SUPPORTING INFORMATION

DIASTEREOMERIC REISSERT COMPOUNDS OF ISOQUINOLINE & 6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINE IN STEREOSELECTIVE SYNTHESIS

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General Procedures:

Unless otherwise noted commercial reagent grade materials were used without purification. Benzene, toluene and CH_2Cl_2 were distilled from calcium hydride and stored over 4Å molecular sieves. DMF was used as received, or vacuum distilled, and stored over 4Å molecular sieves. Diethyl ether was dried over freshly made sodium ribbon and distilled. THF was predried over KOH followed by anhydrous $NaSO_4$ and distilled under argon from potassium using benzophenone as an indicator. *n*-Butyllithium was used as a nominally 2.4 M solution in hexane as purchased; periodically, this solution was titrated against a known weight of 2,6-dimethoxybenzyl alcohol and the molarity of the solution recalculated. All reactions involving organic solvents were performed under an inert atmosphere of argon or nitrogen.

Melting points were determined in capillaries and are corrected. Infrared spectra were determined on neat samples (liquids) or KBr pellets (solids). NMR spectra were obtained on 80, 270 and 400 MHz instruments using tetramethylsilane as an internal standard; the following abbreviations are used in describing ^{1}H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad); coupling constants (*J* values) are given in Hz . Variable temperature ^{1}H NMR spectra were obtained on a 200 MHz instrument. Elemental analyses were determined by commercial laboratories. All optical rotations (α) were obtained at the sodium D-line at 25^{o}C on a polarimeter at least 30 min after turning on the instrument. The polarimeter cell was carefully washed with acetone and dried under nitrogen; the volume of the cell was 1 mL and the path length (*l*) was 1 dm. A solution of the analyte of concentration *c* (g/mL) was made by weighing a sample directly into a volumetric flask on the analytical balance. The solution was added to the cleaned cell and the optical rotation was taken. The polarimeter was calibrated by use of a sample of commercial (-)-menthol. Specific rotations are reported as $[\alpha]_D^{25}$ {= α/lc}

without units (degree•mL/g•dm) followed by "[c (in g/dL), solvent]"; for neat compounds we report α_D^{25}.[S1] HPLC was performed on a dual pump model with UV detection set at a wavelength of 254 nm. The columns used were a Pirkle covalent phenylglycine modified spherisorb S5NH column (4.6 x 250 mm) and a Chiralcel OD column (4.6 x 250 mm); HPLC grade solvents for the mobile phase were deaerated using a nitrogen bubbler prior to use. X-ray crystallography was performed with $M_oK\alpha$ (λ=0.71073 Å) radiation source at 298°K. Solution was achieved by direct methods using SHELXTL PLUS. Refinement was by Full-Matrix Least Squares riding model. Fixed isotropic U was used to place the hydrogen atoms. High resolution fast atom bombardment mass spectra (HR FAB MS) were obtained using xenon in the positive ion mode; the matrix was 3-nitrobenzoic acid-poly(ethylene glycol) (NBA-PEG).

Chromatographic Treatment of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitriles [(*S*)-8/(*R*)-8]. A sample was fractionated by automated flash chromatography by slow gradient elution with hexanes:ethyl acetate from 100:0 to 90:10. In the proton NMR spectra (Figure S1a) the ratios of the signals for the *Z*-isomers at 6.39 ppm (H_1) and 6.87ppm (H_3) vs. those for the *E*-isomers at 6.18 and 6.22 ppm (both signals together, H_1) and 7.02 ppm (H_3) over the 6 fractions range from 60:40 to 64:36. On the other hand the ratios of the signals for H_1 of the two diastereomers at 6.18 and 6.22 ppm change significantly in sequence from 31:69 to 38:62 to 45:55 to 53:47 to 61:39 to 66:34, respectively. Moreover, the low temperature spectrum of fraction 1 (Figure S1b) shows that the individual H_3 signals for the *Z*- and *E*-urethane isomers are each comprised of ~60:40 diastereomers in contrast to the original sample (Figure 1c) in which the two diastereomers were present in essentially equal proportions. In ~30 other Reissert compounds we observed that the predominant *Z*-isomers produce chemical shifts for H_3 that are upfield relative to the *E*-isomers; for H_1 the opposite trend is observed because of its proximity to

the carbonyl oxygen in the *Z*-isomer. The change in diastereomeric ratio (as judged by the ratio of the minor upfield H_1 signals at 6.18 and 6.22 ppm) most notably affects the H_3 signals at 6.9 ppm and the upfield portion of the H_4 signals at 6.0 ppm; this is consistent with the assignment of the *Z*-urethane configuration to these signals, which places the menthyl moiety in the vicinity of H_3 and H_4. The lack of effect of diastereoisomerism on the less well-resolved signals of the *E*-urethanes (H_3 at 7.0 ppm and the downfield portion of the H_4 signals at 6.0 ppm) results from the menthyl moiety being remote from these protons. On the other hand, the sensitivity of the H_1 signals at 6.18 and 6.22 ppm reflects their proximity to the menthyl moiety in the *E*-urethanes.

***l*-Menthoxyacetic Acid.** Using a reported procedure [S2] this compound was made from *l*-menthol and chloroacetic acid. Pure (-)-menthoxyacetic acid was obtained by vacuum distillation, bp 112-115°C/0.3 torr. α_D^{25} = -92.4° (neat). Reported [S2a] bp 134-7°C/2 torr, α_D^{25} = -92.4 (neat). FTIR (neat): ν 3600-2600 (O-H), 2870 (C-H), 1762 (C=O), 1732 (C=O), 1455, 1237, 1127 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$); δ 0.80-1.10 (m, 12 H), 1.20-2.20 (m, 5 H), 3.19 and 3.21 (0.5 each H, t, J=12), 4.06 and 4.24 (1H each, d, J=18), 10.01 (s, 1 H).

(-)-Menthoxyacetyl Chloride. A solution of (-)-menthoxyacetic acid in thionyl chloride was allowed to reflux for 24 h and then cooled to room temperature. The excess thionyl chloride was distilled (1 atm., 70°C) from the product, which was purified by distillation under reduced pressure, bp 80-82°C/0.3 torr. FTIR (neat): ν 2800 (C-H), 1798 (C=O), 1455, 1237, 1127 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.80-1.10 (m, 12 H), 1.20-2.20 (m, 5 H), 3.19 and 3.21 (0.5 each H, t, J=12), 4.45 (s, 2 H, $COCH_2$). α_D^{25} = -92.1 (neat). Reported bp 117-120°C/3 torr, α_D^{25} = -89.6° (neat). [S2b]

Aryl 1-Isoquinolyl Carbinyl *l*-Menthyl Carbonates. Condensation of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitriles [(*S*)-**8**/(*R*)-**8**] with aromatic aldehydes was carried out at –40°C in

DMF as described. Benzaldehyde, *o*-tolualdehyde, veratraldehyde and *o*-anisaldehyde afforded the corresponding carbonates **5**, R = *d*-menthyl, R' = aryl. The products were analyzed by HPLC on a Pirkle column (See Table S1 and Figures S6 and S7 below). Because these doubly benzylic carbinol esters racemized rapidly (over a period of a few days or less), no attempt was made to isolate and purify them.

Racemic 1-Isoquinolyl Phenyl Carbinol

a. By the Phase Transfer Method: [S3] Aqueous NaOH (50%, 7 mL) was added to a well stirred solution of the Reissert compound **1a**, R=C_6H_5, (1.0 g, 3.9 mmol) in benzene (35 mL), benzaldehyde (3.9 mL, 39 mmol) and trimethylbenzylammonium chloride (74 mg, 3.9 mmol) and the mixture was allowed to stir for 24 h. The very thick mixture was diluted with water (200 mL). The benzene layer was washed with water (2 x 30 mL), aq. sat'd $NaHCO_3$ (3 x 30 mL), and $NaHSO_3$ (10 x 30 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to yield the crude alcohol (750 mg, 85%), which was purified by recrystallization from ethanol, mp 113-115°C (reported [S4] mp 114-116°C). FTIR (KBr): ν 3500-2500 (O-H), 2900 (C-H), 1550 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.20 (s, 1 H), 6.23 (s, 1 H), 7.20-7.40 (m, 5 H), 7.42-7.52 (m, 1 H), 7.60-7.80 (m, 2 H), 7.80-7.85 (m, 1 H), 7.85-8.00 (m, 1 H), 8.50-8.60 (m, 1 H). LR MS (DICI): m/z 339 (8%, M^+), 234 [100%, $(M-C_6H_5CO)^+$], 217 [95%, $(M-C_6H_5COOH)^+$], 105 (80%, $C_6H_5CO^+$), 77 (80%, $C_6H_5^+$).

b. By the NaH/DMF Method via 3, R = α-$C_{10}H_7$, R' = C_6H_5: [S5] NaH (60%, 100 mg, 2.5 mmol) was added to a well stirred solution of the compound **1a**, R=α-$C_{10}H_7$ [S6] (700 mg, 2.26 mmol) and benzaldehyde (0.30 mL, 3.0 mmol) in DMF (20 mL) at 0°C. The mixture was stirred for 1.7 h at 0°C and quenched into ice-water (200 mL) and extracted with ether (2x40 mL) and ethyl acetate (2x40 mL). The combined extract was washed with water (2x20 mL), saturated aq.

$NaHSO_3$ (2x20 mL) and water (4x20 mL). The extract was dried (Na_2SO_4) and concentrated to yield the crude ester, 620 mg (75%). Recrystallization (hexane-ethyl acetate) afforded the pure ester **3**, R = α-$C_{10}H_7$, R' = C_6H_5 as a colorless crystalline solid, mp 134-137°C. ^{1}H NMR ($CDCl_3$) δ: 7.2-7.7 (m, 11H), 7.85 (m, 2H), 7.91 (s, 1H, CHO), 8.05 (d, J=8, 1H), 8.41 (t, J=8, 1H), 8.59 (d, J=8, 1H), 8.94 (d, J=8, 1H). Anal. Calcd. for $C_{27}H_{19}NO_2$: C 83.27, H 4.92, N 3.60. Found: C 83.52, H 4.97, N 3.58.

A solution of the naphthoate ester in THF (15 mL), water (15 mL), EtOH (15 mL) and NaOH (0.5 g) was allowed to reflux overnight. The product was isolated and purified as in the procedure above to yield the alcohol (82%). Spectral data were identical to those of the compound prepared by the phase transfer method above.

Racemic 1-Isoquinolyl *tert*-Butyl Carbinol (16).

a. By the NaH/DMF Method via 3, **R=α-$C_{10}H_7$, R'=*tert*-Bu:** By the above method Reissert compound **1a**, R= α-$C_{10}H_7$ [S6] and pivaldehyde yielded 100% of the **3**, R=α-$C_{10}H_7$, R'=*tert*-Bu, mp 136-137°C (hexane-ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.17 (s, 9H), 6.73 (s, 1H, CHO), 7.45-7.75 (m, 6H), 7.85 (m, 2H), 8.02 (d, J=8, 1H), 8.42 (dd, J=1, 7; 1H), 8.54 (bd, J=7, 1H), 8.56 (d, J=7, 1H), 8.88 (bd, J=7, 1H). Anal. Calcd. for $C_{25}H_{23}NO_2$:C 81.27, H 6.28, N 3.79. Found: C 81.24, H 6.24, N 3.90.

The naphthoate ester was hydrolyzed (88%) to *rac*-**16**, mp 101-102°C, purified by several recrystallizations from ethyl acetate/hexane. Spectral data of this sample were identical with those of the sample synthesized by the PTC method (below).

B. By the PTC Method: The method described above with **1a**, R=C_6H_5 and pivaldehyde produced (25%) the alcohol, mp 100-101°C. FTIR (KBr): ν 3300-3500 (O-H) and 2810-2600 (C-H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 9 H), 4.58 (d, J=8, 1 H), 5.34 (d, J=8, 1 H), 7.55-7.75

(m, 3 H), 7.84 (d, J=8, 1 H), 8.18 (d, J=8, 1 H), 8.50 (d, J=8, 1 H). Anal. Calcd. for $C_{14}H_{17}NO$:C 78.10, H 7.98, N 6.51. Found: C 77.97, H 7.98, N 6.34.

Optical Purity Analysis of Isoquinolyl Alcohols

a. Attempts to Form Diastereomeric Derivatives: A set of model reactions of racemic 1-isoquinolyl phenyl carbinol with acetyl chloride to form the acetate **3**, R=CH_3, R'=C_6H_5 showed that the best conditions for the esterification were in refluxing toluene with pyridine as the base (96% yield). Then *l*-(-)-menthyl chloroformate and cholesteryl chloroformate were used as chiral esterification reagents with racemic 1-isoquinolyl phenyl carbinol. The chloroformates were found not to be reactive enough toward the tertiary alcohol; these reactions did not proceed to high conversion under any of the conditions used. N-Phenylsulfonylprolyl chloride was also tried, but without success.

The synthesis of diastereomeric silyl acetals from racemic 1-isoquinolyl phenyl carbinol, *l*-menthol and dimethyldichlorosilane[S7] also proved problematic because of the difficulty in forming the silyl acetals quantitatively and isolation of the pure product; Si-CH_3 peaks from side products also interfered with NMR analysis.

b. Use of Chiral Shift Reagents and Chiral Solvents: The chiral lanthanide shift reagents tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) {Eu(hfc)$_3$} and tris[3-(hexafluoropropylhydroxymethylene)-(+)-camphorato]praseodynium (III) {Pr(hfc)$_3$} were applied in a 1:5 mole ratio to racemic 1-isoquinolyl phenyl carbinol and *rac*-**16**. Also the chiral amines *R*-(+)-1-(α-napthyl)ethyl amine and *S*-(-)-α-methylbenzylamine were used in a 3:1 ratio relative to racemic 1-isoquinolyl phenyl carbinol and *rac*-**16**. These techniques proved unsuccessful due to problems with line broadening.

c. Use of Quinine as a Chiral Solvating Agent: For racemic 1-isoquinolyl phenyl carbinol in $CDCl_3$ ^1H NMR singlets for the methine and hydroxyl protons occur at 6.40 and 6.38 ppm in $CDCl_3$, respectively. In the case of racemic 1-isoquinolyl *tert*-butyl carbinol (*rac*-**16**) one doublet (J=6.8 Hz) each for the methine (H_α, 5.25 ppm) and hydroxyl signals (4.50 ppm) (Figure S9a) was identifiable by exchanging the compound with D_2O, resulting in two singlets, a broad OH signal and a sharp H_α peak. H_8 of **16** appears as a doublet at 8.13 ppm (Figure S9a).

Quinine was employed as a chiral solvating agent (CSA).[S8] When racemic 1-isoquinolyl phenyl carbinol was mixed with quinine (3 eq.), the signal for the methine (H_α) proton was shifted into a complex splitting pattern in the aromatic region, making interpretation extremely difficult.

Rac-**16** was mixed with quinine in a molar ratio of 1:≥3 [e. g., 10 mg (46 μmol) of *rac*-**16** and 53 mg (164 μmol) of quinine] and dissolved in a minimal amount of $CDCl_3$ in a vial. Ten drops of D_2O were then added and the sample was shaken vigorously for 1 h. Molecular sieves were added and the sample was allowed to stand for 5 min. The sample was filtered into an NMR tube and the minimum amount of $CDCl_3$ was added to allow NMR determination. The H_α protons displayed two singlets (Figure S9b) and proton H_8 appeared as an overlapping pair of doublets (Figure S9b inset). Integration of the outer peaks for H_8 was used as a verification of the enantiomeric ratio determined by integration of the methine (H_α) singlets; for the racemate, this yielded a 50.0:50.0 composition with a standard error of the mean, σ_n, of ±0.7 percent (n = 20). In the case of the pure enantiomer only one of the methine singlets was present at 5.21 ppm and only one of the H_8 doublets at 8.13 ppm (Figure 6).

1-Alkyl-2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitriles and 1-Alkyl-2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitriles. To a solution of the Reissert

compound 1:1 (*S*)-**8**:(*R*)-**8** or (*S*)-**11** (2.7 mmol) and alkyl halide (2.7 mmol) in 10 mL of DMF at –40°C under N_2 was added 0.5 g (3 mmol) of 80% NaH. After 3 h the mixture was quenched with water and extracted 3x with ether. The ether solution was washed with water 6x, dried ($MgSO_4$) and evaporated to yield the crude product, which was analyzed by HPLC on a Pirkle phenylglycine column (See Table S1 and Figures S11-S13 below). No attempt was made to isolate and purify these compounds.

1-Deuterio-2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile [(*S*)-8-*d*:(*R*)-8-*d*]. To a stirred solution of 1.0 g (2.7 mmol) of 1:1 (*S*)-**8**:(*R*)-**8** and 2.0 mL (32 mmol) of CS_2 in 30 mL of DMF at ambient temperature under N_2 was added 90 mg (≈3.0 mmol) of ≈80% NaH in mineral oil. The red-orange mixture was stirred for 2 h and quenched by addition of 25 mL of D_2O. The solid was filtered, washed with water and dried. ^{1}H NMR ($CDCl_3$) indicated that the peaks for H_1 at 6.23, 6.28 and 6.43 ppm were diminished to ~20% of the integrations for signals assigned to H_3 and H_4 (Figure S14). A control experiment was carried out in the same manner except quenching was accomplished by addition of H_2O; this resulted in complete recovery of the starting Reissert compound with 1:1 diastereomeric ratio as determined by the ^{1}H NMR spectrum.

Quenching of the Anion from 2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitrile [(*S*)-11]. This transformation was carried out with NaH, CS_2 and H_2O as described for deuteration of (*S*)-**8**/(*R*)-**8** above. A mixture of (*S*)-**11**/(*R*)-**11** resulted. See Figure S2.

6,7-Dimethoxy-3,4-dihydroisoquinoline (17). This compound was made following known procedures for the syntheses of 3,4-dihydroisoquinolines.[S9] Anhyd. formic acid (7.00 g, 152 mmol) was refluxed with 3,4-dimethoxyphenethylamine (10.00 g, 55.2 mmol) for 3 h, protected by a Drierite tube. The solution was allowed to cool to room temperature, whereupon it

solidified. Toluene (50 mL) was added. Phosphorous oxychloride (30 mL, 0.20 mol) was added cautiously through the condenser. The Drierite tube was reattached and the homogeneous solution was refluxed for 1 h, cooled to room temperature and diluted with petroleum ether (bp 40-60 °C). The solvent was decanted from a brown viscous oil, which was dissolved in hot ethanol. The alcohol solution was poured into 350 mL of dilute HCl. The aq. solution was extracted with benzene. The aq. acidic medium was made basic with 50% aq. NaOH with cooling by the addition of ice. The basic aq. solution was extracted with benzene (3 x 50 mL). The collected organic phase was dried using Na_2SO_4 and then filtered. The benzene was removed using a rotoevaporator to give 9.60 g (90 % yield) of an orange oil, which was used in Reissert compound syntheses: (lit. bp 152-158 °C/0.8-0.9 torr, [S9a] bp 120 °C/0.01 torr [S10]); IR 3003, 1630 cm^{-1}, ^1H NMR δ 2.63 (t, J = 8, 2 H), 3.68 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.63 (s, 1 H), 6.76 (s, 1 H), 8.18 (s, 1 H); ^{13}C NMR δ 24.6, 47.1, 55.9, 56.0, 110.5, 110.6, 121.4, 129.7, 147.8, 151.3, 159.4.

1-Methyl-6,7-dimethoxy-3,4-dihydroisoquinoline. This compound was synthesized in a manner analogous to that above from 3,4-dimethoxyphenethylamine and acetic acid in 68% yield as a yellowish-white solid, mp 107.0 - 107.9°C (hexane-ethyl acetate) (lit. mp 108°C,[S11a] 106-107°C,[S11b] 106°C,[S11c] 102-104°C,[S11d] 105-106°C [S11e]). IR ν 2964, 2941, 2924, 3077, 1626, 1603, 1571 cm^{-1}; ^1H NMR δ 2.40 (s, 3 H), 2.63 (t, J = 8, 2 H), 3.61 (m, 2 H), 3.89 (s, 6 H), 6.67 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR δ 23.1, 25.6, 46.8, 55.8, 56.2, 109.4, 110.4, 122.4, 131.1, 147.5, 150.9, 163.3.

