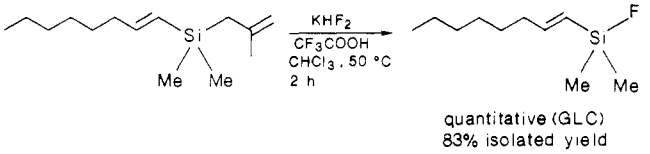
methallyl-Si moiety is deemed to be a protected form of F-Si. An example follows.



quantitative (GLC)
83% isolated yield

In conclusion, the study reported herein has shown that fluorine substituent(s) on the silyl group of alkenylsilanes accelerate the F^--promoted cross-coupling reactions of alkenylsilanes with alkenyl iodide. By choosing the appropriate catalyst and solvent, we could perform a highly stereospecific, chemoselective synthesis of a conjugated polyene system free from any stereoisomers. Thus, the silicon-based cross-coupling reaction may find wide application in the field of total synthesis of natural products. Research in this area is in progress in our laboratories.

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Articles

Synthesis of (1*S*,2*R*)- and (1*S*,2*S*)-1-Amino[2-^{2}H]cyclopropane-1-carboxylic Acids: The Total ^{1}H NMR Assignment of *Cyclo*[ACC-α-methyl-Phe]

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An asymmetric synthesis of stereospecifically monodeuteriated ACC's, (1*S*,2*R*)- and (1*S*,2*S*)-1-amino[2-^{2}H]-cyclopropane-1-carboxylic acids, is described. The reduction of methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate with $^2H_2$ gas in the presence of the asymmetric reduction catalysts, (*R*,*R*)-dipamp and (*S*,*S*)-chiraphos, afforded, after acid hydrolysis, (2*S*,3*R*)-[2,3-$^2H_2$]- and (2*R*,3*S*)-[2,3-$^2H_2$]homoserine lactones, respectively. The chiral synthon bis(lactim ethers) were derived from the chiral auxiliary reagent (*R*)-(+)-2-methyl-3-phenylalanine by coupling with the above dideuteriated homoserine lactones by utilizing standard procedures. The cyclopropane ring systems are formed by treating each bis(lactim ethers) derivative with butyllithium. The stereochemistry of this intramolecular cyclization to form the cyclopropane ring is discussed. The desired cyclopropane derivatives are obtained by successive treatments with first 0.25 N HCl and then heating at reflux with 6 N HCl. The proton NMR assignment has been made for all four diastereotopic hydrogens of ACC when incorporated into the diketopiperazine ring [bis(lactim ethers) derivative] {*cyclo*[ACC-α-methyl-Phe]} as well as in the underivatized parent compound.

Introduction

The various enzymatic steps in the biosynthetic pathway in which *S*-adenosyl-L-methionine (SAM) is converted to ethylene, the plant-ripening hormone, have recently been the subject of investigation in a number of laboratories.[1a-p] Our laboratory has been involved in the investigation of the stereochemistry of the enzymatic reaction in which the PLP-dependent enzyme ACC synthase converts SAM into the immediate biosynthetic precursor of ethylene, 1-aminocyclopropane-1-carboxylic acid (ACC), in the rate-limiting step, the partial results of which have been recently reported by both our group[1m] and the Arigoni group.[1n]

In our approach to answer[2] the final question remaining concerning the stereochemical mechanism of ACC synthase, namely the enzymatic events at the α-amino acid center, it became necessary to determine the chemical shift values of (or differentiate between) all four of the hydrogen

(1) For examples, see the following: (a) Adams, D. O.; Yang, S. F. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 170-174. (b) Boller, T.; Herner, R. C.; Kende, H. *Planta* **1979**, *145*, 293-303. (c) Yu, Y.-B.; Adams, D. O.; Yang, S. F. *Arch. Biochem. Biophys.* **1979**, *198*, 280-286. (d) Adlington, R. M.; Aplin, R. T.; Baldwin, J. E.; Rawlings, B. J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086-1087. (e) Hoffman, N. E.; Yang, S. F.; Ichihara, A.; Sakamura, S. *Plant. Physiol.* **1982**, *70*, 195-199. (f) Adlington, R. M.; Baldwin, J. E.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 290-292. (g) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1983**, *48*, 5143-5144. (h) Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207-7209. (i) Oskouee, S. K.-; Jones, J. P.; Woodard, R. W. *Biochem. Biophys. Res. Commun.* **1984**, *121*, 181-187. (j) Peiser, G. D.; Wang, N. E.; Hoffman, N. E.; Yang, S. F.; Liu, H. W.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3059-3063. (k) Baldwin, J. E.; Adlington, R. M.; Lajore, G. A.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1496-1498. (l) Pirrung, M. C.; McGeehan, G. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1044-1045. (m) Ramalingam, K.; Lee, K.-M.; Woodard, R. W.; Bleecker, A. B.; Kende, H. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7820-7824. (m) Wiesendanger, R.; Martinoni, B.; Boller, T.; Arigoni, D. *Experientia* **1986**, *42*, 207-209. (o) Pirrung, M. C. *Biochemistry* **1986**, *25*, 114-119. (p) Wiesendanger, R.; Martinoni, B.; Boller, T.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1986**, 238-239.

(2) After completion of this synthesis, the Arigoni group published the results from a study involving one regiospecifically dideuteriated SAM analogue, which indicates that the stereochemical event(s) at the α-amino acid center of SAM involve inversion of configuration (or an odd number of inversions), see ref 1p. We have synthesized both [2*S*,3*R*,4*S*,*S*(*S*)]- and [2*S*,3*S*,4*R*,*S*(*S*)]-3,4-$^2H_2$]SAM, incubated with them individually with ACC synthase, measured the ^{1}H NMR of the resulting ACC's, and, based on the chemical shift values obtained from the present work and the information presented in ref 17, have determined the stereochemical outcome of the events at the α-center to involve an inversion of configuration, which is in agreement with their findings.

0022-3263/89/1954-0270$01.50/0

atoms attached to the two prochiral methylene carbons of ACC. The most direct and reliable method for this assignment would be the preparation of ACC's that are stereospecifically labeled with deuterium via routes in which the stereochemistry of each reaction is known with certainty. Methods have been published for the synthesis of [2,2,3,3-$^2H_4$]ACC,[1d,3] (±)-[2,2-$^2H_2$]ACC,[3] *cis*-[2,3-$^2H_2$]-ACC,[1f,h,3] and (±)-*trans*-[2,3-$^2H_2$]ACC.[1f,h,3] These synthetic routes involve either dialkylation of a Schiff-base protected glycine ester[1d,f,h] or dialkylation of ethyl isocyanoacetate with the appropriately deuteriated dibromoethane or 2-bromoethyl tosylate species.[3] The dialkylation of ethyl isocyanoacetate with 1,2-dibromoethane was originally utilized by Schollkopf in the preparation of nonlabeled ACC.[4]

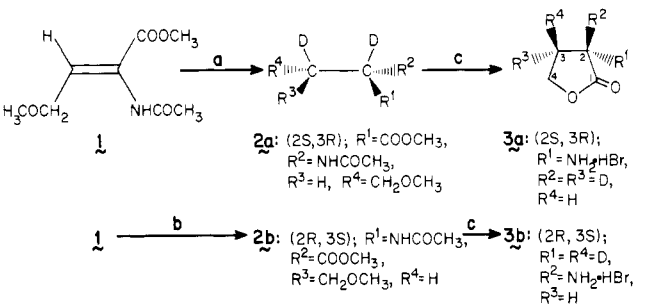
Recently, three elegant syntheses of optically active [2,2-$^2H_2$]ACC have been communicated.[5a,b] However, to date, no methods for the synthesis of the total diastereomeric mixture of monodeuteriated ACC's or either of the enantiomeric pairs have appeared, much less the synthesis of a single optically active stereospecifically monodeuteriated ACC.[6] This paper reports the synthesis of two of the four possible stereospecifically monodeuteriated ACC's (the other two are available via the same methodology) and the ^{1}H-NMR assignment of ACC and its diketopiperazine derivative, *cyclo*-[(*R*)-2-methyl-3-phenylalanyl-1-aminocyclopropane-1-carboxylic acid] bis(lactim methyl ether) {*cyclo*[ACC-α-methyl-Phe]}.

