Synthesis of Stereospecific Deuterium-Labeled Homoserines and Homoserine Lactones

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Received August 12, 1987

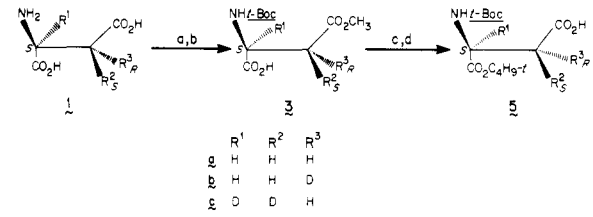
The syntheses of the stereospecific deuteriated derivatives (2*S*,4*R*)- and (2*S*,4*S*)-[4-^{2}H]homoserine lactone hydrochlorides, (2*S*,3*R*)-[3-^{2}H]- and (2*S*,3*S*)-[2,3-$^2H_2$]homoserine lactone hydrochlorides, and (2*S*,3*R*,4*R*)-[3,4-$^2H_2$]- and (2*S*,3*S*,4*S*)-[2,3,4-$^2H_3$]homoserine lactone hydrochlorides as well as the homoserine derivatives themselves have been synthesized in eight simple steps from the appropriate aspartic acids via a route designed for maximal synthetic versatility. The enantiomeric excesses at carbon 4 of the deuteriated homoserines are *R* = 78% (98% ^{2}H) and *S* = 82% (98% ^{2}H) and at carbon 3 *R* = 100% (98% $^2H_2$) and *S* = 100% (95% ^{2}H).

L-Homoserine ((2*S*)-2-amino-4-hydroxybutanoic acid) is a pivotal amino acid utilized in a variety of pyridoxal phosphate (PLP) dependent enzymatic reactions.[1] These enzyme reactions convert L-homoserine derivatives such as *O*-acetyl-L-homoserine, *O*-phosphoryl-L-homoserine, and *O*-succinyl-L-homoserine into L-methionine,[2] L-threonine,[3] and L-cystathionine,[4] respectively. PLP-catalyzed reactions which carry out elimination–replacement reactions at the γ-carbon of amino acids generally require the abstraction of both the α-hydrogen atom and the β-hydrogen atom to form the key intermediate, a fully conjugated β,γ-unsaturated imine (vinylglycine).[1] In order to study the mechanism of these enzymatic transformations, it is necessary to prepare both regio- and stereospecific deuteriated homoserines. In this paper, we report the synthesis of the stereospecific deuteriated derivatives (4*R*)- and (4*S*)-L-[4-^{2}H]homoserine lactone hydrochlorides, (2*S*,3*R*)-[3-^{2}H]- and (2*S*,3*S*)-[2,3-$^2H_2$]homoserine lactone hydrochlorides, and (2*S*,3*R*,4*R*)-[3,4-$^2H_2$]- and (2*S*,3*S*,4*S*)-[2,3,4-$^2H_3$]homoserine lactone hydrochlorides as well as several of the homoserine derivatives themselves.

Results and Discussion

We have recently reported[5] a totally chemical synthesis of (4*R*)- and (4*S*)-D,L-[4-^{2}H]homoserine, which utilized (*R*)- and (*S*)-Alpine borane[2,6,7] (Aldrich Chemical Company), to introduce the chirality at the C-4 position. The method produces sufficient quantities of stereospecifically deuteriated D,L-homoserine in high enantiomeric excess at the 4 position but is long and laborious (eight steps), gives a poor overall yield (5%), produces a D,L mixture at the α-carbon center, and is not readily applicable to the synthesis of homoserines stereospecifically labeled at both the 3- and 4-position. We therefore decided to pursue a more general method which might prove applicable to the synthesis of homoserine lactones stereospecifically deuteriated at either the 3- or 4-carbon atom or specifically dideuteriated at both the 3- and 4-carbon atom.

Scheme I[a]



[a] (a) CH_3OH/HCl; (b) $(Boc)_2O$; Na_2CO_3/dioxane/H_2O; (c) DCCI/DMAP/*t*-BuOH/CH_2Cl_2; (d) 1 N NaOH/acetone/H_2O.

