# ENANTIOSELECTIVE SYNTHESIS OF 1S,3S,5S- and 1R,3S,5R-2-AZABICYCLO[3.3.0]OCTANE-3-CARBOXYLIC ACID STARTING FROM L-SERINE[§]

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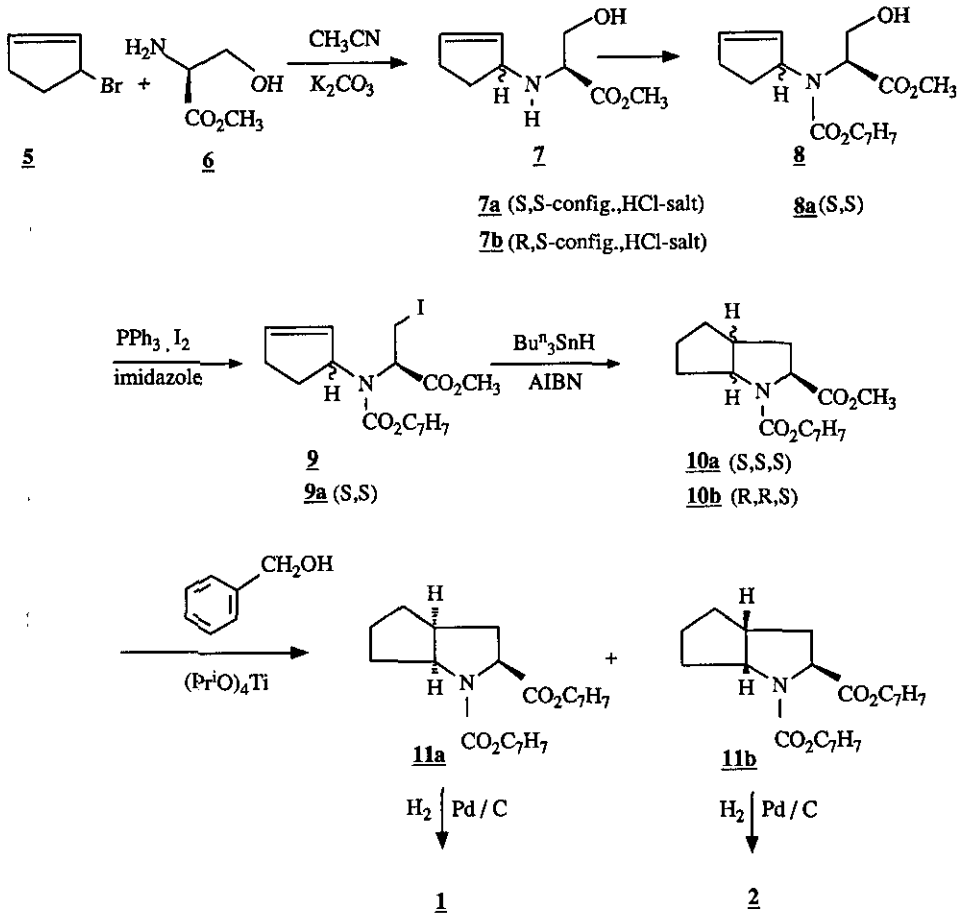
Abstract - (1S,3S,5S)- and (1R,3S,5R)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid have been synthesized by intramolecular radical cyclisation of methyl 2-(S)-[N-benzyloxycarbonyl-N-(2-cyclopenten-1-yl)amino]-3-iodopropionate and subsequent reactions.

(1S,3S,5S)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid 1 and (1R,3S,5R)-2-azabicyclo[3.3.0]octane-3-carboxylic acid 2 are precursors of the highly potent angiotensin converting enzyme inhibitors 3[1,2] (ramiprilat) and 4[2]. In order to prepare these inhibitors for investigating the structure activity relationship in vitro[2a] we had to synthesize 1 and 2 as intermediates. Recently, we reported the synthesis of racemic 1[2,3] and 2[2]. To avoid the resolution of the racemic benzyl ester of 1 or 2 in preparing 3 and 4[2,3] we looked for an enantioselective synthesis. It was reported that carbon radicals derived from the side chain of optically active α-amino acid derivatives react with olefins to give functionalized α-amino acids under retention of configuration at C-2 of the amino acid[4,5]. Consequently, we believed that an intramolecular radical cyclization of an appropriate optically active olefinic α-amino acid derivative should provide 1 and 2 with the correct configuration at C-3 of the bicyclic system.

| $R^1$ | $R^2$ | | |
|---|---|---|---|
| H | H | 1 | 2 |
| H | $COCH(CH_3)-NH-CH(CO_2H)-CH_2-CH_2-C_6H_5$ | 3 | 4 |
| $CH_3$ | $CH_3$ | 13 | |

Treatment of 3-bromocyclopentene 5 with L-serine methyl ester 6 afforded a diasteromeric mixture of the L-serine derivative 7 in 36 % yield, which was acylated with benzyl chloroformate to give 8 in 90 % yield (Scheme I). The compound 8 was treated with iodine, triphenylphosphine and imidazole in benzene[6] to give the iodo compound 9 in 45 % yield. The key compound 9 was subjected to radical cyclization with tri-n-butyltin hydride in benzene in the presence of 2,2'-azoisobutyronitrile (AIBN). A diasteromeric mixture containing 10 a and 10 b was obtained in 88 % yield. To separate the isomers, 10 a and 10 b have been transesterified with benzyl alcohol and titanium tetraisopropoxide[7] to give the benzyl esters 11 a and 11 b in 78 % yield in a ratio of 1.25:1. The diastereomers could be separated easily by column chromatography on silica gel. Upon hydrogenation of 11 a or 11 b with 10 % palladium on carbon in ethanol the desired proline derivatives 1 and 2 were each obtained in 92 % yield.

**Scheme I**



We found that diastereomer 7 a could be separated out from the isomeric mixture 7 by several recrystallisations of the HCl salt in acetonitrile. The extent of separation could be followed by pmr (270 MHz) of the free base in $CD_3OD$ observing the relative intensities of the well separated signals of the olefinic protons tentatively assigned to C-2 (5.70 ppm and 5.76 ppm). The compound 7 a was subjected to the same reaction sequence described above to give the pure isomer 10 a via 8 a and 9 a. Configuration of 1 and 2 has been determined by comparison of the pmr spectra of authentic samples of 1[3] and 2[8]. The optical purity of 1 and 2 was > 99 %. The determination of the optical purity of 1 was possible by pmr measurements of the N-methyl methyl ester derivative 13 in the presence of the shift reagent S-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol and by quantitative evaluation of the enantiomers of 1 on HPTLC pre-coated plates ®CHIR with concentrating zones (E. Merck, Darmstadt). The optical purity of 2 was determined using the method of H. Frank et al.[10]

## EXPERIMENTAL

Melting points were determined by the capillary method and are uncorrected. Infra-red (ir) spectra were determined with a Perkin Elmer 683 spectrophotometer and pmr spectra were recorded with a Bruker AM 270 spectrometer operating at 270 MHz and using tetramethylsilane (≈ 0.0 ppm) as internal reference. Mass spectra were obtained with a Kratos MS 80 spectrometer and the optical rotation values with a Perkin Elmer 141 polarimeter. The gas chromatograph Varian 3700 was used. The quantitative evaluation of the high performance thin layer chromatography (HPTLC) was performed with a TLC/HPTLC scanner (Fa. CAMAG, Muttenz, Switzerland). Column chromatography was performed on Merck silica gel ®Si 60 $F_{254}$.

