Conformational Analysis of 5-Lipoxygenase Inhibitors: Role of the Substituents in Chiral Recognition and on the Active Conformations of the (Methoxyalkyl)thiazole and Methoxytetrahydropyran Series

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The investigation of the SAR of 5-lipoxygenase (5-LO) inhibition of a series of racemic (methoxyalkyl)thiazoles, exemplified by compound 7 (ZM-211965), has led to other active, racemic derivatives in which the thiazole moiety has been replaced by an ester or an ether. Furthermore, the cyclization of the ethers has given a highly potent, but achiral series, the methoxytetrahydropyrans (methoxyTHP), exemplified by 41 (ZD-2138) presently under clinical evaluation. More recent structural investigations have led to chiral members of this series bearing a 2-methyl substituent in the tetrahydropyran ring. The potential for enantioselectivity in each of the three noncyclic, racemic series led us to synthesize the pure enantiomers ((*R*)-**13c**, (*S*)-**13c**, (*R*)-**13d**, (*S*)-**13d**, (*R*)-**15c**, (*S*)-**15c**, (*R*)-**16b**, (*S*)-**16b**, and (*R*)-**16c**, (*S*)-**16c**) and to determine their absolute configuration. The biological activity of each enantiomer was evaluated in intact mouse macrophages and in human whole blood and showed that, of these three series, only the thiazole is enantioselective and that the active configuration is (*S*) (being between 2 and 3 orders of magnitude more potent than the (*R*) isomer in mouse macrophages). Conformational analysis using systematic conformational searching, molecular mechanics, and semiempirical methods has been performed on the chiral compounds, and the results have helped to explain the enantioselectivity in the thiazole series and to define the role of the substituents around the quaternary carbon. Simultaneously in the achiral tetrahydropyran (THP) series, the critical role of the methoxy substituent has been examined through the synthesis of the ethyl (**24b**), ester (**22b**), methoxymethyl ether (**26**), hydroxymethyl (**25b**), aldehyde (**27b**), ketone (**29b**), hydroxy (**31b**), and methyl (**23b**) analogues and by analysis of their biological and conformational properties. This approach, complemented by the results of a similar study carried out on the *Z* and *E* isomers of the chiral ethyl-2-methylTHP derivative (**39b** and **40b**), has also led to the characterization of the active conformation in this series. The whole study has identified new elements to clarify the 3D structural requirements of the 5-LO active site.

Introduction

We have recently reported the discovery of the (methoxyalkyl)thiazoles, a novel series (A) of nonredox, orally active, and selective 5-lipoxygenase (5-LO) inhibitors, exemplified by ZM-211965 (**7**, Table 1).[1,2a-e] Structure–activity relationships (SAR) within this series indicated that inhibition arose from specific interactions between enzyme and inhibitors. SAR from this series of relevance to this paper (Table 1) can be summarized as follows: (1) both methoxy and thiazolyl groups were required for inhibition (**1**, **2**); (2) comparison of the potencies of conformationally constrained indans **3** (0.7 μM) and **4** (>40 μM) and tolyl derivatives **5** ($\cong$0.75 μM) and **6** (40 μM) indicated the crucial spacial arrangement of methoxy and thiazolyl groups relative to the attachment point of the naphthylmethoxy group; (3) (+)-**3** was substantially more potent than (−)-**3**, indicating enantioselective inhibition of these enantiomers;[3] (4) the position of the thiazolyl nitrogen was important: 2- and 4-thiazolyl isomers **7** and **8** were equipotent but 5-thiazolyl **9** was 10-fold less potent.

Studies in which the thiazolyl group of **7** was replaced by various functional groups afforded the active ester (B) and ether (C) series (Scheme 1). Elaboration of the ether series C by the incorporation of rings in order to restrict conformational mobility resulted in the achiral 4-methoxytetrahydropyrans (4-methoxyTHPs, D). One member of this series, **41** (ZD-2138), is currently under clinical evaluation.[4a] More recent developments in the 4-methoxyTHP series include the introduction of a 2-methyl substituent in the tetrahydropyran ring (series E, R = MeO).[4b] Similarities between the SAR of (methoxyalkyl)-thiazole and 4-methoxyTHP series implies that each binds at the same locus on 5-LO with several binding points in common.[4a] In this paper, we describe the preparation and biological properties of pure enantiomers in series A, B, and C through resolution of a common intermediate, 2-(3′-(benzyloxy)-5′-fluorophenyl)-2-hydroxybutyric acid, **11b** (Scheme 2). The absolute configuration of series A–C was assigned based on the X-ray determination of the quinine salt of (−)-**11b**.[5] The synthesis and in vitro potency of several analogues of the 4-methoxyTHP derivative in both achiral (D) and chiral (E) series are also described. Application of conformational analysis to model compounds in series A–E has been used in an attempt to identify the active conformations and to gain insight into the binding site on 5-LO.

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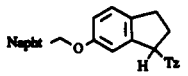
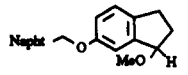
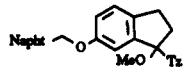
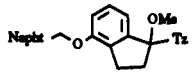
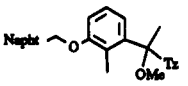
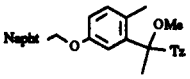
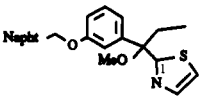
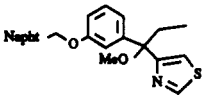
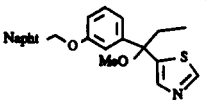
Table 1. Some Important SAR in the Thiazole Series[a]

compound		human whole blood 5-LO IC_{50} (μM)[b]
	1	>40 (2)
	2	>40 (2)
	3 (+)-3 (−)-3	0.7 ± 0.2 (4) 0.5 ± 0.2 (3) >40 (3)
	4	>40 (1)
	5	0.51–0.99
	6	40 (1)
	7	0.4 ± 0.1 (3)
	8	0.6 ± 0.1 (3)
	9	6.3 (1)

[a] Napht = 2-naphthyl; Tz = 2-thiazolyl. [b] IC_{50}'s ± SE (number of determinations). Where only two determinations were made, both results are given.

Biological Tests

Eicosanoid Generation in Murine Peritoneal Macrophages. Inhibition of LTC4 and PGE2 synthesis in plasma-free cultures of peritoneal macrophages was evaluated as described by Foster et al.[6]

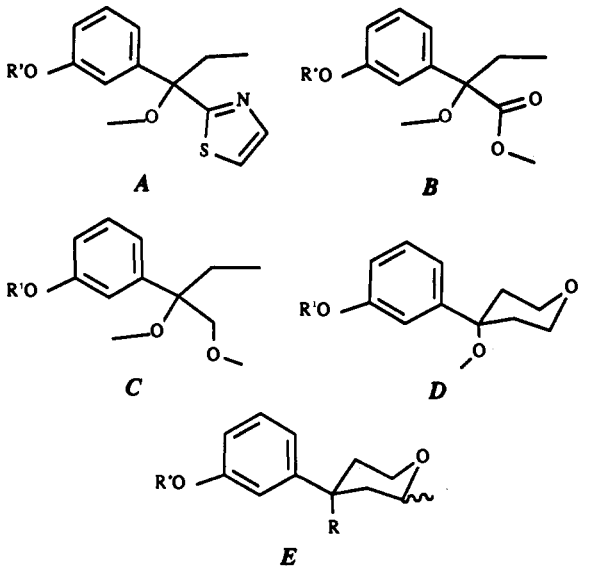
Eicosanoid Generation in Whole Blood. The potency and selectivity of 5-LO inhibitors were evaluated by studying eicosanoid generation in A-23187-stimulated and heparinized human whole blood as described by Foster et al.[6]

Statistical Analysis. IC_{50} values were calculated using an iterative, four-parameter curve-fitting program. Statistical analysis showed 95% confidence limits to be ±5.4-fold and ±2.6-fold for mouse macrophage and human whole blood assays, respectively. Differences between means were assessed by Student's paired t test with $p < 0.05$ regarded as significant.

Chemistry

The simplest way to construct a quaternary carbon substituted simultaneously by phenyl, ethyl, hydroxyl, and thiazolyl groups is to add successively a lithiothiazole and then an ethyl organometallic derivative, or the converse, to a phenylcarbonyl function.[2b] This method could not be applied to obtain the enantiomeric isomers of the present series since there is no possibility in the sequence of resolving either an intermediate or any of the end-products. Instead, we employed the hydroxy acid (*R,S*)-**11b** obtained in three steps from 1-bromo-3,5-difluorobenzene and isobutyl 2-ketobutyrate and resolved it using (−)-phenylethylamine and quinine (Scheme 2). The crystal structure was determined for the quinine salt and the *R*-configuration thus assigned to (−)-**11b**.[5] The following syntheses were performed in each enantiomeric series. The carboxylic acid group of **11b** was converted to a thiazole ring by reduction of the corresponding methyl ester to aldehyde **12c** followed by condensation with 1,4-dithiane-2,5-diol and ammonia providing the thiazolidine **12d** which was oxidized to thiazole **13a**.[7] The rest of the synthesis was straightforward as it involved deprotection of the phenolic function and condensation with either 2-(bromomethyl)naphthalene or *N*-methyl-6-(bromomethyl)quinol-2-one. The same final sequence has been applied to the resolved intermediates **12a** to give the methoxy esters **16b** and **16c**. The resolved hydroxy acid **11b** was converted to the diol **14b** which afforded the dimethoxy compound **15c** after methylation, deprotection, and alkylation as before. The achiral tetrahydropyranyl ring was built up from ethyl *m*-(benzyloxy)phenylacetate **17** using bis(2-chloroethyl) ether to give the intermediate **18** (Scheme 3). Similarly, the chiral 2-methyltetrahydropyranyl ring was made using diiodo ether **33** (Scheme 5). In the achiral THP series, the ethyl carboxylate function of **18** was reduced to the key hydroxymethyl compound **19** and then to the methyl analogue **20b**. The hydroxymethyl compound **19** was converted to the ethyl derivative **24a** via the aldehyde **21a** and the alkene **21b** intermediates. The same sequence was used to synthesize the *Z* and *E* isomers of the 2-methyl-4-ethyltetrahydropyran derivatives **39a** and **40a**. The aldehyde **21a** was also converted into the alcohol intermediate **28a** by a Grignard reaction and the ketone **29a** was obtained by oxidation of the alcohol intermediate **28b** after deprotection of **28a**. All the benzyl protection groups were removed by catalytic hydrogenation, and alkylation gave the end products **22b**, **23b**, **24b**, **25b**, **27b**, **29b**, **39b**, and **40b** (Schemes 3 and 5). Compound **25b** was further methylated to **26**. The 4-hydroxytetrahydropyranyl derivative **31b** (Scheme 4) was made from the intermediate **30**[4a] following the same final sequence as just described.

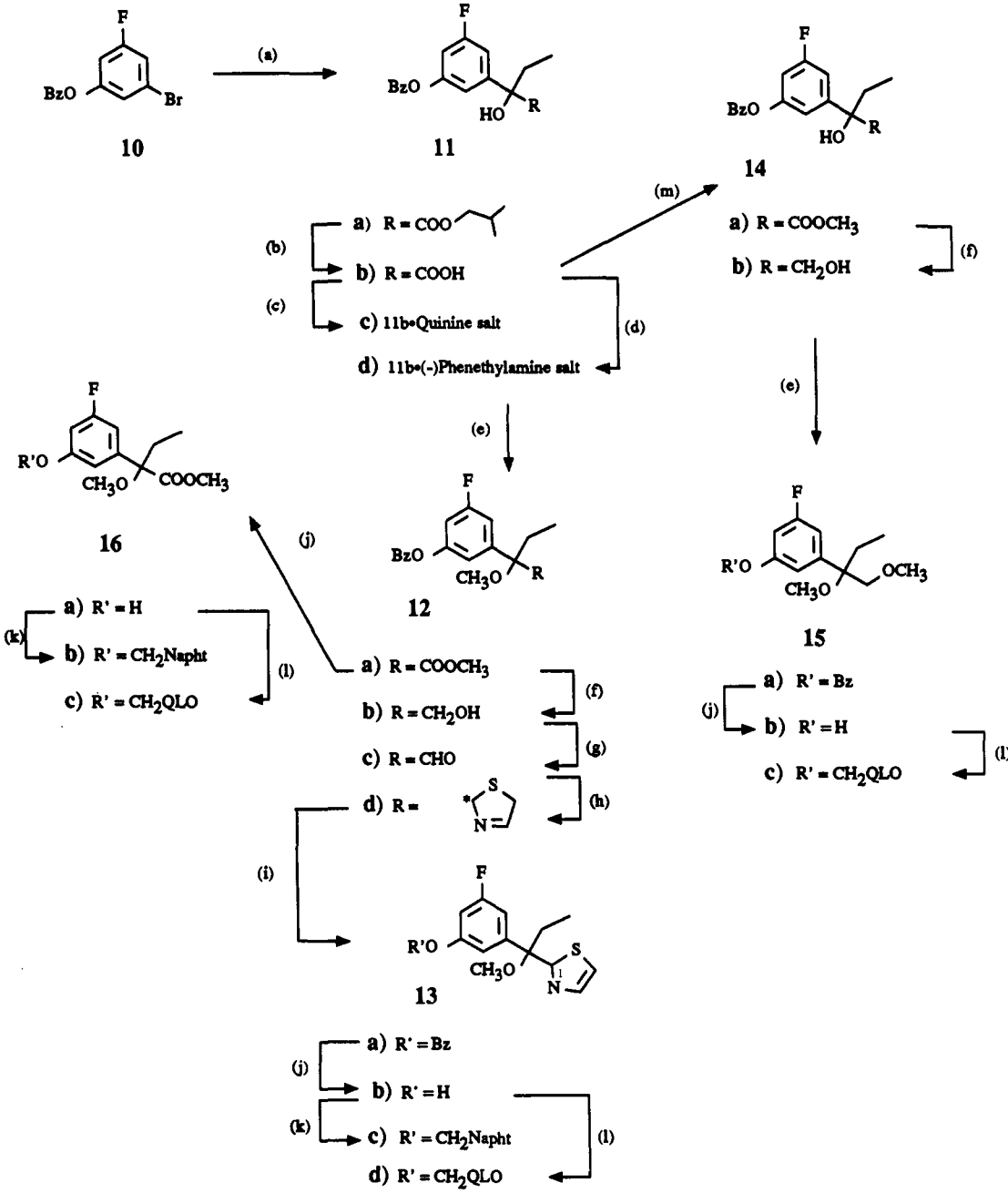
Scheme 1. General Structures of the Series Studied



