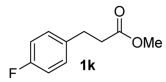
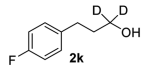
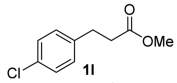
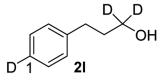
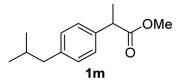
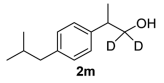
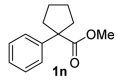
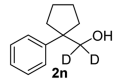
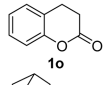
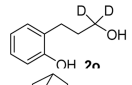
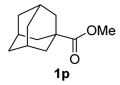
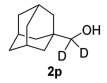
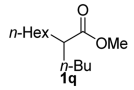
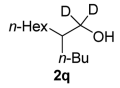
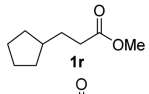
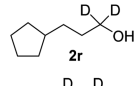
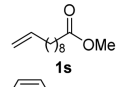
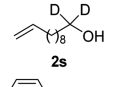
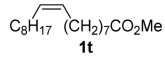
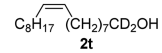
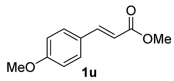
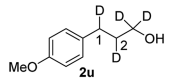
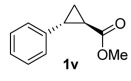
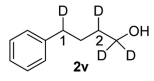
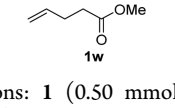
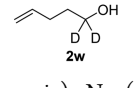
The substrate scope investigations demonstrate that high levels of D_2 incorporation are general across a range of aliphatic ester and lactone substrates (Table 3). Significantly, no impact on the D_2 incorporation or yield was observed with sterically hindered substituents (entries 7 and 9), which compares 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.

Interestingly, when 6.5 equiv of sodium was used, the 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 and 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 to 10 mmol) resulted in excellent yield and D_2 incorporation (entry 1). High D_2

DOI: 10.1021/acs.joc.6b02950
J. Org. Chem. 2017, 82, 1285–1290

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



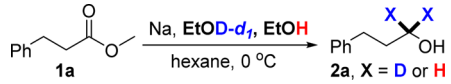
entry	substrate	product	yield (%)[b]	[D_2] (%)[c]
1[d]	 1a	 2a	93	96
2	 1i	 2i	91	93
3	 1j	 2j	81	92
4	 1k	 2k	87	94
5[e]	 1l	 2l	81	94[f]
6	 1m	 2m	92	95
7	 1n	 2n	95	96
8	 1o	 2o	77	91
9	 1p	 2p	95	97
10	 1q	 2q	75	95
11	 1r	 2r	80	97
12	 1s	 2s	95	94
13	 1t	 2t	95	91
14[e]	 1u	 2u	78	91[g]
15[e]	 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]In 95% [D_1] at C_1. [g]In 94% [D_1] at C_1 and 74% [D_1] at C_2. [h]In 93% [D_1] at C_1 and 89% [D_1] at C_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.

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

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

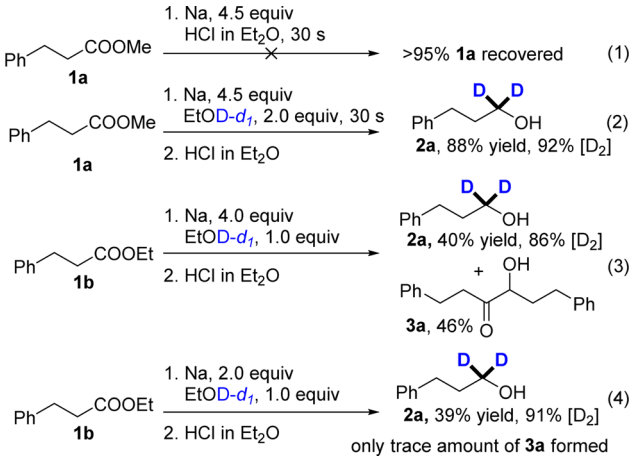


entry	EtOD/H (equiv)	EtOD/H (ratio)	addition method[b]	yield (%)[c]	[D_2] (%)[c]
1	4.5	1:1	A	94	82
2	4.5	1:1	B	95	50
3	4.5	1:1	C	93	11
4	4.5	2:1	A	96	88
5	4.5	8:1	A	95	91

[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.