### N-(2-(1R,S)-Cyclopenten-1-yl)-L-serine methyl ester 7.

Solid $K_2CO_3$ (135 g, 0.977 mol) was added to L-serine methyl ester hydrochloride (34.2 g, 0.29 mmol) in dry acetonitrile (200 ml). 3-Bromocyclopentene [ prepared from cyclopentene (51.6 g, 0.757 mol) and N-bromosuccinimide (43.5 g, 0.244 mol) in $CCl_4$ (139 ml)[11]] was added to this mixture while cooling with ice. The mixture was allowed to reach room temperature and was stirred at this temperature for 2 h. After filtration and concentration of the solution the residue was chromatographed on silica gel using $CH_2Cl_2$ as eluant to give 7 (14.8 g, 36 %) as colourless oil. Pmr ($CD_3OD$) δ 1.57 (1H,m), 2.06-2.53 (3H,m), 3.48 (1H,t,J=6Hz), 3.70-4.05 (6H,m), 5.70 (0.5H,m), 5.76 (0.5H,m), 5.90 (1H,m). Anal. Calcd for $C_9H_{15}NO_3$: C 58.36; H 8.16; N 7.56. Found: C 58.10; H 8.12; N 7.32.

N-(2-(1S)-Cyclopenten-1-yl)-L-serine methyl ester hydrochloride **7 a.**

The compound 7 (5 g, 27.0 mmol) was treated with ethanolic HCl (27.0 ml, 1N) in ethyl acetate (50 ml) to give the diastereomeric mixture of hydrochlorides (5.11 g, 87 %), mp 150-160°C.

A sample was recrystallized several times from dry acetonitrile to yield 7 a, mp 179-180°C, $[\alpha]_D^{22}$ -67.5° (c = 0.85 in $CH_3OH$); $[\alpha]_D^{22}$ of the free base -111.7° (c = 0.865 in $CH_3OH$). 7 a contained 6 % of the (R,S)-diastereomer. Pmr of the free base ($CD_3OD$) δ 1.55 (1H,m), 2.10-2.34 (2H,m), 2.35-2.53 (1H,m), 3.47 (1H,t,J=6Hz), 3.72 (5H,m), 3.87 (1H,m), 5.70 (0.06H,m), 5.76 (0.94H,m), 5.90 (1H,m). Ms (CI), m/z 186 $(M+H)^+$. Anal. Calcd for $C_9H_{16}ClNO_3$: C 48.76; H 7.28; N 6.32; Cl 15.99. Found: C 48.52; H 7.30; N 6.15; Cl 15.85.

N-(2-(1R)-Cyclopenten-1-yl)-L-serine methyl ester hydrochloride **7 b.**

Crystals obtained from the mother liquors of 7 a were recrystallized several times from ethyl acetate and $CH_2Cl_2$ to yield 7 b, mp 152-154°C, containing 13 % of the (S,S)-diastereomer. $[\alpha]_D^{22}$ +82.8° (c = 0.61 in $CH_3OH$), $[\alpha]_D^{22}$ of the free base +38.3° (c = 0.88 in $CH_3OH$). Pmr of the free base ($CDCl_3$) δ 1.56 (1H,m), 2.05-2.33 (2H,m), 2.38-2.53 (1H,m), 3.47 (1H,t,J=6Hz), 3.72 (5H,m), 3.82 (1H,m), 5.70 (0.87H,m), 5.76 (0.13H,m). MS (CI), m/z 186 $(M+H)^+$. Anal. Calcd for $C_9H_{16}ClNO_3$: C 48.76; H 7.28; N 6.32; Cl 15.99. Found: C 48.66; H 7.14; N 6.10; Cl 15.80.

N-Benzyloxycarbonyl-N-(2-(1R,S)-cyclopenten-1-yl)-L-serine methyl ester **8.**

The compound 7 (0.5 g, 2.7 mmol) was suspended in saturated aqueous $NaHCO_3$ solution (7.5 ml), benzyl chloroformate (0.47 g, 2.77 mmol) was added with ice cooling and the mixture stirred for 80 min. After usual work up and column chromatography of the residue on silica gel using $CH_2Cl_2$/ethyl acetate (95:5) as eluant 8 (0.8 g, 90 %) was obtained as colourless oil. Pmr ($CDCl_3$) δ 1.50-1.80 (1H,m), 2.20-2.70 (3H,m), 3.30-3.90 (6H,m), 4.25 (1H,m), 4.95-5.52 (3H,m), 5.60-5.73 (1H,m), 6.00 (1H,m), 7.37 (5H,br s). Ir ($CHCl_3$) 3470 (OH), 1740, 1700 (C=O), 1620, 1580 (C=C) $cm^{-1}$. Ms (EI), m/z 319 ($M^+$). Anal. Calcd for $C_{17}H_{21}NO_5$: C 63.93; H 6.63; N 4.39. Found: C 63.81; H 6.50; N 4.38.

N-Benzyloxycarbonyl-N-(2-(1S)-cyclopenten-1-yl)-L-serine methyl ester **8 a.**

The compound 7 a (1.29 g, 6.97 mmol, containing 6 % of the (R,S)-diastereomer) was treated as described above to give 8 a (2.2 g, 99.6 %) as colourless oil. $[\alpha]_D^{22}$ -112.6° (c = 1.45 in $CH_3OH$). Pmr ($CDCl_3$) δ 1.50-1.80 (1H,m), 2.20-2.70 (3H,m), 3.30-3.90 (6H,m), 4.25 (1H,m), 4.95-5.52 (3H,m), 5.62 (0.06H,m), 5.69 (0.94H,m), 6.00 (1H,m), 7.73 (5H,br s). Ir ($CHCl_3$) 3480 (OH), 1740, 1700 (C=O), 1620, 1590 (C=C) $cm^{-1}$. Ms (FAB), m/z 320 $(M+H)^+$. Anal. Calcd for $C_{17}H_{21}NO_5$: C 63.93;

H 6.63; N 4.39. Found: C 63.74; H 6.65; N 4.20.

Methyl 2-(S)-[N-benzyloxycarbonyl-N-(2-(1R,S)-cyclopenten-1-yl)amino]-3-iodopropionate **9.**

Triphenylphosphine (5.55 g, 21.16 mmol) and imidazole (1.44 g, 21.16 mmol) was dissolved under nitrogen in dry benzene (95 ml). Iodine (4.62 g, 18.2 mmol) in dry benzene (40 ml) was added dropwise to the solution at room temperature. After a yellow precipitate had separated the mixture was stirred for 10 min. Then, at room temperature and protecting from light, 8 (4.3 g, 13.48 mmol) in dry benzene (27 ml) was added dropwise. The mixture was stirred at room temperature for 5 h. It was then poured onto ether/water. The ethereal solution was washed with water, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel using cyclohexane/ethyl acetate (9:1) as eluant to obtain 9 (2.62 g, 45.3 %) as colourless oil. Pmr ($CDCl_3$) $\delta$ 1.70-2.60 (4H,m), 3.24-4.10 (6H,m), 5.00-5.37 (3H,m), 5.70 (0.5H,m), 5.84 (0.5H,m), 6.05 (1H,m), 7.33 (5H,br s). Ir ($CHCl_3$) 1750, 1705 (C=O), 1615, 1590 (C=C) $cm^{-1}$. Ms (FAB), m/z 429 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}INO_4$: C 47.56; H 4.70; N 3.26. Found: C 47.60; H 4.65; N 3.12.

