27A as a colorless oil: R_f 0.53 (40% EtOAc/petroleum ether); $[\alpha]_D$ +10.0° (c 0.23, $CHCl_3$); IR 3600-3300, 2980, 2940, 1750-1730, 1460, 1290, 1080, 1015, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, Δν = 15.3), 2.699 (ab, 1 H, J = 11.3 Hz, Δν = 15.3), 2.631 (abx, 1 H, J, J' = 12.5, 2.8 Hz, Δν = 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, H_2O), 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 $C_{33}H_{50}BrO_9$ (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: (1*R*)-[1-^{2}H]- and (1*S*)-[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-^{2}H]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*-1*R* resonance appearing *downfield* from the *pro*-1*S* resonance. This result was contrary to the empirical rule that the *pro*-1*S* hydrogen resonance of primary alcohol camphanates appears downfield of the *pro*-1*R* hydrogen resonance in the presence of europium.

In order to probe the stereochemistry involved in the biosynthesis of acivicin[2] and blasticidin[3] 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 **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 formulation[5] 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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(1) Career Development Awardee of the National Cancer Institute (CA 00880), 1979-1984.
(2) Ju, S.; Palaniswamy, V. A.; Gould, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 6429-6430.
(3) Prabhakaran, P. C.; Woo, N. T.; Yorgey, P. S.; Gould, S. J. *Tetrahedron Lett.* **1986**, *27*, 3815-3818.
(4) Williams-Ashman, H. G.; Pegg, A. E. In *Polyamines in Biology and Medicine*; Morris, D. R., Marton, L. J., Eds.; Marcel Dekker: New York, 1981; Chapter 2.
(5) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274-275.
(6) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.
(7) (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211-5213. (b) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *Ibid.* **1979**, *101*, 2352-2355.
(8) (a) Parry, R. J. *J. Chem. Soc., Chem. Commun.* **1978**, 294-295. (b) Parry, R. J.; Trainor, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 5243-5244. (c) Aberhart, D. J.; Lin, H. J.; Weiller, B. H. *Ibid.* **1981**, *103*, 6750-6752. (d) Parry, R. J.; Minta, A. *Ibid.* **1982**, *104*, 871-872. (e) Parry, R. J.; Naidu, M. V. *Ibid.* **1982**, *104*, 3217-3219. (f) Parry, R. J.; Rao, S. P.; Mueller, J. *Ibid.* **1982**, *104*, 339-340. (g) Aberhart, D. J.; Russel, D. J. *Ibid.* **1984**, *106*, 4907-4910. (h) Aberhart, D. J.; Gould, S. J.; Lin, H. J.; Thiruvengadam, T. K.; Weiller, B. H. *Ibid.* **1983**, *105*, 5461-5470. (i) Schwab, J. M.; Klassen, J. B. *Ibid.* **1984**, *106*, 7217-7227. (j) Schwab, J. M.; Klassen, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 296-297.

