4-Methoxy-2-methyltetrahydropyrans: Chiral Leukotriene Biosynthesis Inhibitors, Related to ICI D2138, Which Display Enantioselectivity

Graham C. Crawley,* Malcolm T. Briggs, Robert I. Dowell, Philip N. Edwards, Patricia M. Hamilton, John F. Kingston, Keith Oldham, David Waterson, and David P. Whalley

Chemistry 1 Department, ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

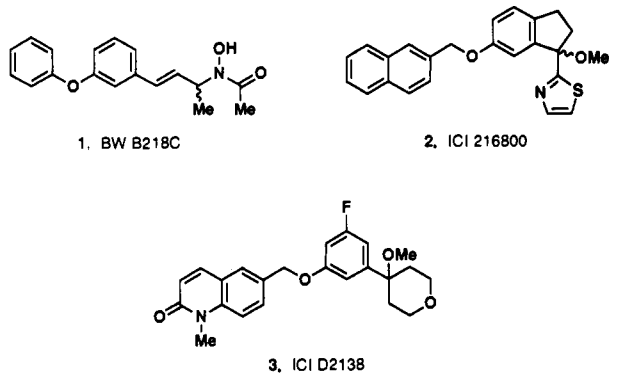
Received July 27, 1992

Leukotrienes (LTs) are a family of important inflammatory mediators produced by an enzymic cascade which is initiated by the action of 5-lipoxygenase (5-LPO) on arachidonic acid. LTB_4 is a potent chemotactic agent and inflammatory mediator[1] and the peptidoleukotrienes LTC_4 and LTD_4 are powerful spasmogens in bronchial and vascular tissues.[2] It is believed that limiting the biosynthesis of LTs through inhibition of 5-LPO will provide clinical benefits in a number of inflammatory conditions such as asthma and rheumatoid arthritis that are associated with elevated levels of LTs.

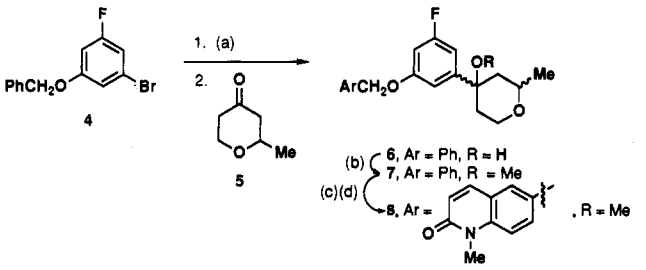
While various series of 5-LPO inhibitors are known, in few of these are distinct structure–activity relationships evident and, in particular, where chiral inhibitors have been resolved, it is rare to observe enantioselectivity. For example, there is no difference in inhibitory potency between the enantiomers of BW B218C (1)[3] (Chart I). In contrast, we have reported an exception to this trend with (methoxyalkyl)thiazoles, a chiral series exemplified by ICI 216800 (2), whose enantiomers showed marked differences in potency in various in vitro and in vivo systems.[4,5] More recently, we have described further developments emanating from the (methoxyalkyl)thiazoles that lead to 4-methoxytetrahydropyrans, a related series of 5-LPO inhibitors.[6] One member of this series, ICI D2138 (3), is under clinical investigation. The 4-methoxytetrahydropyrans described to date are achiral and we now wish to report that chiral members of this series bearing 2-methyl substitution on the tetrahydropyran ring, i.e. 8, exhibit enantioselective inhibition of LT biosynthesis.

The four diastereomers of 8 were prepared by analogy with the route previously described for 3[6] using (*R*)- or (*S*)-2-methyltetrahydropyranone (5) (Scheme I). The lithio- or Grignard reagents of 4 were treated with either (*R*)- or (*S*)-5 and each pyranone produced a mixture of two diastereomeric hydroxy compounds 6 arising from addition to the ketone either cis or trans to the 2-methyl substituent. These diastereomers were readily separated chromatographically. Using (±)-5[7] to define reaction conditions, it was found that lithio 4 generated 6 in a cis:trans ratio of 1:3 whereas with the Grignard reagent the ratio was 2:1. NOE experiments[8] on the diastereomers of 7 confirmed predictions from molecular mechanics calculations using AESOP[9] that the lowest energy conformations are as indicated in Chart II. That is, the ring conformations are dominated by a requirement for the 2-methyl substituents to be equatorial, resulting in the 4-aryl group being equatorial in the cis compounds and occupying the axial position in the trans compounds.

