Rearrangement of α-Amino Cyclopropanone Hydrate: A Novel Route to Labeled Amino Acids

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Introduction

Amino acids specifically labeled with stable isotopes are valuable tools for the investigation of proteins at the atomic level. Indeed, the combination of stable isotope labeling and multidimensional NMR spectroscopy is a highly efficient method for the structural study of proteins and peptides in solution.[1] Furthermore, labeled amino acids are of prime importance in the elucidation of many enzyme mechanisms.[2]

The classical methods for the synthesis of deuterium-labeled amino acids involve either isotopic exchange[3] or deuteriogenation of a suitable precursor that incorporates a double bond.[4] Herein, we report a new route to regioselectivelly deuterated amino acids. Our approach derives from a 1932 observation by Lipp et al.[5] who reported the expeditious fragmentation of cyclopropanone hydrate into propanoic acid (Scheme 1).

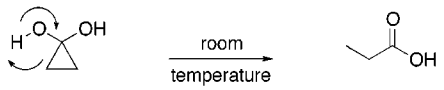
In principle, an α-amino cyclopropanone hydrate such as **1** should display the same reactivity and, hence, rearrange either to the corresponding α-amino acid **2a** (alanine) or *β*-amino acid **2b** (Scheme 2). Furthermore, as the ring opening of the cyclopropane presumably occurs with internal proton transfer, the incorporation of a deuterium label on the hydrate moiety should afford labeling of the resulting amino acid.

Results and Discussion

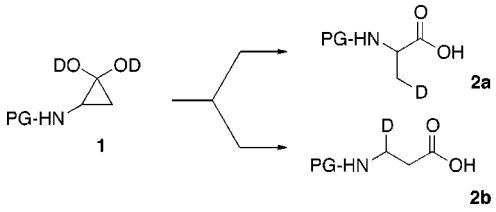
To corroborate this hypothesis, the preparation of four different potential precursors (**7a**−**d**) of amino acids was undertaken (Scheme 3). Our syntheses started from the appropriate α-bromo aldehyde[6] that was protected as a 1,2-benzenedimethyloxy acetal. The choice of 1,2-benzenedimethyloxy acetal as hydrate protecting group was governed by its facile removal through catalytic reduction. In a deuterium atmosphere, this should permit the incorporation of a deuterium label on both oxygen atoms and thereby install the labeling source for the ensuing oxygen to carbon isotope transfer. Bromine *β*-elimination,[7] followed by catalytic cyclopropanation[8] of the resulting ketene acetal **4a**−**d** with diazoacetonitrile afforded cyclopropyl nitrile **5a**−**d**. The nitrile group was hydrolyzed with KOH in *t*-BuOH,[9] and the resulting amide **6a**−**d** was converted to the corresponding cyclopropyl *N*-methyl carbamate **7a**−**d** through DIB-mediated Hofmann rearrangement.[10]

The four different precursors were subjected to deuteriogenolysis in anhydrous EtOAc in the presence of Pd/C. The results are summarized in the Table 1. As expected, the rearrangement of substrates **7a**,**b** afforded the corresponding α-amino acids (*β*-deuterated alanine

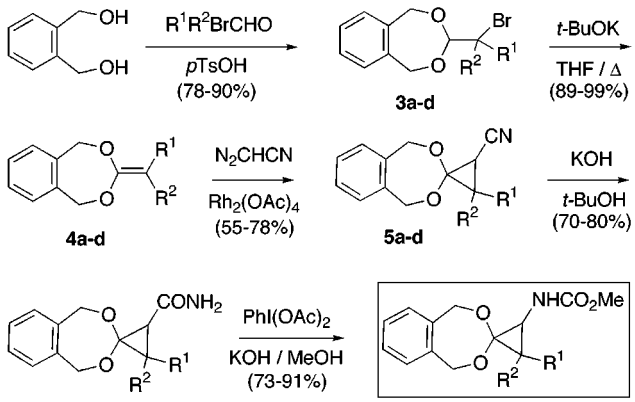
Scheme 1



Scheme 2



Scheme 3



7a R^1 = H, R^2 = H
7b R^1 = H, R^2 = Ph
7c R^1 = Me, R^2 = Me
7d R^1 = H, R^2 = Et