Results and Discussion

The synthesis of (1*S*,2*R*)- and (1*S*,2*S*)-[2-^{2}H]ACC's described in this paper may be divided into three major segments: (a) the synthesis of (2*S*,3*R*)-[2,3-$^2H_2$]- and (2*R*,3*S*)-[2,3-$^2H_2$]homoserine lactones; (b) coupling of the two homoserine lactones to (2*R*)-*N*-Boc-2-methyl-3-phenylalanine hydroxysuccinimide ester followed by cyclization of the deprotected dideuteriated dipeptide lactones to the dideuteriated diketopiperazines and conversion into bis(lactim ether) derivatives; and (c) intramolecular cyclization of the protected dideuteriated diketopiperazines to afford the monodeuteriated spirocyclopropane dilketopiperazine derivatives, which were cleaved to give the target monodeuteriated ACC's.

Previously our laboratory had prepared (2*S*,3*R*)-[3-^{2}H]- and (2*S*,3*S*)-[2,3-$^2H_2$]homoserine lactones from (2*S*,3*R*)-[2,3-^{2}H]- and (2*S*,3*S*)-[2,3-$^2H_2$]aspartic acids.[7] The necessary deuteriated aspartic acids were obtained by the method of Young[8] by incubation of the appropriately *E* dideuteriated ammonium fumarate with the enzyme L-aspartase (commercially available but relatively expensive) in H_2O or by incubation of ammonium fumarate with the enzyme L-aspartase in ^2H_2O. A maximum yield of 40% for the deuteriated aspartic acids was obtained by this enzymatic process. The further elaboration of these aspartic acids to the corresponding deuteriated homoserine lactones required an additional six steps, which proceeded in only 21% overall yield. An alternative synthesis of stereospecifically deuteriated homoserine lactones was therefore sought that would require neither the use of enzyme nor as many steps in their preparation.

Scheme I[a]



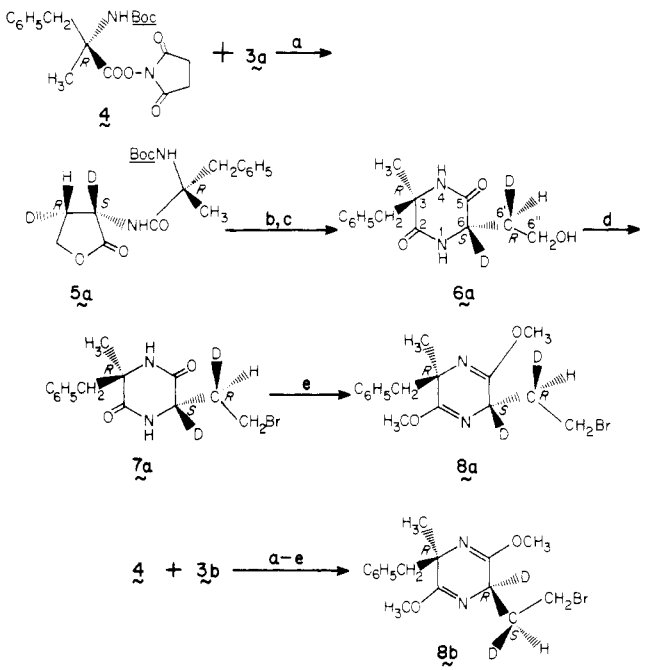
[a] (a) (*R*,*R*)-Dipamp, $^2H_2$(gas), 3 h, 50 psi, 24 °C, 89%; (b) (*S*,*S*)-chiraphos, $^2H_2$ (gas), 3 h, 50 psi, 24 °C, 91% (c) 48% HBr, heat at reflux, 75%.

Recently Scott et al.[9] prepared a number of methyl (*E*)- and (*Z*)-2-acetamido-3-alkylacrylates and reduced them in the presence of a number of chiral asymmetric reduction catalysts and reported the relative enantiomeric purity at the α-amino acid center of the reduction products. Reduction of methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate (1) with either (cycloocta-1,5-diene)[(*R*,*R*)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine]]rhodium tetrafluoroborate [(*R*,*R*)-dipamp] or (bicyclo-[2.2.1]hepta-2,5-diene)[(2*S*,3*S*)-bis(diphenylphosphino)-butane]rhodium perchlorate[(*S*,*S*)-chiraphos], respectively, afforded *N*-acetyl-*O*-methyl-L- or *N*-acetyl-*O*-methyl-D-homoserine methyl esters with enantiomeric purities of 86% *S* and 87% *R* at the α-amino acid center, respectively. Since these hydrogenation catalysts gave protected homoserine derivatives of reasonably high enantiomeric purity, we decided to reduce methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate (1) with $^2H_2$ gas in the presence of either (*R*,*R*)-dipamp or (*S*,*S*)-chiraphos. Since catalytic reductions with H_2 or $^2H_2$ gas proceed by cis addition to the olefin, the resulting asymmetric center produced by addition of a deuterium atom to carbon atom 3 of 1 during reduction should have enantiomeric purity comparable to that of the asymmetric α-amino acid center formed by addition of a deuterium atom to carbon atom 2. Reduction of the acrylate 1 with (*R*,*R*)-dipamp in the presence of $^2H_2$ gas afforded (2*S*,3*R*)-*N*-acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester (**2a**) in 89% yield while reduction of acrylate 1 with (*S*,*S*)-chiraphos in the presence of $^2H_2$ gas produced the enantiomer of **2a**, (2*R*,3*S*)-*N*-acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester (**2b**), in 91% yield (see Scheme I). The protected, dideuteriated homoserine derivatives **2a** and **2b** were heated under reflux with 48% aqueous HBr to afford (2*S*,3*R*)-[2,3-$^2H_2$]homoserine lactone hydrobromide (**3a**) in 95% ee at the amino acid center and (2*R*,3*S*)-[2,3-$^2H_2$]homoserine lactone hydrobromide (**3b**) in 84% ee at the amino acid center in yields of 75%. This methodology represents a significant improvement over the previously published methods[7,8] for the synthesis of homoserine lactones that are stereospecifically labeled with deuterium at carbon atom 3.

With the large-scale preparation of deuteriated homoserine lactones **3a** and **3b** completed, we proceeded to

(3) Ramalingam, K.; Kalvin, D.; Woodard, R. W. *J. Labelled Compd. Radiopharm.* **1984**, *31*, 833–841.
(4) Schollkopf, U.; Harm, R.; Hoppe, D. *Justus Liebigs Ann. Chem.* **1973**, 611–618.
(5) (a) Hill, R. K.; Prakash, S. R.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Liu, H. W.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 795–796. (b) Subramanian, P. K.; Woodard, R. W. *J. Org. Chem.* **1987**, *52*, 15–18.
(6) A reviewer has kindly brought to our attention that Dr. Richard K. Hill's group at the University of Georgia has prepared a monodeuteriated ACC in a stereospecific manner, but to the best of our knowledge this procedure has not been reported in the literature.
(7) Ramalingam, K.; Woodard, R. W. *J. Org. Chem.* **1988**, *53*, 1900–1903.
(8) Young, D. W.; Gani, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2393–2398.
(9) Scott, J. W.; Keith, D. D.; Nix, G., Jr.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D., Jr.; Yang, R. *J. Org. Chem.* **1981**, *46*, 5086–5093.

