Synthesis of (*R*)- and (*S*)-1-Amino[2,2-$^2H_2$]cyclopropane-1-carboxylic Acids

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The synthesis of (*R*)- and (*S*)-1-amino[2,2-$^2H_2$]cyclopropane-1-carboxylic acids of biological interest is described. The stereochemistry of the reaction of the lithio derivative of (*R*)-(−)-2,5-dimethoxy-3-benzyl-3-methyl-3,6-dihydropyrazine with 2-halo 1,1-dideuteriated ethyl tosylate or 2-halo 1,1-dideuteriated ethyl triflates is discussed as well as the stereochemistry of the reaction with methyl triflate and deuterium chloride. The intramolecular cyclization to form the three-membered ring is also discussed in terms of stereochemistry. The configurations of the newly formed center(s) of chirality in both the mono- and dialkylated products are derived from ^1H NMR.

The achiral natural product 1-aminocyclopropane-1-carboxylic acid (ACC) is the key intermediate in the bioconversion of methionine to the fruit-ripening hormone ethylene[1] and is the substrate for the enzyme ACC deaminase from *Pseudomonas sp.* which fragments the cyclic amino acid to ammonia and α-ketobutyrate.

The syntheses of stereospecifically labeled ACCs have been reported,[2,3] but the procedures used gave 1:1 mixtures of enantiomers. These ACCs were used to probe the mechanism of ethylene biosynthesis.[3] Recently two syntheses of (*R*)- and (*S*)-1-amino-[2,2-$^2H_2$]cyclopropane-1-carboxylic acids, utilized to probe the mechanism of the pyridoxal phosphate dependent enzyme ACC deaminase, have appeared;[4] however, they are multistep procedures and require an independent method for assessing the percent of enantiomeric excess (% ee) of the isomers.

Herein, we describe a simple synthesis of (*R*)- and (*S*)-[2,2-$^2H_2$]ACC based, in part, on the Schöllkopf[5] approach to asymmetric synthesis and one which also allows for the direct assessment of % ee.

We chose as our chiral agent (*R*)-(+)-2-methyl-3-phenylalanine (1), which was prepared from phenylacetone[6] in a convenient four-step sequence in 49% overall yield by a modified asymmetric Strecker synthesis[7] first described by Weinges and co-workers.[8] This amino acid was chosen because it lacks an α-hydrogen and therefore the cyclo[α-methyl-Phe-Gly] derived can only be alkylated at the C-6 position. The synthesis of the cyclo[α-methyl-Phe-Gly] began with the esterification of the phenylalanine derivative with methanolic HCl,[9] and the resulting methyl ester **2** was condensed[10] with *N*-*t*-Boc-glycine to give the dipeptide methyl ester **3**. Following the procedure of Nitecki,[11] the dipeptide methyl ester **3** was cyclized, after treating with formic acid, by boiling in a mixture of *sec*-butanol and toluene (2:1)[12] to yield the 2,5-diketopiperazine (**4**). The piperazine **4** was then converted into the bis(lactim ether) **5** by treatment with trimethyloxonium tetrafluoroborate.[13]

Our initial approach to the synthesis of the target compounds was the reaction of 2-halo 1,1-dideuteriated ethyl tosylates (or 2-halo-2,2-dideuteriated ethyl tosylates) with the lithio derivative of the bis(lactim ether) **5** to, it was hoped, obtain a mixture of products in which both the halide and tosylate had been displaced. These two alkylated products would be separated and intramolecularly cyclized via treatment with butyllithium, independently, to form both desired stereoisomers from one common chiral synthon and one common regiospecifically deuteriated ethane derivative. Unfortunately when 2-bromo-1,1-dideuteriated ethyl tosylate was used as the alkylating agent a single product was obtained in which *only* the bromide had been displaced and the reaction had proceded only in modest yield. In order to obtain a mixture of alkylated products, to increase the overall yield, and to increase the leaving potential of the alcohol function, the hydroxyl group was converted into a triflate instead of a tosylate since the triflate leaving group potential is 3×10^4 greater than that of a tosylate and 1.5×10^5 times greater than that of a bromide ion.[14] That this is actually the case was quite apparent when it was found that upon treatment of the lithio derivative of the bis(lactim ether) **5** with 2-halo 1,1-dideuteriated ethyl triflate only an alkylated bromo derivative was obtained, indicating exclusive displacement of the triflate moiety. Since the yields of monoalkylated derivatives of **5** were substantially better with the triflate compared to the tosylate, the triflates were chosen as the alkylating derivatives. The triflates were prepared from the corresponding alcohols by utilizing the standard triflic anhydride/pyridine in methylene chloride method.[15] These reagents are fairly stable at room temperature and conveniently stored at 0 °C for months without appreciable decomposition. The triflates were, however, prepared immediately before needed and characterized from spectral data.