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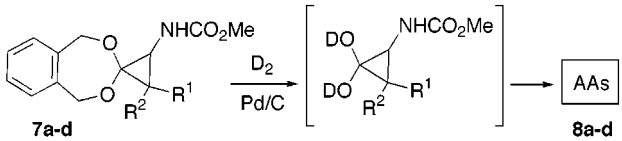
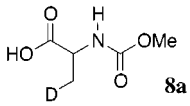
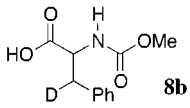
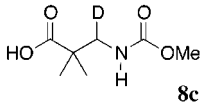
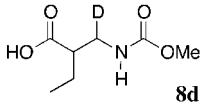
Table 1. Deuteriogenolysis of Amino Acid Precursors

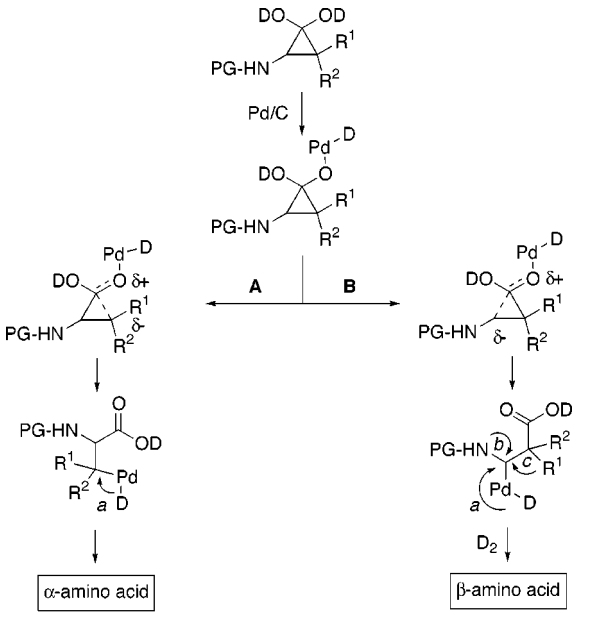


7a-d **8a-d**

substrate	R^1	R^2	product	yield[a] (%)	i.e.[b] (%)
7a	H	H	 **8a**	95	80
7b	H	Ph	 **8b**	93	93
7c	Me	Me	 **8c**	93	71
7d	H	Et	 **8d**	84	74

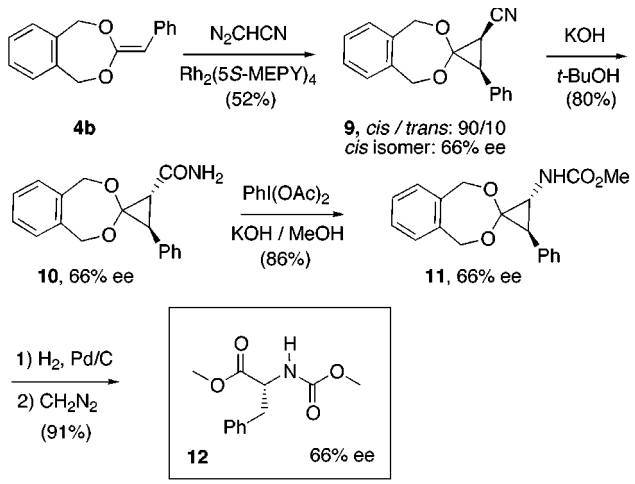
[a] Yields obtained after treatment of the crude reaction mixture with diazomethane. The amino acid was isolated as its methyl ester. [b] Isotopic enrichments were determined by mass spectrometry.

