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Synthesis of α,α-dideutero-β-amino esters

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ABSTRACT

A straight forward entry to α,α-dideutero-β-amino esters starting from the corresponding imines and deuterated acetonitrile has been developed involving a two-step process.

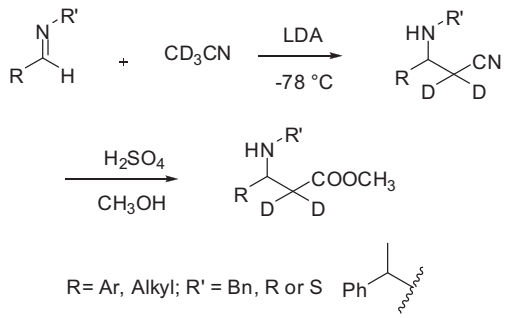
β-Amino acids and β-peptides have acquired a place of prominence mainly because of their pharmaceutical potential. Unique features of β-peptides when compared to their α-analogues are: increased metabolic stability, higher structural diversity and formation of well-defined structures.[1] These features make β-peptides important peptido-mimetics with various biological activities. β-Amino acids are also found to be the components of many natural products such as Taxol,[2] Cryptophycin 1,[3] Jusplankinolide,[4] Bestatin[5] etc. β-Amino acids are also the precursors of bioactive β-lactams.[6]

Deuterium is a non-radioactive labeling atom which has found an important place in the pharmaceutical industry as a marker atom, a tool to explore bio-availability and protein structure elucidation, giving insight into their secondary and tertiary structures. It has been explored by the pharmaceutical industry for better binding to enzymes, better bio-availability, and slower hydrolysis to metabolites.[7] Some of the deuterated pharmaceuticals reported are: paroxetine, reyataz, rimonabant, mosapride, venlafaxine, deuterated atorvastatin etc.[8]

There are limited examples in the literature for the stereo-selective and atom-efficient synthesis of α-deuterated amino acids, which when commercially available, are expensive.[9] With this background and in continuation of our interest in deuteration chemistry[10] as well as in peptido-mimetics we conceived a program to synthesize α,α-dideutero-β-amino acids to add to the repertoire of unusual β-amino acids that are already synthesized in our group.[11]

Synthesis of α,-α-dideuterated-β-amino acids has been reported earlier where the available α-amino acids have been modified.[12] However, this method has a disadvantage that amino acids which are available commercially can only be used. The synthetic scheme becomes multi-step if one chooses to synthesize α-amino acids first and then modify them to get the deuterated derivatives.

We envisaged the synthesis of unusual β-amino acids with dideuteration at α,α-position using easily accessible starting materials. Thus, CD_3CN was used as the source of deuterium. Aldehydes were converted to the corresponding imines by classical reaction and imines were the starting materials for the two-step synthesis for dideutero amino acids. The imines were treated with CD_3CN in the presence of LDA at −78 °C to get nitriles. Hydrolysis of the nitrile group with sulfuric acid in methanol gave the corresponding methyl esters of α,α-dideutero-β-amino acids in a 55–75% yield over 2 steps. The esters obtained were characterized using ^1H NMR, mass, IR, ^{13}C NMR etc. Chiral induction to get the enantiomers was carried out by substituting benzylamine with *R*-or *S*-α-phenylethylamine (Scheme 1).



Scheme 1. Synthesis of α,α-dideutero-β-amino acids via benzyl imines.

