To a solution of 2-[(4-methoxyphenyl)methyl]cyclopentaneacetonitrile in anhydrous CH_2Cl_2 (70 mL) at −78 °C was added BBr_3 (55.1 mmol, 55.1 mL of a 1 M solution in CH_2Cl_2). The reaction was stirred for 18 h while the reaction was allowed to warm to room temperature and additional BBr_3 (10.4 mmol, 10.4 mL of a 1 M CH_2Cl_2 solution) was added. After 24 h, saturated $NaHCO_3$ was added, the organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was chromatographed with a gradient of hexane/EtOAc varying from 3:1 to 2:1 to give 10.43 g (100%) of 2-(4-hydroxybenzyl)cyclopentaneacetonitrile: ^1H NMR ($CDCl_3$) δ 1.2–2.7 (m, 12 H), 5.5 (br s, 1 H), 6.7 (d, J = 8 Hz, 2 H), 7.0 (d, J = 8 Hz, 2 H) ppm; IR (neat) 3600–3160, 2260, 1520, 1220 cm^{-1}; HRMS M^+ calcd for $C_{14}H_{17}NO$ m/z 215.1310, found m/z 215.1305.

A mixture of 2-(chloromethyl)quinoline hydrochloride (1.47 g, 6.85 mmol), DMSO (10 mL), NaOH (0.50 g, 12.44 mmol), and 2-[(4-hydroxyphenyl)methyl]cyclopentaneacetonitrile (1.34 g, 6.22 mmol) was stirred at ambient temperature for 21 h. The reaction was poured into H_2O and extracted with EtOAc. The organic extracts were combined and washed with H_2O and brine and then dried (Na_2SO_4) and evaporated. The residue was chromatographed with a petroleum ether/EtOAc gradient varying from 9:1 to 2:1 to give crude product. This material was recrystallized from petroleum ether/EtOAc to give **49b** (2.1 g, 95%): mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 1.2–2.7 (m, 12 H), 5.4 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.1 (d, J = 9 Hz, 2 H), 7.5 (t, J = 7 Hz, 1 H), 7.7 (m, 3 H), 8.1 (d, J = 9 Hz, 1 H), 8.2 (d, J = 9 Hz, 1 H) ppm; IR (nujol) 2240, 1600, 1070, 830 cm^{-1}; HRMS M^+ calcd for $C_{24}H_{24}N_2O$ m/z 356.1888, found m/z 356.1909. Anal. ($C_{24}H_{24}N_2O$) C, H, N.

2-[[4-(Quinolin-2-ylmethoxy)phenyl]methyl]cyclopentane-1-acetic Acid (46). Compound **46b** (2.0 g, 5.6 mmol) was dissolved in EtOH (100 mL) and 10% NaOH (10 mL) was added. The solution was heated at reflux for 48 h and stirred at ambient temperature for 4 days. Additional 10% NaOH (10 mL) was added and the solution was heated at reflux for 24 h. The solvent was removed and the residue was diluted with H_2O (100 mL). The aqueous solution was washed with Et_2O then made acidic with 10% HCl (pH 6). The precipitated solid was filtered and pure **46** (0.6 g, 21% yield) was obtained after flash chromatography using a 5% IPA in $CHCl_3$ solution: mp 131–132 °C; ^1H NMR ($CDCl_3$) δ 1.2–2.8 (m, 12 H), 5.4 (s, 2 H), 6.9 (d, J = 9 Hz, 2 H), 7.0 (d, J = 9 Hz, 2 H), 7.5 (t, J = 7 Hz, 1 H), 7.7 (m, 3 H), 8.1 (d, J = 8 Hz, 1 H), 8.2 (d, J = 8 Hz, 1 H), 10.6 (br s, 1 H) ppm; IR (KBr) 3260–2400, 1710, 1520, 830 cm^{-1}; HRMS M^+ calcd for $C_{24}H_{25}NO_3$ m/z 375.1834, found m/z 375.1829. Anal. ($C_{24}H_{25}NO_3 \cdot 0.25H_2O$) C, H, N.