Molecular Modeling

To study the conformational properties of series **A–E**, simplified models were used in which the fluorine atom from the central phenyl ring and the naphthyl- or quinolone-containing side chains were omitted. Molecular

Scheme 2. Synthesis of the Thiazole, Ester, and Ether Series[a,b]



[a] (a) Mg, Et_2O, isobutyl 2-ketobutyrate; (b) K_2CO_3, H_2O/MeOH, 80 °C; (c) (−)-quinine, EtOH/diisopropyl ether, HCl (2 N); (d) (−)-phenylethylamine, diisopropyl ether, HCl (2 N); (e) NaH, 15-crown-5, CH_3I, DMF; (f) $AlLiH_4$, Et_2O; (g) DMSO, oxalyl chloride, CH_2Cl_2, −60 °C; (h) Na_2SO_4, 1,4-dithiane-2,5-diol, NH_3, THF, reflux; (i) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, C_6H_6, reflux; (j) H_2, Pd/C, 50 psi, EtOH; (k) 2-(bromomethyl)naphthalene, K_2CO_3, DMF; (l) *N*-methyl-6-(bromomethyl)-2-quinolone, K_2CO_3, DMF; (m) CH_2N_2, Et_2O.[b] Napht = 2-naphthyl; QLO = *N*-methyl-2-quinolon-6-yl.

models were constructed on an Evans & Sutherland PS390 computer terminal applying the ZENECA in-house molecular modeling package VIKING and using the standard geometries implemented in this program.

Conformational Analysis

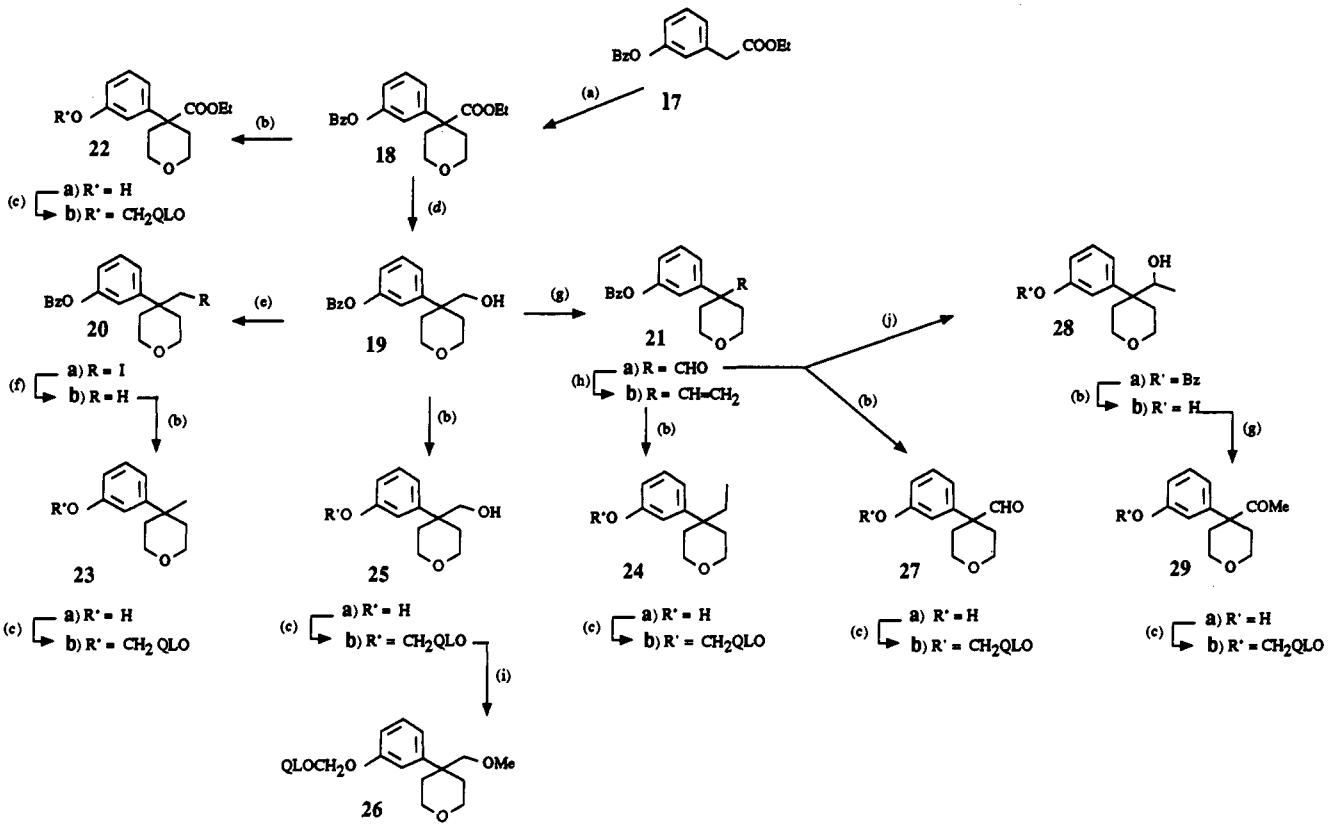
Series A–C. Preliminary systematic conformational searches for sterically allowed conformations were performed with Marshall's algorithm[8] and using a 20° incremental step. Conformations within 5 kcal of the minimum were optimized with the in-house molecular mechanics program AESOP,[9] which employs MM2 force field parameters. This led to a reduced number of different low-energy conformations. This approach was then refined by optimizing geometries and total energies of the remaining conformations with the MNDO molecular orbital procedure implemented in AMPAC.[10,11]

Series D, E. The torsional driver option in AESOP was used to evaluate torsional energy profiles for rotation of 4-substituted THPs about the phenyl ring in 30° increments, for both the phenyl equatorial and phenyl axial forms. The geometries of the energy minima were relaxed to determine the lowest energy conformations.

Results

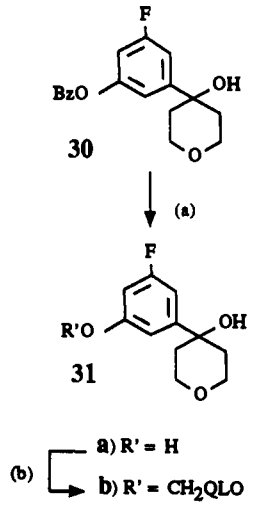
The structures and *in vitro* inhibitory potencies of LT biosynthesis for the pure enantiomers of series A–C are shown in Table 2. In thiazole series A the (*S*)-**13c** and (*S*)-**13d** were between 2 and 3 orders of magnitude more potent than the corresponding (*R*) enantiomers in zymo-

Scheme 3. Synthesis of the Tetrahydropyranyl Series[a,b]



[a] (a) NaH, 15-crown-5, DMF, NaI, bis(2-chloroethyl) ether; (b) H_2, Pd/C, 30 psi, EtOH; (c) *N*-methyl-6-(bromomethyl)-2-quinolone, K_2CO_3, DMF; (d) $AlLiH_4$, Et_2O; (e) I_2, PPh_3, imidazole, CH_3CN/diglyme, 110 °C; (f) H_2, Pd/C, Et_3N, 70 psi, EtOAc; (g) DMSO, oxalyl chloride, CH_2Cl_2, −70 °C, NEt_3; (h) $MePPh_3Br$, *n*-BuLi, THF; (i) NaH, 15-crown-5, CH_3I, DMF; (j) CH_3MgBr, THF. [b] QLO = *N*-methyl-2-quinolon-6-yl.

Scheme 4. Synthesis of the Tetrahydropyranyl Series[a-c]



[a] The synthesis of compound **30** has been described in ref 4a. [b] QLO = *N*-methyl-2-quinolon-6-yl. [c] (a) H_2, Pd/C, 30 psi, EtOH; (b) *N*-methyl-6-(bromomethyl)-2-quinolone, K_2CO_3, DMF.

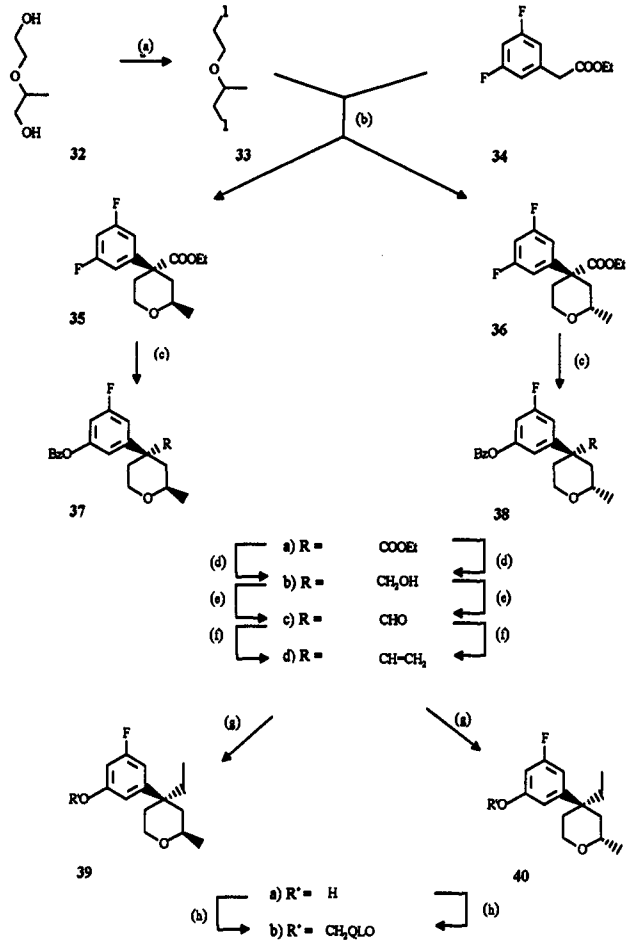
san-stimulated murine macrophages, but enantioselectivity was much reduced in ionophore-stimulated human whole blood.[12] The active indan enantiomer (+)-3 is 50-fold more potent than (−)-3, but their absolute configurations remain unknown.[3] The enantiomers in series B (**16b**, **16c**) and C (**15c**), however, showed no enantioselectivity in either macrophages or blood.

In the THP series D (Table 3), compounds with methoxy (**41**, 0.027 μM), carbethoxy (**22b**, ≅0.05 μM), or acetyl (**29b**, ≅0.07 μM) substituents at the 4-position were most potent in human whole blood with potency somewhat reduced with methoxymethyl (**26**, 0.17 μM), ethyl (**24b**, ≅0.14 μM), and methyl (**23b**, 0.44 μM) substituents whereas hydroxymethyl (**25b**, 2.3 μM), aldehydo (**27b**, ≅7.6 μM), and hydroxy (**31b**, 1.1 μM) substituted compounds were substantially less potent. In the chiral THP series E the *Z*-isomer of the 4-ethyl-2-methyl derivative (**39b**, 0.06 μM) had similar potency to **41** and was 30-fold more potent than the *E*-isomer (**40b**).