1-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline. This compound was synthesized in a manner analogous to that above from 3,4-dimethoxyphenethylamine and phenylacetyl chloride in 47% yield as a whitish solid, mp 86.5-90.7°C (lit. ~80°C, [S12a] 84-85°C, [S12b] 81.8-85.9°C [S12c] 87°C [S12d]),

which was not further purified: IR ν 3027, 1623, 1604 cm^{-1}; ^1H NMR δ 2.64 (t, 2 H), 3.71 (s, 3 H), 3.74 (m, 2 H), 3.86 (s, 3 H), 4.04 (s, *J* = 8, 2 H), 6.64 (s, 1 H), 6.94 (s, 1 H), 7.25 (m, 5 H); ^{13}C NMR δ 25.7, 43.4, 47.1, 55.1, 55.9, 110.0, 110.4, 121.6, 121.9, 126.3, 128.4, 131.7, 138.2, 147.3, 150.7, 165.2.

1-*i*-Propyl-6,7-dimethoxy-3,4-dihydroisoquinoline. This compound was made analogously from 3,4-dimethoxyphenethylamine and 2-methylpropionic acid in 80% yield as an orange oil (lit. bp 126-129°C/0.5 mm,[S13a] 128-129°C/1.2 mm,[S13b]). IR ν 2969, 1624, 1606 cm^{-1}; ^1H NMR δ 1.12 (d, *J* = 7, 6 H), 2.49 (t, *J* = 8, 2 H), 3.11 (m, 1 H), 3.52 (t, *J* = 8, 2 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 6.62 (s, 1 H), 6.96 (s, 1 H); ^{13}C NMR δ 20.3, 25.2, 31.0, 46.0, 55.0, 55.6, 62.8, 108.5, 110.0, 120.9, 131.3, 146.9, 150.1, 170.1.

(*S*)-α-Methylbutyryl chloride. Thionyl chloride (5.98 g, 50.2 mmol) was added to (*S*)-α-methylbutyric acid, 98%, $\alpha_D^{25} = +19°$ (neat), (5.13 g, 50.2 mmol) in a reflux apparatus connected to a drying tube. The solution was warmed at 30-40 °C with stirring for 23 h and placed under aspirator pressure to remove excess thionyl chloride. The compound was distilled under aspirator pressure, affording a colorless oil; IR: 1793 cm^{-1}. Alternatively, the crude compound was used without distillation.

8-Phenyl-*l*-menthyl chloroformate. 8-Phenyl-*l*-menthol, 98%, $[\alpha]_D^{25} = -26$ (c = 2.0, C_2H_5OH) (0.90 g, 3.9 mmol) was stirred under argon with pyridine (0.31 g, 3.9 mmol) in benzene (4 mL). Triphosgene (0.38 g, 1.3 mmol) in benzene (5 mL) was added dropwise. After the 2 d of stirring, the mixture was filtered. The benzene was removed *in vacuo* to give 0.85g (75%) of colorless oil: IR (neat): ν 1770 cm^{-1}; ^1H NMR δ 0.90 (m, 5 H), 1.14 (m, 2 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.63 (m 2 H), 2.02 (m, 2 H), 4.81 (m, 1 H), 7.20 (m, 1 H), 7.33 (m, 4 H); ^{13}C NMR δ 21.5, 26.5, 26.8, 27.0, 31.4, 24.2, 39.9, 41.0, 50.7, 83.9, 88.7, 125.5, 128.2, 149.8. This was used without

further purification.

Reaction of the anion of 1-Cyano-2-(*l*-menthoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*S*)-19 with water. To a stirred solution of (*S*)-**19** (0.50 g, 1.3 mmol) in DMF (25 mL) at 1°C was added NaH as a 60% dispersion in mineral oil (0.05 g, 1 mmol). The yellow mixture was stirred at 1°C for 15 min and the anion was quenched with H_2O (1 mL). The yellow color disappeared immediately. Stirring was continued for 3.2 h and the mixture was poured into 250 mL of ice water and filtered to give 0.5 g of yellowish white solid. Two peaks were obtained in the HPLC characteristic of the two diastereomers of **19** (Figure S18).

Use of Butyllithium in the Methylation of 2-(*l*-Menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*S*)-19. To a stirred solution of (*S*)-**19** (1.00 g, 2.50 mmol) in THF (15 mL) at -78°C under argon was added *n*-butyllithium (2.62 mmol). The mixture was stirred for 20 min, during which time it turned yellow. Iodomethane (0.39 g, 2.8 mmol) was added via syringe. The mixture was warmed with an ice bath. Stirring was continued for 4 h. The color of the mixture faded to colorless in 20 min. Saturated aq. NH_4Cl (10 mL) was added to the mixture followed by H_2O (15mL). The solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was washed with brine and dried using anhyd. Na_2SO_4. The solvent was removed *in vacuo* to give 1.13 g (100%) of an oil, which crystallized upon standing. The ^1H NMR spectrum of the unpurified material was essentially identical to that of **25a** described in the text; the ratio of the two 1-methyl signals at 1.89 and 1.86 ppm in toluene-d_8 was 51:49. $[\alpha]_D^{25}$ = -44.8 (c = 2.11, $CHCl_3$).

To a stirred solution of (*S*)-**19** (0.40 g, 1.0 mmol) in THF (15 mL) at -78°C under argon was added *n*-butyllithium (1.05 mmol). The mixture was stirred for 20 min, during which time it turned yellow in color. The reaction temperature was lowed to -100°C. Iodomethane (0.16 g,

1.1 mmol) was added via syringe. Stirring was continued for 5 h at -100°C. The yellow color of the anion disappeared after 1.5 h of stirring. Saturated aq. NH_4Cl (10 mL) was added to the mixture followed by H_2O (15mL). The solution was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phase was washed with brine and dried using anhyd. Na_2SO_4. The ^1H NMR spectrum of the unpurified material was essentially identical to that of **25a** given above; the ratio of the two 1-methyl signals at 1.90 and 1.87 ppm in toluene-d_8 was 54:46. $[\alpha]_D^{25}$ = -39.6 (c = 0.450, $CHCl_3$).

1-*i*-Propyl-2-(*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (25b) from (*S*)-19 using LDA as the base. To freshly distilled diisopropylamine (0.11 g, 1.1 mmol) in THF (10 mL) *n*-butyllithium (1.13 mmol) was added under argon at -20°C. The temperature was raised to rt and stirring continued for 15 min. The resulting diisopropylamide in THF was cooled to -78°C. (*S*)-**19** (0.41 g, 1.0 mmol) in THF (25 mL) was added dropwise. The mixture turned yellow. Stirring was continued for 10 min. 2-Iodopropane (0.19 g, 1.1 mmol) was added to the mixture via syringe. The mixture was stirred at -78°C for 3 h. The yellow color had faded slightly. The mixture was allowed to come to rt and stirred for an additional 12 h, by which time the color had changed to a light red. Aq. NH_4Cl (10 mL) followed by H_2O (20 mL) were added to the mixture. The aq. solution was reduced in volume *in vacuo* until an oil in H_2O appeared. The aq. solution/oil was extracted with CH_2Cl_2 (3 x 15-20 mL). The combined organic phase was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was removed *in vacuo* to give 0.44 g (98% yield) of a dark yellow oil. The crude compound was crystallized once from a mixture of ethanol and hexane and twice from a mixture of ethyl acetate and hexane: mp 128-131°C: $[\alpha]_D^{25}$ = -53.1 (c=0.700, $CHCl_3$); IR ν 2243, 1698 cm^{-1}; ^1H NMR δ 0.61 (m, 3 H), 0.78 (m, 3 H), 0.88 (m, 6 H), 1.06 (m, 6 H), 1.45 (m, 2 H), 1.66 (d, J = 7, 2 H), 1.88 (m, 1

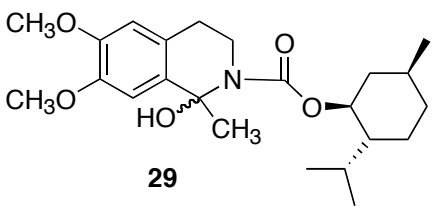
H), 2.10 (t, *J* = 7, 1 H), 2.61 (d, *J* = 7, 1 H), 2.86 (m, 1 H), 3.19 (m, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.23 (m, 1 H), 4.71 (m, 1 H), 6.61 (s, 1H), 7.02 (d, *J* = 8, 1 H); ^{13}C NMR δ 16.0, 16.4, 18.9, 20.7, 21.9, 23.6, 26.6, 29.0, 31.4, 34.2, 36.6, 41.2, 41.4, 41.8, 47.3, 47.4, 55.9, 56.1, 63.2, 63.4, 111.0, 112.3, 119.8, 121.9, 128.4, 147.1, 148.9, 154.9. The IR, ^{1}H NMR and ^{13}C NMR spectrum were identical to those obtained for **25b** using NaH/DMF.

Cyanoacylation of 1-Substituted 3,4-Dihydroisoquinolines: General Procedure.

To a stirred solution of 0.50 g of the substituted 3,4-dihydroisoquinoline, 1.1 equivalent of TMSCN, and 0.10 equivalent of anhyd. $AlCl_3$ in 20 mL of CH_2Cl_2 was added 1.1 equivalent of acid chloride. After 3-6 days of stirring at room temperature (monitored by TLC), 1 mL of H_2O was added and stirring was continued for 1 day. The organic phase was washed 3x each with H_2O, 10% HCl, H_2O, 10% NaOH, and H_2O and then once with brine. The organic phase was dried over anhyd. Na_2SO_4 and evaporated to give the crude product.

1-Methyl-2-(*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (25a) by cyanoacylation. After 6 days, an orange oil in 100% yield. In the ^{1}H NMR spectrum obtained in toluene-d_8 the ratio of the integrations of the 1-methyl signals at 1.89 and 1.86 ppm was 44:56, respectively. Use of other reaction temperatures (0 and -26ºC) yielded the same diastereomeric ratio.

1-Methyl-2-(*l*-menthoxycarbonyl)-1-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (29). When the cycanoacylation reaction to form **25a** above was terminated by quenching with water after 3 days, the crude product (72%) was shown to be a mixture of 4 compounds by TLC; trituration with ether yielded (14%) the material with the lowest R_f and it was purified by column chromatography (SiO_2, 10% *i*-PrOH/hexane) and recrystallization



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(ethanol, then hexane-ethyl acetate) as silky colorless needles of **29**, mp 125-126ºC; IR (KBr): ν 3375, 1678 cm^{-1}; ^1H NMR δ 0.75 (d, *J* = 7, 3 H), 0.87 (m, 7 H), 1.00 (m, 2 H), 1.25 (m, 1 H), 1.42 (m, 2 H), 1.62 (m, 2 H), 1.84 (m, 1 H), 1.96 (m, 1 H), 2.58 (s, 2 H), 3.03 (t, *J* = 7, 2 H), 3.44 (m, 2 H), 3.92 (s, 6 H), 4.48 (m, 1 H), 5.10 (m, 1 H), 6.75 (s, 1 H), 7.22 (s, 1 H); ^{13}C NMR δ 16.6, 20.7, 22.0, 23.8, 26.4, 29.2, 31.3, 34.2, 34.4, 41.6, 42.4, 47.4, 56.0, 56.3, 113.7, 114.7, 129.8, 134.5, 147.0, 152.0, 156.5, 199.8. Anal. Calcd. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.45; Found: C, 67.60; H, 8.48, N, 3.54.

1-Benzyl-2-(*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (25c) by cyanoacylation. Crude yield: 86% of a brown viscous oil, purified by flash chromatography to give a colorless oil, which solidified under vacuum. The solid was recrystallized from a mixture of hexane and ethyl acetate: mp 106-109°C. $[\alpha]_D^{25}$ = -22.3 (c = 0.713, $CHCl_3$). The IR, ^{13}C and ^1H NMR spectra were identical to the compound made by benzylation of dihydro-Reissert compound **19**, but the melting point was 2-3°C lower and the optical rotation was 20° lower. The diastereomers could not be separated by chromatography or recrystallization.

1-Methyl-(8'-phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinoline (26a) by cyanoacylation. 90% yield of a golden yellow amorphous solid whose IR and NMR spectra were essentially identical to the product prepared by methylation of **20**. $[\alpha]_D^{25}$ = -50.4 (c = 0.630, $CHCl_3$). The integration ratio of the 1-methyl signals at 1.90 and 1.87 ppm in toluene-d_8 was 62:38, respectively.

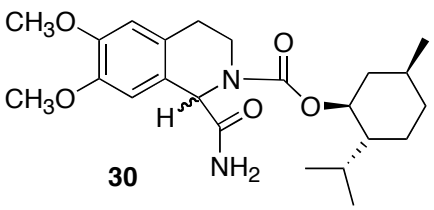
Transformations of Chiral Dihydro Reissert Compounds and Alkylated Derivatives

With a view toward ultimate production of isoquinoline alkaloids, several transformations of alkylated chiral dihydro Reissert compounds were explored. Attempted

reductions of 1-methyl-2-(*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**25a**) and 1-benzyl-(*l*-menthoxycarbonyl)-1-cyano-2-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**25c**) to N-formyl derivatives (as precursors to N-methyl analogs) using sodium borohydride, sodium borohydride in diglyme, sodium borohydride in diglyme with aluminium chloride, diisobutylaluminium hydride and lithium aluminium hydride all at various temperatures resulted in recovery of only starting material.

Treatment of (*S*)-**19**with hydrogen peroxide under basic conditions in DMSO led to quantitative conversion of the cyano moiety to the amide (**30**).

2-(*l*-menthoxycarbonyl)-1-carboxamido-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (30) by hydrolysis of [(*S*)-19] with hydrogen peroxide and base. A solution of (*S*)-**19** (0.76 g, 1.9 mmol) in DMSO (15 mL) with K_2CO_3 (0.20 g, 1.6 mmol) was cooled to 0 °C using an ice H_2O bath. Aq. hydrogen peroxide (30%, 0.35 mL) was added to the mixture, which was warmed to room temperature and stirred for 12 h. H_2O (10 mL) was added and the resultant mixture was poured into H_2O (35 mL). The precipitate was filtered to give 1.16 g (100%) of a white solid, which was recrystallized once from ethanol, twice from a mixture of hexane and ethyl acetate and once from toluene, affording pure **30**: mp 167-168°C; $[\alpha]_D^{25}$ = -60.0 (c = 0.160, $CHCl_3$); IR (KBr): ν 3364, 3174, 1695, 1657 cm^{-1}; ^1H NMR δ 0.75 (d, *J* = 7, 3 H), 0.95 (m, 9 H), 1.46 (m, 2 H), 1.67 (d, *J* = 7, 2 H), 1.87 (br, 1 H), 2.03 (m, 1 H), 2.80 (br, 2 H), 3.58 (br, 1 H), 3.85 (br s, 7 H), 4.64 (br m, 1 H), 5.46 (m, 1 H), 5.96 (br m, 1.5 H), 6.73 (br m, 2.5 H); the ^1H NMR spectrum showed traces of ethyl acetate; ^{13}C NMR δ 16.6, 22.7, 22.0, 23.7, 26.6, 28.1, 31.5, 34.3, 40.6, 41.4, 41.6, 47.4, 56.0, 56.1, 58.1, 111.5, 127.1, 127.6, 140.8, 141.3, 147.9, 148.8, 173.4. Anal. Calcd. for $C_{23}H_{34}N_2O_5$•0.50($CH_3COOC_2H_5$): C, 64.91; H, 8.27; N,



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6.06; Found: C, 64.61; H, 8.07; N, 6.53.

Table S1

Reactions of Diastereomeric Isoquinoline Reissert Compounds [a]

Reissert Compound	Electrophile	Product	Yield (%)	Diastereomeric Product Ratio
1:1(*S*)-**8**:(*R*)-**8**	C_6H_5CHO	**5**, R = *d*-menthyl, R' = C_6H_5	95	55:45 [b]
1:1(*S*)-**8**:(*R*)-**8**	*o*-$CH_3C_6H_4CHO$	**5**, R = *d*-menthyl, R' = *o*-$CH_3C_6H_4$	100	66:34 [b,c]
1:1(*S*)-**8**:(*R*)-**8**	*o*-$CH_3OC_6H_4CHO$	**5**, R = *d*-menthyl, R' = *o*-$CH_3OC_6H_4$	100	62:38 [b,d]
1:1(*S*)-**8**:(*R*)-**8**	3,4-$(CH_3O)_2C_6H_3CHO$	**5**, R = *d*-menthyl, R' = 3,4-$(CH_3O)_2C_6H_3$	61	51:49 [b]
1:1(*S*)-**8**:(*R*)-**8**	D_2O	(*S*)-**8**:(*R*)-**8**	100	1:1 [b,e]
(*S*)-**11**	H_2O	(*S*)-**11**:(*R*)-**11**	100	51:49 [b,f]

[a] In DMF at –40°C using NaH as base.
[b] By HPLC with a Pirkle phenylglycine column (99:1 hexane:isopropanol, 1 mL/min); listed in order of elution.
[c] See Figure S6.
[d] See Figure S7.
[e] See Figure S14.
[f] See Figure S2.

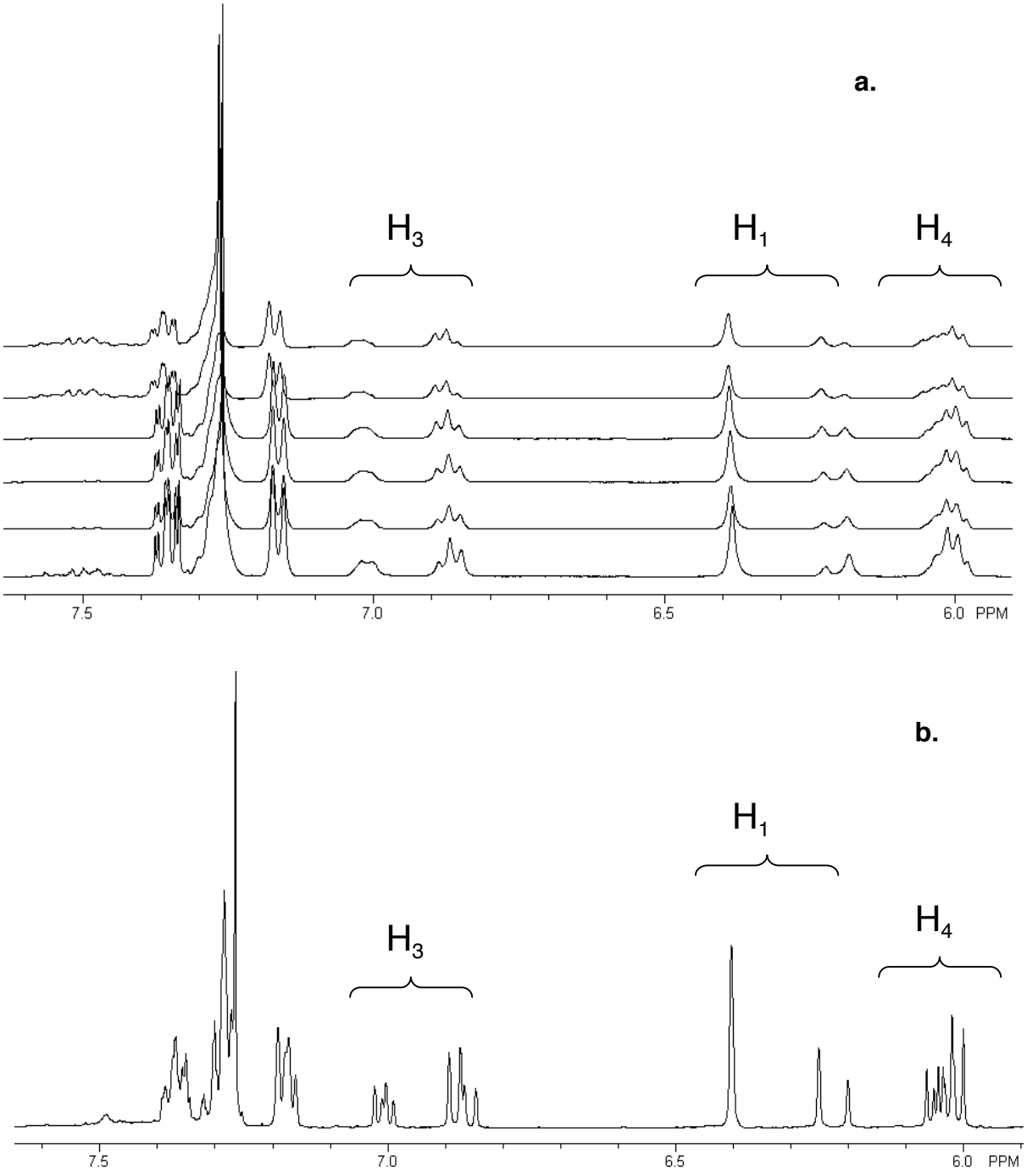

Figure S1. Partial 400 MHz ^{1}H NMR spectra of chromatographic fractions of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile [(*S)*-**8**/(*R)*-**8**] in $CDCl_3$: **a, top**) fractions 1, 3, 5, 7, 9 and 11 (top to bottom) at 23^{o}C and **b, bottom**) fraction 1 at -20^{o}C.