We began the synthesis of the desired cyclopropanes by the reaction of the bis(lactim ether) **5** directly with 1 equiv of butyllithium in tetrahydrofuran (THF) at −78 °C to form the lithio derivative which reacted with regiospecifically deuterium labeled 2-haloethyl triflates[15-17] to se-

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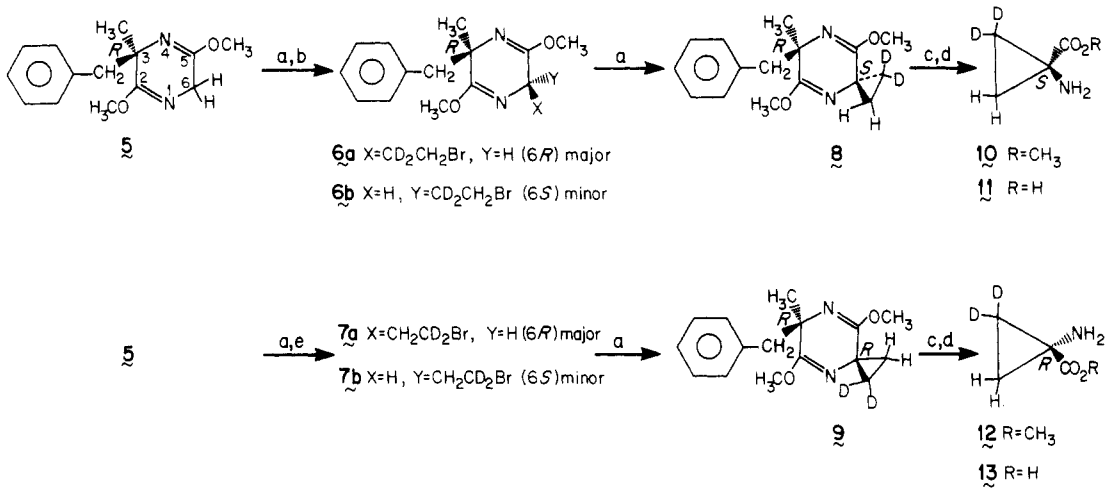
0022-3263/87/1952-0015$01.50/0

Scheme I[a]



[a] (a) BuLi; (b) $BrCH_2CD_2OTf$; (c) 0.25 N HCl; (d) 6 N HCl; (e) $BrCD_2CH_2OTf$.

Table I. Diastereomeric Excess of Various Alkylation Reactions

	first alkylation			second alkylation		
	% product (compd)			% product (compd)		
alkylating agent	trans	cis	% yield	trans	cis	% yield
$BrCH_2CD_2OTs$	90	10	26			
$BrCD_2CH_2OTs$	90	10	25			
$BrCH_2CD_2OTf$	22 (**6b**)	78 (**6a**)	86	27 (**9**)	73 (**8**)	55
$ClCH_2CD_2OTf$	20	80	88	27 (**9**)	73 (**8**)	51
$BrCD_2CH_2OTf$	20 (**7b**)	80 (**7a**)	88	28 (**8**)	72 (**9**)	55
$CH_3I(CD_3I)$	85	15	80	98	2[20]	70
$CD_3I(CH_3I)$	84	16	82	98	2[20]	71
CH_3OTf	50	50	85			
CD_3OTf	50	50	84			
DCl/D_2O	77	23	82			

lectively displace the triflate group (Scheme I) to afford a mixture of diastereomers **6a** and **6b** (4:1) in high yields (Table I). Surprisingly, the 2-haloethyl group had entered at C-6 cis to the bulky benzyl group at C-3 (in violation of Schöllkopf's observations) to induce the *R* configuration at C-6.