The route chosen is comparable to the natural biosynthesis of homoserine from aspartic acid which first involves the NADPH reduction of aspartic acid to aspartate semialdehyde and then further reduction of the aldehyde to homoserine. *N*-(*tert*-Butyloxycarbonyl)-L-aspartic acid 1-*tert*-butyl ester (**5a**), an important synthon in our study since it is the precursor to our synthetic "aspartate semialdehyde," was prepared from L-aspartic acid (**1a**) as outlined in Scheme I. The esterification of L-aspartic acid (**1a**) to its 4-methyl ester[8] (**2a**) was accomplished in 88% yield with methanolic HCl. After the 4-methyl L-aspartate hydrochloride was converted into the corresponding *N*-*t*-Boc derivative **3a** in 72% yield by treatment with di-*tert*-butyl dicarbonate and sodium carbonate in aqueous dioxane, the α-carboxylic acid group was esterified with *tert*-butyl alcohol, dicyclohexylcarbodiimide (DCC), and 4-(dimethylamino)pyridine (DMAP) to give the 1-*tert*-butyl 4-methyl *N*-(*tert*-butyloxycarbonyl)-L-aspartate (**4a**). Selective partial hydrolysis[9] of the diester with aqueous 1 N NaOH in acetone afforded the monoester **5a**. The 1-*tert*-butyl *N*-(*tert*-butyloxycarbonyl)-L-aspartate (**5a**) was treated with ethyl chloroformate in the presence of triethylamine and the resultant ethyl ester reduced with sodium borodeuteride in D_2O to yield *N*-(*tert*-butyloxycarbonyl)-L-[4,4-$^2H_2$]homoserine 1-*tert*-butyl ester (**6a**). The alcohol function of the homoserine derivative was oxidized[10] chromium(IV) oxide–pyridine to give the deuteriated aspartate semialdehyde derivative **7a** which was then stereospecifically reduced (Scheme II) with (*R*)- and (*S*)-Alpine borane to yield the (4*S*)- and (4*R*)-L-[4-^{2}H]-

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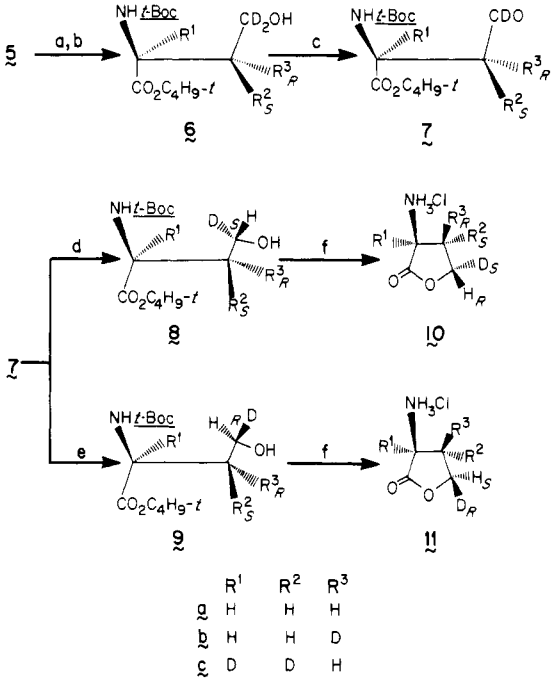
0022-3263/88/1953-1900$01.50/0

Scheme II[a]



[a] (a) $ClCO_2C_2H_5/(C_2H_5)_3N/THF$; (b) $NaBD_4/D_2O$; (c) $CrO_3/C_5H_5N/CH_2Cl_2$; (d) (*R*)-Alpine borane; (e) (*S*)-Alpine borane; (f) HCl/C_2H_5OH.

homoserine derivatives **8a** and **9a**, respectively. Removal of the protecting groups of **8a** and **9a** with ethanolic HCl afforded the lactone hydrochlorides **10a** and **11a** in enantiomeric excesses of 78% and 82%, respectively, as determined from ^1H NMR by the previously described methodology.[5]

The synthesis of the (2*S*,3*R*)-[3-^2H]- and (2*S*,3*S*)-[2,3-$^2H_2$]homoserine lactone hydrochlorides was accomplished in 21% overall yield from the stereospecifically deuteriated aspartic acids **1b** (ca. 95% ^2H incorporation) and **1c** (ca. 98% $^2H_2$ incorporation), respectively, which were obtained enzymatically from the reaction of fumaric acid and [2,3-$^2H_2$]fumaric acid with NH_4^+ in the presence of aspartase as previously described[12] (Scheme III).

