NMR spectra, and Dr. J. C. Gilbert for exchanging manuscripts after learning of our similar synthetic approaches.

Registry No. (±)-**2**, 61505-17-7; (±)-^{3}H-**2**, 105164-40-7; **5**, 81328-62-3; **6**, 4342-60-3; (±)-**7**, 104762-26-7; (±)-**8** (acid) (isomer 1), 105164-34-9; (±)-**8** (acid) (isomer 2), 105164-35-0; (±)-**8** (isomer 1), 105164-36-1; (±)-**8** (isomer 2), 105164-37-2; (±)-**8** (methyl ester) (isomer 1), 104762-29-0; (±)-**8** (methyl ester) (isomer 2), 104762-30-3; (±)-**9**, 104762-32-5; (±)-**10**, 104762-31-4; ^{3}H-**10**, 105164-38-3; (±)-^{3}H-**10**-al, 105164-39-4; 2-methyl-1-cyclopentene-1-carboxylic acid, 67209-77-2; (±)-trichodienal, 82096-03-5.

Asymmetric Synthesis of (*R*)- and (*S*)-[2-^{2}H$_1$]Glycine

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Chiral glycine[1] has become an increasingly important substance for the study of numerous biochemical reactions and serves as a starting material for stereospecific conversions into other important, labeled compounds such as chiral acetic[2] and chiral glycolic[3] acids. A number of syntheses of chiral glycine have been reported[1] that involve one or two enzyme-mediated transformations or involve unambiguous chemical syntheses from chiral, nonracemic starting materials such as other amino acids or sugars. The somewhat capricious nature of the enzyme-mediated syntheses and the tediousness of the multistep chemical syntheses make this deceptively simple molecule a challenging and important target for efficient asymmetric synthesis. We recently reported[4] a new asymmetric synthesis of α-amino acids based on the chiral electrophilic glycinate **2**. In this paper, we further demonstrate the utility of this method by reporting an efficient two-step stereospecific synthesis of (*R*)- and (*S*)-[2-^{2}H$_1$]glycine from the readily available[4] glycinates **1**.

Bromination of (−)-5(*S*),6(*R*)-**1** as previously described[4] furnishes the bromide **2** as a white solid (Scheme I). Reduction of **2** with D_2 at 40 psi in the presence of catalytic $PdCl_2$ in D_2O/THF at 25 °C for 40 h directly furnishes (*S*)-[2-^{2}H$_1$]glycine in 51–54% yield. The isotopic purity of this material at C-2 was determined to be at least 84–90% and the optical purity (% ee) was established at 77–82% according to the procedure of Armarego et al.[5] Specifically, acylation of **3** with (−)-camphanyl chloride (**4**) furnished the amides (**5a,b**, which were examined by ^{1}H NMR (Scheme II). Comparison of the resonances near δ 4 with that of the amides **5c** prepared from racemic [2-^{2}H$_1$]glycine obtained from racemic **1** rigorously established the stereochemical purities of (*S*)- and (*R*)-**3**. The isotopic purity was similarly obtained by comparing the ^{1}H NMR spectra of the camphanyl amide **5d** of glycine with those of the chiral glycine derivative (Figure 1).

The stereochemical outcome of the reduction clearly indicates that the C–D bond is formed from the sterically less encumbered face of the presumed putative imine **6** (Scheme III).

It is noteworthy that reduction of (−)-5(*S*),6(*R*)-**2** with Bu_3SnD followed by hydrogenolysis (H_2/Pd/C) produced