2-[[4-(Quinolin-2-ylmethoxy)phenyl]methyl]-1-(5-tetrazolylmethyl)cyclopentane (47). A mixture of **46b** (7.6 g, 21.2 mmol), NaN_3 (4.1 g, 63.7 mmol), NH_4Cl (3.4, 63.7 mmol), and anhydrous DMF was heated on an oil bath at 110–120 °C. After 5 h the reaction was cooled and additional NaN_3 (4.1 g, 63.7 mmol) and NH_4Cl (3.4 g, 63.7 mmol) were added. The reaction was then heated for another 63 h. The mixture was cooled and poured into H_2O (400 mL), and 10% NaOH (20 mL) was added. The basic aqueous solution was washed with Et_2O (5 × 200 mL) and this solution was made acidic with 10% HCl (pH 6). The precipitated solid was filtered and purified by silica gel chromatography using a 5% MeOH in $CHCl_3$ solution to give **47** (6.0 g, 71%): mp 136–138 °C; ^1H NMR ($CDCl_3$) δ 1.2–3.0 (m, 12 H), 5.3 (s, 2 H), 6.8 (m, 4 H), 7.7 (m, 4 H), 8.0 (d, J = 8 Hz, 1 H), 8.2 (m, 1 H), 10.6 (br s, 1 H) ppm; IR (KBr) 3100–2400, 1510, 1250, 830 cm^{-1}; HRMS M^+ calcd for $C_{24}H_{25}N_5O$ m/z 399.2059, found m/z 399.2082. Anal. ($C_{24}H_{25}N_5O$) C, H, N.

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Stereospecific Synthesis, Assignment of Absolute Configuration, and Biological Activity of the Enantiomers of 3-[[[3-[2-(7-Chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic Acid, a Potent and Specific Leukotriene D_4 Receptor Antagonist

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The enantiomers of the leukotriene D_4 antagonist 3-[[[3-[2-(7-chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]thio]methyl]thio]propionic acid (L-660,711)(MK-571) have been prepared, their absolute stereochemistry has been assigned as *S* for (+)-1 and *R* for (−)-1 by X-ray analysis of a synthetic intermediate (**5**), and the biological activity of the enantiomers has been explored. Unexpectedly, the enantiomers are both comparably biologically active with (+)-1 slightly more intrinsically active at the LTD_4 receptor in vitro.

Introduction

We have recently described the development[1] and pharmacology[2] of (±)-3-[[[3-[2-(7-chloroquinolin-2-yl)-(*E*)-ethenyl]phenyl][[3-(dimethylamino)-3-oxopropyl]-thio]methyl]thio]propionic acid (**1**), (MK-571), a novel, potent, and selective antagonist at the leukotriene D_4 receptor. A large-scale synthesis has also recently been described.[3] The pharmacological profile of **1**[2] (high intrinsic potency, excellent oral bioavailability and oral activity, and long duration of action in a variety of species) indicates that this compound has the potential to define

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(1) Zamboni, R.; Jones, T. R.; Belley, M.; Champion, E.; Charette, L.; Dehaven, R.; Frenette, R.; Gauthier, J. Y.; Leger, S.; Masson, P.; McFarlane, C. S.; Pong, S. S.; Piechuta, H.; Rokach, J.; Thérien, M.; Williams, H. W. R.; Young, R. N. *J. Med. Chem.*, accepted for publication.

(2) Jones, T. R.; Zamboni, R.; Belley, M.; Champion, E.; Charette, L.; Ford-Hutchinson, A. W.; Frenette, R.; Gauthier, J. Y.; Leger, S.; Masson, P.; McFarlane, C. S.; Piechuta, H.; Rokach, J.; Williams, H. W. R.; Young, R. N.; Dehaven, R.; Pong, S. S. *Can. J. Physiol. Pharmacol.* **1989**, *67*, 17.

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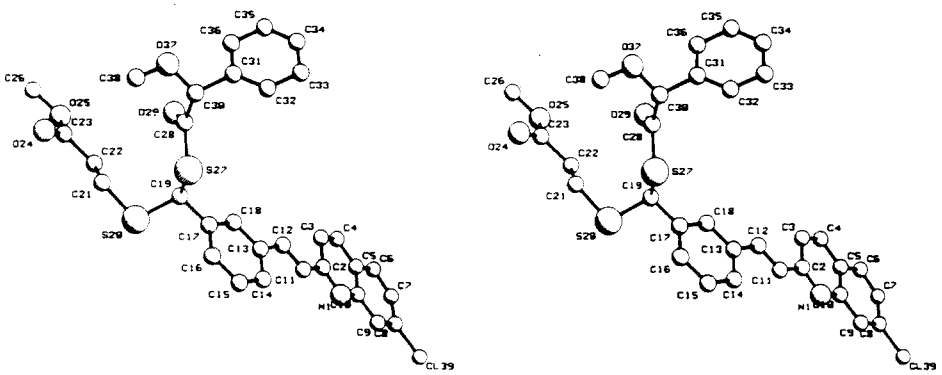
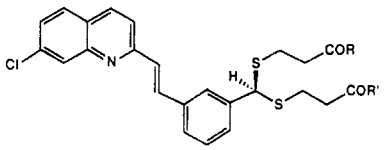