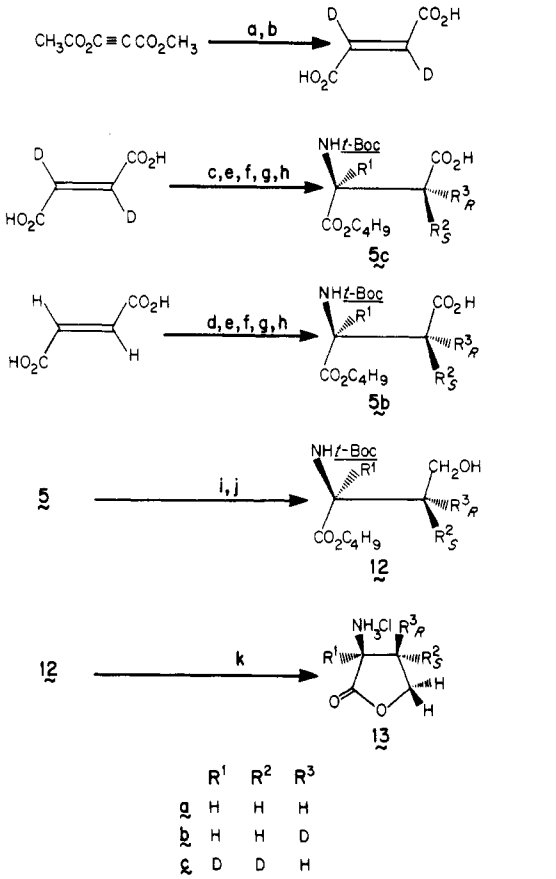
The above reaction sequences were also utilized to prepare the (2*S*,3*R*,4*R*)-[3,4-$^2H_2$]- and (2*S*,3*S*,4*S*)-[3,4-$^2H_3$]homoserine lactone hydrochlorides by starting with aspartic acids **1b** and **1c**, stereospecifically deuteriated at carbon atom 3, and following the route described to prepare the (2*S*,4*R*)- and (2*S*,4*S*)-4-^2H]homoserine lactone hydrochlorides. Although neither **8b** (2*S*,3*R*,4*S*)-[3,4-$^2H_2$] nor **9c** (2*S*,3*S*,4*R*)-[2,3,4-$^2H_3$] were synthesized in this study, their synthesis could be readily accomplished by reducing **7b** and **7c** with (*R*)- and (*S*)-Alpine borane, respectively.

In conclusion, we have reported a synthesis of the title compounds, in very good overall yield, in which the % ee at the 4- and 3-position were excellent. The synthesis gives only the naturally occurring L isomer (2*S*).

Experimental Section

General Methods. All melting points were obtained on a Mel-temp apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Varian EM-360 60-MHz, a Bruker WM 360-MHz, or an IBM WP 270-MHz NMR spectrometer in $CDCl_3$, Me_2SO-d_6 and D_2O. Samples dissolved in $CDCl_3$ and Me_2SO-d_6 are reported in ppm downfield from tetramethylsilane, while samples in D_2O are reported downfield from 3-(trimethylsilyl)-propionic acid sodium salt. All spectral and physical properties of the deuteriated compounds were found to be comparable to the nondeuteriated compounds.

Scheme III[a]



[a] (a) Ph_3P/D_2O; (b) 10% KOH; (c) L-aspartase/NH_4Cl/H_2O; (d) L-aspartase/ND_4Cl/D_2O; (e) CH_3OH/HCl; (f) $(Boc)_2O$; Na_2CO_3/dioxane/H_2O; (g) DCCI/DMAP/*t*-BuOH/CH_2Cl_2; (h) 1 N NaOH/acetone/H_2O; (i) $ClCO_2C_2H_5/(C_2H_5)_3N/THF$; (j) $NaBH_4/H_2O$; (k) HCl/C_2H_5OH.

All organic and inorganic reagents were purchased from the usual sources and were used without further purification. Organic solvents were dried by the standard methods.[13] TLC plates (silica) were purchased from Analtech. The plates were visualized by spraying with Ninhydrin. Medium grade silica gel (Merck, 70–230 mesh) was used for column chromatography.

4-Methyl L-Aspartate Hydrochloride (2a). Aspartic acid (2.6 g, 0.019 mol) was dissolved in dry methanol (20 mL) containing dry hydrogen chloride (1.5 g) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The excess methanol was removed and dry diethyl ether was added. The precipitate was filtered and dried to yield 3.12 g (88%) of the 4-methyl ester hydrochloride, mp 190–192 °C dec (lit.[8] mp 193 °C dec): ^1H NMR (Me_2SO-d_6) δ 2.94 (d, 2 H, *J* = 5.5 Hz, 3-C*H*$_2$), 3.64 (s, 3 H, COOC*H*$_3$), 4.20 (t, 1 H, *J* = 5.5 Hz, C α-*H*).