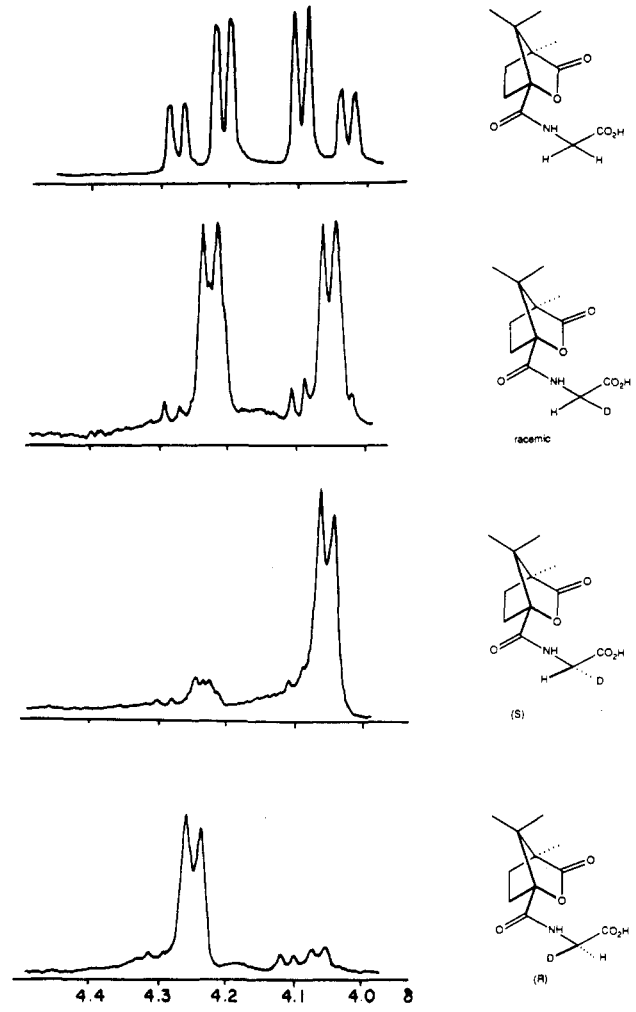

Figure 1. ^{1}H NMR spectra of camphanyl amides at 270 MHz between δ 4.0 and 4.4: (a) **5d**; (b) **5c**; (c) **5a**; (d) **5b**.

(*R*)-**3**, in 60% ee (ie., the *reverse* stereochemical outcome from the hydrogenolysis).

Similarly, the conversion of (+)-5(*R*),6(*S*)-**1** into (*R*)-**3** proceeds with equal efficiency. Although the optical purity of the chiral glycine obtained by the present method is slightly lower than that reported previously,[1,5] the relatively high overall chemical yield and experimental simplicity of this synthesis render this contribution a practical alternative to the significantly more laborious syntheses.[1] Furthermore, since the isotopic atom is introduced in the very last transformation, this methodology should be particularly appealing to those interested in synthesizing [2-^{3}H$_1$]glycine.

Experimental Section

(*S*)-[2-^{2}H$_1$]Glycine. The bromide (−)-5(*S*),6(*R*)-**2** (0.274 mmol, 1 equiv) is dissolved in dry THF (5 mL) and D_2O (1 mL) and placed in a pressure bottle that had been base washed with NaOD/D_2O. To this solution was added $PdCl_2$ (14.6 mg, 0.082 mmol, 0.3 equiv) and the vessel was charged with D_2 at 40 psi.

† Fellow of the Alfred P. Sloan Foundation, 1986–1988. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee, 1986–1988.

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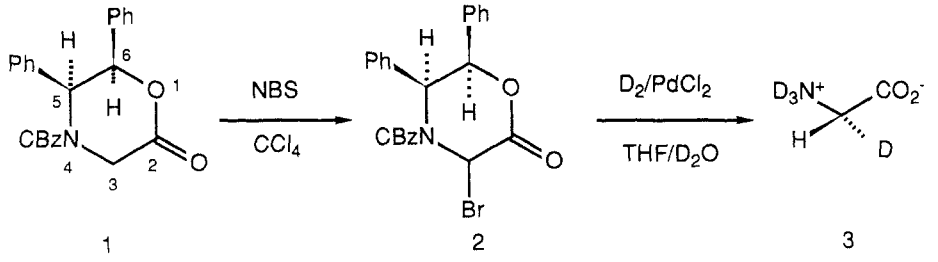
Scheme I