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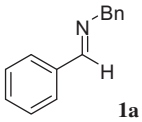
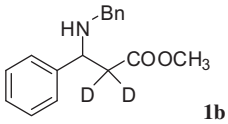
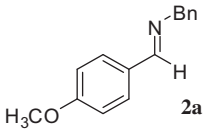
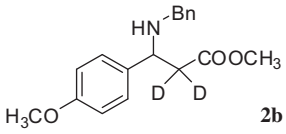
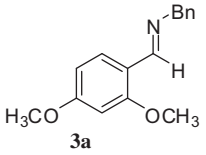
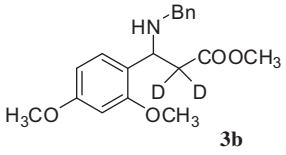
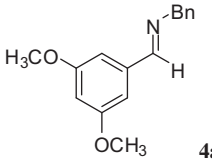
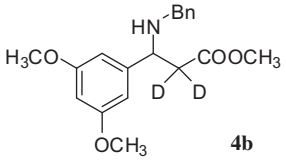
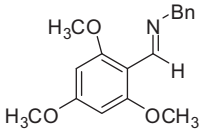
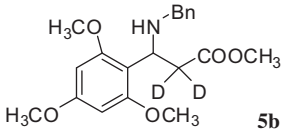
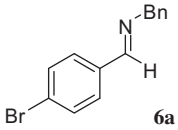
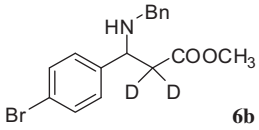
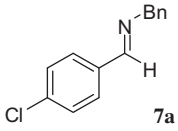
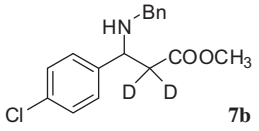
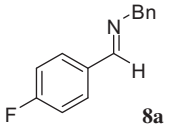
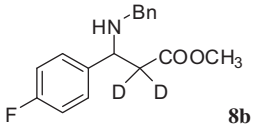
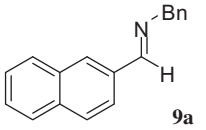
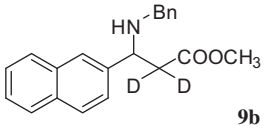
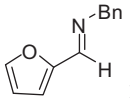
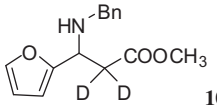
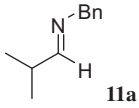
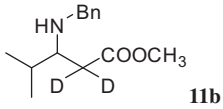
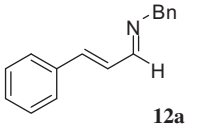
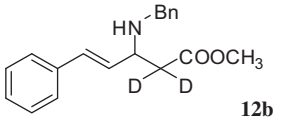
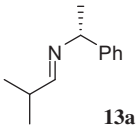
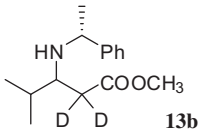
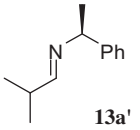
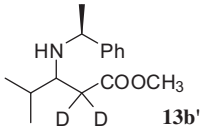
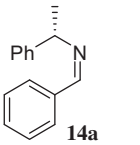
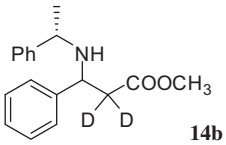
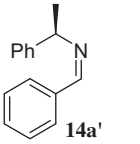
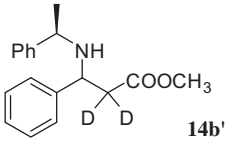
Table 1
Synthesis of α,α-dideutero-β-Amino acid esters

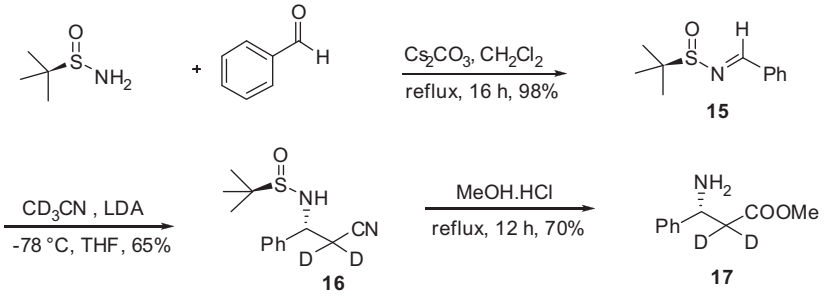
Entry	Imine	β-Amino acid (as methyl ester)	Yield (%)[a]
1	 **1a**	 **1b**	55
2	 **2a**	 **2b**	60
3	 **3a**	 **3b**	65
4	 **4a**	 **4b**	62
5	 **5a**	 **5b**	70
6	 **6a**	 **6b**	75
7	 **7a**	 **7b**	70
8	 **8a**	 **8b**	65
9	 **9a**	 **9b**	70
10	 **10a**	 **10b**	60
11	 **11a**	 **11b**	72
12	 **12a**	 **12b**	70

[a] Yield of the product after two steps (nucleophilic addition, hydrolysis/esterification).

Table 2
Enantioselective α,α-dideutero-β-Amino acid esters

Entry	Imine	β-Amino acid (as methyl ester)	Yield (%)[a]
1	 **13a**	 **13b**	60/99[b]
2	 **13a'**	 **13b'**	60/99[b]
3	 **14a**	 **14b**	70/99[b]
4	 **14a'**	 **14b'**	70/99[b]

[a] Yield of the product after two steps (nucleophilic addition, hydrolysis/esterification).
[b] % ee determined by Chiral HPLC using ChiralCel OD-H column.



Scheme 2. Synthesis of α, α-dideutero-β-amino acids via *tert*-butylsulfinimines.