The configuration at C-6 of these alkylated products was assigned based on their ^1H NMR spectra. The ^1H NMR spectrum of the parent compound **5** shows signals at δ 2.84 and 3.66 (d, AB, 2 H, J = 20.53 Hz) due to the C-6 hydrogen atoms. On the basis of the ^1H NMR studies of Kopple[18] on the diketopiperazine cyclo[Phe-Gly] and of Woodard[19] on the diketopiperazines cyclo[L-Phe-L-Ala], cyclo[L-Phe-D-Ala], cyclo[L-Phe-AiBA], and cyclo[D-Phe-ACC] the ^1H NMR signal at δ 2.84 of **5** was assigned to the hydrogen atom cis to the benzyl group at position C-3 and the other signal at δ 3.66 to be the hydrogen atom trans to the benzyl group. In the case of the major diastereomer **6a**, the C-6 hydrogen atom signal appears at δ 3.87 (s), indicating a cis addition of the 2-bromo-1,1-dideuterioethyl group had occurred and that the major diastereomer had the 6*R* configuration. The 6*S* configuration of the minor isomer was also confirmed by ^1H NMR.

This difference in the stereochemistry of the monoalkylated product between the 2-halo-1,1-dideuteriated ethyl tosylate and the 2-halo-1,1-dideuteriated ethyl triflate as alkylating agents is quite interesting. In the case of the tosylate the approach of the electrophile was trans to the bulky 3-benzyl group and therefore obeys Schöllkopf's observation; however, in the case of the triflate the approach of the electrophile was cis to the bulky 3-benzyl group and therefore violates Schöllkopf's rule. Since in the synthesis of the target molecule described below a second alkylation step (albeit an internal alkylation) was necessary, any stereochemistry at the C-6 position would be lost, due to the removal of the C-6 hydrogen atom and rehybridization from sp^3 to sp^2, so that the initial inverse approach is only of academic interest.

To further investigate this anti-Schöllkopf-type addition of electrophiles generated by a triflate leaving group, methyl triflate was prepared and added to the lithio derivative of the bis(lactim ether) **5**. The stereochemistry at the C-6 position, as determined from the ^1H NMR of the alkylated product, was totally racemic (i.e., a 50:50 mixture of 6*S* and 6*R*), indicating a total lack of asymmetric induction by the chiral synthon. The stereochemistry of the alkylation of the lithio derivative of the bis(lactim ether) **5** with methyl iodide has been previously reported from our laboratory[20] to be 4:1 trans/cis addition (i.e. 6*S*/6*R*).

To explore the possible role(s) of the triflate anion function, 1 mol of lithium triflate was added to a reaction mixture in which methyl iodide had been added to the lithio derivative of the bis(lactim ether) **5**. The ratio of cis to trans addition remained unchanged from that of just methyl iodide, indicating that the lithium triflate generated during the alkylation of the lithio derivative of the bis(lactim ether) **5** with methyl triflate probably did not play

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a significant role in the steric course of the addition of the electrophile.

As further evidence that this violation of Schöllkopf's rule cannot be simply explained by a unimolecular S_n1-type ionization, quenching the lithium anion of **5** with dilute DCl in deuterium oxide gave only a monodeuteriated product in which the deuterium was incorporated preferentially in the trans C-6 position (6*S*/6*R* = 4/1). This implies that a positively charged alkylating species, formed via an S_n1 process, does not adversely affect the approach of the attacking nucleophile. This is also true in the case of 2-haloethyl triflate as the alkylating species. Since the alkylating species in an S_n1-type reaction would be a 2-haloethyl cation, one would expect scrambling of the deuteriums in the product if an ethyl bromonium cation were formed. Since no scrambling of deuterium in the monoalkylated products was observed, it is presumed that the C-6 anion attacks the 2-haloethyl triflate in an S_n2-type process to directly displace the triflate function. As can be seen from Table I only compounds with triflates as the leaving group gave an anomalous reversal in stereochemistry in a monoalkylation reaction.

