The Synthesis of (5*R*)- and (5*S*)-[5-^{3}H]-L-Ornithine

Ronald J. Parry*, Shyhchen Ju and Bill J. Baker

Department of Chemistry, Rice University, Houston Texas 77251

Summary

A practical synthesis of (5*R*)- and (5*S*)-[5-^{3}H]-L-ornithine is described. The key steps in the synthesis are the reduction of [*formyl*-^{3}H]-5-hexenal with *S*- or *R*-Alpine Borane to (1*R*)- and (1*S*)-[1-^{3}H]-5-hexen-1-ol and the use of the Evans electrophilic azidation of chiral imide enolates to introduce the α-amino group of ornithine. The stereochemistry expected for the Alpine Borane reduction was verified by NMR analysis of the camphanate ester derived from reduction of [*formyl*-^{2}H]-5-hexenal with *R*-Alpine Borane.

Key Words: L-ornithine, tritium, stereospecific labeling, Alpine Borane, electrophilic azidation, camphanate ester.

Introduction

In conjunction with biosynthetic studies of the nucleoside antibiotic sinefungin,[1] a need arose for (5*R*)- and (5*S*)-[5-^{3}H]-L-ornithine. The synthesis of these forms of labeled ornithine had been previously reported by Townsend *et al.*,[2] but the final step of the synthesis proceeded in very low yield. We therefore devised a more satisfactory synthesis of (5*R*)- and (5*S*)-[5-^{3}H]-L-ornithine.

Results and Discussion

The synthesis (Scheme 1) began with 5-hexen-1-ol (**1**) which was oxidized with PCC to 5-hexenal (**2**). Reduction of **2** with sodium [^{3}H]borohydride (100mCi) gave (1*RS*)-[1-^{3}H]-5-hexen-1-ol (**1a**) in quantitative yield (radiochemical yield 26%). Oxidation of the tritiated alcohol followed by reduction[3] of the labeled aldehyde with *S*- or *R*-Alpine Borane proceeded smoothly to produce (1*R*)- and (1*S*)-[1-^{3}H]-5-hexen-1-ol (**3**, **4**), respectively, (yield 44% for two steps). The stereospecifically tritiated alcohols having been obtained, they were converted to the corresponding mesylates (95%). The mesyl groups were then displaced by treatment of the sulfonate esters with sodium azide in DMF to produce the stereospecifically tritiated azides **5** and **6**. Since the displacement reaction takes place at a primary center, it was expected to proceed with inversion of configuration.[4] The tritiated azides **5** and **6** were next oxidized with ruthenium trichloride and sodium

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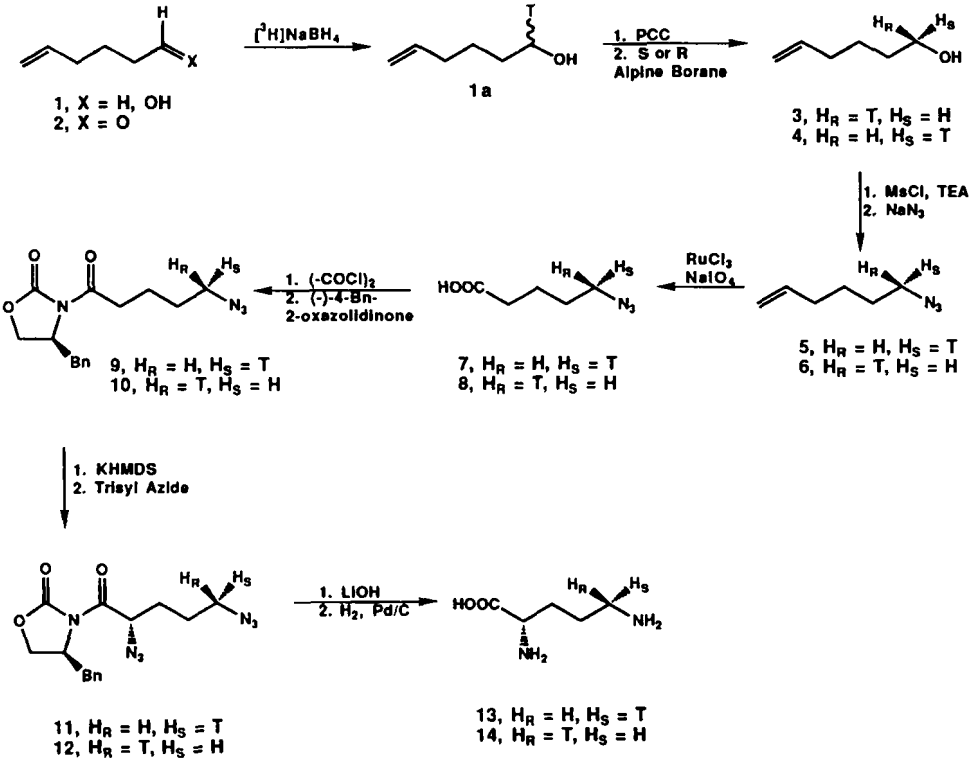
periodate[5] to yield the 5-azidopentanoic acids **7** and **8** (50% yield from the mesylates). These stereospecifically tritiated acids were then coupled to (*S*)-(-)-4-benzyl-2-oxazolidinone by standard methods[6] (56%), generating the acylated oxazolidinones **9** and **10**. Treatment of **9** and **10** with

