Highly Diastereoselective Alkylation of 3-Substituted Tetrahydroisoquinolines

Axel Monsees, Sabine Laschat,* and Ina Dix

Institut für Organische Chemie der Technischen Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

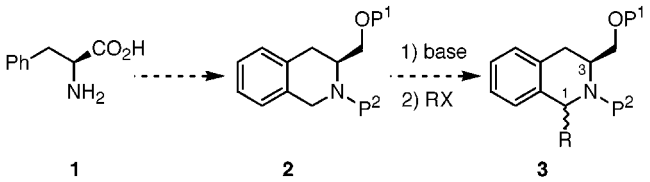
Peter G. Jones

Institut für Anorganische und Analytische Chemie der Technischen Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

Received June 9, 1998

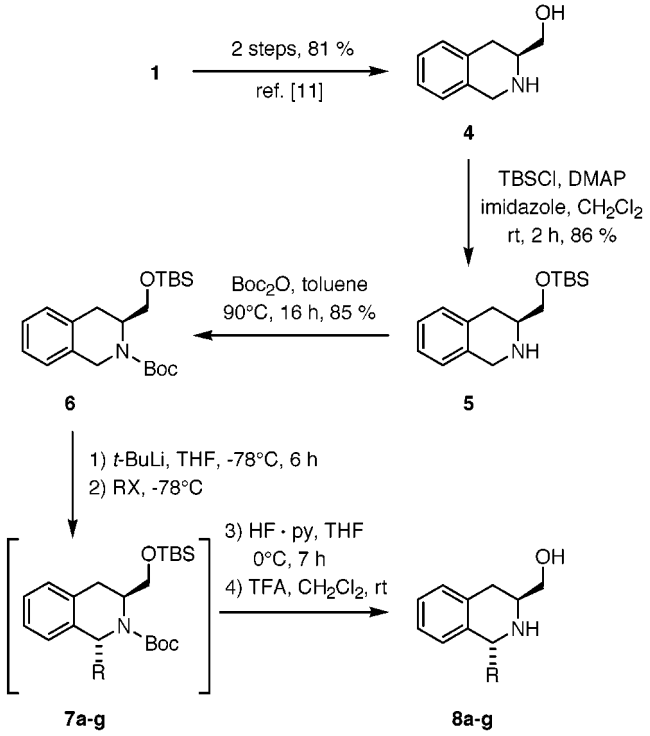
Until now, much synthetic effort has been devoted to the asymmetric synthesis of optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines,[1] because they are part of many naturally occurring alkaloids and their nonnatural derivatives and exhibit important biological activities.[2] The stereocenter at C-1 of the tetrahydroisoquinoline can be introduced either directly via Pictet−Spengler[3−5] and Bischler−Napieralski cyclization/asymmetric hydrogenation,[5,6] nucleophilic attack to an N-substituted isoquinolinium salt,[7] or electrophilic attack at the corresponding carbanion.[8] Recently a cyclization using electrophilic selenium reagents has been reported.[9] Another method utilizes the addition of chiral phenylacetaldehyde acetals to acylimines.[10] However, several of the above-mentioned methods, in particular the Pictet−Spengler reaction, are hampered by the fact that the presence of an activated aromatic system is required. Thus we envisaged as an alternative approach the diastereoselective alkylation of suitably protected 3-substituted tetrahydroisoquinoline **2** to give the chiral 1,3-disubstituted derivative **3**. Compound **2** should be easily available in enantiomerically pure form from L-phenylalanine **1** (Scheme 1). The results toward this end are described below.

Scheme 1



1 **2** **3**

Scheme 2



7a-g **8a-g**

R	7	Crude yield [%]	8	Yield [%]	%de
Me	**a**	98	**a**	31	98
Et	**b**	94	**b**	40	95
n-Pr	**c**	98	**c**	36	98
i-Pr	**d**	97	**d**	31	99
n-Bu	**e**	95	**e**	39	98
n-C_5H_{11}	**f**	99	**f**	42	97
CH_2OMe	**g**	96	**g**	23	99

As reported earlier, phenylalanine **1** was converted to the enantiomerically pure amino alcohol **4** via Pictet−Spengler cyclization followed by reduction with $LiAlH_4$ (Scheme 2).[11] Treatment of **4** with TBSCl and subsequent protection of the nitrogen atom with Boc_2O yielded tetrahydroisoquinoline **6**. Compound **6** was deprotonated with *t*-BuLi in THF at −78 °C and then alkylated with various electrophiles. As shown in Scheme 2, alkylation proceeded in all cases with good yields and high diastereoselectivities (95−99% de), giving the trans-1,3-disubstituted tetrahydroisoquinolines **7a**−**g** as the major products. Diastereomeric ratios of **7** were determined by capillary GC of the crude product. Monitoring the alkylation by GC revealed almost quantitative conversion.