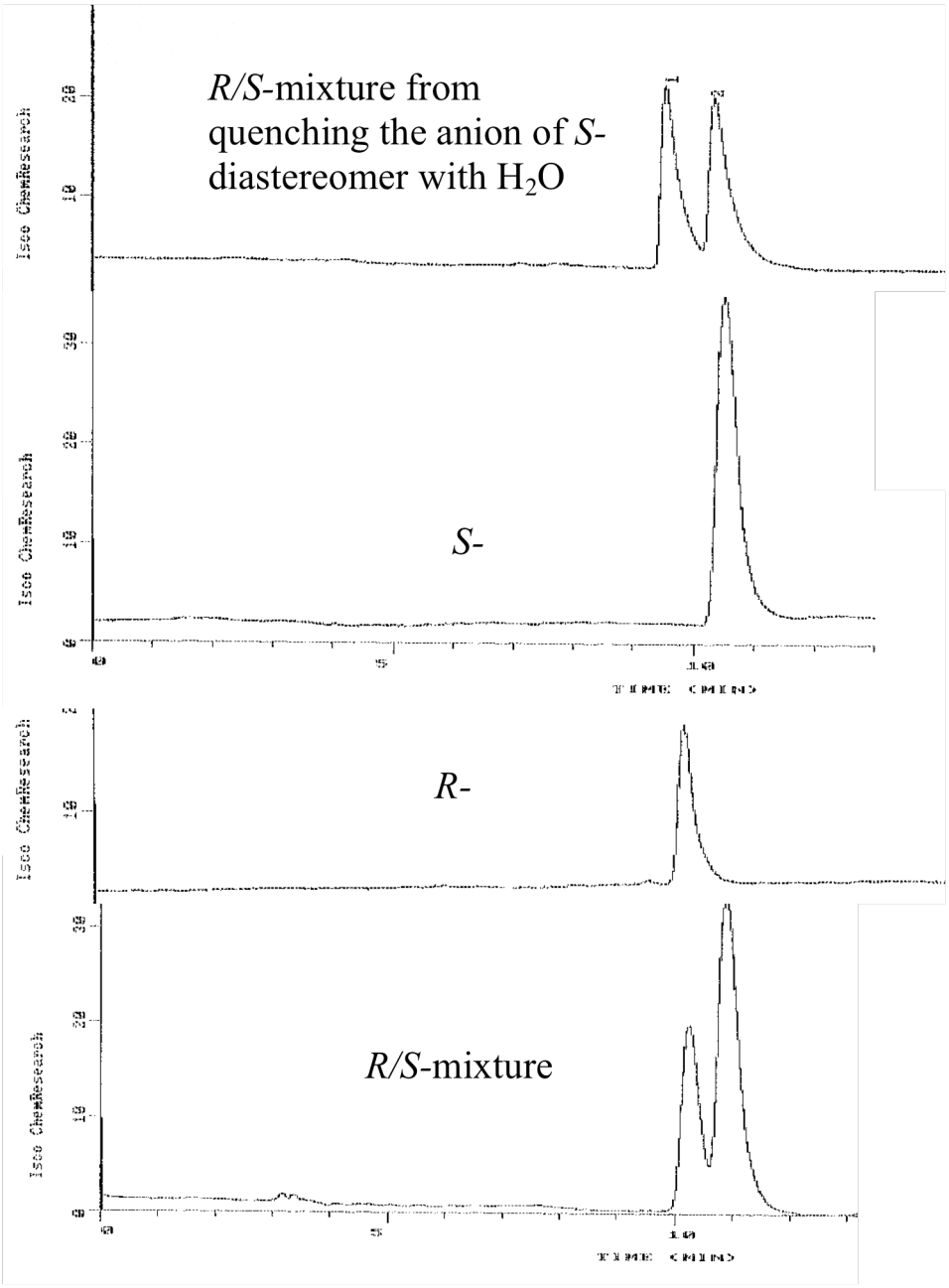

Figure S2. HPLC traces (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitriles (**11**), from bottom up: mixture as isolated, pure *R*-diastereomer, pure *S*-diastereomer (see Figure S3 for X-ray crystal structure of the *S*-diastereomer) and 51:49 mixture after quenching the anion of (*S)*-**11** with H_2O.

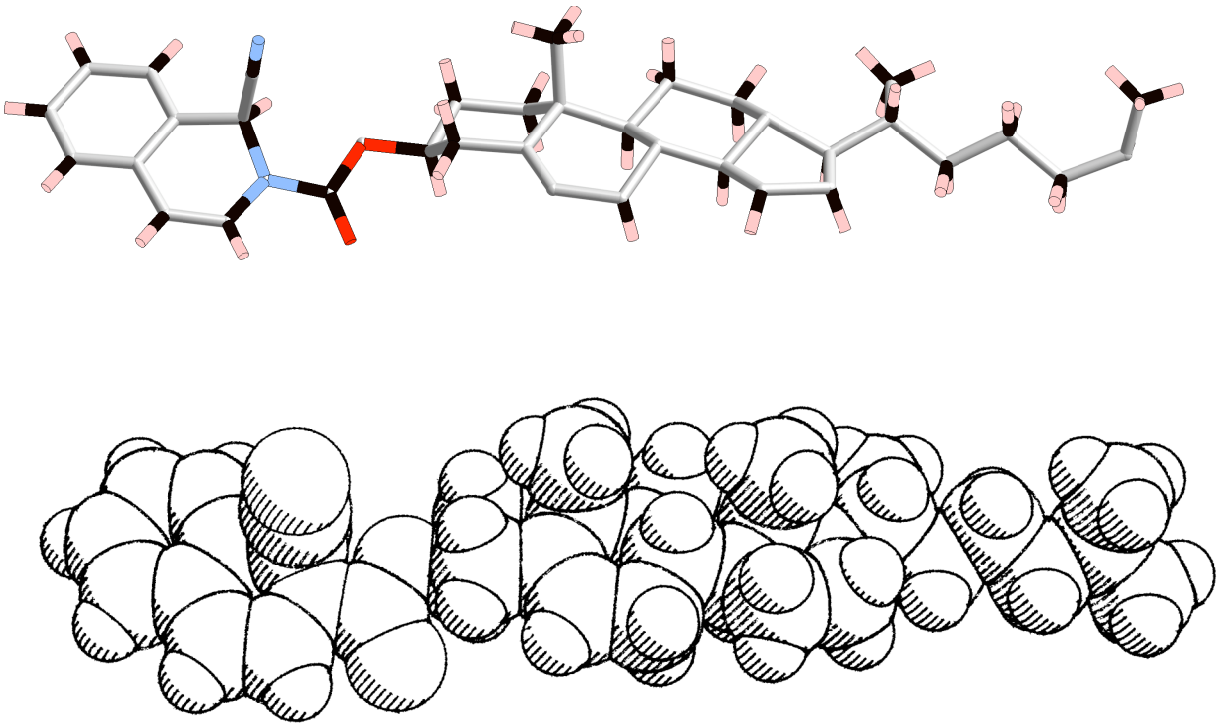

Figure S3. X-ray crystal structure of diastereomerically pure *S*-2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitrile [(*S*)-**11**]: stick (top) and space filling (bottom) representations.

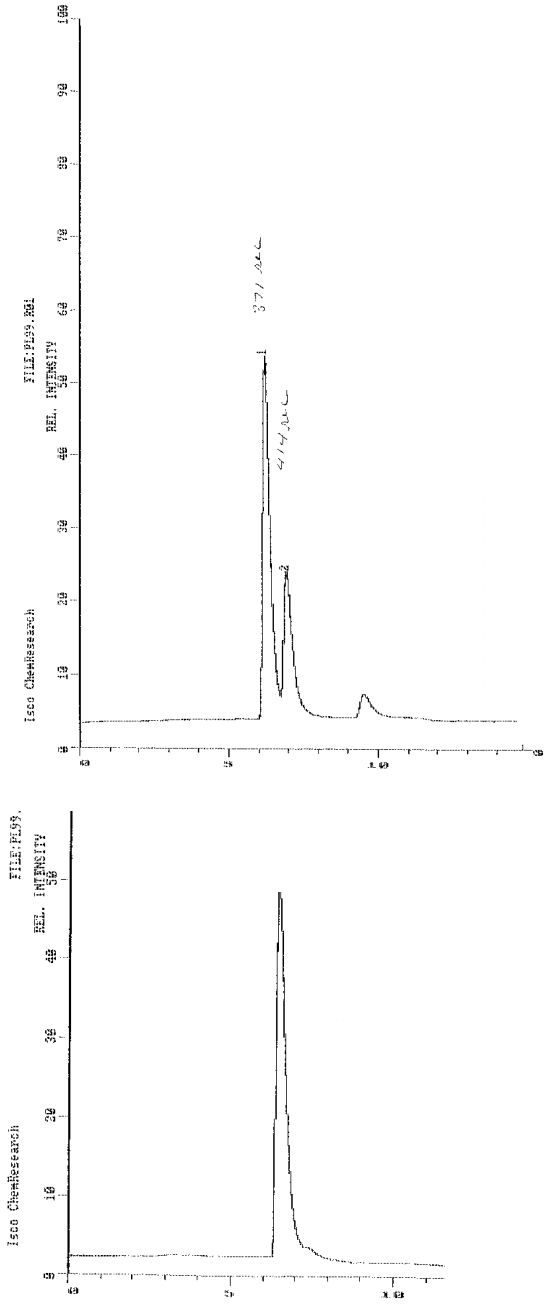

Figure S4. HPLC traces (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-isoquinolyl *tert*-butyl carbinyl *l*-menthyl carbonate (**12**) derived from 1:1 (*S)*-**8**:(*R)*-**8** and pivaldehyde. a, top) as made mixture of *R*- and *S*-diastereomers and b, bottom) pure *S*-diastereomer after a single recrystallization (see Figure S5 for the X-ray crystal structure).

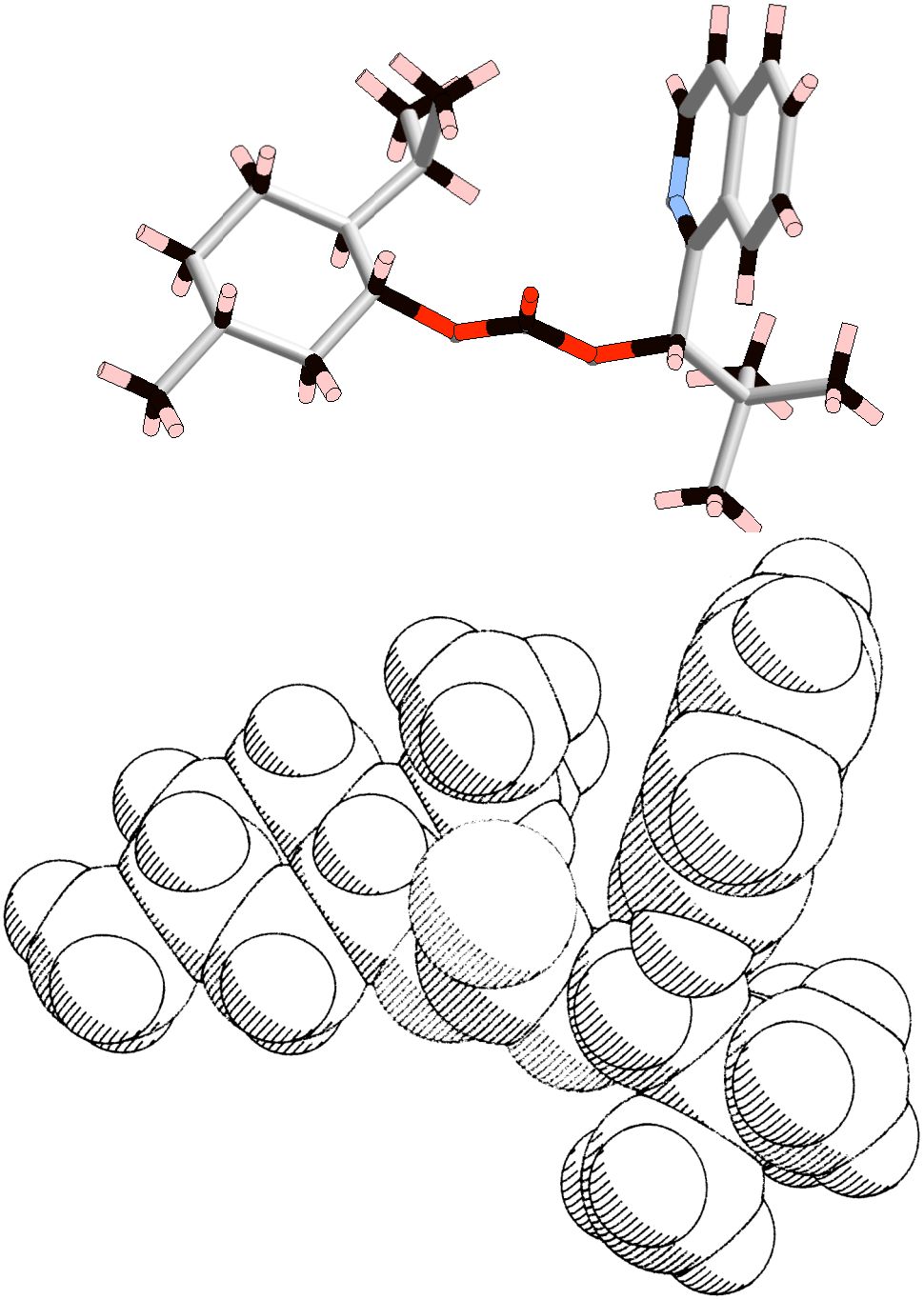

Figure S5. X-ray crystal structure of diastereomerically pure 1-isoquinolyl *tert*-butyl carbinyl *l*-menthyl carbonate [(*S*)-**12**]: stick (top) and space filling (bottom) representations.

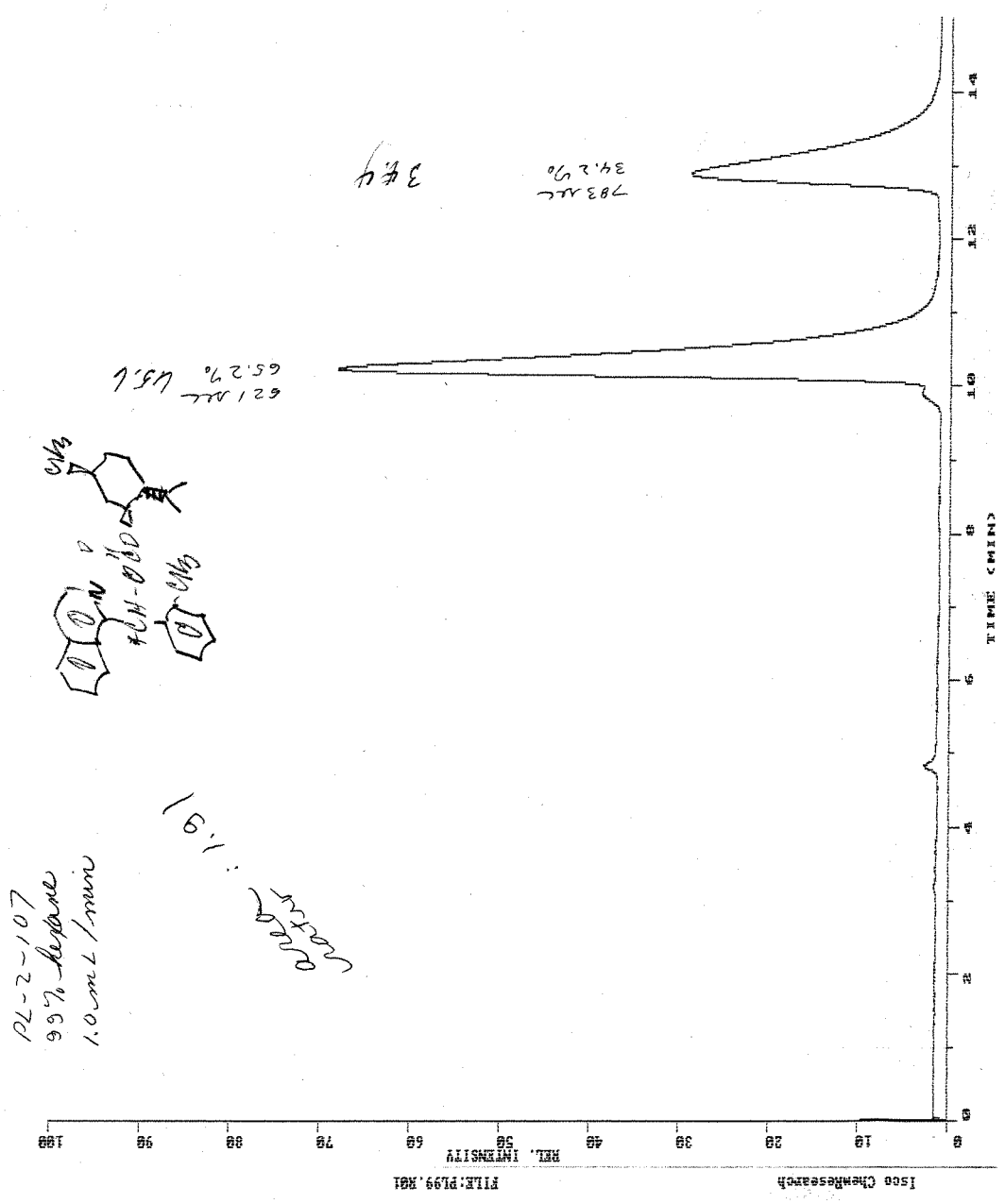

Figure S6. HPLC trace (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-isoquinolyl *o*-tolyl carbinyl *l*-menthyl carbonate **(5**, R = *d*-menthyl, R' = *o*-$CH_3C_6H_4$) derived from 1:1 (*S)*-**8**:(*R)*-**8** and *o*-tolualdehyde. The ratio of diastereomers is 66:34. The ^{1}H NMR spectrum indicates that there is no residual starting material; furthermore, there are two doublets for H_8 (8.54 and 8.58 ppm) in a ratio of 62:38, respectively, as well as two *o*-CH_3 signals (2.53 ppm) in a ratio of 68:32.