Chart I

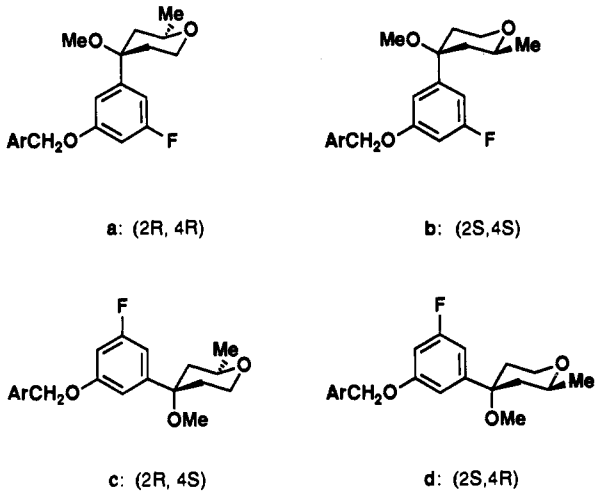


Scheme I[a]



[a] Reagents: (a) *n*-BuLi, THF, −70 °C or Mg, THF; (b) NaH, MeI, DMF, room temperature; (c) H_2, 10% Pd/C, EtOAc; (d) 6-(bromomethyl)-1-methylquinol-2-one, K_2CO_3, DMF, room temperature.

Chart II



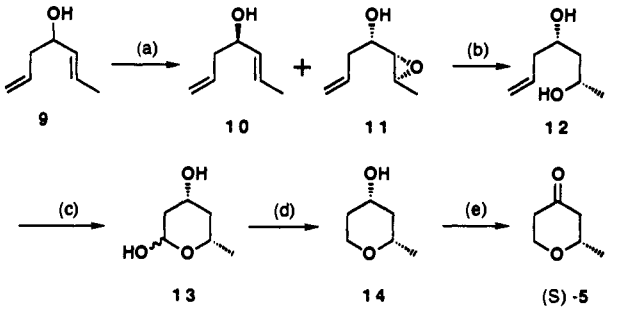
7, Ar = Ph; 8, Ar = 1-methyl-2-quinolone-6-yl

(*S*)-2-Methyltetrahydropyranone [(*S*)-5] was prepared[10] as indicated in Scheme II. A Sharpless kinetic resolution of 9[11] using catalytic conditions[12] gave epoxide 11, which was reduced with Red-Al to the 1,3-diol 12.[13] Ozonolysis converted 12 to the epimeric lactols 13, which, after protection of the hydroxyl functions, were reduced with Et_3SiH/TMSOTf[14] to the pyranol 14. Oxidation provided (*S*)-5 with an ee ≥ 95%. Assignment of the *S*-configuration follows[15] from the Sharpless epoxidation and was confirmed by comparison with (±)-5 and (*R*)-5[16] using HPLC on a chiral support.[17] For synthetic purposes, (*R*)-5 was obtained from resolution with (+)-1-methylbenzylamine of *cis*-2-methyl-4-pyranol hemiphthalate ester. Hydrolysis of the resolved phthalate and oxidation gave (*R*)-5 with an ee ≥ 90%.

The isomers of 8 were evaluated in vitro for inhibition

0022-2623/93/1836-0295$04.00/0

Scheme II[a]



[a] Reagents: (a) $Ti(OiPr)_4$, (+)-DIPT (0.1 equiv), TBHP, molecular seives, CH_2Cl_2, -20 °C; (b) 3.4 M Redal in toluene, THF, 0 °C; (c) O_3, MeOH, -20 °C; (d) (1) EtOH, HCl; (2) Et_3SiCl, imidazole, DMF, room temperature; (3) Et_3SiH, TMSOTf, -20 °C; (e) CrO_3, acetone.

Table I

no.	abs config	$[\alpha]_D$,[a] deg	analysis[b,c]	IC_{50} human whole blood,[d,e] μM	IC_{50} mouse macrophages,[e] nM
8a	2*R*,4*R*	+10.9	CHN	0.14 (0.053–0.36)	8 (1.8–36)
8b	2*S*,4*S*	-12.7	CHN	1.76 (0.68–4.58)	60 (13–270)
8c	2*R*,4*S*	-1.8	HN;C[f]	0.67 (0.26–1.74)	9 (2–41)
8d	2*S*,4*R*	+1.6	CHN	0.017 (0.0065–0.044)	0.4 (0.09–1.8)

[a] 29 °C c = 0.5 g/100 mL (CH_2Cl_2). [b] Analyses for C, H, and N were within ±0.4% of the theoretical value except where indicated otherwise. [c] **8a**, mp 118–120 °C; **8b**, mp 128–30 °C; **8d**, mp 91–3 °C; **8c** was an oil. [d] Mean of two determinations each performed in duplicate. [e] 95% confidence limits are shown in parentheses. [f] C: calcd, 70.1; found, 69.1. Calcd for $C_{24}H_{27}FNO_4$ $(M + H)^+$ 412.1924, found 412.1925; purity > 98% by HPLC analysis.

of LTB_4 synthesis in A-23187-stimulated human whole blood and of LTC_4 synthesis in plasma protein-free cultures of zymosan-stimulated mouse macrophages (Table I).[18] In these systems, the enantiomeric pair **8c,d** showed potency differences of 39- and 22-fold in whole blood and macrophages, respectively. The alternate pair **8a,b**, exhibited a potency difference of 13-fold in whole blood with a slightly reduced ratio being observed in macrophages.[19] Importantly, the same enantiomer in each pair was the more potent in both test systems. However, the enantiomer **8d** bearing a 2(*S*)-methyl was the more potent in the **8c,d** pair while the 2(*R*) enantiomer **8a** was more potent in the **8a,b** pair. The consistency of the potency ratios between enantiomers in whole blood and in macrophages indicated that the potency differences observed in blood did not arise from differential binding to plasma proteins.

