Chiral Dioxolane Inhibitors of Leukotriene Biosynthesis: Structure–Activity Relationships and Syntheses Using Asymmetric Dihydroxylation

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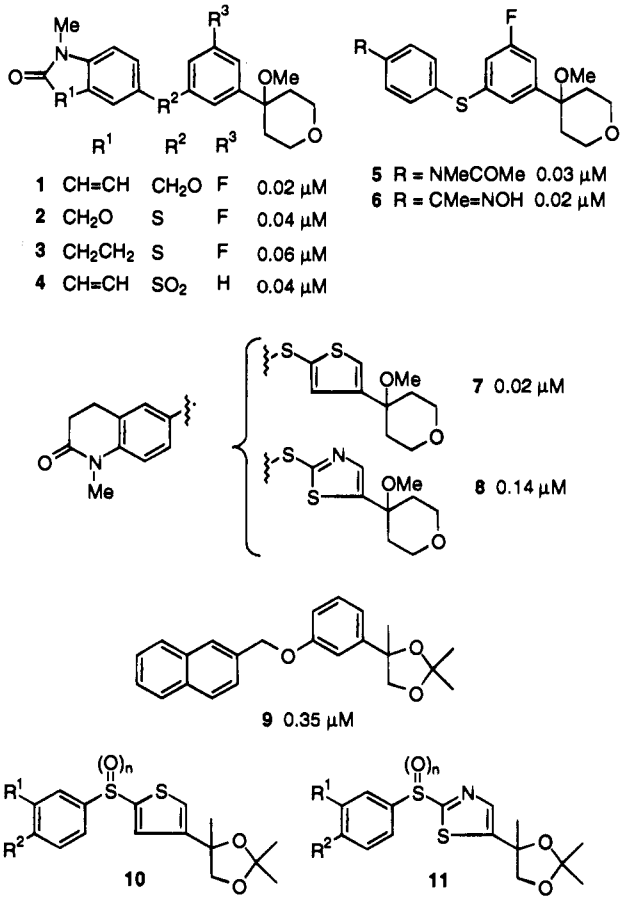
1,3-Dioxolanes have been described as chiral inhibitors of 5-lipoxygenase (5LO). In the present work, this series has been developed further to provide agents which showed comparable or superior potency *in vivo* to ZD2138, a methoxytetrahydropyran inhibitor of 5LO, which is currently undergoing clinical evaluation. An asymmetric synthesis was developed to these dioxolanes based on asymmetric dihydroxylation. (*S*)-*N*-Methyl-4′-[[4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)thien-2-yl]thio]acetanilide ((*S*)-**10d**) inhibited leukotriene B_4 (LTB_4) synthesis in A23187-stimulated human whole blood *in vitro* with IC_{50} 0.039 μM, 25-fold more potent than (*R*)-**10d**. *In vivo*, (*S*)-**10d** inhibited LTB_4 synthesis by 70% in zymosan-inflamed air pouch exudate in rat 10 h after an oral dose of 1.5 mg/kg. Structure–activity relationship considerations suggested that the dioxolane and methoxytetrahydropyran series are related, a conclusion which can be supported by molecular modeling.

5-Lipoxygenase (5LO) is the first enzyme in the biosynthesis of leukotrienes (LTs) from arachidonic acid. LTs are a family of important biological molecules. LTC_4 and LTD_4 are powerful bronchial spasmogens and LTB_4 is a potent inflammatory mediator. Because of these properties, LTs are implicated in the pathology of a number of diseases such as asthma, rheumatoid arthritis, and inflammatory bowel disease. Extensive research has been devoted to two approaches to LT modulation, namely LTC_4/LTD_4 receptor antagonism and 5LO inhibition, and both have provided agents which are in late stage clinical evaluation for the treatment of asthma.[1,2] As both spasmogenic and inflammatory LT components of asthma are addressed, a 5LO inhibitor may produce additional clinical benefit compared with a receptor antagonist. We have developed 4-methoxytetrahydropyrans (4-MeO-THPs) that are potent and selective 5LO inhibitors from which **1** (ZD2138) and **2** (ZD7717) were chosen for clinical evaluation.[3] Currently, phase II trials in asthma and rheumatoid arthritis are underway with **1**.

Our research has shown[4] that structural variation of **1** is possible while retaining potent inhibition of LT biosynthesis *in vitro*. For example (Chart 1), the 2-quinolone ring system has been replaced by benzoxazinone (**2**), dihydroquinolone (**3**), and substituted phenyl groups (**5**, **6**). Thiophene and thiazole, when appropriately substituted, have proved effective alternatives to the central benzene ring (**7**, **8**), and thio (**2**, **3**, **5**–**8**) and (often) sulfone (**4**) can replace the methyleneoxy linking group. With most of these compounds, similar inhibition to **1** was observed *in vivo*. A common feature of the aforementioned structures, however, is the 4-MeO-THP, and in order to broaden the structural diversity within our collection of 5LO inhibitors, we sought alternatives to this ring system which conferred equivalent or enhanced inhibitory potency following oral administration. Much work had been carried out to this end and a number of novel potent inhibitors *in vitro* discovered, but frequently these lacked the oral potency of 4-MeO-THPs. Illustrative is a series of dioxolanes,[5] exemplified by **9**, in which the most effective oral agents were still roughly 5–10-fold less potent than **1**. We undertook a further evaluation of the dioxolane series in which the thiophene, thiazole, and other changes embodied in **2**–**8** that had proved successful for 4-MeO-THPs were incorporated into target structures **10** and **11**. This study resulted in the discovery of potent orally

Chart 1[a]



[a] IC_{50}s shown are for inhibition of LTB_4 synthesis in A23187-stimulated human whole blood.

