27A as a colorless oil: $R_f 0.53$ (40% EtOAc/petroleum ether); $[\alpha]_D$ +10.0° (c 0.23, CHCl₃); IR 3600-3300, 2980, 2940, 1750-1730, 1460, 1290, 1080, 1015, 920 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.381 (d, 1 H, J = 8.5 Hz), 7.113 (d, 1 H, J = 3.1 Hz), 6.671 (dd, 1 H, J, J' = 8.5, 3.1 Hz), 5.015 (dt, 1 H, J, J' = 9.2, 5.7 Hz), 5.00 (m, 1 H), 4.528 (dd, 1 H, J, J' = 7.6, 4.9 Hz), 3.914 (dd, 1 H, J, J' = 10.7, 2.1 Hz), 3.90 (m, 1 H), 3.798 (s, 3 H), 3.348 (dt, 1 H, J, J' = 2.7, 10.7 Hz), 3.256 (s, 3 H), 2.738 (abx, 1 H, J, J' = 11.3, 4 Hz, $\Delta v = 15.3$), 2.699 (ab, 1 H, J = 11.3 Hz, $\Delta v = 15.3$), 2.631 (abx, 1 H, J, J' = 12.5, 2.8 Hz, $\Delta v = 12.5$ 150), 2.439 (dd, 1 H, J, J' = 15.4, 2.3 Hz), 2.42 (br s, 1 H), 2.248 (dd, 1 H, J, J' = 12.2, 11 Hz), 1.90 (m, 1 H), 1.70–1.20 (20 H, H₂,O), 1.169 (d, 3 H, J = 6.4 Hz), 0.895 (s, 3 H), 0.811 (s, 3 H), 0.809 (d, 3 H, J= 6.4 Hz, 0.794 (d, 3 H, J = 6.1 Hz), 0.746 (d, 3 H, J = 6.7 Hz); exact mass calcd for C33H50BrO9 (MH+) 669.2638, found 669.2648.

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Supplementary Material Available: General experimental conditions; experimental details for 8a, 20b-27B, attempted deprotection of 23A, Barton oxidation and Mosher esters of 8, 8a, and 17 (18 pages). Ordering information is given on any current masthead page.

Synthesis of Chirally Deuteriated Phthalimidopropanols and Evaluation of Their Absolute Stereochemistry

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Abstract: (1R)- $[1-^{2}H]$ - and (1S)- $[1-^{2}H]$ -3-phthalimido-1-propanols were synthesized by two independent routes and were initially analyzed for absolute stereochemistry by ¹H NMR spectroscopy of the derived (-)-camphanate esters, 8a and 8b, in the presence of Eu(fod)₃. As subsequently determined by conversion of one of the sample alcohols to 1(S)-[1-²H]heptanol and analysis of its (-)-camphanate by Eu(dpm)₃/¹H NMR, the europium-induced shift of the phthalimidopropanol camphanate resonances resulted in the pro-1R resonance appearing downfield from the pro-1S resonance. This result was contrary to the empirical rule that the pro-1S hydrogen resonance of primary alcohol camphanates appears downfield of the pro-1R hydrogen resonance in the presence of europium.

In order to probe the stereochemistry involved in the biosynthesis of acivicin² and blasticidin³ and in the reaction catalyzed by the enzyme spermidine synthase (EC 2.51.16),⁴ ornithine, 1, arginine, 2, and decarboxylated S-adenosyl-L-methionine (dcSAM), 3, each chirally deuteriated at C-3, were needed. An activated form of chirally deuteriated phthalimidopropanol ${\bf 4}$ was envisioned as the key intermediate, which could be converted to the above chirally deuteriated precursors as illustrated in Scheme I. Two independent routes for the synthesis of 4 were developed. In each case the chirality at the labeled center was analyzed by ¹H NMR of the (-)-camphanate derivative in the presence of europium. The results reported here unequivocally establish the absolute stereochemistry of each sample and reveal that the presence of the phthalimido group altered the camphanate-europium interaction from the well-accepted empirical formulation⁵ and would, if undetected, have led to erroneous conclusions.

Results

One synthesis of 4 applied a purely chemical route whereby chirality was introduced by stereospecific reduction of the deuteriated aldehyde 6a (Figure 1). Commercially available ethyl 3-chloropropionate, 5, was reduced with $LiAlD_4$ and the resulting 3-chloro-1,1-dideuteriopropanol was converted into 1,1-dideuteriophthalimidopropanol in 50-55% overall yield. This product was oxidized to deuterio aldehyde 6a, by using Swern's procedure,⁶ in 95% yield. Portions of the deuterio aldehyde were reduced to a chirally deuteriated phthalimidopropanol, 7a or 7b, with either S-Alpine-Borane or R-Alpine-Borane (Aldrich), respectively.7

The stereochemistry of the Midland reduction could be assumed from the large number of literature precedents:^{7,8} reduction of a deuteriated aldehyde with R-Alpine-Borane yields the S alcohol and with S-Alpine-Borane yields the R alcohol. Rather than rely