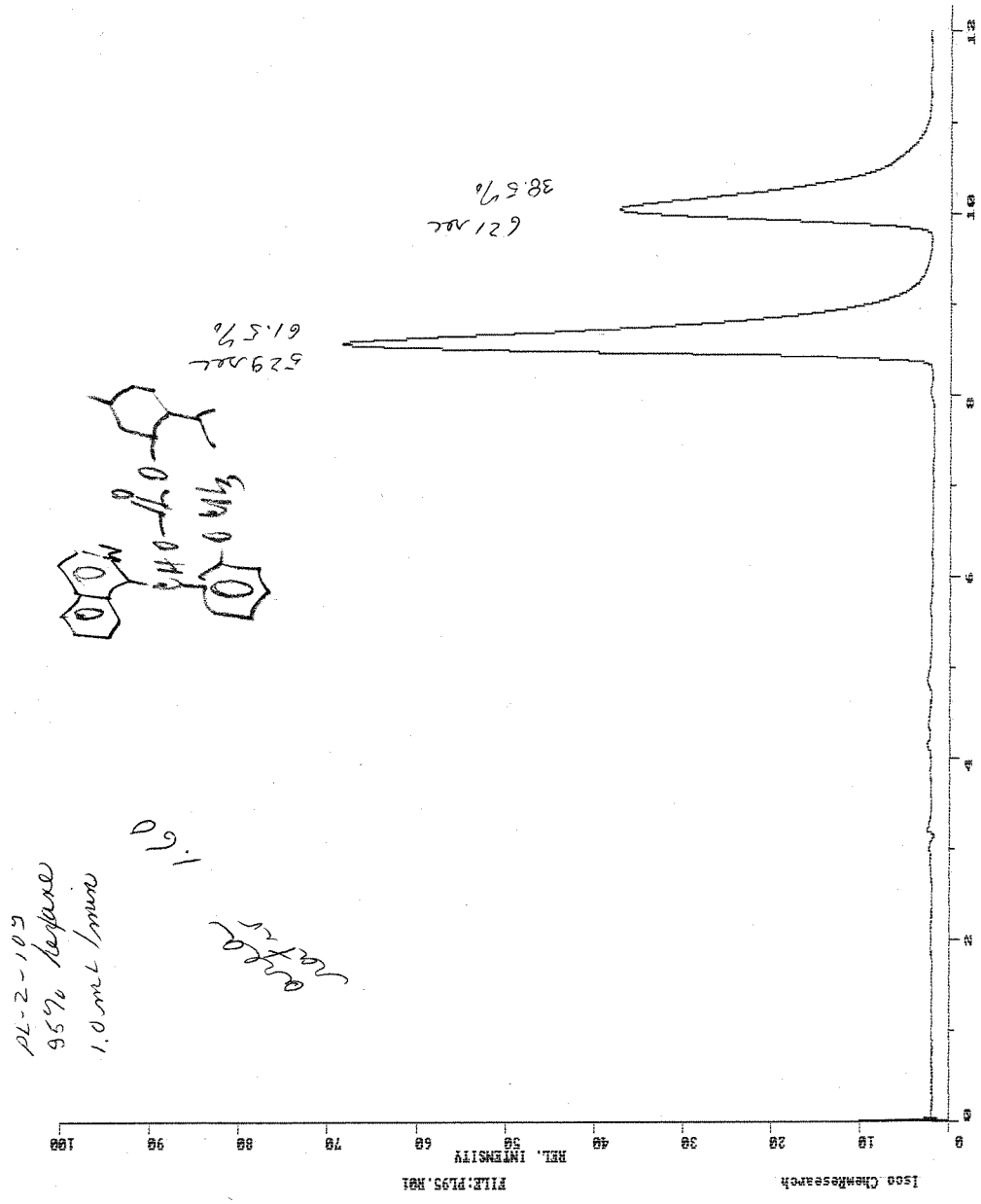

Figure S7. HPLC trace (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-isoquinolyl *o*-anisyl carbinyl *l*-menthyl carbonate (**5**, R = *d*-menthyl, R' = *o*-$CH_3OC_6H_4$) derived from 1:1 (*S)*-**8**:(*R)*-**8** and *o*-anisaldehyde. The ratio of diastereomers is 62:38. The ^{1}H NMR spectrum indicates that there is no residual starting material; furthermore, there are two doublets for H_8 (8.51 and 8.56 ppm) in a ratio of 62:38, respectively, as well as two OCH_3 signals (3.90 and 4.00 ppm) in a ratio of 71:28.

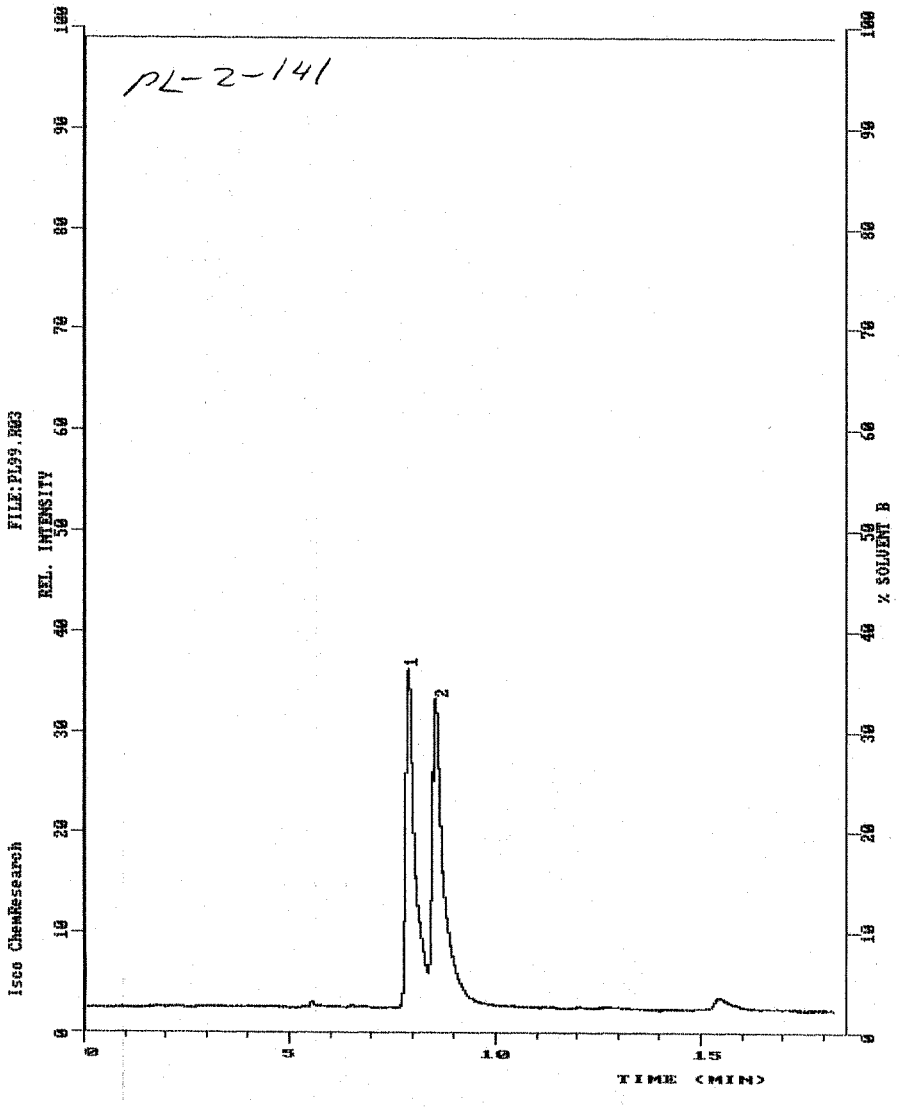

Figure S8. HPLC trace (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-isoquinolyl *tert*-butyl carbinyl cholesteryl carbonate (**15**) derived from diastereomerically pure (*S)*-**11** and pivaldehyde. The ratio of diastereomers is 52:48. The peak at 15.5 min is due to an impurity.

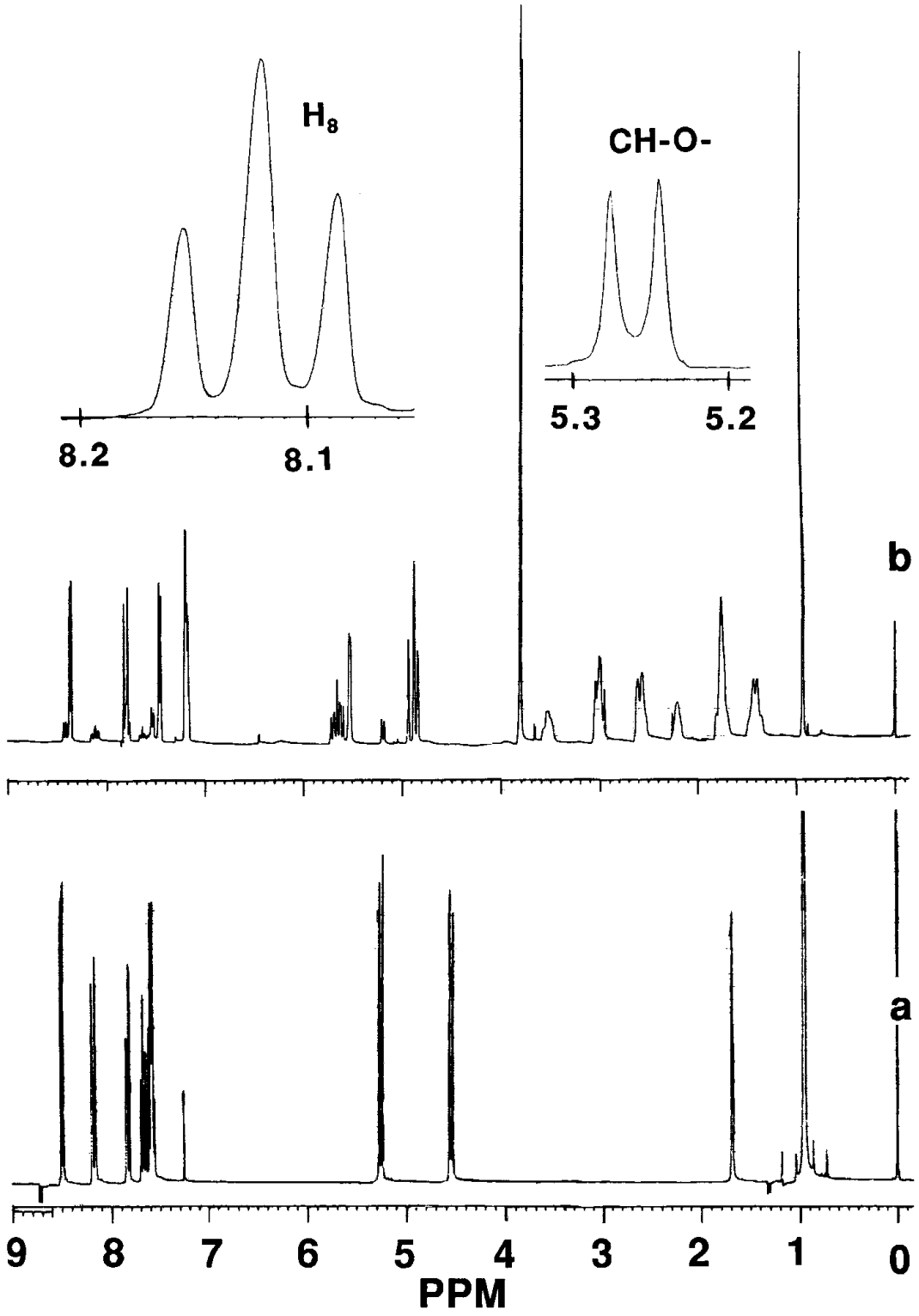

Figure S9. 270 MHz ^{1}H NMR spectra of **a**) bottom, racemic 1-isoquinolyl *tert*-butyl carbinol (**16**) and **b**) top, **16** and quinine (1.0:3.6 molar ratio) after exchange with D_2O at 25°C in $CDCl_3$. The peak at 1.7 ppm in (**a**) is due to H_2O. The peaks at ca. 7.2 ppm in (**a**) and (**b**) are due to $CHCl_3$.

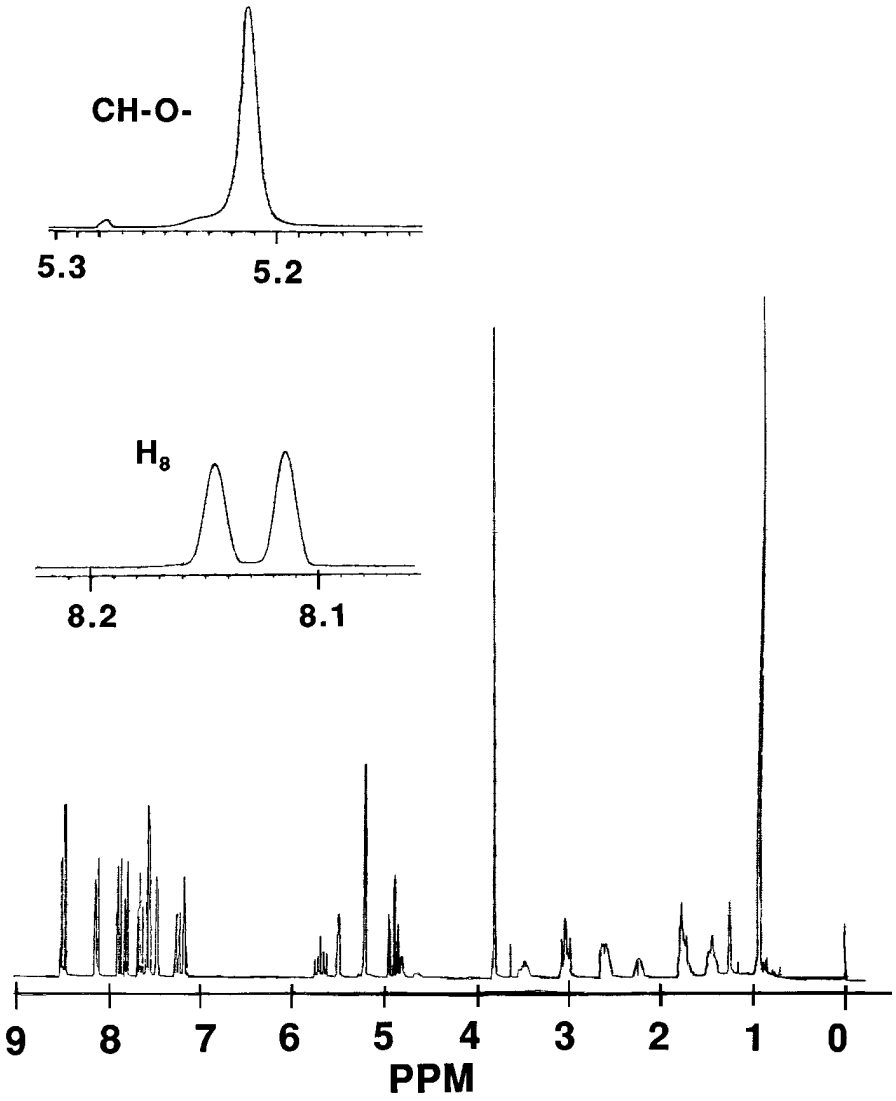

Figure 10. 270 MHz ^{1}H NMR spectrum of *S*-(-)-1-isoquinolyl *tert*-butyl carbinol [(*S*)-**16**] and quinine (1:3 molar ratio) after exchange with D_2O in $CDCl_3$ at 25°C. Integration of the singlets at 5.21 and 5.28 indicates a purity of 99%.

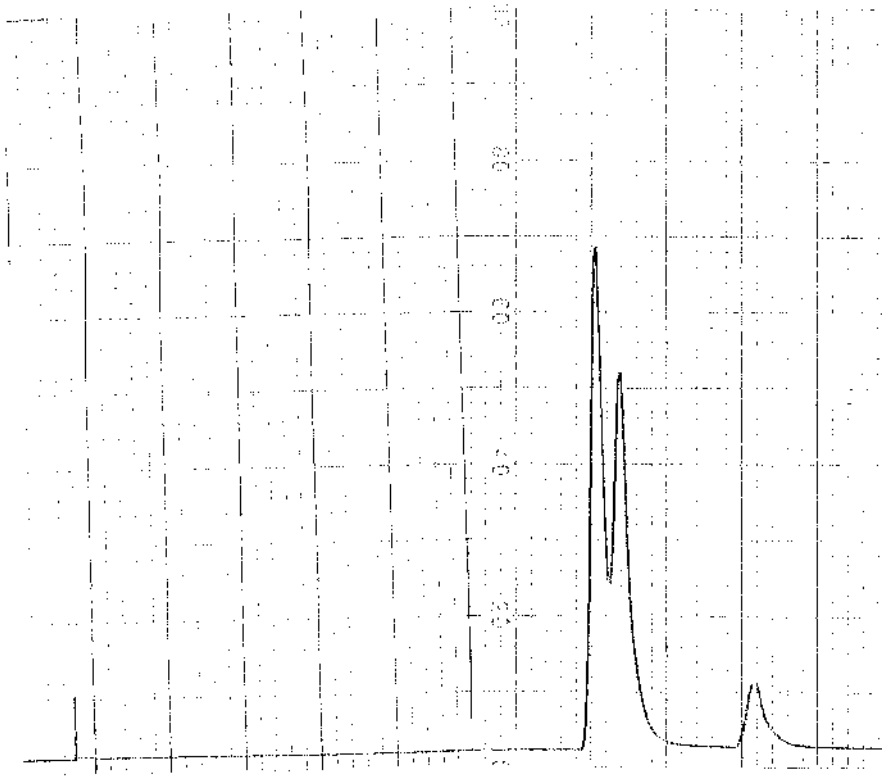

Figure S11. HPLC trace (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-methyl-2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**22a**) derived from 1:1 (*S)*-**8**:(*R)*-**8** and methyl iodide. The ratio of diastereomers is ~50:50. The small signal at higher elution time is starting material.