Scheme 4



8a and phenylalanine **8b**, respectively) in high yield and high isotopic purity. A 5 to 10% increase in isotopic enrichment was observed with deuteriogenolysis in methanol-*d* (>99% D). Surprisingly, substrates **7c**,**d** exclusively furnished the labeled *β*-amino acid. In all cases the rearrangement is highly regioselective. The difference in reactivity between amino acid precursors **7a**,**b** and **7c**,**d** may be rationalized by two pathways, A and B (Scheme 4), in which palladium plays a key role in the rearrangement of the cyclopropanone hydrate. Indeed, it has recently been reported that Pd/C catalyzes the ring opening of cyclopropanols.[11] On the basis of this report, we suggest that, in the first step, a palladium alkoxide is formed by oxidative addition of Pd(0) to the hydrate

Scheme 5



group. The hydrate oxygen atoms then act as electron donors and the cyclopropane carbon atoms as electron acceptors. The relative stability of the indicated partial negative charge could be one of the factors that directs the cyclopropane rearrangement. For example, R substituents on substrate **7b** (R^1 = H and R^2 = Ph) promote stabilization of the partial negative charge at the adjacent carbon atom through the electron-withdrawing effect of the phenyl ring. It is also conceivable that, for **7a** (R^1 = H and R^2 = H), the formation of a partial negative charge takes place preferentially on the unsubstituted methylene carbon. However, the rearrangement of **7c**,**d** (R^1 = alkyl or H, R^2 = alkyl) employs pathway B, where the electron-rich alkyl groups center the incipient negative species on carbon adjacent to nitrogen. Subsequent ring opening generates a *σ*-Pd complex[11] that undergoes either reductive- (a) or *β*-elimination (b or c) followed by in situ reduction by D_2 gas. In the case of α-amino acids, reductive elimination (a) appears to be the only active process (no labeling was detected other than on the side chain). However, for *β*-amino acids[12] *β*-elimination (b and/or c) is probably also operative. Indeed, **8d** was labeled in two positions, namely on the methylene carbon atom adjacent to nitrogen (H/D: 0.26) and on the methine carbon atom adjacent to the carboxylic group (H/D: 0.87).

The same strategy was applied with success to the synthesis of optically enriched D-phenylalanine **12** (Scheme 5) using, as the key step, an asymmetric Rh_2(5*S*-MEPY)$_4$ mediated cyclopropanation.[13] This afforded the chiral cyclopropane **9** with a *cis*/*trans* ratio of 90/10. The cis isomer (66% ee) was isolated by column chromatography and converted into the corresponding amide **10**. It should be noted that the center adjacent to the nitrile moiety was fully inverted during the basic hydration step, leading to trans cyclopropane **10** without any loss of optical purity. The amide group was then rearranged stereospecifically[14] to carbamate **11** using DIB. Finally,

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palladium-catalyzed hydrogenolysis of **11** led to *N*-methyl carbamate D-phenylalanine methyl ester **12** in 91% yield with an enantiomeric excess[15] of 66%. The utilization of hydrogen instead of deuterium for the benzyl deprotection step was dictated by the necessity to avoid the introduction of a second chiral center (on the side chain) that would have complicated the assignment of absolute stereochemistry to the amino acid.

In conclusion, we have shown that the rearrangement of α-amino cyclopropanone hydrates provides an easy route to amino acid derivatives. The method was extended to the synthesis of optically enriched D-phenylalanine derivative (66% ee). The approach developed here permits the incorporation of isotopic labeling and is particularly well adapted for the preparation of radioactively labeled amino acids using, for example, tritium gas.

Experimental Section

General Methods. ^{1}H NMR, ^{13}C NMR, and ^{2}H NMR spectra were recorded at 300, 75, and 46 MHz using residual $CHCl_3$ (7.25 ppm), $CDCl_3$ (77 ppm), and $CDCl_3$ (7.25 ppm) as internal standard, respectively. Flash column chromatography was performed on Merck silica gel (60 Å, 230−400 mesh). All reactions were performed under Ar in a flame-dried flask using anhydrous solvents. HRMS were recorded at the "Centre Régional de Mesures Physiques de l'Ouest". Reagents were purchased from Aldrich Chemical Co.