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h. N₂H₄ H₂O, MeOH, 1 TsCl, El₃N, CH₂Cl₂, 1 Ac₂O, AcOH, NaNO₂,

k. Na₂CO₃, CCl₄, Δ; † Bu₂CuLi, Et₂O, m Bu₄NF

Figure 1. Synthesis of $(1R)-[1-^2H]$ - and $(1S)-[1-^2H]$ phthalimidopropanols, 7a and 7b, and conversion of 7b to $1(S)-[1-^2H]$ heptanol. Portions of the ¹H NMR spectra (400 MHz) of their (-)-camphanates—8a, 8b, and 14a—in the presence of Eu(fod)₃ corresponding to hydrogens at C-1 are shown to the right of each structure.

on analogy, the stereochemistries at C-1 of 7a and 7b were analyzed by using the method of Gerlach and Zagalak,⁵ which has been widely used in stereochemical studies.⁹ Thus, each was converted to its corresponding (-)-camphanate, 8a or 8b, respectively, by stirring with (-)-camphanoyl chloride in methylene chloride in the presence of triethylamine.

The second route to 4 made use of a combination of enzymatic and chemical processes. γ -Aminobutyric acids 9a and 9b of known chirality were generated with glutamate decarboxylase,¹⁰ but the chirally labeled center was subsequently altered in a stereocontrolled manner to replace nitrogen with oxygen (Figure 2).¹¹

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This involved thermal rearrangement¹² of a nitroso sulfonamide derived from **9a** and **9b** to afford the tosylate **10a** or **10b**. To check their chirality and optical purity, each was converted to its acetate, **11a** and **11b**, respectively, with tetrabutylammonium acetate in acetone. The acetates were hydrolyzed with methanolic HCl, and the resulting alcohols were esterified with (-)-camphanoyl chloride in pyridine to give **8a** and **8b**, respectively.

For reasons of solubility, $Eu(fod)_3$ was adopted for the chirality analysis. As a solution of unlabeled camphanate **8** was titrated with the shift reagent, it was observed that the resonances for the prochiral hydrogens adjacent to the phthalimido group began to shift and resolve first. However, with the addition of ca. 80 mol % of shift reagent, the desired prochiral methylene resonances were resolved. When the labeled samples **8a** and **8b**, prepared as shown in Figure 1, were similarly treated, results opposite to those expected were obtained. The spectrum of the camphanate obtained via *R*-Alpine-Borane reduction had the smaller peak in the higher field resonance, indicating the deuterium was in the *pro-R* position, while the complementary result was obtained with the sample from *S*-Alpine-Borane (Figure 1). By all literature precedents, ^{5,8b,c,g,h,9,10} in the presence of europium the *pro-S* hydrogen resonance should shift further downfield than the *pro-R* hydrogen resonance.

Analysis of **8a** and **8b**, prepared as shown in Figure 2, revealed that the sample **8a**, produced from (R)-GABA, contained the bulk of the deuterium (79%) in the downfield resonance, and the complementary result was obtained from the sample **8b**, derived from (S)-GABA. The same results were obtained with the

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Reagents

a, Glutamate decarboxylase; b. Phthalic anhydride, c. EtO-C(O)Cl, Et_3N , d. NaN_3, e. t-BuOH, Δ ; f. N₂H₄, g. TsCl,

h. Phthalic anhydride; Η NaNO₂, AcOH; J. Na₂CO₃, dioxane, Δ, k. Bu₄NOAc, acetone; H H Cl. MeOH, m. (-)-Camphanoyl chloride, pyridine.

Figure 2. Synthesis of (1R)- $[1-^2H]$ - and (1S)- $[1-^2H]$ phthalimidopropanol tosylates, 10a and 10b, and their conversion to the acetates and (-)-camphanates. Portions of the ¹H NMR spectra (200 MHz) of the acetates in the presence of Eu(hfc)₃ and of the camphanates in the presence of Eu(fod)₃ corresponding to hydrogens at C-1 are shown to the right of each structure.

Scheme I



acetates 11a and 11b in the presence of the chiral shift reagent $Eu(hfc)_3$ (Figure 2).

In view of the surprising results from the first synthesis, it was clear that either the Midland reduction or the camphanate analysis had proceeded in contradiction to the literature precedents. To resolve this ambiguity and establish the correct absolute stereochemistry of all samples, the phthalimidopropanol **7b**, derived from the *R*-Alpine-Borane reduction, was converted to one of the chirally deuteriated 1-heptanols, which can be used as absolute configurational standards. These have been unambiguously synthesized and have been analyzed by using the camphanate method.^{8ij}

Phthalimidopropanol 7b was protected as its t-BDMS ether, and the phthalimido group was removed by treatment with methanolic hydrazine. Several attempts were made to deaminate the resulting *t*-BDMS-protected aminopropanol **12a**, including direct halodeamination¹³ as well as conversion of the amino function to a good leaving group followed by treatment with nucleophiles.¹⁴ Success was achieved when the amine was converted to the *N*-nitroso sulfonamide and then to the tosylate **13a** upon heating at reflux in CCl_4 .¹² The tosylate was then treated with lithium di-*n*-butylcuprate,¹⁵ yielding the *t*-BDMS ether of