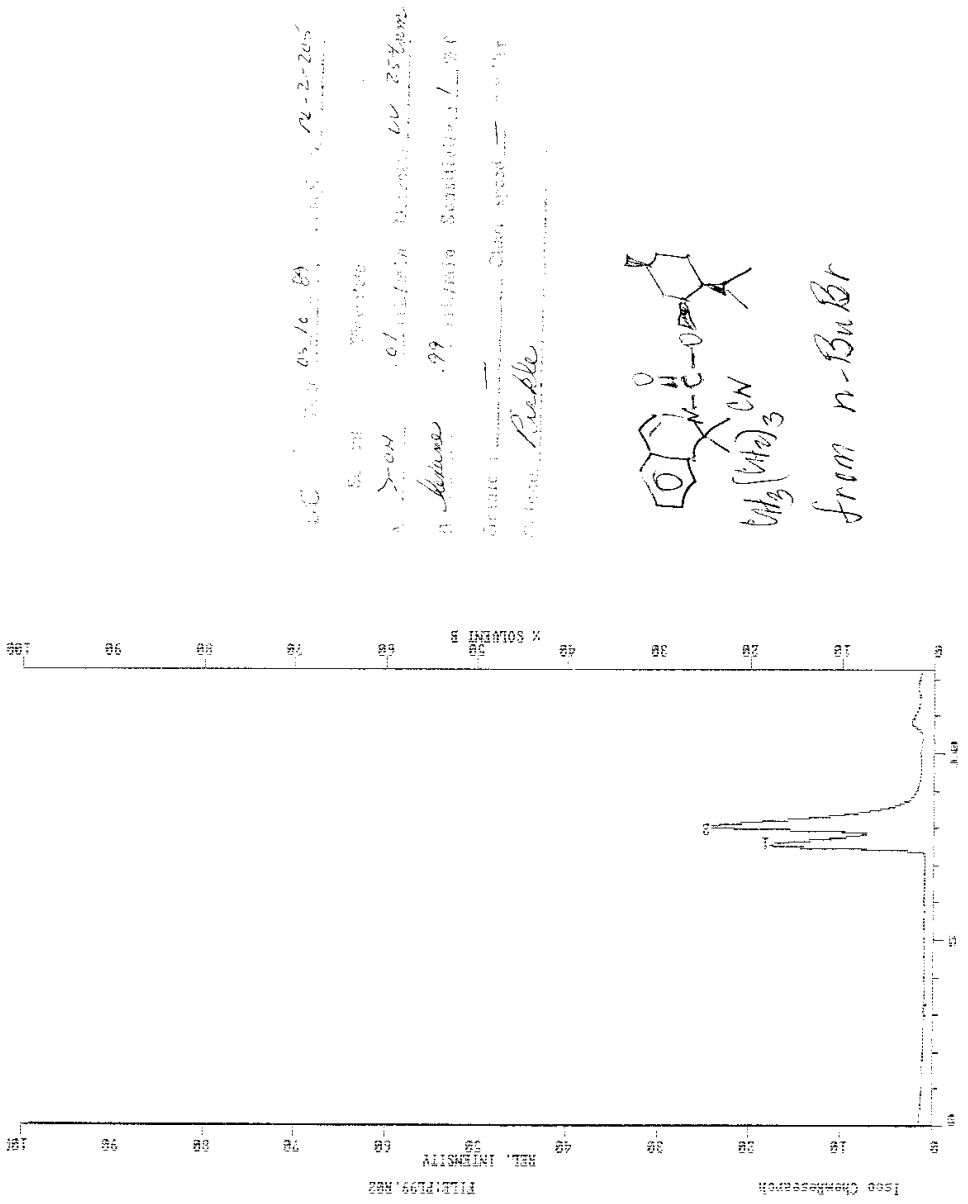

Figure S12. HPLC trace (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-*n*-butyl-2-*l*-menthyloxycarbonyl-1,2-dihydroisoquinaldonitrile (**22b**) derived from 1:1 (*S)*-**8**:(*R)*-**8** and *n*-butyl bromide. The ratio of diastereomers is 36:64. The small peak at ~11 min is residual starting material.

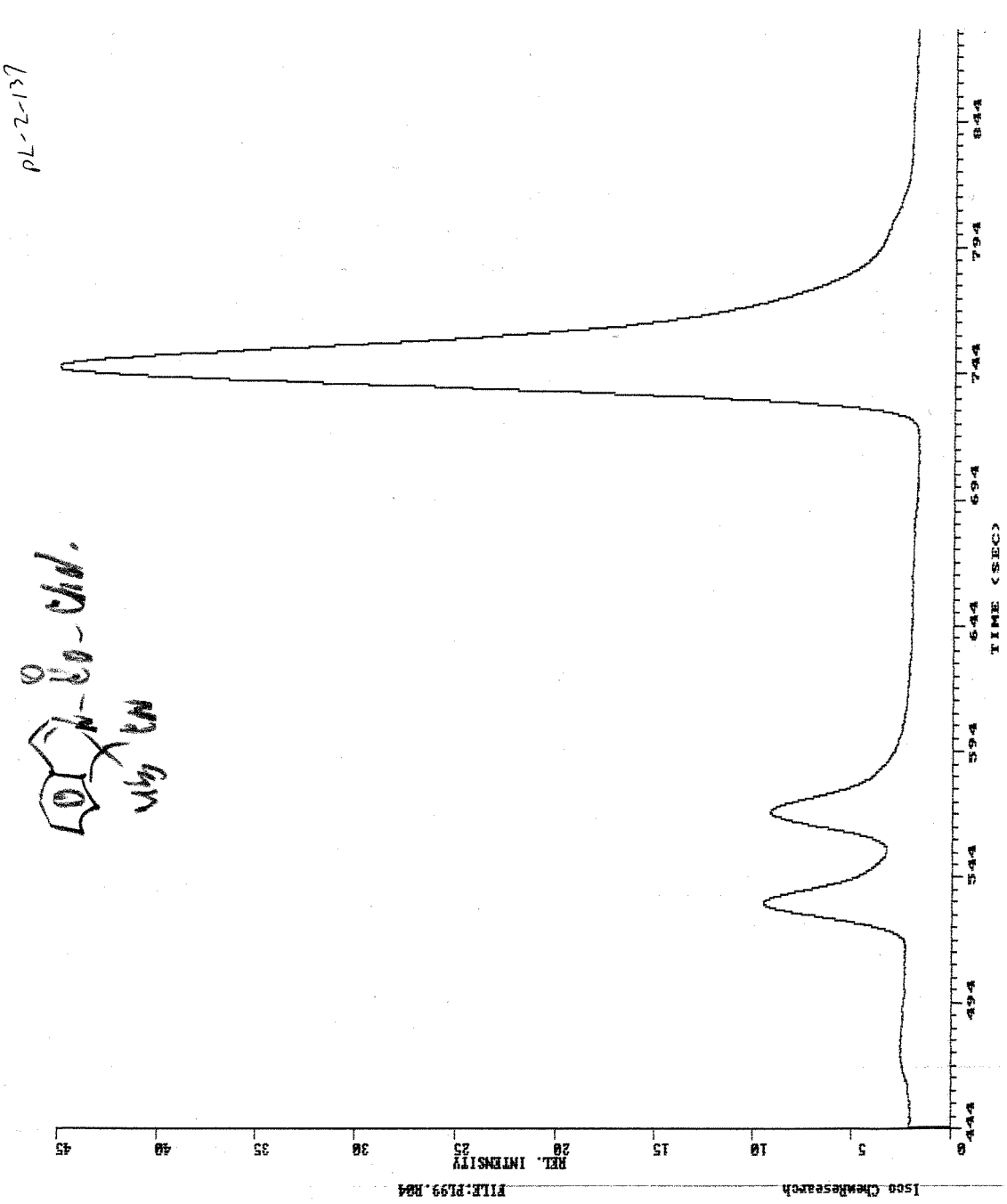

Figure S13. HPLC trace (4.6 x 250 mm Pirkle covalent phenylglycine column, 99:1 hexane: ethyl acetate, 1.0 mL/min, 254 nm detection) for 1-methyl-2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitrile (**23a**) derived from diastereomerically pure (*S)*-**11** and methyl iodide. The ratio of diastereomers is 55:45. The large peak at ~750 seconds is residual (*S)*-**11**; conversion 15%.

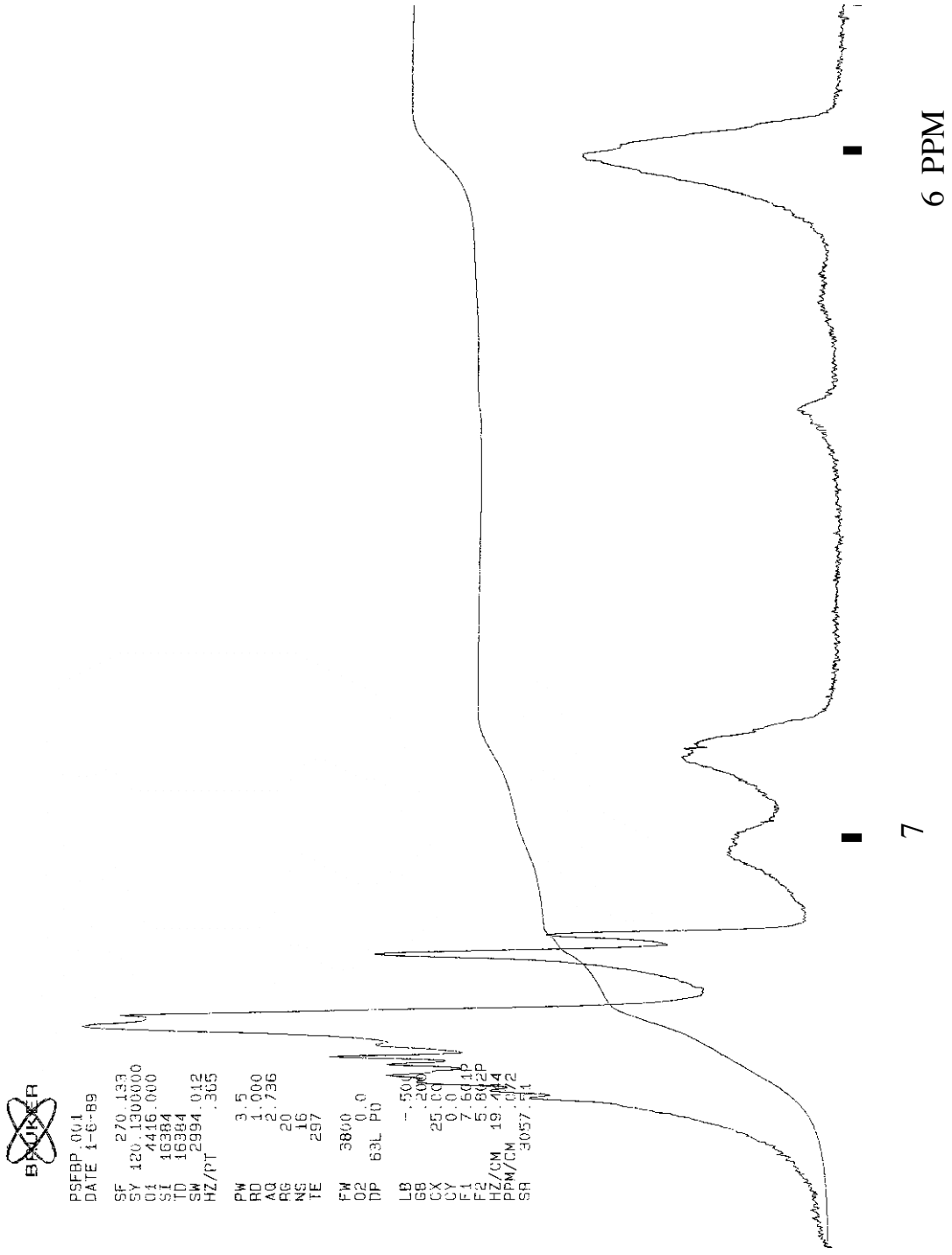

Figure S14. Partial 270 MHz 1H NMR spectrum of a sample of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile [(*S)*-**8**/(*R)*-**8**] prepared by quenching the anion with D_2O. The signals for H_1 at 6.18, 6.22 and 6.38 ppm have been greatly diminished, c.f., Figure 1b.

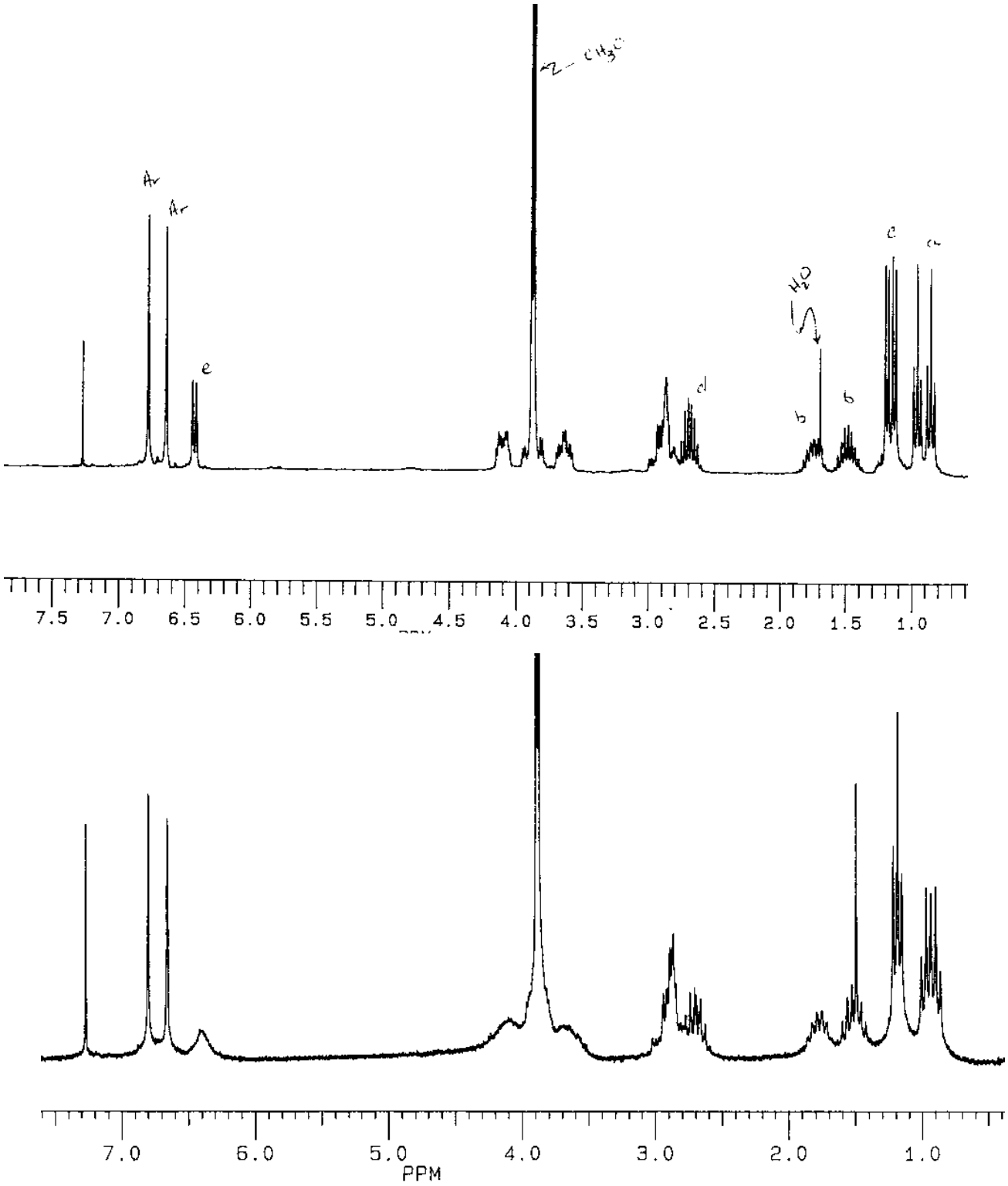

Figure S15. ^{1}H NMR spectra of 2-[(*S*)-α-methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(18)** (200 MHz, $CDCl_3$) a, top) at ambient temperature, b, bottom) at 50°C. The peak at 7.3 ppm is due to $CHCl_3$.

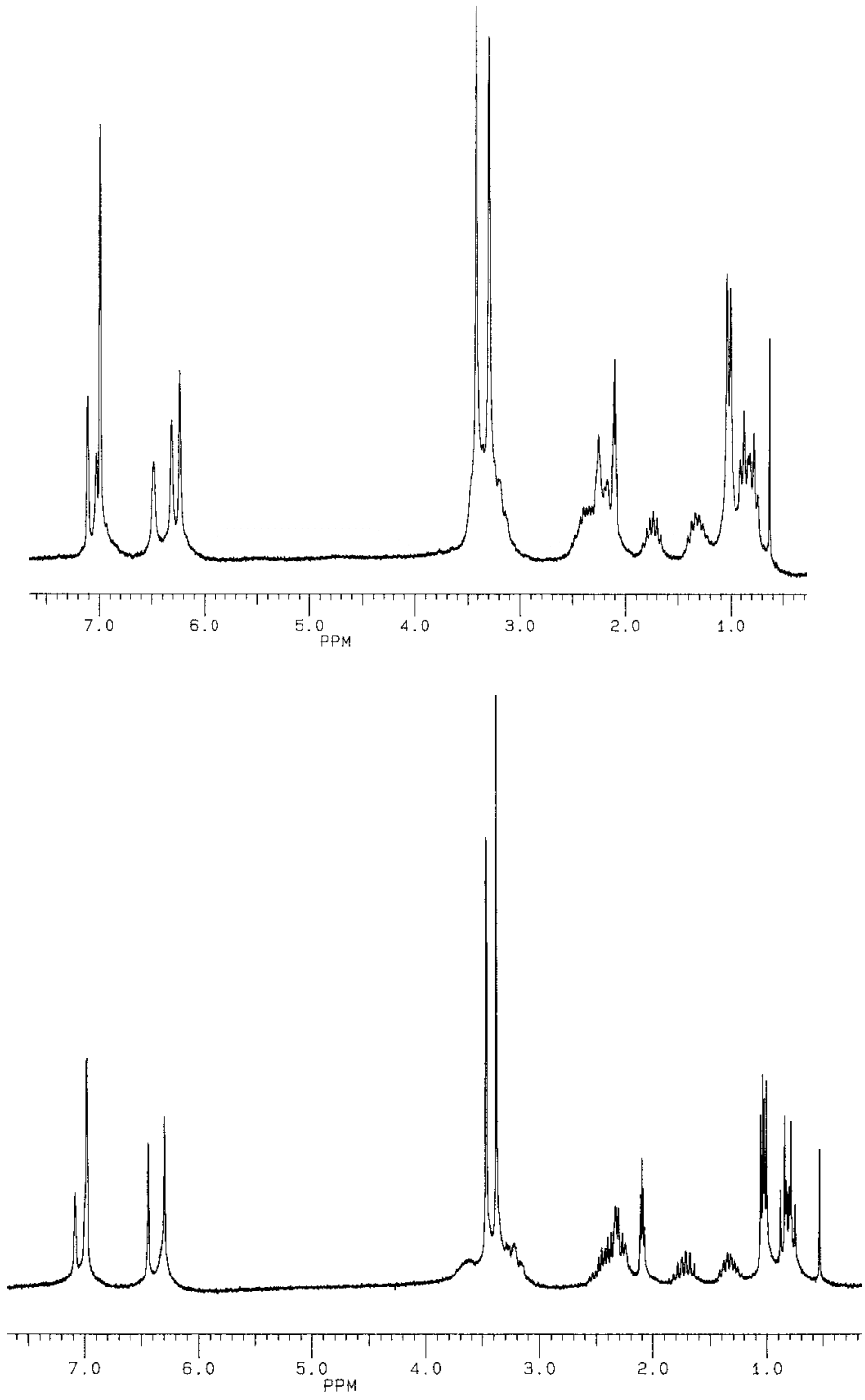

Figure S16. ^{1}H NMR spectra of 2-[(*S*)-α-methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(18**) (200 MHz, toluene-d_8) a, top) at ambient temperature. b, bottom) at 70ºC. The signals at 2.1 and 7.0 ppm are due to the solvent.

