

Synthesis of Structural Analogs of Leukotriene B₄ and Their Receptor Binding Activity

William D. Kingsbury,*† Israil Pendrak,† Jack D. Leber,† Jeffery C. Boehm,† Brenda Mallet,† Henry M. Sarau,† James J. Foley,† Dulcie B. Schmidt,† and Robert A. Daines†

Departments of Medicinal Chemistry and Pharmacology, SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939

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Structural analogs of leukotriene B₄ (LTB₄) were designed using a preferred conformation of LTB₄ (1). Appending an aromatic ring scaffold between LTB₄ carbons 7 and 11 led to quinoline analogs 3 and 15. A similar modification to the LTB₄ structure between carbons 7 and 9 led to the pyridine analogs 41 and 46. The compounds of this study were evaluated in receptor binding assays using [³H]LTB₄ and intact human DMSO differentiated U-937 cells. The first analog prepared, quinoline 3, displayed moderate potency in the LTB₄ receptor binding assay ($K_i = 0.9 \mu\text{M}$). Modification of 3 by appending an aromatic ring between carbons 2 and 4 of the acid side chain produced a dramatic increase in receptor binding (15, $K_i = 0.01 \mu\text{M}$); a further improvement in receptor binding was achieved in the pyridine series (e.g., 41; $K_i = 0.001 \mu\text{M}$). The LTB₄ receptor agonist/antagonist activity of the test compounds was determined using a functional assay that relies upon intracellular calcium mobilization induced by LTB₄. Of the analogs prepared in this report only 47 demonstrated LTB₄ receptor antagonist activity.

Leukotriene B₄ (LTB₄, 1), a product of 5-lipoxygenase-catalyzed oxygenation of arachidonic acid, is postulated to be a mediator of inflammation and has been implicated in a variety of human inflammatory diseases. The known pathophysiological responses of LTB₄ include potent neutrophil chemotactic activity, the promotion of adherence of polymorphonuclear leukocytes (PMNs) to the vascular endothelium, stimulation of the release of lysosomal enzymes and superoxide radicals by PMNs, and an increase in vascular permeability.¹ Furthermore, the proinflammatory actions of LTB₄ have been demonstrated *in vivo*: topical application of LTB₄ on human skin promotes the infiltration of PMNs and other inflammatory cells,² intradermal injection of LTB₄ results in the accumulation of neutrophils at the injection site,³ and intravenous injection of LTB₄ causes rapid but transient neutropenia.⁴ These phenomena coupled with the presence of elevated concentrations of LTB₄ in psoriatic lesional skin,⁵ in colonic mucosa associated with inflammatory bowel disease,⁶ in synovial fluid from patients with active rheumatoid arthritis,⁷ and in gouty effusions⁸ support the involvement of LTB₄ in human inflammatory diseases. LTB₄ is produced by mast cells, PMNs, monocytes, alveolar macrophages, peritoneal macrophages, and keratinocytes. The synthesis of LTB₄ can be induced in these cells by the calcium ionophore A23187, opsonized zymosan particles, antigen, the chemotactic peptide formylmethionylleucylphenylalanine (FMLP), aggregated immunoglobulins (IgG, IgE, and IgA), and bacterial exotoxins.

The pharmacological effects of LTB₄ are mediated through its interaction with specific cell surface receptors that have been characterized on PMNs, monocytes, U-937 cells, lymphocytes, mast cells, smooth muscle cells, and endothelial cells, as well as on various tissues such as spleen, lung, heart, brain, small intestine, uterus, and kidney.⁹ The major proinflammatory activity of LTB₄ is thought

to involve a receptor-mediated induction of aggregation and the adhesion of inflammatory cells, especially PMNs, to venular endothelial cells. Furthermore, it has been postulated that LTB₄ synergizes with other chemotactic factors, such as C5a, to amplify the inflammatory response.¹ Thus, the availability of potent, selective LTB₄ receptor antagonists will be useful in elucidating the role of LTB₄ in human inflammatory diseases.

A number of LTB₄ receptor antagonists have been described (Figure 1). SM-9064¹⁰ and U-75302¹¹ are structurally related to LTB₄, and both exhibit partial agonist activity; LY-223982¹² and SC-41930¹³ are structurally related to the LTD₄ receptor antagonist FPL-55712. Recent reports describe the high affinity, orally active LTB₄ receptor antagonists ONO 4057¹⁴ and RG-14893.¹⁵

In the present study, we describe the results of our efforts to identify structural leads to unique LTB₄ receptor antagonists. The strategic approach focused on building ring-fused analogs of LTB₄ that would restrict the conformational freedom of the molecule. Thus, a series of quinoline (3 and 15) and pyridine (41 and 46) LTB₄ analogs was synthesized. The receptor binding affinities as well as the functional activity at the human LTB₄ receptor(s) of the analogs were determined. Based on the formative results of this study, high-affinity (e.g., low-nanomolar) LTB₄ receptor antagonist were identified.^{16,17}

Chemistry

Our initial strategy focused on the use of LTB₄ (1) as a template to design structurally rigid analogs of LTB₄. To begin this process, it was necessary to select a representative conformation of LTB₄. This was complicated by the conformational flexibility of LTB₄ and by the lack of conformational information related to LTB₄ at the receptor. However, high-field nuclear magnetic resonance studies of an aqueous solution of the potassium salt of LTB₄ support a preferred conformation of LTB₄ in which the conjugated double bonds exist in a coplanar arrangement with *s-trans* stereochemistry about the 7,8- and 9,10-bonds.¹⁸ Also, the SAR of closely related analogs

* Department of Medicinal Chemistry.

† Department of Pharmacology.

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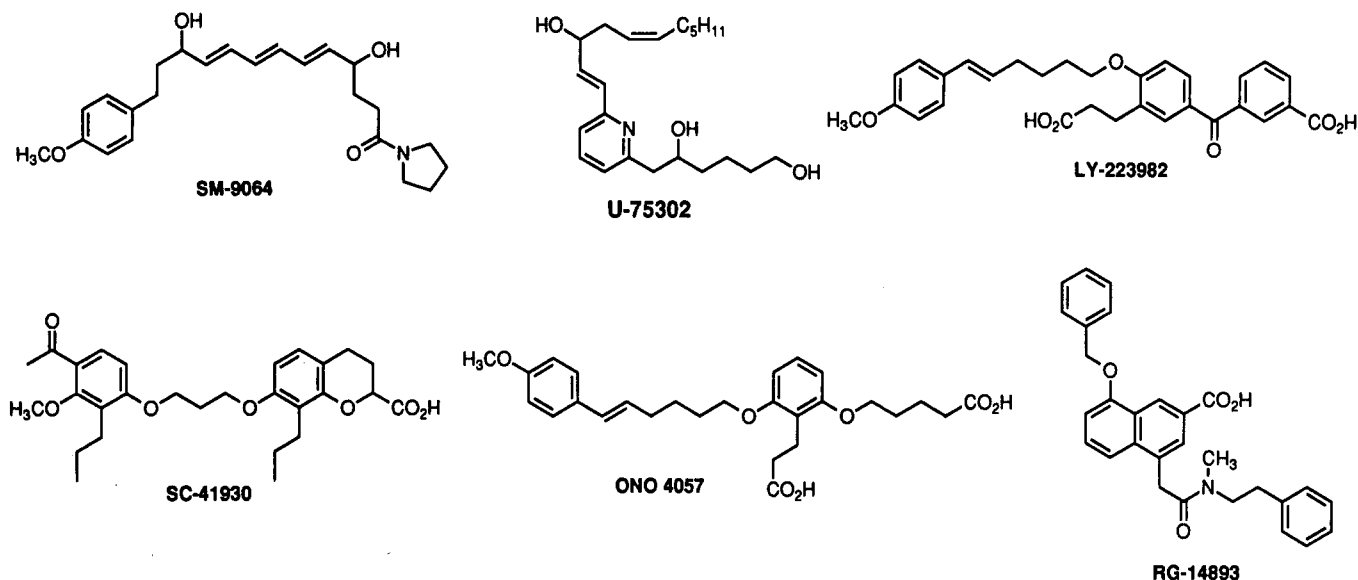


Figure 1.