Synthesis of Acetals 3a−d. 7-Bromomethyl-5,9-dihydro-6,8-dioxa-benzocycloheptene **3a** was synthesized according to literature procedures.[7] For **3b−d**, a typical experimental procedure is given for the synthesis of 7-(1-bromo-1-phenylmethyl)-5,9-dihydro-6,8-dioxa-benzocycloheptene **3b**. To a solution of 2-bromo-2-phenylacetaldehyde[6] (1.8 g, 9 mmol, 1 equiv) in 70 mL of toluene were added 1,2-benzenedimethanol (1.37 g, 1.1 equiv) and *p*-TsOH (0.2 g, cat). The mixture was heated to reflux for 3 h in a Dean−Stark apparatus, cooled to room temperature, and diluted with 50 mL of Et_2O. The organic layer was washed with 10% $NaHCO_3$, and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Acetal **3b** was obtained pure as white crystals after recrystallization from Et_2O (2.30 g, 80% yield). ^{1}H NMR ($CDCl_3$) δ 4.78−5.06 (m, 5H), 5.32 (d, J = 6.1 Hz, 1H), 7.19−7.49 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 53.1, 71.7, 107.7, 127.3, 127.5, 127.6, 128.5, 128.7, 138.2, 138.3.

7-Bromomethyl-5,9-dihydro-6,8-dioxa-benzocycloheptene 3a (white crystals, 7.31 g, 90% yield): ^{1}H NMR ($CDCl_3$) δ 3.48 (d, J = 5.1 Hz, 2H), 4.95 (s, 4H), 5.15 (t, J = 5.1 Hz, 1H), 7.19−7.28 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 31.4, 71.7, 105.7, 127.3, 127.6, 138.3.

7-(1-Bromo-1-methylethyl)-5,9-dihydro-6,8-dioxa-benzocycloheptene 3c (white crystals, 3.90 g, 85% yield): ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 6H), 4.82 (s, 1H), 4.98 (s, 4H), 7.22−7.29 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 29.0, 64.5, 73.7, 112.5, 127.8, 139.0.

7-(1-Bromopropyl)-5,9-dihydro-6,8-dioxa-benzocycloheptene 3d (white crystals, 3.50 g, 78% yield): ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.3 Hz, 3H), 1.80−1.93 (m, 1H), 2.02−2.15 (m, 1H), 3.97−4.04 (m, 1H), 4.94−5.02 (m, 5H), 7.19−7.27 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 11.8, 26.5, 56.9, 72.1, 72.3, 108.3, 126.1, 127.4, 127.6, 129.0, 138.5, 138.6.

Synthesis of Ketene Acetals 4a−d. A typical experimental procedure is given for the preparation of 7-methylene-5,9-dihydro-6,8-dioxa-benzocycloheptene **4a**. To a solution of 7-bromomethyl-5,9-dihydro-6,8-dioxa-benzocycloheptene **3a** (7.20 g, 29,6 mmol, 1 equiv) in 150 mL of anhydrous THF was added portionwise at 0 °C *t*-BuOK (3.65 g, 1.1 equiv). The mixture was heated to reflux for 1 h, cooled to room temperature, and diluted with 50 mL of Et_2O. The solution was filtered over Celite, and the solvents were removed under reduced pressure. The crude was pure enough and was used without further purification. Ketene acetal **4a**[17] was obtained as a white solid (4.80 g, 99% yield). ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 2H), 5.09 (s, 4H), 7.10−7.28 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 69.4, 72.0, 126.1, 127.4, 135.8, 164.2. MS (CI/NH_3): 163 (M + 1, 100).

7-Benzylidene-5,9-dihydro-6,8-dioxa-benzocycloheptene 4b (white needles, 0.89 g, 99% yield): ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 2H), 5.28 (s, 3H), 7.13−7.53 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 71.3, 73.4, 88.4, 125.0, 126.0, 126.6, 127.3, 127.4, 127.7, 128.2, 135.4, 136.0, 159.4. MS (CI/NH_3): 239 (M + 1, 100). IR (KBr): 1677 (C=C).