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Figure 3. Conversion of (1S)- $[1-^2H]$ phthalimidopropanol, 7b, to (-)-camphanate 8b and conversion to acetate 11a via the mesylate. Portions of the ¹H NMR spectra (400 MHz) of 8b and 11a in the presence of Eu(fod)₃ and Eu(hfc)₃, respectively, are shown to the right of each structure.

chirally deuteriated heptanol, which was deprotected with tetrabutylammonium fluoride to give chirally deuteriated heptanol. This was converted to its (-)-camphanate derivative **14a** (see Figure 1). The 400-MHz ¹H NMR spectrum of **14a** was analyzed in the presence of 80 mol % of Eu(dpm)₃, and the smaller peak was now the downfield resonance, revealing that the alcohol, in fact, had the *S* configuration (see Figure 1). The same primary center had seemed to have the *R* configuration when it had been analyzed as the (-)-camphanate of the phthalimido alcohol (see Figure 1).

A potential ambiguity still remained with the second route, whereby it had been assumed that the acetolyses of 10a and 10b (Figure 2) had proceeded with inversion of configuration. This was shown to indeed be the case (see Figure 3). Alcohol 7b, obtained from the first route, now known to have the S configuration, was converted to the mesylate 15b and then treated with tetra-*n*-butylammonium acetate in acetone. The resulting acetate 11a was analyzed by 400-MHz ¹H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)₃. This was compared with the spectrum of phthalimidopropanol (-)-camphanate (8b) taken in the presence of Eu(fod)₃. The results indicated that the mesylate had undergone total inversion as expected.

Discussion

The analysis of chirality of deuteriated primary alcohols from the ¹H NMR spectra of their (-)-camphanate derivatives in the presence of europium has been a valuable tool for nearly 15 years. A number of such studies have relied on the empirical correlation that the *pro-S* resonance is shifted further downfield than the *pro-R* resonance, first noted by Gerlach and Zagalak,⁵ while others have also converted the labeled alcohol to a primary configurational standard.

From the results of the present study it is clear that simple reliance on the empirical rule for camphanates would have led to erroneous conclusions. The initial results, however, indicated that either this rule or the generally accepted prediction for Midland reduction of aldehydes was inoperative. The results of our analysis of the deuteriated heptanol clearly reveal that the Midland reduction had proceeded in the normal fashion: *R*-Alpine-Borane reduced the deuteriated aldehyde to the *S* alcohol; and *S*-Alpine-Borane reduced it to the *R* alcohol. It is possible that the phthalimide moiety in 8 caused complexation with europium in a manner that altered the normal juxtaposition relative to the camphanate and the relevant prochiral hydrogens.

Experimental Section

General Methods. ¹H NMR and ¹³C NMR spectra were recorded either on a Bruker AM 400 (400.13 and 100.61 MHz, respectively), on a Varian FT-80A (80 and 20 MHz, respectively), or on a Varian XL200 (200 MHz) spectrometer. All chemical shifts for ¹H and ¹³C NMR spectra are reported in parts per million relative to tetramethylsilane (Me₄Si, δ 0.00). Infrared spectra were recorded in wavenumbers on either a Nicolet 5DXB FT-IR or a Perkin-Elmer 727B spectrometer. Low-resolution mass spectra were taken on a MAT CH-7 spectrometer. High-resolution mass spectra were taken on a Kratos MS 50 TC spectrometer. Melting points were taken on a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed by R. Johnson at Desert Analytics (Tucson, AZ). Flash chromatography was carried out with use of silica gel (EM Reagents, Keiselgel 60, 230-400 mesh). Analytical thin-layer chromatography (TLC) was carried out on precoated Keiselgel 60 F₂₅₄ (either 0.2-mm aluminum sheets or 0.25-mm glass plates) and visualized by long- and/or short-wave UV.

Materials. All solvents were reagent grade and used directly as purchased except for tetrahydrofuran (THF), which was distilled over sodium with benzophenone ketyl as indicator, and methylene chloride, which was distilled over calcium hydride.

N-(3-Hydroxypropyl)phthalimide. To a mechanically stirred suspension of LiAlH₄ (2.5 g, 0.066 mol) in absolute ether (150 mL) at 0 °C under N₂ was added ethyl 3-chloropropionate, 5, (15 g, 0.11 mol) dropwise over 30 min while the temperature was kept at 0 °C. After the addition, the mixture was warmed to room temperature, stirred for 3 h, and then cooled to 5 °C in an ice bath. Excess LiAlH₄ was quenched by successive addition of H₂O (2.4 mL), NaOH (15% solution, 2.4 mL), and H₂O (7.2 mL). The mixture was stirred for 30 min and allowed to settle for 2 h, and the resulting white precipitate was removed by vacuum filtration. The residue was thoroughly washed with ether, and the combined filtrates were evaporated under reduced pressure to give 3-chloropropanol.