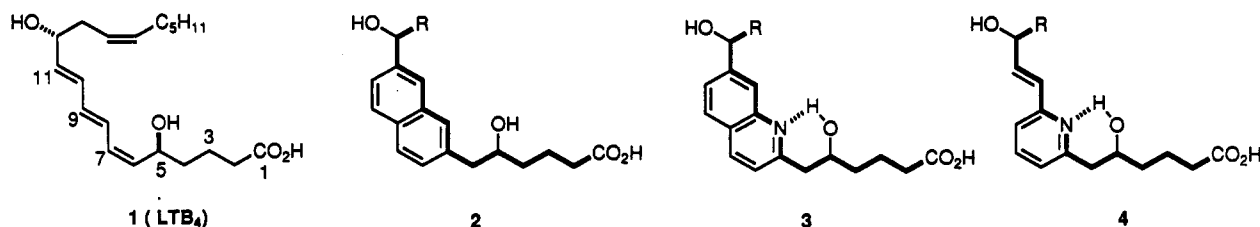


Figure 2.

of LTB₄ demonstrated the importance of the triene geometry, and the stereochemical requirement for the 5(*S*)- and 12(*R*)-hydroxyl groups. Based on this information, conformer 1 was selected as a reasonable template for use in the design process (Figure 2).

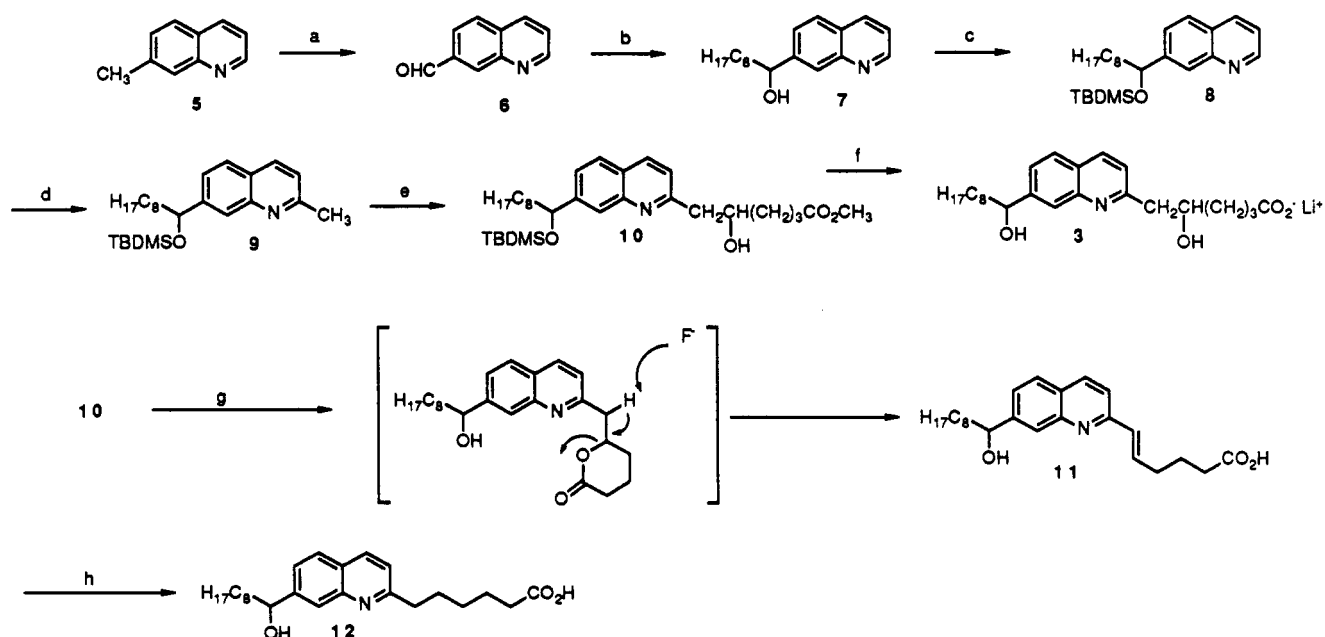
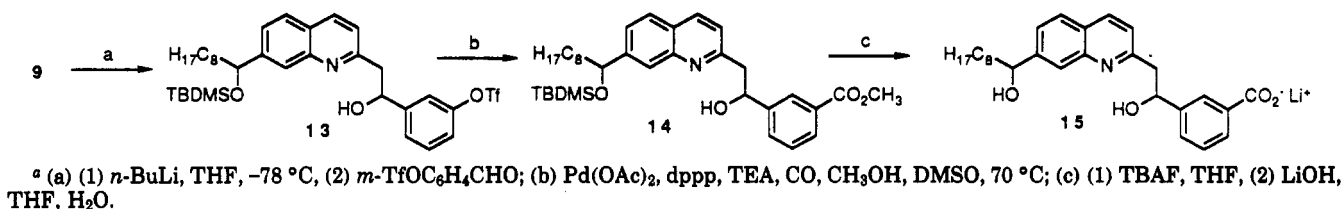
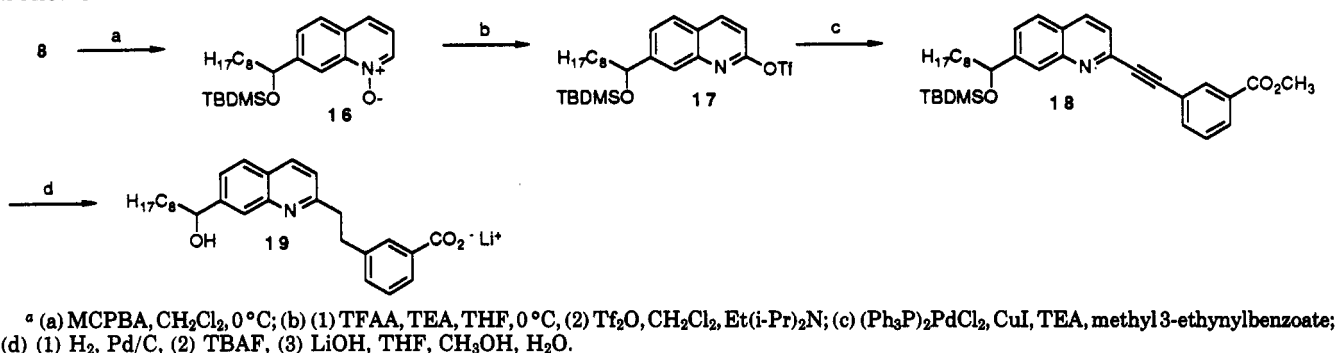
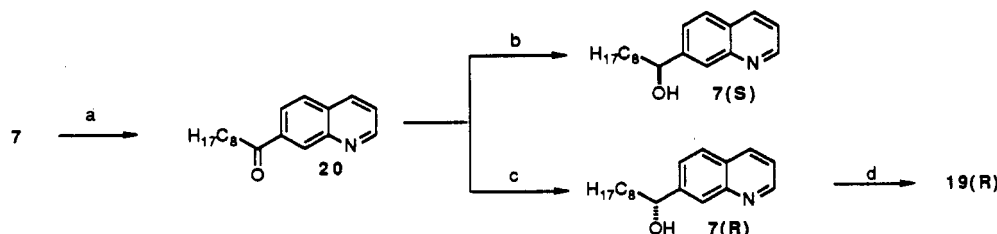
Joining carbon atoms 7–11 into an aromatic ring system led to the initial target structure 2. Although 2 incorporates a rigid mimic of the *trans*-diene backbone of 1, it does not mimic the C-6,7 *cis* olefin geometry present in LTB₄ and thus permits variability with regard to the orientation of the C-5 hydroxyl group. However, the quinoline structure 3 allows for hydrogen bonding between the C-5 hydroxyl and the quinoline nitrogen and affords a conformational mimic of the desired C-6,7 *cis*oid geometry present in LTB₄. An additional target molecule, pyridine 4, preserves the hydrogen bond between the C-5 hydroxyl and the pyridine ring nitrogen but provides a greater degree of flexibility in the olefinic lipid portion of the molecule. Thus, this strategy defined our approach to the design of target molecules.