7-Isopropylidene-5,9-dihydro-6,8-dioxa-benzocycloheptene 4c (white powder, 1.34 g, 95% yield): ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 6H), 5.06 (s, 4H), 7.10−7.13 (m, 2H), 7.24−7.27 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 16.2, 71.7, 87.7, 126.2, 127.2, 136.7, 153.2. MS (CI/NH_3): 191 (M + 1, 100). IR (KBr): 1720 (C=C).

7-Propylidene-5,9-dihydro-6,8-dioxa-benzocycloheptene 4d (pale yellow oil, 1.81 g, 89% yield): ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.3 Hz, 3H), 2.08 (m, 2H), 4.19 (t, J = 7.3 Hz, 1H), 5.06 (s, 2H), 5.09 (s, 2H), 7.09−7.26 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 15.1, 17.8, 71.4, 72.6, 87.3, 126.0, 126.3, 127.2, 127.3, 136.2, 136.4, 158.0. MS (CI/NH_3): 191 (M + 1, 100). IR (KBr): 1699 (C=C).

Synthesis of Cyclopropyl Nitriles 5a−d. A typical experimental procedure is given for the synthesis of **5b**. To a refluxing solution of ketene acetal **4b** (0.5 g, 2.1 mmol, 1 equiv) and $Rh_2(OAc)_4$ (1 mol %) in 5 mL of CH_2Cl_2 was added over a period of 8 h, via a seringe pump, diazoacetonitrile[16] (25 mL of a 0.1 M soln in CH_2Cl_2, 1.2 equiv). The solution was cooled to room temperature and filtered over Celite, and the solvent was removed under reduced pressure. Chromatography over silica (hexane:EtOAc, 9:1) allowed the separation of each diastereomer (ratio: 1/1) which were obtained in a combined 55% yield (0.320 g, white powder). Cis cyclopropyl nitrile **5b (9)**: R_f 0.3 (hexane:EtOAc, 8:2). ^{1}H NMR ($CDCl_3$) δ 2.48 (d, J = 10.3 Hz, 1H), 2.99 (d, J = 10.3 Hz, 1H), 4.95−5.18 (m, 4H), 7.17−7.52 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 18.0, 34.7, 71.0, 71.3, 94.6, 115.6, 127.1, 127.3, 127.8, 128.5, 129.2, 131.3, 137.0. Trans cyclopropyl nitrile **5b**: R_f 0.4 (hexane:EtOAc, 8:2). ^{1}H NMR ($CDCl_3$) δ 2.27 (d, J = 6.7 Hz, 1H), 3.13 (d, J = 6.7 Hz, 1H), 4.80 (m, 2H), 5.08 (d, J = 14.4 Hz, 1H), 5.26 (d, J = 14.4 Hz, 1H), 7.10−7.42 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 17.8, 37.4, 71.2, 71.3, 95.0, 117.3, 127.1, 127.3, 127.7, 127.9, 128.6, 132.5, 137.0, 137.2.

Cyclopropyl Nitrile 5a. Addition of diazoacetonitrile over a period of 5 h at room temperature, **5a** was obtained in 66% yield (3.84 g, white powder). R_f 0.2 (hexane:EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 2H), 2.04 (dd, J = 7.0 and 9.8 Hz, 1H), 4.95−5.28 (m, 4H), 7.26−7.37 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 11.3, 21.0, 71.5, 93.4, 117.9, 127.3, 127.4, 127.8, 127.9, 137.1, 137.3.