(1) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.
(2) (a) Herbert, R. B. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Philipson, J. D.; Roberts, M. F.; Zenk, M. H., Eds.; Springer-Verlag: Berlin, 1985, p. 213. (b) Shamma, M. *Isoquinoline Alkaloids, Chemistry and Pharmacology*; Academic Press: New York, 1972. (c) Kametani, T. *The Chemistry of the Isoquinoline Alkaloids*; Elsevier: Amsterdam, 1969.
(3) Cox, A. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(4) (a) Sotomayor, N.; Dominguez, E.; Lete, E. *Tetrahedron* **1995**, *51*, 12159. (b) Bravo, P.; Crucianelli, M.; Farina, A.; Meiller, S. V.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **1998**, *435*, 5. (c) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327.
(5) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kisinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877.
(6) (a) Morimoto, T.; Suzuki, N.; Achiwa, K. *Tetrahedron Asym.* **1998**, *9*, 183. (b) Gosmann, G.; Guillaum, D.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 4369.
(7) (a) Ludwig, M.; Beer, H.; Lotter, H.; Wanner, K. Th. *Tetrahedron Asym.* **1997**, *8*, 2693. (b) Wanner, K. Th.; Praschak, I.; Höfner, G.; Beer, H. *Arch. Pharm. Med. Chem.* **1996**, *329*, 11. (c) Barbier, D.; Marazano, C.; Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1998**, *63*, 1767. (d) Comins, D. L.; Badawi, M. M. *Heterocycles* **1991**, *32*, 1869. (e) Richter-Addo, G. B.; Knight, D. A.; Dewey, M. A.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 11863. (f) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932.
(8) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.
(9) Wirth, T.; Fragale, G. *Synthesis* **1998**, 162.
(10) Wünsch, B.; Nerdinger, S. *Tetrahedron Lett.* **1995**, *36*, 8003.
(11) Monsees, A.; Laschat, S.; Kotila, S.; Fox, T.; Würthwein, E.-U. *Liebigs Ann./Recueil* **1997**, 533.