Scheme 1: *Synthesis of (5S)- and (5R)-[5-3H]-L-Ornithine*

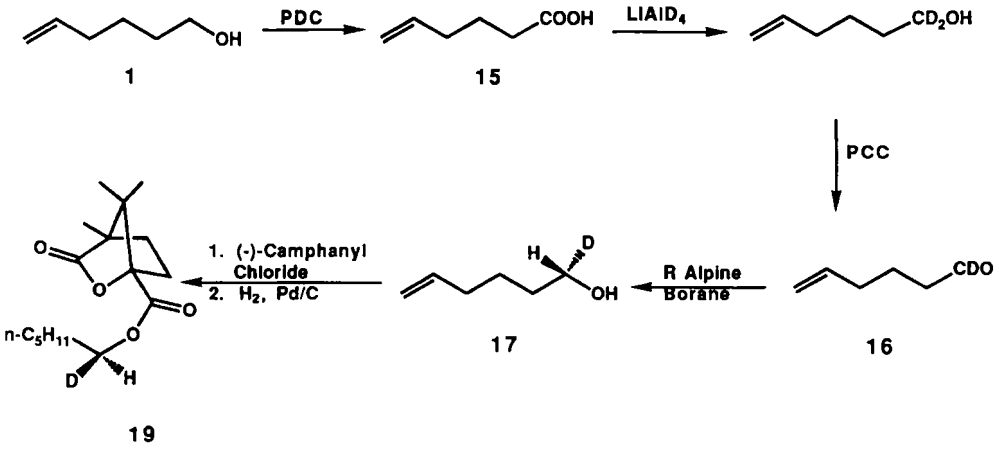


potassium bis(trimethylsilyl)amide followed by 2,4,6-triisopropylbenzenesulfonyl azide[7] resulted in the stereospecific introduction of an azide function with formation of the diazides **11** and **12** (46-66%). The yield of the azidation reaction was highly dependent upon the quality of the base employed and the diazides exhibited chromatographic behavior that was almost identical to that of the monoazides. Conversion of the diazides into stereospecifically tritiated forms of L-ornithine (**13**, **14**) was accomplished by base-catalyzed removal of the chiral auxiliary (76%) followed by reduction of the azide functions with hydrogen and palladium (92%). The overall chemical yield of L-ornithine was *ca.* 8% while the overall radiochemical yield was *ca.* 4%. The stereospecificity of the electrophilic azidation reaction was determined by measurement of the optical rotation of unlabeled L-ornithine hydrochloride obtained via the route in Scheme 1. The rotation exhibited by the

L-ornithine indicated that the enantiomeric excess of the L-isomer was 82.5%. For reasons that are unclear, this degree of stereospecificity is somewhat lower than has been reported for other amino acids synthesized by the electrophilic azidation process.[7]