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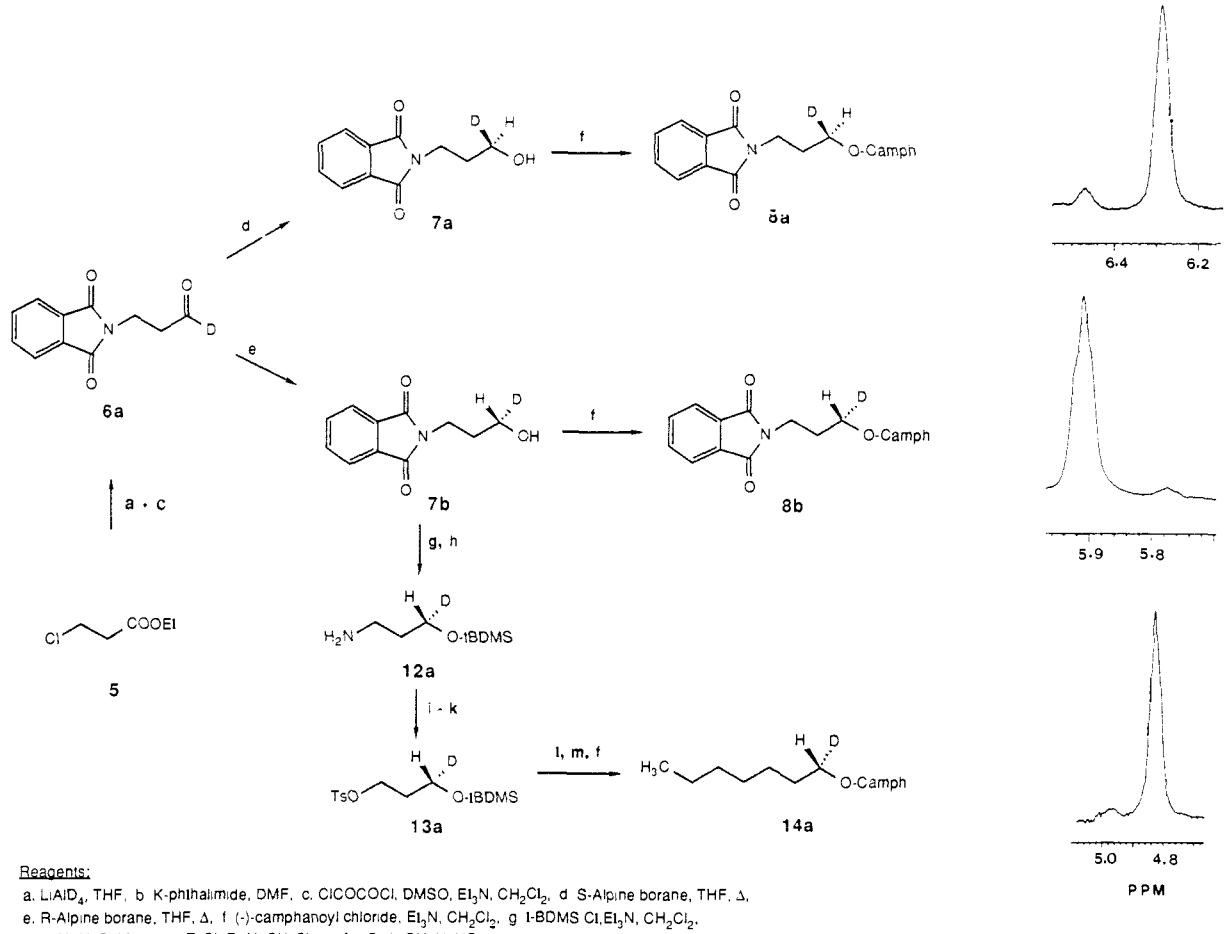


Figure 1. Synthesis of (1*R*)-[1-^{2}H]- and (1*S*)-[1-^{2}H]phthalimidopropanols, **7a** and **7b**, and conversion of **7b** to 1(*S*)-[1-^{2}H]heptanol. Portions of the ^{1}H NMR spectra (400 MHz) of their (-)-camphanates—**8a**, **8b**, and **14a**—in the presence of Eu(fod)$_3$ corresponding to 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] This involved thermal rearrangement[12] 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

(9) (a) Fuganti, C.; Ghiringhelli, D.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1975**, 846–847. (b) Armarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. I* **1976**, 2229–2237. (c) Cane, , D. E.; Murthy, P. P. N. *J. Am. Chem. Soc.* **1977**, *99*, 8327–8329. (d) Kitchin, J. P.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. I* **1979**, 1384–1385. (e) Drengler, K. A.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 856–857. (f) Coates, R. M.; Cavender, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 6358–6359. (g) Polavarapu, P. L.; Nafie, L. A.; Benner, S. A.; Morton, T. H. *Ibid.* **1981**, *103*, 5349–5354. (h) Benner, S. A.; Rozzell, J. D., Jr.; Morton, T. H. *Ibid.* **1981**, *103*, 993–994. (i) Orr, G. R.; Gould, S. J. *Tetrahedron Lett.* **1982**, *23*, 3139–3142. (j) Schwab, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 1876–1878. (k) Kobayashi, K.; Jadhav, P. K.; Zydowsky, T. M.; Floss, H. G. *J. Org. Chem.* **1983**, *48*, 3510–3512. (l) Schwab, J. M.; Li, W. B.; Thomas, L. P. *J. Am. Chem. Soc.* **1983**, *105*, 4800–4808. (m) Rhodes, Y. E. *Tetrahedron Lett.* **1983**, *24*, 4959–4962. (n) Iwaski, S.; Furukawa, J.; Takakis, I. M.; Okuda, S. *Ibid.* **1983**, *24*, 5257–5260. (o) Furukawa, J.; Iwasaki, S.; Okuda, S. *Ibid.* **1983**, *24*, 5261–5264. (p) Rozzell, J. D.; Benner, S. A. *J. Org. Chem.* **1983**, *48*, 1190–1193.