Methyl 2-(S)-[N-benzyloxycarbonyl-N-(2-(1S)-cyclopenten-1-yl)amino]-3-iodopropionate **9 a.**

The compound 8 a (2.2 g, 6.84 mmol, containing 6 % of the (R,S)-diastereomer) was treated as described above to give 9 a (1.54 g, 52.5 %) as colourless oil. $[\alpha]_D^{22}$ -96.7° (c = 0.95 in $CH_3OH$). Pmr ($CDCl_3$) $\delta$ 1.92 (1H,m), 2.20-2.60 (3H,m), 3.23-4.10 (6H,m), 5.00-5.37 (3H,m), 5.70 (0.94H,m), 5.84 (0.06H,m), 6.04 (1H,m), 7.33 (5H,br s). Ir ($CHCl_3$) 1750, 1705 (C=O), 1615, 1590 (C=C) $cm^{-1}$. Ms (FAB), m/z 429 $(M+H)^+$. Anal. Calcd for $C_{17}H_{20}INO_4$: C 47.56; H 4.70; N 3.26. Found: C 47.40; H 4.55; N 4.50.

Mixture of methyl N-benzyloxycarbonyl-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylate **10 a** and methyl N-benzyloxycarbonyl-(1R,3S,5R)-2-azabicyclo[3.3.0]octane-3-carboxylate **10 b.**

The compound 9 (3.224 g, 7.56 mmol), 2,2'-azoisobutyronitrile (AIBN, 0.521 g) and tri-n-butyltin hydride (2.310 g, 7.94 mmol) were dissolved in dry benzene (260 ml) and refluxed under nitrogen for 4 h. After evaporation in vacuo the residue was taken up in ether (100 ml). The ethereal solution was stirred with aqueous KF solution (10 %, 100 ml) for 30 min. After filtration the solution was dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel using cyclohexane/ethyl acetate (4:1) as eluant to give 10 a and 10 b (2.1 g, 88 %) as a 1.3:1 mixture of diastereomers (determined by HPLC: Partisil column, mobil phase cyclohexane/DME 50:1, 220 nm). Pmr ($CDCl_3$) $\delta$ 1.22-2.03 (7H,m), 2.10 (0.5H,m), 2.42 (0.5H,m), 2.72 (1H,m), 3.50-3.80 (3H,m), 4.30 (1H,m), 4.44 (1H,m), 4.96-5.24 (2H,m), 7.27-7.40 (5H,m). Ir ($CHCl_3$)

1750, 1710 (C=O), 1590 (C=C) $cm^{-1}$. Ms (EI), m/z 303 ($M^+$). Anal. Calcd for $C_{17}H_{21}NO_4$: C 67.30; H 6.98; N 4.62. Found: C 67.01; H 7.02; N 4.55.

Methyl N-benzyloxycarbonyl-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylate **10 a.**

The compound 9 a (1.466 g, 3.42 mmol, containing 6 % of the (R,S)-diastereomer) was treated as described above to give 10 a (0.884 g, 81 %) as colourless oil. $[\alpha]_D^{22}$ +5.7° (c = 1.13 in $CH_3OH$). Pmr ($CDCl_3$) δ 1.23-1.90 (5H,m), 1.97 (2H,m), 2.40 (1H,m), 2.68 (1H,m), 3.53-3.78 (3H,m), 4.28 (1H,m), 4.42 (1H,m), 5.02-5.20 (2H,m), 7.28-7.40 (5H,m). Ir ($CHCl_3$) 1750, 1705 (C=O), 1585 (C=C) $cm^{-1}$. Ms (CI), m/z 304 $(M+H)^+$. Anal. Calcd for $C_{17}H_{21}NO_4$: C 67.30; H 6.98; N 4.62. Found: C 67.24; H 6.80; N 4.60.

Benzyl N-benzyloxycarbonyl-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylate **11 a** and benzyl N-benzyloxycarbonyl-(1R,3S,5R)-2-azabicyclo[3.3.0]octane-3-carboxylate **11 b.**

The mixture of 10 a and 10 b (1 g, 3.3 mmol) was dissolved in benzyl alcohol (10 ml), titanium tetraisopropoxide (0.337 g, 1.19 mmol) was added dropwise, and the mixture was stirred at 90°C for 4 h in vacuo (20 mm Hg). The benzyl alcohol was then removed in vacuo, the residue was taken up in ether and the ethereal solution was washed with aqueous HCl (2N), saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution after the precipitate had been removed by filtration. After drying over sodium sulfate the solution was concentrated in vacuo. The residue was chromatographed on silica gel using cyclohexane/ethyl acetate (9:1) as eluant. The compound 11 b (0.422 g, 34 %) eluted first, followed by the more polar 11 a (0.553 g, 44 %), both are colourless oils.

11 a: $[\alpha]_D^{22}$ -2.8° (c = 1.09 in $CH_3OH$). Pmr ($CDCl_3$) δ 1.30 (1H,m), 1.50 (1H,m), 1.60-2.10 (5H,m), 2.42 (1H,m), 2.68 (1H,m), 4.28 (1H,m), 4.49 (1H,m), 4.95-5.27 (4H,m), 7.32 (10H,m). Ir ($CHCl_3$) 1750, 1705 (C=O) $cm^{-1}$. Ms (EI), m/z 379 ($M^+$). Anal. Calcd for $C_{23}H_{25}NO_4$: C 72.80; H 6.64; N 3.69. Found: C 72.53; H 6.62; N 3.58.

11 b: $[\alpha]_D^{22}$ -101.6° (c = 0.82 in $CH_3OH$). Pmr ($CDCl_3$) δ 1.41-1.95 (7H,m), 2.10 (1H,m), 2.74 (1H,m), 4.34 (1H,m), 4.48 (0.5H,dd,$J_1$=3Hz,$J_2$=9Hz), 4.55 (0.5H,dd,$J_1$=3Hz,$J_2$=9Hz), 4.92-5.23 (4H,m), 7.28 (10H,m). Ir ($CHCl_3$) 1745, 1710 (C=O) $cm^{-1}$. Ms (EI), m/z 379 ($M^+$). Anal. Calcd for $C_{23}H_{25}NO_4$: C 72.80; H 6.64; N 3.69. Found: C 72.60; H 6.50; N 3.58.

When 10 a (0.878 g, 2.89 mmol) was used as starting material, 11 a (0.836 g, 76 %) was obtained. A small amount of 11 b (0.06 g, 5.5 %) was found, resulting from the (R,S)-diastereomer in 9 a (6 %). 11 a and 11 b of this run showed identical pmr-spectra (270 MHz) to those obtained from 10 a and 10 b described above.

(1S,3S,5S)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid **1**.

The compound 11 a (0.5 g, 1.32 mmol) obtained from the mixture of 10 a and 10 b or obtained only from 10 a was dissolved in ethanol (10 ml), Pd/C (10 %, 50 mg) was added and the mixture hydrogenated for 6 h at room temperature. The catalyst was removed by filtration, the solution was concentrated in vacuo and the residue was treated with ethyl acetate to afford 1 (186 mg, 91 %) as colourless crystals, mp 235-238°C. $[\alpha]_D^{22}$ -53.1° (c = 0.52 in $CH_3OH$). Pmr ($D_2O$) δ 1.58 (1H,m), 1.69-1.95 (4H,m), 2.02 (2H,m), 2.62 (1H,m), 3.00 (1H,m), 4.15 (1H,dd,$J_1$=2Hz,$J_2$=8Hz), 4.20 (1H,m). Ir (KBr pellet) 1620, 1580 (C=O) $cm^{-1}$. Ms (CI), m/z 156 $(M+H)^+$. Anal. Calcd for $C_8H_{13}NO_2$: C 61.91; H 8.44; N 9.03. Found: C 61.84; H 8.20; N 8.86. The optical purity was > 99 % determined by quantitative thin layer chromatography (HPTLC pre-coated plates ®CHIR with concentrating zone 2.5 cm (E. Merck, Darmstadt); eluant: ethanol/i-propanol/water 60/10/30 (v/v/v); migration distance: 20 cm; detection: plates were dipped in 0.5 % ninhydrin in ethanol/acetic acid 98/2 followed by heating up to 120°C for 10 min; evaluation with TLC/HPTLC scanner (CAMAG, UV 410 nm)). Using benzyl (1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylate[3] as starting material 1 was obtained with identical pmr spectrum (270 MHz), $[\alpha]_D^{22}$ -52.2° (c = 0.5 in $CH_3OH$), mp 236-238°C.