The conformational analysis performed on the simplified model of thiazole **7** gave 10 conformers corresponding to energy minima within 2.5 kcal mol^{-1} of the lowest energy conformation. Only four of these conformers, shown for their (*S*)-enantiomers in Figure 1, were compatible with the knowledge that the conformationally constrained indan (**3**) and tolyl (**5**) analogues were also active. The two lowest energy conformations (ΔE = 0.1 kcal mol^{-1}) differed only in that either the methoxy group (TZ0) or the ethyl group (TZ1) was close to the plane of the phenyl ring (torsion angles 10° and 9°, respectively) with the thiazolyl above or below the plane. In these two conformations the orientation of the thiazolyl and methoxy groups were such that the thiazolyl nitrogen and methoxy lone pairs were oriented in opposite directions with torsional angles [O–C–C–N] of −120° and −176° for TZ0 and TZ1, respectively. The converse situation in which the thiazolyl nitrogen and methoxy oxygen lone pairs were oriented in the same direction corresponded to TZ3 and TZ9 (1.4 and 2.3 kcal mol^{-1} more energetic than TZ0 and TZ1, respectively). The lower energy of TZ0 and TZ1 was expected based on electronic repulsion which will occur between oxygen and nitrogen lone pairs in TZ3 and TZ9.

A similar conformational pattern was obtained in the simplified model of ester **16** (Figure 2). Among the various conformers identified, the most stable EST0 had the methoxy group close to the plane of the aromatic ring

Scheme 5. Synthesis of the 2-Methyltetrahydropyranyl Series[a,b]



[a] (a) I_2, imidazole, PPh_3, Et_2O/CH_3CN; (b) NaH, THF, reflux; (c) NaH, benzyl alcohol, *N*-methylpyrrolidone, 50 °C; (d) $AlLiH_4$, Et_2O; (e) DMSO, oxalyl chloride, CH_2Cl_2, −70 °C, NEt_3; (f) $MePPh_3Br$-*n*-BuLi, THF; (g) H_2, Pd/C, 30 psi, EtOH; (h) *N*-methyl-6-(bromomethyl)-2-quinolone, K_2CO_3, DMF.[b] QLO = *N*-methyl-2-quinolon-6-yl; Bz = benzyl.

(torsional angle 11°) with the ethyl and ester functions above and below the plane and the carbonyl oxygen and methoxy oxygen lone pairs opposed. The second most stable conformer EST1, which was only 0.5 kcal mol^{-1} higher in energy, had the ethyl group in the plane of the aromatic ring.[13]

In the ether series for the model of **15**, as already observed in the other two noncyclic series, the two most stable conformations had either methoxy (ETH0) or ethyl (ETH1) coplanar with the phenyl ring (Figure 3) but there was only 0.3 kcal mol^{-1} between these two states. Other low-energy conformations presented various orientations of the ether chain.

In the achiral THP series D, for models of **22–27**, **29**, **31**, and **41** with the phenyl ring positioned equatorially, the most stable conformation identified had one of the THP carbons (3 or 5) nearly eclipsing the aromatic ring. This is illustrated in Figure 4 (left) for the methoxyTHP model in which the phenylTHP torsion angle was 2°. This torsion angle varied within the range 1°–17° depending on the substituent at position 4, but these changes corresponded to negligible changes in energy. The optimized conformations for each of these model compounds were determined with an axial phenyl and are illustrated by the methoxyTHP example in Figure 4 (right). The major difference between all these analogues lies in the stability of the equatorial versus the axial phenyl conformations, as indicated by the difference in energy between the equatorial and axial conformations ΔE_{ax-eq} (Table 3). The value ΔE_{ax-eq} was determined for each pair (Table 3) and, by employing $\Delta E = -RT \ln K$, was used to calculate the percentage of equatorial form present in the gas phase at 25 °C.[14] These calculations indicated that when R was methoxy or hydroxy the phenyl group was essentially in the equatorial position whereas when R was ethyl, methoxymethyl, hydroxymethyl, or methyl the major conformer had phenyl axial. In the chiral 2-methylTHP series E, the ring conformations were dominated by the requirement for the 2-methyl group to be equatorial, resulting in the phenyl group being equatorial in the *Z* isomer (**39b**) and axial in the *E* isomer (**40b**).[15]

Discussion

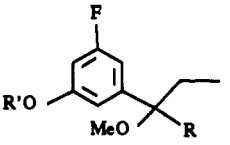
The absence of enantioselective inhibition observed in the ester (**16b**, **16c**) and ether (**15c**) series suggests that in these series two of the three substituents, methoxy or ethyl or ester/ether, can be interconverted without greatly influencing the enzymatic recognition of these inhibitors. The possibility of interconversions involving the ester group of **16b** and **16c** or the ether group of **15c**, however, seems unrealistic, since these substituents most probably take the place of the thiazole, whose presence and spatial position is crucial for activity (Table 1), confirmed by the stereoselectivity of the thiazole series. The equivalence between the methoxy and the ethyl substituents appears more realistic, as these groups have similar steric and lipophilic properties. In contrast, the thiazole series A (**13c**, **13d**) displays enantioselective inhibition, the (*S*) isomer being the more active enantiomer. This means that the methoxy group prefers not to occupy the ethyl site in the enzyme and vice versa although conformational analysis suggests that the two configurations corresponding to this interconversion are energetically almost equally likely.

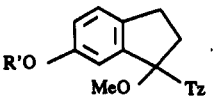
In order to gain an understanding of the active conformation and enantioselectivity of the thiazole series A, the conformationally constrained indane **3** which has similar potency to **13** has been included in the analysis. However, in view of the similarity in size and shape of methoxy and ethyl groups, conformations TZ0 and TZ3 have been kept under consideration to accommodate the possibility that the ethyl group in compounds of series A could occupy the position adopted by the methoxy in indan **3**. As with the series A model, the lowest energy conformation of indan **3** has its thiazole nitrogen and methoxy lone pairs oriented in opposite (INDS0 or INDR0) rather than the same (INDS1 or INDR1) direction with an energy difference of 1.9 kcal mol^{-1} between the two states (Figure 5). It is worth mentioning that in the 4-thiazolyl derivative (**8**) the nitrogen atom also prefers to point away from the methoxy group.[16] The equipotency between those compounds suggests that these stable conformations correspond to the active orientation of the thiazole.

Although the two lowest energy conformations of series A, TZ0 and TZ1, are equivalent in energy, it can be seen that TZ1 matches the low energy indan conformation INDS0 whereas TZ0 matches the higher energy indan conformer INDR1. TZ1 is therefore the more likely active conformation for the noncyclic thiazole series and suggests that (*S*)-**3** is the active indan enantiomer.[3]

This analysis provides an explanation for the observed enantioselectivity of series A: the methoxy substituent cannot be inverted with the ethyl because it ensures the

Table 2. Structure, Physical Data, and Biological Activity of the Separated Enantiomers in the Ester, Ether, Thiazole, and Indan Series[a]





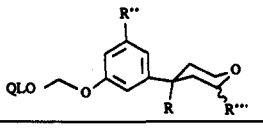
Indan

				IC_{50} (μM)[c]			
compd	R'	R	$[\alpha]^{20}_D$	mouse mϕ 5-LO	S/R[d]	human whole blood 5-LO	S/R[d]
(*S*)-**16b**	CH_2Napht	COOMe	−17.3	0.0050 ± 0.0014 (3)	0.4	0.33–0.12	0.6
(*R*)-**16b**			+23.3	0.0013–0.0046		0.22–0.07	
(*S*)-**16c**	CH_2QLO	COOMe	−20.5	0.0123–0.0551	0.4	0.34–0.08	0.7
(*R*)-**16c**			+22.9	0.0096 ± 0.0045 (3)		0.11–0.09	
(*S*)-**15c**	CH_2QLO	CH_2OCH_3	−12.6	0.045 (1)	1	0.07 (1)	7
(*R*)-**15c**			+16.5	0.048 (1)		0.52 (1)	
(*S*)-**13c**	CH_2Napht	Tz	+42.8	0.0007 (1)	700	0.74–0.34	>16
(*R*)-**13c**			−40.7	0.513 (1)		>10–6.5	
(*S*)-**13d**	CH_2QLO	Tz	+46.6	0.0016–0.0006	100	0.41 (1)	11[e]
(*R*)-**13d**			−38.5	0.2006–0.0499		4.5 (1)	
(+)-**3**[b]	CH_2Napht	indanyl	ee > 95%	<0.030 (1)	>50	0.5 ± 0.2 (3)	>80
(−)-**3**[b]			ee > 95%	1.25–1.70		>40 (3)	

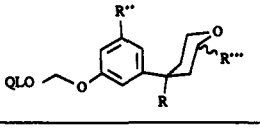
[a] Napht = 2-naphthyl; QLO = *N*-methyl-2-quinolon-6-yl; Tz = 2-thiazolyl. [b] The physical and biological data reported have been published in ref 2b. [c] IC_{50}'s ± SE (number of determinations). Where only two determinations were made, both results are given. [d] S/R is the mean value of the ratios calculated from data obtained in the same experiments. [e] Measurement not performed on the same day.

Table 3. Structure, Physical Data, Biological Activity, and Conformational Behavior of the THP Derivatives Studied[a]

Equatorial



Axial



compd	R	R''	R'''	human whole blood 5-LO IC_{50} (μM)[d]	ΔE_{ax-eq} (kcal/mol)	% of equatorial form
41[b]	OCH_3	F	H	0.027 ± 0.005 (6)	1.6	93
24b	C_2H_5	H	H	0.15–0.13	−0.8	21
22b	$COOC_2H_5$	H	H	0.07–0.03	0.3[c]	63[c]
26	CH_2OCH_3	H	H	0.17 (1)	−1.0	15
25b	CH_2OH	H	H	2.3 (1)	−1.3	10
29b	$COCH_3$	H	H	0.10–0.04	0.3	61
27b	COH	H	H	9.9–5.3	0.3	62
31b	OH	F	H	1.1 (1)	2.0	97
23b	CH_3	H	H	0.44 (1)	−0.6	27
39b	C_2H_5	F	CH_3(Z)	0.06 (1)	2.2	97
40b	C_2H_5	F	CH_3(E)	1.9 (1)	−5.4	0.01

[a] QLO = *N*-Methyl-2-quinolon-6-yl. [b] The physical and biological data reported have been published in ref 4b. [c] Calculations have been performed on the methyl ester analogue. [d] IC_{50}'s ± SE (number of determinations). Where only two determinations were made, both results are given.

correct orientation of the thiazole fragment which is also an energetically stable conformation. In the ester and ether series, the inversion of the ethyl and methoxy groups creates no difficulty in orienting the ester or ether groups for optimum binding; thus no enantioselectivity exists.[17] This analysis also implies an important role for the thiazole nitrogen in the interaction with the enzyme, possibly as a hydrogen bond acceptor. This would require optimal positioning of the thiazolyl nitrogen for hydrogen-bond formation and is consistent with the observation that 2- and 4-thiazolyl compounds **7** and **8** had similar potency, but 5-thiazolyl **9** was significantly less potent.[18]

Although the THP series is slightly divergent from the common template found in the noncyclic thiazole, ester, and ether series, the SAR data detailed in ref 4a clearly show that the left-hand side chain (R'O in Scheme 1), the central phenyl ring, and the methoxy groups occupy the active site in the same way. In the most stable conformation, the phenyl ring was co-planar with the C3–C4 bond of the THP ring. In this conformation, the C3–C4 bond occupies an equivalent position to the ethyl groups in TZ1, EST1, and ETH1. However, the THP oxygen cannot be fitted on oxygen of either ester or ether functions of series B and C nor on thiazole nitrogen of series A. The biological data given in Table 3 show that in series D the replacement of the methoxy (**41**) by an ethyl (**24b**) or an ether (**26**) leads to a decrease in potency whereas the replacement by an ester (**22b**) does not significantly change it. This observation apparently contradicts the previous conclusion that the acyclic methoxy and ethyl substituents are equivalent. This apparent anomaly can be explained by considering the THP ring conformations. Indeed, in the best derivative, the 4-methoxyTHP (**41**), the equatorial phenyl form is present in 93%, which strongly suggests that this is the active conformation. Only 21% of the ethyl derivative **24b** adopts this conformation. We could consider that if 100% of this active form were present, the in vitro potency would be equal to the methoxyTHP analogue (0.03 μM). The same conclusion can be made for the ester (**22b**), ether (**26**), and ketone (**29b**) derivatives.

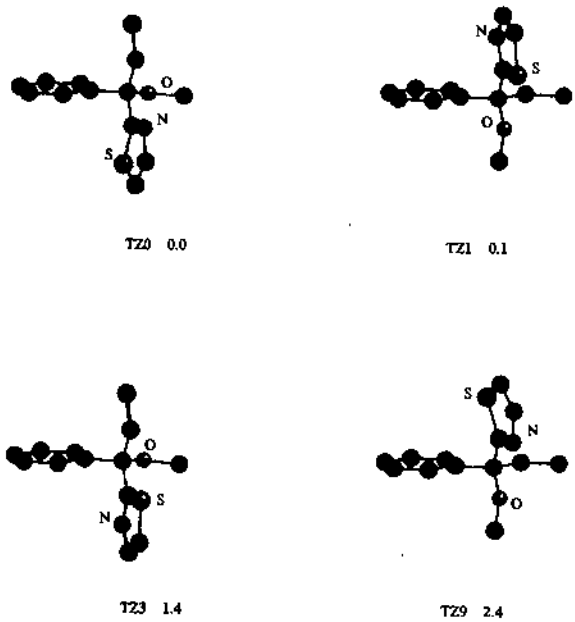


Figure 1. Four of the 10 energy minima obtained for the (methoxypropyl)thiazole series A (MNDO calculations). The values given are the energy differences (in kilocalories per mole) above the lowest energy conformation TZ0.