The synthesis of the title compound is completed via an intramolecular Schöllkopf alkylation performed on the mixture of diastereomers **6a** and **6b** in THF at −78 °C by treating with butyllithium. The mixture of diastereomers was not separated since treatment with butyllithium converted the C-6 from an sp^3 hybridization to an sp^2 hybridization, therefore all stereochemical information at C-6 was lost. Although one would expect the alkylating group to enter intramolecularly from the trans face, an unusual ring closure occurred to give predominantly **8** (**8**/**9**, 3:1) in which the intramolecular addition of the alkyl group was cis to the benzyl group, indicating an anti-Schöllkopf addition. The 6*S* configuration of **8** was derived from high-field ^1H NMR data.[16] The methylene hydrogen atoms at δ 0.13 and 0.5 (d, AB, 2 H, *J* = 4.12 Hz) which are located within the shielding cone of the aromatic ring (benzyl group) suffer an upfield shift of Δδ 0.6 as compared to those at δ 0.69 and 1.13 (d, AB, 2 H, *J* = 4.10 Hz) in the minor isomer **9**.

The synthesis of the title compound **11** was completed by hydrolysis of the adduct **8** (de 46%) with 0.25 N HCl at room temperature for 48 h. This cleavage gave both (*R*)-2-methyl-3-phenylalanine methyl ester (**2**) and (*S*)-1-amino[2,2-$^2H_2$]cyclopropane-1-carboxylic acid methyl ester (**10**) hydrochlorides. These esters were further hydrolyzed (6 N HCl, heated to reflux, 1 h) to give the corresponding amino acids which were separated by chromatography. Similarly, the *R* isomer of [2,2-$^2H_2$]ACC **13** was obtained in 44% ee from the reaction of the lithio derivative of **5** and 2-bromo-2,2-dideuterioethyl triflate, via the intermediate bis(lactim ether) **9**, obtained from the ethers **7a** and **7b**, as shown in the bottom portion of Scheme I.

Although the Schöllkopf-type of addition to the lithio derivative of **5** was unpredictive in this study, the use of the bis(lactim ether) to synthesize the target compounds was successful since both stereoisomers of [2,2-$^2H_2$]ACC were obtained in reasonable % ee from one common synthon. The use of 2-methyl-3-phenylalanine as the chiral agent was also very successful since it allowed one to use the ^1H NMR of the product bis(lactim ether) to determine the % ee directly without the use of any added chiral shift reagent.

Experimental Section

Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian EM-360 60-MHz, Bruker WM-360-MHz, and IBM WP 270-MHz spectrometers, and chemical shifts values are reported in ppm downfield from tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer. Mass spectra were recorded on a Finnigan 4021 mass spectrometer by the University of Michigan Chemistry Department Instrumentation Service. Optical rotations were measured in a 1-dm cell at 25 °C on a Perkin-Elmer Model 141 polarimeter, and *c* is expressed in g/100 mL.

Column chromatography was performed using E. Merck Silica Gel 60, 70–230 mesh ASTM, and elutions were carried out with 19:1 hexane/ethyl acetate (v/v) followed by 9:1 hexane/ethyl acetate unless otherwise noted. Analytical thin-layer chromatography was performed on Analtech, Inc. 20 × 20 cm plates precoated with Silica Gel G. Tetrahydrofuran and 1,2-dimethoxyethane were distilled from $LiAlH_4$ immediately prior to use. Dichloromethane was distilled from P_2O_5 under nitrogen. All organic solvent extracts were dried with Na_2SO_4 and removed in vacuo by using a rotary evaporator (water aspirator vacuum) unless stated otherwise. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