Methyl N-methyl-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylate **13**.

The compound 1 (0.1 g, 0.65 mmol) was dissolved in methanol (4 ml). To the solution was added at room temperature dropwise an ethereal solution of diazomethane (obtained from N-methyl-N-nitroso-p-toluolsulfonamid (2.14 g, 0.01 mmol) and ethanolic KOH (0.4 g KOH in 10 ml ethanol)) until the solution remained slightly yellow. Nitrogen was bubbled through the solution which was then concentrated in vacuo. The residue was chromatographed on silica gel using cyclohexane/ethyl acetate (4:1) as eluant to obtain 13 (55 mg, 47 %) as colourless oil. $[\alpha]_D^{22}$ -54.6° (c = 1.53 in $CH_3OH$). Pmr ($CDCl_3$, 400 MHz) δ 1.22-1.82 (7H,m), 2.29 (1H,m), 2.35 (3H,s), 2.57 (1H,m), 2.81 (1H,dd,$J_1$=3Hz,$J_2$=6Hz), 2.98 (1H,dd,$J_1$=5Hz,$J_2$=6Hz), 3.74 (3H,s). Ir (neat) 1750, 1730 (C=O) $cm^{-1}$. Ms (CI), m/z 184 $(M+H)^+$. Anal. Calcd for $C_{10}H_{17}NO_2$: C 65.54; H 9.35; N 7.65. Found: C 65.23; H 9.31; N 7.48. The optical purity of 13 was > 99 % determined by 400 MHz-pmr measurement in the presence of S-(+)-1-(9-anthryl)-2.2.2-trifluoroethanol: addition of S-(+)-1-(9-anthryl)-2.2.2-trifluoroethanol (40 mg) to a $CDCl_3$-solution of rac.13 (5 mg in 0.5 ml $CDCl_3$) resulted in a diastereotopic split of the N-$CH_3$ signals (S,S,S-isomer: 2.25 ppm (s); R,R,R-isomer: 2.05 ppm (s)). Racemic 13 was obtained by the following procedure:

Methyl N-methyl-(1SR,3SR,5SR)-2-azabicyclo[3.3.0]octane-3-carboxylate **rac. 13**.

Racemic 1[3] (0.5 g, 3.22 mmol) was suspended in dry DMF (5 ml) and diisopropylethylamine (0.833 g, 6.45 mmol) was added. Methyl iodide (0.915 g, 6.45 mmol) was added dropwise to the suspension at room temperature and stirred for 16 h. The mixture was poured into water and the aqueous solution was extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel to yield rac. 13 (170 mg, 29 %) as colourless oil. Pmr and ms was identical with the spectra of optical pure 13. Anal. Calcd for $C_{10}H_{17}NO_2$: C 65.54; H 9.35; N 7.65. Found: C 65.28; H 9.50; N 7.41.

(1R,3S,5R)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid 2.

The compound 11 b (64 mg, 0.17 mmol) was dissolved in ethanol (10 ml), Pd/C (10 %, 10 mg) was added and the mixture hydrogenated for 1 h at room temperature. The catalyst was removed by filtration, the solution was concentrated in vacuo and the residue was treated with ethyl acetate to give 2 (22 mg, 85 %) as colourless crystals, mp 220°C. The optical purity was > 99 % determined by the method of H. Frank[10]. $[\alpha]_D^{22}$ -47.2° (c = 0.4 in $CH_3OH$). Pmr ($D_2O$) δ 1.50-2.17 (7H,m), 2.33 (1H,m), 2.94 (1H,m), 4.21 (1H,dd,$J_1$=$J_2$=7Hz), 4.31 (1H,ddd,$J_1$=4Hz,$J_2$=$J_3$=7Hz). Ir (KBr pellet) 1620, 1585 (C=O) $cm^{-1}$. Ms (CI), m/z 156 $(M+H)^+$. Anal. Calcd for $C_8H_{13}NO_2$: C 61.91; H 8.44; N 9.03. Found: C 61.63; H 8.51; N 8.74.

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§ Dedicated to Prof. Sir Derek Barton on the occasion of his 70th birthday

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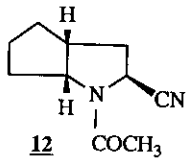
8. Authentic 2 has been prepared by hydrolysis of racemic 12[9] with aqueous HCl (6 N) followed by treatment with ion exchange resin (®Amberlite IRA-93, $OH^-$) to bring the pH to 5, colourless crystals, mp 220°C. Pmr ($D_2O$) δ 1.50-2.17 (7H,m), 2.33 (1H,m), 2.94 (1H,m), 4.21 (1H,dd,$J_1$=$J_2$=7Hz), 4.31 (1H,ddd,$J_1$=4Hz, $J_2$=$J_3$=7Hz). Ir (KBr pellet) 1620, 1585 (C=O) $cm^{-1}$. Ms (CI), m/z 156 $(M+H)^+$. Anal. Calcd for $C_8H_{13}NO_2$: C 61.91; H 8.44; N 9.03. Found: C 61.79; H 8.25; N 8.78.



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# ASYMMETRIC DITHIOACETALS III: THE PREPARATION OF THE ENANTIOMERS OF 3-((((3-(2-(7-CHLOROQUINOLIN-2-YL)-(E)-ETHENYL)PHENYL)-3-DIMETHYLAMINO-3-OXOPROPYL-THIO)METHYL)THIO)PROPIONIC ACID (L-660,711) (MK-571), AN ANTAGONIST OF LEUKOTRIENE $D_4$†

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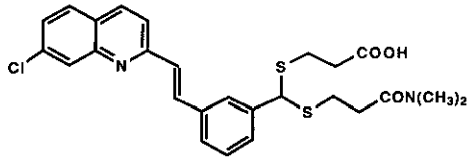
Abstract - The application of a novel method for the preparation of chiral dithioacetals to the synthesis of the enantiomers of L-660,711, an antagonist of leukotriene $D_4$, is described. Reaction of 3-(t-butyldiphenylsilyloxymethyl)-benzaldehyde or isophthalaldehyde with (R)-(-)-α-methoxyphenylthiolacetic acid and N,N-dimethyl-3-mercaptopropionamide provides diastereomeric acylthioalkylthio-acetals (10,11 or 17a,b) which are readily separable and can be subsequently deacylated with sodium methoxide and the resultant thiolate anion alkylated with methyl acrylate to provide enantiomeric dithioacetals (12a,b or 14a,b) which are converted to the enantiomers of L-660,711.

## INTRODUCTION

The leukotrienes $C_4$, $D_4$ and $E_4$ are postulated as important mediators in the ethiology of human asthma. These leukotrienes exert their potent biological effects through interaction with specific cellular receptors and in the human lung they are thought to act on a common receptor on which leukotriene $D_4$ exerts the most potent effects[1]. Over the past several years a number of specific receptor antagonists of leukotriene $D_4$ have been developed and are currently being evaluated as potentially novel therapies for bronchial asthma[2].