Scheme II[a]



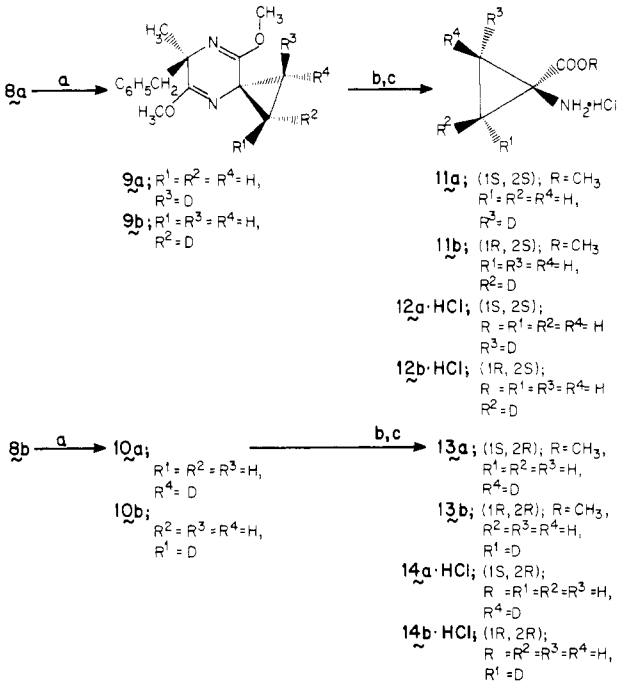
[a] (a) $(C_2H_5)_3N/CH_2Cl_2$, 5 °C; (b) 98% HCO_2H, 24 °C; (c) toluene, heat at reflux; (d) $Ph_3P/Br_2/DMF$, 0 °C; (e) $(CH_3)_3OBF_4/CH_2Cl_2$, 40 °C.

incorporate these lactones into dipeptides with our chiral auxiliary amino acid for conversion into the target diketopiperazines. In a procedure analogous to that used by Kemp and McNamara[10] for the synthesis of L,L-ethyl 3-amino-2-oxopiperidine-6-carboxylate, the lactones **3a** and **3b** were coupled to the hydroxysuccinimide ester[11] of (2*R*)-*N*-Boc-2-methyl-3-phenylalanine (**4**) to give the protected dipeptide lactones **5a** and **5b**, which were intramolecularly cyclized to the diketopiperazines **6a** and **6b**. The diketopiperazines **6a** and **6b** were brominated via $P(phenyl)_3/Br_2$[12] to afford the dideuteriated bromodiketopiperazines **7a** and **7b**, which were then converted to the bis(lactim ethers) **8a** and **8b** (Scheme II).

The synthetic procedure for the formation of the cyclopropane ring from the protected diketopiperazines **8a** and **8b** is comparable to the intermolecular alkylation methodology, which Schollkopf[13] has employed in the enantioselective synthesis of a variety of α-branched amino acids and which our laboratory has recently utilized for the synthesis of stereospecifically dideuteriated ACC.[5b] The bis(lactim ethers) **8a** and **8b** were treated with *n*-BuLi at −78 °C to effect an intramolecular cyclization to yield predominantly the bis(lactim ether) cyclopropane diketopiperazines **9a** and **10a**, respectively [**9a**/**9b** = **10a**/**10b** = 3/1].[5b,14]

Several unsuccessful attempts were made to separate the diastereomers **9a** and **10a** from their minor contaminant isomers **9b** and **10b** by semipreparative HPLC (RP-C18 column).

Scheme III[a]



[a] (a) BuLi/THF, −78 °C; (b) 0.25 N HCl, 24 °C; (c) 6 N HCl heat at reflux.

The configuration of the newly formed center of chirality at C-6 in **9a** was derived from high-field ^1H NMR spectra. Bose et al.[15] have demonstrated that cyclic dipeptides containing aromatic amino acid residues adopt a boat shape for the heterocyclic ring and the "folded conformation" for the aromatic side chain. Our group and others have reported[5a,b,16] that the four diastereotopic hydrogen atoms of ACC, when incorporated into a diketopiperazine ring, appear as eight-line multiplets (AA'BB') at δ 0.13, 0.50, 0.70, and 1.13 with equal intensity in the ^1H NMR spectrum. The signals at δ 0.13 and 0.50 were assigned[5a,b,16] to hydrogen atoms (located within the shielding cone of the aromatic ring) attached to the *pro-R* methylene carbon and δ 0.70 and 1.13 to hydrogen atoms attached to the *pro-S* methylene carbon. The crucial task of assigning individual resonances remained unsolved.

The ^1H NMR spectrum of the product isolated from the cyclization step **8a** → **9a** shows signals at δ 0.17, 0.56, 0.71, and 1.20 as multiplets with intensity ratios 0.8:1.0:0.95:0.3, which suggest that intramolecular cis addition[5b] has occurred in that step to induce a new chiral center at C-6 to give **9a** contaminated with **9b** [**9a**/**9b** (*S*/*R* at C-6) = 3/1] and that the signal (least intensity) at δ 1.20 could be assigned to the *pro-S* hydrogen (R3 in **9b**) and hence δ 0.71 to the *pro-R* hydrogen (R4 in **9a** and **9b**) attached to the *pro-S* methylene carbon. From the intensity ratios, it is not unreasonable to assign the signal (higher intensity) at δ 0.56 to the *pro-R* hydrogen (R1 in **9a** and **9b**) and hence δ 0.17 to the *pro-S* hydrogen (R2 in **9a**) attached to the *pro-R* methylene carbon.

The assignments made above were further confirmed from the ^1H NMR spectra of the reaction product mixture **10a** and **10b** [**10a**/**10b** (*S*/*R* at C-6) = 3/1] from step **8b** → **10a** in which the ACC protons appeared at the same positions as above except with the intensity ratios 1.0:0.8:0.3:0.95. Alternatively, the 6*R* diastereomers **9b** and

(10) Kemp, D. S.; McNamara, P. E. *J. Org. Chem.* **1984**, *49*, 2286–2288.
(11) The hydroxysuccinimide ester of *N*-Boc-α-methyl-(*R*)-phenylalanine was prepared by the method of Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839–1845.
(12) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964–965.
(13) For a review of this methodology, see: Schollkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091 and references contained therein.
(14) The configuration at C-6′ is reversed during the cyclization step **8a** to **9a** and **8b** to **10a** when the order of priority of groups attached to it changes.
(15) Bose, A. K.; Manhas, M. S.; Tavares, R. F.; Van der Veen, J. M.; Fujiwara, H. *Heterocycles* **1977**, *7*, 1227–1270.
(16) Woodard, R. W. *J. Org. Chem.* **1985**, *50*, 4796–4799.

10b may be obtained as the major isomers, if the syntheses were started from (2*S*)-2-methyl-3-phenylalanine as chiral auxiliary reagent. The other two isomers, however, were not synthesized since the assignment had been firmly established with the two isomers presently prepared.