(10) (a) Santaniello, E.; Kiehle, M. G.; Manzocchi, A.; Bosisio, E. *J. Chem. Soc., Perkin Trans. I* **1979**, 1677–1679. (b) Pontoni, G.; Coward, J. K.; Orr, G. R.; Gould, S. J. *Tetrahedron Lett.* **1983**, *24*, 151–154.

(11) Experimental details of the conversion of **9a** and **9b** to **10a** and **10b**, respectively, are given in the accompanying paper on the spermidine synthase reaction.

(12) (a) White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6008–6010. (b) White, E. H. *Ibid.* **1955**, *77*, 6011–6014.

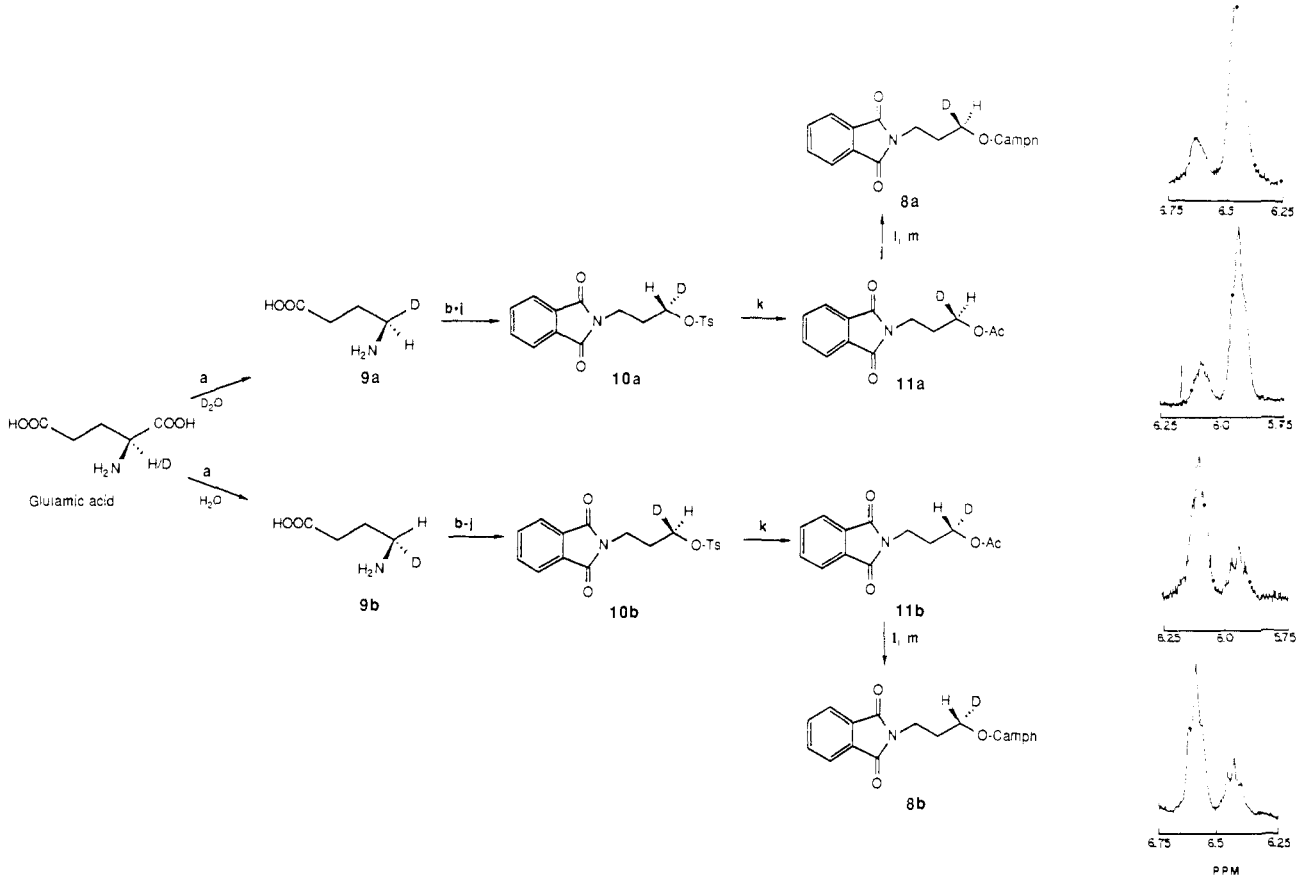
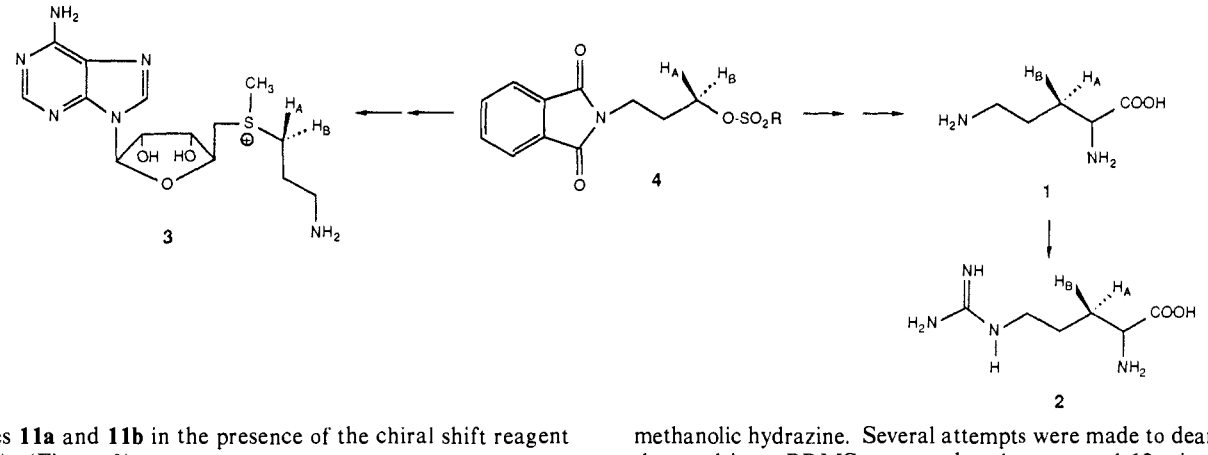