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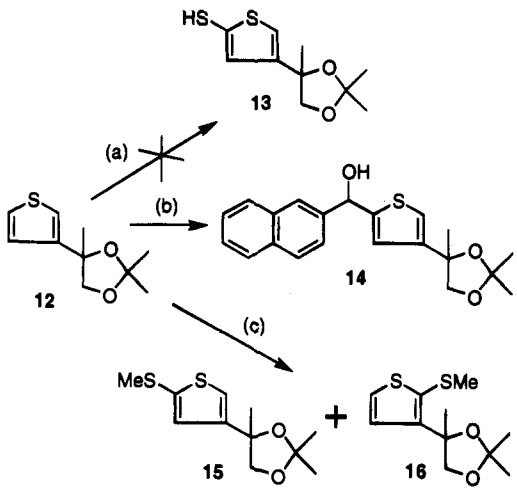
Scheme 1[a]



[a] Reagents: (a) (1) LDA, (2) S; (b) (1) LDA, (2) 2-naphthaldehyde; (c) (1) BuLi, (2) MeSSMe.

active dioxolane inhibitors of LT biosynthesis and is the subject of this report.

Synthetic Chemistry

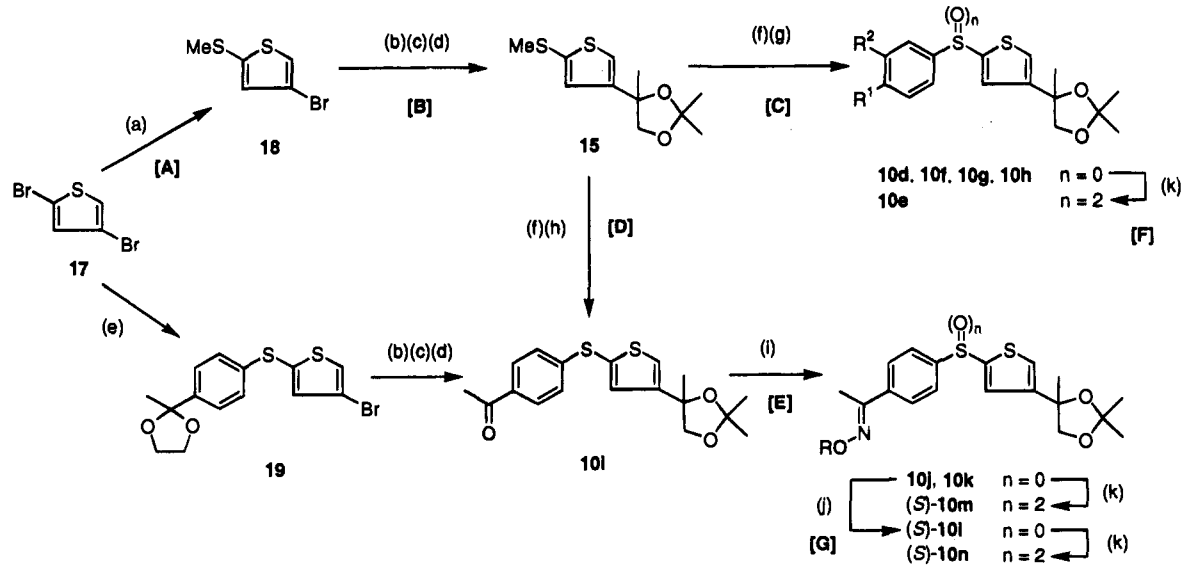
For the synthesis of thiophene-containing dioxolanes, we envisaged that thiol **13** would be a versatile intermediate in that reaction with bromo and iodo compounds would allow the generation of a variety of target structures (Scheme 1). Our first attempt at the synthesis of **13** involved treatment of the thiophene anion of **12**, generated by LDA, with sulfur. However, no thiol product could be detected, even after reaction with LAH to reduce polysulfides. The formation of the required anion was demonstrated by the isolation of **14** as the sole product after reaction with 2-naphthaldehyde, but disappointingly, exposure of the anion to MeSSMe gave both regioisomers **15** and **16**, each in 20–25% yield. In view of this result, we turned our attention to generating thiophene anions through lithium exchange with 2-bromothiophene derivatives (Scheme 2). Lithiation of 2,4-dibromothiophene with *n*-BuLi generated only the 2-anion which on reaction with MeSSMe gave **18** in 74% yield. The 4-bromo substituent of **18** was transformed using standard methods to **15**. The MeS group of **15** was cleanly demethylated by 3 equiv of MeSNa (DMF, 130 °C), but attempts to isolate and characterize the thiol led to extensive degradation. However, we found that crude Na thiolate could be reacted successfully with a variety of aryl halides. For example, reaction with *N*-methyl-4-iodoacetanilide in the presence of CuCl and K_2CO_3 gave **10d** and with 4-fluoroacetophenone provided **10i** in 89% and 73% yields, respectively. **10i** was also prepared through the intermediacy of **19** whereby the thiophene substituents were introduced in the reverse order. Further elaboration of **10i** furnished the oxime derivatives shown in Table 1.

For the syntheses of resolved dioxolanes, the Sharpless asymmetric dihydroxylation (AD) was employed (Scheme 3).[6] The requisite thiophene alkene substrate **21** was prepared from 3-acetyl-2-bromothiophene (**20**) by Wittig olefination followed by lithiation and quench with MeSSMe. Treatment of alkene **21** with AD-mix-α or AD-mix-β produced resolved diols (*S*)-**22** and (*R*)-**22** in 95% and 98% yields, respectively, and enantiomeric excesses (ees) of ≥98%. Optical purities and absolute configurations were determined by ^1H NMR experiments with a chiral shift reagent and comparison with a pair of enantiomeric diols of known absolute configurations.[7] Resolved thiazole diols were prepared similarly. Alkene **24**, prepared by reaction of 5-lithio-2-(thiomethyl)thiazole with acetone followed by dehydration, gave the diols (*R*)-**25** and (*S*)-**25** in yields of 95% and 76% with AD-mix-α and AD-mix-β, respectively.[8] Each diol **25** had an ee of 98.5%. The resolved thiophene and thiazole diols were converted to target compounds using the methods described in Scheme 2. In fact, the AD routes proved so efficient and convenient that it was easier to prepare resolved compounds directly than synthesize racemates, and no racemic thiazole target compounds were synthesized.