The crude product was reacted with potassium phthalimide (35.3 g, 0.19 mol) in dry DMF (100 mL) at 120 °C for 4 h. After the mixture was cooled to room temperature, CHCl₃ (150 mL) was added, and the mixture was poured into water (500 mL). The organic layer was repeatedly washed with water and dried (Na₂SO₄) and on removal of solvent under reduced pressure gave a white, crystalline solid, which was recrystallized from 95% EtOH to give 11.0 g (49% from 5) of pure phthalimido alcohol: mp 75-76 °C (litt.¹⁶ mp 75-79 °C); IR (CHCl₃)

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3550, 1725, 1450 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ 7.77 (m, 4 H), 3.86 (t, 2 H, J = 6.4 Hz), 3.59 (t, 2 H, J = 6 Hz), 2.55 (br s, 1 H), 1.87 (tt, 2 H, J = 6 Hz).

N-(3-Hydroxy[3,3-²H₂]**propyl)phthalimide.** Via the above procedure, ethyl 3-chloropropionate, **5**, (15 g, 0.11 mol) was reduced with LiAlD₄ and then converted to 11.5 g (51% from **5**) of deuteriated phthalimido-propanol: ¹H NMR (80 MHz, CDCl₃) δ 7.79 (m, 4 H), 3.86 (t, 2 H, J = 8 Hz), 2.51 (s, 1 H), 1.87 (t, 2 H, J = 8 Hz).

N-(3-Oxopropyl)phthalimide (6). Oxalyl chloride (0.32 mL, 3.52 mmol) was taken up in dry CH_2Cl_2 (25 mL) and stirred under N_2 at -60 °C. To this was added dry DMSO (0.6 mL, 7.04 mmol) in dry CH_2Cl_2 (5 mL), and the resulting mixture was stirred for 5 min. The phthalimidopropanol (0.765 g, 3.2 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise to the reaction flask with continuous stirring, while the temperature was maintained below -50 °C. After 25 min, Et₃N (2.3 mL, 16 mmol) was added dropwise, and the resulting paste was allowed to warm to room temperature and stirred for 5 min. Water (50 mL) was added, the phases were separated, and the CH_2Cl_2 layer was washed successively with 1% HCl, 5% Na₂CO₃, and H₂O. It was then dried (Na₂SO₄) and concentrated in vacuo to give a white solid, which was recrystallized from CH_2Cl_2 -hexane to give 0.59 g (91% yield) of pure 6: mp 126-127 °C (lit.¹⁷ mp 125-126 °C); ¹H NMR (80 MHz, CDCl₃) δ 9.82 (t, 1 H, J = 1.3 Hz), 7.7-7.9 (m, 4 H), 4.04 (t, 2 H, J = 7 Hz), 2.87 (dt, 2 H, J = 7, 1.3 Hz).

N-(3-Oxo[3-²H]propyl)phthalimide (6a). Via the above procedure, the dideuteriophthalimido alcohol (11 g, 53 mmol) was converted into 9.84 g (91% yield) of deuterio aldehyde 6a: ¹H NMR (80 MHz, CDCl₃) δ 7.78 (m, 4 H), 4.04 (t, 2 H, J = 9 Hz), 2.87 (t, 2 H, J = 9 Hz).

Reduction of N-(3-Oxopropyl)phthalimide. A solution of the aldehyde 6 (500 mg, 2.5 mmol) in dry THF (10 mL) was added dropwise to the stirred reagent, R- or S-Alpine-Borane (6 mL, 0.5 M solution, 3 mmol), under N₂. After 10 min, the mixture was heated at reflux for 2 h and cooled to room temperature, and the solvent was removed under reduced pressure. The resulting gum was taken up in anhydrous ether (50 mL) and cooled in an ice bath. Ethanolamine (0.2 mL, 3.2 mmol) was added, and the mixture stirred for 20 min. The white precipitate that formed was removed by filtration under vacuum, and the filtrate was concentrated under reduced pressure to give a yellowish oil, which was subjected to flash column chromatography (SiO₂, 1:1 hexane-EtOAc) to give 380 mg (75%) of pure alcohol. The ¹H NMR spectrum was the same as that of N-(3-hydroxypropyl)phthalimide.

Reduction of N-(3-Oxo[3-²H]propyl)phthalimide. The above procedure was followed to convert the deuterio aldehyde (a total of 4.5 g, 22.05 mmol in two batches) into 2.65 g (58% yield) of (3R)-[3-²H]alcohol 7a by using S-Alpine-Borane (a total of 47.5 mL, 0.5 M solution, 24.7 mmol in two batches). Similarly the deuterio aldehyde (a total of 4.5 g, 22.05 mmol in two batches) was reduced to 3.6 g (80% yield) of (3S)-[3-²H]alcohol 7b by using R-Alpine-Borane (a total of 47.5 mL, 24.7 mmol in two batches): mp 126-127 °C; ¹H NMR (80 MHz, CDCl₃) δ 7.81 (m, 4 H), 3.86 (t, 2 H, J = 6.2 Hz), 3.61 (t, 1 H, J = 1.2 Hz), 2.55 (s, 1 H), 1.92 (q, 2 H, J = 6.2 Hz).