We have recently described the discovery and synthesis of a novel, potent, specific and orally active leukotriene $D_4$ antagonist (L-660,711)[3] (1) which contains an unusual asymmetric dithio-




(+) or (-) L-660711 (1)

†Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.

acetal moiety as a key structural feature. Our original synthesis provided the compound as a racemic mixture. It was thus important to prepare significant quantities of the pure enantiomers of 1 in order to fully evaluate the *in vivo* and *in vitro* biological activities of this important new drug. As classical resolution techniques failed to provide these enantiomers we were forced to develop novel synthetic procedures to prepare asymmetric[4] and chiral[5] dithioacetals and the application of this methodology to the preparation of the enantiomers of L-660,711 (1) is the subject of this report.

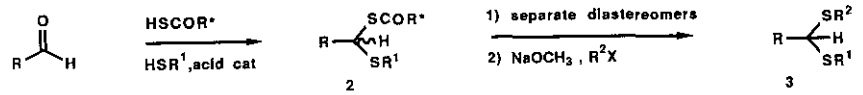
## DISCUSSION

There are very few reports of the preparation of acyclic asymmetric dithioacetals in the literature[6] and we are unaware of any published reports of successful resolution of such a species[7]. However, as 1 contains a carboxylic acid group this functionality could possibly serve to aid in the resolution in racemic 1. Before attempting classical resolution techniques we required a method to assess the chiral purity and hence the success of our attempts. Preparation of several chiral esters (by carbodiimide condensation of 1 with (R)-methyl α-hydroxyphenylacetate, l-borneol, (S)-(+)-2-butanol, (+)-isopinocampheol and l-menthol) or amides (from (-)-α-methylbenzylamine) gave diastereomeric adducts which were not readily resolved by reversed phase hplc and which did not provide any readily resolved signals in the pmr spectra which could serve as a measure of enantiomeric purity. In the end we found that the esters prepared by condensation of 1 and (-)-2,2,2-trifluoro-1-(9-anthryl)-ethanol exhibited resolved signals in the pmr spectra (particularly at 4.97 and 4.98 ppm for the thioacetal methine protons) which could be used to quantitatively assess chiral purity of the enantiomers of 1 with an accuracy >95% e.e.

With this method in hand we sought to resolve 1 via classical techniques (selective crystallization of the (-)-ephedrine, brucine or (-)-cinchonidine salts, chromatographic separation of the diastereomeric esters described above). These efforts were uniformly unsuccessful. With respect to ester formation it appeared that the relative similarity of the two chains and the remoteness of the two chiral centres in such diastereomeric derivatives mitigated against the success of such techniques.

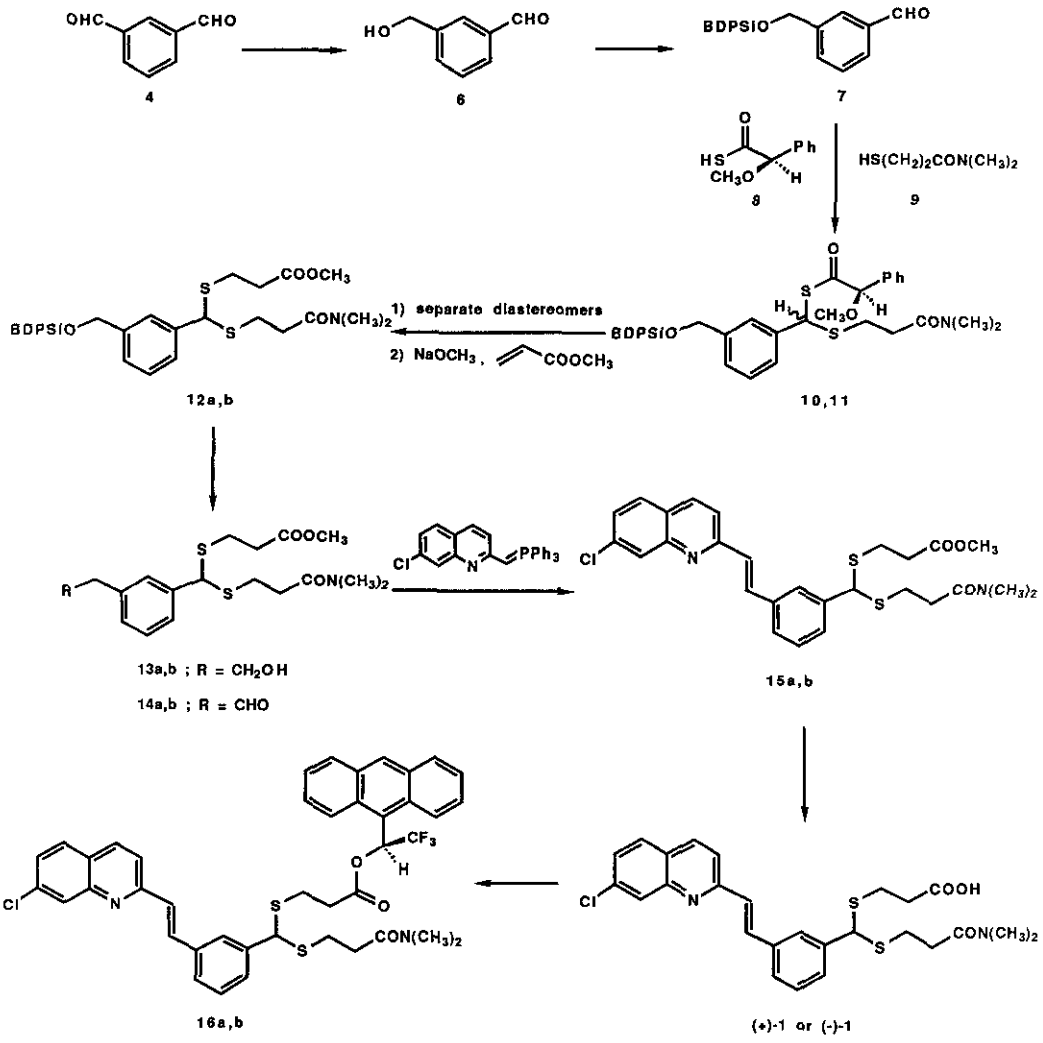
We therefore applied the novel synthetic methodology we have recently developed for the preparation of asymmetric dithioacetals[4,5] (Scheme 1) to successfully achieve this goal. In this procedure aldehydes are reacted with one equivalent each of a thiol acid and thiol to provide essentially exclusively the *mixed* acylthioalkylthioacetals (2). When a chiral thiol acid (such as (R)-(-)-α-methoxyphenylthiolacetic acid) is used in this reaction the derived

Scheme 1



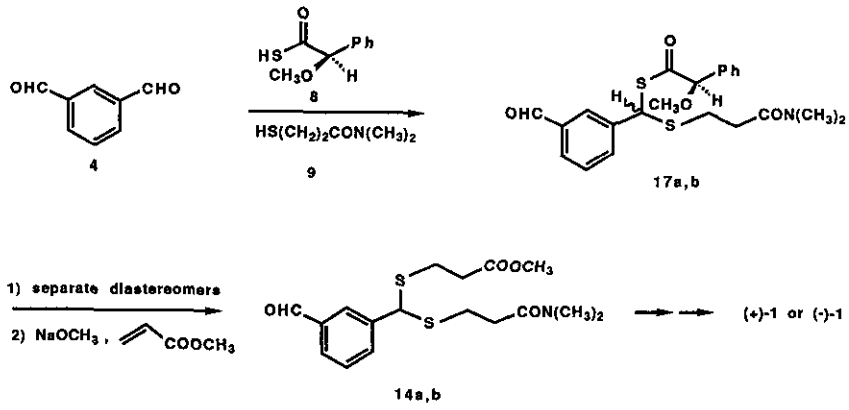

diastereomeric mixed dithioacetals are generally easily separable by chromatographic techniques. Subsequent deacylation of these mixed adducts (2) with sodium methoxide at a low temperature proceeds to provide the intermediate thiolate anions which can be alkylated with a variety of electrophiles to provide chiral dithioacetals (3) without any loss of enantiomeric purity[5].