Biological Results and Discussion[9,10]

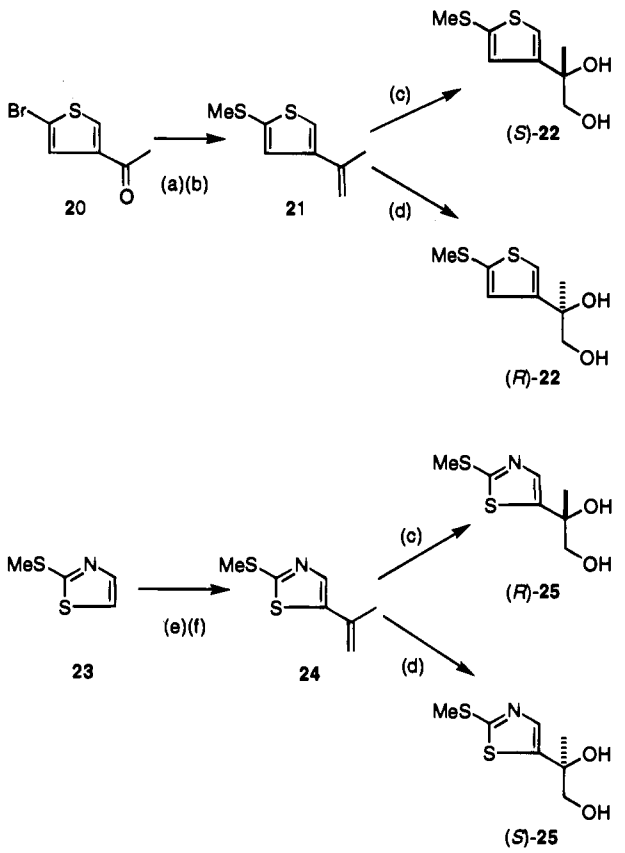
Compounds were evaluated for inhibition of LT biosynthesis *in vitro* using A 23187-stimulated human

Scheme 2[a]



[a] Reagents: (a) (1) BuLi, (2) MeSSMe; (b) (1) BuLi, (2) $MeCOCH_2OTHP$; (c) H^+; (d) $Me_2C(OMe)_2$, H^+; (e) (1) BuLi, (2) 4-[$MeC(OCH_2)_2$]PhS; (f) MeSNa; (g) ArI, CuCl, K_2CO_3; (h) 4-fluoroacetophenone; (i) $NH_2OH{\cdot}HCl$, NaOAc; (j) (1) NaH, (2) $BrCH_2CN$; (k) $KHSO_5$, NaOAc. Note: capital letters in square brackets refer to the general synthetic methods indicated in Table 2 and the Experimental Section.

Scheme 3[a]



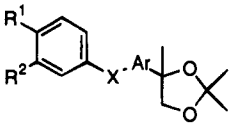
[a] Reagents: (a) $Ph_3P{=}CH_2$; (b) (1) BuLi, (2) MeSSMe; (c) AD-mix-α; (d) AD-mix-β; (e) (1) BuLi, (2) acetone; (f) $BF_3{\cdot}Et_2O$.

whole blood (Table 1). The bicycles benzoxazinone and dihydro-2-quinolone, employed advantageously in 4-MeO-THPs **2** and **3**, also produced potent inhibitors when applied in the thiophene–dioxolane series, i.e., **10c,a**. However, **10b** with the linking group extended to CH_2S was substantially less effective. The seco-analogue of **10a**, **10d**, had similar potency as did the sulfonamides **10f,h**. Removing the N-Me fragment from the seco-amide group produces **10i** which was somewhat less potent than **10d**, but the "reversed" amide **10g** had considerably reduced potency. The oxime **10j** was a potent inhibitor, significantly more potent than the O-Me oxime **10k**.

For routine evaluation *in vivo*, compounds were examined for inhibition of LTB_4 synthesis in zymosan-inflamed rat air pouch exudate 3 h after oral administration. Of the compounds described so far, only **10d** (ED_{50} 0.5 mg/kg) exhibited comparable oral potency[11] to **1**, and in order to be able to assess this compound fully *in vivo*, we prepared resolved materials. Comparison of the enantiomers of **10d** *in vitro* demonstrated an eudismic ratio of 25 with (*S*)-**10d** the eutomer. A similar ratio has been observed with enantiomeric 4-methoxy-2-methyltetrahydropyrans.[12]

With resolved intermediates now available, various derivatives of the oxime (*S*)-**10j** were prepared. In contrast to the O-Me oxime **10k**, the cyanomethylated compound (*S*)-**10l** was slightly more potent than **10j** *in vitro* and also active *in vivo* (ED_{50} 0.5 mg/kg po). The presence of the oxime provided a point of attachment by which water-solubilizing groups could be appended in attempts to enhance oral potency. For example, the *N*-morpholinoethoxy ((*S*)-**10o**) group was introduced,