Thus, the enantioselective inhibition of LT biosynthesis first observed among (methoxyalkyl)thiazole inhibitors is now extended to chiral members of the related series of 4-methoxytetrahydropyrans. This is in marked contrast with other chiral series of LT biosynthesis inhibitors for which no enantioselectivity has been observed. The in vivo activity of **8a–d** will be reported separately.

Acknowledgment. We thank Howard Beeley for the NOE experiments and Richard Gaskell for ee determinations.

References

(1) McMillan, R. M.; Foster, S. J. Leukotriene B_4 and Inflammatory Disease. *Agents Actions* **1988**, *24*, 114–119.
(2) O'Donnell, M.; Welton, A. Comparison of the Pulmonary Pharmacology of Leukotrienes and PAF: Effects of their Antagonists. In *Therapeutic Approaches to Inflammatory Disease*; Lewis, A. J., Doherty, N. S., Ackerman, N. R., Eds.; Elsevier: New York, 1989; pp 169–193.
(3) Salmon, J. A.; Garland, L. G. Leukotriene Antagonists and Inhibitors of Leukotriene Biosynthesis as Potential Therapeutic Agents. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhäuser Verlag: Basel, Boston, Berlin, 1991; pp 9–90.
(4) 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.
(5) 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.
(6) 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.
(7) Hanschke, E. The Prins Reaction. III. The Reaction of Allylcarbinol with Aldehydes and Ketones. *Chem. Ber.* **1955**, *88*, 1053–1061.
(8) In the ^1H NMR spectra of *cis*-7 and *trans*-7, the coupling constants of the C-2 methine protons [*cis* (C_6D_6), $J_{ax\text{-}ax}$ = 11.04, $J_{ax\text{-}eq}$ = 4.8; *trans* ($CDCl_3$), $J_{ax\text{-}ax}$ = 11.2, $J_{ax\text{-}eq}$ = 4.9] indicate that, in both, the tetrahydropyran rings adopt chair conformations with the 2-methyl substituents equatorial. One-dimensional NOE studies were used to determine the configuration at C-4. Irradiation of the *ortho* protons of the 4-phenyl substituent produced enhancements of the H_{3eq}, H_{5eq} and H_{3ax}, H_{5ax} protons in the spectrum of *cis*-7 and enhancements of the H_{2ax}, H_{6ax} and H_{3eq}, H_{5eq} protons of *trans*-7. In addition, irradiation of the methoxy group in *cis*-7 produced enhancements of the H_{2ax}, H_{6ax} and H_{3eq}, H_{5eq} protons. These results are consistent with the configurations and conformations for 7 shown in Chart II.
(9) AESOP is an in-house molecular mechanics program (Masek, B. B.; ICI Americas, 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* **1980**, *12*, 395.
(10) Crawley, G. C.; Edwards, P. N.; Girodeau, J.-M. M. M. Eur. Pat. 385662, 1990.
(11) Roush, W. R.; Brown, R. J. Total Synthesis of Carbohydrates. 3. Efficient, Enantioselective Syntheses of 2,6-Dideoxyhexoses. *J. Org. Chem.* **1983**, *48*, 5093–5101.
(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masumune, H.; Sharpless, K. B. Catalytic Asymmetric Epoxidation and Kinetic Resolution: Modified Procedures Including in Situ Derivatization. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
(13) Slow addition of Redal at 0 °C avoids formation of 1,2-diol: Walker, R. P., personal communication.
(14) Bennek, J. A.; Gray, G. R. An Efficient Synthesis of Anhydroalditols and Allyl C-Glycidols. *J. Org. Chem.* **1987**, *52*, 892–897.
(15) Rossiter, B. E. Synthetic Aspects and Applications of Asymmetric Epoxidation. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1985, Vol. 5, pp 193–308.
(16) The absolute configuration of (*R*)-6, prepared by enzymic reduction of (±)-6 followed by oxidation, has been determined from its CD spectrum using the octant rule, see: Haslegrave, J. A.; Jones, J. B. Enzymes in Organic Synthesis. 25. Heterocyclic Ketones as Substrates of Horse Liver Alcohol Dehydrogenase. Highly Stereoselective Reduction of 2-Substituted Tetrahydropyran-4-ones. *J. Am. Chem. Soc.* **1982**, *104*, 4666–4671.
(17) Chiralcel OB using *i*-PrOH/hexanes (5:95) as eluant.
(18) 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.
(19) Differences between IC_{50} values of each enantiomeric pair in the macrophage assay were assessed for statistical significance based on variability of standard data. *P*-values were 0.06 for **8a** vs **8b** and 0.005 for **8c** vs **8d**.