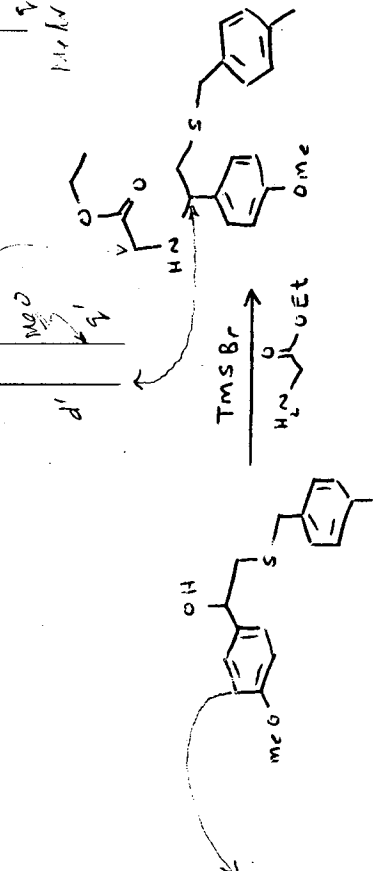
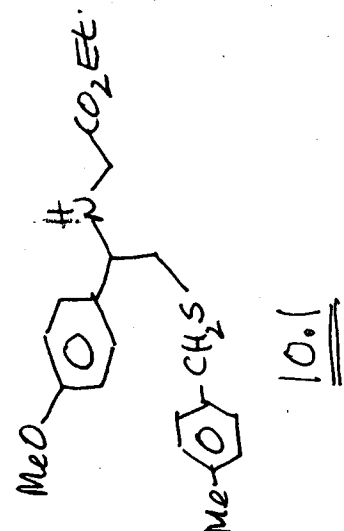
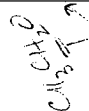
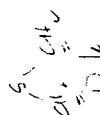
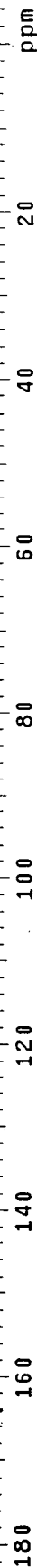


Pulse Sequence: apt

125 MHz APT in CDCl₃ (ref. to CDC13 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe CH, CH3 positive; C, CH2 negative
 date: Sep 20 2002 seqfil: apt hz/mm: 104.17 sweep width [Hz]: 25000 spectrometer: lbd5 file: exp
 acq.time [s]: 2.0 relax.time [s]: 0.5 dig.res. [Hz/pt]: 0.38 # of scans: 898



Bk 13 p 115



100 MHz APT in acetone (ref. to acetone @ 29.8 ppm), temp 27.8 C -> actual temp = 27.0 C, asw400 probe
CH, CH3 positive; C, CH2 negative

acetone

Pulse Sequence: apt

21.151
20.592
20.395
20.197
20.000
19.806
19.608
19.411

36.275
34.790

62.509
55.791

138.051
135.492
131.075
130.258
130.000
125.741
115.714

162.039

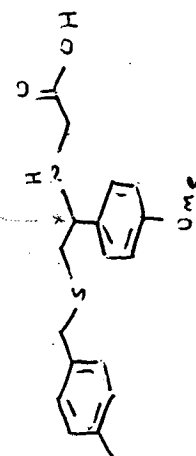
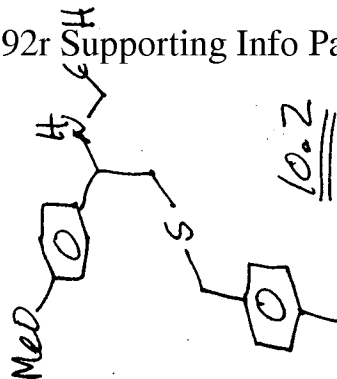
178.344

S ↑ 5
T 3
D ↓ 5
Q 2

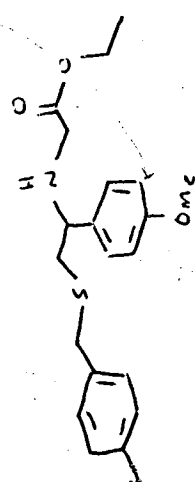
see expansion
48.0

MeO

MeO



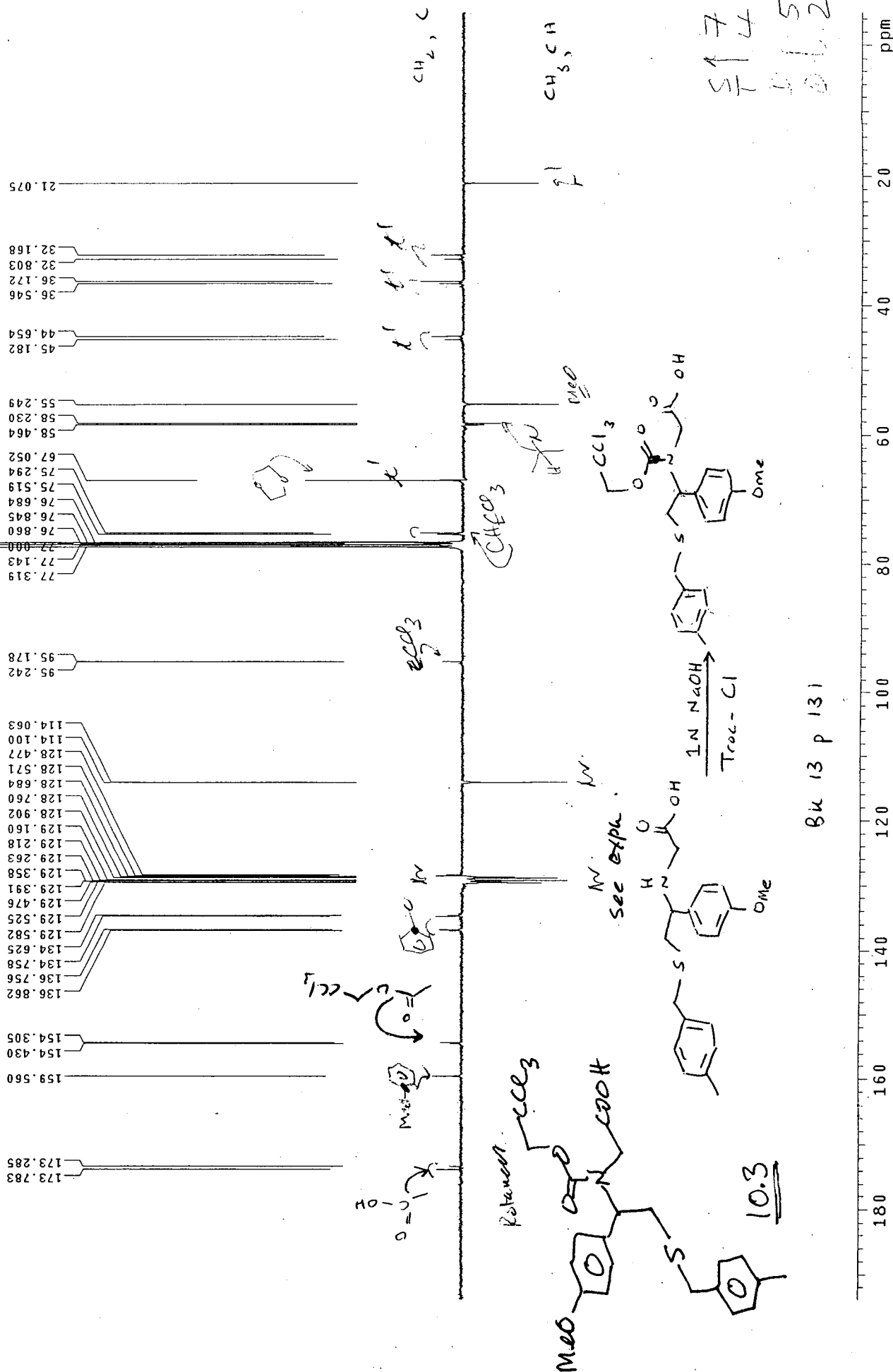
1N NaOH
dioxane-
water



Bk 13 p 129

180 160 140 120 100 80 60 40 20 ppm

100 MHz APT in CDCl₃ (ref. to CDC13 @ 77.0 ppm), temp 27.8 C -> actual temp = 27.0 C, asw400 probe
 CH, CH3 positive; C, CH2 negative
 date: Sep 26 2002 seqfil: apt
 acq.time[s]: 2.0 relax.time[s]: 0.5
 hz/mm: 83.33 sweep width[Hz]: 20000 spectrometer: i300
 dig.res.[Hz/pt]: 0.31 # of scans: 18600
 file: /mnt/d600/clivenmrdata/Soleiman/SEPT2002/SH13131-C.fid
 Pulse Sequence: apt

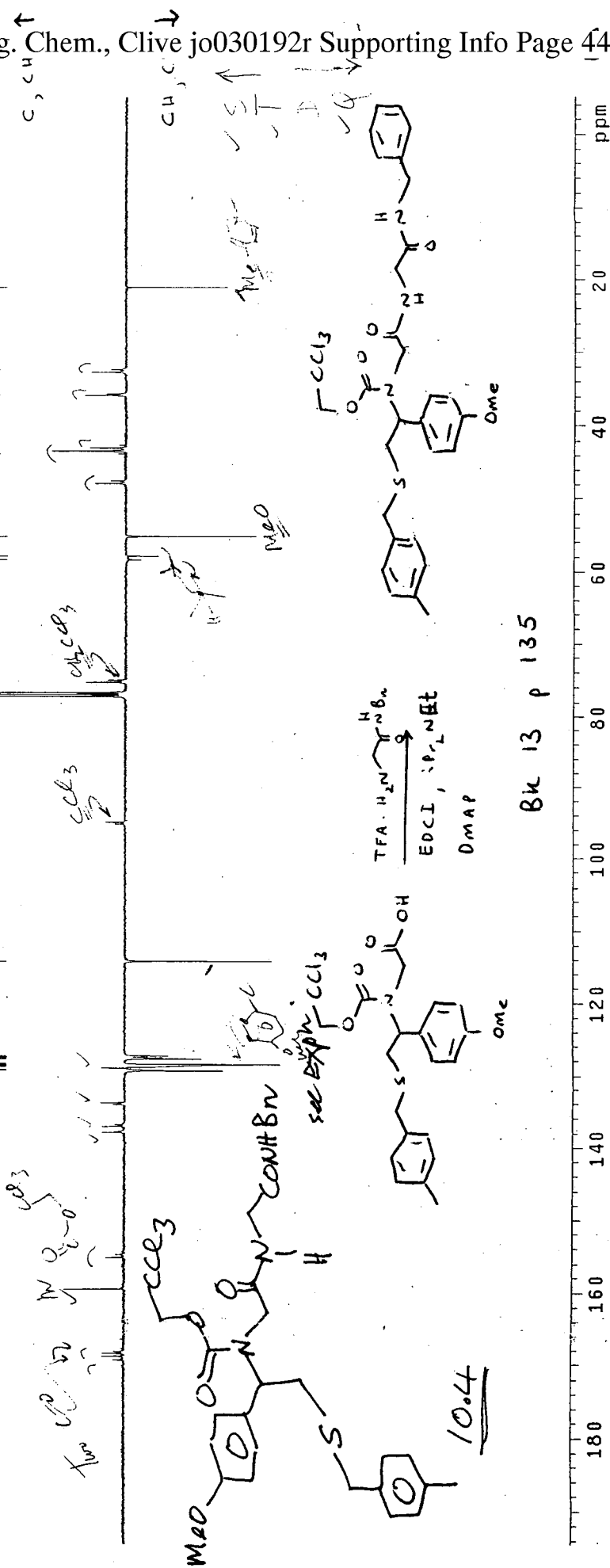
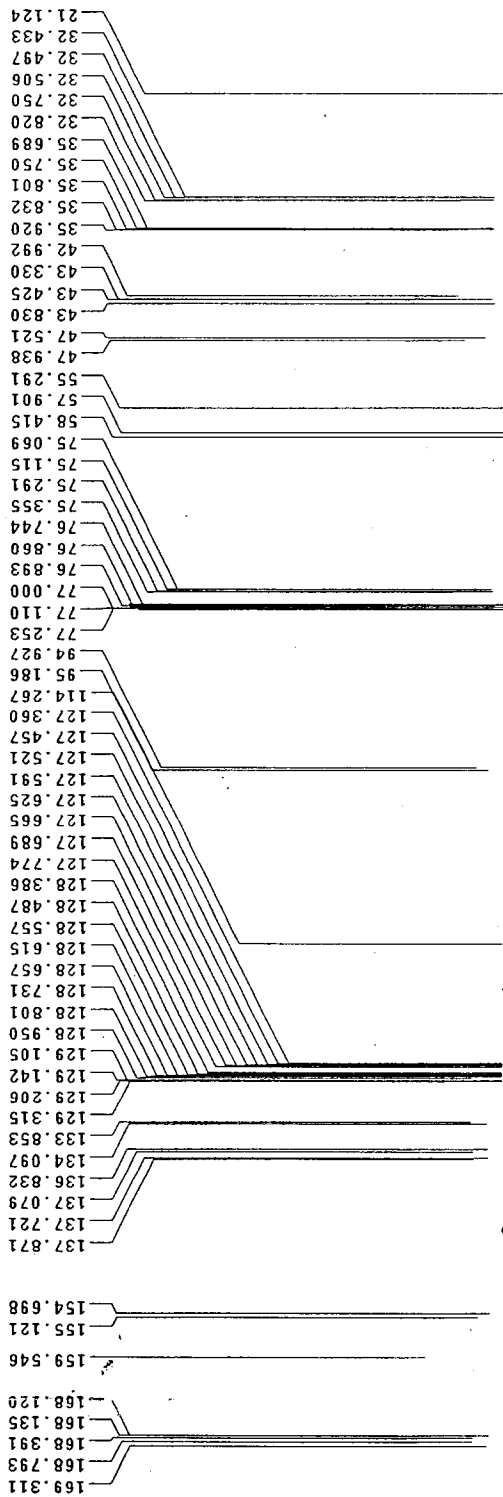