(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 nondeuterium-labeled product as the major product (entry 3). These results indicate that only 2 equiv of the proton donor is involved in the Bouveault−Blanc reduction under these conditions and rules out the four proton transfer process.[16] In addition, the use of premixed 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-determining step.[8a]

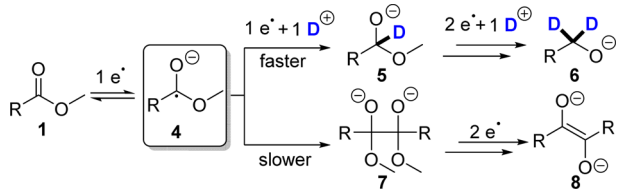
Control reactions (eqs 1 and 2) demonstrated that (a) ester reduction by Na/HCl is not observed (eq 1); (b) in the reaction with 2.0 equiv of EtOD-d_1, Na was all consumed within 30 s (eq 2). Moreover, in the presence of 4.0 equiv of Na and 1.0 equiv of EtOD-d_1, **2a** was formed in 40% yield and 88% D_2 incorporation, and 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 (eqs 2−4) indicate that anions are selectively protonated by the proton donor (c.f., intramolecular proton transfer), which may lead to the

DOI: 10.1021/acs.joc.6b02950
J. Org. Chem. 2017, 82, 1285−1290

Scheme 2. Proposed Mechanism for the Reductive Deuteration of Esters Using Na/EtOD-d_1



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 cost, 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 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 ultraviolet 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 and δ = 77.1 ($CDCl_3$) for ^{13}C NMR. Multiplicities for coupled signals are designated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, and 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 (2.25−4.00 mmol) followed by Na reagent (2.25 mmol) under N_2 at 0 °C, and the resulting 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 ^{1}H NMR ($CDCl_3$, 400/500 MHz) to obtain the deuterium incorporation and yield using internal standard ($MeNO_2$) and compared 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 °C, and the resulting solution was stirred vigorously. After 5 min at 0 °C, 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 (0.500 mmol), EtOD (2.25 mmol), and Na dispersion in oil (2.25 mmol) for 5 min at 0 °C, after chromatography (hexanes-10% EtOAc/hexane), afforded **2a** in 67 mg and 97% yield as a colorless oil. D_2 incorporation = 94%. ^{1}H 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 °C afforded **2a** in 67 mg and 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 °C and 10 min at rt afforded **2a** in 66 mg and 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 °C and 10 min at rt afforded **2a** in 56 mg and 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 °C afforded **2a** in 65 mg and 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 °C afforded **2a** in 53 mg and 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 °C afforded **2a** in 61 mg and 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 °C afforded **2a** in 68 mg and 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 °C, after chromatography (hexanes-10% EtOAc/hexane), afforded **2a** in 1.28 g and 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 (4.50 mmol) followed by Na dispersion in oil (4.50 mmol) in an open flask at 0 °C, and the resulting solution was stirred vigorously. After 5 min at 0 °C, the temperature was increased 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) to afford **2a** in 127 mg and 92% yield as a

DOI: 10.1021/acs.joc.6b02950
J. Org. Chem. 2017, 82, 1285−1290

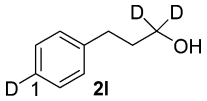
colorless oil. D_2 incorporation = 90%. Spectroscopic properties matched those previously described.

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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2i** in 76 mg and 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2j** in 75 mg and 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2k** in 68 mg and 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).* 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2l** in 56 mg and 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-D} = 24.4), 61.6 (m), 34.1, 32.1.



2l

2-(4-Isobutylphenyl)propan-1,1-d_2-1-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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2m** in 89 mg and 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2n** in 85 mg and 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 °C and 5 min at rt, after chromatography (hexanes-30% EtOAc/hexane), afforded **2o** in 59 mg and 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 °C, after chromatography (hexanes-10% EtOAc/hexane), afforded **2p** in 80 mg and 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.

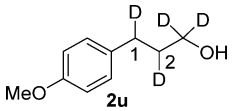
2-Butyloctan-1,1-d_2-1-ol **2q**[13] *(Table 3, entry 10).* According to the general procedure, the reaction of methyl 2-butyloctanoate (0.500 mmol), EtOD (2.25 mmol), and Na dispersion in oil (2.25 mmol) for 5 min at 0 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2q** in 71 mg and 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2r** in 52 mg and 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2s** in 82 mg and 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2t** in 128 mg and 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.

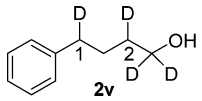
3-(4-Methoxyphenyl)propan-1,1,2,3-d_4-1-ol **2u**[13] *(Table 3, entry 14).* According to the general procedure (except that a mixture of hexane (2.5 mL) and Et_2O (2.0 mL) was used as the solvent), the reaction of methyl (*E*)-3-(4-methoxyphenyl)acrylate (0.500 mmol), EtOD (3.25 mmol), and Na dispersion in oil (3.25 mmol) for 5 min at 0 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2u** in 66 mg and 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).



2u

DOI: 10.1021/acs.joc.6b02950
J. Org. Chem. 2017, 82, 1285−1290

4-Phenylbutan-1,1,2,4-d_4-1-ol **2v**[11d] *(Table 3, entry 15).* 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 °C and 5 min at rt, after chromatography (hexanes-10% EtOAc/hexane), afforded **2v** in 51 mg and 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-D} = 19.4), 31.8 (t, J_{C-D} = 19.0), 27.4.