In a typical study benzaldehyde imine **1a** was alkylated with CD_3CN mediated by LDA in THF followed by sulfuric acid catalyzed hydrolysis in methanol which furnished **1b** in 55% yields. The deuterium enrichment was found to be over 99% based on ^2H NMR which helped us infer that during anion generation, there was no exchange of D with H, the reaction being carried out with care under anhydrous conditions (anhydrous THF and nitrogen atmosphere). To substantiate our protocol various substituted aryl imines (Table 1, entries 2–9), heteroaryl imine (entry 10) and aliphatic imine (entry 11) provided the corresponding α,α-dideutero-β-amino acid methyl esters (over a 60% yield for 3 steps-alkylation, hydrolysis, esterification). It was also observed that cinnamaldehyde imine (entry 12) provided **12b** in over a 70% yield. This indicated that substituents on the aromatic ring as well as unsaturation in conjugation to aromatic ring do not have any effect on the synthesis of nitriles/esters.

To further demonstrate the utility of this strategy in synthesizing enantioselective α,α-dideutero-β-amino acids, the imines **13a**, **13a′**, **14a**, **14a′** were prepared from aldehyde and chiral amine (*R* and *S*-phenylethylamine) (Table 2, entries 1–4). The reactions of these imines, under described conditions, provided **13b**, **13b′**, **14b** and **14b′**, respectively, in 9:1 diastereomeric ratio.[14]

Attempts to deprotect **6b** using Pd/C-ammonium formate resulted in an inseparable mixture of compounds.[13] Similarly, NIS-catalyzed reaction also provided the mixture of products. Deprotection of the chiral auxiliary using Pd/C-H_2 was also not successful.

Several attempts to obtain deuterated amino esters from both **6b** and **14b** failed by reported deprotection protocols. A change in the protecting group was attempted and thus the reaction of benzaldehyde was carried out with *tert*-butylsulfinamide to give imine **15**. LDA-mediated reaction of deuterated acetonitrile with **15** gave dideuterated nitrile **16**. Treatment of **16** with methanolic HCl smoothly converted the nitrile group to the methyl ester and simultaneously deprotected the chiral auxiliary. The resulting dideutero-amino ester **17** was characterized by ^1H NMR, ^{13}C NMR, and optical rotation (Scheme 2). The absolute stereochemistry of the new stereo-center generated was predicted based on the literature.[15]

In summary, we present here a very simple synthetic strategy for the preparation of unusual α,α-dideutero-β-amino esters starting from respective benzylimines and *tert*-butyl sulfinimines.[16] Even though, products obtained from benzyl imines could not be converted to free amino acids, the problem was circumvented by

using *tert*-butyl sulfinimide route. Further work is in progress to generalize the protocols.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H NMR spectra for compounds **1–16** and intermediates) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.004.

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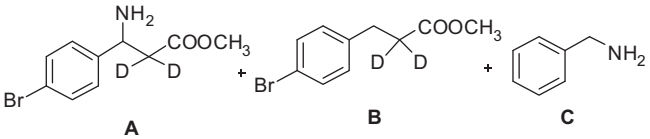
13. (a) Leplae, P. R.; Umezawa, N.; Lee, H.-S.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 5629; (b) The reaction of **6b** under Pd/C-ammonium formate provided the following mixture of products based on LCMS in ratio 40.77 (Phenylethylamine, **C**), 37.45 (amino ester, **A**) and 19.98 (ester without amino group, **B**).