Bk 13 p 131

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125 MHz APT in CDC13 (r.f. to CDC13 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
CH, CH3 positive; C, CH2 negative
date: Sep 29 2002      sqf1: apt      hz/mm: 104.17 sweep width [Hz]: 25000      spectrometer: i300      file: /mnt/d600/c1ivenmrdata/Soleiman/SEPT2002/SH13135_C.fid
acq.time[s]: 2.0      relax.time[s]: 0.5      dig.res. [Hz/pt]: 0.38      # of scans: 4864      Pulse Sequence: apt

```



Bk 13 p 135

525 MHz APT in CDCl₃ (ref. to CDCl₃ @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe



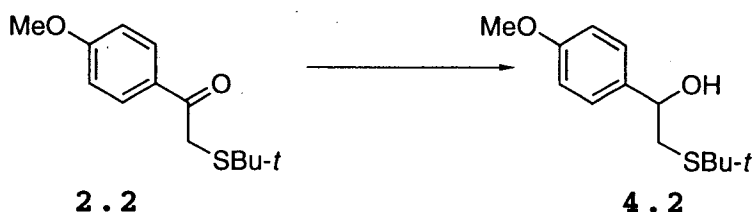
6 signals.
See notation

General procedures

Unless stated to the contrary, all reactions were done under dry N₂, and the general procedures used previously³² were followed. The symbols s', d', t', and q' used for ¹³C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, the assignments being made from APT spectra. Optical rotations were measured at 20 °C with a Perkin Elmer 241 Polarimeter, using a sodium lamp.

The **a** or **b** designation in compound numbers indicates whether a particular compound originates from the chromatographically faster- or slower-running series, respectively, as determined from the earliest point at which separation of isomers was possible.

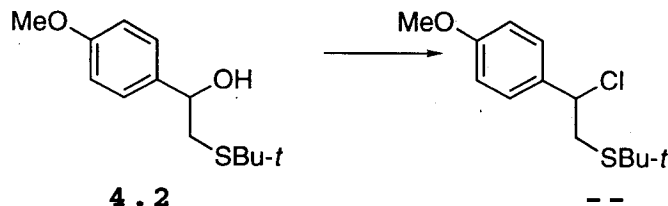
2-*tert*-Butylsulfanyl-1-(4-methoxyphenyl)ethanol (**4.2**).



NaBH₄ (400 mg, 10.6 mmol) was added in four approximately equal portions at 15-min intervals to a stirred and cooled (0 °C) solution of ketone **2.2** (826 mg, 3.47 mmol) in dry MeOH (15 mL), and stirring was continued for 30 min at 0 °C. The solvent was evaporated and the residue was dissolved in a 1:1 mixture of water and EtOAc (80 mL) and stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer and extracts were dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:3 EtOAc-hexanes, gave **4.2** (760 mg; 92%) as a colorless oil: FTIR (CDCl₃ cast) unexceptional; ¹H NMR (CDCl₃, 500 MHz) δ 1.33 (s, 9 H), 2.72-2.77 (m containing a broad singlet, 2 H in all), 2.88-2.92 (m, 1 H), 3.78 (s, 3 H), 4.67 (dd, *J* = 9.4, 3.8 Hz, 1 H), 6.84-6.85 (m, 2 H), 7.25-7.27 (m, 2 H); ¹³C NMR (CDCl₃, 125 MHz) δ 31.2 (q'), 38.7 (t'), 42.7 (s'), 55.3 (q'), 72.1 (d'), 113.8 (d'), 126.9 (d'), 134.9 (s'), 159.1

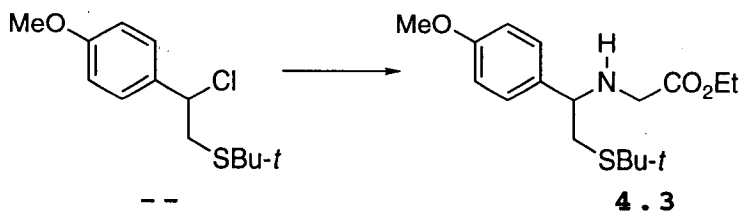
(s'); exact mass m/z calcd for $C_{13}H_{20}O_2S$ 240.1184, found 240.1187.

1-(2-*tert*-Butylsulfanyl-1-chloroethyl)-4-methoxybenzene.



$SOCl_2$ (347 μ L, 4.67 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **4.2** (1.22 g, 4.67 mmol) in dry CH_2Cl_2 (6 mL). After 2 h the mixture was diluted with Et_2O (80 mL), washed with saturated aqueous $NaHCO_3$ (3 x 40 mL), dried ($MgSO_4$) and evaporated to give the crude chloride (1.16 g, 96%) as a pale yellow oil: 1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 9 H), 3.21 (d, J = 8.0 Hz, 2 H), 3.78 (s, 3 H), 4.93 (t, J = 7.6 Hz, 1 H), 6.84–6.88 (m, 2 H), 7.28–7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.9 (q'), 37.4 (t'), 43.1 (s'), 55.2 (q'), 62.3 (d'), 114.0 (d'), 128.7 (d'), 132.2 (s'), 159.7 (s'). The chloride was used crude.

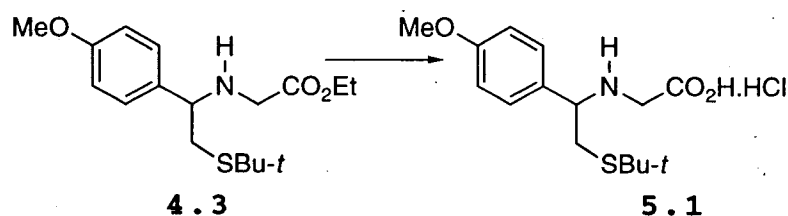
[2-*tert*-Butylsulfanyl-1-(4-methoxyphenyl)ethylamino]-acetic Acid Ethyl Ester (4.3).



Freshly distilled (distilled under water pump vacuum) $H_2NCH_2CO_2Et$ (204 mg, 1.98 mmol) was added in one lot to a stirred solution of the above crude chloride (233 mg, 0.901 mmol) in dry CH_2Cl_2 (2.5 mL), and stirring was continued for 6 h (tlc control, silica, 1:3 $EtOAc$ -hexane), by which point all the chloride had reacted. Some flash chromatography silica gel was added and the

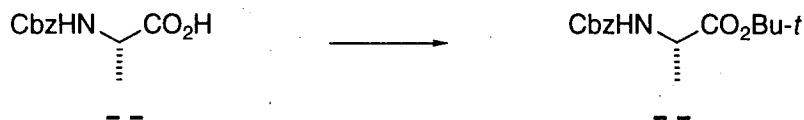
mixture was evaporated at room temperature. The residual solid was placed on top of a column made up with flash chromatography silica gel (2 x 20 cm), and elution with 1:5 EtOAc-hexane gave **4.3** (189 mg, 64%), identical with material obtained from **4.2**, by use of Me₃SiBr.

[2-*tert*-Butylsulfanyl-1-(4-methoxyphenyl)ethylamino]-acetic Acid Hydrochloride (5.1).



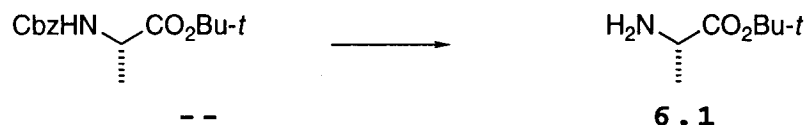
NaOH (1.29 g, 32.4 mmol) was added to a stirred solution of ester **4.3** (1.034 g, 3.18 mmol) in 1:1 THF-water (28 mL). After 4 h the mixture was diluted with water (25 mL) and washed with Et₂O (3 x 25 mL). The aqueous layer was cooled (0 °C), acidified to pH 1-2 with concentrated hydrochloric acid and then evaporated to dryness. The residue was mixed with MeOH (100 mL) and the mixture was warmed slightly. The mixture was filtered, and the filtrate was evaporated to give amino acid hydrochloride **5.1** (1.06 g, 100%) as a pale yellow foam: FTIR (CDCl₃ cast) 3400-2400 (br), 1690 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz) δ 1.30 (s, 9 H), 3.19 (dd, J_{AB} = 12.9 Hz, J_{AX} = 9.5 Hz, 1 H), 3.27-3.30 (m, 1 H), 3.62 (ABq, Δν_{AB} = 28.8 Hz, J_{AB} = 17.0 Hz, 2 H), 3.81 (s, 3 H), 4.40 (dd, J = 9.6, 6.0 Hz, 1 H), 7.00 (dd, J = 6.8, 1.9 Hz, 2 H), 7.38 (dd, J = 6.8, 2.1 Hz, 2 H); the ¹H NMR (300 MHz) spectrum run in DMSO-d₆ showed broad signals, with integration corresponding to 24 H; ¹³C NMR (CDCl₃, 125 MHz) δ 31.2 (q'), 31.9 (t'), 44.2 (s'), 46.4 (t'), 56.1 (q'), 63.4 (d'), 115.7 (d'), 125.7 (s'), 131.1 (d'), 162.1 (s'), 168.7 (s'); exact mass m/z calcd for C₁₅H₂₃NNaO₃S (M + Na) 320.1296, found 320.1297.

(*S*)-2-(Benzyloxycarbonylamino)propionic Acid *tert*-Butyl Ester.



A solution of *t*-butyl trichloroacetimidate [$\text{Cl}_3\text{CC}(=\text{NH})\text{OBu-}t$] (13.8 g, 63.2 mmol) in dry cyclohexane (distilled from CaH_2) (60.9 mL) was added over 10 min to a stirred and cooled (0°C) solution of (*S*)-2-(benzyloxycarbonylamino)propionic acid (7.05 g, 31.6 mmol) in dry CH_2Cl_2 (30.4 mL), followed by $\text{BF}_3\cdot\text{OEt}_2$ (610 μL , 4.81 mmol), which was also added over ca 10 min. Stirring was continued for 14 h and the mixture was neutralized with solid NaHCO_3 (5 g). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:9 acetone-hexanes, gave the protected alanine³³ (7.72 g, 87%) as a colorless oil: $[\alpha]_D^{20} -28.4^\circ$ (*c* 1, EtOH); FTIR (CHCl_3 cast) 3339, 1723 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.36 (d, $J = 7.1$ Hz, 3 H), 1.44 (s, 9 H), 4.20-4.27 (m, 1 H), 5.05-5.12 (m, 2 H), 5.30-5.41 (br m, 1 H), 7.28-7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 18.8 (q'), 27.9 (q'), 50.1 (d'), 66.7 (t'), 81.8 (s'), 128.0 (d'), 128.3 (d'), 128.4 (d'), 136.4 (s'), 156.5 (s'), 172.1 (s'); exact mass m/z calcd for $\text{C}_{15}\text{H}_{21}\text{NNaO}_4$ ($M + \text{Na}$) 302.1363, found 302.1362.

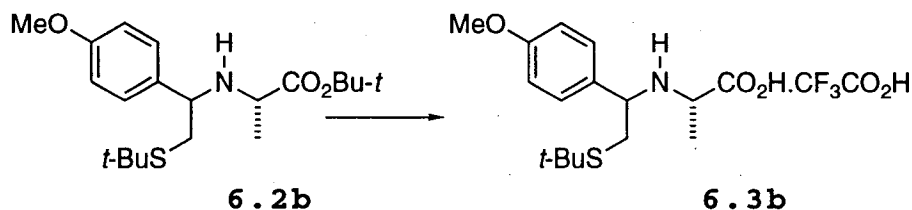
(2*S*)-2-Aminopropionic Acid *tert*-Butyl Ester (6.1).²⁴



10% Pd-C (778 mg, 25% weight of starting material) was added slowly, under a continuous stream of N_2 , to a solution of the above carbamate (3.11 g, 7.84 mmol) in dry MeOH (60 mL). The flask was purged with H_2 gas and the mixture was stirred under a H_2 atmosphere, using a balloon. After 6 h, the mixture was filtered through a Celite pad (3 x 5 cm), using MeOH (25 mL). The combined filtrate and washings were carefully evaporated (the product is