Synthesis of the initial target, 3, is shown in Scheme I. Selenium dioxide oxidation of 7-methylquinoline (5) afforded aldehyde 6. Treatment of 6 with octylmagnesium bromide afforded alcohol 7. Compound 7 was protected as the silyl derivative 8 and reacted with methylolithium to give the 2-methylquinoline derivative 9. Initial attempts to acylate the quinoline methyl group by formation of the 2-methylquinoline lithium salt followed by reaction with methyl 4-formylbutanoate resulted in low yields of the desired alcohol 10, likely a result of anion attack at the ester or enolization of the ester–aldehyde. Titanium anion complexes have been reported to react selectively with aldehydes.¹⁹ Thus, the titanium anion of 9 on reaction with methyl 4-formylbutanoate provided improved yields

of 10 (e.g., 30%). Treatment of 10 with HF in pyridine provided the diol–ester which was hydrolyzed to the target dihydroxyquinolinecarboxylate 3. Compound 11 was formed unexpectedly from 10 when tetrabutylammonium fluoride (TBAF) was used in the deblocking step. This product can be rationalized by initial lactone formation followed by fluoride-mediated proton abstraction causing elimination–lactone ring opening; catalytic reduction of 11 afforded 12.

Compound 15 was prepared as shown in Scheme II. In this case, 13 could be prepared by reaction of the lithium anion of 9 with the substituted benzaldehyde. Palladium-catalyzed carbonylation²⁰ of 13 afforded the ester 14 which was treated first with TBAF to remove the silyl group and then hydrolyzed to afford compound 15. Compound 19, the “C-5” deshydroxy analog of 15, was prepared as shown in Scheme III. *m*-Chloroperbenzoic acid oxidation of 8 afforded the *N*-oxide 16 that on reaction with TFAA afforded the corresponding 2-hydroxyquinoline.²¹ Conversion of the 2-hydroxyquinoline to triflate 17 and palladium-catalyzed coupling with methyl 3-ethynylbenzoate afforded the alkyne 18.²² Reduction of the alkyne, removal of the silyl protecting group, and hydrolysis provided 19.

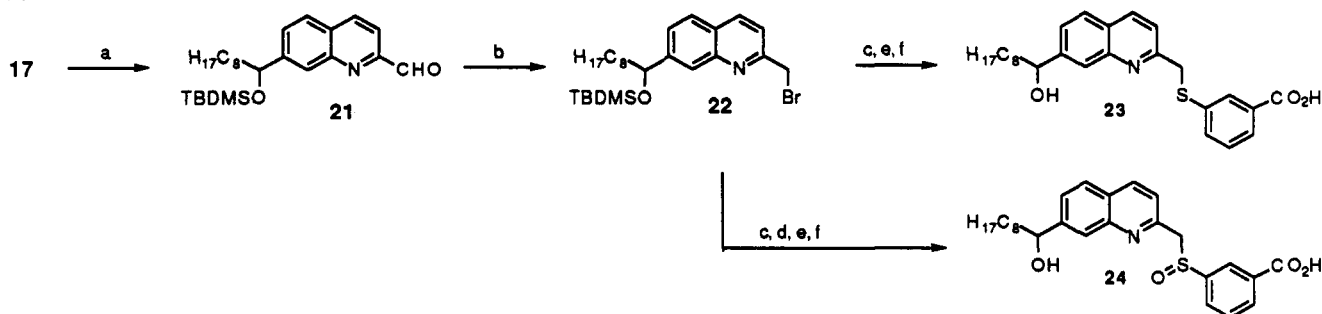
The 12(*R*), 5(*S*) stereochemistry of the LTB₄ hydroxyl groups has been reported to be important in terms of receptor binding potency.²⁸ Therefore, an effort was made to examine the consequence of the hydroxyl stereochemistry in this series. Preliminary experiments revealed that (*R,S*)-7 could be resolved by HPLC using an asymmetric Pirkle column.²³ The asymmetric synthesis of (*R*)-7 and (*S*)-7 was achieved as shown in Scheme IV. Manganese dioxide oxidation of 7 afforded ketone 20. Stereoselective reduction of 20 with (–)-Ipc₂BCl afforded (*S*)-7, whereas

Scheme I^aScheme II^aScheme III^aScheme IV^a

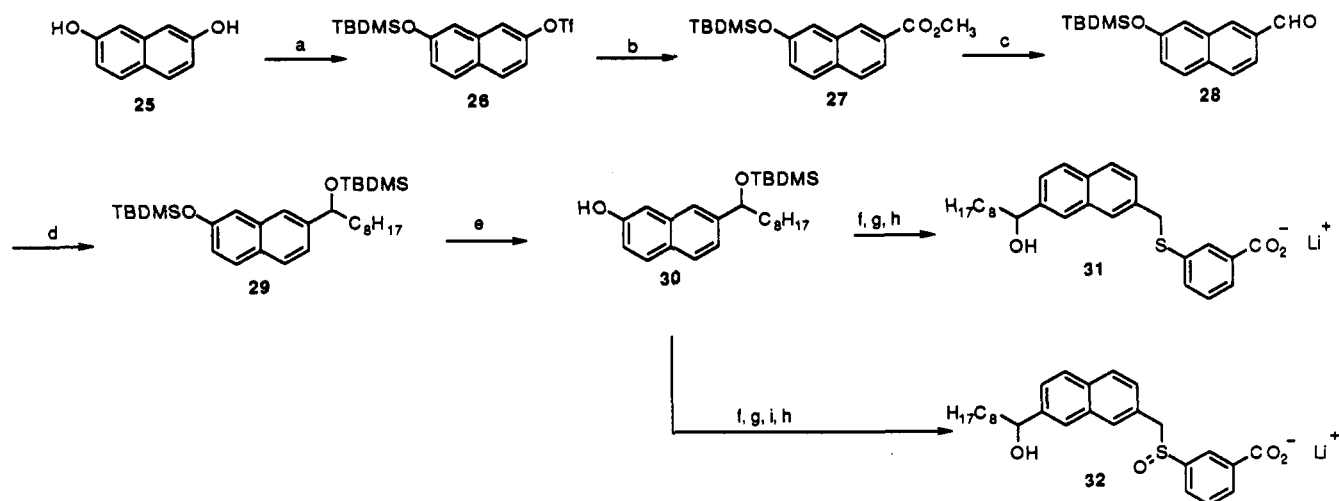
reduction of **20** using $(+)\text{-Ipc}_2\text{BCl}$ afforded $(R)\text{-7}$.²⁴ The enantiomeric excess of each was judged to be $>98\%$ as measured by NMR-GC analysis of the Mosher esters.²⁵ $(R)\text{-19}$ was prepared from $(R)\text{-7}$ according to Scheme III via $(R)\text{-8}$ and contained $<3\%$ of $(S)\text{-19}$ as determined by Pirkle column HPLC. The stereochemical assignment was

based on literature analogy²⁴ and supported by the receptor binding activity observed for this enantiomer in comparison to $(R,S)\text{-19}$.

Compounds **23** and **24** represent sulfur analogs of **19** and **15**, respectively, and were prepared as shown in Scheme V. The triflate **17** afforded the corresponding methyl ester

Scheme V^a

^a (a) (1) Pd(OAc)₂, dppp, TEA, CO, DMSO, CH₃OH, 65 °C, (2) DIBAL, CH₂Cl₂, -78 °C; (b) (1) NaBH₄, CH₃OH, 0 °C, (2) Ph₃P, CBr₄, CH₂Cl₂; (c) ArSH, K₂CO₃, DMF; (d) MCPBA, CH₂Cl₂, 0 °C; (e) TBAF, THF; (f) LiOH, THF, H₂O.