Table 1. Inhibition of LT Biosynthesis by Compounds **10** and **11**



no.[a]	R^1	R^2	X	Ar[b]	human whole blood IC_{50} (μM)[c]
10a	$NMeCOCH_2CH_2$		S	thio	0.10
10b	NMeCOCH=CH		CH_2S	thio	6.93
10c	$NMeCOCH_2O$		S	thio	0.040
10d	NMeCOMe	H	S	thio	0.15, 0.070
10e	NMeCOMe	H	SO_2	thio	0.84
10f	$NMeSO_2Me$	H	S	thio	0.16
10g	CH_2CONEt_2	H	S	thio	3.22
10h	SO_2NMe_2	H	S	thio	0.21
10i	COMe	H	S	thio	0.60
10j	CMe=NOH	H	S	thio	0.040
10k	CMe=NOMe	H	S	thio	0.27
(*S*)-**10d**	NMeCOMe	H	S	thio	0.040, 0.037
(*R*)-**10d**	NMeCOMe	H	S	thio	1.18, 0.75
(*S*)-**10j**	CMe=NOH	H	S	thio	0.040
(*S*)-**10l**	$CMe{=}NOCH_2CN$	H	S	thio	0.010
(*S*)-**10m**	CMe=NOH	H	SO_2	thio	0.090
(*S*)-**10n**	$CMe{=}NOCH_2CN$	H	SO_2	thio	0.050
(*S*)-**10o**	$CMe{=}NOCH_2CH_2$-$N(CH_2CH_2)_2O$	H	S	thio	1.51
(*R*)-**11a**	$NMeCOCH_2CH_2$		S	thiaz	0.060
(*R*)-**11b**	NMeCOMe	H	S	thiaz	0.070, 0.30
(*S*)-**11b**	NMeCOMe	H	S	thiaz	6.21
(*R*)-**11d**	CMe=NOH	H	S	thiaz	0.13
(*R*)-**11e**	CMe=NOH	H	SO_2	thiaz	0.20
(*R*)-**11f**	$CMe{=}NOCH_2CN$	H	S	thiaz	0.030
(*R*)-**11g**	$CMe{=}NOCH_2CN$	H	SO_2	thiaz	0.12
(*R*)-**11c**	COMe	H	S	thiaz	0.39

[a] Ref 9. [b] thio = 2,4-thiopheneyl; thiaz = 2,5-thiazolyl. S or SO_2 is appended to the 2-position of thiophene and thiazole rings. [c] 95% confidence limits for IC_{50} values were ±2.6-fold.

but this change reduced potency considerably *in vitro*, and the compound was of no interest *in vivo* (ED_{50} >1.5 mg/kg po).

Potency in the thiazole series paralleled in many respects that of the thiophene series. Thus, dihydro-2-quinolone (*R*)-**11a**, *N*-methylacetanilide (*R*)-**11b**, and oxime (*R*)-**11d** were all potent inhibitors *in vitro*. (*R*)-**11b** has the same absolute configuration as (*S*)-**10d** and was 33-fold more potent than (*S*)-**11b** *in vitro*. In common with the thiophene series, the cyanomethylated derivative (*R*)-**11f** was a potent inhibitor *in vivo* (ED_{50} 0.5 mg/kg po); however, (*R*)-**11b** was less potent orally (ED_{50} > 1.5 mg/kg po) than its thiophene counterpart **10d**.

An advantage of S-linking groups, over the CH_2O of **1**, is that they allow conversion to sulfone, and this modification could lead to improved oral potency in two ways. Firstly, lowering lipophilicity relative to the sulfide would be expected to increase aqueous solubility. Secondly, placement of the electron-withdrawing SO_2 group adjacent to the two aryl rings could provide these rings with some protection from possible oxidative metabolism. However, in this instance, although the sulfones of oximes and *O*-(cyanomethyl)oximes in the thiophene ((*S*)-**10m**, (*S*)-**10n**) and thiazole ((*R*)-**11e**, (*R*)-**11g**) series were not significantly different from the corresponding sulfides ((*S*)-**10j**, (*S*)-**10l**; (*R*)-**11d**, (*R*)-**11f**) *in vitro*, none of these compounds showed enhanced potency *in vivo* (ED_{50}s >1.5 mg/kg po).

The thiophene acetanilide (*S*)-**10d** was chosen for evaluation alongside **1** in the rat air pouch assay but

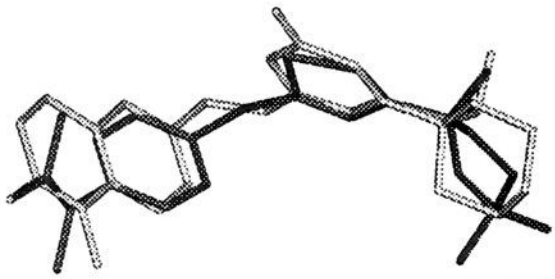


Figure 1. Overlay generated in Sybyl using multifit of **1** (light gray) and (S)-**10d** (dark gray).

at the more discriminating time point of 10 h postdose. Tested in this way, **1** and (*S*)-**10d** showed 49% ($p < 0.01$) and 70% ($p < 0.001$) inhibition of LTB_4 synthesis at 1.5 mg/kg po, respectively.

Although at first sight the dioxolanes may appear to represent a departure from the 4-MeO-THP series, much of the structure–activity relationship (SAR) presented here indicates that the two series are indeed related. For example, all the features of the 4-MeO-THP structures **2**–**8**, when applied in the dioxolane series, have also provided potent inhibitors. One way of rationalizing these observations is depicted in Figure 1, in which (*S*)-**10d** has been modeled on **1** using the multifit algorithm provided in Sybyl.[13] In this overlay, all the important structural elements[14] of 4-MeO-THPs are matched in close spatial proximity by features present in (*S*)-**10d**, *viz.* a tertiary benzylic carbon atom, a benzylic substituent (OMe or Me) providing conformational restriction or space filling, and ring oxygen atoms and amidic carbonyls available for H-bonding to the enzyme.

In conclusion, we have developed efficient asymmetric syntheses of thiophene- and thiazole-containing dioxolanes. The enantiomeric pairs (*R*)-**10d**, (*S*)-**10d** and (*R*)-**11b**, (*S*)-**11b** demonstrated enantioselective inhibition of LT biosynthesis. Enantioselective inhibition of LT biosynthesis remains rare, and this work provides further examples. This study extends earlier work on 5LO-inhibiting dioxolanes[15] and demonstrates that potency *in vivo* equal or superior to ZD2138 (**1**) is achievable with dioxolanes following oral administration. In particular, the dioxolane group offers an alternative pharmacophore to 4-MeO-THP for providing potent oral inhibitors of LT biosynthesis. One disappointing aspect of these newer dioxolanes was the difficulty of inducing target compounds to crystallize, even those exhibiting high ees. Lack of crystallinity complicates drug purification during manufacture, and for this reason, further preclinical work on (*S*)-**10d** was curtailed.