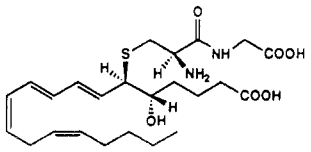
Figure 1. A computer-generated stereodrawing of **5** showing the atom labeling. Hydrogen atoms are eliminated for clarity.

the role of leukotriene D_4 (LTD_4) (**2**) in human disease states. It is currently undergoing clinical testing in normal and asthmatic subjects[4] to determine if it may represent a significant new therapy for asthma.



S-(+)-**1** : R=N(CH$_3$)$_2$; R'=OH

R-(-)-**1** : R=OH ; R'=N(CH$_3$)$_2$



LTD_4 (**2**)

Discussion

The development of **1** evolved closely with the elaboration and refinement of a model of the leukotriene D_4 receptor based on analysis of biological data available in the literature on leukotriene analogues and antagonists.[5] In keeping with this model, **1** embodies a planar lipophilic backbone with extended conjugation, coupled to two polar chains, one ionizable and the other not. Limited literature examples (i.e. the C-1 amide analogue of LTD_4 is equiactive with LTD_4[6]) suggest that the amide group in **1** should correspond to the C-1 carboxy group of LTD_4.

As **1** is a racemate, it was important to determine if one enantiomer was intrinsically more potent than the other at the receptor. This knowledge was important not only for guiding the drug development but also in allowing us to further test and refine our receptor model. Therefore it was necessary to prepare the enantiomers of **1**, assign absolute stereochemistry, and characterize their biological activities, and this is the subject of the present report.

A stereospecific synthesis of the (+) and (-) enantiomers has been developed[7,8] and more recently the enantiomers have been prepared by an enzymatic hydrolysis of the prochiral dimethyl ester analogue of **1**.[9] Unfortunately attempts to obtain either enantiomer or synthetic intermediates as crystals suitable for X-ray analysis were unsuccessful. Thus an alternative stereospecific synthesis was developed to provide a crystalline intermediate for X-ray analysis.

In the previous synthesis[8] and in the one described herein we have prepared diastereomeric adducts with (*R*)-(-)-α-methoxyphenylthiolacetic acid as key intermediates which in principle could be amenable to the NMR-based method of determination of absolute stereochemistry recently published by Trost et al.[10] for *O*-methylmandelate esters. Although it seemed possible that that method could be extended to our series, it was not formally proven for sulfur analogues or thioacetals, and therefore we considered it imperative to prove the absolute stereochemistry by X-ray analysis.

Chemistry

Aldehyde **3** was readily obtained from the condensation of 7-chloroquinaldine and isophthalaldehyde.[1,3] Earlier attempts to react this aldehyde with thiols and thiolacetic acid led to extensive spontaneous conjugate addition of the thiolacid to the styryl double bond. We found however that this side reaction could be suppressed by the use of a radical inhibitor (2,6-di-*tert*-butyl-4-methylphenol (BHT)) and low temperature. Thus the BF_3·OEt_2-catalyzed condensation of (*R*)-(-)-α-methoxyphenylthiolacetic acid, methyl 3-mercaptopropionate, and **3** in the presence of BHT produced the diasteromeric alkyl acyl dithioacetals **4** and **5** (74% isolated yield), which were readily separated by chromatography (Scheme I). Diastereomer **5** could also be obtained pure by selective crystallization of the mixture. Recrystallization of **5** provided monoclinic crystals, which were subjected to X-ray analysis (vide infra), which indicated that the dithioacetal center had the *S* configuration based on the known stereochemistry of the chiral auxiliary

(3) McNamara, J. J.; Leazer, J. L.; Bhupathy, M.; Amato, J. S.; Reamer, R. A.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3718.