A B C

14. The diastereomeric ratio was determined by HPLC and enantiomeric excess by chiral HPLC for major diastereomer.
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16. *General procedures for the synthesis of α,α-dideuterated-β-amino acids*:
Preparation of imines:
A 100 mL round bottomed flask was charged with benzaldehyde (2 mL, 1 mmol) in methanol (10 mL). Benzyl amine (2.1 mL, 1 mmol) was added to it followed by potassium carbonate (catalytic) till the reaction mixture was alkaline. The solution was allowed to stir at room temperature overnight. After completion of the reaction, it was filtered through a bed of celite and concentrated on rotavapor at low temperature. This imine was then dissolved in dry THF under nitrogen atmosphere and stored for the next step. Yield 3.31 g (90%).
General procedure for the preparation of racemic deuterated nitriles:
A thoroughly dried flask purged with nitrogen, was charged with diisopropylamine (1.03 mL, 1 mmol) in dry THF (3 mL) and cooled to −10 °C. Then, *n*-BuLi 2.5 M (6.2 mL, 1 mmol) was added slowly to it. The reaction mixture was allowed to stir for 20 min and then cooled to −78 °C. Deuterated acetonitrile (0.5 mL 2 mmol) in 3 mL of dry THF was added to the solution. After about 30 min freshly prepared imine (2 g, 1 mmol) dissolved in dry THF (10 mL) was added slowly to the mixture. The reaction mixture was then stirred at −78 °C for about 4 h, then quenched with saturated NH_4Cl solution, and extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Upon drying under vacuum, the resulting compound was further subjected to purification by column chromatography. Yield 1.95 g (80%)
General procedure for β-amino esters:
In a 25 mL round bottomed flask nitrile (100 mg, 1 mmol) was dissolved in methanol (3 mL) and cooled to 0 °C. Then 1 mL conc. H_2SO_4 was added dropwise to this reaction mixture and refluxed for 4 h (or till the reaction was complete). The reaction was quenched with sodium bicarbonate till pH neutral, the solid was filtered under vacuum, and washed with methanol. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography. Yield 0.039 g (69%).
Spectral data for representative new compounds:
Methyl 3-(benzylamino)-2, 2-dideutero-3-phenylpropanoate (***1b***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.40 (m, 10H), 3.94 (d, *J* = 4.5 Hz, 1H), 3.68 (dd, *J* = 12.8, 27.2 Hz, 1H), 3.62 (s, 3H), 3.52 (dd, *J* = 12.8, 24.9 Hz, 1H), 2.18 (br, 1H); ^{2}H NMR ($CHCl_3$, 83.3 MHz) δ 2.65 (s, 2D); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 140.4, 139.4, 129.0, 128.7, 128.6, 128.2, 127.7, 127.3, 127.2, 127.0, 126.9, 58.7, 58.2, 51.3, 29.7; IR (KBr) *ν* 3614, 2923, 2853, 1645, 1453, 1219, 771, 700 cm^{-1}; MS (EI) *m/z* 272 [M]$^+$. HRMS (ESI) *m/z* calcd for $C_{17}H_{17}D_2NO_2$: 272.1614, found 272.1618 [M+H]$^+$.
Methyl 3-(benzylamino)-2, 2-dideutero-3-(4-methoxyphenyl) propanoate (***2b***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.48 (m, 6H), 6.88 (d, *J* = 8.5 Hz, 4H), 5.12 (s, 1H), 4.15 (d, *J* = 7.04 Hz, 1H), 4.12 (d, *J* = 7.0 Hz, 1H), 3.83 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 135.7, 135.6, 133.4, 133.3, 129.8, 129.7, 127.7, 127.6, 64.2, 60.2, 34.3, 33.5, 26.8; IR (KBr) *ν* 3465, 2923, 2853, 1637, 1465, 1256, 692 cm^{-1}; MS (EI) *m/z* 301.5 [M]$^+$.
Methyl 3-(benzylamino)-2,2-dideutero-3-(4-bromophenyl)propanoate (***6b***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.50 (m, 9H), 4.01 (d, *J* = 9.8 Hz, 1H), 3.65 (s, 3H), 3.50 (d, *J* = 6.8 Hz, 2H), 2.00 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 141.2, 139.7, 132.2, 131.8, 129.0, 128.5, 128.2, 127.8, 127.2, 127.1, 121.3, 58.0, 51.8, 51.2, 29.7; IR (KBr) *ν* 3465, 3028, 1730, 1454, 1254, 1009, 819, 734, 699, 594 cm^{-1}; MS (EI) *m/z* 349.9[M]$^+$.
