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†

Robert N. Young*, Jacques Yves Gauthier, Michel Thérien, and Robert Zamboni

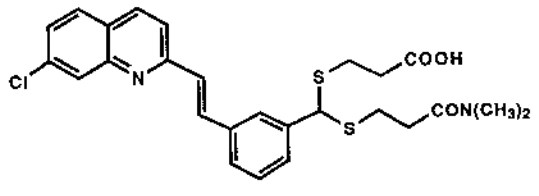
Merck Frosst Center for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Quebec, Canada H9R 4P8

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.

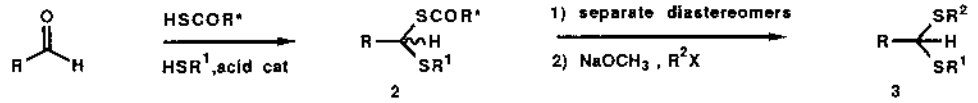
DISCUSSION

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.

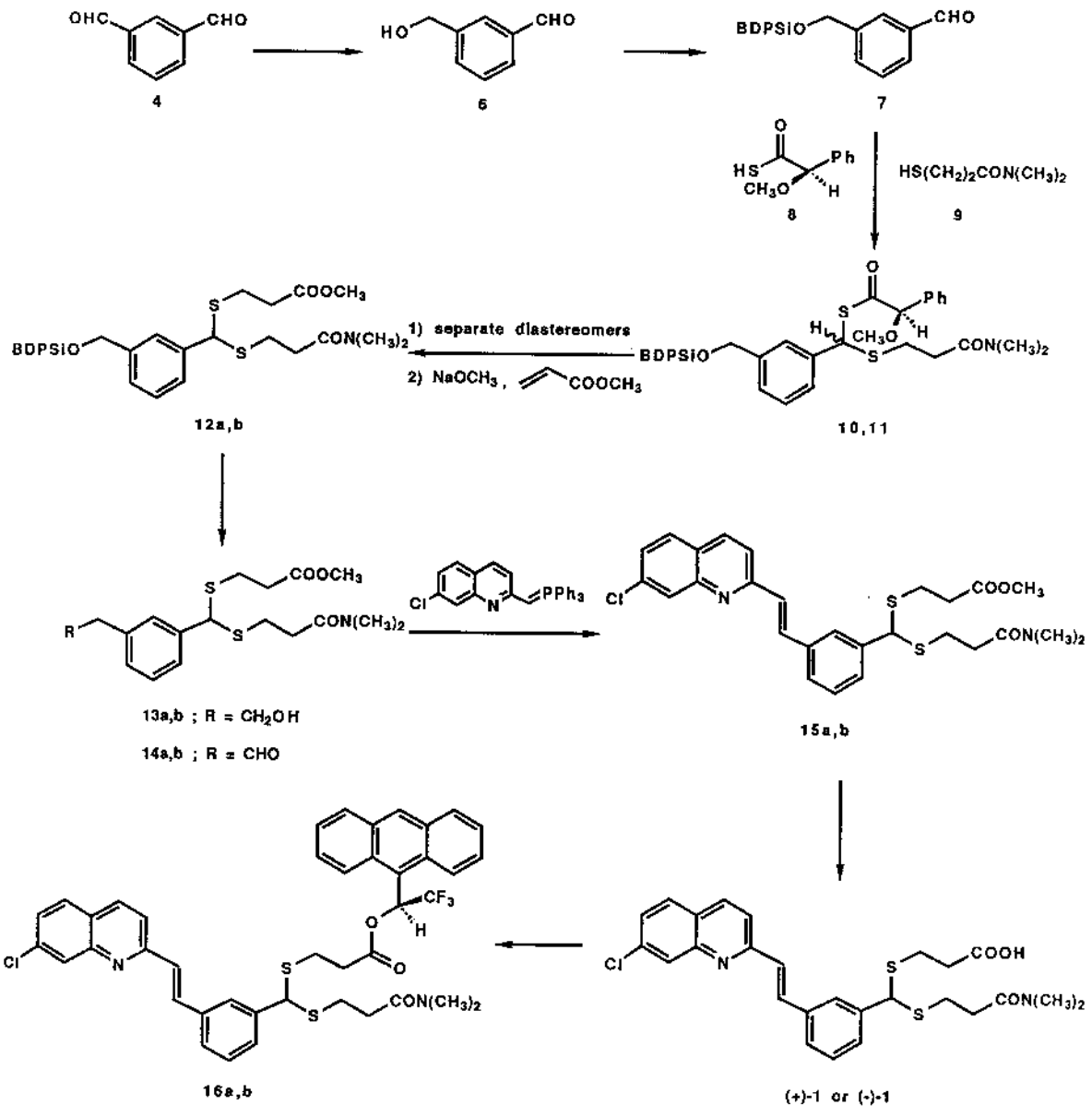
We therefore applied the novel synthetic methodology we have recently developed for the preparation of asymmetric dithioacetals[4,5] (Scheme 1) to successfully achieve this goal. In this procedure aldehydes are reacted with one equivalent each of a thiol acid and thiol to provide essentially exclusively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