Scheme VI^a

^a (a) (1) TBDMSCl, DMF, imidazole, 0 °C, (2) Tf₂O, pyridine, 0 °C; (b) Pd(OAc)₂, dppp, TEA, CO, DMSO, CH₃OH, 65 °C; (c) (1) DIBAL, CH₂Cl₂, -78 °C, (2) MnO₂, CH₂Cl₂; (d) C₈H₁₇MgBr, THF, -25 °C, (2) TBDMSOTf, lutidine, CH₂Cl₂, 0 °C; (e) K₂CO₃, CH₃OH, THF; (f) (1) Tf₂O, pyridine, (2) Pd(OAc)₂, dppp, TEA, CO, DMSO, CH₃OH, 65 °C, (3) DIBAL, CH₂Cl₂, -78 °C, (4) Ph₃P, CBr₄, CH₂Cl₂, (5) ArSH, K₂CO₃, DMF; (g) TBAF, THF; (h) LiOH, THF, CH₃OH, H₂; (i) MCPBA, CH₂Cl₂, 0 °C.

by standard palladium-catalyzed carbonylation in methanol. Reduction of the methyl ester with DIBAL afforded aldehyde 21. Sodium borohydride reduction of 21 gave the corresponding alcohol which on reaction with triphenylphosphine and carbon tetrabromide afforded bromide 22. Reaction of 22 with methyl 3-mercaptopbenzoate followed by desilylation and hydrolysis afforded sulfide 23. Sulfoxide 24 was prepared from 22 by a similar process.

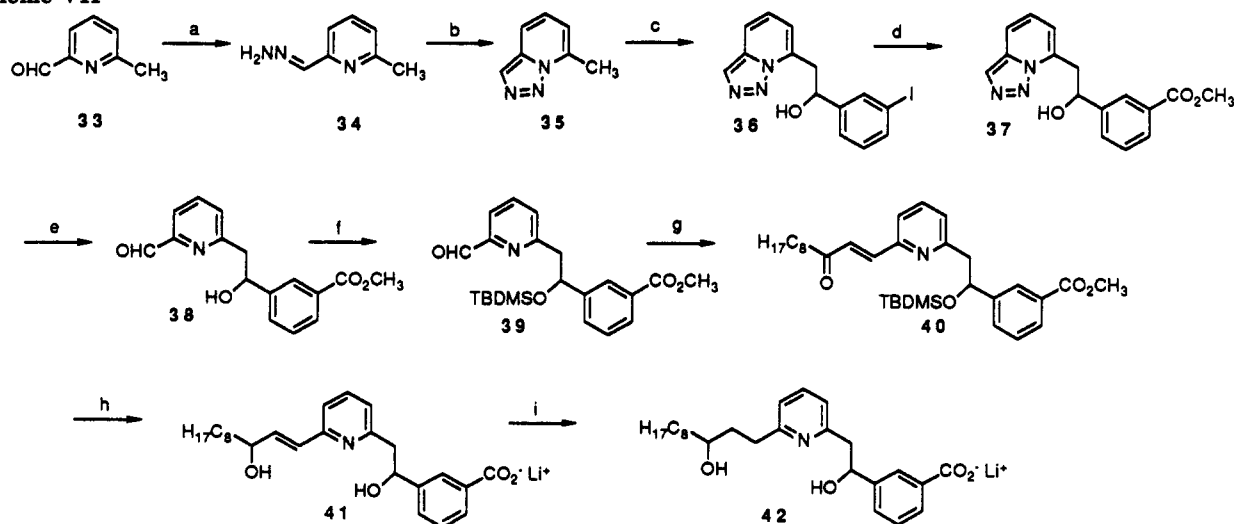
The naphthalene analogs 31 and 32 were prepared as shown in Scheme VI. Dihydroxynaphthalene 25 was converted to the silyl triflate 26. Palladium-catalyzed carbonylation afforded the ester 27 which was converted to the aldehyde 28. Reaction of 28 with octylmagnesium bromide followed by silylation afforded 29. Selective deprotection of the phenolic silyl group gave intermediate 30 which was converted to 31 and 32 by procedures comparable to those described for the preparation of 23 and 24.

Pyridines 41, 42, 46, and 47 were prepared as shown in Schemes VII and VIII. Compound 35 was prepared according to the method of Jones and Sliskovic²⁶ starting with aldehyde 33. The triazolopyridine 35 was converted to the lithium anion which afforded alcohol 36 on reaction with 3-iodobenzaldehyde. All attempts to bypass the use of the triazolo protecting group resulted in substantially lower yields. Palladium-catalyzed carbonylation of iodide 36 afforded ester 37. Removal of the triazolo protecting group by initial bromination followed by hydrolysis

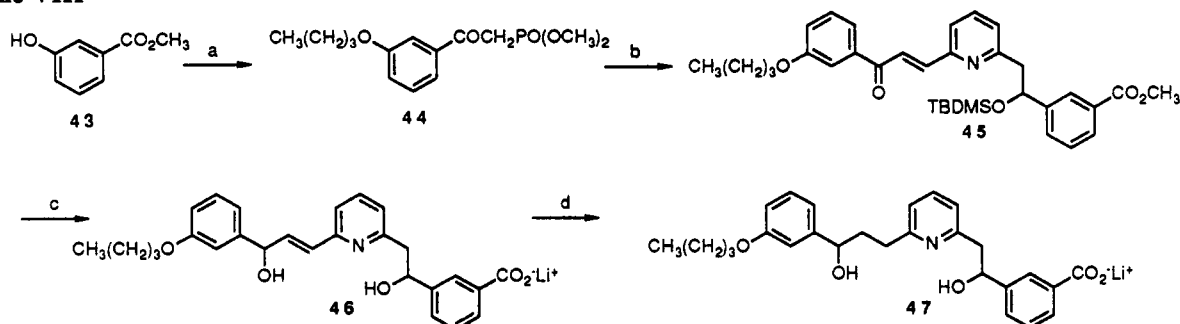
afforded aldehyde 38. Silylation of alcohol 38 followed by Wittig reaction afforded ketone 40. Reduction of the ketone, removal of the silyl protecting group, and hydrolysis gave the desired pyridine diol 41; reduction of 41 afforded 42. Compounds 46 and 47 were prepared by a similar route (Scheme VIII).

Results and Discussion

The LTB₄ receptor binding and functional cellular assay data for the test compounds are shown in Tables I and II. Although human polymorphonuclear leukocytes (PMNs) are considered to be the primary target inflammatory cells, they represent a potential biological hazard, and their use was reserved to evaluate only the potentially interesting high-affinity compounds. Thus, the receptor binding studies described in this paper were done using intact differentiated human monocyte/macrophage U-937 cells. U-937 cells are a stable transformed cell line that express LTB₄ receptors which appear identical in binding assays to the LTB₄ receptors found on human PMNs.²⁷ The U-937 cell binding assay is very reproducible, and quantitative K_i values were determined by measuring the ability of the compounds to compete with [³H]LTB₄ for binding to the receptor. All compounds that demonstrated reproducible high affinity (K_i ≤ 0.1 μM) in the primary U-937 cell assay were confirmed in a PMN receptor binding assay. The experimental results (K_is) from the U-937 and the PMN assays usually were found to be comparable, but

Scheme VII^a

^a (a) H_2NNH_2 , 100 °C; (b) $\text{K}_3\text{Fe}(\text{CN})_6$, NaHCO_3 , H_2O , 90 °C; (c) LDA, 3-iodobenzaldehyde, Et_2O ; (d) $\text{Pd}(\text{OAc})_2$, dppp, TEA, CO, DMSO, CH_3OH , 75 °C; (e) (1) Br_2 , CH_2Cl_2 , 0 °C, (2) AgNO_3 , EtOH , H_2O ; (f) TBDMSTf, lutidine, CH_2Cl_2 , 0 °C; (g) $\text{H}_{17}\text{C}_8\text{COCH}_2\text{PO}(\text{OEt})_2$, THF, NaH ; (h) (1) NaBH_4 , CH_3OH , -10 °C, (2) TBAF, THF, 0 °C, (3) LiOH , THF, CH_3OH , H_2 ; (i) H_2 , Pd/C, EtOH .