volatile) to yield amine **6.1** (1.84 g, 89%) as a pale yellow oil: $[\alpha]_D^{20} +2.3^\circ$ (c 1, CHCl₃); FTIR (CHCl₃ cast) 1732 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.29 (d, J = 7.0 Hz, 3 H), 1.43 (s, 9 H), 2.33 (br s, 2 H), 3.43 (q, J = 7.0 Hz, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 20.4 (q'), 28.0 (q'), 50.6 (d'), 81.0 (s'), 175.1 (s'); exact mass m/z calcd for C₇H₁₆NO₂ (M + H) 146.1181, found 146.1183. Examination of the Mosher amide showed (¹⁹F NMR) showed no epimerization. The Mosher amides of racemic material give separated ¹⁹F NMR signals at δ -69.6 and -69.4 ppm.

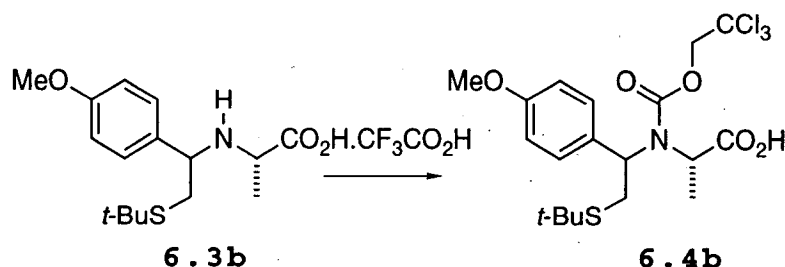
(2S)-2-[2-tert-Butylsulfanyl-1-(4-methoxyphenyl)-ethylamino]propionic Acid Trifluoroacetate (6.3b).



CF₃CO₂H (1 mL) was added to a stirred and cooled (0 °C) mixture of **6.2b** (375 mg, 1.02 mmol) and PhOMe (190 μ L), and stirring was continued for 5 h at 0 °C. Evaporation of the solvents and flash chromatography of the residue over silica gel (2 x 15 cm), using 8:92 and then 1:1 MeOH-CH₂Cl₂, gave **6.3b** (318 mg, 73%) as a white solid: $[\alpha]_D^{20} -4.7^\circ$ (c 1, MeOH); mp 137-142 °C; FTIR (MeOH cast) 1678, 1613 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz) δ 1.28 (s, 9 H), 1.44 (d, J = 7.1 Hz, 3 H), 3.19 (dd, J_{AB} = 12.3 Hz, J_{AX} = 10.1 Hz, 1 H), 3.23 (dd, J_{AB} = 12.6 Hz, J_{BX} = 4.9 Hz, 1 H), 3.45-3.50 (m, 1 H), 3.79 (s, 3 H), 4.29 (dd, J_{AX} = 9.8 Hz, J_{BX} = 5.4 Hz, 1 H), 6.95-6.96 (m, 2 H), 7.34-7.37 (m, 2 H) (two protons not observed in this spectrum); ¹³C NMR (CDCl₃, 125 MHz) δ 15.4 (q'), 31.2 (q'), 31.3 (q'), 43.2 (s'), 49.8 (d'), 55.8 (q'), 61.8 (d'), 115.4 (d'), 126.8 (s'), 130.8 (d'), 161.9 (s') (one carbon not observed in this spectrum); exact mass m/z calcd for C₁₆H₂₅NNaO₃S (M + Na) 334.1453, found 334.1454. We did not establish if the compound is the trifluoroacetate salt or the

zwitterion; the % yield is based on the assumption that the compound is the trifluoroacetate salt.

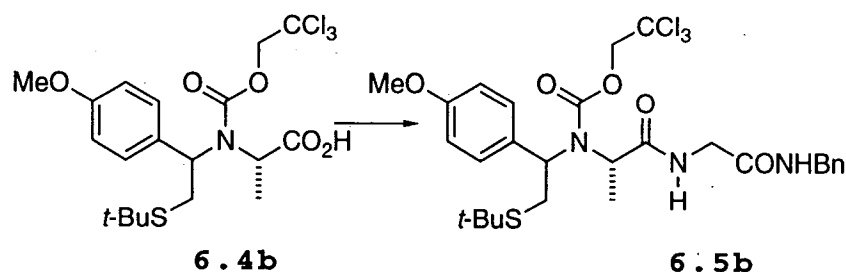
(2*S*)-2-[[2-*tert*-Butylsulfanyl-1-(4-methoxyphenyl)-ethyl](2,2,2-trichloroethoxycarbonyl)amino]propionic Acid (6.4b).



Neat $\text{Cl}_3\text{CCH}_2\text{OCOC1}$ (260 μL , 1.88 mmol) and 1 N NaOH (245 μL) were added simultaneously by syringe over 4 h to a stirred and cooled (0 $^\circ\text{C}$) suspension of **6.3b** (294 mg, 0.691 mmol) in 1 N NaOH (1.10 mL). When addition was complete the cold bath was removed and stirring was continued for 11 h, by which time all **6.3b** had reacted. The mixture was cooled (0 $^\circ\text{C}$), acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:99, 2:99 and then 4:96 MeOH- CH_2Cl_2 , gave **6.4b** (337 mg, 100%) as a white foam: $[\alpha]^{20}_{\text{D}} -0.9^\circ$ (c 1.0, MeOH); mp 64–65 $^\circ\text{C}$; FTIR (MeOH cast) 1713, 1611 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) (mixture of rotamers) δ 0.97 (d, J = 6.8 Hz, 1.1 H), 1.03 (d, J = 6.8 Hz, 1.5 H), 1.33 (s, 3.8 H), 1.35 (s, 5.2 H), 3.08–3.18 (m, 2 H), 3.67–3.74 (m, 1 H), 3.79 (s, 3 H), 4.69–4.75 (m, 1 H), 4.87–5.02 (m, 1 H), 4.94 (ABq, $\Delta\nu_{\text{AB}}$ = 48.2 Hz, J_{AB} = 12.0 Hz, 1 H), 5.54–5.61 (m, 1 H), 6.87–6.89 (m, 2 H), 7.24–7.27 (m, 2 H) (one proton not observed in this spectrum); ^{13}C NMR (CDCl_3 , 100 MHz) (mixture of rotamers) δ 14.6 (q'), 16.1 (q'), 28.4 (s'), 28.9 (s'), 30.8 (q'), 43.1 (t'), 43.4 (t'), 52.1 (d'), 52.8 (d'), 55.2 (q'), 59.1 (d'), 59.5 (d'), 75.2 (d'), 75.5 (d'), 94.7 (s'), 95.3 (s'), 114.2 (d'), 128.4 (s'), 129.6 (d'), 129.7 (d'), 152.8 (s'), 153.7

(s'), 159.7 (s'), 175.0 (s'), 175.3 (s'); exact mass m/z calcd for $C_{19}H_{26}Cl_3NNaO_5S$ ($M + Na$) 508.0495, found 508.0495.

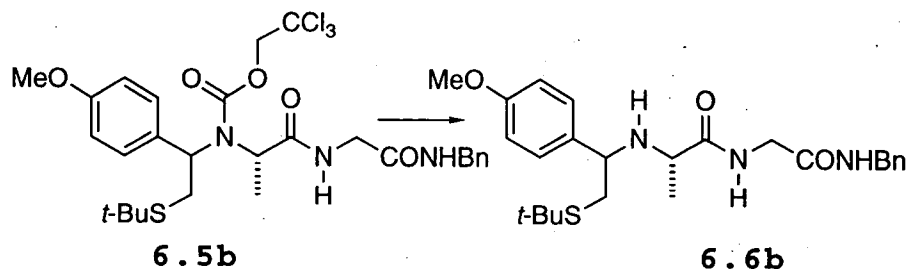
[(1*S*)-1-[(Benzylcarbamoylmethyl)carbamoyl]ethyl][2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethyl]carbamic Acid 2,2,2-Trichloroethyl Ester (6.5b**).**



O-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (186 mg, 0.556 mmol) was added to a stirred mixture of acid **6.4b** (271 mg, 0.578 mmol), Et_3N (233 μ L, 1.67 mmol) and the amine salt $CF_3CO_2H \cdot H_2NCH_2CONHBn^{25}$ (161 mg, 0.578 mmol) in MeCN (3 mL). The mixture was stirred for 4 h, diluted with EtOAc (25 mL) and washed successively with 1 N hydrochloric acid (2 x 15 mL) and saturated aqueous $NaHCO_3$ (2 x 15 mL). The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 4:96 MeOH- CH_2Cl_2 , gave **6.5b** (314 mg, 89%) as a white crystalline solid: $[\alpha]_D^{20} +26.9^\circ$ (c 1.0, $CHCl_3$); mp 74-76 $^\circ C$; FTIR ($CHCl_3$ cast) 1695, 1612 cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, $J = 6.8$ Hz, 3 H), 1.35 (s, 9 H), 3.05 (dd, $J_{AB} = 11.9$ Hz, $J_{AX} = 3.5$ Hz, 1 H), 3.21 (dd, $J_{AB} = J_{BX} = 11.9$ Hz, 1 H), 3.58 (dd, $J = 17.1, 5.0$ Hz, 1 H), 3.66 (m, 1 H), 3.78 (s, 3 H), 3.99 (d, $J = 12.0$ Hz, 1 H), 4.19 (dd, $J = 14.9, 4.3$ Hz, 1 H), 4.39 (dd, $J = 17.1, 7.6$ Hz, 1 H), 4.54 (d, $J = 12.0$ Hz, 1 H), 4.67 (dd, $J = 14.8, 7.2$ Hz, 1 H), 5.61 (dd, $J = 11.7, 3.3$ Hz, 1 H), 6.85-6.87 (m, 2 H), 7.20-7.33 (m, 7 H), 7.33-7.35 (m, 1 H), 7.91 (br t, $J = 6.0$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q'), 29.8 (s'), 30.9 (q'), 43.1 (t'), 43.2 (t'), 53.2 (d'), 55.4 (q'), 57.7 (d'), 74.7 (t'), 95.1 (s'), 114.4 (d'), 127.4 (d'), 127.9 (d'), 128.6 (d'), 128.9 (d'),

129.3 (s'), 138.4 (s'), 153.4 (s'), 159.9 (s'), 169.1 (s'), 171.3 (s') (one carbon not observed in this spectrum); exact mass m/z calcd for $C_{28}H_{36}Cl_3N_3NaO_5S$ ($M + Na$) 654.1339, found 654.1339.

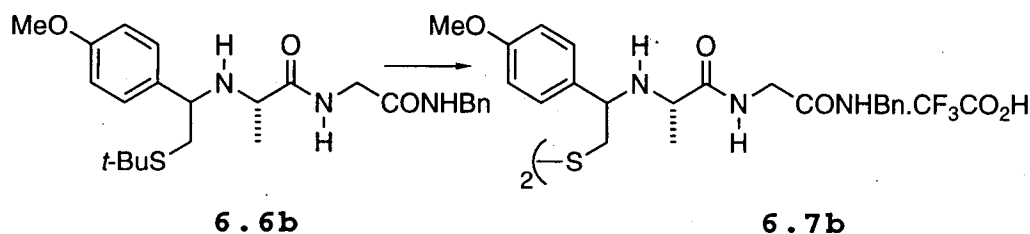
(2*S*)-*N*-(Benzylcarbamoylmethyl)-2-[2-*tert*-butyl-sulfanyl-1-(4-methoxyphenyl)ethylamino]propionamide (6.6b).



Cd powder (1.32 g, 11.7 mmol) was added in one portion to a stirred solution of **6.5b** (258 mg, 0.410 mmol) in 1:1 DMF-AcOH (9 mL). Stirring was continued for 5 h at room temperature, and the mixture was filtered through a Celite pad (2 x 4 cm), using EtOAc (50 mL). The combined filtrates and washings were evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 5:100 MeOH-CH₂Cl₂, gave **6.6b** (258 mg, 87%) as a glassy liquid: $[\alpha]^{20}_D +18.0^\circ$ (c 1.0, CHCl₃); FTIR (CH₂Cl₂ cast) 3304, 1653, 1610 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.24 (d, $J = 7.1$ Hz, 3 H), 1.30 (s, 9 H), 2.11 (br s, 1 H), 2.68 (dd, $J_{AB} = 12.5$ Hz, $J_{AX} = 10.0$ Hz, 1 H), 2.78 (dd, $J_{AB} = 12.6$ Hz, $J_{BX} = 3.8$ Hz, 1 H), 2.90-2.98 (m, 1 H), 3.65-3.81 (m containing a singlet at δ 3.70, 5 H in all), 4.32 (dd, $J_{AB} = 14.9$ Hz, $J_{AX} = 5.7$ Hz, 1 H), 4.39 (dd, $J_{AB} = 14.8$ Hz, $J_{BX} = 5.9$ Hz, 1 H), 6.75-6.78 (m, 2 H), 6.81-6.85 (m, 1 H), 7.17-7.28 (m, 7 H), 7.94 (br t, $J = 5.2$ Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 17.9 (q'), 31.0 (q'), 36.6 (s'), 42.7 (t'), 43.16 (t'), 43.24 (t'), 53.1 (q'), 55.5 (d'), 61.2 (d'), 114.0 (d'), 127.3 (d'), 127.4 (d'), 127.6 (d'), 128.3 (d'), 128.6 (d'), 134.2 (s'), 138.0 (s'), 159.2 (s'), 168.8 (s'), 175.6 (s'); exact mass m/z calcd for $C_{25}H_{36}N_3O_3S$ ($M + H$) 458.2477, found 458.2476. The compound had ee = 99.5% [HPLC, ChiralCel OD-H column, 5% EtOH-