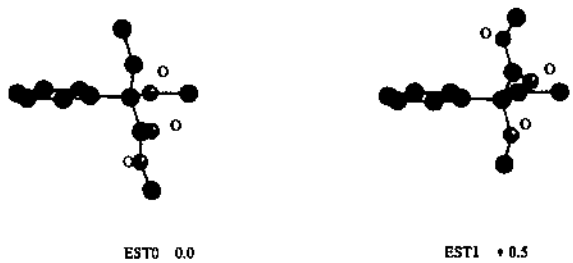


Figure 2. The two first energy minima obtained for the methoxy ester series B (MNDO calculations). The values given are the energy differences (in kilocalories per mole) above the lowest energy conformation EST0.

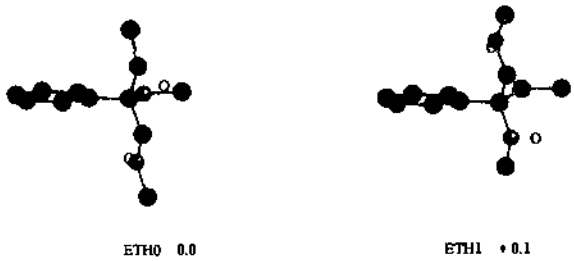


Figure 3. The two first energy minima obtained for the methoxy ether series C (MNDO calculations). The values given are the energy differences (in kilocalories per mole) above the lowest energy conformation ETH0.

The *Z* and *E* isomers of the 4-ethyl-2-methylTHP were prepared to confirm this hypothesis. This gave derivatives **39b** and 40b, in which the phenyl substituents adopted almost exclusively equatorial and axial conformations, respectively, and in which the former was some 30-fold more potent than its isomer. It is worthwhile noting that whereas calculations predict that the chiral ethyl derivative **39b** would exist in 97% of the equatorial phenyl form, its in vitro potency (0.06 μM) is slightly lower than that of the 4-methoxyTHP (41, 0.027 μM). This can be explained by the fact that series E is enantioselective and that the *Z* and *E* derivatives are racemic mixtures of active and less active enantiomers.[4b] The hydroxy compound 31b,

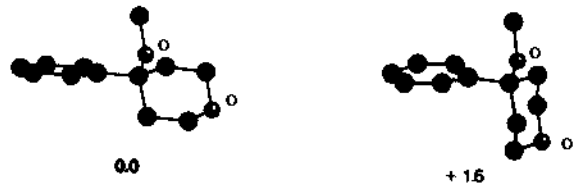


Figure 4. The most stable conformation of the methoxyTHP derivative respectively in the equatorial phenyl form (left) and axial phenyl form (right). The values given are the energy differences (in kilocalories per mole) above the lowest energy conformation (equatorial form, (left), AESOP calculation).

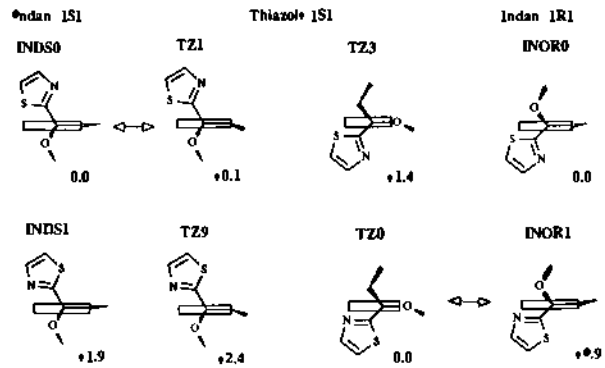


Figure 5. Schematic representation of the allowed conformations in the thiazole series: (methoxypropyl)thiazolyl and indan derivatives. The numbers represent the MNDO energy differences (in kilocalories per mole) above the most stable conformations in each series.

which exists predominantly in the equatorial phenyl form, was 50-fold less potent than 41, indicating that occupancy of this conformer alone was insufficient to achieve high potency. Similarly, the aldehydo and acetyl derivatives **27b** ($\cong$7.6 μM) and **29b** (0.07 μM) were calculated to exist to the same degree in conformations with phenyl equatorial, and yet **29b** was at least 2 orders of magnitude more potent than 27b. Another example is given by hydroxymethyl 25b (2.3 μM) and methoxymethyl ether 26 (0.17 μM). Also, the methylTHP (23b, 0.44 μM) is less potent than the ethyl (24b, $\cong$0.14 μM) or methoxy (41) derivatives. From these observations, a two-atom chain at the benzylic quaternary carbon in the THP series, with the second atom fulfilling a lipophilic or space-filling role, appeared to be an extra requirement for potent inhibition.

Conclusions

The resolution of the chiral (methoxypropyl)thiazoles, esters, and ethers derivatives 13c, 13d, 15c, 16b, and 16c and the determination of their absolute configurations has shown that, of these three noncyclic series, only the thiazole series exhibited enantioselective inhibition of 5-LO and that the more active configuration was (S). These observations complemented by the results of conformational analysis performed on these noncyclic series and on the THP series has allowed us to define more closely the role of the substituents around the quaternary benzylic carbon of each series. We conclude that the methoxy group is important, not only because it interacts with the enzyme, but also because it ensures that the necessary conformations are adopted for successful binding to the enzyme. In the (methoxyalkyl)thiazole series, it correctly orientates the thiazole ring, possibly enabling a specific interaction between the thiazolyl nitrogen and the enzyme, and in the achiral THP series it ensures a high proportion of the active equatorial phenyl conformation. Providing these

requirements are fulfilled, the methoxy group can be replaced by ethyl, ester, ketone or other functions but not by hydrophilic groups.

Experimental Section

All reactions (excluding catalytic hydrogenations) were performed in an inert (argon or nitrogen) atmosphere. Organic solutions were dried over $MgSO_4$. All evaporations were carried out in vacuo with Büchi rotary evaporators. Melting points were determined on a Reichert Jung microscope or a Mettler FP62 and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. ^1H NMR spectra were recorded on a JEOL FX90Q instrument except when noted and are reported as δ values (parts per million) relative to Me_4Si as internal standard. Mass spectra were recorded on VG1212 or VG7250SA machines. IR spectra were recorded on a Perkin-Elmer 781 infrared spectrophotometer. Optical rotations were measured on a Thorn NPL243 polarimeter. Elemental analyses were recorded with a Carlo Erba 1106 apparatus, and results obtained were within ±0.4% of the theoretical value except when noted. Water content was determined by a Karl Fisher method. All commercially available chemicals were used as supplied by the manufacturer. Column chromatography was performed on silica gel 60 (70–230 mesh) from E. Merck (Darmstadt, Germany). All enantiomeric pairs have been submitted to chromatographic analysis using either Cyclobond I DMP or Pirkle covalent phenylglycine under various conditions. No useful separation could be observed. Enantiomeric excesses (ee) have been determined on resolved compounds by NMR spectroscopy using optical shift reagent.

(*RS*)-Isobutyl 2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutyrate [(*RS*)-11a]. The preparation of the Grignard reagent was initiated by gently heating a mixture of magnesium (2.64 g, 0.11 mol), a few drops of dibromoethane, and 10% of a solution of 3-(benzyloxy)-5-bromofluorobenzene (10) (31 g, 0.11 mol) in dry Et_2O (150 mL). When reflux was obtained, the remaining solution was added dropwise at such a rate that the reflux was maintained without external heating. At the end of the reaction the mixture was allowed to cool to room temperature and a solution of isobutyl 2-ketobutyrate (15 g, 0.10 mol) in Et_2O (20 mL) was added dropwise. The mixture was stirred overnight and then partitioned between Et_2O and a saturated aqueous ammonium chloride solution. The organic phase was washed with brine, dried, and evaporated. The residue (37 g) was purified by column chromatography using CH_2Cl_2/petroleum ether (3/1, v/v) as eluant giving (*RS*)-11a as an oil (16.3 g, 47.3%): ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 0.90 (t, 3 H), 1.25 (d, 3 H), 1.45–1.65 (m, 2 H), 1.65–2.20 (m, 2 H), 4.80–5.05 (m, 1 H), 5.10 (s, 2 H), 6.50–7.10 (m, 3 H), 7.25–7.50 (m, 5 H).

(*RS*)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutyric Acid [(*RS*)-11b]. A mixture of (*RS*)-11a (10 g, 0.028 mol), potassium carbonate (5.4 g), water (5 mL), and methanol (42 mL) was heated at 80 °C for 4 h. The mixture was evaporated, and the residue was partitioned between Et_2O and water. The aqueous layer was acidified to pH 2 by the addition of 2 N aqueous HCl and extracted with EtOAc. The organic phase was washed with brine, dried, and evaporated to give white crystals (7.1 g, 84.5%): mp 104.5–105.5 °C; ^1H NMR (DMSO-d_6) δ 0.70 (t, 3 H), 2.00 (m, 2 H), 3.00–3.70 (m, 1 H), 5.30 (s, 2 H), 6.75–7.20 (m, 3 H), 7.30–7.55 (m, 5 H); EIMS 304 ($M^{\cdot+}$). Anal. ($C_{17}H_{17}FO_4 \cdot 0.25H_2O$) C, H.

(*R*)-(−)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutyric acid [(*R*)-11b]. A mixture of (*RS*)-11b (8.5 g, 0.28 mol) and quinine ($[\alpha]^{20}_{546} = -154° \pm 3°$ (*c* = 1.5, $CHCl_3$)) (9.07 g, 0.28 mol) was dissolved in EtOH in excess. After stirring for 30 min the solution was evaporated. The residue was dissolved in a minimum of hot EtOH (28 mL). The resulting solution was diluted with diisopropyl ether (230 mL) and left to stand for 2 d at room temperature. The crystals were filtered off (7.13 g), and the mother liquors were evaporated to give 11.12 g of residue which was used to obtain (*S*)-11b. The crystalline quinine salt (7.02 g) was recrystallized in a mixture of EtOH (35 mL) and diisopropyl ether (300 mL) to give 11c (4.93 g, 70%): mp 195.5–196.5 °C. 11c (4.93 g) was partitioned between 2 N aqueous HCl and Et_2O. The organic layer was washed with water and brine, then dried and evaporated to give (*R*)-11b as a white solid (2.24 g, 26%): mp 114–115 °C; $[\alpha]^{20}_D = -23° \pm 0.5°$ (*c* = 1, $CHCl_3$), ^1H NMR ($CDCl_3$) spectrum identical to (*RS*)-11b. A sample of (*R*)-11b was esterified with diazomethane to give (*R*)-14a and submitted to ^1H NMR in the presence of Europium salts[21] to show an optical purity greater than 95%.

(*R*)-Methyl 2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutyrate [(*R*)-14a]. A solution of diazomethane[22] in Et_2O was added dropwise to a solution of (−)-11b (2.24 g, 7.37 mmol) in Et_2O (35 mL). After addition, the mixture was stirred for 10 min and evaporated in vacuo to dryness to obtain an oily product (2.27 g, 97%): ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.80–2.40 (m, 2 H), 3.85 (s, 3 H), 5.10 (s, 2 H), 6.50–7.60 (m, 8 H).

(*S*)-(+)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutyric Acid [(*S*)-11b]. The method liquors of the crystallizations of 11c were pooled and evaporated to dryness. The residue (13.52 g) was partitioned between 2 N aqueous HCl and Et_2O. The organic phase was washed with brine, dried, and evaporated to give 5.34 g (0.017 mol) of partially resolved 11b which was mixed with (−)-1-phenylethylamine ($[\alpha]^{20}_{546} = -45° \pm 2°$ (*c* = 10, EtOH)) (2.13 g, 0.017 mol) in diisopropyl ether (320 mL). The mixture was left to stand 2 d at room temperature. The crystals were filtered, dried (5.79 g, 77%), and recrystallized in EtOH/diisopropyl ether (20:500 mL) to give 11d (2.71 g, 36%) as white crystals (mp 150.5–150.8 °C). 11d (2.10 g) was partitioned between 2 N aqueous HCl and Et_2O. The organic layer was washed with water and brine, dried, and evaporated to give (*S*)-11b as a white solid (1.86 g, 22%): mp 113.0–114.0 °C; $[\alpha]^{20}_D = +24.8° \pm 0.5°$ (*c* = 1, $CHCl_3$). ^1H NMR ($CDCl_3$) spectrum identical to (*RS*)-11b. A sample of (*S*)-11b was esterified with diazomethane to give (*S*)-14a and submitted to ^1H NMR in the presence of Europium salts[21] to show an optical purity greater than 95%.