In order to complete the synthesis, the bis(lactim ethers) **9a** and **10a** (50% de at C-6) were hydrolyzed with 0.25 N hydrochloric acid at room temperature to afford (2*R*)-2-methyl-3-phenylalanine methyl ester hydrochloride and (1*S*,2*S*)- or (1*S*,2*R*)-1-amino[2-^{2}H]cyclopropane-1-carboxylic acid methyl ester hydrochloride (**11a** and **11b** or **13a** and **13b**), respectively. The methyl esters were further hydrolyzed, by heating them to reflux in 6 N HCl, to the corresponding amino acids. The target (1*S*,2*S*)- and (1*S*,2*R*)-1-amino[2-^{2}H]cyclopropane-1-carboxylic acids (**12a** and **14a**, 50% de at C-1) were separated by preparative thin-layer chromatography from the chiral auxiliary reagent (2*R*)-2-methyl-3-phenylalanine, which could be recycled.

The mixture of monodeuteriated ACC's (**12a** and **12b**) displays two multiplets centered at δ 1.04 and 1.18 with an intensity ratio 3:2 whereas the nondeuteriated ACC hydrogen atoms resonate essentially at the same chemical shift but as multiplets of equal intensities. This implies that the two diastereotopic hydrogen atoms cis to the carboxylate function of ACC appear downfield relative to the other two diastereotopic hydrogen atoms trans to the carboxylate function, which is in agreement with our earlier observations.[17] This assignment is further substantiated from the ^{1}H NMR spectrum of the mixture **14a** and **14b**, which shows the two multiplets with an intensity ratio 2:3.

The use of an aromatic α-methyl amino acid, as the chiral auxiliary agent in this synthesis, was essential since our research group[5b,16] as well as other groups[5a] have demonstrated that the spatial orientation of this aromatic ring causes significant changes in the chemical shifts of the cyclopropane methylene protons when ACC is incorporated into a diketopiperazine, which is prepared from an aromatic α-amino acid. The cyclopropane methylene protons that are cis to the aromatic ring are shifted upfield relative to the cyclopropane methylene protons, which are trans to the aromatic ring. Therefore this particular diketopiperazine ring system is not only useful as a chiral synthon but also serves the dual role of being an important handle for the determination of the enantiomeric purity of the deuteriated ACC product. (In this particular case the diastereomeric purity of the bis(lactim ether) synthetic intermediate is being assessed.) Another important aspect of the synthesis described here is that bromination of the deuteriated homoserine diketopiperazines and subsequent intramolecular cyclization of the protected deuteriated bromo diketopiperazines via attack at the brominated center to afford the deuteriated ACC's do not involve reactions that affect either the deuterium label or the chirality of the deuteriated C-3 center of the homoserine portion of the diketopiperazine. Therefore it is not critical for the bromination to be stereospecific (as it would had the deuteriation been at the C-4 center of the homoserine portion) nor is it critical whether the intramolecular displacement reaction occurs with inversion or retention of configuration at the C-4 position. Furthermore, the stereochemistry at the carbon 2 of the starting homoserine lactones **3a** and **3b** and whether there is an H or D at that center does not matter since both the label and stereochemistry are lost during the reaction with butyllithium, which removes the hydrogen at the C-2 center. The stereochemistry at the α-methyl amino acid center is, however, critical in dictating the stereochemistry at the amino acid center of ACC.

(17) Subramanian, P. K.; Ramalingam, K.; Norton, S.; Woodard, R. W. *Spectrosc. Lett.* **1986**, *19*, 1059–1069.

Conclusion

The synthesis described represents the first report of the preparation of ACC's that are stereospecifically labeled with one deuterium atom on a single cyclopropane methylene. The synthesis does not require enzymes for the introduction of asymmetry on the C-3 carbon of homoserine, nor does it require a multistep synthesis from specifically deuteriated aspartic acids. The starting material acrylate **1**, is readily available.[9] Application of the Schollkopf methodology[13] to the preparation of the bis(lactim ether) diketopiperazines **9a** and **10a** led to deuteriated ACC's of relatively high enantiomeric purity. These purities are readily determined from the high-field ^{1}H NMR spectra of the protected deuteriated diketopiperazines **9a** and **10a** due to the dramatic changes in the chemical shifts of the cyclopropane ring protons caused by their differences in spatial orientation relative to the aromatic ring, which is located above the 2,5-diketopiperazine ring structure. The compounds available from the present synthesis also make it possible to assign unequivocally the resonances of all four diastereotopic hydrogen atoms in the ^{1}H NMR spectrum of ACC when incorporated into a diketopiperazine ring system containing an aromatic amino acid of known absolute configuration.

Experimental Section

All melting points are uncorrected. All literature melting points are for the nondeuteriated compounds. ^{1}H NMR spectra were recorded at 60, 270, or 360 MHz in $CDCl_3$, Me_2SO-d_6, and D_2O. Samples dissolved in D_2O were reported in ppm downfield from sodium 3-(trimethylsilyl)propanate.

Inorganic and organic reagents were purchased from the usual chemical sources and were used without further purification. Tetrahydrofuran was predried over calcium hydride and distilled from lithium aluminum hydride under a nitrogen atmosphere with triphenylmethane as indicator. Dichloromethane was distilled from phosphorus pentoxide and stored under nitrogen atmosphere over 4A molecular sieves. Methanol was heated to reflux over magnesium metal turnings, which were activated with iodine crystals; the dried methanol was finally distilled from a magnesium methoxide slurry. Anhydrous methanol was purified further for asymmetric deuterogenation reactions by shaking under 40 psi of deuterium gas with Raney nickel catalyst for 8 h at room temperature, filtration of the catalyst, and finally redistillation. The methanol was stored under a nitrogen atmosphere and thoroughly degassed for 15–20 min with prepurified nitrogen prior to its use as a solvent in all asymmetric deuteriogenation reactions. All other organic solvents were of reagent grade and were used without further purification.

The asymmetric hydrogenation catalysts used in this study: (cycloocta-1,5-diene)[(*R*,*R*)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine]]rhodium tetrafluoroborate [(*R*,*R*)-dipamp] and (bicyclo[2.2.1]hepta-2,5-diene)[(2*S*,3*S*)-bis[(diphenylphosphino)butane]]rhodium perchlorate [(*S*,*S*)-chiraphos] were prepared by the methods of Vineyard et al.[18] and Fryzuk et al.[19] The catalysts were stored dessicated under an inert atmosphere or in vacuo. The reagents used in the preparation of the catalysts were purchased from Strem Chemicals Inc. and from Aldrich Chemical Co. Deuterium gas (20-L lecture bottle) was purchased from Matheson, Inc.

(*R*,*R*)-1,2-Ethanedioylbis[(*o*-methoxyphenyl)phenylphosphine] was kindly donated by Dr. William S. Knowles of Monsanto

(18) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952.

(19) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262–6267.

Chemical Co. while methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate (1) was kindly donated by Dr. John W. Scott of Hoffman-LaRoche, Inc. The asymmetric deuteriogenation reactions were performed on a Parr hydrogenation apparatus at ambient temperature under 50 psi of $^2H_2$ (gas) in a manner analogous to that described by Scott et al.[9] (*R*)-α-Methylphenylalanine was prepared by the recently published method of Subramanian et al.[20]

Solvents were evaporated in vacuo with a rotary evaporator (water aspirator vacuum) at 40–90 °C unless stated otherwise. Medium-grade silica gel (Merck 70–230 mesh) was used for column chromatography. R_f values of purified compounds were recorded from TLC plates (silica Analtech), which were visualized by ultraviolet irradiation from a Mineralight short-wave UV lamp, iodine chamber visualization, or by spraying with an ethanolic solution of ninhydrin.