hexane].

(2*S*)-*N*-(Benzylcarbamoylmethyl)-2-[2-[2-[(1*S*)-1-[(benzylcarbamoylmethyl)carbamoyl]ethylamino]-2-(4-methoxyphenyl)ethyl]disulfanyl]-1-(4-methoxyphenyl)ethylaminolpropionamide Bis(Trifluoroacetate) (6.7b).



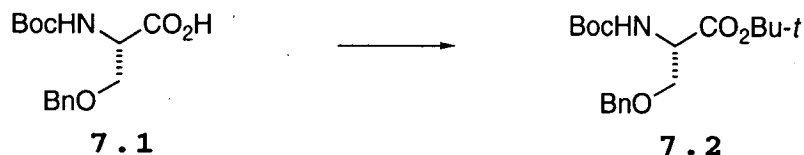
In this experiment the initial thiol product was not protected from air.

CF₃CO₂H (1.0 mL) was added to thioether **6.6b** (156 mg, 0.341 mmol) contained in a flask immersed in an ice-bath. The mixture was stirred and PhOMe (62 μ L), followed by Hg(OAc)₂ (109 mg, 0.342 mmol) were added. Stirring was continued for 25 min and the solvent was evaporated. The residue was dissolved in MeCN (15 mL) and H₂S gas was bubbled through the solution for 2 min. The resulting black suspension was filtered through a tightly packed Celite column (2 x 4 cm) and the solid was washed with several portions of MeCN. Evaporation of the combined filtrate and washings, and flash chromatography of the residue over silica gel (2 x 18 cm), using 4:100 MeOH-CH₂Cl₂, gave **6.7b** (124 mg, 70%) as a pale brown oil: [α]_D²⁰ -7.0 (c 0.74, MeOH); FTIR (MeOH, cast) 3291, 1651 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz) δ 1.31 (d, *J* = 7.0 Hz, 6 H), 2.72-2.83 (m, 4 H), 3.13-3.20 (m, 2 H), 3.71-3.83 (m containing a singlet at δ 3.73, 12 H in all), 4.37 (s, 4 H), 6.81-6.85 (m, 4 H), 7.18-7.29 (m, 14 H); ¹³C NMR (CD₃OD, 125 MHz) (mixture of rotamers) δ 18.2 (q'), 18.5 (q'), 31.6 (t'), 43.4 (t'), 44.2 (t'), 46.4 (t'), 55.8 (q'), 56.4 (q'), 60.7 (d'), 64.7 (d'), 115.1 (d'), 128.2 (d'), 128.45 (d'), 128.52 (d'), 129.5 (d'), 130.05 (d'), 130.12 (d'), 139.7 (s'), 160.8 (s'), 160.9 (s'), 170.96 (s'), 171.01 (s'); ¹⁹F NMR (CD₃OD, 376.5 MHz) δ -77.2; exact

mass m/z calcd for $C_{42}H_{53}N_6O_6S_2$ ($M + H$) 801.3463, found 801.3467.

We assume the product is the bis-trifluoroacetate salt.

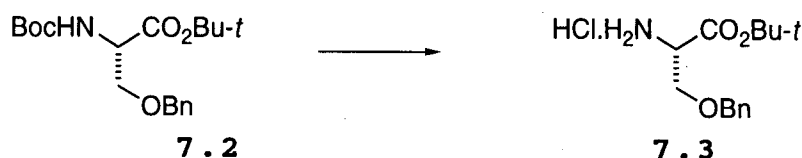
(2*S*)-3-Benzoyloxy-2-(*tert*-butoxycarbonylamino)-propionic Acid *tert*-Butyl Ester (7.2).



The following²⁹ is the best procedure for making the *t*-butyl ester, as epimerization, if any, appears to be very slight.

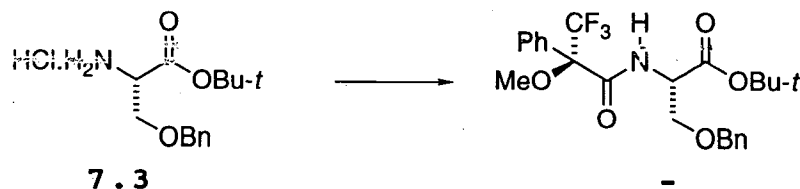
A solution of *t*-butyl trichloroacetimidate [$\text{Cl}_3\text{CC}(=\text{NH})\text{-OBu-t}$] (13.9 g, 63.6 mmol) in dry cyclohexane (60.9 mL) was added over 10 min to a stirred and cooled (0 °C) solution of **7.1** (8.98 g, 30.4 mmol) in dry CH_2Cl_2 (30.4 mL), followed by $\text{BF}_3\cdot\text{OEt}_2$ (610 μL , 4.81 mmol), which was also added over ca 10 min. Stirring was continued for 14 h and the mixture was neutralized with solid NaHCO_3 (5 g). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:9 acetone-hexanes, gave **7.2** (6.76 g, 63%) as a pale yellow oil: $[\alpha]^{20}_{\text{D}} +8.0^\circ$ (c 1, CHCl_3) [lit.^{24a} $[\alpha]^{20}_{\text{D}} -15.0^\circ$ (c 1, CHCl_3)]; FTIR (CH_2Cl_2 cast) 1716 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 1.432 (s, 9 H), 1.435 (s, 9 H), 3.64 (dd, $J_{\text{AB}} = 9.3\text{ Hz}$, $J_{\text{AX}} = 3.1\text{ Hz}$, 1 H), 3.83 (dd, $J_{\text{AB}} = 9.3\text{ Hz}$, $J_{\text{BX}} = 3.1\text{ Hz}$, 1 H), 4.28-4.32 (m, 1 H), 4.50 (ABq, $\Delta\nu_{\text{AB}} = 30.8\text{ Hz}$, $J_{\text{AB}} = 12.1\text{ Hz}$, 2 H), 5.35 (d, $J = 8.4\text{ Hz}$, 1 H), 7.24-7.34 (m, 5 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 28.0 (q'), 28.4 (q'), 54.4 (d'), 70.5 (t'), 73.3 (t'), 79.7 (s'), 81.9 (s'), 127.4 (d'), 127.6 (d'), 128.3 (d'), 137.6 (s'), 155.4 (s'), 169.5 (s'); exact mass m/z calcd for $\text{C}_{19}\text{H}_{29}\text{NNaO}_5$ ($M + \text{Na}$) 374.1943, found 374.1945.

(2*S*)-2-Amino-3-benzoyloxypropionic Acid *tert*-Butyl Ester Hydrochloride (7.3).



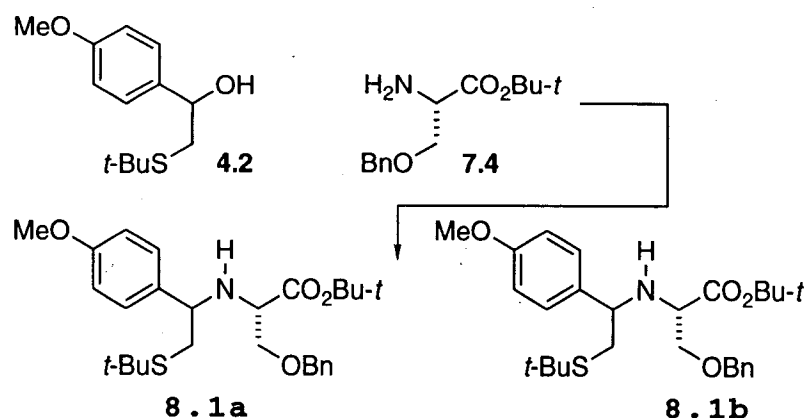
Dry HCl gas was passed into cold (0 °C) EtOAc (50 mL) for 20 min and the solution was allowed to warm slowly to room temperature. A portion of this solution (7.5 N³⁰ 17.3 mL, 129.8 mmol) was added to a stirred solution of **7.2** (made by use of *t*-butyl trichloroacetimidate, 6.758 g, 19.24 mmol) in EtOAc (86 mL) contained in a round-bottom flask fitted with a rubber septum, and stirring was continued overnight. The resulting precipitate was collected and washed with Et₂O. Recrystallization from MeOH-EtOAc, gave **7.3** (1.676 g, 34%) as a white solid. Evaporation of all the filtrates and mother liquors gave material that was resubjected to the initial acid treatment. In this way a further crop of **7.3** was obtained, but this material had an ee of 57%. The first crop (34%) had: mp 181-183 °C; FTIR (MeOH cast) 3700-3400 (br), 1736 cm⁻¹; ¹H NMR (CD₃OD, 500 MHz) δ 1.48 (s, 9 H), 3.78 (dd, *J*_{AB} = 10.4 Hz, *J*_{AX} = 3.1 Hz, 1 H), 3.90 (dd, *J*_{AB} = 10.4 Hz, *J*_{BX} = 4.2 Hz, 1 H), 4.13 (dd, *J*_{AX} = 3.1 Hz, *J*_{BX} = 4.2 Hz, 1 H), 4.57 (ABq, Δ*V*_{AB} = 58.3 Hz, *J*_{AB} = 12.0 Hz, 2 H), 7.26-7.34 (m, 5 H); ¹³C NMR (CD₃OD, 100 MHz) δ 28.1 (q'), 54.9 (d'), 68.2 (t'), 74.6 (t'), 85.3 (s'), 129.2 (d'), 129.24 (d'), 129.55 (d'), 138.4 (s'), 167.6 (s'); exact mass *m/z* calcd for C₁₄H₂₂NO₃ (M + H) 252.1600, found 252.1604.

(2*S*)-3-Benzoyloxy-2-[(2*S*)-(3,3,3-trifluoro-2-methoxy-2-phenylpropionylamino)]propionic Acid *tert*-Butyl Ester (Mosher Amide).



Et₃N (23.1 μ L, 0.165 mmol) was added to a stirred and cooled (0 °C) mixture of (-)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (77.2 mg, 0.330 mmol) and amine hydrochloride **7.3** (47.4 mg, 0.165 mmol) in dry CH₂Cl₂ (1.5 mL), followed by *N*-(3-dimethylamino)propyl-*N*-ethylcarbodiimide (64.5 mg, 0.330 mmol). Stirring was continued at 0 °C for 3 h by which time all **7.3** had reacted (tlc control, silica, 1:4 EtOAc-hexanes). Evaporation of the mixture gave the crude Mosher amides: The ¹⁹F NMR spectrum (CDCl₃) indicated an ee of $\geq 94\%$ [δ -69.16 (minor diastereoisomer), -69.11 (major diastereoisomer)]. Flash chromatography over silica gel (1 x 15 cm), using 1:4 EtOAc-hexanes, gave the Mosher amides (72.6 mg, 94%) as a colorless oil, care being taken to collect all fractions containing Mosher amides: [α]_D²⁰ +18.1° (c 0.7, CH₂Cl₂); FTIR (CH₂Cl₂ cast) 3428, 1739, 1700 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.47 (s, 9 H), 3.49 (s, 3 H), 3.62 (dd, *J* = 9.6, 3.1 Hz, 1 H), 3.82 (dd, *J* = 9.6, 3.1 Hz, 1 H), 4.40 (ABq, $\Delta\nu_{AB}$ = 16.1 Hz, *J*_{AB} = 12.1 Hz, 2 H), 4.63-4.66 (m, 1 H), 7.13-7.15 (m, 2 H), 7.21-7.35 (m, 6 H), 7.44 (br d, *J* = 8.0 Hz, 1 H), 7.50-7.51 (m, 2 H); ¹³C NMR (CDCl₃, 125 MHz) δ 28.1 (q'), 53.1 (q'), 55.2 (d'), 69.6 (t'), 73.3 (t'), 82.7 (s'), 83.9 (q, *J* = 26.3 Hz), 122.5 (s'), 124.8 (s'), 127.4 (d'), 127.6 (d'), 127.7 (d'), 128.3 (d'), 129.3 (d'), 132.8 (s'), 137.4 (s'), 165.9 (s'), 168.4 (s'); exact mass *m/z* calcd for C₂₄H₂₈F₃NO₅Na (M + Na) 490.1812, found 490.1818.

(2*S*)-3-Benzoyloxy-2-[2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethylamino]propionic Acid *tert*-Butyl Ester (less polar isomer) (8.1a) and (more polar isomer) (8.1b).