Scheme VIII^a

^a (a) (1) K_2CO_3 , $\text{C}_4\text{H}_9\text{I}$, DMF, 90 °C, (2) $\text{LiCH}_2\text{PO}(\text{OCH}_3)_2$, THF, -78 °C; (b) (1) NaH , THF, 45 °C, (2) **39**, THF; (c) (1) NaBH_4 , CH_3OH , -10 °C, (2) TBAF, THF, 0 °C, (3) LiOH , THF, CH_3OH , H_2 ; (d) H_2 , Pd/C, EtOH .

Table I. Quinoline and Naphthalene Analogs: Inhibition of [^3H]LTB₄ Binding on Human U-937 cells and LTB₄-Induced Calcium Mobilization Using Human PMNs

compd	whole cell K_i (μM)	PMN agonist (%)
3	0.9	63
11	1.4	45
12	2.8	58
15	0.01	74
(<i>R,S</i>)- 19	0.1	66
(<i>R</i>)- 19	0.05	56
23	0.6	85
24	0.14	98
31	9	23
32	0.5	56

sometimes differences did occur (higher affinity in PMN assays; results not shown). All compounds were evaluated in a secondary intact human PMN functional assay for agonist activity. This assay monitors the LTB₄, or test compound, mediated increase in intracellular calcium utilizing the fluorescent calcium indicator fura 2 to quantitate the maximal intracellular calcium level achieved. Human peripheral blood PMNs were used for this assay because the LTB₄-induced calcium response is significantly greater in these cells than it is in U-937 cells, thus providing a more sensitive assay. Indeed, during the initial stages of this investigation, it was discovered that compounds which were without significant agonist activity in the U-937 cell assay were in fact partial agonists in the PMN cell assay.

Table II. Pyridine Analogs: Inhibition of [^3H]LTB₄ Binding on Human U-937 Cells and LTB₄-Induced Calcium Mobilization Using Human PMNs

compd	whole cell K_i (μM)	PMN agonist (%)
U-75302	0.7	100
41	0.001	86
42	0.06	84
46	0.003	56
47	1	4

The receptor binding affinity of the initial target compound (**3**, $K_i = 0.9 \mu\text{M}$) provided support for our strategic approach. However, **3** demonstrated partial agonist activity (63%) in the PMN functional assay (in contrast to the absence of agonist activity in the U-937 cell assay). Since the goal of this investigation was to identify LTB₄ receptor antagonists, structural modifications of **3** were made in an attempt to eliminate the LTB₄ receptor agonist activity while maintaining or enhancing the LTB₄ receptor binding affinity.

The "C-5" deoxy analog of LTB₄ has been reported to retain high affinity LTB₄ receptor binding;²⁸ compounds **11** and **12** represent "C-5" deoxy analogs of **3**. The binding affinity observed with these compounds is consistent with that observed for LTB₄ analogs; the "C-5" hydroxyl group is not a requirement for receptor binding, although the "C-5" deoxy analog of LTB₄ is slightly less potent than

LTB₄. Both derivatives 11 and 12 demonstrated agonist activity in the human PMN LTB₄ receptor functional assay.

The effect of side-chain modification on receptor binding and agonist activity was investigated by joining an aromatic ring to the acid side chain between carbons 2 and 4, resulting in compound 15. This modification produced a dramatic increase in binding affinity, compound 15 being 100-fold more potent than 3 (i.e., K_{is} of 0.9 and 0.01 μM for 3 and 15, respectively). In this case, the "C-5" deoxy analog 19 (K_{i} = 0.1 μM) was found to have reduced potency of 1 order of magnitude compared with that of 15. While both 15 and 19 demonstrated high-affinity LTB₄ receptor binding, they also were found to be partial agonists in the PMN functional cell assay.

Since all of the test compounds were either diastereomeric or enantiomeric mixtures, it was of interest to determine if the stereochemistry of one of the hydroxyl groups would have an effect on either the potency or the agonist activity. The hope was that the receptor antagonist activity would be retained in one stereoisomer while the agonist activity would be a property of the other stereoisomer. While the 5-deoxy analog of LTB₄ is 10 times less potent than LTB₄, the 12-deoxy LTB₄ analog is 300 times less potent than LTB₄.²⁸ Therefore, we decided to prepare the 5-deoxy analog 19 with the (*R*) stereochemistry since this stereoisomer would correspond to the C-12 hydroxyl stereochemistry of natural LTB₄. (*R*)-19 was found to have approximately twice the receptor binding potency of (*R,S*)-19. Unfortunately, (*R*)-19 was found to be a partial agonist in the human PMN functional cell assay. Since the more potent stereoisomer was found to be a partial agonist, we concluded that the best approach to take in trying to separate the antagonist/agonist properties would be to vary the position of the functional groups on the lead molecules. For this reason, stereochemical issues were not addressed for the duration of this investigation.

To determine the effect of replacing the hydroxymethyl group with a sulfoxide in the chain linking the aromatic rings, sulfide 23 was prepared. A comparison of the receptor binding affinity of 23 with 19 revealed that this substitution resulted in a loss in LTB₄ binding affinity but an increase in agonist activity. Likewise, sulfoxide 24 demonstrated a 10-fold reduction in receptor binding affinity as compared to the analogous alcohol 15; 24 also demonstrated agonist activity comparable in magnitude to that observed for LTB₄.

Replacement of the quinoline ring system with the naphthalene ring system was investigated. Naphthalene derivatives 31 and 32 were found to be 4–15-fold less potent than the corresponding quinoline analogs 23 and 24; decreased agonist activity was observed for 31 and 32 relative to 23 and 24.

During the course of this work, Upjohn reported the synthesis of the LTB₄ receptor antagonist U-75302 (Figure 1).¹¹ In view of the structural similarities between U-75302 and the quinoline receptor antagonists of this investigation (e.g., 3), and considering the substantial increase in receptor binding affinity obtained by adding an aromatic ring between C-2 and C-4 (e.g., 3 to 15), compound 41 was prepared (Scheme VII). Compound 41 was found to be significantly (700-fold) more potent than U-75302 in the LTB₄ binding assay (Table II) and approximately 1 order of magnitude more potent than that of the analogous

quinoline 15 (Table I). Saturation of the side chain afforded 42, a compound that was 60 times less potent than 41; again both analogs 41 and 42, like U-75302, were found to be functional agonists at the LTB₄ receptor.

Variation of the lipid tail was investigated to determine whether changes in this portion of the molecule would have an effect either on receptor binding or agonist activity. Insertion of an aromatic ring into the lipid side chain afforded 46. This change did not diminish the LTB₄ binding affinity but did result in a reduction in agonist activity. Reduction of the side chain afforded 47. This derivative demonstrated substantial reduction (300-fold) in receptor binding affinity, but more encouragingly, it did not demonstrate significant LTB₄ receptor agonist activity in the human PMN functional assay at concentrations up to 100 μM . Thus, 47 represents the first LTB₄ receptor antagonist prepared in this series. Although the potency of 47 was too low to be of further interest, it did provide a lead for further modification (see accompanying paper, ref 16).