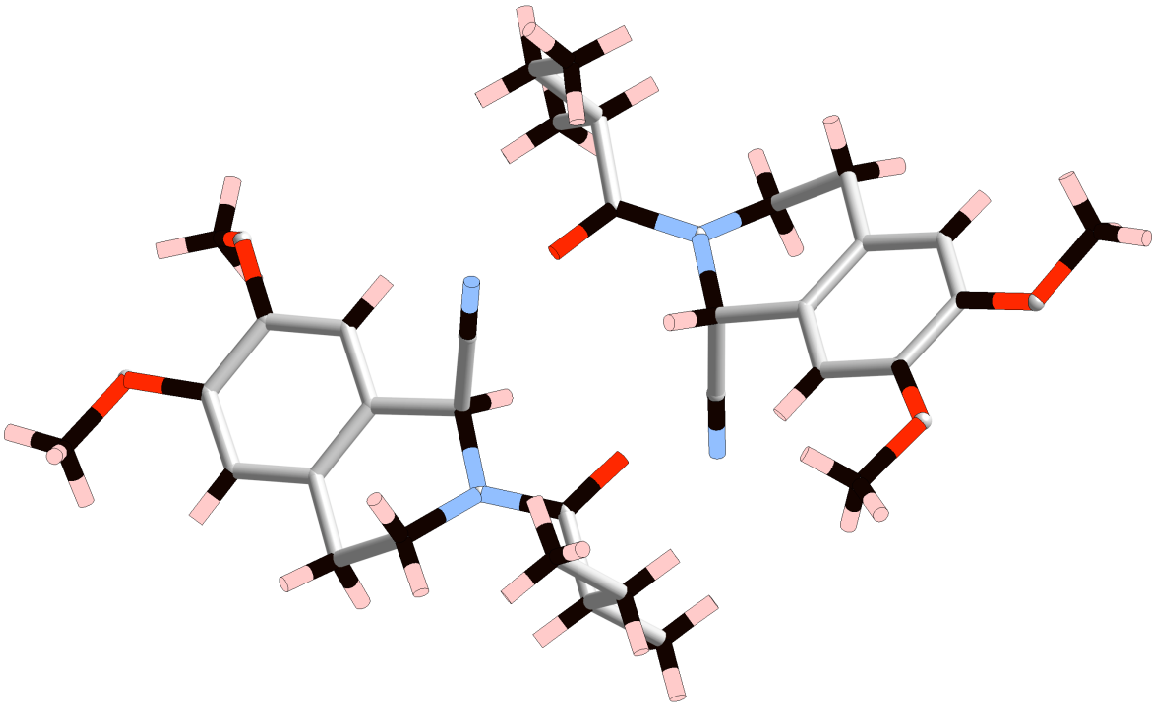

Figure 17. X-ray crystal structure of mixed diastereomers of 2-(*S*-α-methylbutyryl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**18**).

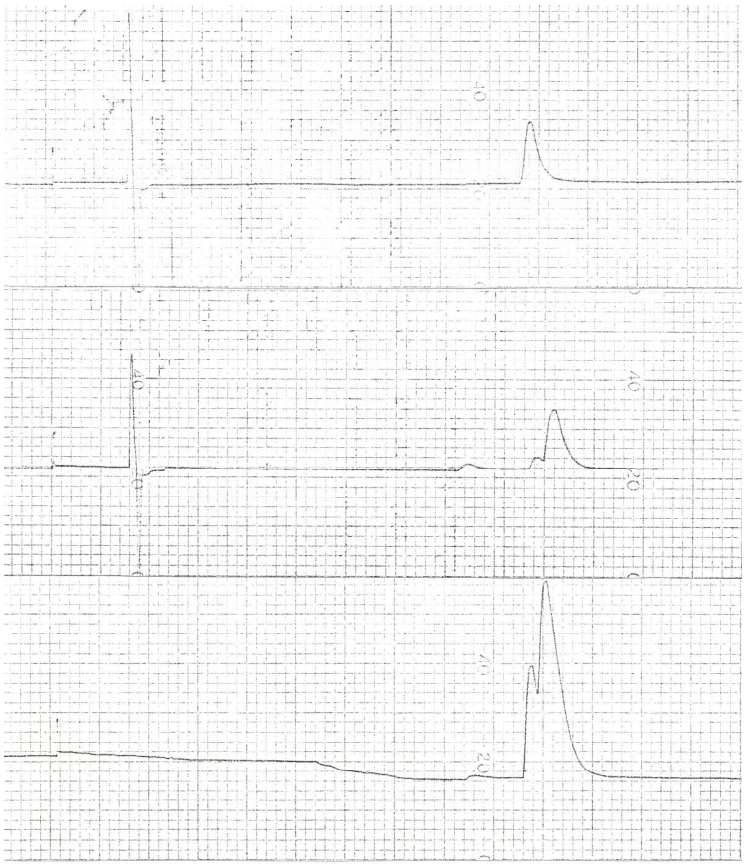

Figure S18. HPLC traces for 2-(*l*-menthoxycarbonyl)-l-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**19**). Top trace, compound (*S*)-**19**. Middle trace, compound (*R*)-**19**. Bottom trace, a mixture of compounds (*S*)-**19** and (*R*)-**19**. 4.6 x 250 mm normal phase silica gel column, 10% ethyl acetate in hexane, 2 mL per min. The higher melting *S*-form exhibited a retention time of 9.60 min while the lower melting *R*-diastereomer exhibited a retention time of 10.2 min.

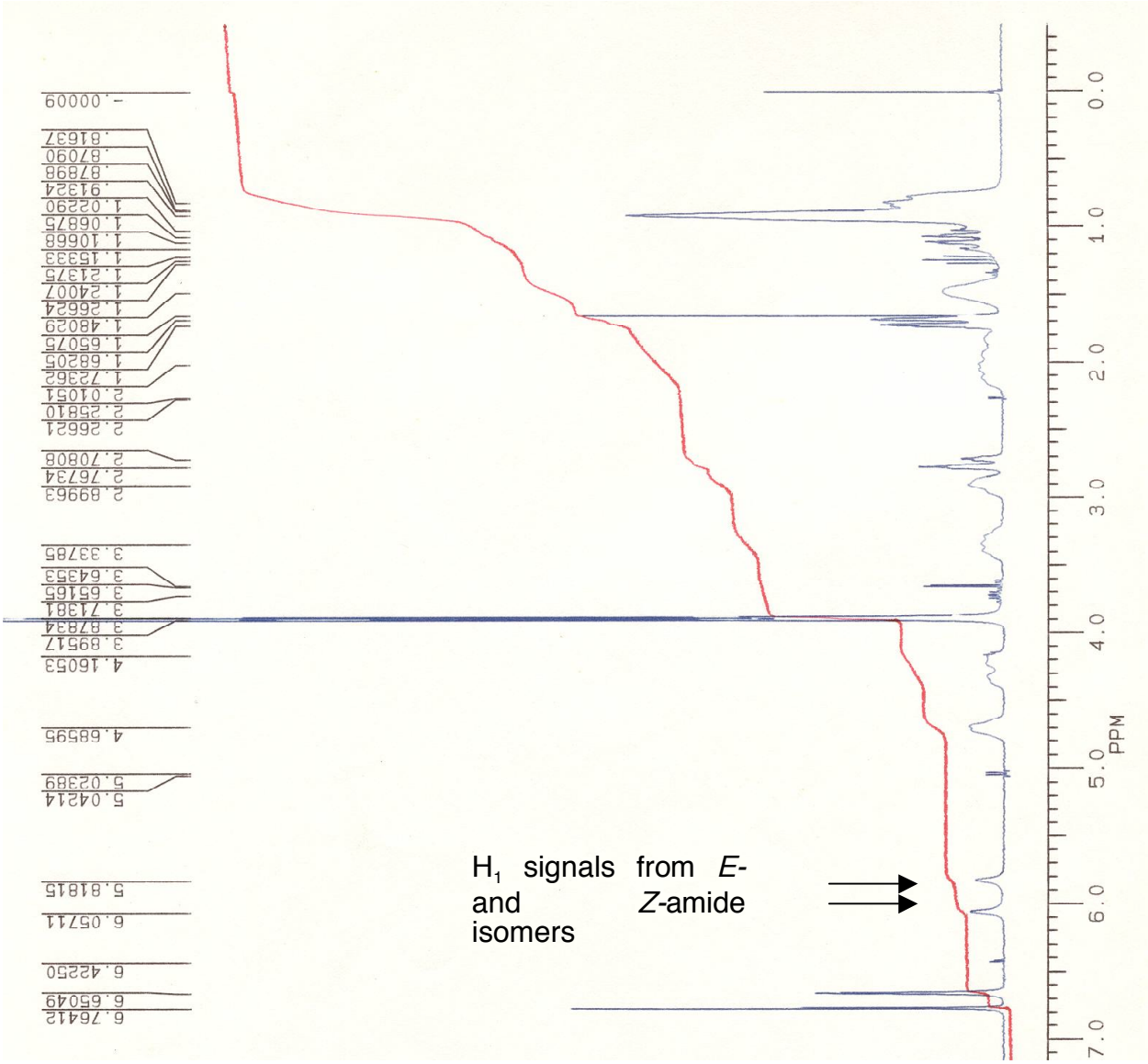

Figure S19. ^{1}H NMR spectrum (270 MHz, $CDCl_3$) of (1*S*)-2-(*l*-menthoxycarbonyl)-l-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-**19**] at ambient temperature.

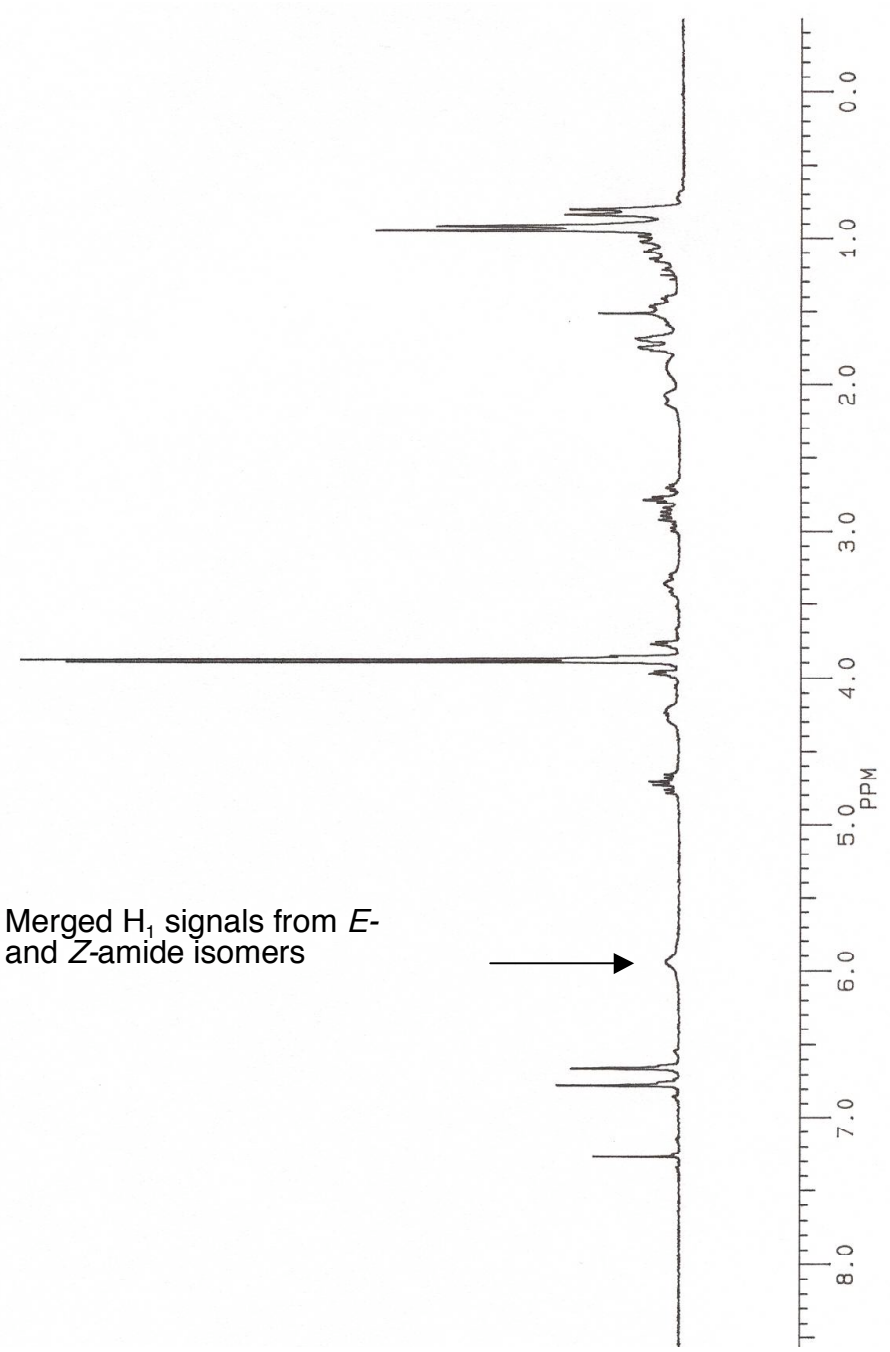

Figure S20. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of (1*S*)-2-(*l*-menthoxycarbonyl)-l-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-**19**] at 45ºC.

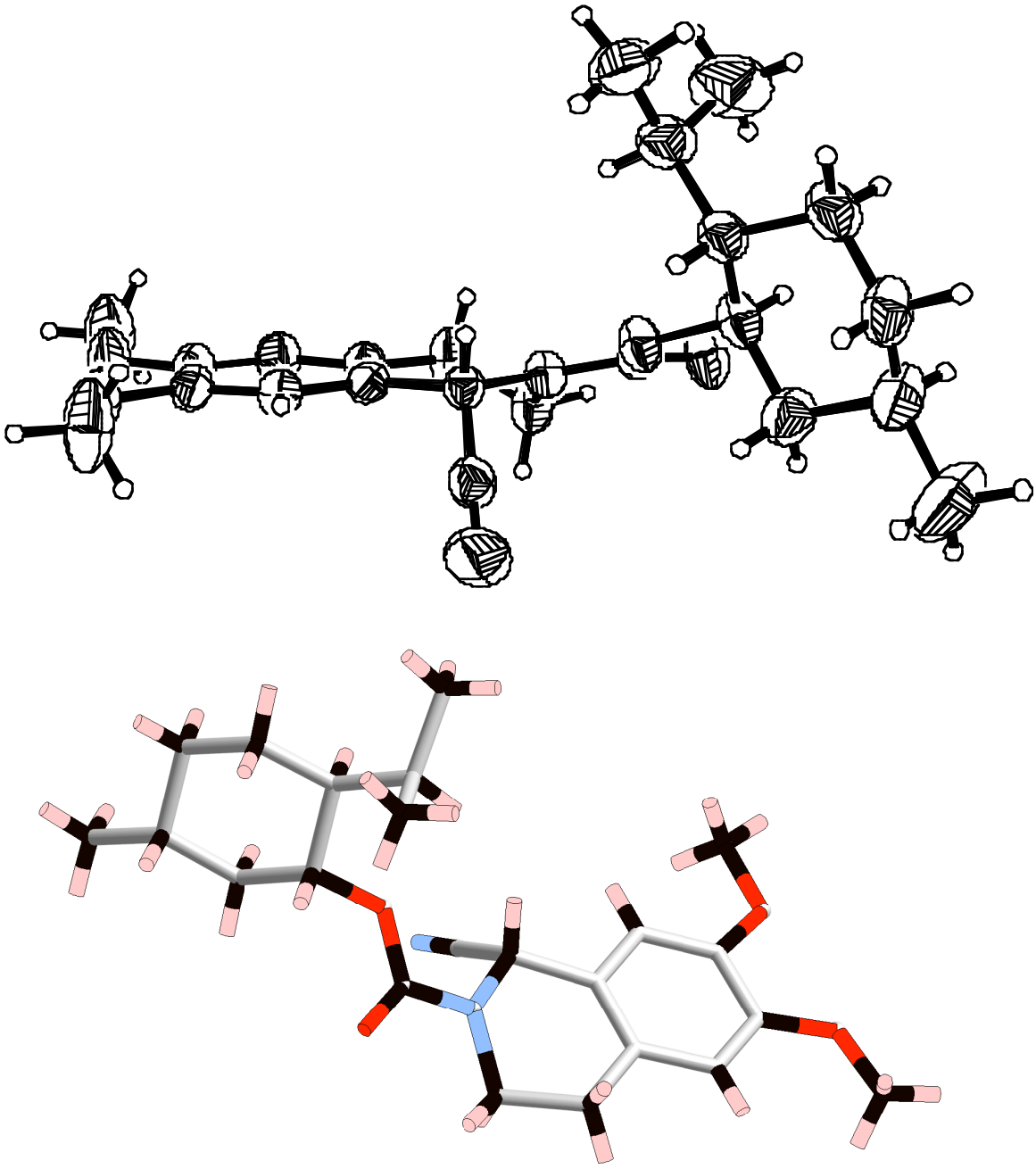

Figure 21. X-ray crystal structure of diastereomerically pure *S*-2-*l*-menthoxycarbonyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-**19**]: ORTEP drawing (top) and stick (bottom) representations.

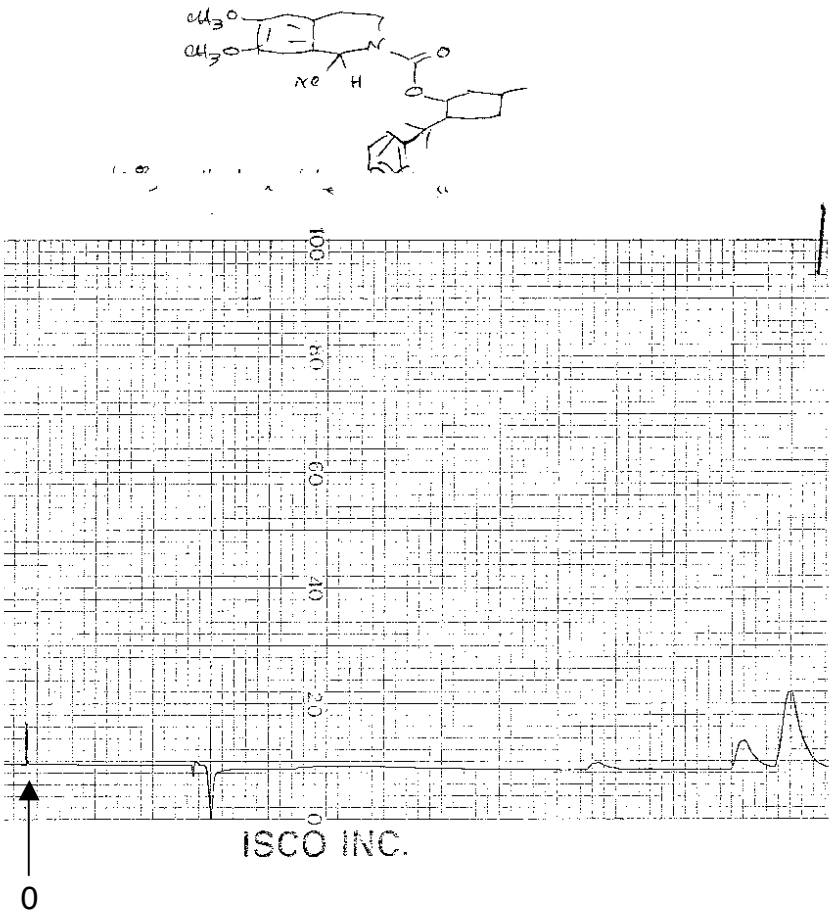

Figure S22. HPLC trace for 2-(8'-phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**20**): 4.6 x 250 mm normal phase silica gel column, 15% ethyl acetate in hexane, 1 mL per min, 254 nm uv detection. The area ratio of peaks with retention times of 11.7 vs. 12. 5 min was 20:80, respectively. The peak at 9.4 min is an unknown impurity.