The absolute configuration of the isotopic label in the resulting ornithines was determined by analyzing the stereochemistry of a sample of (1-$^2H_1$)-5-hexen-1-ol (**17**) prepared from [*formyl*-$^2H_1$]-5-hexenal (**16**) by reduction with *R*-Alpine Borane (Scheme 2). The synthesis of **16** was accomplished by oxidation of 5-hexen-1-ol (**1**) to 5-hexenoic acid (**15**) with PDC in DMF,[8] reduction of the acid to (1-$^2H_2$)-5-hexenol with lithium aluminum deuteride, and oxidation of the dideuterio

Scheme 2: *Analysis of Chirality of (1S)-(1-$^2H_1$)-5-Hexen-1-ol*



alcohol to **16** with PCC. On the basis of much literature precedent,[9] the reduction of **16** with *R*-Alpine Borane was anticipated to yield (1*S*)-(1-$^2H_1$)-5-hexen-1-ol (**17**). This expectation was confirmed by conversion of **17** into its (-)-camphanate ester **18**, reduction of the ester to yield hexanoyl camphanate (**19**), and analysis of the chirality of the deuterium label in **19** by the method of Zagalak and Gerlach,[10] which has been widely employed in stereochemical studies.[11] The ^1H NMR spectrum of **19** in the presence of the shift reagent Eu(DPM)$_3$ revealed that the isotopic label had the expected *S* configuration and that the optical purity of the label was *ca.* 90%.[12]

To summarize, a useful synthesis of (5*R*)- and (5*S*)-[5-^3H]-L-ornithine has been developed. The synthesis proceeds in satisfactory overall yield and it allows the preparation of L-ornithine with high specific activity, since the introduction of tritium is accomplished with labeled sodium borohydride.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on either a Jeol FX-90Q (90MHz) or an IBM AF300 (300MHz) spectrometer using $CDCl_3$ as solvent, unless otherwise noted. Chemical shifts are given in parts per million downfield from tetramethylsilane. All melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. Mass spectra were run on Finnegan 3300 and CEC 111021-110B mass spectrometers. Analytical thin layer chromatography was performed with precoated Merck silica gel type 60 F-254 glass plates (0.25 mm layers) or with Merck cellulose F glass plates (0.1 mm layers). Column chromatography was performed using Merck silica gel (200-400 mesh) or Merck microcrystalline cellulose (Avicel). Chemical reagents were purchased from Aldrich Chemical Company, while the tritiated sodium borohydride was obtained from American Radiolabeled Chemicals, Inc.

Synthesis of L-Ornithine.

(1*RS*)-[1-^{3}H]-5-Hexenol (1a). 5-Hexenol (1.0 g, 10 mM) was added with stirring under nitrogen to a suspension of PCC (3.23 g, 15 mM) in 40 mL of dichloromethane. After 1.5 h, the mixture was cooled to 4° C and stirred at this temperature for an additional 12 h. Diethyl ether (20 mL) was then added and the crude supernatant passed through a Florisil column to remove highly colored impurities. Elution of the column with additional ether yielded a dilute solution of 5-hexenal (2) which was concentrated by removal of the ether at 40° C. The crude 5-hexenal was dissolved in 30 mL of absolute ethanol, the solution cooled in an ice bath, and sodium [^{3}H]borohydride (0.64 mM, 100 mCi) added with stirring. The solution was then stirred for 2.5 h, at the end of which time unlabeled sodium borohydride (0.60 g, 16 mM) was added and the reduction allowed to proceed overnight. The solvent was removed *in vacuo* and the residue partitioned between 15% aqueous NaOH and dichloromethane. After repeated extraction of the aqueous phase, the combined organic phases were dried over anhydrous $MgSO_4$, and the solvent removed *in vacuo*. The crude alcohol was purified by flash chromatography (SiO_2, hexane:ethyl acetate, 4:1) to yield 1.0 g (*ca.* 100%) of (1*RS*)-[1-^{3}H]-5-hexenol with a total activity of 26 mCi: TLC (SiO_2, hexane:ethyl acetate, 4:1, R_f = 0.36); ^{1}H NMR: δ 5.5-6.0 (m, 1H, vinyl H), 5.0 (m, 2 H, vinyl H), 3.6 (t, 2 H, CH_2OH), 2.0 (m, 2 H, allylic CH_2), 1.4-1.8 (m, 4 H); ^{13}C NMR: d 138.5, 114.4, 62.2, 33.3, 31.9, 24.9.