Experimental Section

General. All reactions were performed in argon atmospheres. Organic extracts were dried over $MgSO_4$ before evaporation *in vacuo* using rotary evaporators. NH_4Cl refers

Table 2. Physical and Synthetic Data for Compounds **10** and **11** and Key Intermediates

no.	formula	anal.	mp (°C)	$[\alpha]^{25}_D$[a] deg	method (yield, %)
10a	$C_{20}H_{23}NO_3S_2$	CHN	oil		A[b] (17)
10b	$C_{21}H_{23}NO_3S_2 \cdot 0.25DMF$	CHN	oil		C[c] (87)
10c	$C_{19}H_{21}NO_4S_2$	CHN	oil		C[d] (14)
10d	$C_{19}H_{23}NO_3S_2$	HN; C[e]	oil		C (89)
10e	$C_{19}H_{23}NO_5S_2 \cdot 0.6Tol$	CHN	oil		F (80)
10f	$C_{18}H_{23}NO_4S_3 \cdot 0.2Tol$	CHN	oil		C (54)
10g	$C_{22}H_{29}NO_3S_2$	HN; C[f]	oil		C (51)
10h	$C_{18}H_{23}NO_4S_3 \cdot 0.2Tol$	CHN	oil		C (90)
10i	$C_{18}H_{20}O_3S_2$	CHNS	oil		D (73); B (32)
10j	$C_{18}H_{21}NO_3S_2$	HN; C[g]	oil		E (93)
10k	$C_{19}H_{23}NO_3S_2$	HN; C[h]	oil		E (97)
(*S*)-**10d**	$C_{19}H_{23}NO_3S_2$	CHNS	oil	+9.9 ($c = 0.5$)	C (90)
(*R*)-**10d**	$C_{19}H_{23}NO_3S_2$	CHNS	oil	−10.9 ($c = 0.5$)	C (89)
(*S*)-**10j**	$C_{18}H_{21}NO_3S_2$	CHNS	oil		E (99)
(*S*)-**10i**	$C_{18}H_{20}O_3S_2$	CHS	oil		D (71)
(*S*)-**10l**	$C_{20}H_{22}N_2O_3S_2$	CHNS	oil		G (82)
(*S*)-**10m**	$C_{18}H_{21}NO_5S_2 \cdot 0.33Tol$	CHN	oil		F (81)
(*S*)-**10n**	$C_{20}H_{22}N_2O_5S_2$	CHNS	oil		F (72)
(*S*)-**10o**	$C_{24}H_{32}N_2O_4S_2$	CHNS	oil		G[i] (71)
(*R*)-**11a**	$C_{19}H_{22}N_2O_3S_2$	CHNS	oil		C (78)
(*R*)-**11b**	$C_{18}H_{22}N_2O_3S_2$	CHN	77–78	−11.9 ($c = 0.5$)	C (72)
(*S*)-**11b**	$C_{18}H_{22}N_2O_3S_2$	CHNS	76–77	+11.7 ($c = 0.3$)	C (70)
(*R*)-**11c**	$C_{17}H_{19}NO_3S_2$	HN; C[j]	oil		D (76)
(*R*)-**11d**	$C_{17}H_{20}N_2O_3S_2$	CHNS	75–78		E (90)
(*R*)-**11e**	$C_{17}H_{20}N_2O_5S_2$	CHNS	154–156		F (37)
(*R*)-**11f**	$C_{19}H_{21}N_3O_3S_2$	HN; C[k]	oil		G (94)
(*R*)-**11g**	$C_{19}H_{21}N_3O_5S_2 \cdot 0.2Tol$	CHN	oil		F (62)
12	$C_{10}H_{14}O_2S$		liq		B (43)
(*S*)-**15**	$C_{11}H_{16}O_2S_2$	CHS	liq		*m*
19	$C_{14}H_{13}BrO_2S_2$	CH; Br[l]			A (78)
21	$C_8H_{10}S_2$	CH	oil		*m*
22	$C_8H_{12}O_2S_2$	CH	40–42		*m*
(*S*)-**22**	$C_8H_{12}O_2S_2$	CHS	72–74	+14.8 ($c = 0.5$)	*m*
(*R*)-**22**	$C_8H_{12}O_2S_2$	CHS	73–74	−14.5 ($c = 0.5$)	*m*
(*S*)-**25**	$C_7H_{11}NO_2S_2$	CHN	107–109	−7.4 ($c = 0.2$)	*m*
(*R*)-**25**	$C_7H_{11}NO_2S_2$	CHNS	107–109	+7.0 ($c = 0.3$)	*m*
27	$C_{20}H_{22}O_4S_2$	CH	120–122		*m*

[a] Recorded in CH_2Cl_2 solution. [b] Prepared using bis-(3,4-dihydro-2-oxo-1-methylquinol-6-yl) disulfide (refs 4b,c) and **28**. [c] Prepared from the thiol generated from **15**, 6-(bromomethyl)-1-methylquinol-2-one (ref 3), and K_2CO_3 at room temperature. [d] Prepared from 1-methyl-6-mercaptobenzoxazin-2-one (ref 4a) and **28**. [e] C: calcd, 60.45; found, 60.0. [f] C: calcd, 62.97; found, 62.3. [g] C: calcd, 59.48; found, 60.0. [h] C: calcd, 60.45; found, 59.9. [i] *N*-(2-Chloroethyl)morpholine used as alkylating agent. [j] C: calcd, 58.43; found, 57.9. [k] C: calcd, 56.55; found, 57.0. [l] Br: calcd, 22.37; found, 21.6. [m] See the Experimental Section.

to a saturated aqueous solution. Chromatography refers to flash chromatography and was performed as described.[16] Melting points are uncorrected.