2b. (2*S*,3*R*)-[3-^2H] was prepared (91%) in an analogous manner from (2*S*,3*R*)-[3-^2H]aspartic acid[12] (ca. 95% ^2H), mp 190–192 °C dec: ^1H NMR (Me_2SO-d_6) δ 2.96 (d, 1 H, *J* = 5.5 Hz, 3-C^2H_R*H*$_S$), 3.65 (s, 3 H, COOC*H*$_3$), 4.17 (d, 1 H, *J* = 5.4 Hz, Cα-*H*).

2c. (2*S*,3*S*)-[2,3-$^2H_2$] was similarly prepared (87%) from (2*S*,3*S*)-[2,3-$^2H_2$]aspartic acid[12] (ca. 98% $^2H_2$), mp 190–192 °C dec: ^1H NMR (Me_2SO-d_6) δ 2.94 (s, 1 H, 3-C^2H_S*H*$_R$), 3.64 (s, 3 H, COOC*H*$_3$).

4-Methyl *N*-(*tert*-Butyloxycarbonyl)-L-aspartate (3a). To a stirred solution of sodium carbonate (10.6 g, 0.1 mol) in dioxane-water (2:1, 300 mL) was added 18.3 g (0.1 mol) of 4-methyl

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aspartate hydrochloride at 0 °C. When the evolution of carbon dioxide had ceased, sodium carbonate (10.6 g, 0.1 mol) was added followed by the addition of di-*tert*-butyl dicarbonate (24.0 g, 0.11 mol), and the reaction mixture was stirred at 0 °C for an additional 1 h. A white precipitate was formed within 30 min. The reaction mixture was then stirred at room temperature for 12 h. The dioxane was removed and the residue was poured onto ice–water (200 mL) and the cold solution washed with diethyl ether to remove nonacidic impurities. The aqueous solution was acidified (pH 2.5) with a solution of $NaHSO_4$ and extracted with diethyl ether (3 × 150 mL). The combined ether extracts were washed with water and dried. The solvent was removed on a rotary evaporator to afford the title compound as a colorless oil (20.0 g, 81%), homogeneous on TLC (silica gel, hexane–acetone 7:3), which was suitable for the preparation of **4a**. ^1H NMR ($CDCl_3$): δ 1.45 (s, 9 H, -NCOO-*t*-C_4H_9), 2.83 (d, 2 H, 3-CH_2), 3.71 (s, 3 H, $COOCH_3$), 4.60 (m, 1 H, Cα-*H*), 5.5 (d, 1 H, N*H*), 11.4 (s, 1 H, COO*H*).

3b. (2*S*,3*R*)-[3-^2H], 75.3% yield; oil: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, -NCOO-*t*-C_4H_9), 3.02 (d, 1 H, J = 3.86 Hz, 3-$C^2H_RH_S$), 3.71 (s, 3 H, $COOCH_3$), 4.63 (q, 1 H, Cα-*H*), 5.5 (d, 1 H, J = 7.5 Hz, N*H*), 11.5 (s, 1 H, COO*H*).

3c. (2*S*,3*S*)-[2,3-$^2H_2$], 78.5% yield; viscous oil: ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, -NCOO-*t*-C_4H_9), 2.83 (s, 1 H, 3-$C^2H_SH_R$), 3.71 (s, 3 H, $COOCH_3$), 5.71 (s, 1 H, N*H*), 11.9 (s, 1 H, COO*H*).

1-*tert*-Butyl 4-Methyl *N*-(*tert*-Butyloxycarbonyl)-L-aspartate (4a). To a cooled (0 °C) solution of **3a** (12.35 g, 0.05 mol), 4-(dimethylamino)pyridine (0.5 g) and *tert*-butyl alcohol (4.0 g, 5.1 mL, 0.055 mol) in dry methylene chloride was added with stirring *N*,*N*′-dicyclohexylcarbodiimide (12.38 g, 0.06 mol), and the reaction mixture was stirred at 0 °C for 2 h. After stirring for 12 h at room temperature, the dicyclohexylurea which formed was filtered and the filtrate taken up in 400 mL of diethyl ether. The organic layer was washed with 1 N HCl (2 × 100 mL), a saturated aqueous solution of sodium bicarbonate (2 × 100 mL), and water (2 × 100 mL) and dried (Na_2SO_4). The residue, an oil, was dissolved in ethyl acetate (50.0 mL) and evaporated onto silica gel (10.0 g). This was dry-loaded onto a 200-g silica gel column packed in hexane–acetone (7:3) and eluted with 700 mL of hexane–acetone (7:3), 15-mL fractions being collected. Fractions 22–45 were concentrated to give 12.8 g of chromatographically pure **4a** (85%): ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.84 (dd, 2 H, 3-CH_2), 3.70 (s, 3 H, $COOCH_3$), 4.45 (m, 1 H, Cα-*H*), 5.42 (br s, 1 H, N*H*).