N-[3-[(Methylsulfonyl)oxy]propyl]phthalimide (15). The following procedure is typical. To a stirred solution of *N*-(3-hydroxypropyl)-phthalimide (1.00 g, 4.8 mmol) and methanesulfonyl chloride (0.42 mL, 5.36 mmol) in dry CH₂Cl₂ (50 mL) at −78 °C under N₂ was added Et₃N (0.75 mL, 5.36 mmol) dropwise. After 1 h, the paste was warmed to room temperature, stirred at 25 °C for 2 h, and poured into cold H₂O (50 mL). The CH₂Cl₂ layer was separated, dried (Na₂SO₄), and recrystallized from 95% EtOH to give 1.38 g (100%) of a white solid: mp 132–133 °C; IR (CHCl₃) 3300, 3130, 1770, 1378 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ 7.8 (m, 4 H), 4.25 (t, 2 H, J = 6 Hz), 3.84 (t, 2 H, J = 6.5 Hz), 3.05 (s, 3 H), 2.15 (tt, 2 H, J = 6 Hz); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.24, 134.16, 131.99, 123.35, 67.21, 37.45, 34.44, 28.28. Anal. Calcd for C₁₂H₁₃NO₅S: C, 50.87; H, 4.63; N, 4.94; S, 11.32. Found: C, 51.17; H, 4.46; N, 4.83; S, 11.07.

N-[3(R)-[(Methylsulfonyl)oxy][3-²H]propyl]phthalimide (15a) and N-[3(S)-[(Methylsulfonyl)oxy][3-²H]propyl]phthalimide (15b). Via the above procedure (3R)-[3-²H]alcohol 7a (2.1 g, 10.2 mmol) and (3S)-[3-²H]alcohol 7b (2.0 g, 9.7 mmol) were each converted into their mesylates, 15a (2.75 g, 95%) and 15b (2.7 g, 95%), respectively: ¹H NMR (80 MHz, CDCl₃) δ 7.8 (m, 4 H), 4.25 (t, 1 H, J = 6.1 Hz), 3.84 (t, 2 H, J = 6.6 Hz), 3.04 (s, 3 H), 3.15 (q, 2 H, J = 6 Hz). N-(3-Acetoxypropyl)phthalimide (11). A. N-(3-Bromopropyl)-

N-(3-Acetoxypropyl)phthalimide (11). A. N-(3-Bromopropyl)phthalimide (Aldrich) (268 mg, 1 mmol) was dissolved in 10 mL of acetone together with 1.301 g (4.32 mmol) of tetra-*n*-butylammonium acetate, and the reaction mixture was stirred for 8 h at ambient temperature, protected from atmospheric moisture by means of a CaCl₂

(17) Atkinson, R. O.; Poppelsdorf, F. J. Chem. Soc. 1952, 2448.

drying tube. The reaction solvent was then removed in vacuo, the residue was partitioned between EtOAc and H_2O (5 × 50 mL), and the dried organic extract was concentrated in vacuo to give a crystalline solid product; yield, 236 mg (99%). Recrystallization from Et₂O-petroleum ether gave 170 mg (72%) of needlelike crystals, mp 62-63 °C (lit.¹⁸ mp 63.5-65 °C): ¹H NMR (CDCl₃) δ 7.75 (m, 4 H, Ar), 4.12 (t, 2 H, J = 6 Hz, CH₂O), 3.81 (t, 2 H, J = 7 Hz, CH₂NPhT), 2.05 and 2.01 (overlapping t and s, 5 H, CH₂ and CH₃).

The \hat{R} isomer 11a was obtained by reaction of 10a¹¹ (50 mg, 0.134 mmol) and 250 mg (0.831 mmol) tetra-*n*-butylammonium acetate in 15 mL acetone as described above for 11. The desired acetate was isolated as described above and purified by flash chromatography with hexanes-EtOAc (1.5:1) as the eluting solvent to give 26 mg (81%) of 11a as a colorless oil: ¹H NMR (CDCl₃) δ 4.10 (t, 1 H, J = 3 Hz, CHDO), all other resonances as observed for 11.

The S isomer 11b was obtained from $10b^{11}$ by identical procedures with those described above for the synthesis of the R isomer 11a: ¹H NMR (CDCl₃) identical with the R acetate 11a derived from 10a. The chiral acetates 11a and 11b could be distinguished from one another by the use of the chiral NMR shift reagent Eu(hfc)₃ (Figure 2).

B. Alternatively, the acetate **11a** was prepared from the mesylate **15b** with the following procedure. The mesylate **15b** (60 mg, 0.21 mmol) and tetra-*n*-butylammonium acetate (340 mg, 1.13 mmol) were stirred at room temperature in dry acetone (5 mL) for 15 h. Acetone was removed in vacuo, and the resulting solid was taken up in CH₂Cl₂ (10 mL) and washed with H₂O (2 × 15 mL). The organic layer was dried over Na₂SO₄. Solvent removal gave 53 mg (100%) of crystalline product, which was recrystallized from hexane-ethyl acetate to give 49 mg (95%) of **11a**: ¹H NMR (400 MHz, CDCl₃) δ 7.7-7.9 (m, 4 H), 4.12 (t, 1 H, J = 6 Hz), 3.80 (t, 2 H, J = 6.7 Hz), 1.9-2.1 (m, 5 H).