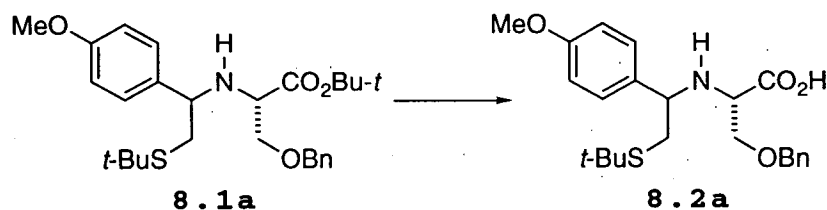
The free amine **7.4** was liberated from its HCl salt as follows: Solid NaOH (233 mg, 5.82 mmol) was added to a stirred solution of **7.3** (1.67 g, 5.80 mmol) in water (20 mL). The pH was adjusted to 8-9 by addition of solid NaOH and the mixture was extracted with Et₂O. The combined organic extracts were dried and evaporated, and the resulting amine (**7.4**) (1.47 g, ca 100%) was used immediately.

Me₃SiBr (390 μ L, 2.93 mmol) was added dropwise to a stirred and cooled (0 $^{\circ}$ C) solution of alcohol **4.2** (704 mg, 2.93 mmol) in dry CH₂Cl₂. After 40 min, a solution of **7.4** (1.47 g, 5.87 mmol) in dry CH₂Cl₂ (3 mL) was injected in one portion. Stirring was continued for 3 h without recharging the cold bath. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 25 cm), using 4:12:100 *t*-BuOMe-Et₂O-petroleum ether (35-60 $^{\circ}$ C), gave the faster-eluting diastereoisomer **8.1a** (422 mg, 30%) as a colorless oil. The slower-eluting fraction was resubjected to flash chromatography over silica gel (3.5 x 25 cm), using 1:9 EtOAc-hexanes, to obtain **8.1b** (539 mg, 38%) as a colorless oil. Isomer **8.1a** had: $[\alpha]_D^{20}$ -60.0 $^{\circ}$ (*c* 1.0, CH₂Cl₂); FTIR (CH₂Cl₂ cast) 3311, 1730 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.29 (s, 9 H), 1.44 (s, 9 H), 2.66 (dd, *J*_{AB} = 12.1 Hz, *J*_{AX} = 9.3 Hz, 1 H), 2.75 (dd, *J*_{AB} = 12.2 Hz, *J*_{BX} = 4.7 Hz, 1 H), 2.72-2.80 (br s, 1 H), 3.08 (t, *J* = 5.1 Hz, 1 H), 3.49 (dd, *J*_{AB} = 9.0 Hz, *J*_{AX} = 5.4 Hz, 1 H), 3.57 (dd, *J*_{AB} = 9.1 Hz, *J*_{BX} = 4.7 Hz, 1 H), 3.74 (dd, *J*_{AX} = 9.2 Hz, *J*_{BX} = 4.8 Hz, 1 H), 3.76 (s, 3 H), 4.44 (ABq, $\Delta\nu_{AB}$ = 22.1 Hz, *J*_{AB} = 12.2 Hz, 2 H), 6.79-6.82 (m, 2 H), 7.19-7.28 (m, 7 H); ¹³C NMR (CDCl₃, 125

MHz) δ 28.2 (q'), 31.1 (q'), 37.4 (t'), 42.4 (s'), 55.3 (q'), 59.3 (d'), 60.2 (d'), 72.0 (t'), 73.1 (t'), 81.1 (s'), 113.8 (d'), 127.3 (d'), 127.4 (d'), 128.1 (d'), 128.4 (d'), 134.7 (s'), 138.1 (s'), 158.9 (s'), 172.3 (s'); exact mass m/z calcd for $C_{27}H_{40}NO_4S$ (M + H) 474.2678, found 474.2675.

Isomer **8.1b** had: $[\alpha]^{20}_D +22.2^\circ$ (c 1.0, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1731 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (s, 9 H), 1.35 (s, 9 H), 2.50 (br s, 1 H), 2.73-2.80 (m, 2 H), 3.31 (t, $J = 4.6$ Hz, 1 H), 3.56-3.61 (m, 2 H), 3.73-3.61 (overlapping signals containing a singlet at δ 3.74, 4 H in all), 4.49 (ABq, $\Delta\nu_{AB} = 14.5$ Hz, $J_{AB} = 12.1$ Hz, 2 H), 6.78-6.81 (m, 2 H), 7.19-7.29 (m, 7 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.1 (q'), 31.2 (q'), 36.5 (t'), 42.3 (s'), 55.3 (q'), 59.7 (d'), 60.4 (d'), 70.3 (t'), 73.3 (t'), 81.0 (s'), 113.8 (d'), 126.9 (d'), 127.5 (d'), 128.2 (d'), 128.4 (d'), 134.7 (s'), 138.0 (s'), 158.9 (s'), 171.9 (s'); exact mass m/z calcd for $C_{27}H_{40}NO_4S$ (M + H) 474.2678, found 474.2679.

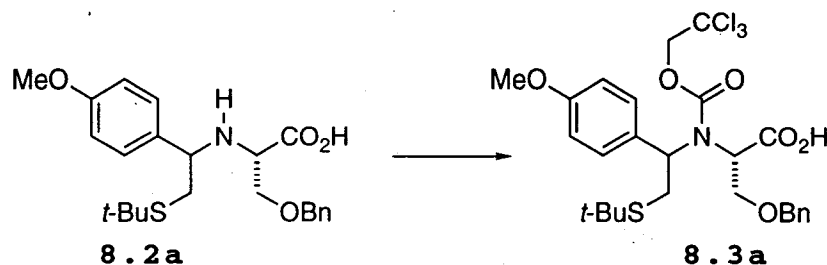
(2S)-3-Benzoyloxy-2-[2-tert-butylsulfanyl-1-(4-methoxyphenyl)ethylamino]propionic Acid (8.2a).



$Me_3SiOSO_2CF_3$ (323 μ L, 1.79 mmol) was added dropwise to a stirred and cooled (0 $^\circ$ C) solution of ester **8.1a** (422 mg, 0.893 mmol) in dry CH_2Cl_2 (6.6 mL). Stirring was continued for 6 h without recharging the cold bath and the mixture was applied directly to a silica gel column (2 x 15 cm). Flash chromatography, using 4:100 MeOH- CH_2Cl_2 , gave **8.2a** (338 mg, 90%) as a pale yellow solid: $[\alpha]^{20}_D +2.4^\circ$ (c 1.0, MeOH); mp 172-176 $^\circ$ C; FTIR (MeOH cast) 3600-2000, 1613 cm^{-1} ; 1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (s, 9 H), 2.81-2.89 (m, 2 H), 3.32-3.34 (m, 1 H), 3.47 (dd, $J = 9.9, 3.9$ Hz, 1 H), 3.68-3.82 (m containing a singlet at δ 3.75, 5

H in all), 4.33 (ABq, $\Delta\nu_{AB} = 44.7$ Hz, $J_{AB} = 11.8$ Hz, 2 H), 6.76-6.79 (m, 2 H), 7.11-7.30 (m, 7 H) (two protons not observed in this spectrum); ^{13}C NMR (CDCl_3 , 125 MHz) δ 31.0 (q'), 35.6 (s'), 42.9 (t'), 55.3 (q'), 59.5 (d'), 62.5 (d'), 69.2 (t'), 73.0 (t'), 114.2 (d'), 127.6 (d'), 127.7 (d'), 128.2 (d'), 128.3 (d'), 137.3 (s'), 159.5 (s'), 172.3 (s') (one carbon not observed in this spectrum); exact mass m/z calcd for $\text{C}_{23}\text{H}_{32}\text{NO}_4\text{S}$ ($M + H$) 418.2047, found 418.2052.

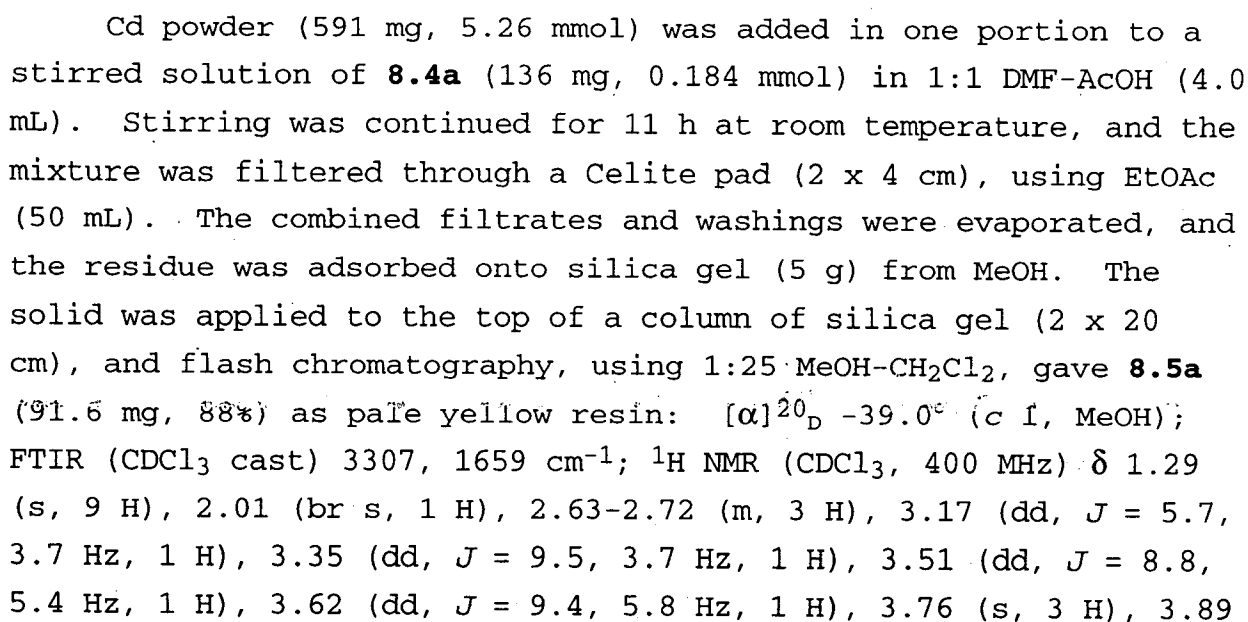
(2*S*)-3-Benzoyloxy-2-[[2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethyl](2,2,2-trichloroethoxycarbonyl)-aminolpropionic Acid (8.3a).



A solution of $\text{Cl}_3\text{CCH}_2\text{OCOCl}$ (228 μL , 1.65 mmol) in dioxane (1 mL) and 0.5 N NaOH (430 μL , 215 mmol) were added simultaneously by syringe pump over 4.5 h to a stirred and cooled (0 $^\circ\text{C}$) solution of **8.2a** (308 mg, 0.827 mmol) in 1 N NaOH (0.99 mL). When addition was complete the cold bath was removed and stirring was continued for 14 h. The mixture was diluted with water (5 mL), adjusted to pH 3-4 with 1 N hydrochloric acid, and extracted with Et_2O (2 x 15 mL). The combined extracts were dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 8:100 MeOH- CH_2Cl_2 , gave **8.3a** (174 mg, 38%) as a white foam: $[\alpha]_D^{20} -34.5^\circ$ (c 1.0, CHCl_3); FTIR (CDCl_3 cast) 1714 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) (mixture of rotamers) δ 1.22 (s, 3.9 H), 1.28 (s, 5.1 H), 2.93-3.01 (m, 1 H), 3.14-3.24 (m, 1 H), 3.75 (s, 3 H), 3.76-3.80 (m, 1 H), 3.88-3.96 (m, 1 H), 4.04-4.07 (m, 1 H), 4.46-4.58 (m, 2.6 H), 4.70-4.75 (m, 1 H), 4.94 (d, $J = 11.9$ Hz, 0.42 H), 5.42 (dd, $J = 9.6, 6.4$ Hz, 1 H), 6.81 (d, $J = 8.5$ Hz, 2 H),

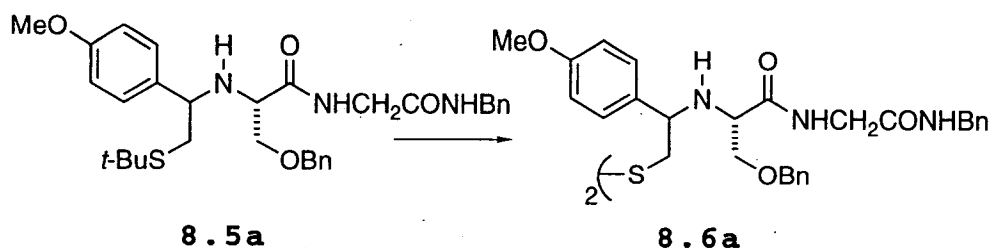
[(1*S*)-1-[(Benzylcarbamoylmethyl)carbamoyl]-2-benzyl-oxyethyl][2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethyl]-carbamic Acid 2,2,2-Trichloroethyl Ester (8.4a).

(2S)-N-(Benzylcarbamoylmethyl)-3-benzyloxy-2-[2-tert-butylsulfanyl-1-(4-methoxyphenyl)ethylamino]propionamide (8.5a).



(dd, $J = 16.5, 5.9$ Hz, 1 H), 4.10–4.20 (m, 3 H), 4.27–4.39 (m, 2 H), 6.76 (d, $J = 8.4$ Hz, 2 H), 6.85 (s, 1 H), 7.02 (d, $J = 8.6$ Hz, 2 H), 7.12–7.32 (m, 10 H), 8.44 (t, $J = 6.5$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 31.0 (q'), 36.7 (s'), 42.7 (t'), 43.1 (t'), 43.4 (t'), 55.2 (q'), 59.7 (d'), 62.1 (d'), 71.1 (t'), 72.7 (t'), 114.0 (d'), 127.3 (d'), 127.48 (d'), 127.54 (d'), 127.8 (d'), 128.40 (d'), 128.48 (d'), 128.54 (d'), 134.0 (s'), 137.4 (s'), 138.0 (s'), 159.1 (s'), 169.1 (s'), 173.3 (s'); exact mass m/z calcd for $\text{C}_{32}\text{H}_{42}\text{N}_3\text{O}_4\text{S}$ 564.2891 ($M + H$), found 564.2896.

(2*S*)-*N*-(Benzylcarbamoylmethyl)-2-[2-[2-[(1*S*)-1-[(benzylcarbamoylmethyl)carbamoyl]-2-benzyloxyethyl-amino]-2-(4-methoxyphenyl)ethyldisulfanyl]-1-(4-methoxyphenyl)ethylamino]-3-benzyloxypropionamide (and corresponding thiol) (8.6a).

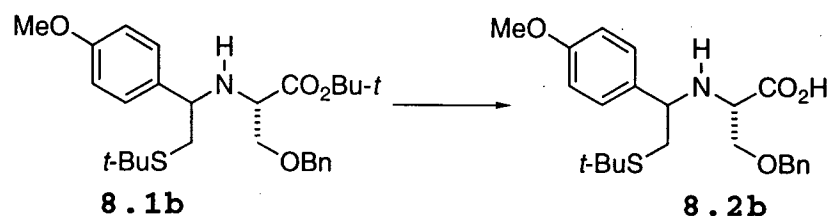


In this experiment the initial thiol product was not protected from air.