(1*R*)-[1-^{3}H]-5-Hexen-1-ol (3). By the procedure outlined above, (1*RS*)-[1-^{3}H]-5-hexen-1-ol (1.0 g, 26 mCi) was oxidized with PCC to [*formyl*-^{3}H]-5-hexenal (*ca.* 0.98 g). The crude

aldehyde was dissolved in dry THF (10 mL) and the solution added dropwise with stirring under nitrogen to 20 mL of a 0.5 M solution of *S*-Alpine Borane in THF. After 10 min the mixture was heated at reflux for 2 h and then allowed to cool to room temperature. The solvent was removed *in vacuo*, the residue dissolved in diethyl ether (50 mL), and the resulting solution cooled in an ice bath. Ethanolamine (0.66 mL, 1.06 eq.) was added and the mixture stirred on ice for 20 min. The white precipitate was removed by vacuum filtration and the filtrate concentrated *in vacuo* to give a yellowish oil that was purified by flash chromatography (SiO_2, hexane:ethyl acetate, 4:1). The yield of pure (1*R*)-[1-^{3}H]-5-hexen-1-ol was 0.44 g (44%).

(1*R*)-[1-^{3}H]-5-Hexenyl Methane Sulphonate. The sample of (1*R*)-[1-^{3}H]-5-hexen-1-ol obtained from *S*-Alpine Borane reduction was diluted with unlabeled alcohol to give a total weight of 1.0 g (10 mM). The diluted alcohol was dissolved in dichloromethane (15 mL) and triethylamine (2.0 mL, 14.3 mM) added. The resulting solution was cooled to 0° C and freshly distilled methanesulfonyl chloride (1.0 mL, 12.9 mM) added dropwise with stirring. The reaction mixture was then allowed to warm to room temperature while stirring overnight. The mixture was poured into a mixture of ice and saturated $NaHCO_3$ solution. The organic layer was removed, and the aqueous layer extracted with 2 x 10 mL of dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent removed *in vacuo* to yield 1.72 g (95%) of tritiated mesylate as a colorless oil: TLC (SiO_2 hexane:ethyl acetate, 4:1, R_f = 0.24); ^{1}H NMR: δ 5.65 (1 H, m, vinyl H), 5.0 (2 H, m, vinyl H), 4.2 (2 H, t, CH_2OMs), 3.0 (3 H, s, CH_3SO_2), 2.1 (2 H, d, allylic H), 1.4-2.0 (m, 4 H). The preparation of the unlabeled mesylate has been previously reported.[13]

(5*S*)-[5-^{3}H]-5-Azidopentanoic Acid (7). The stereospecifically tritiated (1*R*)-mesylate (1.72 g, 9.6 mM) was dissolved in dry DMF (20 mL), sodium azide (1.43 g, 22 mM) added, and the mixture stirred for 20 h at room temperature. Water (20 mL) was added and the diluted reaction mixture extracted several times with diethyl ether. The combined ether extracts were back washed with water and then dried over anhydrous $MgSO_4$. The ether was removed *in vacuo* at room temperature in order to avoid loss of the relatively volatile azide. The crude azide was chromatographed (SiO_2, diethyl ether) and the fractions containing the (5*S*)-[5-^{3}H]-5-azido-1-hexene were carefully concentrated *in vacuo*. The purified azide was dissolved in a mixture of carbon tetrachloride (21.5 mL) and acetonitrile (21.5 mL). Water (35 mL) and sodium periodate (0.15 g, 47 mM) were added, and the mixture cooled in an ice-bath. Ruthenium trichloride trihydrate