(4) For preliminary clinical abstracts, see: (a) Kips, J. C.; Joos, J.; Margolskee, D.; Dehepeleire, I.; Rogers, J. D.; Pauwels, R.; Van Der Straeten, M. *L-660,711, A Potent Antagonist of LTD_4-Induced Bronchoconstriction in Man*, Proceedings of the American Thoracic Society Meeting, Cincinnati, OH, May 14–17, 1989. (b) Van Hecken, A.; DeSchepper, P. J.; Margolskee, D. J.; Hsieh, J. Y. K.; Rokinette, R. S.; Buntinx, A.; Rogers, J. D. *Human Kinetics and Tolerability of Intravenous MK-571; A New Leukotriene (LT) D_4 Receptor Antagonist*, Proceedings of IV World Conference on Clinical Pharmacology and Therapeutics, Mannheim, Heidelberg, July 23–28, 1989.

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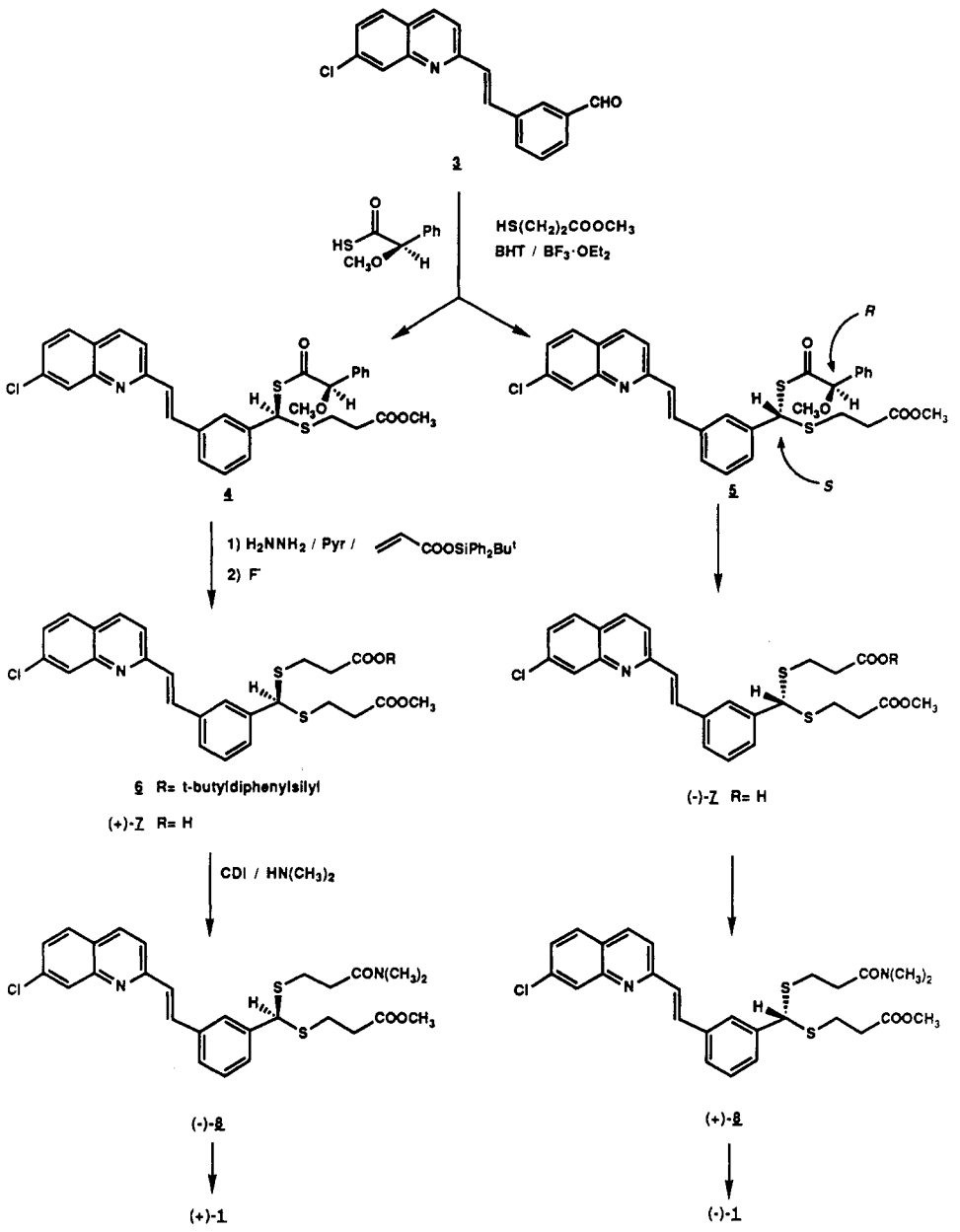
(9) Hughes, D. L.; Bergan, J. J.; Amato, J. S.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 1787.