(2*S*,3*R*)-*N*-Acetyl-*O*-methyl[2,3-$^2H_2$]homoserine Methyl Ester (2a). A Parr hydrogenation bottle was charged with 7.00 g (37.4 mmol) of methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate (1) and 6.0 mL of dry, degassed methanol. To the solution was added 0.283 g (3.74×10^{-4} mol) of (*R*,*R*)-dipamp catalyst. After addition of the catalyst, the contents of the hydrogenation bottle were degassed for several additional minutes with prepurified nitrogen. The bottle was connected to a Parr hydrogenation apparatus, which was fitted with a lecture bottle (20 L) of deuterium gas. The hydrogenation bottle was evacuated (water aspirator vacuum), charged to approximately 15 psi with deuterium gas, and evacuated. The Parr bottle was again charged with deuterium gas and evacuated. Finally, the Parr bottle was charged with deuterium gas to a pressure of 50 psi and shaken for 3 h at room temperature at 50 psi. The reaction mixture was diluted with methanol and evaporated onto 10 g of silica gel. The silica gel containing the preabsorbed product **2a** was placed onto a chromatography column (2 × 45 cm) containing 60 g of silica gel. The column was eluted with 2:1 ethyl acetate/hexane. Column fractions (2 and 3, 150 mL each) that contained (2*S*,3*R*)-*N*-acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester **2a** [as determined by TLC (1:1 ethyl acetate/hexane)] were combined and evaporated, and the residue was placed under high vacuum at room temperature. The residue slowly solidified to afford 6.34 g (89% yield) of a white, crystalline solid. The solid was recrystallized from anhydrous ether at −20 °C, mp 52–54 °C (lit.[9] mp 62.5–64.5 °C for nondeuteriated compound), R_f (0.20) ethyl acetate/hexane (2:1). Repeated recrystallizations of the product from ether at −20 °C failed to raise the melting point to that of the reported value[9] for the nondeuteriated compound: IR (KBr) 3300, 3100–2800, 1750, 1665, 1535, 1440, 1380, 1270, 1200, 1160, 1100 cm^{-1}; IR ($CHCl_3$)[9] 3430, 1745, 1675, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s and m, 4 H, $NHCOCH_3$ and 3-$C^2H_RH_S$), 3.36 (s, 3 H, OCH_3), 3.52 (d, 2 H, J = 6 Hz, 4-CH_2OCH_3), 3.76 (s, 3 H, $COOCH_3$), 6.75 (br s, 1 H, $NHCOCH_3$).

(2*R*,3*S*)-*N*-Acetyl-*O*-methyl[2,3-$^2H_2$]homoserine Methyl Ester (2b). In a manner analogous to that described for the preparation of (2*S*,3*R*)-*N*-acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester (**2a**), 3.33 g (0.0178 mol) of methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate (1) was reduced with 0.128 g (1.78×10^{-4} mol) of (*S*,*S*)-chiraphos in the presence of deuterium gas (50 psi, 3 h, room temperature) to afford 3.03 g (91% yield) of (2*R*,3*S*)-*N*-acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester (**2b**): mp 52–54 °C (lit.[9] mp 62.5–64.5 °C for nondeuteriated compound); R_f (0.20) ethyl acetate/hexane (2:1); IR (KBr) 3300, 3100–2800, 1750, 1665, 1535, 1440, 1380, 1270, 1200, 1160, 1100 cm^{-1}; IR ($CHCl_3$)[9] 3430, 1745, 1675, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s and m, 4 H, $NHCOCH_3$ and 3-$C^2H_SH_R$), 3.36 (s, 3 H, OCH_3), 3.52 (d, 2 H, J = 6 Hz, 4-CH_2OCH_3), 3.76 (s, 3 H, $COOCH_3$), 6.74 (br s, 1 H, $NHCOCH_3$).

(2*S*,3*R*)-[2,3-$^2H_2$]Homoserine Lactone Hydrobromide (3a). (2*S*,3*R*)-*N*-Acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester (**2a**) (1.0 g, 5.2 mmol) was dissolved in 5.0 mL of 48% aqueous HBr and heated to reflux with stirring for 16 h. The aqueous HBr was removed in vacuo. The residue was resuspended in absolute ethanol (5 × 20 mL), and the absolute ethanol was evaporated each time. The semicrystalline residue was placed under high vacuum, resuspended in acetone, collected, and air-dried. The solid was recrystallized from the minimal amount of absolute ethanol to afford 0.72 g (74.8%) of (2*S*,3*R*)-[2,3-$^2H_2$]homoserine lactone hydrobromide (**3a**) as a white, crystalline solid: mp 245–248 °C (lit.[21] mp 242–244 °C for the nondeuteriated compound); R_f (0.53), 1-propanol/water (9:5); $[\alpha]^{25}_D$ −19.9° (c = 1.02, H_2O) [lit.[21] value for L-homoserine lactone hydrobromide $[\alpha]^{27}_D$ −21.0° (c = 1.0, H_2O)]; ^1H NMR (^2H_2O) δ 2.61 (d, 1 H, J = 5.6 Hz, 3-$C^2H_RH_S$), 4.27 and 4.44 (t and d, 2 H, J = 7.5 Hz and J = 9.2 Hz, 4-CH_2).

(2*R*,3*S*)-[2,3-$^2H_2$]Homoserine Lactone Hydrobromide (3b). In an analogous manner for the preparation of homoserine lactone hydrobromide (**3a**), (2*R*,3*S*)-*N*-acetyl-*O*-methyl[2,3-$^2H_2$]homoserine methyl ester (**2b**) (1.0 g, 5.2 mmol) was reacted with 5.0 mL of 48% aqueous HBr to afford 0.70 g (72.7%) of 2*R*,3*S*)-[2,3-$^2H_2$]homoserine lactone hydrobromide (**3b**): mp 245–248 °C (lit.[21] mp 242–244 °C for the nondeuteriated compound); R_f (0.53), 1-propanol/water (9:5); $[\alpha]^{25}_D$ +17.7° (c = 0.982, H_2O) [lit.[21] value for D-homoserine lactone hydrobromide $[\alpha]^{27}_D$ +21.0° (c = 1.0, H_2O)]; ^1H NMR (270 MHz, ^2H_2O) δ 2.61 (d, 1 H, J = 4.8 Hz, 3-$C^2H_SH_R$), 4.27 and 4.44 (t and d, 2 H, J = 8.0 Hz and J = 9.4 Hz, 4-CH_2).

(2*R*)-(−)-*N*-[(1,1-Dimethylethyl)oxycarbonyl]-2-methyl-3-phenylalanine. A mixture of (*R*)-(+)-2-methyl-3-phenylalanine (5.38 g, 30 mmol) and sodium carbonate (6.36 g, 60.0 mmol) was dissolved in dioxane/water (1:2, 150 mL), and the solution was cooled to 5 °C. Di-*tert*-butyl dicarbonate (6.55 g, 30.0 mmol) was added, and the resulting mixture was stirred at 5 °C for 3 h and at room temperature overnight. After removing the dioxane under reduced pressure, the solution was extracted with ethyl acetate (2 × 25 mL). The aqueous layer was acidified with an aqueous $KHSO_4$ solution to pH 2–3 and then extracted with ethyl acetate (3 × 50 mL). The organic extract was dried (Na_2SO_4), and the solvent was removed under vacuum to yield the crude product as a white foam, which was purified by gravity column chromatography, eluting with hexane/ethyl acetate (3:2): yield 5.6 g (66.8%); $[\alpha]^{27}_D$ −19.0° (c = 1.4, C_2H_5OH); ^1H NMR (Me_2SO-d_6) δ 1.20 (s, 3 H, CH_3), 1.41 (s, 9 H, $C(CH_3)_3$), 2.94, 3.48 (AB, d, J = 13.26 Hz, 2 H, $C_6H_5CH_2$), 6.63 (s, 1 H, NH), 7.08–7.26 (m, 5 H, C_6H_5). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58. Found: C, 64.65; H, 7.50.