(0.07 g, 0.26 mM) was added with stirring and stirring continued for 10 min at 0° C, after which time the ice-bath was removed and stirring at room temperature continued overnight. Dichloromethane (40 mL) was then added, the two phases separated, and the aqueous phase extracted repeatedly with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a dark oil. This oil was chromatographed (SiO_2, hexane:ethyl acetate, 1:1) to yield 0.61 g (50%) of (5*S*)-[5-^{3}H]-5-azidopentanoic acid as a colorless oil: TLC (SiO_2,1:1 hexane:ethyl acetate, R_f = 0.32); ^{1}H NMR: δ 9.0 (1 H, broad s, COOH), 3.2 (2 H, t, CH_2N_3), 2.4 (2 H, t, $\mathbf{CH_2}$COOH), 1.4-2.0 (4 H, m). The acid could not be distilled without decomposition and it gave no molecular ion on electron impact.

N-{(5*S*)-[5-^{3}H]-5-Azidopentanoyl}-(4*S*)-4-benzyl-2-oxazolidinone (9). (5*S*)-[5-^{3}H]-5-Azidopentanoic acid (**7**, 0.61 g, 4.2 mM) was dissolved in dry benzene (25 mL), the solution cooled in an ice-bath, and oxalyl chloride (0.74 mL, 8.5 mM) added dropwise with stirring. The cooling bath was removed and the mixture stirred at room temperature for 17 h. The solution was then concentrated *in vacuo* and the residual oxalyl chloride chased out of the reaction mixture with dry THF (3 x 10 mL). Finally, the residual acid chloride was dissolved in dry THF (5 mL) in preparation for the next step. (-)-(4*S*)-Benzyl-2-oxazolidinone (1.12 g, 6.3 mM) was dissolved in dry THF (25 mL), the solution cooled to -78° C, and n-butyl lithium (2.53 mL of 2.5 M solution in hexane, 6.3 mM) added dropwise with stirring under N_2. After 20 min stirring at -78°, the THF solution of the crude acid chloride was added at -78°, and stirring at this temperature continued for 30 min. The reaction temperature was then raised to 0° and stirring continued for 30 min. Excess saturated aqueous NH_4Cl solution was added, the mixture concentrated *in vacuo*, and the residue partitioned between ether and saturated aqueous $NaHCO_3$. After repeated extractions, the combined ether phases were dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (SiO_2, hexane:ethyl acetate, 5:1) to yield **9** as a colorless oil (0.72 g, 56% yield from **7**; sp. act. = 4.88 mCi/mM): TLC (SiO_2, hexane:ethyl acetate, 5:1, R_f = 0.25); ^{1}H NMR (300 MHz): δ 7.3 (5 H, m, ArH), 4.6 (1 H, m, ArCH$_2$**CH**), 4.1 (2 H, d, CH_2OCO), 3.2 (2 H, t, CH_2N_3), 2.9 (2 H, m, $ArCH_2$), 2.7 (2 H, t, $CH_2\mathbf{CH_2}CO$), 1.5-1.9 (4 H, m); ^{13}C NMR (75 MHz): δ 172.5, 153.3, 135.1, 129.3, 128.8, 127.2, 66.1, 54.9, 50.9, 37.7, 34.8, 28.1, 21.2; ^{13}C NMR (DEPT): **CH**: 129.3, 128.8, 127.2, 54.9; $\mathbf{CH_2}$: 66.1, 50.9, 37.7, 34.8, 28.1, 21.2. The product could not be distilled and gave no molecular ion on electron impact.