(*S*)-Methyl 2-[3-(benzyloxy)-5-fluorophenyl]-2-hydroxybutyrate [(*S*)-14a] was obtained similarly to (*R*)-14a (95%): oil; ^1H NMR ($CDCl_3$) spectrum identical to (*R*)-14a.

(*S*)-(−)-Methyl 2-[3-(Benzyloxy)-5-fluorophenyl]-2-methoxybutyrate [(*S*)-12a]. Sodium hydride (2.37 g, 60% in oil, 0.059 mol) was added slowly under argon to a mixture of hydroxy acid (*S*)-11b (5.15 g, 0.017 mol) and 16-crown-5 (20 drops) in DMF (60 mL). Iodomethane (9.62 g, 0.067 mol) was added rapidly, and the mixture was stirred overnight at room temperature before being partitioned between water and ether. The organic phases were washed with brine, dried, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 as eluant to give (*S*)-12a as a yellow oil (5.11 g, 91%): $[\alpha]^{20}_D = -22.3° \pm 0.4°$ (*c* = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 1.90–2.60 (m, 2 H), 3.21 (s, 3 H) 3.70 (s, 3 H), 5.04 (s, 2 H), 6.50–7.00 (m, 3 H), 7.20–7.50 (m, 5 H).

The following compounds were obtained similarly:

(*R*)-(+)-Methyl 2-[3-(benzyloxy)-5-fluorophenyl]-2-methoxybutyrate [(*R*)-12a] starting from (*R*)-11b (90.6%): oil; $[\alpha]^{20}_D = +22.6° \pm 0.5°$ (*c* = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.77 (t, 3 H), 2.00–2.50 (m, 2 H), 3.22 (s, 3 H), 3.70 (s, 3 H), 5.04 (s, 2 H), 6.50–7.00 (m, 3 H), 7.30–7.60 (m, 5 H).

(*S*)-2-[3-(Benzyloxy)-5-fluorophenyl]-1,2-dimethoxybutane [(*S*)-15a] starting from (*S*)-14b (77%): oil; ^1H NMR ($CDCl_3$) δ 0.77 (t, 3 H), 1.60–2.20 (m, 2 H), 3.14 (s, 3 H), 3.30 (s, 3 H), 3.58 (d, 2 H), 5.04 (s, 2 H), 6.40–6.90 (m, 3 H), 7.20–7.60 (m, 5 H).

(*R*)-2-[3-(Benzyloxy)-5-fluorophenyl]-1,2-dimethoxybutane [(*R*)-15a] starting from (*R*)-14b (100%): oil; ^1H NMR spectrum identical to (*S*)-15a.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-(methoxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (26) starting from 25b (70%): mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 1.80–2.20 (m, 4 H), 3.20 (s, 3 H), 3.72 (s, 3 H), 3.30–4.00 (m, 6 H), 5.11 (s, 2 H), 6.60–7.80 (m, 9 H). EIMS 394 (MH^+). Anal. ($C_{24}H_{27}NO_4 \cdot 0.05H_2O$) C, H, N; C: calcd, 73.14; found, 72.64.

(*S*)-(+)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-methoxybutanol [(*S*)-12b]. A solution of (*S*)-12a (4.7 g, 0.014 mol) in dry Et_2O (50 mL) was added to a suspension of lithium aluminum hydride (0.54 g, 0.014 mol) in dry Et_2O (150 mL). After the mixture was stirred for 1 h, the excess of hydride was carefully destroyed with water. After the resulting mixture was partitioned between water and Et_2O, the organic phases were dried and evaporated. The residue was purified by column chromatography using a gradient of CH_2Cl_2 to CH_2Cl_2/Et_2O (90/100, v/v) as eluant to give (*S*)-12b as an oil (4.34 g, 100%): $[\alpha]^{20}_D = +1.0° \pm 0.5°$

(c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.86 (t, 3 H), 1.80–2.10 (m, 2 H), 3.16 (s, 3 H), 3.78 (s, 2 H), 5.05 (s, 2 H), 6.50–6.90 (m, 3 H), 7.20–7.60 (m, 5 H).

The following compounds were obtained similarly:

(*R*)-(−)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-methoxybutanol [(*R*)-12b] starting from (*R*)-**12a** (86%): oil, $[\alpha]^{20}_D = -1.0° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.78 (t, 3 H), 1.70–2.10 (m, 2 H), 3.16 (s, 3 H), 3.77 (s, 2 H), 5.05 (s, 2 H), 6.50–7.00 (m, 3 H), 7.25–8.10 (m, 5 H).

(*R*)-(−)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutanol [(*R*)-14b] starting from (*R*)-**14a** (100%): oil, ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 1.60–2.30 (m, 2 H + 2 OH), 3.75 (q, 2 H), 5.10 (s, 2 H), 6.50–7.00 (m, 3 H), 7.20–7.60 (m, 5 H).

(*S*)-(+)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-hydroxybutanol [(*S*)-14b] starting from (*S*)-**14a** (100%): oil; $[\alpha]^{20}_D = +3.4° \pm 0.4°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) spectrum identical to (*R*)-**14b**.

(*S*)-(−)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-methoxybutanal [(*S*)-12c]. A solution of DMSO (1.99 mL, 0.028 mol) in CH_2Cl_2 (8 mL) was added at −60 °C under argon to a solution of oxalyl chloride (30 mL). After 15 min a solution of (*S*)-**12b** (4.30 g, 0.014 mol) in CH_2Cl_2 (12 mL) was added while maintaining the temperature at −60 °C. After 15 min the mixture was allowed to reach room temperature during 1 h before being partitioned between water and CH_2Cl_2. The organic phase was washed with brine, dried, and evaporated. The residue was purified by column chromatography using a gradient of CH_2Cl_2/petroleum ether (50/50, v/v) to CH_2Cl_2 as eluant to give (*S*)-**12c** as an oily product (3.6 g, 85%): $[\alpha]^{20}_D = -2.4° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 1.70–2.25 (m, 2 H), 3.28 (s, 3 H), 5.04 (s, 2 H), 6.50–7.00 (m, 3 H), 7.20–7.60 (m, 5 H), 9.45 (s, 1 H).

The following compound was obtained similarly:

(*R*)-(+)-2-[3-(Benzyloxy)-5-fluorophenyl]-2-methoxybutanal [(*R*)-12c] starting from (*R*)-**12b** (86%): oil; $[\alpha]^{20}_D = +2.6 \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.79 (s, 3 H), 1.80–2.50 (m, 2 H), 3.29 (s, 3 H), 5.03 (s, 2 H), 6.50–7.00 (m, 3 H), 7.20–8.10 (m, 5 H), 9.50 (s, 1 H).

(*S*)-(+)-1-[3-(Benzyloxy)-5-fluorophenyl]-1-(thiazol-2-yl)propyl Methyl Ether [(*S*)-13a]. Sodium sulfate (400 mg, 2.63 mmol) and 1,4-dithiane-2,5-diol (0.86 g, 5.6 mmol) were added to a solution of (*S*)-**12c** (3.4 g, 11 mmol) in anhydrous THF (6 mL). NH_3 was bubbled through the refluxing mixture for 4 h. After evaporation the residue was filtered on silica using CH_2Cl_2 as eluant. After evaporation the oil [(*S*)-**12d**] (0.83 g, 20.5%) was obtained and dissolved in C_6H_6 (8 mL) before adding 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.56 g, 2.4 mmol). The mixture was refluxed for 3 h before being partitioned between water and C_6H_6. The organic phase was washed with brine, dried, and evaporated. The residue was purified by column chromatography using CH_2Cl_2/petroleum ether (50/50, v/v) as eluant to give (*S*)-**13a** as an oily product (0.523 g, 13%): $[\alpha]^{20}_D = +45.8° \pm 0.6°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 2.20–3.00 (m, 2 H), 3.20 (s, 3 H), 5.00 (s, 2 H), 6.50–7.00 (m, 3 H), 7.20–7.60 (m, 6 H), 7.70 (d, 1 H).

Similarly, **(*R*)-(−)-1-(Benzyloxy)-5-fluorophenyl]-1-(thiazol-2-yl)propyl methyl ether [(*R*)-13a]** was obtained starting from (*R*)-**12c** (73%): oil; $[\alpha]^{20}_D = -48.1° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 2.20–3.00 (m, 2 H), 3.20 (s, 3 H), 5.00 (s, 2 H), 6.40–7.00 (m, 3 H), 7.20–7.50 (m, 6 H), 7.70 (d, 1 H).

(*S*)-(+)-1-(3-Hydroxy-5-fluorophenyl)-1-(thiazol-2-yl)-propyl methyl ether [(*S*)-13b]. A solution of (*S*)-**13a** (0.477 g, 1.33 mmol) in EtOAc (10 mL) was hydrogenated over 30% Pd/C (1 g, 50% moist) under 50 psi overnight. After filtration the solvent was evaporated. The residue was purified by column chromatography using a gradient of CH_2Cl_2 to CH_2Cl_2/acetone (95/5, v/v) as eluant to give (*S*)-**13b** as a white solid (0.213 g, 60%): mp 152–153 °C; $[\alpha]^{20}_D = +100.0° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.75 (t, 3 H), 2.20–2.80 (m, 2 H), 3.16 (s, 3 H), 6.00–6.25 (m, 1 H), 6.50–6.80 (m, 2 H), 7.20–7.50 (m, 1 H), 7.69 (d, 1 H).

Similarly, the following compounds were obtained:

(*R*)-(−)-1-(3-Hydroxy-5-fluorophenyl)-1-(thiazol-2-yl)propyl methyl ether [(*R*)-13b] starting from (*R*)-**13a** (67%): mp 151.3–152.3 °C; $[\alpha]^{20}_D = -97.7° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 2.20–3.00 (m, 2 H), 3.17 (s, 3 H), 6.00–6.25 (m, 1 H), 6.50–6.80 (m, 2 H), 7.32 (d, 1 H), 7.70 (d, 1 H).

(*S*)-2-(3-Hydroxy-5-fluorophenyl)-2-methoxybutyl methyl ether [(*S*)-15b] starting from (*S*)-**15a** (95%): oil; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 1.50–2.20 (m, 2 H), 3.17 (s, 3 H), 3.30 (s, 3 H), 3.59 (d, 2 H), 5.10–5.60 (s, broad, 1 H), 6.30–7.00 (m, 3 H).

(*R*)-2-(3-Hydroxy-5-fluorophenyl)-2-methoxybutyl methyl ether [(*R*)-15b] starting from (*R*)-**15a** (96%): oil; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 1.65–2.10 (m, 2 H), 3.17 (s, 3 H), 3.32 (s, 3 H), 3.60 (q, 2 H), 5.09 (s, broad, 1 H), 6.35–6.80 (m, 3 H).

(*S*)-(+)-1-[3-[(Naphth-2-ylmethyl)oxy]-5-fluorophenyl]-1-(thiazol-2-yl)propyl Methyl Ether [(*S*)-13c]. Potassium carbonate (51 mg, 0.37 mmol) was added to a solution of (*S*)-**13b** (90 mg, 0.34 mmol) and 2-(bromomethyl)naphthalene (75 mg, 0.34 mol) in DMF (1.5 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and Et_2O. The etheral phase was washed with brine, dried, and evaporated. The residue was purified by column chromatography using CH_2Cl_2/petroleum ether (50/50, v/v) as eluant to give (*S*)-**13c** (102 mg, 74%): mp 75–76 °C; $[\alpha]^{20}_D = +42.8° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.75 (t, 3 H), 2.20–3.00 (m, 2 H), 3.20 (s, 3 H), 5.16 (s, 2 H), 6.50–8.10 (m, 12 H); EIMS 407 ($M^{\cdot+}$). Anal. ($C_{24}H_{22}FNO_2S$) C, H, N.

Similarly, the following compounds were obtained:

(*R*)-(−)-1-[3-[(Naphth-2-ylmethyl)oxy]-5-fluorophenyl]-1-(thiazol-2-yl)propyl methyl ether [(*R*)-13c] starting from (*R*)-**13b** (68%): mp 79–80 °C; $[\alpha]^{20}_D = -40.7° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.75 (t, 3 H), 2.00–3.00 (m, 2 H), 3.20 (s, 3 H), 6.50–8.00 (m, 12 H); EIMS 407 ($M^{\cdot+}$). Anal. ($C_{24}H_{22}FNO_2S$) C, H, N; C: calcd, 70.74; found, 70.22.

(*S*)-(−)-Methyl 2-[3-[(naphth-2-ylmethyl)oxy]-5-fluorophenyl]-2-methoxybutyrate [(*S*)-16b] from (*S*-**16a** (77%): mp 69.3–70.3 °C; $[\alpha]^{20}_D = -17.3° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 1.90–2.60 (m, 2 H), 3.21 (s, 3 H), 3.70 (s, 3 H), 5.20 (s, 2 H), 6.50–7.10 (m, 3 H), 7.30–8.00 (m, 7 H); EIMS 382 ($M^{\cdot+}$). Anal. ($C_{23}H_{23}FO_4$) C, H.