Figure 2. Synthesis of (1*R*)-[1-^{2}H]- and (1*S*)-[1-^{2}H]phthalimidopropanol tosylates, **10a** and **10b**, and their conversion to the acetates and (−)-camphanates. Portions of the ^{1}H NMR spectra (200 MHz) of the acetates in the presence of Eu(hfc)$_3$ and of the camphanates in the presence 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.[8i,j]

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 halodeamination[13] 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

(13) Doyle, M. P.; Bosch, R. J.; Seites, P. G. *J. Org. Chem.* **1978**, *43*, 4120–4125.

(14) *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Part 2, Chapter 22, pp 929–997.

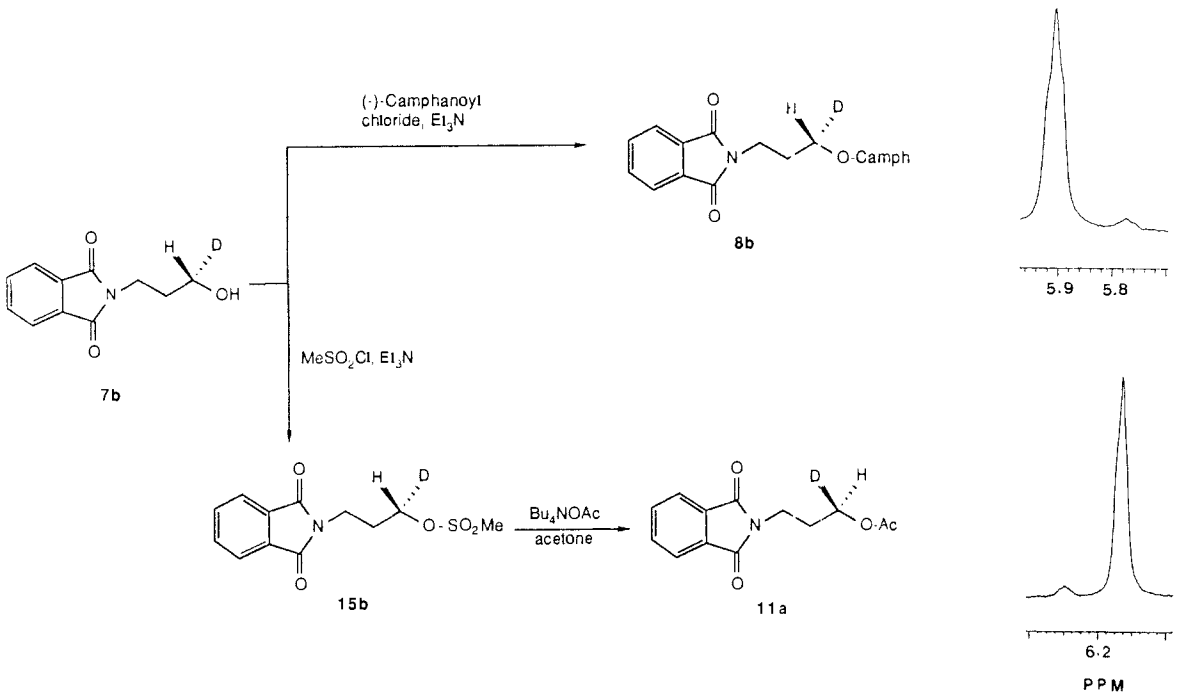


Figure 3. Conversion of (1*S*)-[1-^{2}H]phthalimidopropanol, **7b**, to (−)-camphanate **8b** and conversion to acetate **11a** via the mesylate. Portions of the ^{1}H NMR spectra (400 MHz) of **8b** and **11a** in the presence of Eu(fod)$_3$ and Eu(hfc)$_3$, respectively, are shown to the right of each 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 ^{1}H 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 ^{1}H 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 ^{1}H 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. ^{1}H NMR and ^{13}C 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 ^{1}H and ^{13}C NMR spectra are reported in parts per million relative to tetramethylsilane (Me_4Si, 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 F_{254} (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 $LiAlH_4$ (2.5 g, 0.066 mol) in absolute ether (150 mL) at 0 °C under N_2 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 $LiAlH_4$ was quenched by successive addition of H_2O (2.4 mL), NaOH (15% solution, 2.4 mL), and H_2O (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, $CHCl_3$ (150 mL) was added, and the mixture was poured into water (500 mL). The organic layer was repeatedly washed with water and dried (Na_2SO_4) 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 (lit.[16] mp 75–79 °C); IR ($CHCl_3$)

(15) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777–7782.

(16) Markus, R. L.; O'Brien, J. G. *J. Org. Chem.* **1965**, *30*, 3062–3064.