Method A. 4-Bromo-2-(methylthio)thiophene (18). *n*-BuLi (70 mL, 1.5 M in hexanes, 0.105 mol) was added dropwise to a stirred solution of 2,4-dibromothiophene (25 g, 0.014 mol) in dry ether (400 mL) at −70 °C. After 0.5 h, dimethyl disulfide (10.4 g, 0.11 mol) dissolved in ether (40 mL) was added. The reaction mixture was held at −70 °C for 0.5 h, allowed to warm to 0 °C over 2 h, and added to a mixture of NH_4Cl and ice. The organic phase was separated, the aqueous phase was re-extracted with ether, and the combined ether solutions were washed with water and evaporated. Chromatography (hexanes) gave **18** as a colorless liquid (15.3 g, 70%): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.2 (d, J = 1.5 Hz, 1H), 6.95 (d, J = 1.5 Hz), 2.5 (s, 3H).

Method B. 4-(2,3-Dihydroxyprop-2-yl)-2-(methylthio)-thiophene (22). *n*-BuLi (16.6 mL, 1.5 M in hexanes, 25 mmol) was added dropwise to a stirred solution of **18** (5.2 g, 25 mmol) dissolved in dry ether (150 mL) at −70 °C. After 1 h at −70 °C, 1-hydroxypropan-2-one tetrahydropyran ether (4.3 g, 25 mmol) dissolved in ether (5 mL) was added. The reaction mixture was kept at −70 °C for 1 h, allowed to warm to −30 °C, and added to NH_4Cl (100 mL). The organic phase was separated, the aqueous phase was re-extracted with ether (2 × 50 mL), and the combined ether solutions were washed with water and evaporated. Chromatography (EtOAc:hexanes, 30:70) gave a clear oil (5.35 g) which was dissolved in MeOH (20 mL) and treated with 2 N HCl (3 mL) for 1.5 h. NaOH (2 N, 3.5 mL) was added, MeOH evaporated, and the residue diluted with water and extracted with EtOAc. The extracts were washed with brine, evaporated, and chromatographed (EtOAc:hexanes, 1:1) to give **22** as an oil which slowly crystallized (3.08 g, 60%): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.2 (d, J = 1.5 Hz, 1H), 7.0 (d, J = 1.5 Hz, 1H), 3.75 (dd, J = 11.7, 5 Hz, 1H), 3.6 (dd, J = 11.7, 6.7 Hz, 1H), 2.86 (s, 1H), 2.5 (s, 3H), 2.24 (br t, 1H), 1.5 (s, 3H); MS m/z (CI) 205 [$(M + H)^+$].

2-(Methylthio)-4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-thiophene (15). A solution of **22** (1 g, 4.9 mmol), 2,2-dimethoxypropane (1 mL, 8.2 mmol), and PTSA (10 mg) in acetone (12 mL) was refluxed for 0.75 h, cooled to room temperature, added to aqueous $NaHCO_3$, and extracted with EtOAc. The extracts were washed with brine, evaporated, and chromatographed (EtOAc:hexanes, 5:95) to give **15** as a colorless liquid (0.97 g, 81%): ^1H NMR (CD_3SOCD_3, 200 MHz) δ 7.3 (d, J = 1.5 Hz, 1H), 7.1 (d, J = 1.5 Hz, 1H), 3.95 (AB pattern, 2H), 1.48 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H); MS (CI) m/z 245 [$(M + H)^+$].

Bis(4-acetylphenyl) Disulfide (26). NaSMe (7.7 g, 0.11 mol) was added portionwise to a stirred solution of 4-fluoroacetophenone (12 mL, 0.1 mol) in DMA (50 mL), maintaining the reaction temperature below 35 °C with external ice cooling. The reaction mixture was stirred for 2 h and added to ice/water. Solids were collected and dried at 50 °C *in vacuo* to give 4-(methylthio)acetophenone (15.44 g, 92%). This material was dissolved in DMF (100 mL), NaSMe (15 g, 0.22 mol) added, and the mixture heated at 150 °C for 1.5 h. The reaction mixture was cooled, added to a mixture of 3 N HCl (120 mL) and ice, and extracted with ether (3 × 50 mL). The extracts were washed with brine and evaporated. The crude thiol dissolved in DMSO was left at room temperature for 18 h, added to ice/water (200 mL), and extracted with EtOAc. The extracts were washed with brine, evaporated, and chromatographed (EtOAc:Tol, 10:90) to give **26** as a white solid (8.33 g, 73%): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.9 (d, J = 8.6 Hz, 4H), 7.55 (d, J = 8.4 Hz, 4 Hz), 2.6 (s, 6H); MS (CI) m/z 320 [$(M + NH_4)^+$].

Bis[4-(2-methyl-1,3-dioxolan-2-yl)phenyl] Disulfide (27). A solution of **26** (4.5 g, 15 mmol), ethylene glycol (5 mL, 90 mmol), triethyl orthoformate (10 mL, 60 mmol), and PTSA (250 mg) in toluene (30 mL) was heated at 60 °C for 3 h, cooled, diluted with EtOAc (100 mL), and washed with aqueous K_2CO_3 and brine. Evaporation and trituration with ether and hexanes gave white crystals which were collected and washed with hexanes to give **27** (4.43 g, 76%): mp 126−128 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45 (m, 8H), 4.02 (m, 4H), 3.75 (m, 4H), 1.62 (s, 6H); MS (CI) m/z 391 [$(M + H)^+$].

Method C. *N*-Methyl-4′-[[4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)thien-2-yl]thio]acetanilide (10d). NaSMe (0.54 g, 7.7 mmol) and **15** (0.54 g, 2.2 mmol) dissolved in dry DMF (5 mL) were heated at 130 °C for 0.5 h, cooled, and added to a mixture of dilute citric acid, ether, and ice. The organic phase was separated, the aqueous phase was re-extracted with ether, and the combined ether solutions were washed with brine and evaporated. The crude thiol was dissolved in DMF (5 mL), *N*-methyl-4-iodoacetanilide (0.6 g, 2.2 mmol), K_2CO_3 (0.41 g, 3 mmol), and CuCl (50 mg) were added, and the reaction mixture was stirred and heated at 130 °C for 2 h. After cooling, the reaction mixture was added to ice and aqueous K_2CO_3 and extracted with EtOAc. The extracts were evaporated and chromatographed (EtOAc:hexanes, 1:1) to give **10d** as a colorless oil (0.74 g, 89%): ^1H NMR (CD_3SOCD_3, 200 MHz) δ 7.65 (d, J = 1.5 Hz, 1H), 7.43 (d, J = 1.5 Hz), 7.27 (AB pattern, 4H), 4.0 (AB pattern, 2H), 3.15 (s, 3H), 1.8 (br s, 3H), 1.55 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H); MS (CI) m/z 378 [$(M + H)^+$].