(2*R*)-(+)-*N*-[(1,1-Dimethylethyl)oxycarbonyl]-2-methyl-3-phenylalanine *N*-Hydroxysuccinimide Ester (4). To a stirred solution of (2*R*)-*N*-*t*-Boc-2-methyl-3-phenylalanine (5.60 g, 20 mmol) and *N*-hydroxysuccinimide (2.30 g, 20 mmol) in dry 1,2-dimethoxyethane (100 mL) at 0 °C was added 1,3-dicyclohexylcarbodiimide (4.54 g, 22 mmol), and stirring was continued at 0 °C for 4 h and at room temperature for 8 h. The precipitated urea derivative was filtered off and washed with dry ether (25 mL). The filtrates were combined and dried ($MgSO_4$), and the solvent removed in vacuo. The resulting colorless solid was recrystallized from 2-propanol to give 6.5 g (86.3%) of pure *N*-hydroxysuccinimide ester **4**: mp 174–176 °C; $[\alpha]^{27}_D$ +78.1° (c = 0.82, C_2H_5OH); ^1H NMR (Me_2SO-d_6) δ 1.32 (s, 3 H, CH_3), 1.45 (s, 9 H, $C(CH_3)_3$), 2.81 (s, 4 H, CH_2CH_2), 2.95, 3.57 (AB, d, J = 13.21 Hz, 2 H, $C_6H_5CH_2$), 7.17–7.34 (m, 5 H, C_6H_5), 7.36 (s, 1 H, NH). Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.62; H, 6.43. Found: C, 60.64; H, 6.39.

(*R*)-*N*-[(1,1-Dimethylethyl)oxycarbonyl]-2-methyl-3-phenylalanyl-(2*S*,3*R*)-[2,3-$^2H_2$]-2-amino-4-butyrolactone (5a). To a stirred ice-cold suspension of (2*S*,3*R*)-[2,3-$^2H_2$]-2-amino-4-butyrolactone hydrobromide (**3a**) (0.74 g, 4.0 mmol) in dry dichloromethane (30 mL) was added triethylamine (0.40 g, 4.0 mmol) followed by the *N*-hydroxysuccinimide ester (1.51 g, 4.0 mmol). The reaction mixture was stirred at 5 °C for 8 h and at room temperature for 48 h. It was then washed with water (2 × 10 mL) and dried ($CaCl_2$), and the solvent was removed under vacuum. The crude product was recrystallized from ethyl acetate–hexane to yield 1.0 g (68.2%) of **5a**: mp 201–203 °C; ^1H NMR (Me_2SO-d_6) δ 1.21 (s, 3 H, CH_3), 1.41 (s, 9 H, $C(CH_3)_3$), 2.30 (d, J = 5.32 Hz, 1 H, $C^2H_RH_SCH_2$), 2.98, 3.23 (AB, d, J = 13.55 Hz, 2 H, $C_6H_5CH_2$), 4.21, 4.34 (t, J = 7.67 Hz, 1 H, dd, J = 1.69 Hz, 8.40 Hz, 1 H, C^2HHCH_2), 6.63 (s, 1 H, $(CH_3)_3COCONH$), 7.11–7.28 (m, 5 H,

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C_6H_5), 8.30 (s, 1 H, CONHC^{2}H). Anal. Calcd for $C_{19}H_{24}D_2N_2O_5$: C, 62.96; H, 7.23. Found: C, 62.72; H, 7.32.

(*R*)-*N*-[(1,1-Dimethylethyl)oxycarbonyl]-2-methyl-3-phenylalanyl-(2*R*,3*S*)-[2,3-$^2H_2$]-2-amino-4-butyrolactone (5b). (2*R*,3*S*)-[2,3-$^2H_2$]-2-amino-4-butyrolactone hydrobromide (**3b**) (0.55 g, 3.0 mmol) was suspended in dry dichloromethane (25 mL) at 5 °C, and triethylamine (0.30 g, 3.0 mmol) and (*R*)-*N*-*t*-Boc-2-methyl-3-phenylalanine *N*-hydroxysuccinimide ester (**4**) (1.13 g, 3.0 mmol) were added. After the reaction mixture was stirred at 5 °C for 8 h and at room temperature for 48 h, it was worked up as described for **5a**, yielding 0.8 g (73.5%) of **5b**: mp 200–202 °C (ethyl acetate–hexane); ^{1}H NMR (Me_2SO-d_6) δ 1.22 (s, 3 H, CH_3), 1.42 (s, 9 H, C(CH_3)$_3$), 2.31 (dd, J = 1.63 Hz, 6.30 Hz, 1 H, C^{2}H$_S$H$_R$CH$_2$), 3.05, 3.26 (AB, d, J = 13.54 Hz, 2 H, $C_6H_5CH_2$), 4.20, 4.31 (dd, J = 6.57 Hz, 8.59 Hz, 1 H, dd, J = 1.78 Hz, 8.68 Hz, 1 H, CH^{2}HCH_2), 6.57 (s, 1 H, (CH$_3$)$_3$COCONH), 7.11–7.28 (m, 5 H, C_6H_5), 8.32 (s, 1 H, CONHC^{2}H). Anal. Calcd for $C_{19}H_{24}D_2N_2O_5$: C, 62.96; H, 7.23. Found: C, 63.14; H, 7.40.

(3*R*,6*S*)-3-Benzyl-3-methyl-6-deuterio-6-[(1*R*)-2-hydroxy[1-^{2}H]ethyl]piperazine-2,5-dione (6a). The N-protected dipeptide **5a** (0.91 g, 2.5 mmol) was dissolved in formic acid (98%, 10 mL), and the solution was stirred for 2 h at room temperature. After the excess acid was removed under reduced pressure (bath <30 °C), the residue was triturated with anhydrous ether (3 × 20 mL). The precipitated formate salt was taken up in toluene (25 mL) and stirred vigorously under reflux for 6 h. The resulting mixture was then cooled to 0 °C and filtered, and the residue was recrystallized from methanol to yield 0.46 g (69.7%) of pure piperazine-2,5-dione **6a**: mp 274–276 °C; IR (KBr) 1675 (NHC=O), 3645 cm^{-1} (O—H); ^{1}H NMR (Me_2SO-d_6) δ 1.41 (s, 3 H, CH_3), 1.56 (t, J = 6.62 Hz, 1 H, C^{2}H$_R$H$_S$CH$_2$), 2.67, 3.08 (AB, d, J = 12.95 Hz, 2 H, $C_6H_5CH_2$), 3.30–3.36 (m, 2 H, CH^{2}HCH_2), 4.49 (t, J = 4.96 Hz, 1 H, OH), 7.12–7.25 (m, 5 H, C_6H_5), 7.76 (s, 1 H, NH), 8.21 (s, 1 H, NH). Anal. Calcd for $C_{14}H_{16}D_2N_2O_3$: C, 64.10; H, 6.92. Found: C, 63.99; H, 6.87.