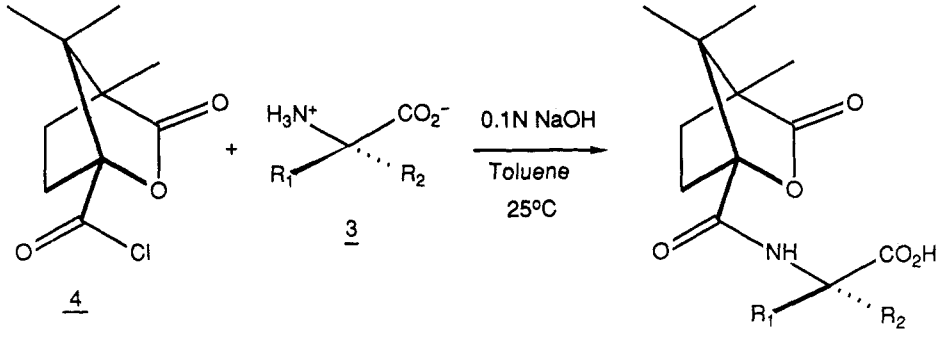


1 2 3

84-90% atom D

77-82% ee

Scheme II



4 3

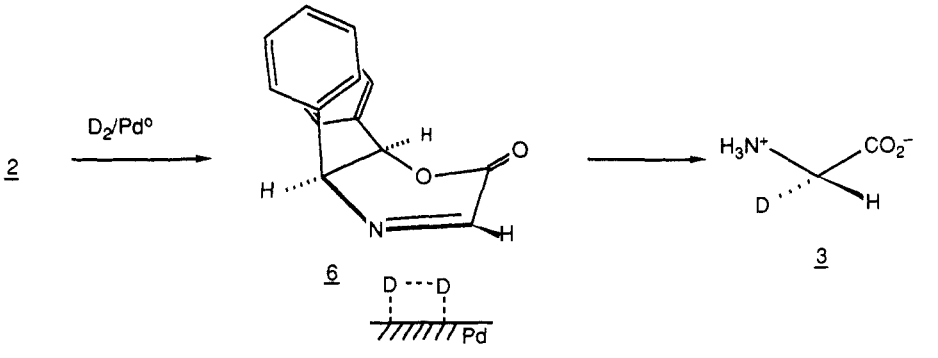
5a, R_1 = H, R_2 = D

b, R_1 = D, R_2 = H

c, R_1, R_2 = H, D

d, R_1 = R_2 = H

Scheme III



6 3

The mixture was allowed to stir for 40 h at 25 °C, and the pressure was reduced to 1 atm and the mixture purged with N_2. The mixture was filtered through a pad of Celite, evaporated to an oily residue, and triturated with CH_2Cl_2, THF, and Et_2O, leaving the insoluble *crystalline* amino acid [23.6 mg (54%)] as its hydrohalogen salt. The free amino acid was obtained by dissolution of the hydrohalogen salt in H_2O (57.5 mg) and eluting the solution with 1 N NH_4OH through an ion-exchange resin (Dowex 50W-X8, 20–50 mesh, in H^+ form after washing with 1 N NaOH and 10% H_2SO_4). Recrystallization from MeOH yielded white crystals: 22.5 mg; mp 235.5 °C dec (lit.[5] mp 234 °C dec); 82% isolated yield (from the amino acid salt); ^1H NMR (270 MHz) δ 3.65 (t).

Determination of Optical Purity (Amides 5). The crude amino acid (as the hydrohalogen salt obtained from the hydrogenolysis (6.9 mg, 0.044 mmol, 1.0 equiv) in 0.1 N NaOH solution (2.2 mL, 0.218 mmol, 5.0 equiv) was added to a stirred solution of (−)-camphanyl chloride (**4**; 18.8 mg, 0.087 mmol, 2.0 equiv) in toluene (1 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then 4.5 h at 25 °C. The mixture was thoroughly extracted with $CHCl_3$ (discarded), the aqueous phase was acidified with 1 N HCl, and the resultant solution was thoroughly extracted with CH_2Cl_2. The combined extracts were evaporated and directly analyzed by ^1H NMR ($CDCl_3$, 270 MHz). The spectroscopic properties of the amides **5** so obtained were identical with those previously reported.[5] The region between δ 4 and 5 was utilized for the determination of optical and isotopic purity as illustrated in Figure 1.[6]

Acknowledgment. We thank the National Science Foundation for their generous support of this work.

Registry No. (−)-(5*S*,6*R*)-**1**, 100516-54-9; (+)-(5*R*,6*S*)-**1**, 105228-46-4; **2**, 100570-94-3; (*S*)-**3**, 62061-66-9; (*R*)-**3**, 62061-53-4; (*S*)-**3**·HBr, 105183-10-6; **4**, 39637-74-6; **5a**, 88315-13-3; **5b**, 88291-60-5; **5d**, 62061-66-9.

(6) The percent ee and isotopic purities were obtained by calculation from the ^1H NMR integrals. Since the peaks from the proteo species **5d** overlap with portions of the peaks from **5a** and **5b**, the resolved portion of the signals at δ 4.3 was accurately integrated and the calculated remaining signals that were not resolved were substracted from the portion of the spectrum between δ 4.0 and 4.1 (for **5a**, for example). Each spectrum was recorded at least twice, and the integrals for each spectrum were measured at least twice, and averaged.