Method F. *N*-Methyl-4′-[[4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)thien-2-yl]sulfonyl]acetanilide (10e). A solution of Oxone (50%, 300 mg) in water (2 mL) containing sufficient NaOAc to bring to pH 5−6 was added to a stirred solution of **10d** (130 mg, 0.35 mmol) in MeOH (4 mL). After 4 h, the reaction mixture was added to water and extracted with EtOAc. The extracts were washed with brine, evaporated, and chromatographed (EtOAc:Tol, 75:25) to give **10e** as a colorless oil (114 mg, 80%): ^1H NMR (CD_3SOCD_3, 200 MHz) δ 8.0 (d, J = 8.7 Hz, 2H), 7.9 (d, J = 1.5 Hz, 1H), 7.85 (d, J = 1.5 Hz, 1H), 7.6 (d, J = 8.7 Hz, 2H), 4.0 (AB pattern, 2H), 3.22 (s, 3H), 1.94 (s, 3H), 1.5 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H); MS (FAB) m/z 410 [$(M + H)^+$].

Method D. 4′-[[4-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-thien-2-yl]thio]acetophenone (10i). Crude thiol, prepared from **15** (1 g, 4.1 mmol) as described in the preparation of **10d**, was dissolved in DMF (8 mL), K_2CO_3 (0.83 g, 6 mmol) and 4-fluoroacetophenone (0.565 g, 4.1 mmol) were added, and the stirred reaction mixture was heated at 130 °C for 1.5 h, cooled, added to ice/water, and extracted with EtOAc. The extracts were evaporated and chromatographed (EtOAc:hexanes, 15:85) to give **10i** as a clear oil (1 g, 73%): ^1H NMR (CD_3SOCD_3, 250 MHz) δ 7.9 (d, J = 8 Hz, 2H), 7.7 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 4.03 (AB pattern, 2H), 1.55 (s, 3H), 1.4 (s, 3H), 1.35 (s, 3H); MS (CI) m/z 349 [$(M + H)^+$].

Method E. 4′-[[4-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-thien-2-yl]thio]acetophenone oxime (10j). A solution of **10i** (400 mg, 1.15 mmol), NaOAc (510 mg, 6.3 mmol), and $NH_2OH·HCl$ (400 mg, 5.75 mL) in EtOH (5 mL) was refluxed for 2 h, cooled, and evaporated. Water was added to the residue which was extracted with EtOAc. The extracts were evaporated and chromatographed (EtOAc:hexanes, 25:75) to give **10j** as a colorless oil (390 mg, 93%): ^1H NMR (CD_3SOCD_3, 200 MHz) δ 11.1 (s, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.6 (d, J = 8 Hz, 2H), 7.4 (d, J = 1.5 Hz, 1H), 7.2 (d, J = 8 Hz, 2H), 4.0 (AB pattern, 2H), 2.15 (s, 3H), 1.55 (s, 3H), 1.4 (s, 3H), 1.35 (s, 3H); MS (FAB) m/z 362 [$(M - H)^-$].

2-(Methylthio)-4-(prop-1-en-2-yl)thiophene (21). *n*-BuLi (1.6 M in hexanes, 37 mL, 57 mmol) was added dropwise to a stirred suspension of Ph_3PMeBr (21.4 g, 60 mmol) in THF (100 mL) cooled in ice. After 1.5 h at room temperature, the ylide solution was recooled in ice and 4-acetyl-2-bromothiophene (11 g, 52.5 mmol) dissolved in THF (60 mL) was added dropwise. The reaction mixture was kept at 10 °C for 1 h and at room temperature for 2 h, added to NH_4Cl, and extracted with ether. The extracts were evaporated and chromatographed (hexanes) to give a colorless liquid (9 g) which was converted, by the procedure used to prepare **18**, to **21** (6.25 g, 70%): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.25 (d, J = 1.5 Hz, 1H), 7.15 (d, J = 1.5 Hz, 1H), 5.3 (s, 1H), 5.02 (m, 1H), 2.5 (s, 3H), 2.1 (s, 3H); MS (CI) m/z 171 [$(M + H)^+$].

2-(Methylthio)-5-(prop-1-en-2-yl)thiazole (24). *n*-BuLi (1.55 M, 60 mL, 92 mmol) and a solution of **23** (10.8 g, 82 mmol) in ether (80 mL) were added dropwise simultaneously to stirred ether (200 mL) cooled to −10 °C. After 0.3 h, acetone (18.4 mL, 252 mmol) in ether (20 mL) was added. After 3.5 h at −10−0 °C, the reaction mixture was added to NH_4Cl and

ice. The organic phase was separated, the aqueous phase was re-extracted with ether, and the combined ether solutions were evaporated. Chromatography (EtOAc:hexanes, 40:60) gave a clear oil (13 g) which was dissolved in CH_2Cl_2 (150 mL), and $BF_3{\cdot}Et_2O$ (16.9 mL, 0.14 mol) was added. After 1 h at room temperature, the reaction mixture was added *carefully* to aqueous K_2CO_3 and extracted with ether, and the extracts were evaporated. Chromatography (EtOAc:hexanes, 6:94) gave **24** as a pale yellow oil (8.7 g, 62%): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.5 (s, 1H), 5.17 (s, 1H), 5.0 (Br s, 1H), 2.7 (s, 3H), 2.1 (br s, 3H); MS (CI) m/z 172 [$(M + H)^+$].