Scheme 2



The successful synthetic routes to the enantiomers of 1 are detailed in Schemes 2 and 3. Our original synthesis of 1 utilized isophthaladehyde (4) and 7-chloroquinaldine as starting materials[3]. To achieve the chiral synthesis we required selective reaction of one of the aldehyde functions of isophthaldehyde and this was achieved by two methods. In the first sequence (Scheme 2) isophthaldehyde was partially reduced with sodium borohydride to provide 3-hydroxymethylbenzaldehyde (6) which was protected as the t-butyldiphenylsilyl ether (7). The ether 7 was then reacted with 1.1 equivalents each of N,N-dimethyl-3-mercaptopropionamide (9) and (R)-(-)-α-methoxyphenylthiolacetic acid (8) under acid catalysis to provide the mixture of diasteromeric mixed acylthioalkylthioacetals (10,11) in good yield. Flash chromatography effected clean separation of these diastereomers to provide 10 (less polar) and 11 (more polar) in 30% and 36% isolated yields respectively. They were then carried on individually in subsequent steps. The less polar diastereomer (10) was reacted at -78°C with sodium methoxide and the liberated thiolate anion was reacted with methyl acrylate to provide the asymmetric dithioacetal 12a (60%) which was treated with tetrabutylammonium fluoride to remove the silyl protecting group and provide the alcohol 13a (84%). Oxidation with manganese dioxide gave the aldehyde 14a (76%). Parallel reactions starting with 11 gave enantiomeric intermediates 12b (74%), 13b (90%) and 14b (74%). In each case the enantiomeric pairs showed equal and opposite optical rotations (see experimental section). Enantiomer 14a was then reacted with the ylid derived from (7-chloroquinolin-2-yl)methyltriphenylphosphonium bromide (prepared from 7-chloroquinaldine by photobromination and subsequent reaction with triphenylphosphine) to provide the ester 15a (96%) which on careful hydrolysis with aqueous lithium hydroxide in DME gave the (+)-enantiomer of 1 ($[\alpha]_D^{25}$ +9.1°) (50%). Similar transformation of the intermediate 14b gave 15b (91%) and the (-)-enantiomer of 1 ($[\alpha]_D^{25}$ -9.2°). Final confirmation of the enantiomeric purity was obtained by conversion of (+)-1 and (-)-1 to the (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol esters (16a,b). Examination at high resolution of the pmr signals for the dithioacetal methine protons allowed estimation of the enantiomeric purity as >95% e.e. in each case. Subsequently a more convergent preparation of the dithioacetalaldehydes (14a,b) was achieved (Scheme 3). Thus isophthalaldehyde (4) was reacted directly with one equivalent each of N,N-dimethyl-3-mercaptopropionamide (8) and R-(-)-α-methoxyphenylthiolacetic acid (9) with p-toluenesulfonic acid to provide (after purification and separation by flash chromatography) the mixed acylthioalkylthioacetals 17a,b (each in 16% isolated yields). The pure diastereomers were reacted with sodium methoxide at -78°C and thence with methyl acrylate (-78°C for 8 hours) to provide the previously obtained chiral dithioacetals 14a (87%) and 14b (83%). Optical rotations of the enantiomers 14a,b obtained in this manner were essentially identical to those obtained by the previous sequence.

Scheme 3




## CONCLUSIONS

A useful and efficient preparation of the enantiomers of L-660,711 (1), a potent leukotriene $D_4$ antagonist bearing an asymmetric dithioacetal moiety, has been achieved. The synthesis demonstrates the utility of the novel procedure for the preparation of asymmetric dithioacetals. We have very recently been able to assign the S configuration to the enantiomer (+)-1 based on X-ray analysis of a related derivative. This study and the biological profile of the two enantiomers will be reported elsewhere.

## EXPERIMENTAL

All melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. $^1H$ Nmr were recorded on Bruker AM 250 or AM 300 spectrometers using tetramethylsilane as internal standard. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by either Guelph Chemical Laboratories Limited, Guelph, Ontario or by Galbraith Laboratories Inc., Knoxville, Tennessee.

2-Bromomethyl-7-chloroquinoline

A solution of 7-chloroquinaldine[8] (177 g, 1 mol), N-bromosuccinimide (178 g, 1 mol), and benzoyl peroxide (1 g) in $CCl_4$ (2 l) was heated at reflux for 2 days under a 150 watt projection flood lamp. The reaction mixture was cooled, passed through a plug of $SiO_2$ (approximately 1 kg) using toluene as eluent. Further chromatography on 2 x 1 kg $SiO_2$ columns using toluene as eluent afforded 120 g of the title compound, mp 112°C (dec.).

$^1$H Nmr ($CDCl_3$) δ: 4.72 (s, 2H), 7.42-7.75 (m, 2H), 7.95-8.15 (m, 2H), 8.35 ppm (d, J = 10 Hz, 1H).

Anal. calc'd for $C_{10}H_7NBrCl$: C, 46.82; H, 2.75; N, 5.46; Br, 31.14; Cl, 13.82. Found: C, 47.13; H, 2.91; N, 5.49; Br, 31.08; Cl, 13.83.

(7-Chloroquinoline-2-yl)methyltriphenylphosphonium bromide

To a suspension of 2-bromomethyl-7-chloroquinoline (120 g, 0.5 mol) in 800 ml of $CH_3CN$ at 60°C was added triphenylphosphine (183 g). The reaction mixture was heated overnight at 60°C, cooled and 400 ml ether was added. The solid was filtered and dried to yield 170 g of phosphonium salt. $^1$H Nmr ($CDCl_3$) δ: 5.90 (d, J = 15 Hz, 2H), 7.50-8.35 p.p.m. (m, 20H).

Anal. calc'd for $C_{28}H_{22}P$ BrCl: C, 64.82; H, 4.27; N, 2.70; Br, 15.40;Cl, 6.83; P, 6.00. Found: C, 64.61, H, 4.27; N, 2.70; Br, 15.41; Cl 6.85; P, 6.42.

3-Hydroxymethylbenzaldehyde (6)

To a solution of isophthalaldehyde (4) (8 g) in ethanol (80 ml) at room temp. was added $NaBH_4$ portion wise, until about 50% reaction was observed by tlc. The reaction mixture was quenched with 25% ammonium acetate, extracted with ethyl acetate, washed with brine (2x), dried over sodium sulfate, filtered and evaporated to dryness. After purification by flash chromatography (50% $Et_2O$/Hex.) 3 g of pure hydroxyaldehyde 6 was obtained.

$^1$H Nmr ($CDCl_3$) δ: 2.45 (s, 1H, OH), 4.78 (s, 2H, $CH_2OH$), 7.50-7.90 (m, 4H, Ar), 10.05 ppm (s, 1H, CHO).

3-t-Butyldiphenylsilyloxymethylbenzaldehyde (7)

To a solution of hydroxyaldehyde 6 (3 g) in methylene chloride (15 ml) and triethylamine (4.1 ml) was slowly added the t-butylchlorodiphenylsilane (8 ml). Finally, 1 crystal of 4-pyrrolidinopyridine was added as a catalyst. The reaction mixture was stirred overnight at room temp. The solution was quenched with 25% ammonium acetate, extracted with ethyl acetate, washed with brine (2x), dried over sodium sulfate, filtered and evaporated to dryness. Purification by flash chromatography (4% AcOEt/Hex), afforded 8.98 g of aldehyde 7.