$\text{CF}_3\text{CO}_2\text{H}$ (2 mL) was added to thioether **8.5a** (85.0 mg, 0.153 mmol) contained in a flask immersed in an ice-bath. The mixture was stirred and PhOMe (32 μL), followed by $\text{Hg}(\text{OAc})_2$ (50.5 mg, 0.158 mmol) were added. Stirring was continued for 25 min and the solvent was evaporated. The residue was dissolved in MeCN (20 mL) and H_2S gas was bubbled through the solution for 2 min. The resulting black suspension was filtered through a tightly packed Celite column (2 x 4 cm) and the solid was washed with several portions of MeCN. Evaporation of the combined filtrate and washings, and flash chromatography of the residue over silica gel (2 x 18 cm), using 4:100 MeOH- CH_2Cl_2 , gave disulfide **8.6a** and the

corresponding thiol (44.4 mg, 58%) as a thick oil: $[\alpha]_D^{20}$ -47.7° ; FTIR (CDCl_3 cast) 3300, 1656, 1609 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 1.58 (br s, 1 H), 2.33 (br s, 1 H), 2.85 (d, $J = 6.2$ Hz, 1 H), 3.20–3.23 (m, 1 H), 3.37–3.41 (m, 1 H), 3.57–3.61 (m, 1 H), 3.71–3.81 (m containing a singlet at δ 3.76, 4 H in all), 3.86–4.10 (m, 2 H), 4.16–4.43 (m, 4 H), 6.76–6.79 (m, 3 H), 6.96–7.03 (m, 2 H), 7.12–7.38 (m, 11 H), 8.14 (br s, 1 H); ^{13}C NMR (CDCl_3 , 125 MHz) (mixture of rotamers) δ 32.2 (t'), 43.1 (t'), 43.2 (t'), 43.3 (t'), 43.4 (t'), 55.2 (q'), 59.7 (d'), 60.3 (d'), 63.5 (d'), 70.8 (t'), 72.7 (t'), 72.8 (t'), 73.0 (t'), 114.0 (d'), 114.1 (d'), 114.2 (d'), 114.3 (d'), 127.3 (d'), 127.4 (d'), 127.49 (d'), 127.53 (d'), 127.6 (d'), 127.7 (d'), 127.8 (d'), 127.9 (d'), 128.0 (d'), 128.39 (d'), 128.4 (d'), 128.55 (d'), 128.61 (d'), 128.67 (s'), 128.72 (s'), 133.0 (s'), 137.40 (s'), 137.42 (s'), 138.0 (s'), 138.1 (s'), 159.2 (s'), 168.8 (s'), 172.90 (s'), 172.94 (s'); ^{19}F NMR (CD_3OD , 376.5 MHz) an old sample that had been kept for 24 h under oil pump vacuum showed only a weak ^{19}F signal at δ -76.1 ; exact mass m/z calcd for disulfide $\text{C}_{56}\text{H}_{65}\text{N}_6\text{O}_8\text{S}_2$ 1013.4305 ($M + H$), found 1013.4301; exact mass m/z calcd for thiol $\text{C}_{28}\text{H}_{33}\text{N}_3\text{NaO}_4\text{S}$ 530.2089 ($M + \text{Na}$), found 530.2082.

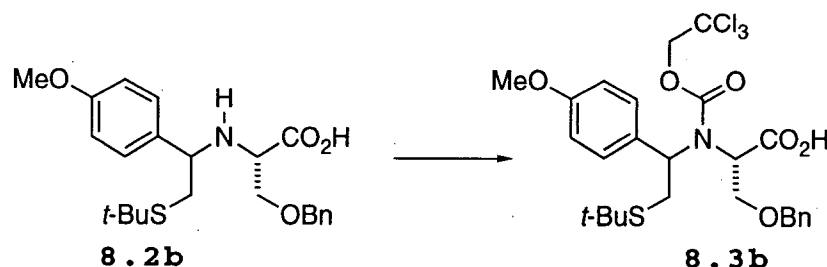
(2*S*)-3-Benzoyloxy-2-[2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethylaminol]propionic Acid (8.2b).



$\text{Me}_3\text{SiOSO}_2\text{CF}_3$ (413 μL , 2.28 mmol) was added dropwise to a stirred and cooled (0°C) solution of ester **8.1b** (539 mg, 1.14 mmol) in dry CH_2Cl_2 (8.5 mL). Stirring was continued for 6 h without recharging the cold bath and the mixture was applied directly to a silica gel column (2 x 15 cm). Flash chromatography, using 4:100 $\text{MeOH}-\text{CH}_2\text{Cl}_2$, gave **8.2b** (403 mg, 84%)

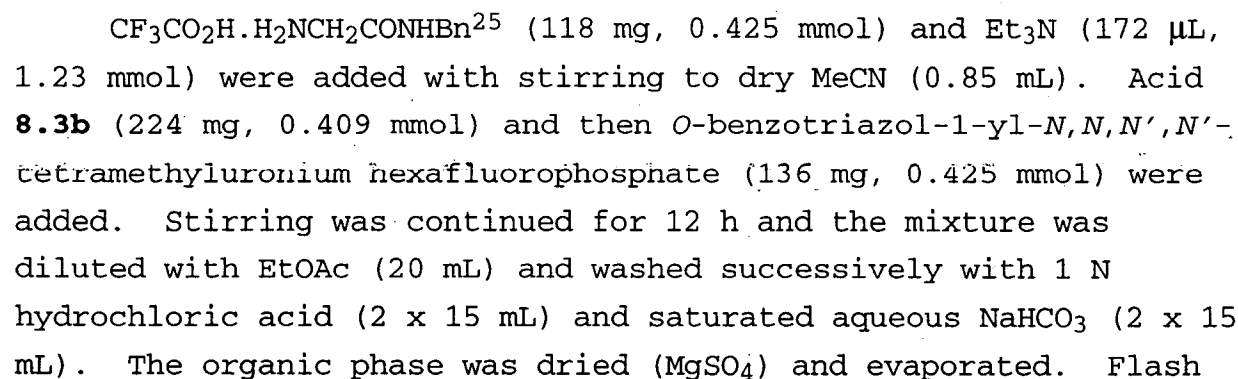
as a pale brown resinous solid: $[\alpha]^{20}_D +3.1^\circ$ (c 1.0, MeOH); FTIR (MeOH cast) 3300-2500, 1640 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 1.23 (s, 9 H), 3.00-3.05 (m, 1 H), 3.16-3.21 (m, 1 H), 3.49-3.50 (m, 1 H), 3.72 (s, 3 H), 3.81-3.90 (m, 2 H), 4.15-4.18 (m, 1 H), 4.47 (ABq, $\Delta\nu_{AB} = 80.5$ Hz, $J_{AB} = 11.7$ Hz, 2 H), 6.80-6.82 (m, 2 H), 7.20-7.29 (m, 7 H), 7.40-8.00 (br s, 2 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 30.8 (q'), 32.9 (s'), 43.4 (t'), 55.2 (q'), 58.9 (d'), 61.9 (d'), 67.1 (t'), 73.5 (t'), 114.6 (d'), 126.4 (s'), 128.0 (d'), 128.1 (d'), 128.4 (d'), 129.5 (d'), 137.2 (s'), 160.3 (s'), 169.9 (s'); exact mass m/z calcd for $\text{C}_{23}\text{H}_{32}\text{NO}_4\text{S}$ (M + H) 418.2047, found 418.2043.

(2S)-3-Benzoyloxy-2-[[2-tert-butylsulfanyl-1-(4-methoxyphenyl)ethyl](2,2,2-trichloroethoxycarbonyl)-amino]propionic Acid (8.3b).



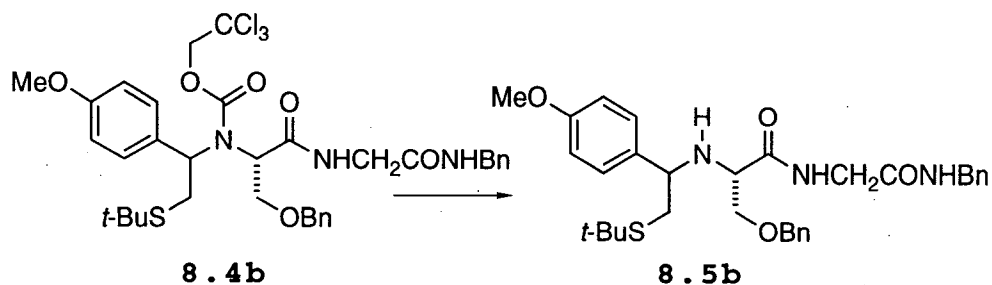
A solution of $\text{Cl}_3\text{CCH}_2\text{OCOCl}$ (300 μL , 2.17 mmol) in dioxane (1 mL) and 0.5 N NaOH (0.56 mL) were added simultaneously by syringe pump over 4.5 h to a stirred and cooled (0 $^\circ\text{C}$) solution of **8.2b** (403 mg, 1.08 mmol) in 1 N NaOH (1.30 mL). When addition was complete the cold bath was removed and stirring was continued for 14 h. The mixture was diluted with water (5 mL), adjusted to pH 3-4 with 1 N hydrochloric acid, and extracted with Et_2O (2 x 15 mL). The combined extracts were dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 8:100 MeOH- CH_2Cl_2 , gave **8.3b** (314 mg, 52%) as a pale yellow foam: $[\alpha]^{20}_D -12.1^\circ$ (c 1.0, CHCl_3); FTIR (CHCl_3 cast) 1715 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) (mixture of rotamers) δ 1.21 (s, 1.26 H), 1.28 (s, 1.46 H), 1.30 (s, 2.30 H), 1.33 (s, 4.0 H), 2.98-3.26 (m, 2

[(1*S*)-1-[(Benzylcarbamoylmethyl)carbamoyl]-2-benzyloxyethyl][2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethyl]carbamic Acid 2,2,2-Trichloroethyl Ester (8.4b).



chromatography of the residue over silica gel (2 x 15 cm), using 1:25 MeOH-CH₂Cl₂, gave **8.4b** (175 mg, 61%) as a white solid: $[\alpha]^{20}_D = -15.1^\circ$ (c 1, CHCl₃); mp 46-51 °C; FTIR (CDCl₃ cast) 3350 (br), 1669, 1611 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) (mixture of rotamers) δ 1.17-1.48 (m, 9 H), 1.73 (s, 0.30 H), 2.48 (dd, $J = 9.8, 5.9$ Hz, 0.37 H), 2.91-3.23 (m, 2 H), 3.65-3.87 (m containing singlet at δ 3.78, 5 H in all), 3.87-4.60 (m, 7 H), 5.42-5.50 (m, 1 H), 6.27 (br s, 0.17 H), 6.65 (br s, 0.20 H), 6.66 (br s, 0.11 H), 6.78-6.90 (m, 2 H), 7.00-7.07 (m, 2 H), 7.17-7.35 (m, 10 H), 7.64 (t, $J = 5.9$ Hz, 0.49 H), 7.79 (br s, 0.17 H); ¹³C NMR (CDCl₃, 100 MHz) (mixture of rotamers) δ 28.9 (t'), 29.6 (t'), 29.8 (t'), 30.3 (q'), 30.8 (q'), 30.9 (q'), 42.9 (t'), 43.2 (s'), 43.4 (t'), 43.6 (t'), 55.2 (q'), 56.3 (d'), 57.8 (d'), 59.7 (d'), 60.9 (d'), 67.8 (t'), 69.8 (t'), 72.9 (t'), 73.5 (t'), 74.9 (t'), 75.2 (t'), 95.1 (s'), 114.1 (d'), 114.4 (d'), 127.2 (d'), 127.3 (d'), 127.4 (d'), 127.6 (d'), 128.0 (d'), 128.1 (d'), 128.3 (d'), 128.4 (d'), 128.5 (s'), 128.7 (d'), 129.6 (d'), 129.7 (d'), 129.8 (d'), 136.7 (s'), 138.2 (s'), 153.7 (s'), 159.7 (s'), 168.7 (s'), 170.3 (s'); exact mass m/z calcd for C₃₅H₄₂Cl₃N₃NaO₆S (M + Na) 760.1752, found 760.1753.

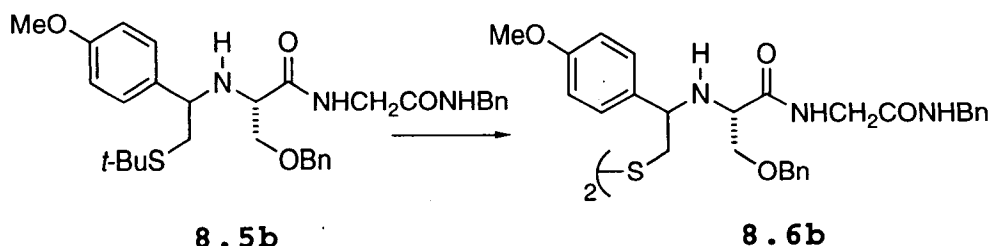
(2*S*)-*N*-(Benzylcarbamoylmethyl)-3-benzyloxy-2-[2-*tert*-butylsulfanyl-1-(4-methoxyphenyl)ethylamino]propionamide (8.5b).



Cd powder (787 mg, 7.00 mmol) was added in one portion to a stirred solution of **8.4b** (185 mg, 0.250 mmol) in 1:1 DMF-AcOH (5.4 mL). Stirring was continued for 4 h at room temperature, and the mixture was filtered through a Celite pad (2 x 4 cm), using EtOAc (50 mL). The combined filtrates and washings were washed with