10.1021/jo9810967 CCC: $15.00
Published on Web 11/26/1998

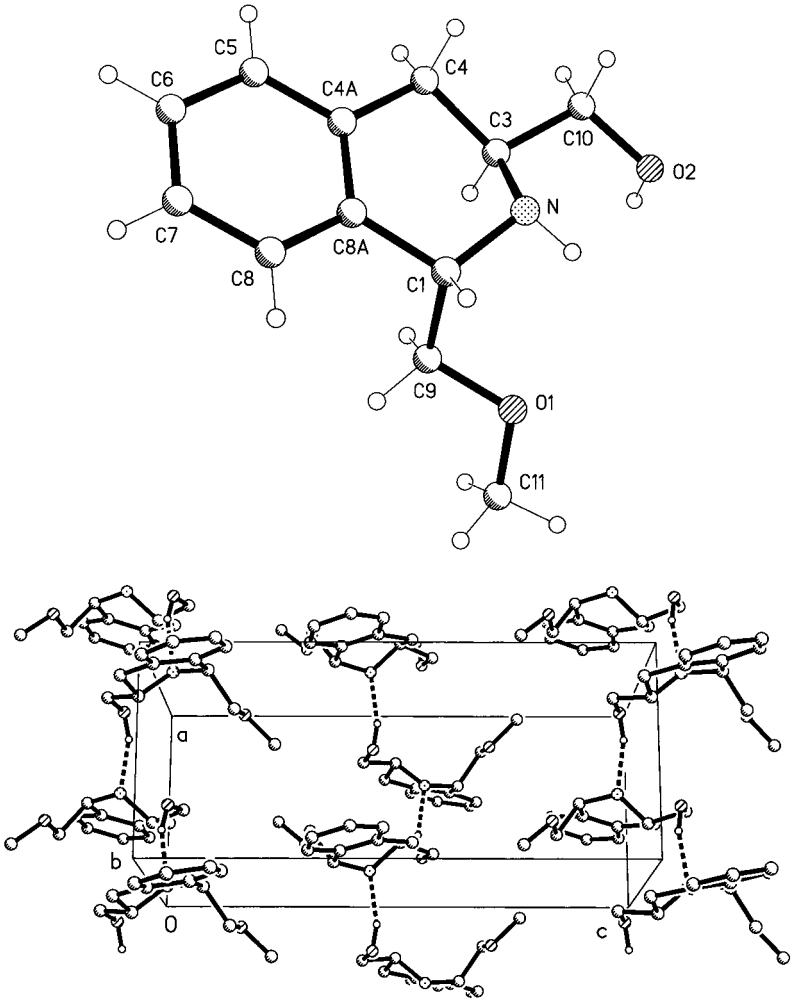


Figure 1. (a) X-ray crystal structure of tetrahydroisoquinoline derivative **8g**. (b) A view of the packing diagram is shown. Selected bond lengths (Å) and angles (°) of the intermolecular hydrogen bond: O2−H02 0.94(1), H02−N 1.89(5), O2−N 2.79(1) Å, O2−H02−N 159(4)°.

The observed diastereoselectivity is probably due to the steric bias from the bulky *tert*-butyldimethylsilyloxy group, which directs the incoming electrophile to the opposite face. This result is in accordance with the observation that sterically more-hindered bases such as LHMDS, NaHMDS, or the use of *t*-BuLi/TMEDA or of *t*-BuLi/sparteine gave only incomplete conversion. The steric bulkiness of both TBS and the Boc group produced considerable line broadening and doubling of NMR signals, so that both ^{1}H and ^{13}C NMR spectra of **7** were not reliable for characterization. As a consequence, crude alkylation products **7a**−**g** were fully deprotected in a two-step protocol using HF·pyridine and TFA to the 1-alkyl-3-hydroxymethyltetrahydroisoquinolines **8a**−**g**. Although reaction control by GC indicated quantitative deprotection, the yields of amino alcohols **8a**−**g** were only moderate. The tendency of compound **8** to form hydrogen bonds (see below) with polar solvents during aqueous workup might explain the decreased yields. It should be emphasized, however, that no change of the diastereomeric ratios of **8a**−**g** during the deprotection (as compared with **7a**−**g**) was observed.[12]

The relative configuration of **8** could be established by an X-ray crystal structure determination of 1-methoxymethyl-substituted derivative **8g** (Figure 1).[13] Although in this particular case three different intermolecular hydrogen bonds between NH−O2, (O2)H−O1, and NH−O1 might be expected, the packing diagram shows that intermolecular hydrogen bonds were only observed between NH and O2.

Experimental Section

All reactions were carried out under argon by using standard Schlenk technique. Solvents were dried and deoxygenated by standard procedures. Analytical TLC was performed on precoated Macherey-Nagel Polygram SIL G/UV$_{254}$ plates (0.25 mm thickness) and products were visualized with a solution of phosphomolybdic acid in EtOH (5%, v/v). Flash chromatography[14] was carried out with Merck silica gel 60 (230−400 mesh). NMR spectra were performed at 300 and 400 MHz (^{1}H), 75 and 100 MHz (^{13}C). Melting points were uncorrected. IR spectra: Nicolet 5DXC FT-IR spectrometer. Optical rotations: 1-dm-cells, 1-mL capacity, room temp. Mass spectra were obtained at 70 eV, NH_3 was used as reactand gas for CI spectra. GC analysis:

(12) In the case of **7d** and **8d** the minor (1*S*, 3*S*)-diastereomers were identified by GC-MS spectra of the crude products. (1*R*, 3*S*)-**7d**: R_t = 22.1 min; GC-MS (EI) *m*/*z* 376 (M − C_3H_7, 9), 276 (M − C_3H_7 − COOtBu, 100), 176 (37), 73 (17), 57 (56). (1*S*, 3*S*)-**7d**: R_t = 22.5 min; GC-MS (EI) *m*/*z* 376 (8), 276 (100), 176 (35), 73 (9), 57 (48). (1*R*, 3*S*)-**8d**: R_t = 15.9 min; GC-MS (CI) *m*/*z* 206 (M + H, 100), 162 (M − C_3H_7, 12), 130 (M − C_3H_7 − CH_2OH − H, 2). (1*S*, 3*S*)-**8d**: R_t = 15.4 min; GC-MS (CI) *m*/*z* 206 (100), 162 (15), 130 (3).

(13) The authors have deposited atomic coordinates for the structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK upon quoting the reference number 106540.

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

HP5-fused silica capillary column (ID 0.32 mm, length 30 m), a temperature program was run from 80 °C with 8 °C min^{-1} up to 280 °C. Diastereomeric ratios of **7** and **8** were determined by capillary GC of the crude products from three independent runs (standard deviation ±0.2%).