Scheme 1



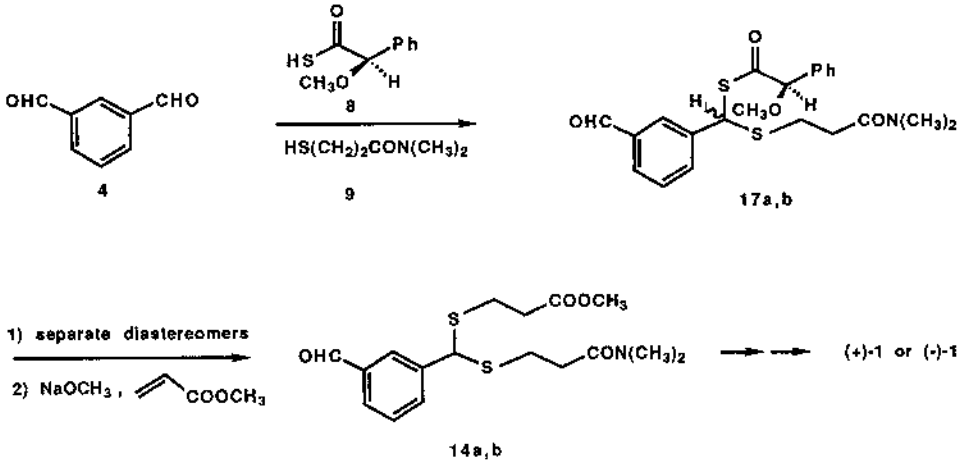
diastereomeric mixed dithioacetals are generally easily separable by chromatographic techniques. Subsequent deacylation of these mixed adducts (2) with sodium methoxide at a low temperature proceeds to provide the intermediate thiolate anions which can be alkylated with a variety of electrophiles to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

^1H 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).

^1H 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).

^1H 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% $NaHCO_3$)

^1H 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 dete 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 slow oxalyl chloride (1.15 ml) and 1 drop of DMF. The solution was slowly warmed to room t stirred 2 h. The solvent was evaporated and the oily residue was coevaporated with (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, t chloride in THF (8 ml) was slowly added. The reaction mixture was stirred for 20 -10°C. The mixture was acidified with 6N HCl, extracted with EtOAc, washed with brin 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 0.2 mol). The ice-bath was then removed and the reaction mixture stirred at room temp. 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 pota t-butoxide (3.622 g, 1 eq.) in 3 portions. The mixture was stirred at room temp. for 1 The reaction mixture was poured over 25% ammonium acetate and methylene chloride. 2N HC added to bring the pH to 7.0-7.5. After two more extractions with methylene chloride organic layers were combined, dried over sodium sulfate, filtered, and evaporated to dry 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, mmol), and N,N-dimethyl-3-mercaptopropionamide (18.24 g, 137 mmol) were dissolved in ben (550 ml). p-Toluenesulfonic acid monohydrate (13 g, 68 mmol) was added and the mixture refluxed for 3 h under a Dean Stark apparatus filled with 3A sieves. Ammonium acetate (2 was added and mixture was extracted with ethyl acetate. The organic extracts were washed w brine (3 x), dried over sodium sulphate, filtered and evaporated to dryness. The residue partially purified on flash chromatography on SiO_2 and then the diastereomers were furt

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.

^1H 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).

REFERENCES

1. C.K. Buckner, R.D. Krell, R.B. Larauusa, D.B. Coursin, P.R. Bernstein, and J.N. Will, J. Pharmac. Exp. Ther., 1986, 237, 558.
2. a) J.H. Fleish, L.E. Rinkema, K.D. Haisch, D. McCullough, F.P. Carr, and R.D. Dillard, Naunyn-Schmiedeberg's Arch. Pharmacol., 1986, 333, 70. b) J.G. Gleason, R.F. Hall, C.D. Perchonock, K.F. Erhard, J.S. Frazee, T.W. Ku, K. Kondrad, M.E. McCartney, S. Mong, S.T. Crooke, G. Chi-Rosso, M.A. Wasserman, T.J. Torphy, R.M. Muceitelli, D.W. Hay, S.S. Tucker, and L. Vickery-Clark, J. Med. CHem., 1987, 30, 959. c) P.R. Bernstein, Y.K. Yee, and D. Snyder, 194th ACS National Meeting, New Orleans, August 30-September 4, 1987, abstracts of meeting.

3. a) R.N. Young, R. Zamboni, and S. Leger, European patent application # 2190377, November 18, 1987. b) R. Zamboni, T.R. Jones, M. Belley, E. Champion, L. Charette, R. Dehaven, R. Frenette, J.Y. Gauthier, S. Leger, P. Masson, C.S. McFarlane, S.S. Pong, H. Piechuta, J. Rokach, M. Thérien, H.W.R. Williams, and R.N. Young, J. Med. Chem., submitted for publication.

4. J.Y. Gauthier, T. Henien, L.Lo, M. Thérien, and R.N. Young, Tetrahedron Letts., 1988, in press.

5. M. Thérien, J.Y. Gauthier, and R.N. Young, Tetrahedron Letts., 1988, in press.

6. a) T. Posner, Chem. Ber., 1903, 36, 296. b) D.T. Gibson, J. Chem. Soc., 1931, 2637. c) D. Paquer, Bull. Soc. Chim. France, 1975, 1439. d) L. Kristenbrugger and J. Voss, Liebigs Ann. Chem., 1980, 472. e) M. Martin and L. Bassery, C.R. Acad. Sci. Paris Ser. C., 1975, 281, 571. f) P. Dubs and R. Stussi, Helv. Chim. Acta, 1978, 61, 2351. g) H. Bohme, H. Bezzenberger, and O. Muller, Arch. Pharmaz., 1973, 306, 268.

7. An attempt to prepare chiral thioacetals using electroreductive methodology by Kristenbrugger and Voss (ref 6d) using a chiral salt medium is reported to have been unsuccessful.

8. C.M. Leir, J. Org. Chem., 1977, 42, 911.

Received, 12th September, 1988