N-{(2*S*),(5*S*)-[5-^{3}H]-2,5-Diazidopentanoyl}-(4*S*)-4-benzyl-2-oxazolidinone (11). Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 5.2 mL, 2.6 mM) was diluted with dry THF (8.4 mL) and the resulting solution cooled to -78° C. A solution of **9** (0.72 g, 2.36 mM) in THF (8.4 mL) precooled to -78° was transferred by cannula into the silyl amide solution and the mixture stirred for 30 min at -78° under N_2. A precooled (-78°) solution of 2,4,6-triisopropylsulfonyl azide[7] (0.875 g, 2.83 mM) in dry THF (8.4 mL) was then added. After a reaction time of 1-2 min, acetic acid (0.62 mL, 4.6 eq.) was added and the reaction allowed to stand overnight. Dichloromethane (30 mL) and brine (30 mL) were added to the reaction mixture, the two phases separated, and the aqueous phase extracted repeatedly with dichloromethane. The combined organic phases were washed with 0.1 N $NaHCO_3$, dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a residue that was purified by flash chromatography: (SiO_2, hexane:ethyl acetate, 5:1) to give 0.38 g of a colorless oil (46%, sp. act. = 6.7 mCi/mM): TLC (5:1 hexane-ethyl acetate, $R_f = 0.17$); ^{1}H NMR(300 MHz): δ 7.2 (5 H, m, ArH), 4.9 (1 H, m, $COCHN_3$), 4.7 (1 H, m, $ArCH_2\mathbf{CH}$), 4.2 (2 H, d, CH_2OCO), 3.3 (2 H, t, CH_2N_3), 2.8 (2 H, q, $ArCH_2$), 1.6-2.0 (4 H, m); ^{13}C NMR (75 MHz): δ 170.3, 152.7, 134.4, 129.2, 128.8, 127.3, 66.5, 59.8, 55.2, 50.4, 37.3, 28.3, 25.3; ^{13}C NMR (DEPT): **CH**: 129.2, 128.8, 127.3, 59.8, 55.2; **CH_2**: 66.5, 50.4, 37.3, 28.3 25.3. The product could not be distilled and gave no molecular ion on electron impact.

(2*S*),(5*S*)-[5-^{3}H]-2,5-Diazidopentanoic Acid. Diazido compound **11** was dissolved in a mixture of THF and water (3:1, 26 mL) and the solution cooled in an ice-bath. The solution was then treated with aqueous lithium hydroxide (1N, 2.6 mL) and stirred for 30 min at 0° under N_2. The reaction was quenched by addition of aqueous $NaHCO_3$ (0.5N, 9 mL), the THF removed *in vacuo*, and the mixture extracted with dichloromethane. The aqueous layer was adjusted to pH 2 and the diazido acid removed by repeated extraction with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the diazido acid as a colorless oil (0.122 g, 66%): ^{1}H NMR: δ 4.0 (1 H, t, CHN_3), 3.3 (2 H, t, CH_2N_3), 1.6-2.1 (4 H, m); ^{13}C NMR (75 MHz): 175.7, 61.3, 50.6, 28.5, 25.1; IR (neat): 2100, 1710 cm^{-1}. The acid could not be distilled without decomposition and it gave no molecular ion on electron impact.

(5*S*)-[5-^{3}H]-L-Ornithine (13). (5*S*)-[5-^{3}H]-2,5-Diazidopentanoic acid (34.5 mg, 0.18 mM) was dissolved in absolute ethanol (3 mL) and 10% palladium on carbon (3 mg) added. The diazido acid was reduced under 80 psi of H_2 for a period of 12 h. The catalyst was then removed by filtration

through Celite and the filtrate taken to dryness *in vacuo*. The crude ornithine was purified by flash chromatography (cellulose, n-butanol:acetic acid:water, 4:2:2). The purified product was a white solid and weighed 32.4 mg (92%, sp. act. = 6.5 mCi/mM): TLC (cellulose, n-butanol:acetone:diethylamine:water, 70:70:35:70, R_f = 0.33); identical R_f and ninhydrin color was exhibited by authentic ornithine; ^{1}H NMR(D_2O): δ 3.83 (1 H, t, **CH**NH_2), 3.07 (2 H, t, **C**H_2NH_2), 1.90 (4 H, m).

(5*R*)-[5-^{3}H]-L-Ornithine (14). (5*R*)-[5-^{3}H]-L-Ornithine (**14**) was synthesized from (1*RS*)-[1-^{3}H]-5-hexenol (1a) in a manner that was identical to that employed to prepare (5*S*)-[5-^{3}H]-L-ornithine (**13**) except for the fact that *R*-Alpine Borane was utilized to reduce [*formyl*-^{3}H]-5-hexenal.