Cyclopropyl Nitrile 5c. Addition of diazoacetonitrile over a period of 3 h under reflux, **5c** was obtained in 78% yield (0.94 g, white powder). R_f 0.3 (hexane:EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.43 (s, 3H), 1.59 (s, 1H), 4.87 (d, J = 14 Hz, 1H), 4.96 (d, J = 14.2 Hz, 1H), 5.05 (d, J = 14 Hz, 1H), 5.21 (d, J = 14.2 Hz, 1H), 7.17−7.30 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 16.9, 19.7, 21.0, 31.1, 70.6, 70.8, 97.7, 116.8, 126.8, 127.0, 127.4, 127.5, 137.0, 137.3.

Cyclopropyl Nitrile 5d. After addition of diazoacetonitrile over a period of 4 h under reflux, **5d** was obtained in 67% yield (0.57 g, white powder) as a 1/1 mixture of diastereomers a and b. R_f 0.4 (hexane:EtOAc, 8:2). ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.3 Hz, 3Ha,b), 1.51−2.01 (m, 4Ha,b), 4.72−4.25 (m, 4Ha,b), 7.18−7.30 (m, 4Ha,b). ^{13}C NMR ($CDCl_3$) δ 12.5, 12.8, 15.0, 15.7, 18.0, 20.1, 32.6, 35.7, 71.0, 71.2, 71.4, 95.3, 95.8, 116.5, 118.1, 126.2, 127.1, 127.3, 127.4, 127.6, 127.8, 137.2, 137.3, 137.5.

Synthesis of Cyclopropyl Amides 6a−d. A typical experimental procedure is given for the synthesis of **6a**. To a solution of cyclopropyl nitrile **5a** (3.8 g, 18.9 mmol, 1 equiv) in 50 mL of freshly distilled *t*-BuOH was added powdered KOH (3.18 g, 3 equiv). The solution was heated to reflux for 4 h, cooled to room temperature, and diluted with 20 mL of H_2O. The precipitate was collected and washed with hexane to afford cyclopropyl

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amide **6a** in 75% yield (3.10 g, white powder). ^{1}H NMR (DMSO-d_6) δ 1.31 (dd, J = 5.5 and 9.6 Hz, 1H), 1.56 (dd, J = 5.5 and 7.1 Hz, 1H), 2.15 (dd, J = 7.1 and 9.6 Hz, 1H), 4.72−5.04 (m, 4H), 6.96 (brs, 1H), 7.27−7.30 (m, 4H), 7.56 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 18.2, 29.6, 70.8, 70.9, 95.2, 127.4, 138.8, 168.5.

Cyclopropyl amide 6b (10). Synthesized from the mixture of diastereomers **5b**, **6b** was obtained as the single trans diastereomer (white powder, 0.250 g, 80%). ^{1}H NMR (DMSO-d_6) δ 2.60 (d, J = 7.3 Hz, 1H), 3.09 (d, J = 7.3 Hz, 1H), 4.62−4.95 (m, 4H), 7.10 (brs, 1H), 7.21−7.31 (m, 9H), 7.69 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 34.4, 35.3, 70.5 (2C), 96.5, 126.3, 127.2, 127.3, 127.9, 128.1, 135.3, 138.3, 138.5, 168.0.

Cyclopropyl Amide 6c. After 12 h under reflux, the reaction was quenched with saturated NaCl and extracted four times with $CHCl_3$ and two times with Et_2O. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. **6c** was obtained, after column chromatography (CH_2Cl_2:EtOH, 95:5) over silica, as a white powder (R_f 0.3, 0.510 g, 70%). ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.40 (s, 3H), 1.76 (s, 1H), 4.28 (d, J = 14.0 Hz, 1H), 5.00 (s, 2H), 5.04 (d, J = 14.0 Hz, 1H), 5.60 (brs, 1H), 6.49 (brs, 1H), 7.15−7.20 (m, 2H), 7.23−7.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 15.2, 21.9, 30.4, 38.0, 70.4, 70.7, 97.6, 126.7, 127.2, 127.5, 137.1, 137.8, 171.2.