(*R*)-(+)-Methyl 2-[3-[(naphth-2-ylmethyl)oxy]-5-fluorophenyl]-2-methoxybutyrate [(*R*)-16b] from (*R*)-**16a** (90%): mp 70.2–71.2 °C; $[\alpha]^{20}_D = +23.3° \pm 0.5°$ (c, = 1, $CHCl_3$); ^1H NMR ($CDCl_3$ δ 0.76 (t, 3 H), 1.95–2.50 (m, 2 H), 3.21 (s, 3 H), 3.68 (s, 3 H), 5.20 (s, 2 H), 6.50–7.10 (m, 3 H), 7.30–8.00 (m, 7 H); EIMS 382 ($M^{\cdot+}$). Anal. ($C_{23}H_{23}FO_4$) C, H.

Using the same procedure, the following compounds were prepared:

(*S*)-(+)-1-[3-[[(*N*-methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-1-(thiazol-2-yl)propyl methyl ether [(*S*)-13d] from (*S*)-**13b** (78%): oil; $[\alpha]^{20}_D = +46.6° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.70 (t, 3 H), 2.20–3.00 (m, 2 H), 3.15 (s, 3 H), 3.65 (s, 3 H), 5.00 (s, 2 H), 6.40–7.80 (m, 10 H); EIMS 439 (MH^+). Anal. ($C_{24}H_{23}FN_2O_3S \cdot 0.1H_2O \cdot 0.17C_3H_6O \cdot 0.06C_6H_7NO$) C, H, N; C: calcd, 65.44; found, 64.53. Water, acetone, and DMF content have been approximated by NMR.

(*R*)-(−)-1-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-1-(thiazol-2-yl)propyl methyl ether [(*R*)-13d from (*R*)-**13b** (68%): oil; $[\alpha]^{20}_D = -38.5° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 2.00–3.00 (m, 2 H), 3.20 (s, 3 H), 3.72 (s, 3 H), 5.06 (s, 2 H), 6.40–7.80 (m, 10 H); EIMS 439 (MH^+). Anal. ($C_{24}H_{23}FN_2O_3S \cdot 0.16H_2O \cdot 0.01CH_2Cl_2$) C, H, N; C: calcd, 65.25; found, 64.70; H: calcd, 5.32; found, 5.82. CH_2Cl_2 content has been approximated by NMR.

(*R*)-(+)-2-[3-[[(*N*-methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-2-methoxybutyl methyl ether [(*R*)-15c] starting from (*R*)-**15b** (58%): oil; $[\alpha]^{20}_D = +16.5° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.78 (t, 3 H), 1.60–2.10 (m, 2 H), 3.16 (s, 3 H), 3.31 (s, 3 H), 3.60 (q, 2 H), 3.72 (s, 3 H), 5.10 (s, 2 H), 6.50–7.00 (m, 4 H), 7.30–7.80 (m, 4 H); EIMS 400 (MH^+). Anal. ($C_{23}H_{26}FNO_4$) C, H, N.

(*S*)-(−)-2-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-2-methoxybutyl methyl ether [(*S*)-15c] starting from (*S*)-**15b** (74%): oil; $[\alpha]^{20}_D = -12.6° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.78 (t, 3 H), 1.50–2.10 (m, 2 H), 3.15 (t, 3 H), 3.31 (t, 3 H), 3.59 (d, 2 H), 3.72 (s, 3 H), 5.10 (d, 2 H), 6.40–7.00 (m, 4 H), 7.20–7.80 (m, 4 H); EIMS 400 (MH^+). Anal. ($C_{23}H_{26}FNO_4$) C, H, N.

(*S*)-(−)-Methyl2-[3-[[(*N*-methyl-2-quinolon-6-yl))methyl]oxy]-5-fluorophenyl]-2-methoxybutyrate [(*S*)-16c] from (*S*)-**16a** (74%): mp 55–56 °C; $[\alpha]^{20}_D = -20.5° \pm 0.5°$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.70 (t, 3 H), 1.80–2.50 (m, 2 H), 3.16 (s, 3 H), 3.64 (s, 3 H), 3.66 (s, 3 H), 5.03 (s, 2 H), 6.40–7.00 (m, 4 H),

7.10–7.60 (m, 4 H); EIMS 414 (MH^+). Anal. ($C_{23}H_{24}FNO_5 \cdot 0.3H_2O$) C, H, N; H: calcd, 5.92; found, 6.36.

(*R*)-(+)-Methyl2-[3-[[(*N*-methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-2-methoxybutyrate [(*R*)-16c] from (*R*)-**16a**] (75%): oil; $[\alpha]^{20}_D = +22.9° \pm 0.5°$ ($c = 1$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3 H), 2.00–2.50 (m, 2 H), 3.23 (s, 3 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 5.10 (s, 2 H), 6.50–7.00 (m, 4 H), 7.30–7.80 (m, 4 H); FABMS 414 (MH^+). Anal. ($C_{23}H_{24}FNO_5 \cdot 0.14EtOAc$) C, H, N; C: calcd, 66.45; found, 67.38; H: calcd, 5.95; found, 6.39.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-(ethoxycarbonyl)-3,4,5,6-tetrahydro-2*H*-pyran (22b) from **22a** (60%): mp 109–110 °C; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H), 1.70–2.70 (m, 4 H), 3.30–4.30 (m, 9 H), 5.10 (s, 2 H), 6.60–7.80 (m, 9 H); EIMS 422 (MH^+). Anal. ($C_{25}H_{27}NO_5$) C, H, N.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (23b) from **23a**, (40%): mp 107–108 °C; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.40–2.60 (m, 4 H), 3.50–3.90 (m, 7 H), 5.12 (s, 2 H), 6.50–7.80 (m, 9 H); EIMS 364 (MH^+). Anal. ($C_{23}H_{25}NO_3 \cdot 0.35H_2O$) C, H, N.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-ethyl-3,4,5,6-tetrahydro-2*H*-pyran (24b) from **24a** (63%): mp 139–140 °C; ^1H NMR ($CDCl_3$) δ 0.56 (t, 3 H), 1.50–2.30 (m, 6 H), 3.40–4.00 (m, 4 H), 3.72 (s, 3 H), 5.12 (s, 2 H), 6.60–7.70 (m, 9 H); EIMS 378 (MH^+). Anal. ($C_{24}H_{27}NO_3 \cdot 0.25H_2O$) C, H, N.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-(hydroxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (25b) from **25a** (71%): mp 60.5–61.5 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.30 (m, 4 H), 3.30–4.00 (m, 6 H), 3.72 (s, 3 H), 5.12 (s, 2 H), 6.60–7.80 (m, 9 H); EIMS 380 (MH^+). Anal. ($C_{23}H_{25}NO_4 \cdot 0.25H_2O$) C, H, N; C: calcd, 71.99; found, 71.37.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-formyl-3,4,5,6-tetrahydro-2*H*-pyran (27b) from **27a** (45%): glass; ^1H NMR ($CDCl_3$) δ 1.80–2.70 (m, 4 H), 3.40–4.20 (m, 4 H), 3.73 (s, 3 H), 5.11 (s, 2 H), 6.60–7.90 (m, 9 H), 9.40 (s, 1 H); EIMS 370 (MH^+). Anal. ($C_{23}H_{23}NO_4 \cdot 0.27H_2O$) C, H, N; C: calcd, 72.31; found, 71.80.

4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-(carboxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (29b) from **29a** (52%): mp 125–126 °C; ^1H NMR ($CDCl_3$) δ 1.90 (s, 3 H), 1.90–2.60 (m, 4 H), 3.73 (s, 3 H), 3.40–4.10 (m, 4 H), 5.10 (s, 2 H), 6.60–7.80 (m, 9 H); EIMS 392 (MH^+). Anal. ($C_{24}H_{25}NO_4 \cdot 0.17H_2O$) C, H, N.

4-[3-[[(*N*-methyl-2-quinolon-6-yl)methyl]oxy]phenyl]-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (31b) from **31a** (34%): mp 181–182 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.20 (m, 4 H), 3.75 (s, 3 H), 3.85–4.00 (m, 4 H), 5.10 (s, 2 H), 6.58–6.98 (m, 4 H), 7.40 (d, 1 H), 7.58–7.70 (m, 3 H); EIMS 383 ($M^{\bullet+}$). Anal. ($C_{22}H_{22}NFO_4$) C, H, N.

(*Z*)-(2*RS*,4*RS*)-4-[3-[[(*N*-Methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-4-ethyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (39b) from **39a** (52%): mp 98.5–99.5 °C (EtOH/pentane); ^1H NMR ($CDCl_3$) δ 0.55 (t, 3 H), 1.25 (d, 3 H), 1.40–2.05 (m, 6 H), 3.75 (s, 3 H), 3.55–4.0 (m, 3 H), 5.10 (s, 2 H), 6.45–6.80 (m, 4 H), 7.30–7.75 (m, 4 H); EIMS 410 (MH^+). Anal. ($C_{25}H_{28}FNO_3$) C, H, N.

(*E*)-(2*SR*,4*RS*)-4-[3-[[(*N*-methyl-2-quinolon-6-yl)methyl]oxy]-5-fluorophenyl]-4-ethyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (40b) from **40a** (68%): oil; ^1H NMR ($CDCl_3$) δ 0.55 (t, 3 H), 1.10 (d, 3 H), 1.20–1.80 (m, 5 H), 2.00–2.25 (m, 1 H), 3.70 (s, 3 H), 3.25–3.90 (m, 3 H), 5.10 (s, 2 H), 6.45–6.80 (m, 4 H), 7.30–7.75 (m, 4 H); EIMS 410 (MH^+). Anal. ($C_{25}H_{28}FNO_3$) C, H, N.

4-[3-(Benzyloxy)phenyl]-4-(ethoxycarbonyl)-3,4,5,6-tetrahydro-2*H*-pyran (18). NaH (60% dispersion in oil, 0.176 g, 4.4 mmol) was added slowly to a stirred solution of **17** (0.540 g, 2 mmol) in dry DMF (10 mL) containing 3 drops of 15-crown-5 at room temperature. After 25 min, sodium iodide (0.3 g, 2 mmol) and bis(2-chloroethyl) ether (0.488 g, 2 mmol) were added. After 12 h, the mixture was acidified with HCl (0.5 N) and extracted with Et_2O (2 × 20 mL). The combined organic solutions were washed with brine (2 × 10 mL), dried, and evaporated. The residue was purified by column chromatography using an increasing gradient of Et_2O in CH_2Cl_2 (0/100 to 5/95, v/v) as eluant to give **18** as a yellow solid (0.325 g, 48%): mp 70–71 °C; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H), 1.75–2.11 (m, 2 H), 2.30–2.60 (m, 2 H), 3.30–4.30 (m, 6 H), 5.05 (s, 2 H), 6.70–7.60 (m, 9 H).

4-[3-(Benzyloxy)phenyl]-4-(hydroxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (19). A solution of the **18** (0.45 g, 1.2 mmol) in anhydrous Et_2O (15 mL) was added dropwise to a suspension of lithium aluminum hydride (0.17 g, 4.47 mmol) in Et_2O (2 mL). After 10 min, the excess of hydride was destroyed by addition of EtOAc (2 mL) and then water (2 mL). The insoluble was decanted and washed with Et_2O (3 × 3 mL). The solvent was dried and evaporated to give **19** as an oil (0.375 g, 100%): ^1H NMR ($CDCl_3$) δ 1.60–2.30 (m, 4 H), 3.30–4.00 (m, 6 H), 5.07 (s, 2 H), 6.70–7.50 (m, 9 H).

Similarly, the following compounds were obtained:

(*E*)-(2*RS*,4*SR*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-(hydroxymethyl)-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (37b) from **37a** (89%): oil; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H), 1.20–2.20 (m, 4 H), 3.55–4.10 (m, 5 H), 5.04 (s, 2 H), 6.50–6.80 (m, 3 H), 7.30–7.50 (m, 5 H).

(*Z*)-(2*SR*,4*RS*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-(hydroxymethyl)-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (38b) from **38a** (93%): oil; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H), 1.25–1.95 (m, 2 H), 2.05–2.30 (m, 2 H), 3.25–3.60 (m, 5 H), 3.75–4.00 (m, 1 H), 5.05 (s, 2 H), 6.55–6.80 (m, 3 H), 7.30–7.50 (m, 5 H).