4b. (2*S*,3*R*)-[3-^2H], 84% yield: ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.93 (br s, 1 H, 3-$C^2H_RH_S$), 3.69 (s, 3 H, $COOCH_3$), 4.5 (q, 1 H, Cα-H), 5.43 (d, 1 H, N*H*).

4c. (2*S*,3*S*)-[2,3-$^2H_2$], 82% yield: ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.96 (s, 1 H, 3-$C^2H_SH_R$), 3.69 (s, 3 H, $COOCH_3$), 5.44 (br s, 1H, N*H*).

1-*tert*-Butyl *N*-(*tert*-Butyloxycarbonyl)-L-aspartate (5a). A solution of **4a** (10.1 g, 0.03 mol) in 150 mL of acetone and 25 mL of water was cooled to 0 °C while 1 N sodium hydroxide (40 mL) was added dropwise over a period of 1 h. The pH of the solution was maintained at 8–8.5 during the addition of 1 N sodium hydroxide. The reaction mixture was then stirred at room temperature for a further 1 h. The solution was then concentrated to about 15 mL and diluted with 50 mL of water. The aqueous solution was washed with diethyl ether, neutralized with 0.5 N HCl, and extracted with diethyl ether (3 × 100 mL). The combined ether extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue, an oil, was solidified upon trituration with hexane. The crude product was recrystallized from hexane: yield 6.41 g (74%), mp 105–106 °C (lit.[9] mp 106 °C); ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 3.0 (dd, 2 H, 3-CH_2), 4.58 (m, 1 H, Cα-*H*), 5.52 (d, 1 H, N*H*), 11.5 (s, 1 H, COO*H*).

5b. (2*S*,3*R*)-[3-^2H], 75% yield: mp 105–106 °C (hexane): ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.98 (br s, 1 H, 3-$C^2H_RH_S$), 4.45 (q, 1 H, Cα-*H*), 5.46 (d, 1 H, N*H*).

5c. (2*S*,3*S*)-[2,3-$^2H_2$], 77% yield: mp 105–106 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.98 (s, 1 H, 3-$C^2H_SH_R$), 5.48 (s, 1 H, N*H*).

***N*-(*tert*-Butyloxycarbonyl)-L-[4,4-$^2H_2$]homoserine *tert*-Butyl Ester (6a).** Compound **6a** was prepared by an adaptation of the procedure by Olson et al.[10] To a stirred solution of ester (13.65 g, 0.0472 mol) and triethylamine (4.78 g, 0.0472 mol) in dry THF (50 mL) was added a solution of freshly distilled ethyl chloroformate (5.12 g, 0.0472 mol) in dry THF (50 mL) at −5 °C under an atmosphere of nitrogen. The reaction mixture was allowed to stir at −5 °C for 45 min after which the precipitated triethylamine hydrochloride was removed by filtration and washed with 10 mL of dry THF. The combined filtrates were added over a period of 30 min to a solution of sodium borodeuteride (3.95 g, 0.094 mol) in 20 mL of D_2O at 10–15 °C. After the addition was complete, the mixture was stirred at room temperature for 4 h, then acidified with 2 N HCl, and extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with $NaHCO_3$ and water, dried, and evaporated. The oily residue was dissolved in 50 mL of ethyl acetate and evaporated onto 10 g of silica gel. The product-laden silica gel was dry-loaded onto a 250-g silica gel column packed in hexane. The column was eluted with 400 mL of hexane–acetone (7:3 v/v) and 10-mL fractions were collected. Evaporation of fractions 20–30 afforded 9.65 g (74%) of **6a** as a clear viscous oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.13 (m, 2 H, 3-CH_2), 3.49 (br s, 1 H, O*H*), 4.35 (m, 1 H, Cα-*H*), 5.36 (d, 1 H, N*H*).