3550, 1725, 1450 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) 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-$^2H_2$]propyl)phthalimide.** Via the above procedure, ethyl 3-chloropropionate, **5**, (15 g, 0.11 mol) was reduced with $LiAlD_4$ and then converted to 11.5 g (51% from **5**) of deuteriated phthalimidopropanol: ^1H NMR (80 MHz, $CDCl_3$) 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, Et_3N (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% Na_2CO_3, and H_2O. It was then dried (Na_2SO_4) 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, $CDCl_3$) 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-^{2}H]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, $CDCl_3$) 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 N_2. 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 (SiO_2, 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-^{2}H]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 (3*R*)-[3-^{2}H]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 (3*S*)-[3-^{2}H]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, $CDCl_3$) 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 CH_2Cl_2 (50 mL) at −78 °C under N_2 was added Et_3N (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 H_2O (50 mL). The CH_2Cl_2 layer was separated, dried (Na_2SO_4), and recrystallized from 95% EtOH to give 1.38 g (100%) of a white solid: mp 132–133 °C; IR ($CHCl_3$) 3300, 3130, 1770, 1378 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.24, 134.16, 131.99, 123.35, 67.21, 37.45, 34.44, 28.28. Anal. Calcd for $C_{12}H_{13}NO_5S$: 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-^{2}H]propyl]phthalimide (15a) and *N*-[3(*S*)-[(Methylsulfonyl)oxy][3-^{2}H]propyl]phthalimide (15b).** Via the above procedure (3*R*)-[3-^{2}H]alcohol **7a** (2.1 g, 10.2 mmol) and (3*S*)-[3-^{2}H]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, $CDCl_3$) 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)-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 $CaCl_2$ 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 Et_2O–petroleum ether gave 170 mg (72%) of needlelike crystals, mp 62–63 °C (lit.[18] mp 63.5–65 °C): ^1H NMR ($CDCl_3$) δ 7.75 (m, 4 H, Ar), 4.12 (t, 2 H, J = 6 Hz, CH_2O), 3.81 (t, 2 H, J = 7 Hz, CH_2NPhT), 2.05 and 2.01 (overlapping t and s, 5 H, CH_2 and CH_3).