4-[3-(Benzyloxy)phenyl]-4-(iodomethyl)-3,4,5,6-tetrahydro-2*H*-pyran (20a). A solution of iodine (1.91 g, 7.5 mmol), triphenylphosphine (1.96 g, 7.5 mmol), and imidazole (0.68 g, 10 mmol) in a mixture of acetonitrile (5 mL) and diglyme and (15 mL) was stirred at room temperature for 15 min. A solution of **19** (1.5 g, 5 mmol) in acetonitrile (2 mL) was added. The resulting mixture was heated at 100 °C for 6 h. It was cooled to room temperature and the acetonitrile evaporated. The residue was diluted with EtOAc (10 mL), washed with aqueous sodium thiosulfate (10% w/v, 10 mL) and brine (2 × 5 mL), dried, and evaporated. The material obtained was purified by column chromatography using CH_2Cl_2/petroleum ether (50/50, v/v) as eluant to give **20a** as a white solid (1.427 g, 70%): mp 76.5–77.5 °C (*n*-pentane); ^1H NMR ($CDCl_3$) δ 1.70–2.50 (m, 4 H), 3.20–4.00 (m, 6 H), 5.06 (s, 2 H), 6.70–7.60 (m, 9 H).

4-[3-(Benzyloxy)phenyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (20b). **20a** (0.58 g, 1.42 mmol) was hydrogenated over Pd/C (10%, 0.2 g) in EtOAc (6 mL) and triethylamine (0.286 g, 2.84 mmol) at 70 psi for 12 h. The mixture was then filtered on Celite and evaporated. Column chromatography of the residue using petroleum ether/EtOAc (85/15, v/v) as eluant gave **20b** as an oil (0.22 g, 55%).

4-[3-(Benzyloxy)phenyl]-4-formyl-3,4,5,6-tetrahydro-2*H*-pyran (21a). A solution of dimethyl sulfoxide (2.62 g, 33 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of oxalyl chloride (2.12 g, 16 mmol) in CH_2Cl_2 (15 mL) at −70 °C. After 15 min a solution of **19** (5 g, 16 mmol) was added dropwise while the temperature was kept below −60 °C. After 1 h at −60 °C, triethylamine (11.7 mL, 83 mmol) was added and the mixture was stirred a further 90 min at −60 °C, before being partitioned between water and CH_2Cl_2. The organic phase was washed with brine (2 × 10 mL), dried, and evaporated. Column chromatography of the residue using CH_2Cl_2 as eluant gave **21a** as a white solid (3.7 g, 64%): mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 1.80–2.50 (m, 4 H), 3.30–4.00 (m, 4 H), 5.05 (s, 2 H), 6.70–7.50 (m, 9 H), 9.40 (s, 1 H); CIMS 297 (MH^+). Anal. ($C_{19}H_{20}O_3$) C, H.

Similarly, the following compounds were prepared:

4-(3-Hydroxyphenyl)-4-(carboxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (29a) from **28b** (77%): mp 120–121 °C; ^1H NMR ($CDCl_3$) δ 1.94 (s, 3 H), 1.90–2.60 (m, 4 H), 3.40–4.10 (m, 4 H), 6.60–7.40 (m, 4 H); EIMS 221 (MH^+). Anal. ($C_{13}H_{16}O_2$) C, H; C: calcd, 70.94; found, 70.21.

(*E*)-(2*RS*,4*SR*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-formyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (37c) from **37b** (91%): oil; ^1H NMR ($CDCl_3$) δ 1.24 (d, 3 H), 1.40–2.10 (m, 2 H), 2.25–2.55 (m, 2 H), 3.35–3.70 (m, 2 H), 3.90–4.15 (m, 1 H), 5.05 (s, 2 H), 6.50–6.75 (m, 3 H), 7.30–7.50 (m, 5 H), 9.39 (s, 1 H).

(*Z*)-(2*SR*,4*RS*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-formyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (38c) from **38b** (88%): oil; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H), 1.65–2.40 (m, 4 H), 3.40–3.75 (m, 2 H), 3.85–4.10 (m, 1 H), 5.05 (s, 2 H), 6.50–6.75 (m, 3 H), 7.30–7.50 (m, 5 H), 9.29 (s, 1 H).

4-[3-(Benzyloxy)phenyl]-4-vinyl-3,4,5,6-tetrahydro-2*H*-pyran (21b). A solution of *n*-butyllithium in hexane (1.6 M, 1.37 mL, 2.2 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (0.78 g, 2.2 mmol) in

anhydrous THF (15 mL) and Et_2O (2 mL). After 2 h at room temperature a solution of **21a** (0.592 g, 2 mmol) in Et_2O (5 mL) was added. The resulting mixture was stirred for 4 h at room temperature and filtered. The precipitate was washed with Et_2O (2 × 10 mL), and the combined organic phases were washed with brine (2 × 5 mL), dried, and evaporated. Column chromatography of the residue using CH_2Cl_2 as eluant gave **21b** as a colorless oil (0.4 g, 70%): ^1H NMR ($CDCl_3$) δ 1.80–2.30 (m, 4 H), 3.50–3.80 (m, 4 H), 4.80–5.30 (m, 2 H), 5.05 (s, 2 H)), 5.68–6.05 (m, 1 H), 6.70–7.50 (m, 9 H).

The following compounds were similarly prepared:

(*Z*)-(2*RS*,4*RS*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-vinyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (37d) from **37c** (79%): oil; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H), 1.40–2.15 (q, 4 H), 3.65–4.05 (m, 3 H), 5.02 (s, 2 H), 5.04 (q, 1 H), 5.27 (q, 1 H), 5.84 (q, 1 H), 6.45–6.80 (m, 3 H), 7.30–7.50 (m, 5 H).

(*E*)-(2*SR*,4*RS*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-vinyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (38d) from **38c** (55%): oil; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H), 1.30–2.40 (m, 4 H), 3.35–3.70 (m, 2 H), 3.80–4.0 (m, 1 H), 4.80 (q, 1 H), 5.05 (q, 1 H), 5.10 (s, 2 H), 5.85 (q, 1 H), 6.60–6.75 (m, 3 H), 7.30–7.50 (m, 5 H).

4-(3-Hydroxyphenyl)-4-ethyl-3,4,5,6-tetrahydro-2*H*-pyran (24a). Compound **21b** (0.4 g, 1.3 mmol) was hydrogenated over Pd/C (10%, 0.05 g) in EtOH (5 mL) 50 psi for 12 h. The mixture was then filtered on Celite and evaporated. Column chromatography of the residue using an increasing gradient of Et_2O in CH_2Cl_2 (0/100 to 10/90, v/v) as eluant gave **24a** as a white solid (0.27 g, 96%): mp 64–65 °C; ^1H NMR ($CDCl_3$) δ 0.57 (t, 3 H), 1.50–2.30 (m, 6 H), 3.30–4.00 (m, 4 H), 4.70–5.30 (broad, s, OH), 6.50–7.30 (m, 4 H).

The following compounds were prepared by the same procedure.

(*S*)-(−)-Methyl 2-(3-hydroxy-5-fluorophenyl)-2-methoxybutyrate [(*S*)-16a] from (*S*)-**12a** (95%): mp 75–76 °C; $[\alpha]^{20}_D$ = −9.9° ± 0.5° (*c* = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 1.90–2.60 (m, 2 H), 3.20 (s, 3 H), 3.70 (s, 3 H), 5.80 (s, OH), 6.40–7.00 (m, 3 H).

(*R*)-(+)-Methyl 2-(3-hydroxy-5-fluorophenyl)-2-methoxybutyrate [(*R*)-16a] from (*R*)-**12a** (97%): mp 75–76 °C; $[\alpha]^{20}_D$ = +9.7° ± 0.5° (*c* = 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H), 2.00–2.60 (m, 2 H), 3.18 (s, 3 H), 3.72 (s, 3 H), 6.13 (s, broad, OH, 1 H), 6.45–7.00 (m, 3 H).

4-(3-Hydroxyphenyl)-4-(ethoxycarbonyl)-3,4,5,6-tetrahydro-2*H*-pyran (22a) from **18** (91%): mp 100–101 °C; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3 H), 1.80–2.50 (m, 4 H), 3.50–4.40 (m, 6 H), 5.10 (s, broad, 1 H), 6.70–7.50 (m, 4 H).

4-(3-Hydroxyphenyl)-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran (23a) from **20b** (92%): mp 94–95 °C; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.20–2.60 (m, 4 H), 3.10–4.30 (m, 4 H), 5.00 (s, broad, OH), 6.50–7.40 (m, 4 H).

4-(3-Hydroxyphenyl)-4-(hydroxymethyl)-3,4,5,6-tetrahydro-2*H*-pyran (25a) from **19** (80%): mp 115–116 °C; ^1H NMR (DMSO-d_6) δ 1.70–2.00 (m, 4 H), 3.00–4.00 (m, 6 H), 4.30–4.60 (s, broad, OH), 6.50–7.30 (m, 4 H), 9.00–9.30 (s, broad, OH).

4-(3-Hydroxyphenyl)-4-formyl-3,4,5,6-tetrahydro-2*H*-pyran (27a) from **21a** (23%): mp 123.1–124.1 °C; ^1H NMR ($CDCl_3$) δ 1.90–2.60 (m, 4 H), 3.40–4.10 (m, 4 H), 5.30 (broad, OH), 6.60–7.50 (m, 4 H), 9.40 (s, 1 H).

4-(3-Hydroxyphenyl)-4-(1-hydroxyethyl)-3,4,5,6-tetrahydro-2*H*-pyran (28b) from **28a** (78%): mp 112.5–113.5 °C; ^1H NMR (DMSO-d_6) δ 0.71 (d, 3 H), 1.60–2.40 (m, 4 H), 2.90–4.00 (m, 5 H), 4.50 (d, OH), 6.50–7.40 (m, 4 H), 8.90–9.40 (broad, 1 OH); CIMS 223 (MH^+). Anal. ($C_{13}H_{18}O_3$) C, H.

4-(3-Hydroxy-5-fluorophenyl)-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (31a) from **30** (79%): mp 158–160 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.20 (m, 4 H), 3.85–4.00 (m, 4 H), 5.00 (s, 1 H), 6.30–6.90 (m, 3 H), 9.70 (broad, 1 OH); CIMS 212 ($M^{\cdot+}$).

(*Z*)-(2*RS*,4*RS*)-4-(3-Hydroxy-5-fluorophenyl)-4-ethyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (39a) from **37d** (92%): oil; ^1H NMR ($CDCl_3$) δ 0.60 (t, 3 H), 1.25 (d, 3 H), 1.30–2.05 (m, 6 H), 3.60–4.05 (m, 3 H), 5.10 (m, 1 H), 6.30–6.65 (m, 3 H).

(*E*)-(2*SR*,4*RS*)-4-(3-Hydroxy-5-fluorophenyl)-4-ethyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (40a) from **38d** (75%): oil; ^1H NMR ($CDCl_3$) δ 0.60 (t, 3 H), 1.15 (d, 3 H), 1.15–2.25 (m, 6 H), 3.25–3.60 (m, 2 H), 3.70–3.95 (m, 1 H), 5.50 (m, 1 H), 6.25–6.60 (m, 3 H).

4-[3-(Benzyloxy)phenyl]-4-(1-hydroxyethyl)-3,4,5,6-tetrahydro-2*H*-pyran (28a). A solution of **21a** (1.184 g, 4 mmol) in anhydrous THF (20 mL) under argon was added to a THF solution of CH_3MgBr (3 M, 2 mL, 6 mmol) and stirred overnight. THF was evaporated, and the residue was dissolved in CH_2Cl_2/water. The organic layer was washed with brine, dried, filtered, and evaporated. The residue was purified by column chromatography using a CH_2Cl_2/Et_2O mixture as eluant to give **28a** as white crystals (77%): mp 118.5–119.5 °C; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3 H), 1.60–2.60 (m, 4 H), 3.20–4.10 (m, 5 H), 5.10 (s, 2 H), 6.80–7.60 (m, 9 H). Anal. ($C_{20}H_{24}O_3$) C, H; C: calcd, 76.95; found, 76.42.

1-Iodo-2-(2-iodoethoxy)propane (33). A mixture of triphenylphosphine (159 g, 0.6 mol), imidazole (41.2 g, 0.6 mol), and iodine (115.5 g, 0.45 mol) in Et_2O (500 mL) and acetonitrile (200 mL) was stirred at room temperature for 0.5 h. A solution of 1-hydroxy-(2-hydroxyethoxy)propane (18.2 g, 0.15 mol) in Et_2O was added dropwise, and the resulting mixture was stirred 3 h and diluted with petroleum ether (3 L). The solution was decanted from a viscous residue and concentrated to about one-fourth of its initial volume. A white solid was filtered off, and the filtrate was evaporated. The oily residue was purified by column chromatography using a gradient of petroleum ether to petroleum ether/CH_2Cl_2 (90/10, v/v) as eluant to give **33** as an oil (30.26 g, 61%): ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H), 3.15–3.85 (m, 7 H).

Ethyl (3,5-Difluorophenyl)acetate (34). Concentrated sulfuric acid (6 mL) was added to a solution of 3,5-difluorophenylacetic acid (20.8 g, 0.12 mol) in EtOH (100 mL). The mixture was stirred at room temperature for 6 h, concentrated, and partitioned between Et_2O (50 mL × 2) and aqueous sodium hydroxide (0.5 N, 150 mL). The organic phase was washed with water and brine, dried, and evaporated to give **34** as an oil (23.4 g, 96.7%) which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H), 3.65 (s, 2 H), 4.20 (q, 2 H), 6.65–6.90 (m, 3 H).