(10) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

Scheme I



(Figure 1). By inference the chirality of the corresponding center in **4** was determined to be *R*. With this crucial information in hand, we then attempted to complete the conversion of **4** to (−)-**8** and **5** to (+)-**8**. Standard conditions[7] (i.e. reaction of **4** with sodium methoxide at −78 °C to generate the intermediate thiolate anion followed by reaction with dimethylacrylamide) failed to provide the desired chiral dithioacetal (−)-**8** in adequate yield. Furthermore, due to the relatively poor reactivity of the acrylamide it was necessary to warm the reaction (to −20 °C) to achieve a measure of conversion and in doing so partial racemization was noted. We then attempted to substitute a more reactive synthetic equivalent of the acrylamide, *tert*-butyldiphenylsilyl acrylate, in the reaction, but again unsatisfactory results were obtained presumably due to competitive transesterification of the silyl ester with sodium methoxide. Finally we found that by utilizing hydrazine in pyridine as nucleophile, transesterification and racemization were avoided and hydrolsis of **4** occurred smoothly at −15 °C with concomitant conjugate addition to *tert*-butyldiphenylsilyl acrylate to provide the desired adduct **6**. Subsequent removal of the silyl ester group (TBAF) afforded (+)-**7** in 80% overall yield from **4**. The stereochemical integrity of the transformation was confirmed by conversion of (+)-**7** to (−)-**8**, which was shown to be optically pure by comparison with an authentic sample obtained by the previous route.[8] Conversion of (−)-**8** to (+)-**1** and (+)-**8** to (−)-**1** has been previously described.[8] Thus we were able to make the assignment of the *R* absolute stereochemistry to (−)-**1** (L-668,019), and *S* to (+)-**1** (L-668,018).[11]

Biological Evaluation of the Enantiomers[12]

In receptor binding studies[13] (+)-**1** was found to be significantly more potent than (−)-**1** as an inhibitor of

(11) It should be noted that the optical rotations of the enantiomers of compounds **7** and **1** are very solvent sensitive. Care should be taken to reproduce and to interpret these data. The signs of rotations quoted for the enantiomers of **1** refer to data obtained in 1% aqueous $NaHCO_3$.

(12) Error calculations are quoted as ± standard error of the mean. ED_{50} values for antigen-induced dyspnea in the rat are quoted with 95% confidence limits. A detailed pharmacological study of (+)-**1** and (−)-**1** will be the subject of a future publication.

(13) Pong, S. S.; Dehaven, R. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 7415.

binding of [^{3}H]LTD$_4$ to guinea pig lung membranes. (+)-1 inhibited binding with an IC_{50} value of 0.77 ± 0.15 nM (n = 4) compared to (−)-1 with an IC_{50} value of 3.2 ± 0.6 nM (n = 4). Similar differences (but not statistically significantly different by the Student's t test) were obtained on isolated human lung membranes. (+)-1: IC_{50} = 3.1 ± 0.9 nM (n = 3). (−)-1: IC_{50} 8.0 ± 3.1 nM (n = 3). (+)-1 was also apparently more potent than the (−)-1 as an antagonist of LTD$_4$-induced contractions of isolated guinea pig trachea[14] although again the differences were not statistically significant. Respective −log K_B values for (+)-1 and (−)-1 were 9.0 ± 0.2 (n = 3) and 8.7 ± 0.11 (n = 5). Interestingly, however, in vivo (+)-1 showed a nonsignificant tendency to be less potent than (−)-1. ED_{50} values for (+)-1 and (−)-1 versus antigen-induced dyspnea in hyperreactive rats[15] were respectively 0.097 (0.068–0.14) and 0.028 mg/kg (0.002–0.32) (rats (n = 5) were dosed po with drug in 1% methocel solution at 1 mL/kg by oral gavage 4 h prior to antigen provocation). This apparently anomalous reversal of potencies may relate to the different pharmacokinetic properties of the enantiomers in the rat.[16]