3-Phthalimido-1(R)-[1-²H]propyl (-)-Camphanate (8a). The acetate 11a (25 mg, 0.105 mmol) was dissolved in 5 mL of dry methanolic HCl, and the resulting solution was stirred for 20 h under N₂ at ambient temperature. At the end of this time, the solvent was removed in vacuo, and the residue was dissolved in 1 mL of pyridine. Addition of 200 mg (0.93 mmol) of freshly sublimed (-)-camphanoyl chloride (Fluka) to the cooled (0 °C) solution, followed by stirring overnight and standard workup conditions led to isolation of the desired product. The product was purified by flash chromatography with hexanes-EtOAc (1:1) as the eluting solvent; yield, 18 mg (45%) of an oil: ¹H NMR (CDCl₃) δ 7.76 (m, 4 H, Ar), 4.27 (t, 1 H, J = 3 Hz, CHDO), 3.82 (t, 2 H, J = 7 Hz, CH₂N), 2.44, 2.10-1.80 and 1.70 (br m, 6 H, CH₂), 1.12 (ds, 6 H, gem-CH₃), 1.0 (s, 3 H, CH₃).

3-Phthalimido-1(S)-[1-²H]propyl (-)-Camphanate (8b). The acetate 11b (25 mg, 0.105 mmol) was converted to the (-)-camphanate 8b exactly as described above for the synthesis of 8a; yield, 20 mg (50%) of an oil. ¹H NMR (CDCl₃) was identical with the *R* derivative 8a derived from 11a.

N-[3-(tert-Butyldimethylsiloxy)propyl]phthalimide. Et₃N (0.19 mL, 1.33 mmol) was added dropwise to a stirred solution of alcohol 7 (205 mg, 1 mmol), t-BDMSCl (200 mg, 1.33 mmol), and a catalytic amount (10 mol %) of 4-(dimethylamino)pyridine in CH₂Cl₂ (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 8 h. After extraction with H_2O (2 × 15 mL), the organic layer was dried (Na₂SO₄). Concentration in vacuo gave an oily residue that was further purified by flash column chromatography (30 g of SiO₂, 6% EtOAc in hexane) to give 300 mg (95% yield) of pure product as a colorless oil: IR (neat) 3076, 2950, 1715, 1395 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.69–7.85 (m, 4 H), 3.79 (t, 2 H, J = 7 Hz), 3.67 (t, 2 H, J = 6.1 Hz), 1.89 (tt, 2 H, J = 6.7 Hz), 0.86 (s, 9 H), 0.03 (s, 6 H); ¹³C NMR (100.6 MHz, CDCl₃) & 168.33, 133.77, 132.34, 123.10, 60.91, 35.60, 31.56, 25.86, 18.24, -5.43; high-resolution mass spectrum calcd for C₁₃H₁₆NO₃Si (M - 57) 262.08993, found 262.08994; EIMS, m/z 262 (100), 204 (17), 160 (11.2). Anal. Calcd for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.88; N, 4.38. Found: C, 63.91; H, 7.91; N, 4.37.

N-[3(*S*)-(*tert*-Butyldimethylsiloxy)[3-²H]propyl]phthalimide. By following the above procedure, (1*S*)-[1-²H]alcohol 7b (0.42 g, 2.05 mmol) was converted to 0.64 g (97% yield) of the *t*-BDMS derivative: ¹H NMR (400 MHz, CDCl₃) δ 7.69–7.85 (m, 4 H), 3.79 (t, 2 H, *J* = 7 Hz), 3.67 (t, 1 H, *J* = 6.1 Hz), 1.89 (dt, 2 H, *J* = 6.7 Hz), 0.86 (s, 9 H), 0.03 (s, 6 H).

3-(*tert*-Butyldimethylsiloxy)propylamine (12). The phthalimido silyl ether (520 mg, 1.62 mmol) was treated with excess methanolic hydrazine (30 mL of 0.2 M solution) and allowed to react at room temperature for 8 h, followed by removal of excess hydrazine and methanol under reduced pressure. The residue was redissolved in 100% EtOH, and the solvent was removed under reduced pressure. The resulting residue was taken

⁽¹⁸⁾ Chapman, J. M., Jr.; Cocolas, G. H.; Hall, I. H. J. Med. Chem. 1979, 22, 1399-1402.

up in CH₂Cl₂ (20 mL), the undissolved solid was removed by filtration, and the solid was washed with CH₂Cl₂ (10 mL). Concentration of the filtrate under reduced pressure and Kugelrohr distillation of the residue (35–40 °C at 5 mmHg) gave 275 mg (89% yield) of pure 12: IR (neat) 3300, 2950, 2850, 1395 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.68 (t, 2 H, J = 6.1 Hz), 2.75 (t, 2 H, J = 7.2 Hz), 1.7 (broad peak, 2 H), 1.6 (tt, 2 H, J = 6 Hz), 0.84 (s, 9 H), 0.03 (s, 6 H); ¹³C NMR (100.6 MHz, CDCl₃) δ 61.24, 39.44, 36.46, 25.95, 18.29, -5.34; high-resolution mass spectrum calcd for C₃H₁₄NOSi (M - 57) 132.0844, found 132.0845; EIMS, m/z 132 (100), 104 (42), 75 (32).