12b. (2*S*,3*R*)-[3-^2H], oil; 66% yield via reduction of **5b** with $NaBH_4/H_2O$: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.13 (m, 1 H, 3-$C^2H_RH_S$), 3.39 (br s, 1 H, O*H*), 3.65 (m, 2 H, 4-CH_2-OH), 4.36 (q, 1 H, Cα-*H*) 5.32 (d, 1 H, N*H*).

12c. (2*S*,3*S*)-[2,3-$^2H_2$], viscous oil; 70% yield via reduction of **5c** with $NaBH_4/H_2O$: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.13 (m, 1 H, 3-$C^2H_SH_R$), 3.47 (br s, 1 H, O*H*), 3.65 (m, 2 H, 4-CH_2-OH), 5.33 (s, 1 H, N*H*).

6b. (2*S*,3*R*)-[3,4,4-$^2H_3$]: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.14 (m, 1 H, 3-$C^2H_RH_S$), 3.43 (br s, 1 H, O*H*), 4.34 (m, 1 H, Cα-*H*), 5.31 (br s, 1 H, N*H*).

6c. (2*S*,3*S*)-[2,3,4,4-$^2H_4$]: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.12 (s, 1 H, 3-$C^2H_SH_R$), 3.47 (br s, 1 H, O*H*), 5.32 (br s, 1 H, N*H*).

1-*tert*-Butyl L-2-[(*tert*-Butyloxycarbonyl)amino]-[4-^2H]-4-oxobutanoate (7a). *N*-(*tert*-Butyloxycarbonyl)homoserine *tert*-butyl ester (**6a**) (9.65 g, 0.035 mol) was oxidized with Collins reagent as described by Ramasamy et al.[10] The aldehyde was purified by column chromatography on silica gel by eluting with a 7:3 mixture of hexane–acetone to yield 6.7 g (70%) of the title compound: ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 3.00 (m, 2 H, 3-CH_2), 4.44 (m, 1 H, Cα-*H*), 5.40 (s, 1 H, N*H*).

7b. (2*S*,3*R*)-[3,4-$^2H_2$], viscous oil; 72% yield from **6b**: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.94 (br s, 1 H, 3-$C^2H_RH_S$), 4.48 (t, 1 H, J = 4.3 Hz, Cα-*H*), 5.34 (br s, 1 H, N*H*).

7c. (2*S*,3*S*)-[2,3,4-$^2H_3$], viscous oil; 69.8% yield from **6c**: ^1H NMR ($CDCl_3$) δ 1.45 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.90 (s, 1 H, 3-$C^2H_SH_R$), 5.36 (s, 1 H, N*H*).

***N*-(*tert*-Butyloxycarbonyl)-(4*S*)-[4-^2H]-L-homoserine *tert*-Butyl Ester (8a).** To a flame-dried 200-mL flask equipped with a magnetic stirrer and a rubber septum was added, under a nitrogen atmosphere, 45 mL of a 0.5 M *R*- (+)-Alpine borane solution in THF. The aldehyde **7a** (3.2 g, 0.0116 mol) was added, and the mixture was stirred for 12 h at room temperature and then heated to reflux for 4 h. After being cooled to room temperature, acetaldehyde (2.5 mL) was added, the mixture was stirred 15 min, and the solvent was removed under water aspirator. The pinene was removed in vacuo at 50 °C. The oily residue was dissolved in dry diethyl ether (200 mL), 2-aminoethanol (2.8 mL, 0.046 mol) was added, and the mixture was stirred for 0.5 h. The precipitate which formed was removed by filtration and washed with ether. The combined ether solutions were washed with water and dried over Na_2SO_4 and the solvent was removed on a rotary evaporator. The clear viscous residue was dissolved in ethyl acetate and preabsorbed onto 5 g of silica gel. The free-flowing powder was transferred to the top of a silica gel (200 g) column packed with hexanes. The column was eluted (25-mL fractions were collected) with 500 mL of hexanes/ethyl acetate (8:2). The residual pinene eluted first (fractions 12–16) followed by the title compound (fractions 17–25). Removal of the solvent afforded 2.83 g (88%) of **8a** as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.46 (s, 18 H, -NCOO-*t*-C_4H_9, O-*t*-C_4H_9), 2.13 (m, 2 H, 3-CH_2), 3.42 (br

s, 1 H, O*H*), 3.68 (m, 1 H, 4-C^{2}H$_S$*H*$_R$-OH), 4.35 (m, 1 H, C*α*-H), 5.13 (d, 1 H, N*H*).