(*S*)-3-(*tert*-Butyldimethylsilyloxy)methyl-1,2,3,4-tetrahydroisoquinoline (5). To a solution of (*S*)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline **4** (3.92 g, 24.0 mmol), imidazole (4.08 g, 60.0 mmol), and 4-*N*,*N*-(dimethylamino)pyridine (0.15 g, 1.23 mmol) in CH_2Cl_2 (40 mL) was added *tert*-butyldimethylsilyl chloride (3.92 g, 26.0 mmol) and the mixture was stirred for 2 h at room temperature. After hydrolysis with sat. NH_4Cl (100 mL) the mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (100 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by flash chromatography on SiO_2 (hexanes:ethyl acetate 15:1) to give a pale yellow oil (5.73 g, 86%). $[\alpha]^{22}_D$ − 47.3° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−7.01 (m, 4H), 4.06 (s, 2H), 3.75 (dd, J = 9.8, 4.0 Hz, 1H), 3.61 (dd, J = 9.8, 6.7 Hz, 1H), 3.01 (m, 1H), 2.64 (d, J = 6.7 Hz, 2H), 0.91 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 134.7, 129.7, 126.5, 126.4, 126.1, 67.2, 55.3, 48.5, 31.4, 26.3, 18.7, −5.0; IR (film) 1252, 1103, 742 cm^{-1}; MS (EI), m/z 277 (M, 44), 276 (53), 262 (31), 220 (61), 132 (100), 115 (78), 91 (45); HRMS (EI) calcd for $C_{16}H_{27}NOSi$ 277.1862, found 277.1869.

(*S*)-*N*-*tert*-Butyloxycarbonyl-3-(*tert*-butyldimethylsilyloxy)methyl-1,2,3,4-tetrahydroisoquinoline (6). To a solution of **5** (13.0 g, 47.0 mmol) in toluene (40 mL) was added Boc_2O (10.0 g, 45.8 mmol). After heating the mixture for 16 h at 90 °C the solvent was removed in vacuo and the crude product was purified by flash chromatography on SiO_2 (hexanes:ethyl acetate 40:1) to yield a colorless oil (15.1 g, 85%). $[\alpha]^{22}_D$ − 24.2° (c = 1.25 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.08 (m, 4H), 4.67 (d, br, J = 16.7 Hz, 1H), 4.25 (d, J = 16.7 Hz, 1H), 3.75 (dd, J = 9.8, 4.0 Hz, 1H), 3.54 (dd, J = 9.8, 5.9 Hz, 1H), 3.29 (s, br, 1H), 2.93 (s, 1H), 2.92 (s, 1H), 1.50 (s, 9H), 0.86 (s, 9H), −0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 136.9, 133.5, 129.1, 128.8, 127.0, 126.7, 83.2, 62.1, 51.7, 50.4, 31.2, 28.5, 25.8, 18.1, −5.5; IR (film) 1698, 753 cm^{-1}; MS (EI) m/z 377 (M, 2), 321 (10), 276 (29), 264 (86), 176 (100), 132 (68); HRMS (EI) calcd for $C_{21}H_{35}NO_3Si$ 377.2386, found 377.2380. Anal. Calcd for $C_{21}H_{35}NO_3Si$: C 66.80; H 9.34; N 3.71. Found: C 66.98; H 9.36; N 3.68.

General Procedure for Preparation of 1,3-Disubstituted Tetrahydroisoquinolines (8). To a solution of **6** (3.77 g, 10.0 mmol) in THF (25 mL) was added dropwise *t*-BuLi (7.50 mL, 12.0 mmol, 1.6 M solution in pentane) at −78 °C and the resulting deep red solution was stirred for 6 h at −78 °C. Alkyl halide (20.0 mmol) then was added. After warming to room temperature overnight, the mixture was hydrolyzed with sat. $NaHCO_3$ and then concentrated in vacuo. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product **7** was dissolved in THF (20 mL) and cooled to 0 °C. Then HF·py (13 mL) was added and the mixture was stirred for 7 h at 0 °C. The mixture was diluted with Et_2O (30 mL) and then poured under ice-cooling into aqueous NH_3 (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (5 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and treated with TFA (10 mL). The mixture was then diluted with CH_2Cl_2 (20 mL) and poured under ice-cooling into aqueous NH_3 (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on SiO_2 ($CHCl_3$/*i*-PrOH 10:1).