3(S)-(*tert*-Butyldimethylsiloxy)[3-²H]propylamine (12a). By the above procedure, the deuterio compound (0.70 g, 2.2 mmol) was converted into 0.24 g (58% yield) of product 12a: ¹H NMR (400 MHz, CDCl₃) δ 3.68 (t, 1 H, J = 5.6 Hz), 2.80 (t, 2 H, J = 6.5 Hz), 2.2 (broad peak, 2 H), 1.66 (dt, 2 H, J = 6.5 Hz), 0.89 (s, 9 H), 0.03 (s, 6 H).

N-[3-(tert-Butyldimethylsiloxy)propyl]-p-toluenesulfonamide (13). A stirred solution of the amine 12 (945 mg, 5 mmol) and p-toluenesulfonyl chloride (1.05 g, 5.5 mmol) in CH₂Cl₂ (15 mL) at 0 °C was treated dropwise with Et₃N (0.76 mL, 5.5 mmol). After 2 h, the reaction mixture was warmed to room temperature, and the stirring was continued for 6 h. The mixture was washed with H_2O (3 × 50 mL), and the organic layer was dried (Na₂SO₄). A crude oily product was obtained after solvent removal, and this was further purified by flash column chromatography (30 g SiO₂, CH_2Cl_2 solvent) to give 1.60 g (93% yield) of pure product as an oil: IR (neat) 3285, 3037, 2950, 1600 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) & 7.30-7.70 (m, 4 H), 5.2 (br t, 1 H), 3.61 (t, 2 H, J = 5.6 Hz), 3.05 (dt, 2 H, J = 6.2 Hz), 2.39 (s, 3 H), 1.62 (tt, 2 H, J = 6.1 Hz), 0.88 (s, 9 H), 0.03 (s, 6 H); ¹³C NMR (100.6 MHz, $CDCl_3$) δ 143.18, 137.13, 129.63, 127.15, 62.17, 43.13, 31.25, 25.86, 21.49, 18.13, -5.51; high-resolution mass spectrum calcd for $C_{12}H_{20}N$ - $O_3SSi (M - 57) 286.0933$, found 286.0935; EIMS, m/z 328 (12), 286 (100), 155 (88), 91 (100). Anal. Calcd for $C_{16}H_{29}NO_3Si$: C, 55.94; H, 8.51; N, 4.07. Found: C, 56.03; H, 8.74; N, 3.78.

N-[3(*S*)-(*tert*-Butyldimethylsiloxy)[3⁻²H]propyl]-*p*-toluenesulfonamide (13a). The above procedure was followed to convert the deuteriated amine 12a (240 mg, 1.26 mmol) into 0.364 g (84% yield) of sulfonamide 13a: ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.54 (m, 4 H), 5.20 (br t, 1 H), 3.63 (t, 1 H, J = 5.4 Hz), 3.08 (dt, 2 H, J = 6.1 Hz), 2.43 (s, 3 H), 1.65 (dt, 2 H, J = 5.8 Hz), 0.87 (s, 9 H), 0.03 (s, 6 H).

1-[(tert-Butyldimethylsilyl)oxylheptane. To a stirred solution of the sulfonamide **13** (171 mg, 0.5 mmol) in glacial acetic acid (0.51 mL) and acetic anhydride (2.5 mL) at 0 °C was added finely powdered NaNO₂ (0.77 g, 11.1 mmol) over a period of 4 h. The stirring was continued for another 12 h at 0 °C, and the mixture was then poured into cold H₂O (15 mL). This was stirred for 15 min and then extracted with ether. The ether layer was washed with H₂O, 5% NaHCO₃, H₂O, and NaCl and dried (Na₂SO₄). Concentration in vacuo gave 0.178 g (96%) of crude product as a yellowish oil: IR (neat) 3044, 2950, 2850, 1600 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.89 (m, 4 H), 3.77 (t, 2 H, *J* = 6.5 Hz), 0.89 (s, 9 H), 0.03 (s, 6 H).

The crude product was refluxed in CCl₄ (15 mL) along with anhydrous Na₂CO₃ (55 mg, 0.52 mmol) under an N₂ atmosphere for 20 h. The solid Na₂CO₃ was removed by filtration, and the filtrate was concentrated under reduced pressure to give 130 mg (79% crude yield) of tosylate as an oil: IR (neat) 3038, 2950, 1600, 1490 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.80 (m, 4 H), 4.15 (t, 2 H, J = 6.5 Hz), 3.65 (t, 2 H, J = 5.7 Hz), 2.48 (s, 3 H), 1.87 (tt, 2 H, J = 5.9 Hz), 0.88 (s, 9 H), 0.03 (s, 6 H).