The *R* isomer **11a** was obtained by reaction of **10a**[11] (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 ($CDCl_3$) 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 ($CDCl_3$) 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 CH_2Cl_2 (10 mL) and washed with H_2O (2 × 15 mL). The organic layer was dried over Na_2SO_4. 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, $CDCl_3$) 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-^{2}H]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 N_2 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 ($CDCl_3$) δ 7.76 (m, 4 H, Ar), 4.27 (t, 1 H, J = 3 Hz, CHDO), 3.82 (t, 2 H, J = 7 Hz, CH_2N), 2.44, 2.10–1.80 and 1.70 (br m, 6 H, CH_2), 1.12 (ds, 6 H, *gem*-CH_3), 1.0 (s, 3 H, CH_3).

3-Phthalimido-1(*S*)-[1-^{2}H]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 ($CDCl_3$) was identical with the *R* derivative **8a** derived from **11a**.

***N*-[3-(*tert*-Butyldimethylsiloxy)propyl]phthalimide.** Et_3N (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 CH_2Cl_2 (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 (Na_2SO_4). Concentration in vacuo gave an oily residue that was further purified by flash column chromatography (30 g of SiO_2, 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, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 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 $C_{13}H_{16}NO_3Si$ (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-^{2}H]propyl]phthalimide.** By following the above procedure, (1*S*)-[1-^{2}H]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, $CDCl_3$) 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

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

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

up in CH_2Cl_2 (20 mL), the undissolved solid was removed by filtration, and the solid was washed with CH_2Cl_2 (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, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 61.24, 39.44, 36.46, 25.95, 18.29, −5.34; high-resolution mass spectrum calcd for $C_5H_{14}NOSi$ (M − 57) 132.0844, found 132.0845; EIMS, m/z 132 (100), 104 (42), 75 (32).

3(*S*)-(*tert*-Butyldimethylsiloxy)[3-^{2}H]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, $CDCl_3$) 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 CH_2Cl_2 (15 mL) at 0 °C was treated dropwise with Et_3N (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 (Na_2SO_4). A crude oily product was obtained after solvent removal, and this was further purified by flash column chromatography (30 g SiO_2, 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, $CDCl_3$) δ 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); ^{13}C 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 $C_{12}H_{20}NO_3SSi$ (M − 57) 286.0933, found 286.0935; EIMS, m/z 328 (12), 286 (100), 155 (88), 91 (100). Anal. Calcd for $C_{16}H_{29}NO_3SSi$: 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-^{2}H]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, $CDCl_3$) 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)oxy]heptane. 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 $NaNO_2$ (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 H_2O (15 mL). This was stirred for 15 min and then extracted with ether. The ether layer was washed with H_2O, 5% $NaHCO_3$, H_2O, and NaCl and dried (Na_2SO_4). 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, $CDCl_3$) δ 7.35–7.89 (m, 4 H), 3.77 (t, 2 H, J = 7.2 Hz), 3.5 (t, 2 H, J = 6.1 Hz), 2.45 (s, 3 H), 1.60 (tt, 2 H, J = 6.5 Hz), 0.89 (s, 9 H), 0.03 (s, 6 H).

The crude product was refluxed in CCl_4 (15 mL) along with anhydrous Na_2CO_3 (55 mg, 0.52 mmol) under an N_2 atmosphere for 20 h. The solid Na_2CO_3 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, $CDCl_3$) 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*-butylcuprate[15] (2.7 mmol) in ether at −78 °C under N_2. 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, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_6H_{21}OSi$ (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-^{2}H]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 Bu_2CuLi to give 95 mg (70% overall) of pure deuteriated ether: ^1H NMR (400 MHz, $CDCl_3$) 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 silyl 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 (Na_2SO_4), 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-^{2}H]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-^{2}H]heptanol.

(−)-Camphanate Derivatives of 7. The following is typical. The alcohol (0.25 mmol) in CH_2Cl_2 was stirred with freshly sublimed (−)-camphanoyl chloride (Fluka, 60 mg, 0.28 mmol) in the presence of Et_3N (39 μL, 0.27 mmol) and a catalytic amount of DMAP (10 mol %) for 10 h. The mixture was then washed with H_2O. The organic layer was dried (Na_2SO_4), 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 ($CHCl_3$) 1170, 1362, 1716, 1754, 3019 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{21}H_{23}NO_6$ 385.15252, found 385.15185. Anal. Calcd for $C_{21}H_{23}NO_6$: 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** → **8**. The oily product was purified by Kugelrohr distillation (45–50 °C, 10 mm): ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 μL of dry $CDCl_3$ (dried over molecular sieves). The sample to be studied was prepared in 450 μL of $CDCl_3$ 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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