(*R*)-(−)-2-Methyl-3-phenylalanine Methyl Ester (2).[9] The title compound was prepared as previously described[9,21] from 10.0 g of (*R*)-(+)-2-methyl-3-phenylalanine (**1**)[7] (55.8 mmol) to yield 9.2 g of **2** (85.3%) as a colorless liquid of bp 106–108 °C (3 mmHg): $[\alpha]_D$ −4.2° (*c* 1.0, methanol), [lit.[21] $[\alpha]_D$ −4.33° (*c* 3.05, methanol)]; IR (film) 1735 cm^{-1} ($COOCH_3$); ^1H NMR (Me_2SO-d_6) δ 1.25 (s, 3 H, CCH_3), 1.38 (s, 2 H, NH_2), 2.80 and 2.92 (d, AB, *J* = 13.05 Hz, $C_6H_5CH_2$), 3.61 (s, 3 H, $COOCH_3$), 7.11–7.30 (m, 5 H, C_6H_5).

(*R*)-(+)-*N*-[*N*-(*tert*-Butoxycarbonyl)glycinyl]-2-methyl-3-phenylalanine Methyl Ester (3).[10] To a stirred solution of (*R*)-(−)-2-methyl-3-phenylalanine methyl ester (**2**) (4.83 g, 25 mmol) in dry dichloromethane (30 mL) at 0 °C was added a solution of *N*-[[(2,2-dimethylethyl)oxy)carbonyl]glycine (4.38 g, 25 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (5.16 g, 25 mmol) in dry dichloromethane (20 mL), followed by the addition of 4-(dimethylamino)pyridine (0.61 g, 5 mmol). The reaction mixture was allowed to stir at 0 °C for 4 h and overnight at room temperature. The urea which formed was removed by filtration, and the solvent was evaporated to yield an oily residue. The residue was dissolved in ether (100 mL) and washed successively with 5% citric acid, a saturated $NaHCO_3$ solution, and water. The organic layer was concentrated to yield the crude peptide **3** as a highly viscous oil. The oily product was purified by column chromatography with ethyl acetate/hexane (3:2) as eluant to yield 7.2 g (82.2%): $[\alpha]_D$ +45.4° (*c* 1.6, methanol); ^1H NMR (Me_2SO-d_6) δ 1.21 (s, 3 H, CCH_3), 1.39 (s, 9 H, $C(CH_3)_3$), 2.98 and 3.23 (d, AB, *J* = 13.2 Hz, $C_6H_5CH_2$), 3.53 (dd merged into t, *J* = 5.82 Hz, 2 H, CH_2NH), 3.58 (s, 3 H, $COOCH_3$), 6.96 (t, *J* = 5.55 Hz, 1 H, CH_2NH), 7.08–7.30 (m, 5 H, C_6H_5), 7.93 (s, 1 H, $NHCOCH_2$).

Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.69; H, 7.48. Found: C, 61.59; H, 7.49.

(3*R*)-(−)-3-Methyl-3-benzyl-2,5-diketopiperazine (4). The procedure of Nitecki and co-workers[11] for converting *t*-Boc-protected dipeptide methyl esters into cyclic dipeptides was modified as follows: the *t*-Boc dipeptide methyl ester **3** (7.0 g, 20.0 mmol) was dissolved in formic acid (125 mL) and stirred for 2 h under a drying tube. The solution was concentrated in vacuo (bath temperature <30 °C) and the residue triturated several times with dry ether to precipitate the formate salt (5.1 g, 86.1%), which was used without further purification. To a solution of the formate salt in *sec*-butanol (200 mL) and toluene (100 mL) was added 1.5 g (17.2 mmol) of morpholine, and the mixture was heated to reflux (96 °C) for 2.5 h. After most of the solvent was removed, the solution was cooled to 0 °C and the resulting solid filtered. The crude product was recrystallized from methanol to give 2.8 g (64.1%) of the title compound **4**: mp 302–304 °C; $[\alpha]_D$ −92.7° (*c* 0.11, DMF); IR (KBr) 1675 cm^{-1} (NHC=O); ^1H NMR (Me_2SO-d_6) δ 1.41 (s, 3 H, CCH_3), 2.51 and 3.34 (d, AB, *J* = 17.46 Hz, 2 H, CH_2), 2.67 and 3.07 (d, AB, *J* = 13.02 Hz, $C_6H_5CH_2$), 7.12–7.28 (m, 5 H, $C_6H_5CH_2$), 7.79 (br s, 1 H, 4-N*H*), 8.25 (br s, 1 H, 1-N*H*).