In summary, compounds 3, 15, 23, and 41 represent examples of novel structural leads with high affinity for human LTB₄ receptors. However, all of the compounds in this study, except for 47, were found to be a receptor agonist. In retrospect, the partial agonist activity of these compounds should not have been very surprising in view of the fact that they were designed as rigid mimics of the natural receptor ligand, LTB₄. As such, they bind to the receptor in a manner similar to that of LTB₄ and therefore result in similar cellular responses. Since our goal is to identify novel LTB₄ receptor antagonists and to determine their potential as antiinflammatory agents, the agonist activity represents a substantial liability. The ability to delete agonist activity, for example compound 47, suggested that variations in the lipid tail of the molecules may be a viable starting point from which to design new synthetic targets. The results of these studies are reported in detail.^{16,17}

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus. Nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AM-250 instrument using CDCl₃ unless otherwise indicated. All ¹H chemical shifts are reported in δ relative to tetramethylsilane (TMS, δ 0.00) as the internal standard. Elemental analyses were performed by the Analytical and Physical Chemistry Department of SmithKline Beecham. Mass spectra were determined by the Physical and Structural Chemistry Department of SmithKline Beecham. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F-254 glass-backed plates or Whatman KC 18 F reversed-phase RP-18 glass-backed plates with the solvent systems indicated. High-performance liquid chromatography (HPLC) was conducted using an Altex Model 110 gradient liquid chromatograph with a UV wavelength detector set at 254 nm. Preparative chromatography was carried out using flash silica gel chromatography²⁹ with the solvents as indicated. Water-soluble compounds were purified by medium-pressure liquid chromatography (MPLC) using Altec columns packed with Merck Licroprep RP-18 (25–40 μm) at a maximum pressure of 60 psi. Methyl 3-ethynylbenzoate was prepared from 3-iodobenzene and (trimethylsilyl)acetylene using standard palladium-catalyzed coupling chemistry.²² 1-(Diethylphosphono)decanone was prepared from diethyl methylphosphonate and methyl nonanoate (Nicolau, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* 1988, 110, 4672–4685).

Quinoline-7-carboxaldehyde (6). 7-Methylquinoline (26 g, 0.18 mol) was heated to 160 °C, and selenium dioxide (13 g, 0.12

mol) was added. The reaction mixture was maintained at 150–155 °C for 12 h, cooled to room temperature, diluted with CH₂Cl₂, and filtered. Hexanes were added to the filtrate, the resulting precipitate was washed with hexanes, the combined organic filtrates were concentrated *in vacuo*, and the residue was purified by flash column chromatography (15–30% EtOAc–hexanes gradient elution) to afford 6 (8.4 g, 46%) as a cream solid: mp 70–72 °C; ¹H NMR δ 10.2 (s, 1H, CHO), 9.05 (dd, 1H, 2-quinolinyl), 8.55 (s, 1H, 8-quinolinyl), 8.2 (br d, 1H, 4-quinolinyl), 8.05 (dd, 1H, 3-quinolinyl), 7.9 (d, 1H, 6-quinolinyl), 7.5 (dd, 1H, 5-quinolinyl).

1-Quinolin-7-ylnonan-1-ol (7). 1-Bromooctane (5.9 g, 30.5 mmol) was added to magnesium turnings (0.9 g, 37 mmol) in THF (40 mL), maintaining a gentle reflux during the addition. When the magnesium was dissolved, the solution was cooled to –15 °C and a solution of 6 (4 g, 25.5 mmol) in THF (20 mL) was added while maintaining the temperature at –15 °C. When addition was complete the reaction mixture was warmed to room temperature, diluted with H₂O, and extracted with EtOAc. The EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash column chromatography (5% EtOAc–hexane) afforded 7 (4.2 g, 61%): mp >250 °C; ¹H NMR δ 8.85 (dd, 1H, 2-quinolinyl), 8.15 (dd, 1H, 4-quinolinyl), 8.0 (br s, 1H, 8-quinolinyl), 7.8 (d, 1H, 3-quinolinyl), 7.6 (dd, 1H, 6-quinolinyl), 7.35 (dd, 1H, 5-quinolinyl), 4.9 (br t, 1H, CHOH), 2.9 (br s, 1H, OH), 1.65–2.0 (m, 2H, aliphatic), 1.25 (br, 12H, aliphatic), 0.9 (t, 3H, aliphatic). Anal. (C₁₈H₂₅NO) C, H, N.

7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]-quinoline (8). A solution of 7 (4 g, 14.8 mmol) in CH₂Cl₂ (60 mL) at –10 °C was treated with 2,6-lutidine (4.3 mL, 37 mmol) followed by the dropwise addition of *tert*-butyldimethylsilyl-trifluoromethanesulfonate (4.3 g, 16.2 mmol). The resulting solution was warmed to room temperature, concentrated, and extracted with EtOAc. The EtOAc fraction was washed with aqueous NaHCO₃, H₂O, and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash column chromatography (hexane) afforded the protected hydroxyquinoline as an amorphous solid (5.1 g, 100% yield).

7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]-2-methylquinoline (9). A solution of tetramethylethylenediamine (4.5 mL, 30 mmol) in THF (100 mL) under Ar at 0 °C was treated with methyl lithium (1.4 M, 21.4 mL, 30 mmol). To this solution was added dropwise a solution of 8 (3.9 g, 2.6 mmol) in THF (75 mL), the reaction mixture was warmed to room temperature, and oxygen was bubbled into the solution for 1 h. The resulting mixture was diluted with H₂O, extracted with EtOAc, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (2% EtOAc–hexane) afforded 9 as an amorphous solid (1.6 g, 40%): ¹H NMR δ 8.15 (d, 1H, 4-quinolinyl), 8.0 (br s, 1H, 8-quinolinyl), 7.8 (d, 1H, 3-quinolinyl), 7.6 (dd, 1H, 6-quinolinyl), 7.6 (dd, 1H, 5-quinolinyl), 2.7 (s, 3H, CH₃), 1.65–2.0 (m, 2H, aliphatic), 1.25 (m, 12H, aliphatic), 0.95 (t, 3H, aliphatic), 0.9 (s, 9H, *t*-BuSi), 0.2 (s, 3H, CH₃Si), –0.2 (s, 3H, CH₃Si).

Titanium Chloride Triisopropoxide. Titanium(IV) isopropoxide (23.7 g, 80 mmol) under Ar at 0 °C was treated with portions of titanium(IV) chloride (5.3 g, 30 mmol) over a 5-min period, and the reaction mixture was warmed to room temperature. Distillation (10.5 Torr, 95–100 °C) afforded the desired product that crystallized upon standing.

Methyl 5-Hydroxy-6-[7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl]hexanoate (10). A solution of 9 (100 mg, 0.25 mmol) in THF (2 mL) was added to a flame-dried flask containing *n*-BuLi (2.5 M, 0.13 mL, 0.33 mmol) and THF (2 mL). The solution was cooled to –78 °C, stirred for 20 min, and treated with a solution of titanium chloride triisopropoxide (79 mg, 0.3 mmol) in THF (2 mL). Stirring was continued for 3 h. Then a solution of methyl 4-formybutanoate (40 mg, 0.3 mmol) in THF (2 mL) was added. Stirring was continued for an 1 h at –78 °C, and the mixture was warmed to room temperature, stirred for 12 h, quenched with H₂O, extracted with EtOAc, dried (MgSO₄), filtered, and concentrated. Flash chromatography (1–10% EtOAc–hexane gradient elution) afforded 10 as an oil (40 mg, 30%): ¹H NMR δ 8.2 (d, 1H, 4-quinolinyl), 7.96 (br s, 1H, 8-quinolinyl), 7.9 (d, 1H, 3-quinolinyl), 7.66 (dd, 1H, 6-quinolinyl),

7.35 (d, 1H, 5-quinolinyl), 5.9 (br s, 1H, CHOSi), 4.95 (br t, 1H), 4.35 (m, 1H, CHOH), 3.8 (s, 3H, CH₃CO₂), 3.28 (d, 1H), 3.15 (m, 2H, CH₂-quinolinyl), 2.56 (m, 2H, CH₂CO₂CH₃), 1.15 (s, 9H, *t*-BuSi), 0.85–2.2 (m, 21H, aliphatic), 0.25 (s, 6H, CH₃Si); MS (CI) 530 (M + H).