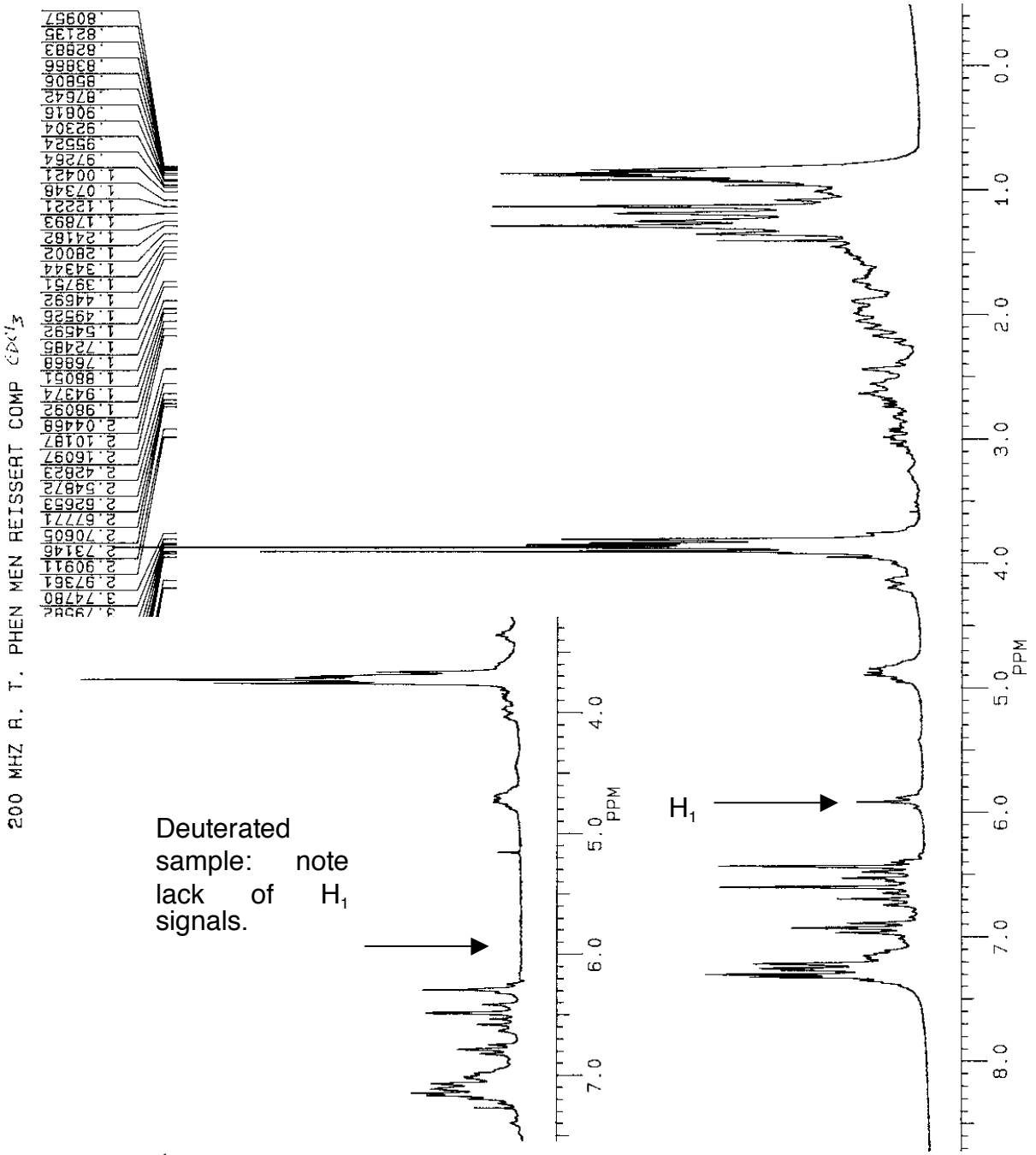

Figure S23. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of 2-(8'-phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**20**) at ambient temperature; inset: deuterated **20** to identify H_1 signals.

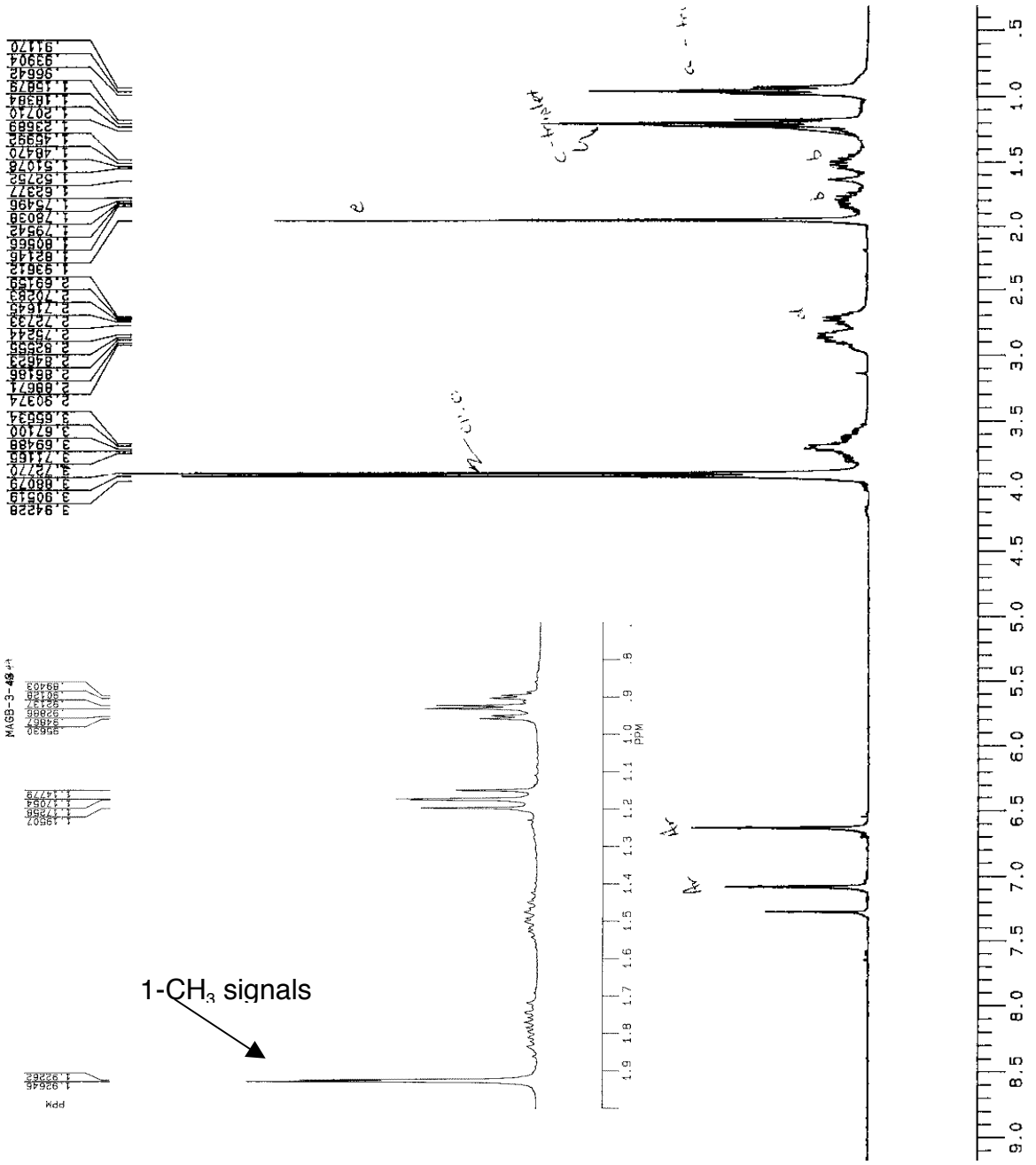

Figure S24. ^{1}H NMR spectrum (270 MHz, $CDCl_3$) of 1-methyl-2-[(*S*)-α-methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**24a**) at ambient temperature.

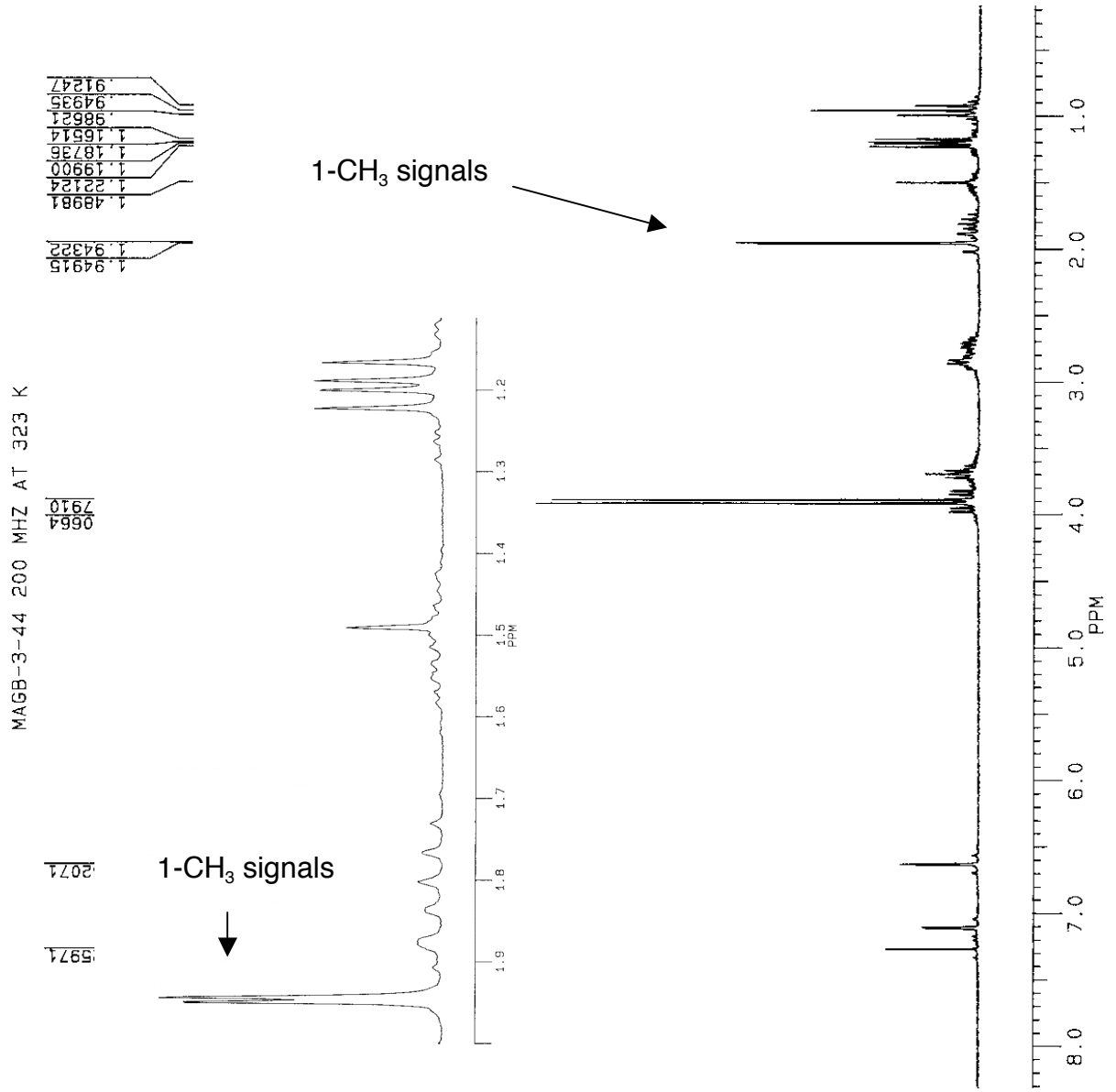

Figure S25. ^{1}H NMR spectrum (200 MHz, $CDCl_3$) of 1-methyl-2-[(*S*)-α-methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**24a**) at 50ºC. The peak at 1.49 ppm is due to water.

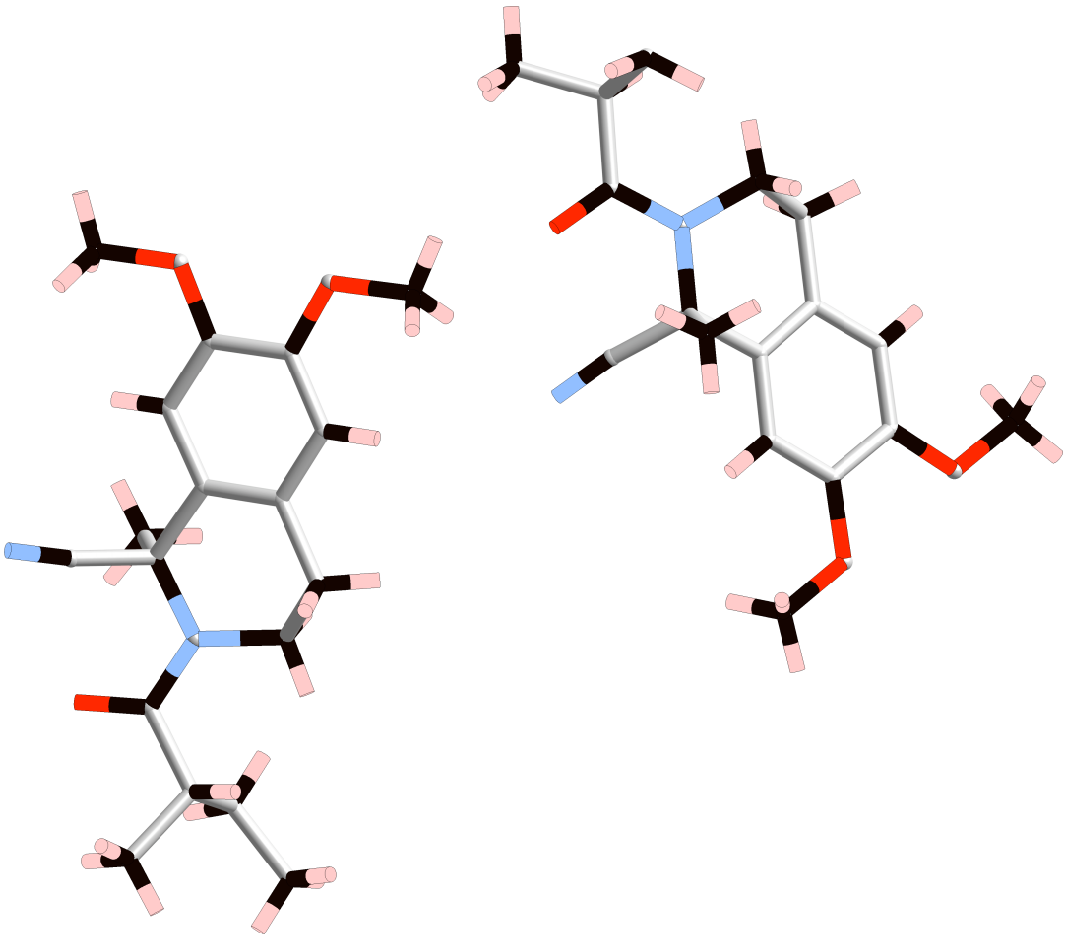

Figure 26. X-ray crystal structure of mixed diastereomers of 1-methyl-2-[(S)-α-methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**24a**).

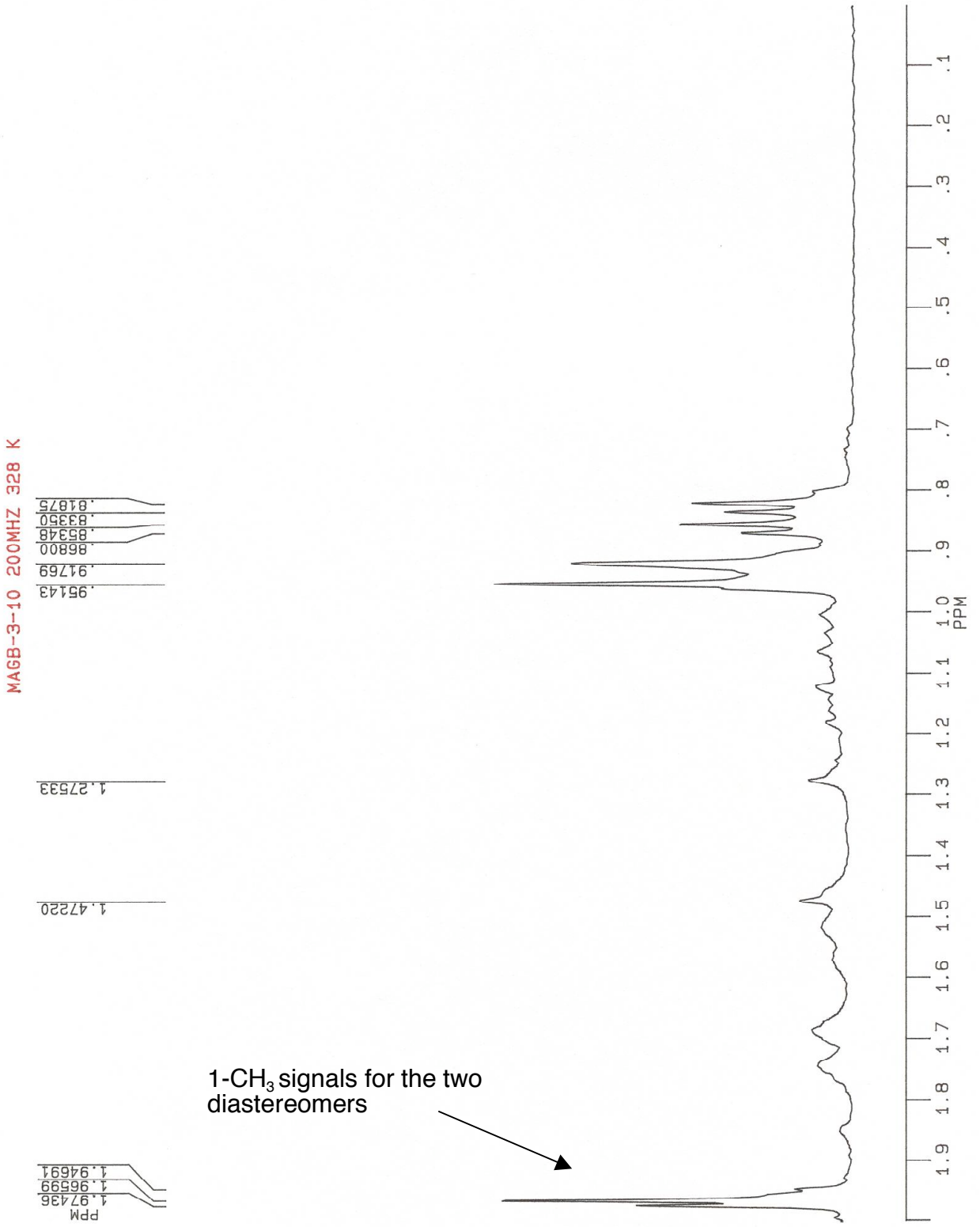

Figure S27. Partial ^{1}H NMR spectrum (200 MHz, toluene-d_8) of 1-methyl-2-(*l*-menthoxycarbonyl)-l-cyano-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **(25a)** at 45ºC.