(1*R*,3*S*)-1-Methyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8a). Yellow solid (0.55 g, 31%), 98% de (by GC); mp. 53 °C; $[\alpha]^{22}_D$ − 23.6° (c = 0.99 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−7.04 (m, 4H), 4.18 (d, J = 6.4 Hz, 1H), 3.70 (dd, J = 10.8, 4.0 Hz, 1H), 3.48 (dd, J = 10.8, 7.4 Hz, 1H), 3.29−3.16 (m, 3H), 2.67 (dd, J = 16.2, 4.0 Hz, 1H), 2.52 (dd, J = 16.2, 10.8 Hz, 1H), 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 133.5, 129.1, 126.3, 126.1, 125.7, 65.0, 50.1, 48.9, 31.0, 23.3; IR (KBr) 3388, 752 cm^{-1}. Before mass spectrometric characterization compound **8a** was converted to the trimethylsilyl ether. MS (EI) m/z 249 (M + $SiMe_3$, 5), 234 (12), 146 (100), 130 (10); HRMS (EI) calcd for $C_{14}H_{23}NOSi$ 249.1544, found 249.1614.

(1*R*,3*S*)-1-Ethyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8b). Yellow oil (0.76 g, 40%), 95% de (by GC); $[\alpha]^{22}_D$ − 19.3° (c = 1.13 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−6.98 (m, 4H), 4.39 (s, br, 2H), 3.87 (dd, J = 8.9, 5.4 Hz, 1H), 3.78 (dd, J = 11.3, 3.5 Hz, 1H), 3.54 (dd, J = 11.3, 7.4 Hz, 1H), 3.27 (m, 1H), 2.63 (s, 1H), 2.62 (s, 1H), 1.80−1.73 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 132.7, 129.2, 126.8, 126.7, 125.9, 64.2, 56.6, 49.1, 29.9, 28.7, 11.0; IR (film) 3314, 739 cm^{-1}; before mass spectrometric characterization compound **8b** was converted to the trimethylsilyl ether. MS (EI) m/z 263 (M + $SiMe_3$, 5), 249 (7), 160 (100); HRMS (EI) calcd for ($C_{15}H_{25}NOSi$ − CH_3) 248.1471, found 248.1506.

(1*R*,3*S*)-1-Propyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8c). Yellow oil (0.74 g, 36%), 96% de (by GC); $[\alpha]^{22}_D$ − 10.4° (c = 1.07 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02−6.92 (m, 4H), 3.84 (dd, J = 9.9, 3.4 Hz, 1H), 3.55 (dd, J = 10.6, 4.0 Hz, 1H), 3.45−3.30 (m, 3H), 3.10−3.07 (m, 1H), 2.52 (dd, J = 16.2, 4.0 Hz, 1H), 2.38 (dd, J = 16.2, 10.6 Hz, 1H), 1.69−1.60 (m, 1H), 1.52−1.32 (m, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 133.4, 129.0, 126.6, 126.0, 125.5, 65.2, 54.6, 48.4, 38.5, 30.9, 19.7, 13.8; IR (film) 3318, 746 cm^{-1}; MS (CI) m/z 206 (M + H, 100), 174 (4), 162 (13); HRMS (CI) calcd for ($C_{13}H_{19}NO$ + H) 206.1545, found 206.1510. Anal. Calcd for $C_{13}H_{19}NO$: C 76.06; H 9.33; N 6.82. Found: C 76.01; H 9.37; N 6.76.

(1*R*,3*S*)-1-(2-Propyl)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8d). Flash chromatography was performed with hexanes:ethyl acetate (12:1) and yielded a yellow oil (0.64 g, 31%), 99% de (by GC); $[\alpha]^{22}_D$ − 12.3° (c = 0.98 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.07 (m, 4H), 3.64 (dd, J = 10.3, 3.9 Hz, 1H), 3.62 (dd, J = 10.3, 3.6 Hz, 1H), 3.40 (dd, J = 10.3, 8.4 Hz, 1H), 3.32 (m, 1H), 2.79 (dd, J = 16.2, 4.5 Hz, 1H), 2.60−2.42 (m, 2H), 2.46 (dd, J = 16.2, 8.6 Hz, 1H), 2.12 (q, J = 6.7 Hz, 1H), 1.06 (d, J = 9.6 Hz, 3H), 0.98 (d, J = 9.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 134.2, 129.2, 127.2, 126.2, 125.1, 65.5, 59.7, 49.9, 32.3, 30.8, 20.8, 18.4; IR (film) 3322, 744 cm^{-1}; MS (CI) m/z 206 (M + H, 100), 162 (16).