The crude tosylate was dried under vacuum and was then dissolved in anhydrous ether (5 mL). This solution was added dropwise to a stirred solution of lithium di-*n*-butylcuprate¹⁵ (2.7 mmol) in ether at -78 °C under N₂. After 6 h, the reaction mixture was worked up in the standard way.¹⁵ Upon Kugelrohr distillation (70 °C/10 mm), 40 mg (35% overall from sulfonamide) of pure product was obtained as colorless oil: IR (neat) 2960, 2856, 1450 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.55 (t, 2 H, J = 6.5 Hz), 1.46 (m, 2 H), 1.23 (m, 8 H), 0.84 (m, 12 H), 0.03 (s, 6 H); ¹³C NMR (100.6 MHz, CDCl₃) δ 63.36, 32.93, 31.89, 29.13, 26.00, 25.80, 25.66, 22.63, 14.07, -5.23; high-resolution mass spectrum calcd for C₆H₂₁OSi (M - 57) 173.1361, found 173.1361. MS (EI), *m/e* 230 (2.6), 173 (100), 132 (20), 75 (48).

1(S)-(tert-Butyldimethylsiloxy)[1-²H]heptane. By following the above procedure, deuteriated sulfonamide 13a (195 mg, 0.57 mmol) gave 210 mg (99% crude) of nitrososulfonamide, which on rearrangement gave 164 mg (82% crude) of tosylate. This was treated with Bu₂CuLi to give 95 mg (70% overall) of pure deuteriated ether: ¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, 1 H, J = 6.5 Hz), 1.55 (m, 2 H), 1.26 (m, 8 H), 0.89 (m, 12 H), 0.03 (s, 6 H).

1-Heptanol. The silvl heptyl ether (115 mg, 0.5 mmol) in THF (5 mL) at room temperature was stirred with tetrabutylammonium fluoride (1 mL, 1.0 M solution) for 21 h. The solvent was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 (10 mL). This solution was washed with H_2O (2 × 10 mL), the organic layer was dried (Na₂-SO₄), and the product was obtained by concentration in vacuo and Kugelrohr distillation (60–65 °C/10 mm) to give 58 mg (100% yield) of 1-heptanol.

1(S)-[1-²H]Heptanol. Via the above procedure, deuteriated silyl heptyl ether (90 mg, 0.39 mmol) was converted into 43 mg (94% yield) of 1(S)-[1-²H]heptanol.

(-)-Camphanate Derivatives of 7. The following is typical. The alcohol (0.25 mmol) in CH₂Cl₂ was stirred with freshly sublimed (-)camphanoyl chloride (Fluka, 60 mg, 0.28 mmol) in the presence of Et₃N (39 μ L, 0.27 mmol) and a catalytic amount of DMAP (10 mol %) for 10 h. The mixture was then washed with H₂O. The organic layer was dried (Na₂SO₄), and solvent removal under reduced pressure gave crude product **8**. This was purified by recrystallization from methylene chloride-hexane, which gave colorless shining flakes: mp 106 °C; IR (CH-Cl₃) 1170, 1362, 1716, 1754, 3019 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ 7.78 (m, 4 H), 4.28 (t, 2 H, J = 6.1 Hz), 3.81 (t, 2 H, J = 6.7 Hz), 1.6–2.7 (m, 6 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 1.0 (s, 3 H); ¹³C NMR (100.6 MHz, CDCl₃) δ 178.03, 168.23, 167.39, 134.08, 132.04, 123.32, 91.12, 62.87, 54.80, 54.12, 34.82, 30.73, 28.97, 27.83, 16.77, 16.68, 9.68; high-resolution mass spectrum calcd for C₂₁H₂₃NO₆: C, 65.43; H, 6.02; N, 3.63. Found: C, 64.97; H, 5.95; N, 3.53.

1-Heptyl Camphanate. The (-)-camphanate of heptanol was prepared as described above for $7 \rightarrow 8$. The oily product was purified by Kugelrohr distillation (45–50 °C, 10 mm): ¹H NMR (400 MHz, CDCl₃) δ 4.20 (t, 2 H, J = 6.6 Hz), 2.43 (m, 1 H), 1.85–2.08 (m, 2 H), 1.67 (m, 3 H), 1.32 (m, 8 H), 1.12 (s, 3 H), 1.06 (s, 3 H), 0.97 (s, 3 H), 0.88 (t, 3 H, J = 6.5 Hz); ¹³C NMR (100.6 MHz, CDCl₃) δ 178.16, 167.57, 91.21, 65.77, 54.80, 54.09, 31.68, 30.67, 29.02, 28.82, 28.61, 25.81, 22.55, 16.80, 14.02, 9.72, 1.02.

Shift-Reagent Study. The appropriate shift reagent was freshly sublimed under reduced pressure before use. A known quantity was weighed out and dissolved in 400 μ L of dry CDCl₃ (dried over molecular sieves). The sample to be studied was prepared in 450 μ L of CDCl₃ with 1% TMS and placed in a 5-mm NMR tube. The ¹H NMR spectrum was first recorded without shift reagent, and then the shift reagent was added in aliquots and the ¹H NMR spectrum was recorded after each addition. The mole percent of shift reagent at which best resolution was observed was noted and used for studies of deuteriated compounds.

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