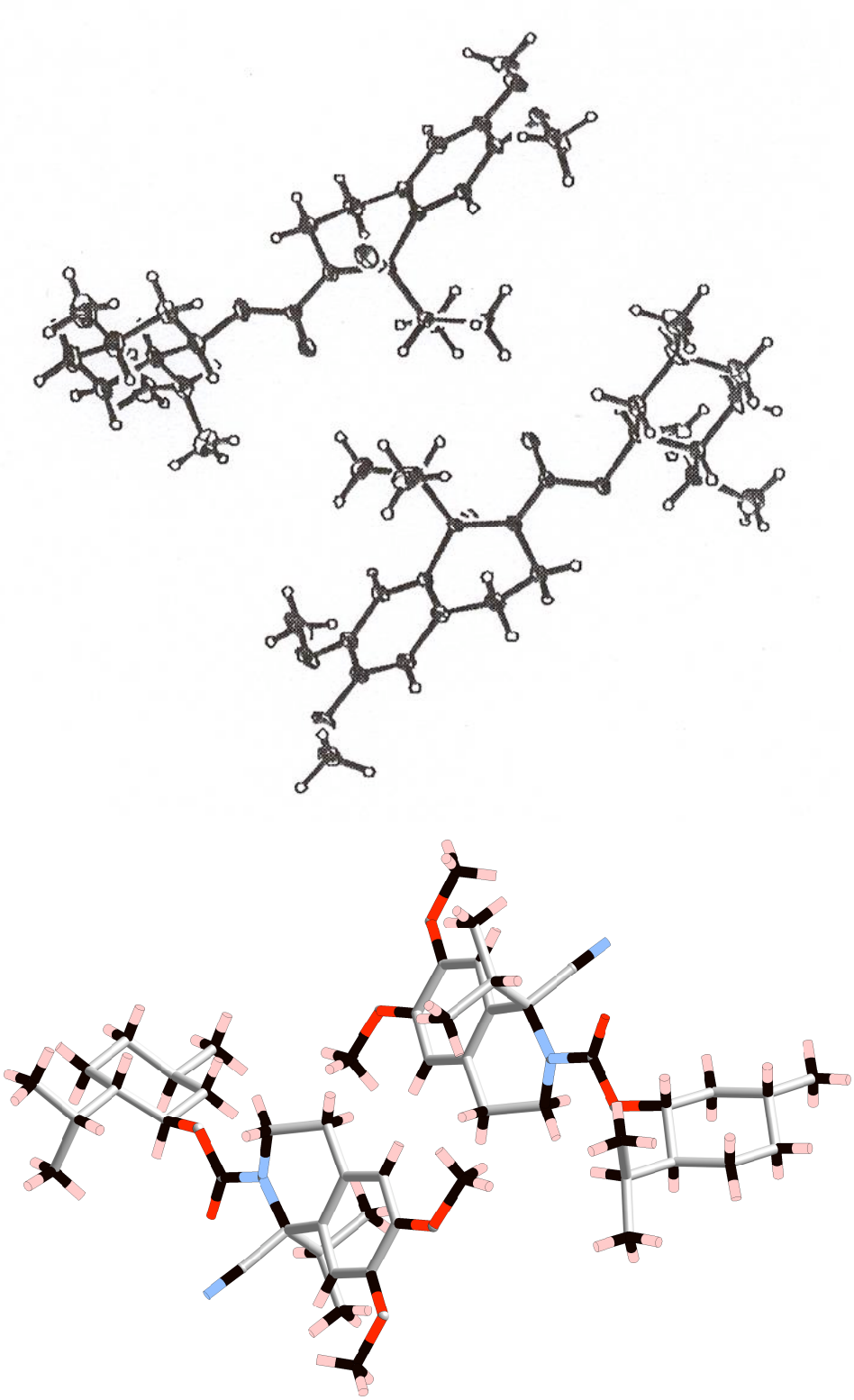

Figure S28. X-ray crystal structure of 1:1 mixture of diastereomers of 1-isopropyl-2-*l*-menthoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquino-line (**25b**): ORTEP drawing (top) and stick (bottom) representations.

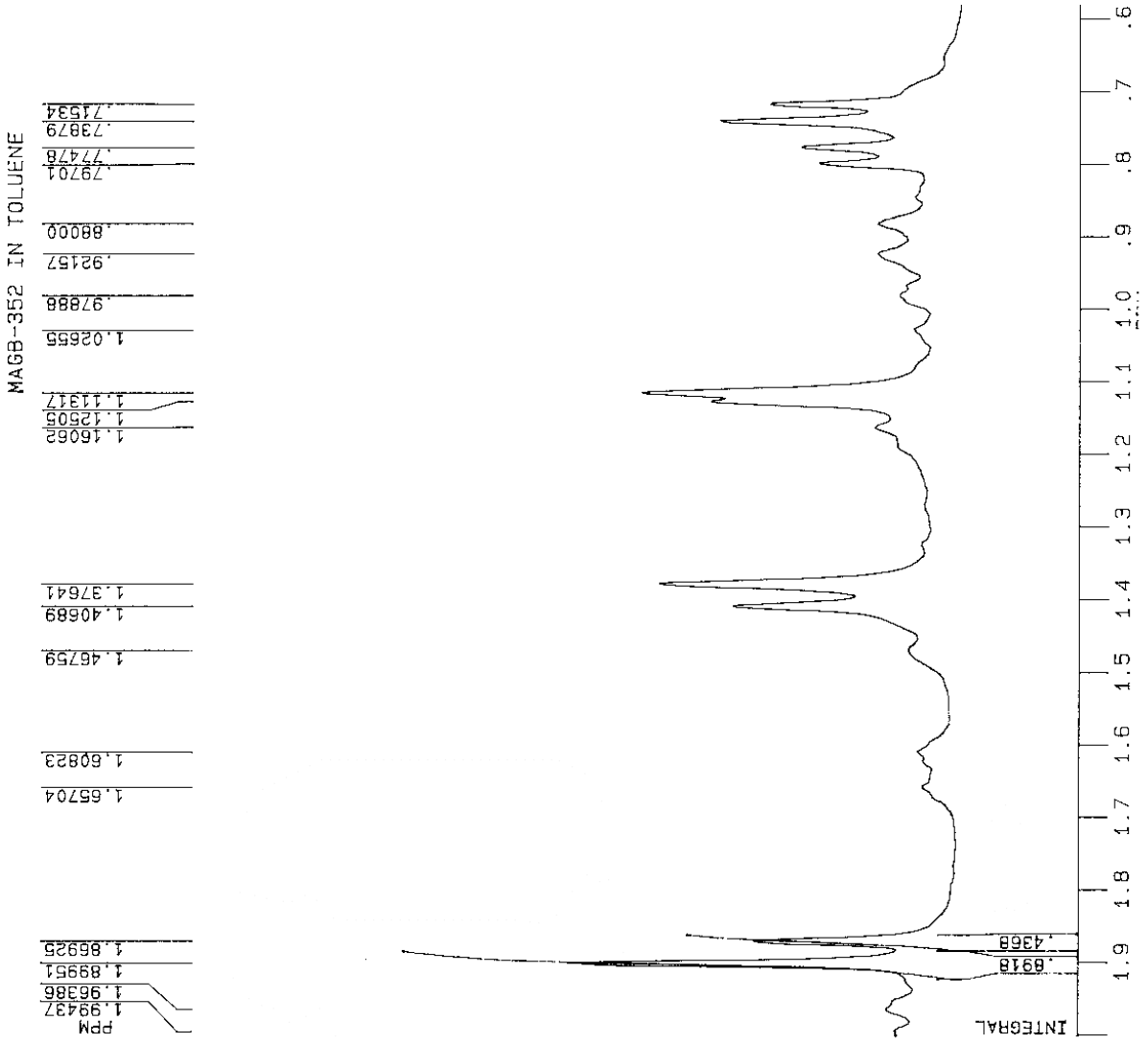

Figure S29. Partial ^{1}H NMR spectrum (200 MHz, toluene-d_8) of 1-methyl-2-(8'-phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(26a)** at 45ºC.

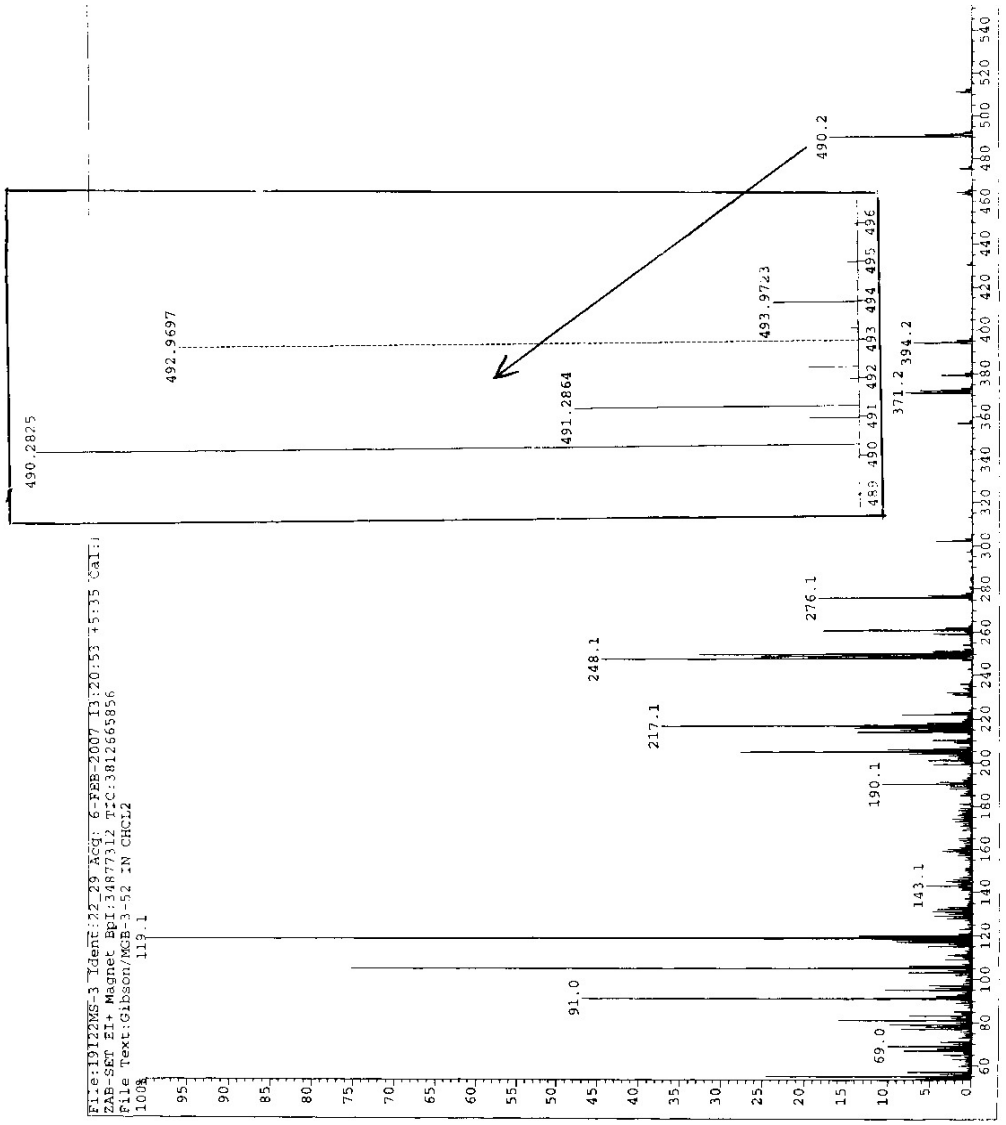

Figure S30. Electron impact mass spectrum of 1-methyl-2-(8'-phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **(26a)**. The inset is the high resolution spectrum; the peak at m/z 492.9697 is a calibration signal. The m/z 394.2 peak is due to loss of the menthyl moiety (C_7H_{12}), apparently via a rearrangement process with migration of the cumyl moiety; the same fragmentation (-m/z 96) is observed in the precursor Reissert compound.

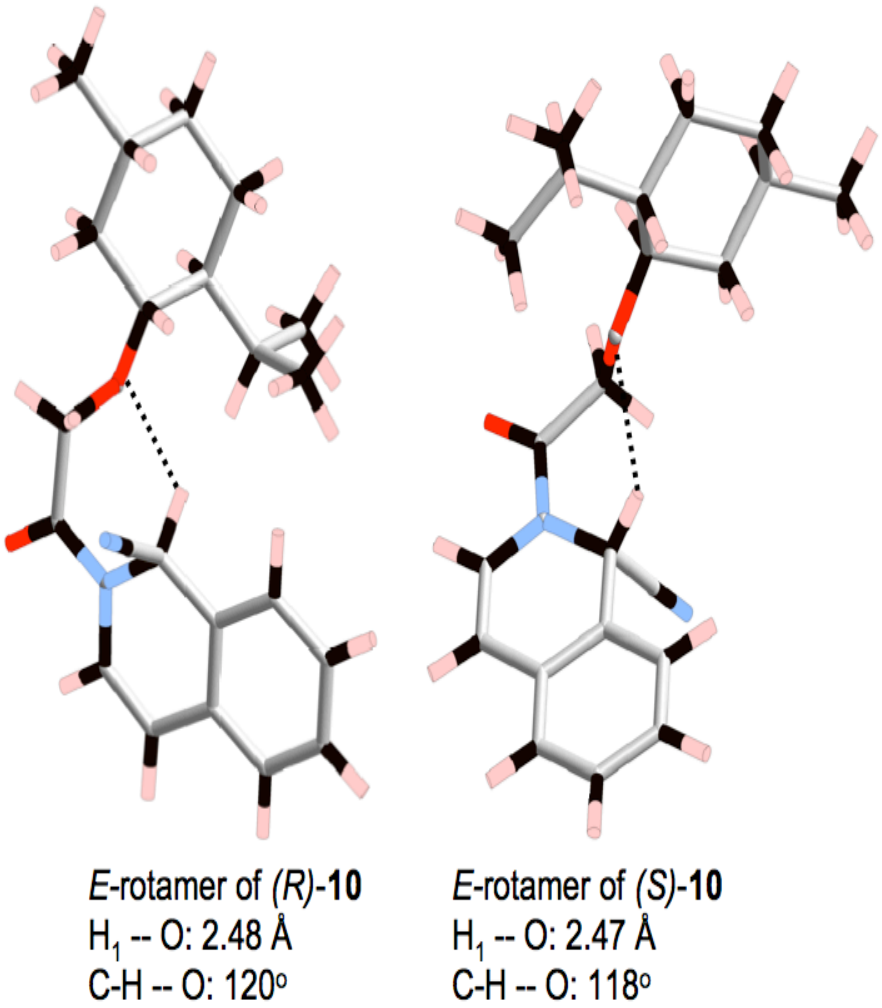

Figure S31. Minimized structures of the *E*-rotamers of (*R*)- and (*S*)-2-menthoxyacetyl-1,2-dihydroisoquinaldonitrile (**10**). The acidic proton H_1 is close to the menthoxy oxygen atom and the C-H-O angles are consistent with a hydrogen bonding interaction. [S14] The calculated energies of the *Z*-rotamers are lower than those of the *E*-rotamers, but molecular mechanics does not take into account possible H-bonding interactions such as those possible here.

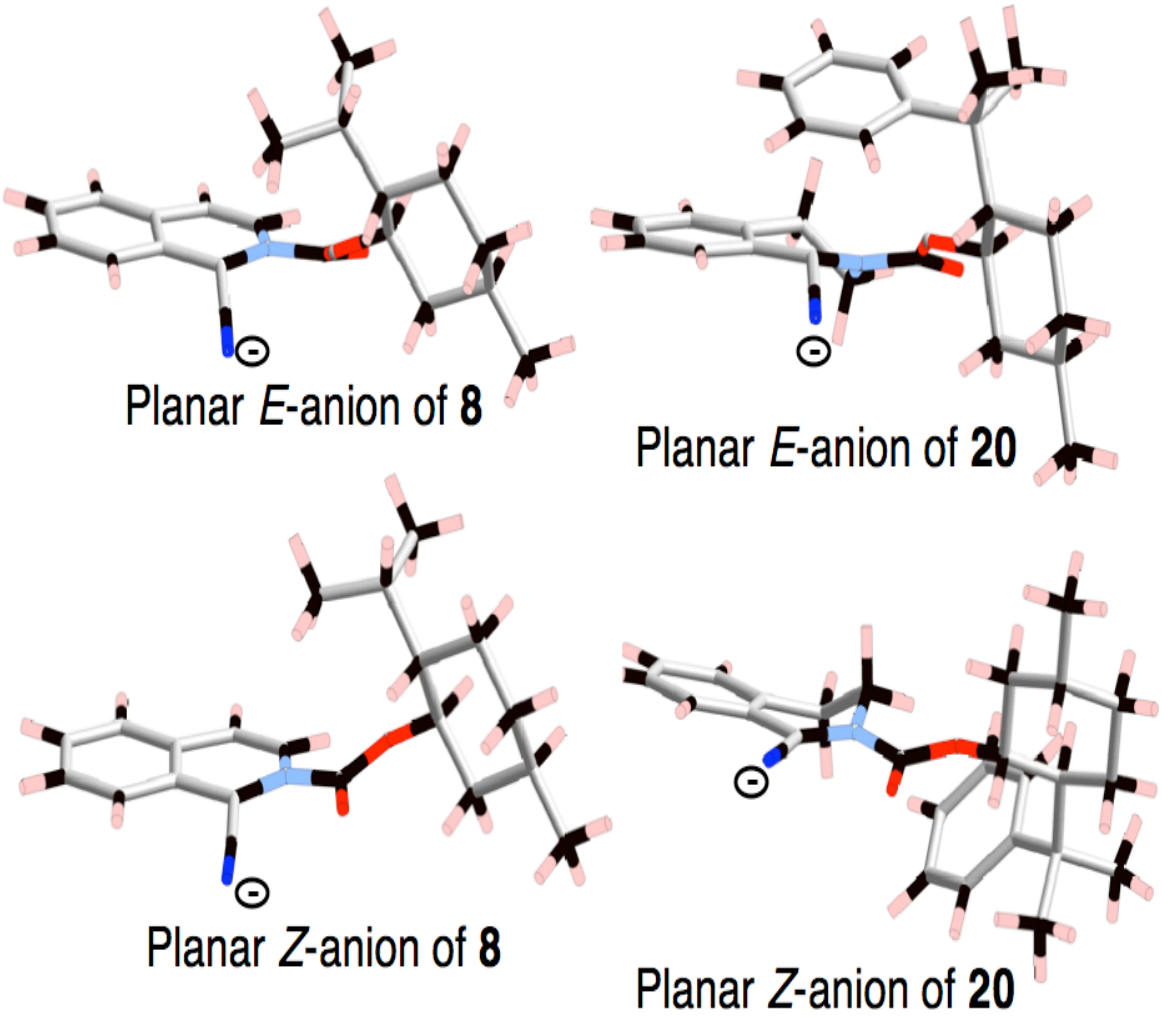

Figure S32. All of the carbanions in this study were benzylic, so most likely they are planar.[S15] Examination of CPK models and the minimized structures above indicate the possible origins of the modest stereoselectivites observed. These structures were minimized (MM2) as the corresponding ketenes and the N atom was then inserted in place of the O atom of the ketene. Both *E*- and *Z*-urethane isomers are shown. On the left are the planar structures for the anion from **8**; in both *E*- and *Z*-forms the menthyl group hinders approach from the top face. Approach of pivaldehyde from the bottom face with the *tert*-butyl group away from the menthyl moiety will lead to the *S*-diastereomer of **12**, experimentally observed as the predominant (82%) product. On the right are the planar structures for the anion from **20.** Here, the *E*- and *Z*-forms

present quite different degrees of steric hindrance. Because of dipolar repulsion of the negative charge of the anion and the carbonyl oxygen, the *E*-isomer should predominate; in this case the phenylmenthyl moiety shields the top face quite effectively. Approach of alkyl halides, e. g., CH_3I, from the bottom face will preferentially lead to the *S*-diastereomers of **26**. Thus, presumably the predominant (e. g., 67% for **26a**) diastereomer in products of alkylation reactions of **20** is the *S*-derivative. The less than perfect stereo-control may be attributed to the presence of some of the *Z*-isomer, in which both faces are accessible.

In the case of 2-cholesteryloxycarbonyl-1-,2-dihydroisoquinaldonitrile (**11**) the lack of diastereoselectivity in forming **15** may be attributed to the lack of steric constraint at the reactive site by the rigid cholesteryl moiety, which as seen in its X-ray structure (Figure S3) is extended away from the isoquinoline portion of the molecule.

These arguments are based on substrate-controlled kinetics, of course. However, molecular mechanics (MM2 and MM3) calculations on the products (*R*)-**12** and (*S*)-**12** from reaction of **8** with pivaldehyde indicated a significant energy difference, 1.1 kcal/mol, favoring the *S*-isomer on the basis of product-controlled kinetics.

As shown below MM2 calculations indicated differences in energies of the diastereomeric dihydro-Reissert compounds as well as their methylated products. The predominance of *S*-diastereomers in the Reissert compounds is consistent with these results. The predicted selective formation of *S*-diastereomers in the methylated products is also consistent with the predictions from the above minimized structure of **20**.

MM2 Calculated Energy Differences and Predicted Fractional Compositions of Dihydro-Reissert Compounds and Methylated Derivatives

Compound	E_R - E_S (kcal/mol)	Predicted Ratio *S*:*R*@ 25°C
18	0.11	55:45
19	0.06	52:48
20	3.33	99.6:0.4
24a	0.15	56:44
25a	0.74	78:22
26a	1.40	91:9

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