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Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47. Found: C, 66.04; H, 6.47.

(3*R*)-(−)-2,5-Dimethoxy-3-benzyl-3-methyl-3,6-dihydropyrazine (5). A mixture of the diketopiperazine **4** (4.37 g, 20 mmol) and 7.4 g (50 mmol) of trimethyloxonium tetrafluoroborate in 100 mL of dry dichloromethane was vigorously (mechanically) stirred at 40 °C for 72 h. The reaction mixture was cooled to room temperature, and a solution of 6 g of potassium carbonate in 25 mL of water was added, the organic layer separated, and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic extracts were evaporated to give a crude residue, which was purified by column chromatography to yield 3.6 g (73%) of **5**: $[\alpha]_D$ −192.3° (*c* 0.555, ethanol); IR (film) 1695 cm^{-1} (C=N); ^1H NMR (Me_2SO-d_6) δ 1.42 (s, 3 H, CCH_3), 2.71 and 3.03 (d, AB, J = 12.77 Hz, 2 H, $C_6H_5CH_2$), 2.84 and 3.66 (d, AB, J = 20.53 Hz, 2 H, 6-*H*), 3.61 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 6.96–7.22 (m, 5 H, $C_6H_5CH_2$).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37. Found: C, 68.42; H, 7.28.

2-Bromo[1,1-$^2H_2$]ethyl Triflate. A solution of 2-bromo[1,1-$^2H_2$]ethanol[16] (2.0 g, 15.8 mmol) and dry pyridine (1.25 g, 15.8 mmol) in 5 mL of dry dichloromethane was added, dropwise with stirring, over a 45-min period, to a solution of triflic anhydride (4.46 g, 15.8 mmol) in 15 mL of dry dichloromethane at 0 °C. After 15 min, the solution was washed with ice-cold water (2 × 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The light-brown residual liquid was filtered through silica gel (hexane/ethyl acetate, 1:1) and the solvent removed under vacuum to give pure 2-bromo[1,1-$^2H_2$]ethyl triflate (3.2 g, 78.4%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 3.60 (s, 2 H, CH_2) IR (film) ν 1418, 1255, 1215, 1140, 980 (OSO_2CF_3) cm^{-1}.

2-Chloro[1,1-$^2H_2$]ethyl Triflate. To a solution of triflic anhydride (4.23 g, 15.0 mmol) in dry dichloromethane (15 mL) at 0 °C was added dropwise a solution of 2-chloro[1,1-$^2H_2$]ethanol[16] (1.24 g, 15.0 mmol) and pyridine (1.19 g, 15.0 mmol) in dry dichloromethane (5 mL) over a period of 45 min. After 15 min, the reaction mixture was worked up as described above to yield 2.4 g (74.4%) of the title triflate: ^1H NMR ($CDCl_3$) δ 3.80 (s, 2 H, CH_2) IR (film) ν 1420, 1255, 1212, 1145, 975 (OSO_2CF_3) cm^{-1}.

2-Bromo[2,2-$^2H_2$]ethyl Triflate. By the above procedure 2-bromo[2,2-$^2H_2$]ethanol[16] (1.27 g, 10.0 mmol) and pyridine (0.79 g, 10.0 mmol) were treated with triflic anhydride (2.82 g, 10.0 mmol) in dry dichloromethane at 0 °C to give 2.0 g (77.2%) of 2-bromo[2,2-$^2H_2$]ethanol triflate: ^1H NMR ($CDCl_3$) δ 4.75 (s, 2 H, CH_2) IR (film) ν 1420, 1255, 1215, 1142, 980 (OSO_2CF_3) cm^{-1}.