Methyl 3-(benzylamino)-2,2-dideutero-4-methylpentanoate (***11b***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.32 (m, 5H), 3.80 (d, *J* = 12.8 Hz, 2H), 3.65 (d, *J* = 8.3 Hz, 3H), 3.42 (s, 1H), 1.0 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 128.5, 128.2, 127.2, 59.0, 51.5, 31.9, 31.1, 29.7, 18.6, 18.5; IR (KBr) *ν* 3348, 3062, 2957, 2853, 1602, 1454, 1250, 1155, 1104, 971, 753, 699 cm^{-1}; MS (EI) *m/z* 238 [M]$^+$; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}D_2NO_2$: 238.1771, found 238.1772 [M+H]$^+$.
(E)-methyl 3-(Benzylamino)-2,2-dideutero-5-phenylpent-4-enoate (***12b***): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.58 (m, 12H), 3.75 (d, *J* = 18.9 Hz, 1H), 3.35 (s, 5H,); ^{2}H NMR ($CHCl_3$, 83.3 MHz) δ 2.65 (s, 2 D); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 152.9, 134.0, 131.3, 129.1, 128.6, 128.5, 37.4, 37.1, 30.0, 29.7; IR (KBr) *ν* 3460, 2925, 2853, 1635, 1453, 751, 698 cm^{-1}; MS (EI) *m/z* 336 [M]$^+$+39; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}D_2NO_2$: 298.1771, found 298.1778 [M+H]$^+$.
4-(Methyl-2,2-dideutero-3-((R)-1-phenylethylamino)pentanenitrile): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.53 (m, 5H), 4.34 (q, *J* = 6.8, 13.2 Hz, 1H), 2.35 (m, 1H), 2.14 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 129.3, 128.9, 127.6, 126.2, 125.5, 120.5, 58.8, 53.4, 36.7, 29.7, 23.8, 22.8; IR (KBr) *ν* 3321, 2924, 2969, 2851, 2195, 1598, 913, 744, 700 cm^{-1}; MS (EI) *m/z* 219 [M]$^+$; $[\alpha]_D^{25}$ + 21.0 (c= 0.1, $CHCl_3$); HPLC retention time for R-(+) isomer it was found to be 5.599 (ee = 99%).
4-(Methyl-2,2-dideutero-3-((S)-1-phenylethylamino)pentanenitrile): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.35 (m, 5H,), 4.28 (q, *J* = 6.8, 12.8 Hz, 1H), 2.12 (m, 1H), 1.92 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 0.94 (dd, *J* = 6.8, 10.6 Hz, 6H), ^{2}H NMR ($CHCl_3$, 83.3 MHz) δ 2.65 (s, 2D); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 129.1, 128.9, 127.6, 126.8, 125.5, 121.4, 53.4, 38.8, 29.7, 23.8, 22.7; IR (KBr) *ν* 3322, 2924, 2969, 2851, 2191, 1594, 913, 795, 700 cm^{-1}; MS (EI) *m/z* 219 [M]; $[\alpha]_D^{25}$ −15.0 (*c* = 0.1, $CHCl_3$); HPLC retention time for S-(−) isomer it was found to be 4.952 (ee = 99%).
3-(Phenyl-2,2-dideutero-3-((R)-1-phenylethylamino)propanenitrile): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (3H, d, *J* = 6.7 Hz), 2.10 (1H, m), 4.28 (1H, q, *J* = 6.6, 13.0 Hz), 4.54 (1H, m), 7.15–7.38 (10H, m); ^{2}H NMR ($CHCl_3$, 83.3 MHz) δ 2.48 (s, 2D); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9, 131.1, 128.6, 115.0, 60.3, 48.5, 29.7, 24.6, 22.7; IR (KBr) *ν* 3434, 2189, 1669, 768 cm^{-1}; MS (EI) *m/z* 253 [M]$^+$; $[\alpha]_D^{25}$ +18.0 (*c* = 0.35, $CHCl_3$); HPLC retention time for R-(+) isomer was found to be 9.195 (ee = 99%) *dr* = 9:1.
3-(Phenyl-2,2-dideutero-3-((S)-1-phenylethylamino)propanenitrile): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, s), 2.14 (1H, m), 3.89 (1H, m), 4.13 (1H, m), 7.10–7.36 (10H, m); ^{2}H NMR ($CHCl_3$, 83.3 MHz): δ 2.40 (s, 2D); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 128.7, 128.5, 128.2, 127.3, 125.4, 117.2, 62.5, 53.2, 29.5, 23.5; IR (KBr) *ν* 3323, 2189, 1594, 1539, 1299, 733, 698 cm^{-1}; MS (EI) *m/z* 253 [M]$^+$; $[\alpha]_D^{25}$ −24.0 (*c* = 0.35, $CHCl_3$); HPLC retention time for S-(-) isomer was found to be 9.023 (ee = 99%).
(S)-N-((R)-2-Cyano 2,2-dideutero-1-phenyl)-2-methylpropane-2-sulfinamide **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.35 (m, 5H), 4.73 (d, *J* = 4.0 Hz, 1H), 3.68 (brs, 1H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 129.2, 126.6, 116.5, 56.4, 54.4, 29.6, 22.6; MS (EI) *m/z* 253 [M]$^+$.+1; $[\alpha]_D^{25}$ −60.0 (*C* = 0.1, $CHCl_3$).
(R)-Methyl 3-amino-2,2-dideutero-3-phenylpropanoate (**17**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 4.34 (S, 1H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 128.9, 128.6, 127.5, 126.2, 52.5, 51.7, 29.6; MS (EI) *m/z* 182 [M]$^+$.+1; $[\alpha]_D^{25}$ +16.0 (*C* = 0.1, $CHCl_3$).