(*S*)-4-(1,2-Dihydroxyprop-2-yl)-2-(methylthio)thiophene ((*S*)-22). A stirred suspension of AD-mix-α (25.2 g) in *t*-BuOH (90 mL) and water (90 mL) was cooled to 0 °C and **21** (3.1 g, 18.2 mmol) added. After 18 h at 0 °C, Na_2SO_3 (10 g, 80 mmol) was added. The reaction mixture was allowed to reach room temperature, added to water, and extracted with EtOAc. The extracts were evaporated and chromatographed (EtOAc: hexanes, 60:40) to give (*S*)-**22** as a white crystalline solid (3.41 g, 92%).

(*R*)-4-(1,2-Dihydroxyprop-2-yl)-2-(methylthio)thiophene ((*R*)-22). This was prepared as a white crystalline solid by the procedure used for the preparation of (*S*)-**22** but substituting AD-mix-β for AD-mix-α (yield 93%).

(*R*)-5-(1,2-Dihydroxyprop-2-yl)-2-(methylthio)thiazole ((*R*)-25). This was prepared as a white crystalline solid by the procedure used for the preparation of (*S*)-**22** but substituting **24** for **21** (yield 95%): ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45 (s, 1H), 3.7 (br AB pattern, 2H), 3.0 (br s, 1H), 2.68 (s, 3H), 2.35 (br s, 3H), 1.6 (s, 3H).

(*S*)-5-(1,2-Dihydroxyprop-2-yl)-2-(methylthio)thiazole ((*S*)-25). This was prepared as a white crystalline solid by the procedure used for the preparation of (*R*)-**22** but substituting **24** for **21** (yield 76%).

Method G. (*S*)-4′-[[4-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)thien-2-yl]thio]acetophenone *O*-(Cyanomethyl)oxime ((*S*)-10l). NaH (60% dispersion in oil, 50 mg, 1.26 mmol) was added to a solution of (*S*)-**10j** (230 mg, 0.63 mmol) in DMF (2 mL), stirred for 1 h, and cooled in an ice bath and $BrCH_2CN$ (150 mg, 1.26 mmol) dissolved in DMF (0.5 mL) added. After 2.5 h, the reaction mixture was added to NH_4Cl and extracted with EtOAc, and the extracts were evaporated. Chromatography (EtOAc:Tol, 5:95) gave (*S*)-**10l** as a colorless oil (208 mg, 82%): ^1H NMR (CD_3SOCD_3, 200 MHz) δ 7.75 (d, J = 1.5 Hz, 1H), 7.73 (d, J = 8 Hz, 2H), 7.52 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 5.15 (s, 2H), 4.1 (AB pattern, 2H), 2.3 (s, 3H), 1.64 (s, 3H), 1.51 (s, 3H), 1.44 (s, 3H); MS (CI) m/z 403 [$(M + H)^+$].

2-Bromo-4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)thiophene (28). NBS (1.6 g, 9.0 mmol) was added to a stirred solution of **12** (1.8 g, 9.0 mmol) in DMF (5 mL) and AcOH (1 mL) cooled in an ice bath. After 1.5 h, the reaction mixture was basified with aqueous K_2CO_3 and extracted with Et_2O. The extracts were washed with water, evaporated, and chromatographed (EtOAc:hexanes, 2.5:97.5) to remove the 2,3-isomer, which was formed in similar yield, to give **28** as a colorless liquid (0.81 g, 32%): ^1H NMR ($CDCl_3$, 250 Hz) δ 7.08 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H), 4.0 (AB pattern, 2H), 1.56 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H).

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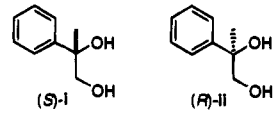
(7) The diols (*S*)-**i** and (*R*)-**ii** were prepared by AD (ref 6) under identical conditions as those used to produce the enantiomers **22** and **25**. AD-mix-α and AD-mix-β gave (*S*)-**i** and (*R*)-**ii**, respectively. The ^1H NMR (400 MHz, $CDCl_3$) spectra of (*S*)-**i** and (*R*)-**ii** in the presence of (*R*)-(+)-1,1′-bi-2-naphthol (RBN) showed the following shifts, where $\Delta_{\alpha-\beta} = \delta_\alpha - \delta_\beta$ and the subscripts indicate the products of AD using AD-mix-α and AD-mix-β, respectively: CH_2 (AB pattern, lower field doublet) $\Delta_{\alpha-\beta}$ 7.2 Hz; MeC $\Delta_{\alpha-\beta}$ − 5.2 Hz. **22**: CH_2 $\Delta_{\alpha-\beta}$ 7.43 Hz, MeC $\Delta_{\alpha-\beta}$ − 3.49 Hz. **25**: MeC $\Delta_{\alpha-\beta}$ − 1.59 Hz. These $\Delta_{\alpha-\beta}$ values correlate with those of (*S*)-**i** and (*R*)-**ii** and allow the absolute stereochemical assignments of **22** and **25** enantiomers as indicated in Scheme 3. Optical purities of **22** and **25** enantiomers were assessed using the shifts in the presence of RBN of the CH_2 and MeS ^1H NMR signals, respectively.



(8) Note the switch in *RS* designation arising from changed priority upon applying the sequence rule to thiophene and thiazole diols.
(9) Throughout the discussion, resolved compounds are referred to with *R* or *S* prefixes whereas racemates are referred to without prefixes.
(10) Biological assays referred to in this paper are described in: McMillan, R. M.; Spruce, K. E.; Crawley, G. C.; Walker, E. R. H.; Foster, S. J. Pre-clinical pharmacology of ICI D2138, a potent orally-active non-redox inhibitor of 5-lipoxygenase. *Br. J. Pharmacol.* **1992**, *107*, 1042–1047.
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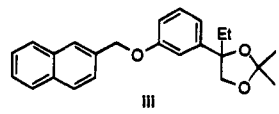
(15) Although no data with broken cell preparations of 5-lipoxygenase are presented on compounds described in this paper, earlier work established that dioxolane derivatives inhibited 5LO. For example, **iii** inhibited 5LO from rat basophilic leukemia cells (ref 10) with an IC_{50} value of 0.011 μM.



III

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