$^1$H Nmr ($CDCl_3$) δ: 1.13 (s, 9H, t-Bu), 4.82 (s, 2H, $CH_2O$), 7.25-7.85 (m, 14H, Ar), 10.05 ppm (s, 1H, CHO).

Dithioacetals 10 and 11

To a solution of aldehyde 7 (8.98 g, 24 mmol) in benzene (90 ml) was added thiol 9 (3.5 g, 26

mmol), thiolacid 8 (4.76 g, 26 mmol) and p-toluenesulfonic acid (2.26 g, 13 mmol). The solution was refluxed for ~ 3.5 h with a Dean-Stark apparatus filled with activated 3A molecular sieves. The solution was cooled to room temp., quenched with 25% ammonium acetate, extracted with EtOAC, washed with brine (3x), dried over sodium sulfate, filtered and evaporated to dryness. The two diastereomers were separated by flash chromatography (10 in. of silica gel), 40% AcOEt/Hex, giving 5.35 g of the less polar compound 10 and 4.51 g of the more polar 11.

10: $[\alpha]_D^{25}$ = +46.4° (c = 2.23, acetone). $^1$H Nmr ($CDCl_3$) δ: 1.12 (s, 9H, t-Bu), 2.45 (t, 2H, J = 7 Hz, $CH_2$), 2.78 (t, 2H, J = 7 Hz, $CH_2$), 2.82 and 2.88 (2s, 6H, $N(CH_3)_2$), 3.42 (s, 3H, $OCH_3$), 4.70 (s, 1H, CH), 4.74 (s, 2H, $CH_2O$), 5.61 (s, 1H, CH), 7.26-7.71 ppm (m, 19H, Ar).

Anal. calc'd for $C_{38}H_{45}NO_4S_2Si$: C, 67.92; H, 6.75; S, 9.54.

Found: C, 67.86; H, 6.98; S, 9.36.

11: $[\alpha]_D^{25}$ = -39.2° (c = 1.98, acetone). $^1$H Nmr ($CDCl_3$) δ: 1.10 (s, 9H, t-Bu), 3.59 (t, 2H, J = 7 Hz, $CH_2$), 3.85 (t, 2H, J = 7 Hz, $CH_2$), 3.95 and 3.96 (2s, 6H, $N(CH_3)_2$), 3.48 (s, 3H, $OCH_3$), 4.72 (s, 2H, $CH_2O$), 4.78 (s, 1H, CH), 5.64 (s, 1H, CH), 7.26-7.85 ppm (m, 19H, Ar).

Preparation of dithioacetal 12a

A solution of dithioacetal 10 (2.6 g, 3.87 mmol) was cooled to -78°C. A solution of sodium methoxide 1M in methanol (3.47 ml, 0.9 eq) was added. After stirring for 10 min (-78°C), methyl acrylate (0.52 ml, 1.5 eq.) was added and the solution was stirred for 2 h at -78°C. The reaction mixture was quenched at low temperature with a saturated solution of ammonium chloride, extracted with EtOAc, washed with brine (3x), dried over sodium sulfate, filtered and evaporated to dryness. Purification by flash chromatography gave 1.4 g of dithioacetal 12a. $[\alpha]_D^{25}$ - 1.62° (c = 1.22, acetone).

$^1$H Nmr ($CDCl_3$) δ: 1.12 (s, 9H, t-Bu), 2.50-2.90 (m, 8H, 4($CH_2$)), 2.91 and 2.92 (2s, 6H, $N(CH_3)_2$), 3.68 (s, 1H, $OCH_3$), 4.77 (s, 2H, $CH_2O$), 5.00 (s, 1H, CH), 7.27-7.72 ppm (m, 14H, Ar).

Anal. calc'd for $C_{33}H_{43}NO_4S_2Si$: C, 64.68; H, 7.10; S, 10.51.

Found: C, 65.03; H, 7.21; S, 10.19.

Compound 11, treated the same way afforded the enantiomer 12b.

$[\alpha]_D^{25}$ + 2.05° (c = 1.84, acetone).

Anal. found: C, 65.08; H, 7.40; S, 10.73.

Preparation of alcohol 13a

To a solution of silyl ether 12a (1.377 g, 2.26 mmol) in THF (25 ml) at room temp. was slowly added tetrabutylammonium fluoride 1M in THF (2.34 ml). The solution was stirred 2 h at room temp. Ethyl acetate was added to the reaction mixture, it was washed with brine (3x), dried over sodium sulfate, filtered and evaporated to dryness. After flash chromatography (40% acetone/hexane), 709 mg of alcohol 13a was obtained. $[\alpha]_D^{25}$ - 4.2° (c = 2.04, acetone).

$^1$H Nmr ($CDCl_3$) δ: 2.50-2.91 (m, 8H, $4(CH_2)$), 2.94 and 2.96 (2s, 6H, $N(CH_3)_2$), 3.70 (s, 3H, $OCH_3$), 4.69 (s, 2H, $C\underline{H}_2OH$), 5.05 (s, 1H, CH), 7.26-7.49 ppm (m, 4H, Ar).

Similar treatment of the enantiomer 12b, afforded the enantiomer 13b $[\alpha]_D^{25}$ + 4.1° (c = 1.78, acetone).

Preparation of aldehyde 14a

To a solution of alcohol 13a (679 mg) in ethyl acetate (30 ml) was added $MnO_2$ (1.3 g). The suspension was stirred overnight at room temp. The suspension was filtered on a pad of silica gel with EtOAc and the solvent was evaporated affording 516 mg of aldehyde 14a

$[\alpha]_D^{25}$ - 6.9° (c = 1.73, acetone).

$^1$H Nmr ($CDCl_3$) δ: 2.56-2.94 (m, 8H, $4(CH_2)$), 2.95 and 2.97 (2s, 6H, $N(CH_3)_2$), 3.70 (s, 3H, $OCH_3$), 5.14 (s, 1H, CH), 7.52, 7.80 and 7.98 (t, J = 7 Hz, t, J = 7 Hz and s, 4H, Ar), 10.03 ppm (s, 1H, CHO).

Anal. calc'd for $C_{17}H_{23}NO_4S_2$: C, 55.26; H, 6.27; S, 17.36.

Found: C, 55.19; H, 6.57; S, 17.06.

The same treatment of the enantiomer 13b afforded the enantiomer 14b $[\alpha]_D^{25}$ +6.7° (c = 1.38, acetone).

Anal. found: C, 55.06; H, 6.57; S, 17.18.

Preparation of olefin 15a

To a suspension of (7-chloroquinolin-2-yl)methyltriphenylphosphonium bromide (809 mg, 1.56 mmol) in THF (15 ml) at -78°C, was added a solution of n-BuLi in Hexane 1.6 M (0.89 ml, 1.43 mmol). The mixture was stirred for 0.5 h at -78°C. Then, aldehyde 14a (480 mg, 1.3 mmol) in THF (4 ml) was slowly added. The mixture was stirred for 0.5 h at -78°C and then warmed to room temp. and stirred for an additional 2 h. A solution of 25% ammonium acetate was added, the mixture was extracted with ethyl acetate, and the extracts were washed with brine (3x), dried over sodium sulfate, filtered and evaporated to dryness. Purification by flash

chromatography afforded 660 mg of olefin 15a.

$[\alpha]_D^{25}$ - 4.2° (c = 1.28, acetone).