Stereospecificity of the Evans Azidation Reaction. In order to determine the stereospecificity of the Evans azidation reaction, the synthesis of unlabeled L-ornithine was carried out according to the preceding reaction conditions, with omission of the steps involved in the introduction of the tritium label. The L-ornithine so obtained was converted to its monohydrochloride and the rotation measured: $[\alpha]_D$ +7.2 (c = 2, H_2O); lit.: $[\alpha]_D$+11.0 (c = 5.5, H_2O).[14]

Analysis of Chirality of (1*S*)-($^2H_1$)-5-Hexen-1-ol.

5-Hexenoic Acid (15). Pyridinium dichromate (13.2 g, 35 mM) was suspended in 25 mL of DMF and 5-hexenol (1.0 g, 10 mM) was added with stirring under N_2. The mixture was stirred overnight and then diluted with water (250 mL). After repeated extraction with ether, the combined ether layers were extracted with excess 10% aq. $NaHCO_3$. The aqueous extract was acidified with 3N HCl to pH 4 and the liberated 5-hexenoic acid recovered by repeated extraction with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and the solvent removed *in vacuo* at room temperature to give the crude acid (0.98 g, 50%) which was pure enough to be used in the next step: TLC (SiO_2, n-hexane:ethyl acetate, 4:1, R_f = 0.23); ^{1}H NMR: δ 8.0 (1 H, bs, COOH), 5.8 (1 H, m, vinyl H), 5.0 (2 H, m, vinyl H), 2.3 (2 H, t, CH_2), 2.1 (2 H, t, CH_2), 1.8 (2 H, m, CH_2).

(1-$^2H_2$)-5-Hexen-1-ol. 5-Hexenoic acid (0.98 g, 8.6 mM) was added dropwise at 0° over a 10 min period to a suspension of lithium aluminum deuteride (0.36 g, 8.6 mM) in anhydrous ether

(15 mL) stirred under N_2. The ice-bath was then removed and the mixture allowed to warm to room temperature. Stirring at room temperature was continued for 3 h, at the end of which time the mixture was cooled in an ice-bath. The excess hydride was quenched by successive addition of water (0.36 mL), 15% aq. NaOH (0.36 mL) and water (1.08 mL) with continuous stirring. After an additional 30 min of stirring, the granular precipitate was removed by vacuum filtration, and the precipitate was washed thoroughly with ether. The combined ether phases were washed with excess 10% aq. $NaHCO_3$ and then dried ($MgSO_4$). Removal of the solvent *in vacuo* at room temperature gave (1-$^2H_2$)-5-hexen-1-ol (0.21 g, 50%); ^1H NMR : δ 6.0-5.5 (1 H, m, vinyl H), 5.0 (2 H, m, vinyl H), 2.0 (2 H, m, allylic CH_2), 1.8-1.4 (4 H, CH_2CH_2); complete deuteration at C-1 was indicated by the absence of a signal for C-1 at 3.6 δ. The alcohol was used without additional purification.