Cyclopropyl Amide 6d. Synthesized from the mixture of diastereomers **5d**. After 3 h under reflux, the reaction was quenched with saturated NaCl and extracted four times with $CHCl_3$ and two times with Et_2O. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. **6d** was obtained as the single trans diastereomer after column chromatography (CH_2Cl_2:EtOH, 95:5) over silica (white powder, R_f 0.4, 0.350 g, 80%). ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 7.3 Hz, 3H), 1.51−1.88 (m, 4H), 4.89−5.05 (m, 4H), 5.61 (brs, 1H), 6.00 (brs, 1H), 7.16−7.26 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 13.3, 20.6, 35.0, 35.4, 71.0, 71.1, 97.6, 127.0, 127.6, 135.2, 137.1, 137.9, 172.2.

Synthesis of Cyclopropyl *N*-Methyl Carbamates 7a−d. A typical experimental procedure is given for the synthesis of **7a**. To a solution of cyclopropyl amide **6a** (2 g, 9.1 mmol, 1 equiv) in 100 mL of anhydrous MeOH was added powdered KOH (1.28 g, 2.5 equiv). The solution was cooled to 0 °C and iodobenzene diacetate (2.94 g, 1 equiv) was added in one portion. The mixture was stirred 20 min at 0 °C and 5 h at room temperature. Water (20 mL) was then added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography over silica (hexane:EtOAc, 6:4) afforded cyclopropyl *N*-methyl carbamate **7a** in 73% yield (white powder, R_f 0.3, 1.67 g). ^{1}H NMR ($CDCl_3$) δ 0.99 (m, 1H), 1.47 (m, 1H), 3.14 (m, 1H), 3.67 (s, 3H), 4.89−5.11 (m, 5H), 7.14−7.25 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 20.9, 34.8, 52.2, 71.0, 71.5, 93.0, 127.4, 127.5, 127.6, 138.2, 138.3, 157.3. HMRS calcd for $C_{13}H_{14}NO_4$ $(M - H)^+$ 248.0922, found 248.0936.

Cyclopropyl *N*-methyl carbamate 7b (11) (white powder, 0.180 g, 86%): R_f 0.5 (hexane:EtOAc, 6:4). ^{1}H NMR ($CDCl_3$) δ 2.42 (d, J = 5.2 Hz, 1H), 3.49 (brs, 1H), 3.70 (s, 3H), 4.70 (m, 2H), 5.08 (m, 2H), 5.18 (brs, 1H), 7.05 (m, 1H), 7.18−7.31 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 38.3, 40.9, 52.3, 71.2, 71.4, 95.1, 126.4, 127.2, 127.5, 127.6, 127.8, 128.3, 136.8, 137.8, 138.2, 157.1. HMRS calcd for $C_{19}H_{19}NO_4$ $(M)^+$ 325.1314, found 325.1333.

Cyclopropyl *N*-methyl carbamate 7c (white powder, 0.240 g, 87%): R_f 0.5 (hexane:EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.31 (s, 3H), 2.71 (d, J = 4.3 Hz, 1H), 3.69 (s, 3H), 4.84−5.08 (m, 5H), 7.14−7.24 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 13.8, 19.7, 27.5, 41.4, 52.2, 70.7, 71.0, 95.5, 127.0, 127.3, 127.5, 138.0, 138.4, 157.6. HMRS calcd for $C_{15}H_{20}NO_4$ $(M + H)^+$ 278.1392, found 278.1389.

Cyclopropyl *N*-methyl carbamate 7d (white powder, 0.120 g, 91%): R_f 0.3 (hexane:EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3H), 1.15−1.19 (m, 1H), 1.47−1.64 (m, 2H), 2.70 (brs, 1H), 3.67 (s, 3H), 4.86−5.09 (m, 5H), 7.16−7.26 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 13.3, 19.5, 34.7, 39.3, 52.0, 70.9, 71.1, 95.4, 127.1, 127.3, 127.4, 138.1, 138.4, 157.3. HMRS calcd for $C_{15}H_{19}NO_4$ $(M)^+$ 277.1314, found 277.1358.