(3*R*,6*R*)-3-Benzyl-3-methyl-6-deuterio-6-[(1*S*)-2-hydroxy[1-^{2}H]ethyl]piperazine-2,5-dione (6b). Via the above procedure, the dipeptide **5b** (0.73 g, 2.0 mmol) was deprotected with 98% formic acid, and the formate salt was cyclized in toluene (20 mL). The crude product was crystallized from methanol to give 0.36 g of **6b** (68.0%) as white needles: mp 273–275 °C; IR (KBr) 1675 (NHC=O), 3650 cm^{-1} (O—H); ^{1}H NMR (Me_2SO-d_6) δ 0.39 (t, J = 5.79 Hz, 1 H, C^{2}H$_S$H$_R$CH$_2$), 1.44 (s, 3 H, CH_3), 2.63, 3.11 (AB, d, J = 13.07 Hz, 2 H, $C_6H_5CH_2$), 3.06 (m, 2 H, CH^{2}HCH_2), 4.28 (t, J = 5.27 Hz, 1 H, OH), 7.10–7.27 (m, 5 H, C_6H_5), 7.74 (s, 1 H, NH), 8.21 (s, 1 H, NH). Anal. Calcd for $C_{14}H_{16}D_2N_2O_3$: C, 64.10; H, 6.92. Found: C, 64.18; H, 6.82.

(3*R*,6*S*)-3-Benzyl-3-methyl-6-deuterio-6-[(1*R*)-2-bromo-[1-^{2}H]ethyl]piperazine-2,5-dione (7a). A mixture of cyclic dipeptide **6a** (0.53 g, 2.0 mmol) and dry triphenylphosphine (0.58 g, 2.2 mmol) was dissolved in dry *N*,*N*-dimethylformamide (10 mL) at room temperature and then cooled to 0 °C. A solution of bromine (0.35 g, 2.2 mmol) in dry DMF (5 mL) was added dropwise over a period of 15 min, and the resultant mixture was stirred at 0 °C for 0.5 h and at 10 °C for an additional period of 8 h. The solvent was removed under reduced pressure, and the residue was rubbed with ether (3 × 20 mL) to give a sticky solid material that was recrystallized from chloroform to yield **7a** (0.55 g, 83.8%), which melted at 263–265 °C: IR (KBr) 1675 cm^{-1} (NHC=O); ^{1}H NMR (Me_2SO-d_6) δ 1.42 (s, 3 H, CH_3), 1.93 (dd, J = 7.81 Hz, 5.89 Hz, 1 H, C^{2}H$_R$H$_S$CH$_2$), 2.68, 3.07 (AB, d, J = 12.97 Hz, 2 H, $C_6H_5CH_2$), 3.35–3.46 (m, 2 H, CH$_2$HCH_2), 7.12–7.28 (m, 5 H, C_6H_5), 7.99 (s, 1 H, NH), 8.34 (s, 1 H, NH); MS, m/e 326 (M − 1)$^+$, 328 (M + 1)$^+$.

(3*R*,6*R*)-3-Benzyl-3-methyl-6-deuterio-6-[(1*S*)-2-bromo-[1-^{2}H]ethyl]piperazine-2,5-dione (7b). The cyclic dipeptide **6b** (0.40 g, 1.5 mmol) was treated with bromine (0.26 g, 1.6 mmol) and triphenylphosphine (0.43 g, 1.6 mmol) in DMF as described for **7a**, and the bromo derivative was purified by recrystallization from methanol/chloroform to afford 0.40 g of **7b** (80.8%), which melted at 260–262 °C: IR (KBr) 1675 cm^{-1} (NHC=O); ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, J = 7.37 Hz, 1 H, C^{2}H$_S$H$_R$CH$_2$), 1.46 (s, 3 H, CH_3), 2.64, 3.12 (AB, d, J = 12.92 Hz, 2 H, $C_6H_5CH_2$), 2.82 (d, J = 7.8 Hz, 2 H, CH^{2}HCH_2), 7.11–7.30 (m, 5 H, C_6H_5), 8.03 (s, 1 H, NH), 8.38 (s, 1 H, NH); MS, m/e 326 (M − 1)$^+$, 328 (M + 1)$^+$.

(3*R*,6*S*)-2,5-Dimethoxy-3-benzyl-3-methyl-6-deuterio-6-[(1*R*)-2-bromo[1-^{2}H]ethyl]-3,6-dihydropyrazine (8a). A mixture of 2,5-diketopiperazine **7a** (0.50 g, 1.5 mmol) and trimethyloxonium tetrafluoroborate (0.74 g, 5.0 mmol) in dry dichloromethane (25 mL) was vigorously stirred at 40 °C for 72 h. The resulting solution was then basified with aqueous potassium carbonate solution, and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (2 × 20 mL), the combined organic extracts were dried ($CaCl_2$), the solvent was removed, and the residual liquid was purified by gravity column, eluting with hexane/ethyl acetate (9:1): yield 0.42 g (77.4%), >95% pure as judged by NMR; IR (film) 1694 cm^{-1} (C=N); ^{1}H NMR (Me_2SO-d_6) δ 1.42 (s, 3 H, CH_3), 1.78 (t, J = 6.60 Hz, 1 H, C^{2}H$_R$H$_S$CH$_2$), 2.72, 3.05 (AB, d, J = 12.73 Hz, 2 H, $C_6H_5CH_2$), 3.34–3.45 (m, 2 H, CH^{2}HCH_2), 3.62 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 6.95–7.21 (m, 5 H, C_6H_5); MS, m/e 354 (M − 1)$^+$, 356 (M + 1)$^+$.

(3*R*,6*R*)-2,5-Dimethoxy-3-benzyl-3-methyl-6-deuterio-6-[(1*S*)-2-bromo[1-^{2}H]ethyl]-3,6-dihydropyrazine (8b). The compound was prepared in the same manner as **8a** from compound **7b** (0.33 g, 1.0 mmol) and trimethyloxonium tetrafluoroborate (0.44 g, 3.0 mmol): yield 0.28 g (78.1%) of **8b** as a colorless liquid, >95% pure as judged by NMR; IR (film) 1694 cm^{-1} (C=N); ^{1}H NMR (Me_2SO-d_6) δ 1.18 (t, J = 7.00 Hz, 1 H, C^{2}H$_S$H$_R$CH$_2$), 1.42 (s, 3 H, CH_3), 2.70, 3.11 (AB, d, J = 12.72 Hz, 2 H, $C_6H_5CH_2$), 2.94 (m, 2 H, CH^{2}HCH_2), 3.63 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 6.93–7.24 (m, 5 H, C_6H_5); MS m/e 354 (M − 1)$^+$, 356 (M + 1)$^+$.

***cyclo*-[(*R*)-2-Methyl-3-phenylalanyl-(1*S*,2*S*)-1-amino[2-^{2}H]cyclopropane-1-carboxylic acid] Bis(lactim methyl ether) (9a).** To a stirred solution of compound **8a** (0.18 g, 0.51 mmol) in dry THF (2 mL) at −78 °C was added a precooled solution of 1.65 N butyllithium (0.34 mL, 0.56 mmol) in hexane by syringe, and stirring was continued for 12 h at −78 °C. The solvent was removed at 40 °C (bath)/14 Torr with a rotary evaporator, and the residual crude product was shaken with phosphate buffer solution (pH 7; 5 mL). The aqueous phase was extracted with ether (2 × 10 mL), the ether extract was dried ($MgSO_4$), the solvent was removed in vacuo, and the residual product was purified by gravity column chromatography, eluting with hexane/ethyl acetate (95:5) to yield 0.1 g (72.0%) of **9a** (de at C-6 50%) of **9a** and **9b** (3:1) as a colorless liquid, >97% pure as judged by NMR: IR (film) 1695 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 0.17 (dd, J = 4.17 Hz, 9.79 Hz, 1 H, 6″-H$_R$H$_S$), 0.56 (m, 1 H, 6″-H$_R$H$_S$), 0.71 (m, 1 H, 6′-H$_R$), 1.52 (s, 3 H, CH_3), 2.78, 3.11 (AB, d, J = 12.81 Hz, 2 H, $C_6H_5CH_2$), 3.62 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 6.99–7.19 (m, 5 H, C_6H_5).