$^1$H Nmr δ: 2.54-2.93 (m, 8H, 4($CH_2$)), 2.94 (s, 6H, $N(CH_3)_2$), 3.70 (s, 3H, $OCH_3$), 5.08 (s, 1H, CH), 7.34-8.14 ppm (m, 11H, Ar + vinyl).

Anal. calc'd for $C_{27}H_{29}N_2O_3S_2Cl$: C, 61.29; H, 5.52; S, 12.12.

Found: C, 61.03; H, 5.68; S, 12.32.

Similarly the enantiomer 14b gave 15b $[\alpha]_D^{25}$ + 3.5° (c = 1.74, acetone).

Anal. found: C, 61.06; H, 5.66; S, 11.91.

Preparation of (+)-1 (and (-)-1)

To a solution of ester 15a (640 mg, 1.21 mmol) in peroxide free 1,2-dimethoxyethane (15 ml) and water (1.5 ml) was added LiOH (1M, 1.8 ml, 1.8 mmol). The solution was stirred for 3 h at room temp. Water was added and the mixture was washed with EtOAc. The aqueous layer was acidified with 1N HCl, extracted with EtOAc, the extracts were washed with brine (2x), dried over $Na_2SO_4$, filtered and evaporated to dryness. The oily residue was coevaporated several times with EtOAc and finally was allowed to crystallize in this solvent overnight at 0°C. Filtration afforded 310 mg of pure (+)-1

$[\alpha]_D^{25}$ + 9.1° (c = 0.88, 1% $NaHCO_3$)

$^1$H Nmr δ: 2.70-3.19 (m, 8H, 4($CH_2$)), 3.00 and 3.02 (2s, 6H, $N(CH_3)_2$), 5.15 (s, 1H, CH), 7.34-8.14 ppm (m, 11H, Ar + vinyl).

Anal. calc'd for $C_{26}H_{27}N_2O_3S_2Cl$: C, 60.63; H, 5.28; N, 5.44; S, 12.45; Cl, 6.88.

Found: C, 60.88; H, 5.38; N, 5.21; S, 12.33; Cl, 6.98.

Similarly 15b was converted to the enantiomer (-)-1 $[\alpha]_D^{25}$ - 9.2° (c = 0.68, 1% $NaHCO_3$).

Anal. found: C, 60.78; H, 5.46; N, 5.35; S, 12.35; Cl, 6.78.

Determination of e.e. of (+)-1 (and (-)-1)

To acid (-)-1 (51 mg) in methylene chloride (0.3 ml) was added 1-cyclohexyl-3-(2-morpholinoethyl)carbodimide metho-p-toluenesulfonate (46 mg, 1.1 eq), (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (30 mg, 1.1 eq.), DMAP (1 crystal) and pyridine (0.1 ml). The solution was stirred for 4 h. The mixture was applied directly to a preparative tlc plate, which after elution with 30% acetone/hexane, afforded the ester 16a. The chemical shift of the methine proton of the dithioacetal of 16a and its diastereomer (from the

(-)- enantiomer of 1) are different (4.97 and 4.98 ppm), thus allowing for the determination of e.e. In our case this value was > 95% for both compounds.

Preparation of thiolacid 8

To (R)-(-)-α-methoxyphenylacetic acid (2 g) in benzene (20 ml) at -10°C was slowly added oxalyl chloride (1.15 ml) and 1 drop of DMF. The solution was slowly warmed to room temp. and stirred 2 h. The solvent was evaporated and the oily residue was coevaporated with toluene (3x). This acid chloride was used as such in the next step. Ir (neat) 1790 $cm^{-1}$ (C=O).

To ethanol (20 ml) at -10°C, anhydrous NaSH (1.34 g, 3 eq.) was added. Then, the acid chloride in THF (8 ml) was slowly added. The reaction mixture was stirred for 20 min at -10°C. The mixture was acidified with 6N HCl, extracted with EtOAc, washed with brine (2x), dried over $Na_2SO_4$, filtered and evaporated to dryness giving 1.64 g of thiolacid 8. $[\alpha]_D^{25}$ = -32.7° (c = 3.1, acetone). Ir (neat) 2550 (SH) and 1700 $cm^{-1}$ (C=O).

Preparation of thiol 9

To N,N-dimethylacrylamide (19.8 g, 0.2 mol) at 0°C was slowly added thiolacetic acid (15.22 g, 0.2 mol). The ice-bath was then removed and the reaction mixture stirred at room temp. for 15 min. On distillation (bp 96-98°C/0.06 torr) 32.24 g of thiolester were obtained.

To the thiolester (5.66 g, 32.34 mmol) in methanol (20 ml) at 0°C was added potassium t-butoxide (3.622 g, 1 eq.) in 3 portions. The mixture was stirred at room temp. for 1.5 h. The reaction mixture was poured over 25% ammonium acetate and methylene chloride. 2N HCl was added to bring the pH to 7.0-7.5. After two more extractions with methylene chloride, the organic layers were combined, dried over sodium sulfate, filtered, and evaporated to dryness, 4.1 g of thiol 8 were obtained as a pale orange oil.

Preparation of aldehyde acetals 17a,b.

Isophthalaldehyde (4) (18.4 g, 137 mmol), (R)-(-)-α-methoxyphenylthiolacetic acid (25 g, 137 mmol), and N,N-dimethyl-3-mercaptopropionamide (18.24 g, 137 mmol) were dissolved in benzene (550 ml). p-Toluenesulfonic acid monohydrate (13 g, 68 mmol) was added and the mixture was refluxed for 3 h under a Dean Stark apparatus filled with 3A sieves. Ammonium acetate (25%) was added and mixture was extracted with ethyl acetate. The organic extracts were washed with brine (3 x), dried over sodium sulphate, filtered and evaporated to dryness. The residue was partially purified on flash chromatography on $SiO_2$ and then the diastereomers were further

separated using a Waters prep 500 HPLC apparatus eluting with hexane - acetone (65:35) to provide a pure diastereomers 17a (more polar, 9.32 g) and 17b (less polar, 8.90 g)

17a: Anal. calc'd for $C_{22}H_{25}NO_4S_2$: C, 61.23; H, 5.84; S, 14.86.
Found: C, 60.95; H, 6.09; S, 14.54.

$^1$H Nmr ($CDCl_3$) δ: 2.51 (t, 2H, J = 7 Hz, $SCH_2$), 2.83 (t, 2H, J = 7 Hz, $CH_2$), 2.88 and 2.91 (2s, 6H, $N(CH_2)_2$), 3.44 (s, 3H, OMe), 4.71 (s, 1H, CH), 6.65 (s, 1H, CH), 7.28-7.97 (m, 9H, Ar), 10.01 ppm (s, 1H, CHO).

Conversion of 17a to the aldehyde 14a

A solution of dithioacetal 17a (9.32 g, 21.6 mmol) in anhydrous THF (236 ml) was treated with a solution of $NaOCH_3$ (1M) in methanol (19.4 ml, 0.9 eq.) at -78°C. After 5 min methyl acrylate (2.92 ml, 1.5 eq.) was added and the mixture was stirred at -78°C for 8 h. A saturated solution of ammonium chloride was added, the mixture was extracted with ethyl acetate, and the organic phase was washed with brine (3 x), dried over sodium sulphate, filtered and evaporated to dryness. Purification by flash chromatography on $SiO_2$ eluting with hexane:acetone (60:40) gave pure 12a (7.08 g, 88%) $[\alpha]_D^{25}$ = -6.6° (c = 1.63, acetone). Similarly 16b (1.974 g) was converted to 12b (1.4 g, 83%) $[\alpha]_D^{25}$ = +6.4° (c = 1.42, acetone).

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