Conclusions

The absolute stereochemistry of the enantiomers of 1 has been assigned as R for the (−) isomer and therefore S for the (+) isomer,[11] assigned on the basis of X-ray analysis of the intermediate **5**. However, analysis of the NMR spectra of **4** and **5** shows that *contrary* to the prediction of the method of Trost et al.[10] for *O*-methylmandelates the methylene resonances of the thiopropionate chain (protons on C-21 and C-22) are significantly shifted upfield in the case of the S,R isomer **5** relative to R,R isomer **4** (see the Experimental Section). Analysis of spectra of simiar intermediates available from our earlier synthesis[8] confirmed the consistency of this observation. It is thus clear that Trost's method of assignment of absolute stereochemistry is not valid for α-methoxyphenylthiolacetic acid derivatives of thioacetals.

Somewhat surprisingly, we have found that the biological activities of the enantiomers of 1 are very similar. In vitro there is a tendency, significant only for inhibition of [^{3}H]LTD$_4$ binding to guinea pig lung membranes, for (+)-1 to be more active at the LTD$_4$ receptor. These differences do not necessarily translate to in vivo activities due to the higher blood levels and longer half-life of the (−) isomer in the rat.[16] With respect to our hypothetical LTD$_4$ receptor model, the trend of these results seems to be in opposition to the prediction that the R enantiomer would be more active. The apparent greater potency of the S enantiomer suggests that we should adjust our receptor model such that the amide group of 1 should be considered to mimic the amide functionality of the cysteinylglycine side chain in LTD$_4$ when binding to the receptor. However, because the differences are small, these data are not sufficiently definitive to allow a firm conclusion to be drawn. Clear evidence of high enantioselectivity in receptor interaction of other classes of leukotriene D$_4$ antagonists has been reported previously.[17] However these compounds (e.g. SK&F 104353 and its enantiomer) contain two asymmetric centers, the thioether and adjacent hydroxyl group, as found in leukotriene D$_4$ itself. It is likely that the hydroxyl grous serves to more rigidly define the orientation of the chains about the thioether center, while in the case of (+)- and (−)-1 the isomers have much more degrees of freedom in the receptor.

Experimental Section

All melting points were determined on a Büchi 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, TN. X-ray diffraction data were collected with an Enraf-Nonius CAD-4 diffractometer.

Preparation of Dithioacetals 4 and 5. To a suspension of the aldehyde **3**[3] (10 mmol, 2.94 g) at −78 °C in dichloroethane (40 mL) was added BHT (1.0 mmol, 220 mg) followed by (*R*)-(−)-α-methoxyphenylthiolacetic acid (10 mmol, 1.8 g), methyl 3-mercaptopropionate (10 mmol, 1.2 g), and BF_3·OEt_2 (25 mmol, 3.54 g). The cold bath was removed and the mixture was stirred for 24 h at room temperature and then saturated NH_4Cl (100 mL) was added. The mixture was extracted with ethyl acetate, and the extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness. Filtration through SiO_2 afforded a 1:1 mixture of the diasteroisomers (4.27 g, 74%). A 2.0-g sample was separated by flash chromatography over SiO_2 eluting with ethyl acetate–hexanes (1:4 then 1:3) to provide the more polar **4** (750 mg) and less polar **5** (810 mg) diastereoisomers. The compounds were recrystallized from ethyl acetate–hexanes (1:3). Crystals of **5** suitable for X-ray analysis were obtained from ethyl acetate.

4: $[\alpha]^{25}_D$ = −106° (c = 0.5, $CHCl_3$): mp 127.5 °C; ^{1}H NMR (CD_3COCD_3) δ 2.70 (m, 2 H), 2.88 (m, 2 H), 3.53 (s, 3 H, OCH_3), 3.67 (s, 3 H, $COOCH_3$), 5.0 (s, 1 H, *CH*OMe), 5.76 (s, 1 H, SC*H*S), 7.35–8.40 ppm (m, 16 H, aromatics and vinyls). Anal. ($C_{31}H_{28}ClNO_4S_2$): C, H, S, Cl, N.