***cyclo*-[(*R*)-2-Methyl-3-phenylalanyl-(1*S*,2*R*)-1-amino[2-^{2}H]cyclopropane-1-carboxylic acid] Bis(lactim methyl ether) (10a).** By the above procedure, compound **8b** (0.3 g, 0.8 mmol) was cyclized with butyllithium (1.65 N, 0.5 mL, 0.84 mmol) in dry THF at −78 °C to give 0.15 g (65%) of bis(lactim ether) **10a** (de at C-6 50%) or **10a** and **10b** (3:1) as a colorless liquid, >97% pure as judged by NMR: IR (film) 1695 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 0.17 (m, 1 H, 6″-H$_R$H$_S$), 0.56 (dd, J = 4.26 Hz, 9.87 Hz, 1 H, 6″-H$_R$H$_S$), 1.20 (m, 1 H, 6′-H$_S$), 1.52 (s, 3 H, CH_3), 2.78, 3.11 (AB, d, J = 12.80 Hz, 2 H, $C_6H_5CH_2$), 3.62 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 6.98–7.20 (m, 5 H, C_6H_5).

(1*S*,2*S*)-1-Amino[2-^{2}H]cyclopropane-1-carboxylic Acid (12a). A mixture of compound **9a** (de at C-6 50%) (0.1 g, 0.37 mmol) and 0.25 N hydrochloric acid (6 mL, 1.5 mmol) was stirred at room temperature for 72 h and extracted with ether (2 × 10 mL), the ether extract was discharged, and the aqueous phase was evaporated in vacuo. The residual products, (**11a**·HCl) and (2*R*)-2-methyl-Phe-OCH$_3$·HCl, were refluxed in 6 N hydrochloric acid (5 mL) for 1 h. After the mixture was cooled to room temperature, 10 mL of water was added, and the entire solution was absorbed onto a column of Dowex 50W-x 8 (H^+ form) cation exchange resin. The column was eluted with water to neutrality followed by 1 N NH_4OH (50 mL). Concentration of the ninhydrin positive fractions of the eluate yielded a mixture of (*R*)-2-methyl-Phe and the title amino acid. The two amino acids were separated by preparative TLC on silica gel with a 2-propanol/ammonia/water (16:3:1) solvent system. The target amino acid (R_f = 0.26) was recrystallized from water/methanol to give 20 mg (54%) of the [^{2}H]ACC **12a** (de at C-1 50%) of **12a** and **12b** (3:1), which melted at 228–230 °C (lit.[22] mp 229–231 °C for the non-

deuteriated analogue): ^{1}H NMR (D_2O) δ 1.04 (m, 2 H, 2-H_R, 3-H_RH_S), 1.18 (m, 1 H, 3-H_RH_S); MS, m/e 103 $(MH)^+$.

(1*S*,2*R*)-1-Amino[2-^{2}H]cyclopropane-1-carboxylic Acid (14a). The title [^{2}H]ACC **14a** was obtained in 50% de at C-1 [or **14a** and **14b** (3:1)] in a manner similar to that for **12a** from 0.1 g (0.37 mmol) of the compound **10a** (de at C-6 50%) by hydrolysis with hydrochloric acid in 48% yield: mp 228-230 °C (water/methanol) (lit.[22] mp 229-231 °C for the nondeuteriated analogue); NMR (D_2O) δ 1.04 (m, 1 H, 3-H_RH_S), 1.19 (m, 2 H, 2-H_S, 3-H_RH_S); MS, m/e 103 $(MH)^+$.

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Syntheses of (1*S*,2*S*,3*S*,4*R*)- and (1*R*,2*R*,3*S*,4*R*)-2,3,4-Trihydroxycyclopentane-1-methanol, Carbocyclic Analogues of α-L-Arabinofuranose and β-D-Ribofuranose[1]

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The title compounds, two carbocyclic analogues of aldopentofuranoses, were synthesized from D-glucose. The key cyclopentane ring formation was achieved under the glycol cleavage reaction of methyl 3-*O*-benzyl-5,6-dideoxy-6-*C*-(methoxycarbonyl)-D-*xylo*-hepto-1,4-furanuronate, which was prepared by a seven-step sequence from D-glucose. The diastereomeric mixture of dimethyl 2-acetoxy-4-(formyloxy)-3-(benzyloxy)cyclopentane-1,1-dicarboxylates was converted into the title compounds through demethoxycarbonylation, Dibal-H reduction, hydroboration of thus formed 1-cyclopentene-1-methanol followed by oxidative workup, and deprotection.

We reported recently the synthesis of enantiomerically pure 2,3,4,5-tetrahydroxycyclohexane-1-methanol and 2,3,4-trihydroxycyclopentane-1-methanol.[2] These polyoxygenated six- and five-membered compounds can be regarded as carbocyclic analogues of carbohydrates. Access to the five-membered carbocycles opens an alternative synthetic approach toward carbocyclic nucleoside antibiotics, which have aroused much interest in recent years owing to their significant antitumor and antimicrobial activities.[3] Our synthesis of these carbocycles relies on the intramolecular aldol cyclization of carbohydrate-derived precursors. Herein, we report syntheses of (1*S*,2*S*,3*S*,4*R*)- and (1*R*,2*R*,3*S*,4*R*)-2,3,4-trihydroxycyclopentane-1-methanol (**1** and **2**, respectively) from D-glucose. The present syntheses are based on a similar approach reported previously.[2f] Compounds **1** and **2** are pseudo-α-L-arabinofuranose and pseudo-β-D-ribofuranose, respectively.[4]

Glycol cleavage of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**3**)[5] with $NaIO_4$ and successive Knoevenagel condensation of the resulting 1,5-dialdofuranose **4** with dimethyl malonate in a mixture of pyridine and acetic anhydride gave α,β-unsaturated diester **5**. 1,4-Conjugate addition of hydride to **5** with $NaBH_4$ gave the saturated diester **6** in an overall yield of 41% from **3**. The isopropylidene group in **6** was then hydrolyzed with aqueous HCl to give **7** as an anomeric mixture. Hydrolysis of the ester groups also occurred partly under these conditions. Unfortunately, we could not find optimal conditions for selective hydrolysis of the isopropylidene group. The glycol in **7** was cleaved with $NaIO_4$ in aqueous MeOH solution. Under the glycol cleavage conditions, the intermediate **8** cyclized spontaneously in an intramolecular aldol fashion. The resulting diastereomeric mixture of the cyclized products **9** and **9′** were acetylated to give **10** and **10′** in a combined yield of 30.5% from **6** (7% of **6** was also recovered at this stage). By careful chromatography on a silica gel column, pure **10** and **10′** were separated in an approximately 5 to 1 ratio. The configurations of the newly introduced asymmetric carbons (C-2) in **10** and **10′** (therefore those in **9** and **9′**) are tentatively assigned as depicted based on ^{1}H NMR (400 MHz) spectra analyses. H-2 of the major isomer **10** appears at δ 5.93 as a doublet with $J_{2,3}$ = 3.4 Hz, while that of **10′** appears at δ 6.01 as a doublet with $J_{2,3}$ = 4.4 Hz. These data indicate that relationship of H-2 and H-3 are trans for **10** and cis for **10′**, respectively.[6] We did not carry out any further experiments for confirmation of the structures of **10** and **10′**. The

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