9a. (4*R*)-[4-^{2}H], viscous oil; 80.7% yield from **7a** via reduction with (*S*)-Alpine borane: ^{1}H NMR ($CDCl_3$) *δ* 1.46 (s, 18 H, -NCOO-*t*-C$_4$*H*$_9$, O-*t*-C$_4$*H*$_9$), 2.13 (m, 2 H, 3-C*H*$_2$), 3.47 (br s, 1H, O*H*), 3.64 (m, 1 H, 4-C^{2}H$_R$*H*$_S$-OH), 4.32 (m, 1 H, C*α*-*H*), 5.13 (d, 1H, N*H*).

9b. (2*S*,3*R*,4*R*)-[3,4-^{2}H$_2$], oil; 82.1% yield from **7b** via reduction with (*S*)-Alpine borane: ^{1}H NMR ($CDCl_3$) *δ* 1.45 (s, 18 H, -NCOO-*t*-C$_4$*H*$_9$, O-*t*-C$_4$*H*$_9$), 2.13 (m, 1 H, 3-C^{2}H$_R$*H*$_S$), 3.39 (br s, 1 H, O*H*), 3.65 (br s, 1 H, 4-C^{2}H$_R$*H*$_S$-OH), 4.36 (br s, 1 H, C*α*-*H*), 5.36 (d, 1 H, N*H*).

8c. (2*S*,3*S*,4*S*)-[2,3,4-^{2}H$_3$], viscous oil; 85% yield from **7c** via reduction with (*R*)-Alpine borane: ^{1}H NMR ($CDCl_3$) *δ* 1.46 (s, 18 H, -NCOO-*t*-C$_4$*H*$_9$, O-*t*-C$_4$*H*$_9$), 2.10 (br s, H, 3-C^{2}H$_S$*H*$_R$), 3.41 (br s, 1 H, O*H*), 3.68 (br s, 1 H, 4-C^{2}H$_S$*H*$_R$), 5.33 (d, 1 H, N*H*).

(4*S*)-[4-^{2}H]-L-Homoserine Lactone Hydrochloride (10a). A solution of *N*-(*tert*-butyloxycarbonyl)-(4*S*)-[4-^{2}H]-L-homoserine 1-*tert*-butyl ester (**8a**) (0.2 g, 0.72 mmol) in 95% ethanolic HCl (25 mL) was heated to reflux for 3 h. The solvent was removed and the residue was dissolved in absolute ethanol (20 mL) and evaporated under vacuum at 40 °C. This procedure was repeated twice more and the residue dried in vacuum. The off-white solid recrystallized from absolute ethanol to yield 52 mg (52%) of **10a**: mp 203–205 °C; ^{1}H NMR (Me_2SO-d_6) *δ* 2.30 and 2.55 (m, 2 H, 3-C*H*$_2$-), 4.42 (d, 1 H, *J* = 8.9 Hz, 4-C^{2}H$_S$*H*$_R$), 4.32 (dd, 1 H, *J* = 11.02 Hz, 8.9 Hz, C*α*-*H*).

11a. (4*R*)-[4-^{2}H]; 57% yield from **9a**; mp 203–205 °C (ethanol): ^{1}H NMR (Me_2SO-d_6) *δ* 2.30 and 2.55 (m, 2 H, 3-C*H*$_2$), 4.27 (m, 1 H, 4-C^{2}H$_R$*H*$_S$), 4.32 (dd, 1 H, *J* = 11.02 Hz, 8.9 Hz, C*α*-*H*).

13b. (2*S*,3*R*)-[3-^{2}H]; 52% yield from **12b**; mp 203–205 °C (ethanol): ^{1}H NMR (Me_2SO-d_6) *δ* 2.53 (m, 1 H, 3-C^{2}H$_R$*H*$_S$), 4.24 and 4.43 (m, d, 3 H, 4-C*H*$_2$ and C*α*-*H*).

13c. (2*S*,3*S*)-[2,3-^{2}H$_2$]; 55.8% yield **12c**; mp 203–205 °C (ethanol): ^{1}H NMR (Me_2SO-d_6) *δ* 2.30 (t, 1 H, *J* = 9.53 Hz, 3-C^{2}H$_S$*H*$_R$), 4.26 and 4.44 (dd, t, 2 H, *J* = 8.9 Hz, 4-C*H*$_2$).