saturated aqueous NaHCO₃ (2 x 10 mL), dried (MgSO₄), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:25 MeOH-CH₂Cl₂, gave **8.5b** (129 mg, 91%) as a pale yellow resin: $[\alpha]^{20}_D$ -4.1° (c 1, MeOH); FTIR (CDCl₃ cast) 3305, 1659 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) (mixture of rotamers) δ 1.29 (br s, 3 H), 1.31 (s, 6 H), 2.64-2.82 (m, 2 H), 3.04-3.06 (m, 1 H), 3.15-3.18 (m, 0.32 H), 3.34 (dd, *J* = 9.5, 3.8 Hz, 0.27 H), 3.50-3.56 (m, 0.34 H), 3.59-3.65 (m, 1 H), 3.69-3.78 (m containing singlet at δ 3.74, 4 H in all), 3.85-3.92 (m, 1 H), 4.03 (dd, *J* = 16.6, 6.6 Hz, 0.6 H), 4.13-4.21 (m, 1.4 H), 4.27-4.37 (m containing singlet at δ 4.36, 2.6 H in all), 6.60 (t, *J* = 5.2 Hz, 0.8 H), 6.73-6.85 (m, 2.4 H), 7.00-7.32 (m, 12 H), 7.99 (br s, 0.1 H), 8.10 (t, *J* = 5.9 Hz, 0.7 H), 8.44 (t, *J* = 6.3 Hz, 0.3 H) (one proton not observed in this spectrum); ¹³C NMR (CDCl₃, 100 MHz) (mixture of rotamers) δ 31.0 (q'), 31.1 (q'), 36.7 (s'), 36.8 (s'), 42.70 (t'), 42.75 (t'), 43.0 (t'), 43.1 (t'), 43.32 (t'), 43.34 (t'), 43.4 (t'), 55.2 (q'), 59.6 (d'), 59.7 (d'), 61.16 (d'), 62.2 (d'), 68.8 (d'), 71.1 (d'), 72.7 (d'), 73.3 (d'), 114.08 (d'), 114.16 (d'), 127.2 (d'), 127.3 (d'), 127.4 (d'), 127.5 (d'), 127.57 (d'), 127.64 (d'), 127.65 (d'), 127.70 (d'), 127.75 (d'), 127.8 (d'), 128.2 (d'), 128.40 (d'), 128.46 (d'), 128.51 (d'), 128.52 (d'), 128.9 (d'), 133.9 (s'), 134.0 (s'), 137.4 (s'), 137.6 (s'), 138.0 (s'), 138.1 (s'), 159.1 (s'), 159.3 (s'), 168.9 (s'), 169.1 (s'), 173.1 (s'), 173.3 (s'); exact mass *m/z* calcd for C₃₂H₄₂N₃O₄S 564.2891 (*M* + *H*), found 564.2893.

(2*S*)-*N*-(Benzylcarbamoylmethyl)-2-[2-[2-[(1*S*)-1-[(benzylcarbamoylmethyl)carbamoyl]-2-benzyloxyethyl-amino]-2-(4-methoxyphenyl)ethyl]disulfanyl]-1-(4-methoxyphenyl)ethylamino]-3-benzyloxypropionamide (and corresponding thiol) (8.6b).

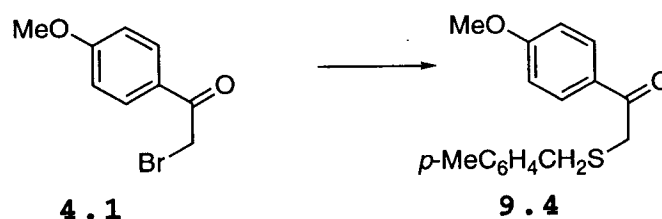


In this experiment the initial thiol product was not protected from air.

$\text{CF}_3\text{CO}_2\text{H}$ (0.5 mL) was added to thioether **8.5b** (95.0 mg, 0.168 mmol) contained in a flask immersed in an ice-bath. The mixture was stirred and PhOMe (32 μL), followed by $\text{Hg}(\text{OAc})_2$ (56.0 mg, 0.177 mmol) were added. Stirring was continued for 25 min and the solvent was evaporated. The residue was dissolved in MeCN (15 mL) and H_2S gas was bubbled through the solution for 2 min. The resulting black suspension was filtered through a tightly packed Celite column (2 x 4 cm) and the solid was washed with several portions of MeCN. Evaporation of the combined filtrate and washings, and flash chromatography of the residue over silica gel (2 x 18 cm), using 4:100 MeOH- CH_2Cl_2 , gave **8.6b** and the corresponding thiol (41.4 mg, 48%) as a pale brown oil: $[\alpha]^{20}_{\text{D}} +4.7^\circ$ (c 1.0, CHCl_3); FTIR (CH_2Cl_2 cast) 3306, 1657 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) (mixture of disulfide and free thiol in a ratio of 3.1:1) δ 1.11-1.33 (m, 1 H), 1.47 (t, $J = 8.3$ Hz, 0.26 H), 2.54-2.82 (m, 2.47 H), 3.07 (t, $J = 3.5$ Hz, 0.78 H), 3.19 (dd, $J = 6.0$, 4.1 Hz, 0.17 H), 4.39 (dd, $J = 9.5$, 4.1 Hz, 0.21 H), 3.53-3.63 (m, 1.74 H), 3.71-3.74 (m containing a singlet at δ 3.74, 4.11 H in all), 3.97-4.04 (m, 1.15 H), 4.16-4.41 (m, 3.54 H), 6.62 (t, $J = 5.7$ Hz, 0.75 H), 6.72-6.84 (m, 2 H), 7.00-7.04 (m, 0.43 H), 7.11-7.35 (m, 9.7 H), 8.04 (t, $J = 5.8$ Hz, 0.69 H), 8.17 (t, $J = 5.9$ Hz, 0.22 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 32.2 (t'), 43.1 (t'), 43.2 (t'), 43.3 (t'), 43.4 (t'), 55.2 (d'), 55.3 (q'), 59.4 (d'), 59.8 (q'), 63.5 (d'), 63.7 (d'), 68.6 (t'), 70.9 (t'), 72.8 (t'), 73.3 (t'), 73.4 (t'), 114.0 (d'), 114.1 (d'), 114.2 (d'), 114.3 (d'), 127.3 (d'), 127.4 (d'), 127.5 (d'), 127.6 (d'), 127.7 (d'), 127.8 (d'), 127.88 (d'), 127.94 (d'), 128.4 (d'), 128.45 (d'), 128.57

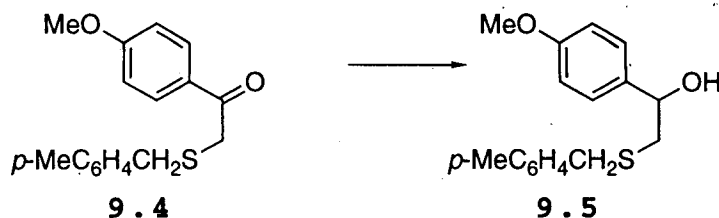
(d'), 128.61 (d'), 128.7 (d'), 132.8 (s'), 133.0 (s'), 137.4 (s'), 137.5 (s'), 138.0 (s'), 159.2 (s'), 159.4 (s'), 168.8 (s'), 172.9 (s'), 173.0 (s'); ^{19}F NMR (CD_3OD , 376.5 MHz) an old sample that had been kept for 24 h under oil pump vacuum showed only a weak ^{19}F signal at δ -76.1; exact mass m/z calcd for disulfide $\text{C}_{56}\text{H}_{65}\text{N}_6\text{O}_8\text{S}_2$ 1013.4305 ($M + H$), found 1013.4301; exact mass m/z calcd for thiol $\text{C}_{28}\text{H}_{33}\text{N}_3\text{NaO}_4\text{S}$ 530.2089 ($M + H$), found 530.2085.

1-(4-Methoxyphenyl)-2-(4-methylbenzylsulfanyl)-ethanone (9.4).⁶



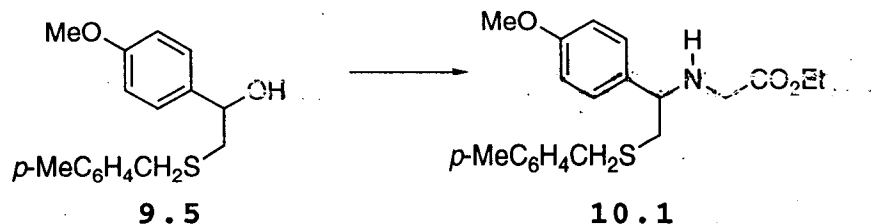
BuLi (2.5 M in hexanes, 7.77 mL, 19.4 mmol) was added in one portion to a degassed (by passage of N_2), stirred and cooled ($0\text{ }^\circ\text{C}$) solution of thioacetic acid *S*-(4-methylphenyl)methyl ester (**9.2**) (3.46 g, 19.2 mmol) in dry THF (60 mL). Stirring was continued for 25 min at $0\text{ }^\circ\text{C}$, and freshly prepared bromide **4.1** (4.40 g, 19.2 mmol) was then added in one portion. The cold bath was removed and the stirring was continued for 13 h. The mixture was diluted with Et_2O (300 mL), washed with water (3 x 100 mL), dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:7 EtOAc-hexanes, gave **9.4** (3.44 g, 62%) as a white solid, which could not be freed of impurities by chromatography. The ^1H NMR spectrum showed the presence of the disulfide $(4\text{-MeC}_6\text{H}_4\text{CH}_2\text{S})_2$. No other data were obtained as the desired product could not be freed of impurities. After reduction of the carbonyl (see formation of **9.5**) a pure product was obtained.

1-(4-Methoxyphenyl)-2-(4-methylbenzylsulfanyl)ethanol (9.5).



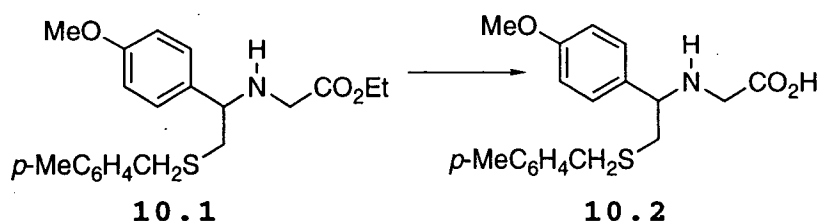
NaBH₄ (142 mg, 3.57 mmol) was added in three equal portions over 45 min to a stirred and cooled (0 °C) solution of **9.4** (341 mg, 1.19 mmol) in 1:1 MeOH-EtOAc (12 mL). After the addition the mixture was stirred at 0 °C for 0.5 h and the solvent was then evaporated. The residue was dissolved in 1:1 water-EtOAc (40 mL), the solution was stirred for 1 h and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic phase and extracts were dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:6 EtOAc-hexanes, gave **9.5** (235 mg, 68%) as a white solid: FTIR (CDCl₃ cast) 3439 (br) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 2.31 (s, 3 H), 2.62 (dd, *J*_{AB} = 13.9 Hz, *J*_{AX} = 9.2 Hz, 1 H), 2.73 (dd, *J*_{AB} = 13.8 Hz, *J*_{BX} = 3.8 Hz, 1 H), 2.76 (br s, 1 H), 3.66 (s, 2 H), 3.76 (s, 3 H), 4.59 (dd, *J*_{AX} = 9.2 Hz, *J*_{BX} = 2.5 Hz, 1 H), 6.82–6.84 (m, 2 H), 7.08–7.09 (m, 2 H), 7.16–7.21 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ 21.1 (q'), 35.9 (t'), 40.9 (t'), 55.3 (q'), 71.4 (d'), 113.8 (d'), 126.9 (d'), 128.7 (d'), 129.2 (d'), 134.6 (s'), 134.7 (s'), 134.8 (s'), 159.1 (s'); exact mass *m/z* calcd for C₁₇H₂₀O₂S 288.1184, found 288.1182.

**[1-(4-Methoxyphenyl)-2-(4-methylbenzylsulfanyl)ethyl-
amino]acetic Acid Ethyl Ester (10.1).**



Me₃SiBr (99 μ L, 0.74 mmol) was injected in one portion to a stirred and cooled (0 $^{\circ}$ C) solution of alcohol **9.5** (204 mg, 0.710 mmol) in dry CH₂Cl₂ (2 mL). Stirring was continued at 0 $^{\circ}$ C for 0.5 h and neat, freshly distilled (distilled under water pump vacuum) H₂NCH₂CO₂Et (146 mg, 1.42 mmol) was added in one portion. The cold bath was removed and stirring was continued for 3 h. The mixture was adsorbed onto silica gel (2 g) from CH₂Cl₂. The solid was applied to the top of a column of silica gel (1.5 x 15 cm), and flash chromatography, using 1:6 EtOAc-hexanes, gave **10.1** (224 mg, 84%) as a colorless oil: FTIR (CHCl₃ cast) 3310 (br), 1735 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.23 (t, *J* = 7.1 Hz, 3 H), 2.30 (s, 3 H), 2.54 (dd, *J*_{AB} = 13.6 Hz, *J*_{AX} = 9.2 Hz, 1 H), 2.56–2.60 (br s, 1 H), 2.65 (dd, *J*_{AB} = 13.6 Hz, *J*_{BX} = 4.6 Hz, 1 H), 3.18 (ABq, $\Delta\nu_{AB}$ = 52.9, *J*_{AB} = 17.5 Hz, 2 H), 3.63–3.73 (m, 3 H), 3.76 (s, 3 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 6.80–6.85 (m, 2 H), 7.07–7.10 (m, 2 H), 7.15–7.20 (m, 4 H); ¹³C NMR (CDCl₃, 125 MHz) δ 14.3 (q'), 21.1 (q'), 35.5 (t'), 39.4 (t'), 48.4 (t'), 55.2 (q'), 59.7 (d'), 60.5 (t'), 113.8 (d'), 128.2 (d'), 128.7 (d'), 129.0 (d'), 133.8 (s'), 134.9 (s'), 136.4 (s'), 158.9 (s'), 172.2 (s'); exact mass *m/z* calcd for C₂₁H₂₇NO₃S 373.1712, found 373.1704.