5: $[\alpha]^{25}_D$ = +104° (c = 0.5, $CHCl_3$); mp 104.3 °C; ^{1}H NMR (CD_3COCD_3) δ 2.58 (m, 2 H), 2.77 (m, 2 H), 3.44 (s, 3 H, OCH_3), 3.61 (s, 3 H, $COOCH_3$), 4.94 (s, 1 H, *CH*OMe), 5.74 (s, 1 H, SC*H*S), 7.35–8.40 ppm (m, 16 H, aromatics and vinyls). Anal. ($C_{31}H_{28}ClNO_4S_2$): C, H, S, Cl, N.

Crystals of 5 formed in space group $P2_1$ with a = 14.704 (4) Å, b = 5.761 (3) Å, c = 17.888 (4) Å and β = 106.17 (1)° for Z = 2 and a calculated density of 1.319 g/cm^3. An automatic four circle diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å) was used to measure 2414 potential diffraction peaks of which 1750 were observed ($I \geq 3\sigma(I)$). Application of a multisolution tangent formula approach to phase solution gave an initial model for the structure[18] which was subsequently refined with least squares and Fourier methods. Anisotropic temperature parameters were refined for the non-hydrogen atoms while isotropic temperature factors were applied to the hydrogens but not refined. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 4F_o^2/\sigma^2(F_o^2)$ was minimized with full-matrix least squares to give an unweighted residual of 0.053.

(14) For a description of methodology, see: Carrier, R.; Cragoe, E.; Ethier, D.; Ford-Hutchinson, A. W.; Girard, Y.; Hall, R. A.; Hamel, P.; Rokach, J.; Share, N. N.; Stone, C. A.; Yusko, P. *Br. J. Pharmacol.* **1984**, *82*, 389.

(15) McFarlane, C. S.; Piechuta, H.; Hall, R. A.; Ford-Hutchinson, A. W. *Prostaglandins* **1984**, *28*, 173.

(16) Comparison of the enantiomers dosed individually as the sodium salts in rats (20 mg/kg, 1% methocel) showed that (−)-1 gave significantly higher blood levels at all time points. At the 4 h postdosing time point, levels of (−)-1 were 5.3 ± 0.7 μM (n = 6) while (+)-1 was 1.5 ± 0.3 μM (n = 5). A detailed study of the pharmacokinetics of (+)- and (−)-1 will be published in the near future. This study defined mean terminal half-lives of (−)-1 and (+)-1 in the rat as 72 and 46 min, respectively. Tocco, D. J.; deLuna, F. A.; Duncan, A. E. W.; Hsieh, J. H.; Lin, J. H. *Drug Metab. Dispos.*, in press.

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(18) The following library of crystallographic programs was used: SHELXS-86, G. M. Sheldrick, University of Gottingen, West Germany, (1986; PLUTO, W. D. S. Motherwell and W. Clegg, University of Cambridge, Cambridge, England, 1978; a version of SDP V.3, Enraf-Nonius, Delft, The Netherlands (1985) locally modified for a Sun Microsystems computer.

Figure 1 is a computer-generated drawing of **5** showing its absolute stereochemistry. All bond distances and angles are within chemically reasonable limits. With the α carbon atom of the methoxyphenylthiolacetate group of **5** known to be *R*, the other chiral carbon atom (C-19) was found to have the *S* configuration.

Preparation of Enantiomeric Dithioacetals (+)-7 and (−)-7. To a −20 °C solution of **4** (0.5 mmol, 290 mg) in dry pyridine (3 mL) was added dropwise a 1 M solution of hydrazine in tetrahydrofuran (0.5 mmol, 500 μL). After 0.5 h *tert*-butyldiphenylsilyl acrylate (1.5 mmol, 465 mg) was added and the mixture was allowed to react for 4 h. It was then quenched with 25% aqueous ammonium acetate (20 mL), extracted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered, and evaporated to dryness with use of toluene to remove pyridine to provide crude **6**. To the cooled (−5 °C) crude **6** in THF (5 mL) was added 1 M n-Bu_4NF in THF (500 μL) and the mixure was stirred 1 h. It was quenched with 25% aqueous ammonium acetate and the organic layer processed as before to give a residue which was purified by chromatography over SiO_2 using acetone–toluene–acetic acid (30:70:0.5) to yield the product (+)-7 (200 mg, 80%): $[\alpha]^{25}_D$ +1.2° (c = 1, acetone) (lit $[\alpha]^{25}_D$ −5.2° ((c = 2, CH_2CL_2)[9]).[11] Anal. ($C_{25}H_{24}ClNO_4S_2$) C, H, N, S.