5-Hydroxy-6-[7-(1-hydroxynonyl)quinolin-2-yl]hexanoic Acid, Lithium Salt (3). A solution of 10 (100 mg, 0.2 mmol) in CH₃CN (11 mL) was treated dropwise with a solution of HF–pyridine (1.1 mL). The resulting mixture was stirred at room temperature under Ar atmosphere for 20 min and concentrated. Flash chromatography (5% CH₃OH–CH₂Cl₂) afforded the corresponding dihydroxy methyl ester (60 mg, 75%) as a yellow oil: ¹H NMR δ 8.05 (d, 1H, 4-quinolinyl), 7.90 (br s, 1H, 8-quinolinyl), 7.75 (d, 1H, 3-quinolinyl), 7.53 (dd, 1H, 6-quinolinyl), 7.20 (d, 1H, 5-quinolinyl), 4.85 (t, 1H, CHOH), 4.19 (m, 1H, CHOH), 3.65 (s, 3H, CH₃O₂C), 3.08 (br dd, 1H, CH-quinolinyl), 2.97 (dd, 1H, CH-quinolinyl), 2.48 (t, 2H, CH₂CO₂CH₃), 1.1–1.95 (m, 18H, aliphatic), 0.82 (t, 3H, CH₃-aliphatic). Anal. (C₂₆H₃₇NO₄·1/8 H₂O) C, H, N.

To a solution of the dihydroxy methyl ester (60 mg, 0.14 mmol) in 1:1 THF–H₂O (2 mL) was added lithium hydroxide monohydrate (31 mg, 0.7 mmol). The solution was stirred at room temperature for 1 h, filtered, and concentrated. MPLC (0–70% CH₃OH–H₂O gradient elution) afforded 3 (30 mg, 53%) as a lyophilized solid: ¹H NMR (CD₃OD) δ 8.22 (d, 1H, 9-quinolinyl), 7.90 (s, 1H, 8-quinolinyl), 7.85 (d, 1H, 3-quinolinyl), 7.55 (dd, 1H, 6-quinolinyl), 7.44 (d, 1H, 5-quinolinyl), 4.80 (t, 1H, CHOH), 4.10 (m, 1H, CHOH), 3.11 (dd, 1H, CH-quinolinyl), 3.02 (dd, 1H, CH-quinolinyl), 2.16 (t, 2H, CH₂CO₂ Li), 1.15–1.95 (m, 18H, aliphatic), 0.85 (t, 3H, CH₃-aliphatic); MS (CI) 402 (M + H). Anal. C, H, N.

6-[7-(1-Hydroxynonyl)quinolin-2-yl]hex-5-enoic Acid (11). A solution of 10 (100 mg, 0.2 mmol) in THF (1 mL) at 0 °C was treated with TBAF (1 M in THF, 1 mL, 1 mmol). The resulting solution was stirred for 5 min at 0 °C, warmed to room temperature, stirred for 48 h, diluted with H₂O, extracted with EtOAc, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (SiO₂, 5% CH₃OH–CH₂Cl₂) afforded 11 (60 mg, 78%) as a white crystalline solid: MS (CI) 384 (M + H). Anal. (C₂₄H₃₃NO₃·1/2 H₂O) C, H, N.

6-[7-(1-Hydroxynonyl)quinolin-2-yl]hexanoic Acid (12). A mixture of 11 (18 mg, 0.03 mmol), EtOH (3 mL), and Pd/C (5%, 20 mg) was hydrogenated on a Parr hydrogenator (60 psi, H₂) for 2 h, filtered, and concentrated to afford 12 as a solid (15 mg, 83%): ¹H NMR (CD₃OD) δ 8.2 (d, 1H, 4-quinolinyl), 7.91 (br s, 1H, 8-quinolinyl), 7.85 (d, 1H, 3-quinolinyl), 7.56 (dd, 1H, 6-quinolinyl), 7.4 (d, 1H, 5-quinolinyl), 4.8 (t, 1H, CHOH), 2.95 (t, 2H, CH₂-quinolinyl), 2.25 (t, 2H, CH₂CO₂H), 1.55–1.95 (m, 4H, aliphatic), 1.15–1.55 (m, 14H, aliphatic), 1.02 (t, 2H, aliphatic), 0.87 (br t, 3H, CH₃-aliphatic); MS (CI) 386 (M + H).

3-[(Trifluoromethyl)sulfonyl]benzaldehyde. To a mixture of 3-hydroxybenzaldehyde (0.5 g, 4 mmol, Aldrich), DMF (2 mL), and sodium hydride (60% oil dispersion, 0.2 g, 20 mmol) was added dropwise a solution containing *N*-phenyltrifluoromethanesulfonamide (1.8 g, 5 mmol, Aldrich) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 12 h, and extracted with EtOAc (50 mL), and the EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) afforded 3-[(trifluoromethyl)sulfonyl]benzaldehyde as an oil (0.3 g, 33%): ¹H NMR δ 10.05 (s, 1H, CHO), 8.0 (d, 1H, aromatic), 7.80 (d, 1H, aromatic), 7.65 (t, 1H, aromatic), 7.55 (dd, 1H, aromatic).

2-[7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl]-1-[3-[(trifluoromethyl)sulfonyl]oxy]phenyl]ethanol (13). A solution of 9 (250 mg, 0.6 mmol) in THF (2 mL) was added dropwise to a solution of *n*-BuLi (0.22 mL, 0.76 equiv, 2.5 M in THF) in THF (2 mL) under Ar at –78 °C. The resulting purple solution was stirred for 1 h, after which 3-[(trifluoromethyl)sulfonyl]benzaldehyde was added, causing the solution to turn light yellow. The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C, stirred for an additional 1 h, diluted with H₂O, and extracted with EtOAc. The EtOAc layer was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) afforded 13 as an oil (0.18 g, 46%): ¹H NMR δ 8.1 (d, 1H aromatic),

8.0 (s, 1H, aromatic), 7.8 (d, 1H, aromatic), 7.7–7.1 (m, 6H, aromatic; quinolinyl), 5.4 (m, 1H, CHOH), 4.9 (t, 1H, CHOSi), 3.3 (d, 2H, CH₂-quinolinyl), 1.8–1.3 (m, 17H, aliphatic), 0.9 (m, 9H, *tert*-butyl), 0.1 (s, 3H, CH₃Si), –0.1 (s, 3H, CH₃Si).

Methyl 3-[1-Hydroxy-2-[7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl]ethyl]benzoate (14). A mixture of 13 (0.18 g, 0.2 mmol), DMSO (1 mL), MeOH (1 mL), Et₃N (8.4 μ L, 2.2 equiv), Pd(OAc)₂ (2.2 mg, 0.04 mmol), and dppp (4.2 mg, 0.06 mmol) was saturated with CO and stirred at 70 °C for 32 h. The mixture was diluted with EtOAc, washed with H₂O, saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (2–5% EtOAc–hexane gradient elution) afforded 14 as an oil (40 mg, 30%).

3-[1-Hydroxy-2-[7-(1-hydroxynonyl)quinolin-2-yl]ethyl]benzoic Acid, Lithium Salt (15). Compound 14 was deprotected and saponified as previously described to afford 15 (11 mg, 65%) as a lyophilized solid: ¹H NMR (CD₃OD) δ 8.15 (d, 1H, aromatic), 8.07 (s, 1H, aromatic), 7.98 (s, 1H, quinolinyl), 7.8 (m, 2H, quinolinyl), 7.6 (d, 1H, aromatic), 7.4 (d, 1H, aromatic), 7.3 (m, 2H, quinolinyl), 5.3 (m, 1H, CHOH), 4.8 (m, 1H, CHOH), 3.4 (d, 2H, CH₂-quinolinyl), 1.8–1.3 (m, 14H, aliphatic), 0.99 (m, 3H, aliphatic); MS (FAB) 436 (M + H).