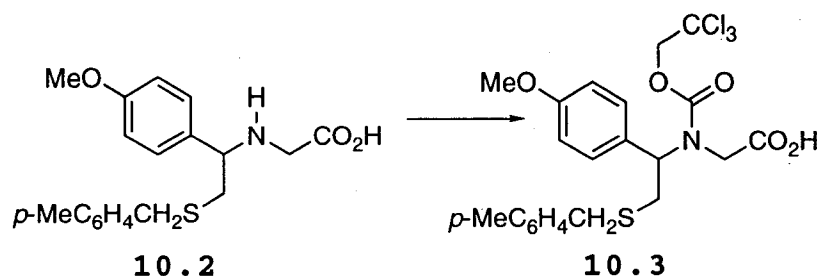
[1-(4-Methoxyphenyl)-2-(4-methylbenzylsulfanyl)ethyl-aminol]acetic Acid (10.2**).**



Aqueous NaOH (1N, 1.80 mL) was added to a stirred solution of ester **10.1** (224 mg, 0.880 mmol) in 1:1 water-dioxane (16 mL). Stirring was continued for 4 h, the mixture was acidified with 1 N hydrochloric acid, the solvent was evaporated and the residue was mixed with MeOH (5 mL), and adsorbed onto silica gel (3 g). The solid was applied to the top of a column of silica gel (1.5 x 15

cm), and flash chromatography, using 1:2:25 AcOH-MeOH-CH₂Cl₂, gave **10.2** (277 mg, 91%) as white solid: mp 165-169 °C; FTIR (microscope) 3600-2100, 1610 cm⁻¹; ¹H NMR (CD₃CO₂D, 400 MHz) δ 1.53 (s, 1 H), 2.28 (s, 3 H), 2.97-3.02 (m, 1 H), 3.18-3.24 (m, 1 H), 3.63 (br s, 2 H), 3.68 (s, 2 H), 3.79 (s, 3 H), 4.36-4.40 (m, 1 H), 6.97 (d, *J* = 8.1 Hz, 2 H), 7.13 (ABq, Δ*v*_{AB} = 32.7 Hz, *J*_{AB} = 7.8 Hz, 4 H), 7.40 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR (CD₃CO₂D, 100 MHz) δ 21.2 (q'), 34.8 (t'), 36.3 (t'), 48.0 (t'), 55.8 (q'), 62.5 (d'), 115.7 (d'), 125.7 (s'), 130.0 (d'), 130.3 (d'), 131.1 (d'), 135.5 (s'), 138.1 (s'), 162.0 (s') (two carbons not observed in this spectrum); exact mass *m/z* calcd for C₁₉H₂₃NNaO₃S 368.1296 (*M* + Na), found 368.1298. We did not establish if the compound is the HCl salt or the zwitterion.

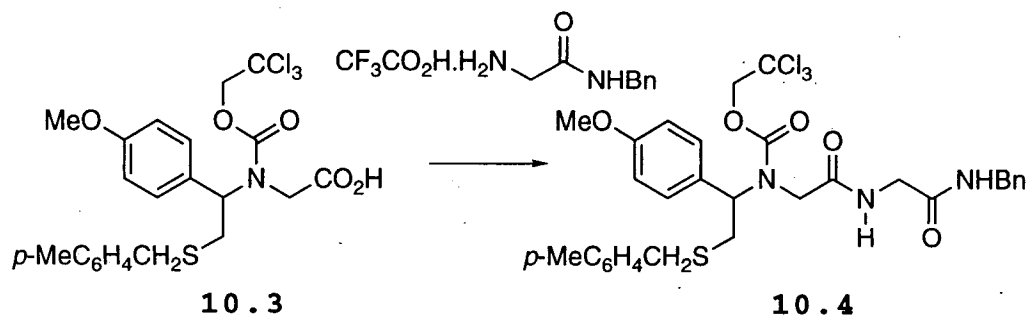
[[1-(4-Methoxyphenyl)-2-(4-methylbenzylsulfanyl)-ethyl](2,2,2-trichloroethoxycarbonyl)amino]acetic Acid (10.3).



Neat Cl₃CCH₂OCOC1 (220 μL, 1.61 mmol) and 1 N NaOH (210 μL) were added simultaneously by syringe over 4.5 h to a stirred and cooled (0 °C) suspension of **10.2** (277 mg, 0.805 mmol) in 1 N NaOH (0.97 mL) and dioxane (1 mL). When addition was complete the cold bath was removed and stirring was continued for 11 h, by which time all **10.2** had reacted. The acidic mixture was extracted with Et₂O and the combined extracts were dried (MgSO₄) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 4:100 MeOH-CH₂Cl₂, gave **10.3** (314 mg, 74%) as an oil: FTIR (CDCl₃ cast) 1716, 1611 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.30 (s, 3 H), 2.94-3.02 (m, 2 H), 3.69 (s, 2 H), 3.70-3.73 (m, 2 H), 3.77

(s, 3 H), 4.72-4.95 (m, 2 H), 5.42-5.49 (m, 1 H), 6.82-6.86 (m, 2 H), 7.07-7.10 (m, 2 H), 7.14-7.20 (m, 4 H); ^{13}C NMR (CDCl_3 , 100 MHz) (mixture of rotamers) δ 21.1 (q'), 32.2 (t'), 32.8 (t'), 36.2 (t'), 36.5 (t'), 44.7 (t'), 45.2 (t'), 55.2 (q'), 58.2 (d'), 58.5 (d'), 67.1 (t'), 75.3 (t'), 75.5 (t'), 76.7 (t'), 95.2 (s'), 114.1 (d'), 128.4 (s'), 128.5 (s'), 128.7 (d'), 128.9 (d'), 129.18 (d'), 129.22 (d'), 129.4 (d'), 129.48 (d'), 129.54 (d'), 134.6 (s'), 134.7 (s'), 136.7 (s'), 136.8 (s'), 154.3 (s'), 154.4 (s'), 159.6 (s'), 173.3 (s'), 173.8 (s'); exact mass m/z calcd for $\text{C}_{22}\text{H}_{24}\text{Cl}_3\text{NNaO}_5\text{S}$ 542.0338 (M + Na), found 542.0335.

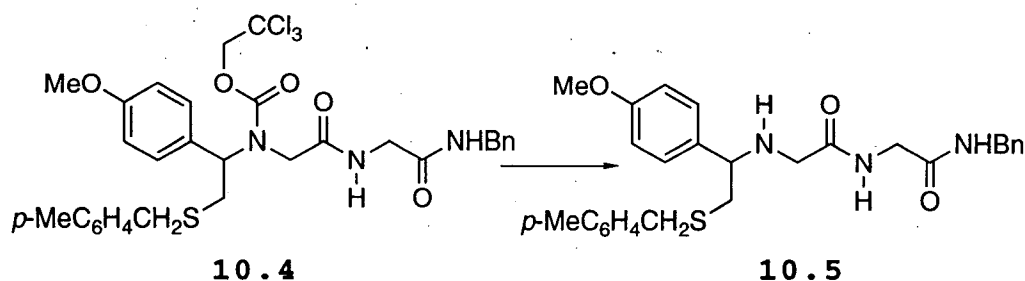
[[(Benzylcarbamoylmethyl)carbamoyl]methyl][1-(4-methoxyphenyl)-2-(4-methylbenzylsulfanyl)ethyl]carbamic Acid 2,2,2-Trichloroethyl Ester (10.4).



i-Pr₂NEt (115 μL , 0.664 mmol) was added to a stirred and cooled (0 $^\circ\text{C}$) mixture of acid **10.3** (314 mg, 0.603 mmol) and $\text{CF}_3\text{CO}_2\text{H} \cdot \text{H}_2\text{NCH}_2\text{CONHBn}$ ²⁵ (184 mg, 0.664 mmol) in dry CH_2Cl_2 (5 mL). After 5 min *N*-(3-dimethylamino)propyl-*N*-ethylcarbodiimide (127 mg, 0.664 mmol) was added, followed by DMAP (3 mg), and the mixture was stirred for 3.5 h without recharging the cold bath. The mixture was diluted with EtOAc (15 mL) and washed successively with 1 N hydrochloric acid (3 mL) and brine (2 x 5 mL), dried (MgSO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 4:100 MeOH- CH_2Cl_2 , gave **10.4** (296 mg, 73%) as a white foam: FTIR (CH_2Cl_2 cast) 3307 (br), 1694, 1660 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 2.29 (s, 3 H), 2.87-3.01 (m, 2 H), 3.47-3.97 (m containing a singlet at δ 3.74, 9 H in all), 4.29-4.45

(m, 2 H), 4.64–4.71 (m, 1 H), 5.38–5.42 (m, 1 H), 6.43 (br s, 1 H), 6.79 (d, $J = 8.0$ Hz, 2 H), 6.92 (br s, 1 H), 7.03–7.28 (m, 12 H); ^{13}C NMR (CDCl_3 , 125 MHz) (mixture of rotamers) δ 21.1 (q'), 32.4 (t'), 32.8 (t'), 35.7 (t'), 35.9 (t'), 43.0 (t'), 43.3 (t'), 43.4 (t'), 43.8 (t'), 47.5 (t'), 47.9 (t'), 55.3 (q'), 57.9 (d'), 58.4 (d'), 75.1 (t'), 75.3 (t'), 94.9 (s'), 95.2 (s'), 114.3 (d'), 127.4 (d'), 127.5 (d'), 127.6 (d'), 127.7 (d'), 127.8 (d'), 128.4 (d'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 128.8 (d'), 129.0 (s'), 129.2 (d'), 129.3 (d'), 129.4 (d'), 133.9 (s'), 134.1 (s'), 136.9 (s'), 137.1 (s'), 137.8 (s'), 137.9 (s'), 154.7 (s'), 155.1 (s'), 159.5 (s'), 168.12 (s'), 168.14 (s'), 168.4 (s'), 168.8 (s'), 169.3 (s'); exact mass m/z calcd for $\text{C}_{31}\text{H}_{34}\text{Cl}_3\text{N}_3\text{NaO}_5\text{S}$ 688.1182 ($M + \text{Na}$), found 688.1183.

***N*-(Benzylcarbamoylmethyl)-2-[1-(4-methoxyphenyl)-2-(4-methylbenzylsulfanyl)ethylamino]acetamide (10.5).**



Cd powder (1.50 g, 13.3 mmol) was added in one portion to a stirred solution of **10.4** (296 mg, 0.444 mmol) in 1:1 DMF-AcOH (9.6 mL). Stirring was continued for 6 h at room temperature, and the mixture was filtered through a Celite pad (2 x 4 cm), using EtOAc (75 mL). The combined filtrates and washings were washed with saturated aqueous NaHCO_3 (2 x 15 mL), dried (MgSO_4), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:100 and then 1:10 $\text{MeOH-CH}_2\text{Cl}_2$, gave **10.5** (204 mg, 93%) as a pale yellow oil: FTIR (CDCl_3 cast) 3297, 1655 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 2.29 (s, 3 H), 2.62 (d, $J = 6.6$ Hz, 2 H), 2.90 (br s, 1 H), 3.04–3.13 (m, 2 H), 3.48 (br t, $J = 6.7$ Hz, 1 H), 3.61–3.75 (m containing a singlet at δ 3.72, 5 H in all), 3.86

(d, $J = 5.0$ Hz, 2 H), 4.36 (d, $J = 5.6$ Hz, 2 H), 6.76-6.81 (m, 3 H), 7.01-7.25 (m, 11 H), 7.73 (br s, 1 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.1 (q'), 36.3 (t'), 38.9 (t'), 43.2 (t'), 43.4 (t'), 49.6 (t'), 55.3 (q'), 60.9 (d'), 114.1 (d'), 127.3 (d'), 127.6 (d'), 128.0 (d'), 128.6 (d'), 128.8 (d'), 129.2 (d'), 133.0 (s'), 134.5 (s'), 136.8 (s'), 137.9 (s'), 159.2 (s'), 168.6 (s'), 172.5 (s'); exact mass m/z calcd for $\text{C}_{28}\text{H}_{33}\text{N}_3\text{NaO}_3\text{S}$ ($M + \text{Na}$) 514.2140, found 514.2144.

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