(1*R*,3*S*)-1-Butyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8e). Flash chromatography was performed with hexanes:ethyl acetate (15:1) and yielded a yellow solid (0.85 g, 39%), 98% de (by GC); mp. 35 °C; $[\alpha]^{22}_D$ − 7.5° (c = 1.20 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−7.05 (m, 4H), 3.95 (dd, J = 10.1, 4.4 Hz, 1H), 3.70 (dd, J = 10.3, 4.0 Hz, 1H), 3.43 (dd, J = 10.3, 8.4 Hz, 1H), 3.22 (m, 1H), 2.75−2.43 (m, 2H), 2.68 (dd, J = 16.2, 4.0 Hz, 1H), 2.49 (dd, J = 16.2, 10.3 Hz, 1H), 1.80−1.34 (m, 6H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 133.6, 129.2, 126.6, 126.0, 125.7, 65.7, 54.9, 48.6, 36.1, 31.1, 29.0, 22.5, 14.0; IR (film) 3318, 746 cm^{-1}; MS (CI) m/z 220 (M + H, 7), 204 (7), 190 (9), 188 (16), 175 (9); HRMS (CI) calcd for $C_{14}H_{21}NO$ + H 220.1701, found 220.1665. Anal. Calcd for $C_{14}H_{21}NO$: C 76.67; H 9.65; N 6.39. Found: C 76.58; H 9.53; N 6.29.

(1*R*,3*S*)-1-Pentyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8f). Flash chromatography was performed with hexanes:ethyl acetate (15:1) and yielded a yellow solid (0.98 g, 42%), 97% de (by GC); mp. 43 °C; $[\alpha]^{22}_D$ − 6.6° (c = 1.01 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.05 (m, 4H), 3.93 (dd, J = 10.3, 3.9 Hz, 1H), 3.72 (dd, J = 10.4, 4.2 Hz, 1H), 3.44 (dd, J = 10.4, 8.4 Hz, 1H), 3.28−3.19 (m, 1H), 2.70−2.38 (m, 2H), 2.68 (dd, J = 16.2, 4.2 Hz, 1H), 2.49 (dd, J = 16.2, 10.6 Hz, 1H), 1.79−1.29 (m, 8H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 133.6, 129.2, 126.6, 126.0, 125.7, 65.7, 54.9, 48.7, 36.4, 31.6, 31.1, 26.5, 22.6, 14.0; IR (KBr) 3316, 742 cm^{-1}; MS (CI) m/z 234 (M + H, 100), 202 (5), 162 (20), 130 (2); HRMS (CI) calcd for ($C_{15}H_{23}NO$ + H) 234.1859, found 234.1885. Anal. Calcd for $C_{15}H_{23}NO$: C 77.21; H 9.93; N 6.00. Found: C 77.30; H 9.73; N 5.87.

(1*R*,3*S*)-1-Methoxymethyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (8g). Yellow solid (476 mg, 23%), 99% de (by GC); mp. 122 °C; $[\alpha]^{22}_D$ − 22.7° (c = 0.98 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.08 (m, 4H), 4.25 (dd, J = 9.8, 3.9 Hz, 1H), 3.71 (dd, J = 10.8, 3.4 Hz, 1H), 3.62 (dd, J = 9.8, 9.8 Hz, 1H), 3.53 (dd, J = 10.8, 7.4 Hz, 1H), 3.47 (dd, J = 9.8, 3.9

Hz, 1H), 3.42 (s, 3H), 3.29−3.20 (m, 1H), 3.25 (s, br, 2H), 2.69−2.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 134.4, 129.2, 126.9, 126.6, 125.6, 74.9, 65.9, 58.8, 54.7, 48.5, 31.1; IR (KBr) 3393, 752 cm^{-1}; MS (CI) *m*/*z* 208 (M + H, 100), 162 (11), 144 (3). Before mass spectrometric characterization, **8g** was converted to the trimethylsilyl ether. HRMS (EI) calcd for $C_{15}H_{25}NO_2Si$ 279.1655, found 279.1622. Anal. Calcd for $C_{12}H_{17}NO_2$: C 69.54; H 8.27; N 6.76. Found: C 69.62; H 8.12; N 6.58.

Acknowledgment. Generous financial support by the Deutsche Forschungsgemeinschaft (Gerhard Hess prize for S.L.) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **5**, **6**, and **8a**−**g** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

JO9810967