Synthesis of Amino Acid Derivatives. A typical experimental procedure is given for the synthesis of 3-[^{2}H]-2-methoxycarbonylamino-propionic acid methyl ester **8a**. A 10 mL flame-dried reaction vessel containing Pd 10 wt % on C (0.053 g, 25 mol %) was air evacuated. A pressure of 0.3 Bar of deuterium gas was introduced at room temperature, and the catalyst was vigorously stirred for 30 min. The gas was evacuated and replaced by a fresh aliquot of D_2. This operation was repeated three times. Cyclopropyl *N*-methyl carbamate **7a** (0.05 g, 0.2 mmol, 1 equiv) in 2 mL of anhydrous EtOAc was then added. The solution was vigorously stirred at room temperature, under 1 Bar of D_2, for 4 h. The catalyst was filtered, and the solvent was removed under reduced pressure. The crude was taken in MeOH and treated, at 0 °C, with diazomethane. After evaporation of the solvent and column chromatography over silica (hexane:EtOAc, 7:3), β-deuterated alanine derivative **8a** (oil, R_f 0.3, 0.035 g) is obtained in 95% yield and 80% isotopic purity. ^{1}H NMR ($CDCl_3$) δ 1.38 (t like, J = 5 Hz, 2H), 3.67 (s, 3H), 3.74 (s, 3H), 4.35 (m, 1H), 5.21 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 18.4 (t), 49.5, 52.2, 52.4, 156.2, 173.5. ^{2}H NMR ($CHCl_3$) δ 1.39. HMRS calcd for $C_6H_{10}DNO_4$ $(M)^+$ 162.0750, found 162.0747.

3-[^{2}H]-2-Methoxycarbonylamino-3-phenylpropionic acid methyl ester 8b (oil, 0.034 g, 93%, 93% i.e.): R_f 0.4 (hexane:EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 3.09 (brd, 1H), 3.65 (s, 3H), 3.71 (s, 3H), 4.64 (t like, J = 5.3 Hz, 1H), 5.11 (brd, 1H), 7.11 (m, 2H), 7.23−7.31 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 37.9 (t), 52.3 (2C), 54.6, 127.1, 128.6, 129.2, 135.6, 156.2, 172.0. ^{2}H NMR ($CHCl_3$) δ 3.09. HMRS calcd for $C_{12}H_{14}DNO_4$ $(M)^+$ 238.1063, found 238.1068.

3-[^{2}H]-2-Methoxycarbonylamino-2,2-dimethylpropionic acid methyl ester 8c was prepared as described for **8a** using 80 mol % of Pd/C and with a reaction time of 12 h (oil, 0.019 g, 93%, 71% i.e.): R_f 0.2 (hexane:EtOAc, 8:2). ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 6H), 3.26 (m, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 5.13 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 22.9, 43.5, 48.4 (t), 52.0, 52.1, 157.3, 177.5. ^{2}H NMR ($CHCl_3$) δ 3.26. HMRS calcd for $C_8H_{14}DNO_4$ $(M)^+$ 190.1063, found 190.1068.

2-(1-[^{2}H]-1-Methoxycarbonylamino-methyl)butyric acid methyl ester 8d was prepared as described for **8c** (oil, 0.017 g, 84%, 74% i.e.): R_f 0.2 (hexane:EtOAc, 8:2). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.52−1.67 (m, 2H), 2.54 (m, 1H), 3.28 (m, 1H), 3.32 (m, residual H), 3.64 (s, 3H), 3.69 (s, 3H), 5.03 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 11.4, 22.8, 41.3 (t), 46.8, 51.7, 52.1, 157.0, 175.3. ^{2}H NMR ($CHCl_3$) δ 2.53, 3.35. HMRS calcd for $C_8H_{14}DNO_4$ $(M)^+$ 190.1063, found 190.1087.

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Supporting Information Available: Reproductions of ^{1}H and ^{13}C NMR spectra of key intermediates **7a−d** and of labeled amino acid derivatives **8a−d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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