(*E*)-(2*RS*,4*SR*)-4-(3,5-Difluorophenyl)-4-ethoxycarbonyl-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (35). Sodium hydride (9.17 g, 60% in oil, 0.229 mol) was added slowly to a solution of ester **34** (17 g, 0.084 mol) in THF (400 mL). The mixture was stirred at room temperature for 1 h, and a solution of diiodo ether **33** (30.28 g, 0.093 mol) in THF (20 mL) was added. The mixture was stirred for 2 h, filtered, and evaporated. The residue was purified by column chromatography using a gradient of petroleum ether to petroleum ether/EtOAc (90/10, v/v) as eluant to give the *Z* and *E* diastereoisomers of **35** as impure fractions. These fractions were purified by Prochrom medium-pressure chromatography using petroleum ether/EtOAc (90/10, v/v) as eluant to give **35** (60%) as the less polar isomer: ^1H NMR ($CDCl_3$)[23] δ d 1.18–1.26 (m, 6 H), 1.40–1.50 (m, 1 H), 1.72–1.84 (m, 1 H), 2.45–2.58 (m, 2 H), 3.49–3.61 (m, 2 H), 3.99–4.06 (m, 1 H), 4.13–4.21 (m, 2 H), 6.66–6.75 (m, 1 H), 6.85–6.95 (m, 2 H).

The more polar isomer gave **(*Z*)-(2*SR*,4*RS*)-4-(3,5-Difluorophenyl)-4-(ethoxycarbonyl)-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (36)** (60%): ^1H NMR ($CDCl_3$)[23] δ d 1.13–1.26 (m, 6 H), 1.40–1.50 (m, 1 H), 1.77–1.87 (m, 1 H), 2.37–2.50 (m, 2 H), 3.37–3.48 (m, 2 H), 3.86–3.92 (m, 1 H), 4.03–4.11 (m, 2 H), 6.69–6.77 (m, 1 H), 6.88–6.97 (m, 2 H).

(*E*)-(2*RS*,4*SR*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-(ethoxycarbonyl)-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (37a). Sodium hydride (258 mg, 60% in oil, 6.46 mol) was added to a solution of benzyl alcohol (582 mg, 5.38 mmol) in *N*-methylpyrrolidone (10 mL). After 0.75 h at room temperature, a solution of **35** (1.35 g, 5.38 mmol) in *N*-methylpyrrolidone (5 mL) was added, the mixture was stirred for 1.5 h at 50 °C, cooled to room temperature, and partitioned between water and Et_2O. The organic phase was washed with brine, dried, and evaporated. The residue was purified by column chromatography using a gradient of petroleum ether to petroleum ether/EtOAc (90/10, v/v) to give **37a** as an oil (756 mg, 45%): ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H), 1.25 (d, 3 H), 1.35–2.00 (m, 2 H), 2.40–2.70 (m, 2 H), 3.35–3.75 (m, 2 H), 3.90–4.10 (m, 1 H), 4.25 (q, 2 H), 5.05 (s, 2 H), 6.50–6.85 (m, 3 H), 7.25–7.45 (m, 5 H).

The following compound was similarly prepared:

(*Z*)-(2*SR*,4*RS*)-4-[3-(Benzyloxy)-5-fluorophenyl]-4-(ethoxycarbonyl)-2-methyl-3,4,5,6-tetrahydro-2*H*-pyran (38a) was obtained from **36** (42%): oil; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H),

1.20 (d, 3 H), 1.50–2.65 (m, 4 H), 3.25–3.65 (m, 2 H), 3.80–4.05 (m, 1 H), 4.10 (q, 2 H), 5.05 (s, 2 H), 6.50–6.85 (m, 3 H), 7.25–7.45 (m, 5 H).

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References

(1) The enzyme 5-lipoxygenase catalyzes the dioxygenation of arachidonic acid at the C-5 position as the first step in the leukotriene biosynthesis pathway, leading to the formation of the 5(*S*)-hydroperoxy-6,8,11,14-eicosatetraenoic acid, which is transformed to leukotriene A4 by dehydration in a second step.

(2) (a) ZM-211965 is equivalent to ICI211965. (b) Bird, T. G. C.; Bruneau, P.; Crawley, G. C.; Edwards, M. P.; Foster, S. J.; Girodeau, J.-M.; Kingston, J. F.; McMillan, R. M. (Methoxyalkyl) Thiazoles: A new series of Potent, Selective, and Orally Active 5-Lipoxygenase Inhibitors Displaying High Enantioselectivity. *J. Med. Chem.* **1991**, *34*, 2176–2186. (c) McMillan, R. M.; Girodeau, J.-M.; Foster, S. J. Selective Chiral Inhibitors of 5-Lipoxygenase with Anti-inflammatory Activity. *Br. J. Pharmacol.* **1990**, *101*, 501–503. (d) Riendeau, D.; Denis, D.; Falgueyret, J.-P.; Percival, M. D.; Gresser, M. J. Catalytic Properties and Reaction Mechanism of 5-Lipoxygenase. In *Prostaglandins, Leukotrienes, Lipoxins and PAF* (Proc. Int. Wash. Spring Symp.), 11th; Bailey, J.-M.; Ed.; Plenum Press: New York, 1991; pp 31–37. (e) McMillan, R. M.; Bird, T. G. C.; Crawley, G. C.; Edwards, M. P.; Girodeau, J.-M.; Kingston, J. F.; Foster, S. J. Methoxyalkyl Thiazoles: A novel series of Potent, Orally Active and Enantioselective Inhibitors of 5-Lipoxygenase. *Agents Actions* **1991**, *34*, 110–112.

(3) An attempted X-ray structure determination of (+)-**3** was insufficiently well resolved to enable unambiguous assignment of its absolute configuration.

(4) (a) Crawley, G. C.; Dowell, R. I.; Edwards, P. N.; Foster, S. J.; McMillan, R. M.; Walker, E. R. H.; Waterson, D.; Bird, T. G. C.; Bruneau, P.; Girodeau, J.-M. Methoxytetrahydropyrans. A New Series of Selective and Orally Potent 5-Lipoxygenase Inhibitors. *J. Med. Chem.* **1992**, *35*, 2600–2609. (b) Crawley, G. C.; Briggs, M. T.; Dowell, R. I.; Edwards, P. N.; Hamilton, P. M.; Kingston, J. F.; Oldham, K.; Waterson, D.; Whalley, D. P. 4-Methoxy-2-methyltetrahydropyrans: Chiral Leukotriene Biosynthesis Inhibitors, Related to ICI D2138, Which Display Enantioselectivity. *J. Med. Chem.* **1993**, *36*, 295–296.

(5) X-ray study. The quininium salt of 2-[3-(benzyloxy)-5-fluorophenyl]-2-hydroxybutyrate was subjected to X-ray crystallographic examination to determine the absolute configuration of the substituted hydroxybutyrate anion relative to the known configuration of the quininium cation.[19,20] This work has been carried out by Professor M. McPartlin of The Polytechnic of North London. Crystal data: $[C_{20}H_{25}N_2O_2]^+[C_{17}H_{16}FO_4]^-$, M = 628.76, orthorhombic, space group $P2_12_12_1$, a = 27.073(4) Å, b = 13.900(3) Å, c = 8.977(2) Å, V = 3378.93 Å^3, Z = 4, $F(000)$ = 1336, D_c = 1.236 g cm^{-3}, μ(Mo Kα) = 0.52 cm^{-1}. A total of 2694 reflections were collected in the range $3° < \theta < 23°$, on a Philips PW1100 diffractometer using graphite monochromated Mo Kα radiation (λ = 0.710 69 Å), with a constant scan width of 0.90°, a weakly diffracting crystal of dimensions 0.46 × 0.39 × 0.18 mm and a θ–2θ scan mode. The data were corrected for Lorentz and polarization factors and equivalent reflections were merged to give a total of 990 unique reflections with $I/\sigma(I) > 2.0$. The structure was solved by direct methods (SHELX-86 program). All the H atoms, apart from those of the ethene substituent of the cation, were included at calculated positions, with thermal parameters of 0.10 Å^2 which were not refined. In the final stages of full-matrix refinement the oxygen atoms of the anion and cation were assigned anisotropic thermal parameters. Weights were applied to the individual reflections as $1/\sigma^2(F)$ and refinement converged at R = 0.0878 and R_w = 0.0823.

(6) Foster, S. J.; Bruneau, P.; Walker, E. R. H.; McMillan, R. M. 2-Substituted Indazolinones: Orally Active and Selective 5-Lipoxygenase Inhibitors with Anti-inflammatory Activity. *Br. J. Pharmacol.* **1990**, *99*, 113–118.

(7) Dubs, P.; Pesaro, M. An Efficient Synthesis of 2-Substituted 1,3-Thiazoles. *Synthesis* **1974**, 294–295.

(8) Motoc, I.; Dammkoehler, R. A.; Mayer, D.; Labanowski, J. Three-dimensional Quantitative Structure-Activity Relationships. I. General Approach to the Pharmacophore Model Validation. *J. Quant. Struct.-Act. Relat.* **1986**, 5(3), 99–105.

(9) AESOP as an in-house molecular mechanics program: Masek, B. B. ZENECA Inc., Wilmington, DE 19897, derived in part from BIGSTRN-3 (QCPE 514), Nachbar, R., Jr.; Mislow, K. *QCPE Bull.* **1986**, *6*, 96. AESOP employs the MM2 force field parameters: see Allinger, N. L. *QCPE Bull.* **1980**, *12*, 395.

(10) Dewar, M. J. S.; Thiel, W. Ground States of Molecules. 38. The MNDO Method. Approximations and Parameters. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.

(11) Dewar Research Group. *QCPE Bull.* **1986**, *6*, 4 (AMPAC, QCPE program no. 506).

(12) The differences between mouse macrophages enantioselectivity (*S*/*R* ratio between 2 and 3 orders of magnitude) and human whole blood enantioselectivity (*S*/*R* ratio of 1 order of magnitude) are intriguing. Bearing in mind that albumin can bind stereoselectively to certain compounds,[24] it can be suggested that the binding to albumin in human blood differs from the (*R*) to the (*S*) isomers, in preference to the (*S*).

(13) The converse orientation of the ester is found in conformations respectively 1.0 and 0.1 kcal/mol more energetic than EST0 and EST1.

(14) ΔS^0 is assumed to be zero.

(15) Extensive nmr studies have been performed on **39b** and **40b**. The data acquired for both isomers indicated that the methyl in the 2-position of the THP is in equatorial orientation. This is shown by the methine hydrogen at C2 having typical axial–axial (10 Hz) and axial–equatorial (2 Hz) vicinal coupling constants. Molecular modeling shows that one chair and one boat conformation put the 2-methyl in equatorial conformation, but the boat conformation are 4.8 and 5.1 kcal/mol for the *Z* and *E* isomers, respectively, more energetic than their corresponding chair conformation (AESOP calculations).[23]

(16) The MNDO energy difference calculated in the 4-thiazolyl derivative between the two conformations corresponding to TZ1 and TZ9 (in the 2-thiazolyl series) is 2.2 kcal/mol.

(17) Contrary to the series A, the problem of the wrong orientation of the ester or methoxymethyl ether functions when the ethyl is out of the aromatic plane does not exist. Indeed, in the ester series the two oxygens of the ester function could nearly equivalently interact with the enzyme. In the ether series, the conformational analysis has shown that the ether substituent always prefers to be in the active orientation (ETH0 and ETH1).

(18) The biological importance of the thiazolyl nitrogen strongly suggests that its key role is assumed by the oxygen atoms of the ester and ether functions in the corresponding noncyclic series. This confirms our previous assumption that in these two series the methoxy or ethyl groups cannot be replaced by the ester or ether substituent, as the putative H-bond acceptor site would be then replaced by a lipophilic methyl group.

(19) Turner, R. B.; Woodward, R. B. In *The alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1953; Vol. 3, pp 1–63.

(20) Lyle, G. G.; Keefer, L. K. The Configurations at C-9 of The Cinchona Alkaloids. NMR Study of The Derived Oxiranes. *Tetrahedron* **1967**, *23*, 3253–3263.

(21) Tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III) derivative.

(22) Prepared and titrated according to the method of Arndt: Arndt, F. In *Organic Syntheses*; Blatt, A. H., Ed.; John Wiley & Sons Inc.: New York, 1943; Collect. Vol. II, pp 165–167.

(23) In addition to the conformational studies,[15] one dimensional noe experiments allow the determination of *Z* and *E* isomers. Irradiation of the methylene group of the ethyl substituent shows a marked effect on the methine hydrogen at C2 for the *Z* isomer and no effect for the *E* isomer. The spectra were recorded on JEOL EX-400 instrument.

(24) Kragh-Hansen, U. Molecular Aspects of Ligand Binding to Serum Albumin. *Pharmacol. Rev.* **1981**, *33* (1), 17–53.