11b. (2*S*,3*R*,4*R*)-[3,4-^{2}H$_2$]; 52% yield from **9b**; mp 203–205 °C (ethanol): ^{1}H NMR (D_2O) *δ* 2.59 (m, 1 H, 3-C^{2}H$_R$*H*$_S$), 4.27 (br s, 1 H, 4-C^{2}H$_R$*H*$_S$), 4.32 (br s, 1 H, C*α*-*H*).

10c. (2*S*,3*S*,4*S*)-[2,3,4-^{2}H$_3$]; 49% yield from **8c**; mp 203–205 °C (ethanol): ^{1}H NMR (D_2O) *δ* 2.28 (d, 1 H, *J* = 7.3 Hz, 3-C^{2}H$_S$*H*$_R$), 4.46 (d, 1 H, *J* = 9.2 Hz, 4-C^{2}H$_S$*H*$_R$).

(4*S*)-[4-^{2}H]-L-Homoserine. The lactone hydrochloride **10a** (20 mg) was dissolved in water (0.2 mL) and applied to a column of Dowex 50W × 4-200 (NH_4^+, 10 mL) and eluted with water followed by 1 N NH_4OH. Ninhydrin-positive fractions were combined and freeze-dried to yield 15 mg (92%) of (4*S*)-[4-^{2}H]-L-homoserine: ^{1}H NMR (D_2O) *δ* 1.81 and 1.91 (m, 2 H, 3-C*H*$_2$), 3.56 (m, 1 H, 4-C^{2}H$_S$*H*$_R$), 3.67 (m, 1 H, C*α*-*H*).

(4*R*)-[4-^{2}H]-L-Homoserine. The title homoserine was prepared from (4*R*)-[4-^{2}H]-L-homoserine lactone hydrochloride (**11a**) as described above in 93% yield: ^{1}H NMR (D_2O) *δ* 1.83 and 1.96 (m, 2 H, 3-C*H*$_2$), 3.57 (m, 1 H, 4-C^{2}H$_R$*H*$_S$), 3.67 (m, 1 H C*α*-H).

Acknowledgment. This work was supported by U.S. Public Health Service Grant GM 36184. We are grateful to the U.S. PHS and the College of Pharmacy for their contribution to the purchase of the IBM 270-MHz NMR.

Hydroboration of Vinyl Ethers with Diisopinocampheylborane[1]

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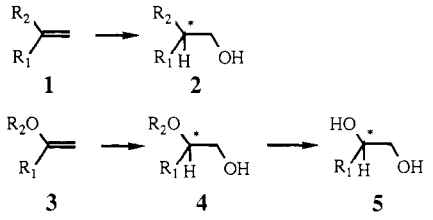
Received August 7, 1987

The reactions of diisopinocampheylborane with cyclic vinyl ethers having an exocyclic oxygen and with acyclic vinyl ethers having groups of varying size attached to oxygen were explored. Evidence of some interaction of the bulkier vinyl ethers with diisopinocampheylborane was obtained, but high enantiomeric excesses were not found. However, the hydroboration–oxidation of benzyl or diphenylmethyl vinyl ethers, followed by cleavage, is a practical route to partially resolved diols.

In the course of synthetic studies directed towards the partial synthesis of vitamin D and analogues of the vitamin, we envisioned the need for resolved terminal epoxides derivable from resolved 1,2-diols. Some examples of such diols have been obtained from resolved precursors, including sugars,[2] malic acid,[3] and amino acids.[4] Others have been made in a recent study of osmium tetraoxide hydroxylation in the presence of resolved amine catalysts.[5] As a possible alternative to these methods, we became intrigued with the possibilities for the formation of resolved diols by hydroboration–oxidation. The only major variable for effecting chiral discrimination in the hydroboration–

Scheme I



oxidation of a specific alkene, e.g., **1** to **2** (Scheme I), is the chiral hydroborating reagent. However, a second variable, the structure of a potentially *cleavable* R_2 group, is present in the vinyl ether **3**, which may be converted via **4** to the specified diol **5**.

R^2 in **3** may interact with a resolved chiral hydroborating agent as a consequence of its bulk, as reported here, or may be a resolved (and bulky) chiral group which can interact with a racemic reagent. The most promising approach, not yet tested in our work, is to combine the types of interaction to provide new examples of double asymmetric induction, a subclass of "double stereodifferentiation".[6]

(1) Partial support by the National Institutes of Health, Grant 5-R01 AM31110-03, is gratefully acknowledged. Partial support from the National Institutes of Health (Grant 1-S10-RR02425) and the National Science Foundation (Grant CHE-8411172) for purchase of the Bruker AM 300 NMR spectrometer is acknowledged.

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