6-Substituted 2,5-Dimethoxy-(3*R*)-3-benzyl-3-methyl-3,6-dihydropyrazines: General Procedure. To a stirred solution of bis(lactim ether) **5** (1.0 g, 4.1 mmol) in dry tetrahydrofuran (10 mL) at −78 °C was added a 1.6 N solution (2.8 mL, 4.5 mmol) of butyllithium in THF by syringe, and stirring was continued for 30 min. Then a precooled solution of the alkylating agent (4.5 mmol) in dry THF (5 mL) was added and stirring continued for 8–12 h at −78 °C. The reaction mixture was allowed to warm to room temperature, the solvent was evaporated under reduced pressure, and the residue was dissolved in ether (25 mL). The ether solution was shaken with water (10 mL), the water layer was back-extracted with ether (2 × 10 mL), and the combined ether layers were dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residual crude products, either **6** [a mixture of **6a** (de 56%) and **6b**] or **7** [a mixture of **7a** (de 60%) and **7b**], depending on the starting triflate, were purified by column chromatography, eluting with hexane/ethyl acetate (9:1).

***cyclo*-[(2*R*)-2-Methyl-3-phenylalanyl[2,2-$^2H_2$]-1-aminocyclopropanecarboxylic acid] Bis(lactim methyl ethers) 8 and 9: General Procedure.** A 1.6 N solution (1.4 mL, 2.2 mmol) of butyllithium in hexane was cooled to −78 °C and added to a solution of compound **6a** or a mixture of **6a** (de 56%) and **6b** (2 mmol) in dry THF (or better DME) at −78 °C. The resulting yellowish brown colored solution was stirred for 8 h and worked up as previously described. The final purification was achieved by silica gel column chromatography using hexane/ethyl acetate (95:5) as eluant to yield **8** (de 46%) contaminated with **9**. The bis(lactim ether) **9** (de 44%) was obtained in the same manner from the monoalkylated ether **7a** (or a mixture of ethers **7a** (de 60%) and **7b**) and purified as described before.

(*S*)-1-Amino[2,2-$^2H_2$]cyclopropane-1-carboxylic Acid (11). A mixture of bis(lactim ether) **8** (de 46%) (0.27 g, 1 mmol) and 16 mL of 0.25 N hydrochloric acid (4 mmol) was stirred at room temperature for 48 h and extracted with ether (2 × 10 mL), the ether extract was discarded, and the aqueous phase was concentrated in vacuo to give a mixture of **10** and **2** hydrochlorides. HCl (5 mL, 6 N) was added to the residue, and the mixture was heated to reflux for 1 h. After the mixture was cooled to room temperature, 10 mL of water was added, and the solution was loaded onto a column of Dowex 50W-X8 (H^+ form) cation-exchange resin. The column was eluted first with water until the eluant was neutral and then with 100 mL of 1 N NH_4OH. Concentration of the ninhydrin positive fractions of the eluate yielded a mixture of chiral auxiliary reagent **1** and the title amino acid **11**. These two amino acids were separated by preparative TLC on silica gel using a 2-propanol/ammonia/water (16:3:1) solvent system. The target amino acid (R_f = 0.26) was crystallized from water/methanol to yield 45 mg (44%) of the [$^2H_2$]ACC **11** (ee 46%), which melted at 228–230 °C (lit.[22] mp 229–231 °C for the nondeuteriated analogue): ^1H NMR (D_2O) δ 1.00, 1.15 (d, AB, 2 H, J = 5.35 Hz, CH_2); MS, m/z 104 (MH^+).

(*R*)-1-Amino[2,2-$^2H_2$]cyclopropane-1-carboxylic Acid (13). The title [$^2H_2$]ACC **13** was obtained in a manner similar to that for **11** from 0.41 g (1.5 mmol) of compound **9** (de 44%) by hydrolysis with hydrochloric acid in 45% yield; mp 229–231 °C (water/methanol) (lit.[22] mp 229–231 °C for the nondeuteriated analogue); ^1H NMR (D_2O) δ 0.99, 1.13 (d, AB, 2 H, J = 5.40 Hz, CH_2); MS, m/z 104 (MH^+).

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