2v

Pent-4-en-1,1-d_2-1-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 °C and 5 min at rt, after chromatography (hexanes-Et_2O), afforded **2w** in 37 mg and 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02950.

^{1}H and ^{13}C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jie_an@cau.edu.cn.

ORCID

Jie An: 0000-0002-1521-009X

Author Contributions

†M.H. and X.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSFC (Nos. 21602248 and 21472236) and the Chinese Universities Scientific Fund for financial support. We thank Professor Ohyun Kwon from UCLA for useful discussions.

■ REFERENCES

(1) (a) Belleau, B.; Burba, J.; Pindell, M.; Reiffenstein, J. *Science* **1961**, *133*, 102. (b) Sanderson, K. *Nature* **2009**, *458*, 269. (c) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (d) Harbeson, S. L.; Tung, R. D. *Annu. Rep. Med. Chem.* **2011**, *46*, 403.

(2) For a review, see: (a) Katsnelson, A. *Nat. Med.* **2013**, *19*, 656. For selected samples, see: (b) Zhang, Y.; Tortorella, M. D.; Wang, Y.; Liu, J.; Tu, Z.; Liu, X.; Bai, Y.; Wen, D.; Lu, X.; Lu, Y.; Talley, J. J. *ACS Med. Chem. Lett.* **2014**, *5*, 1162. (c) Zhu, Y.; Zhou, J.; Jiao, B. *ACS Med. Chem. Lett.* **2013**, *4*, 349.

(3) Mullard, A. *Nat. Rev. Drug Discovery* **2016**, *15*, 219.

(4) Klinman, J. P. *J. Phys. Org. Chem.* **2010**, *23*, 606.

(5) Kurihara, N. *J. Mass Spectrom. Soc. Jpn.* **1998**, *46*, 157.

(6) (a) Mutlib, A. E. *Chem. Res. Toxicol.* **2008**, *21*, 1672. (b) Nag, S.; Lehmann, L.; Kettschau, G.; Toth, M.; Heinrich, T.; Thiele, A.; Varrone, A.; Halldin, C. *Bioorg. Med. Chem.* **2013**, *21*, 6634.

(7) Atzrodt, J.; Derdau, V. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 674.

(8) (a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066. (b) Giagou, T.; Meyer, M. P. *Chem. - Eur. J.* **2010**, *16*, 10616.

(9) For a review, see: (a) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7744. For selected samples, see: (b) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 734. (c) Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456. (d) Neubert, L.; Michalik, D.; Bähn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239.

(10) For selected examples, see: (a) Byun, H. S.; Bittman, R. *Chem. Phys. Lipids* **2010**, *163*, 809. (b) Upshur, M. A.; Chase, H. M.; Strick, B. F.; Ebben, C. J.; Fu, L.; Wang, H.; Thomson, R. J.; Geiger, F. M. *J. Phys. Chem. A* **2016**, *120*, 2684.

(11) (a) Szostak, M.; Spain, M.; Procter, D. J. *Org. Lett.* **2014**, *16*, 5052. For other recent methods for the reduction of carboxylic acid derivatives using SmI_2, see: (b) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 2268. (c) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Commun.* **2011**, *47*, 10254. (d) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 11988.

(12) (a) Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr* **1903**, *137*, 328. (b) Ford, S. G.; Marvel, C. S. *Org. Synth.* **1930**, *10*, 62. (c) Adkins, H.; Gillespie, R. H. *Org. Synth.* **1949**, *29*, 80.

(13) An, J.; Work, D. N.; Kenyon, C.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 6743.

(14) (a) Dye, J. L.; Cram, K. D.; Urbin, S. A.; Redko, M. Y.; Jackson, J. E.; Lefenfeld, M. *J. Am. Chem. Soc.* **2005**, *127*, 9338. (b) Bodnar, B. S.; Vogt, P. F. *J. Org. Chem.* **2009**, *74*, 2598.

(15) The reduction of esters using sodium is a four-electron process.

(16) Barrett, A. G. M. Reduction of Carboxylic Acid Derivatives to Alcohols, Ethers and Amines. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Elsevier Science Ltd, 1991; pp 236−257.

(17) Shi, S.; Szostak, R.; Szostak, M. *Org. Biomol. Chem.* **2016**, *14*, 9151.

(18) For alkali-metal-promoted cyclization reactions, see: Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* **1998**, *63*, 3141.

(19) Bartlett, P. D.; Trahanovsky, W. S.; Bolon, D. A.; Schmid, G. H. *J. Am. Chem. Soc.* **1965**, *87*, 1314.

(20) Tagge, C. D.; Simpson, R. D.; Bergman, R. G.; Hostetler, M. J.; Girolami, G. S.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 2634.

DOI: 10.1021/acs.joc.6b02950
J. Org. Chem. 2017, 82, 1285−1290