(1*S*)-(1-$^2H_1$)-5-Hexen-1-ol (17). Pyridinium chlorochromate (0.66 g, 3.1 mM) was suspended in dichloromethane (8 mL) and (1-$^2H_2$)-5-hexenol (0.21 g, 2.1 mM) was added with stirring under nitrogen. The mixture was stirred in an ice-bath for 14 h and sufficient ether was then added to cause precipitation of most of the chromium salts. The supernatant was passed through a Florisil column in order to eliminate the remaining chromium salts, and the column was washed with additional ether to ensure complete elution of the (*formyl*-$^2H_1$)-5-hexenal. Since the labeled aldehyde is quite volatile, most of the ether was then removed by careful distillation at *ca.* 40°. The undistilled residue was dissolved in dry THF (10 mL) and the resulting solution was added dropwise with stirring under N_2 to a THF solution of *R*-Alpine Borane (0.5M, 4.1 mL). The reaction mixture was stirred at room temperature for 10 min and then refluxed 2 h. The reaction mixture was cooled and the solvent removed *in vacuo*. The residue was dissolved in dry ether and the solution cooled in ice. Ethanolamine (0.13 mL, 1.1 eq.) was added and the mixture stirred 20 min at ice-bath temperature. The white precipitate that formed was removed by vacuum filtration, and the filtrate was concentrated *in vacuo* to give a yellowish oil that was purified by flash chromatography (SiO_2, n-hexane:ethyl acetate, 4:1) to give (1*S*)-(1-$^2H_1$)-5-hexen-1-ol (53.3 mg, 33%); ^1H NMR: δ 6.0-5.5 (1 H, m, vinyl H), 5.0 (2 H, m, vinyl H), 3.6 (1 H, bs, CHDOH), 2.0 (2 H, m, allylic CH_2), 1.8-1.4 (4 H, m, CH_2CH_2).

(-)-Camphanate Ester of (1*S*)-($^2H_1$)-5-Hexen-1-ol (18). To a stirred solution of alcohol **17** (25 mg, 0.25 mM) in dichloromethane (5 mL), (-)-camphanoyl chloride (60 mg, 0.28 mM) was

added. This was followed by triethylamine (39 uL, 0.27 mM) and a catalytic amount of 4-dimethylaminopyridine (10 mol %). The reaction was allowed to proceed at room temperature for 24 h and water was then added. The organic phase was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave the crude ester, which was purified by flash chromatography (SiO_2, n-hexane:ethyl acetate, 6:1) to yield the pure ester **18** (59.4 mg, 85%) as a colorless oil; TLC (SiO_2, n-hexane:ethyl acetate, 6:1, R_f = 0.48); ^{1}H NMR (300 MHz) δ 5.7 (1 H, m, vinyl H), 5.0 (2 H, m, vinyl H), 4.2 (1 H, t, CHDOH), 2.4 (1 H, m), 2.1-1.8 (4 H, m), 1.5 (2 H, m), 1.1 (3 H, s, CH_3), 1.0 (3 H, s, CH_3), 0.9 (3 H, s, CH_3); ^{13}C NMR (75 MHz) δ 178.1, 167.5, 138.0, 114.9, 98.0, 91.1, 65.5, 54.7, 54.1, 33.1, 30.6, 28.9, 27.9, 25.0, 16.72, 16.69, 9.65; ^{13}C NMR (DEPT) **CH_2**: 114.9, 65.5, 33.1, 28.9, 27.9, 25.0; **CH**: 138.0; **CH_3**: 16.72, 16.68, 9.65. The product could not be distilled, and it gave no molecular ion on electron impact.

(-)-Camphanate Ester of (1*S*)-(1-$^2H_1$)-1-Hexanol (19). The (-) camphanate derivative **18** (34.1 mg, 0.12 mM) was dissolved in ethyl acetate (5 mL) and 10% palladium on carbon (3.4 mg) was added. Catalytic hydrogenation was carried out at atmospheric pressure and room temperature for a period of 16 h. The catalyst was then removed by filtration, washed with ethyl acetate, and the combined ethyl acetate fractions taken to dryness *in vacuo* to give the ester **19** as a colorless oil (30.5 mg, 89%). TLC (SiO_2, n-hexane:ethyl acetate, 6:1, R_f = 0.47); ^{1}H NMR δ 4.2 (1 H, t, CHDOH), 2.3 (1 H, m), 2.2-1.8 (2 H, m), 1.9-1.65 (3 H, m), 1.4 (6 H, m), 1.1 (3 H, s, CH_3), 1.05 (3 H, s, CH_3), 0.9 (3 H, s, CH_3), 0.85 (3 H, t, **CH_3CH_2**); ^{13}C NMR (300 MHz) d 178.0, 167.3, 90.9, 65.0, 53.8, 53.0, 31.0, 30.3, 28.7, 25.2, 22.2, 16.52, 16.47, 13.7, 9.5. The product could not be distilled, and it gave no molecular ion on electron impact.

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