Similarly **5** (58 mg) afforded (−)-7 (23 mg): $[\alpha]^{25}_D$ −2.7° (c = 1.5, acetone).

Preparation of Enantiomeric Dithioacetals (+)-8 and (−)-8. To a (−5 °C) solution of (+)-7 (0.1 mmol, 50 mg) in dichloroethane (1 mL) was added 1,1′-carbonyldiimidazole (0.11 mmol, 18 mg). After 0.5 h the mixture was warmed to room temperature for a further 0.25 h and then cooled again to −5 °C. A 1.7 M toluene solution of dimethylamine (1 mmol, 590 μL) was added and the mixture was stirred 0.75 h at −5 °C and then 0.25 h at room temperature. The reaction mixture was then evaporated to dryness and purified by chromatography over SiO_2 using ethyl acetate–hexanes (3:1) to yield the product (−)-8 (42 mg, 80%): $[\alpha]^{25}_D$ = −4.8° (c = 1.6, acetone) (lit. $[\alpha]^{25}_D$ = −4.2° (c = 1.28, acetone);[8] $[\alpha]^{25}_D$ = −5.1° (c = 2, THF)[9]).

Similarly (−)-7 (23 mg) afforded (+)-8 (16 mg): $[\alpha]^{25}_D$ = +4.1° (c = 1.6, acetone) (lit. $[\alpha]^{25}_D$ = +3.5° (c = 1.74, acetone);[8] $[\alpha]^{25}_D$ = +5.0° (c = 2, THF)[9]).

Supplementary Material Available: Tables containing the detailed X-ray experimental, fractional coordinates, temperature parameters, bond distances, and bond angles for 5 (6 pages). Ordering information is given on any current masthead page.

Synthesis and Antimicrobial and Cytotoxic Activities of Pyrrole-Containing Analogues of Trichostatin A

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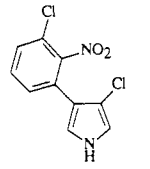
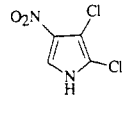
A number of aroylpyrroleacrylic acid derivatives were synthesized by standard procedures and evaluated for cytotoxicity in Vero cells and for capacity to inhibit the multiplication of viruses, bacteria, and fungi. While none of the test compounds showed any activity against bacteria and fungi, most of them inhibited the replication of some DNA viruses at concentrations allowing the exponential growth of uninfected cells. In particular three compounds (**8**, **9c**, and **10h**) showed an antiviral activity at doses that were from 4- to >8-fold lower than the maximum nontoxic doses.

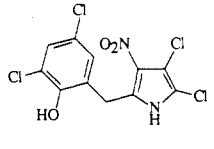
Various naturally occurring antibiotics have been found to display antimycotic activity. Pyrrolnitrin (**1**),[1] pyrrolomycins A (**2**) and B (**3**),[2,3] and the antibacterial pyoluteorin (**4**)[4] belong to the class of pyrrole derivatives that,



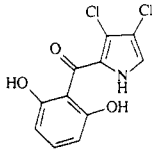
1 Pyrrolnitrin



2 Pyrrolomycin A



3 Pyrrolomycin B



4 Pyoluteorin

since 1965, has been subjected to extensive structural modifications. None of these analogues, however, showed better properties than pyrrolnitrin, which remains the sole therapeutically useful compound.

More recently, trichostatin A (**5**),[5] an antimycotic agent isolated from some strains of *Streptomyces hygroscopicus*, has attracted the attention of chemists[5,6] because of its peculiar structure possessing an unusual *p*-(dimethylamino)benzoyl group and an hydroxamic acid function. Interestingly, in addition to the antimycotic activity, trichostatin A, its glucoside trichostatin C (**6**), and trichostatic acid (**7**) have also been reported to be strong differentiation inducers of Friend leukemia cells.[6-10]

Since we have been engaged in the development of pyrrolnitrin analogues,[11,12] we examined the possibility of

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