Trifluoromethanesulfonic Acid 7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl Ester (17). A solution of 8 (1.4 g, 3.5 mmol) in CH₂Cl₂ (15 mL) at 0 °C was treated with MCPBA (80%, 0.8 g, 3.5 mmol). The solution was stirred for 12 h, warmed to room temperature, diluted with CH₂-Cl₂ (50 mL), washed with NaHCO₃, H₂O, and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (0–1% CH₃OH–CH₂Cl₂ gradient elution) afforded *N*-oxide 16 as an oil (1.2 g, 87%).

A solution of 16 (1.2 g, 3 mmol) in THF (10 mL) under Ar at 0 °C was treated with Et₃N (1.3 mL, 9 mmol) and TFAA (4.2 mL, 30 mmol). After being stirred for 0.5 h, the reaction solution was poured into a mixture containing 5% NaHCO₃, ice, and EtOAc, and the organic phase was separated, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (0–10% EtOAc–hexane gradient elution) afforded 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-ol as a waxy oil (1.2 g, 99%): ¹H NMR δ 7.75 (d, 1H, 4-quinolinyl), 7.45 (d, 1H, aromatic), 7.36 (s, 1H, aromatic), 7.20 (d, 1H, aromatic), 6.69 (d, 1H, 3-quinolinyl), 4.72 (m, 1H, CHOSi), 1.7–1.1 (m, 17H, aliphatic), 0.86 (s, 9H, *t*-BuSi), 0.00 (s, 3H, CH₃Si), –0.17 (s, 1H, CH₃Si).

7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-ol (0.84 g, 2.1 mmol) was treated with dry pyridine (15 mL) under Ar, cooled to –20 °C, and treated with trifluoromethanesulfonic anhydride (1 mL, 6 mmol). The reaction mixture was stirred for 0.5 h at –20 °C, for 0.5 h at 5 °C, and for 12 h at room temperature, diluted with EtOAc, washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (0–10% EtOAc–hexane gradient elution) afforded 17 as an oil (0.73 g, 66%): ¹H NMR δ 8.31 (d, 1H, 4-quinolinyl), 7.86 (m, 2H, aromatic), 7.19 (d, 1H, aromatic), 7.20 (d, 1H, 3-quinolinyl), 4.82 (m, 1H, CHOSi), 1.8–1.2 (m, 17H, aliphatic), 0.89 (s, 9H, *t*-BuSi), 0.08 (s, 3H, CH₃Si), –0.12 (s, 3H, CH₃Si).

Methyl 3-[[7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl]ethynyl]benzoate (18). Compound 17 (0.3 g, 0.5 mmol), methyl 3-ethynylbenzoate (0.09 g, 0.6 mmol), and Et₃N (2 mL) were combined and degassed over a 10-min period with a stream of Ar. Then bis(triphenylphosphine)palladium(II) chloride (Aldrich, 7 mg, 0.01 mmol) and copper iodide (1 mg, 0.05 mmol) were added, and the reaction mixture was stirred under Ar for 6 h, diluted with CH₂Cl₂ (50 mL), washed with H₂O, and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (0–4% EtOAc–hexane gradient elution) afforded 18 as an oil (0.3 g, 96%): ¹H NMR δ 8.36–7.42 (m, 9H, aromatic), 4.85 (t, 1H, CHOSi), 3.93 (s, 3H, CH₃O₂C), 1.9–1.6 (br s, 2H, CH₂CHSi), 1.3–1.2 (br s, 15H, aliphatic), 0.9 (s, 9H, *t*-BuSi), 0.07 (s, 3H, CH₃Si), –0.11 (s, 3H, CH₃Si).

3-[2-[7-(1-Hydroxynonyl)quinolin-2-yl]ethyl]benzoic Acid, Lithium Salt (19). Compound 18 (0.15 g, 0.3 mmol), CH₃OH (20 mL), and 5% Pd/C (0.014 g) were hydrogenated at 50 psi for 3 h. The reaction mixture was filtered, and the solvent was concentrated to afford the reduced silylated methyl ester (0.14 g, 92%): ¹H NMR δ 8.1–6.9 (m, 9H, aromatic), 4.85 (t, 1H, CHOSi),

3.9 (s, 3H, CH₃O₂C), 3.27 (m, 4H, ethylene), 1.8–1.6 (br s, 2H, CH₂CHSi), 1.4–1.2 (br s, 15H, aliphatic), 0.9 (s, 9H, *t*-BuSi), 0.1 (s, 3H, CH₃Si), –0.1 (s, 3H, CH₃Si).

The silyl ester (0.2 g, 0.36 mmol) was deprotected and saponified as previously described to afford, after chromatography (HP-20, H₂O, 50% CH₃OH, 100% CH₃OH), 19 (20 mg): ¹H NMR (free acid) δ 8.22–7.26 (m, 9H, aromatic), 4.89 (t, CHOH), 3.37 (m, 2H, CH₂Ar), 3.23 (m, 2H, CH₂Ar), 1.86 (m, 2H, CH₂CHOH), 1.6–1.2 (br s, 12H, aliphatic), 0.85 (t, 3H, CH₃-aliphatic). Anal. (C₂₇H₃₂LiNO₃) C, H, N.

1-Quinolin-7-ylnonan-1-one (20). A mixture of 7 (4.5 g, 17 mmol), MnO₂ (4.5 g), and CH₂Cl₂ (225 mL) was stirred overnight. The reaction was incomplete (TLC), so therefore an additional 2.3 g of MnO₂ was added; stirring was continued for a total of 48 h. The reaction mixture was filtered and concentrated, and the residue was purified by flash chromatography (0–5% EtOAc–hexanes gradient elution) to afford 20 as an oil (3.9 g, 85%): ¹H NMR δ 8.89 (dd, 1, 2-quinolinyl), 8.58 (s, 1, 8-quinolinyl), 8.1 (n, 2, 3-quinolinyl, 4-quinolinyl), 7.88 (d, 1H, *J* = 6 Hz, 6-quinolinyl), 7.37 (dd, 1H, 5-quinolinyl), 3.02 (t, 2H, *J* = 6 Hz), 1.70 (m, 2H), 1.2 (m, 10H), 0.79 (t, 3H, *J* = 6 Hz).

(S)-1-Quinolin-7-ylnonan-1-ol [(S)-7]. A solution of 20 (0.12 g, 0.44 mmol) in THF (0.5 mL) was added dropwise to a solution of (–)- β -chlorodiisopinocampheylborane (0.3 g, 0.9 mmol) in THF (2 mL) at –25 °C. The resulting solution was stirred for 9 h at –25 °C and concentrated, and the residue was dissolved in Et₂O (4 mL). Diethanolamine (0.2 mL, 0.2 mmol) was added to the Et₂O solution, and the mixture was allowed to stand at room temperature for 4 h. The mixture was filtered, and the solid residue was triturated with Et₂O (3 mL), filtered and washed again with additional Et₂O (2 \times 3 mL), and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (0–50% EtOAc–hexanes gradient elution) to afford (S)-7 as an oil (73 mg, 63%). ¹H NMR was identical to racemic 7. Anal. (C₁₈H₂₅NO) C, H, N.

(R)-1-Quinolin-7-ylnonan-1-ol [(R)-7]. A solution of 20 (1.2 g, 4.4 mmol) in THF (5 mL) was added dropwise to a solution of (+)- β -chlorodiisopinocampheylborane (3.2 g, 9.8 mmol) in THF (5 mL) at –25 °C. The reaction mixture was stirred at –25 °C for 9 h and concentrated, and the residue was dissolved in Et₂O (30 mL). Diethanolamine (2 mL, 2 mmol) was added to the Et₂O solution, and the mixture was allowed to stand at room temperature for 4 h. The resulting mixture was triturated with Et₂O (30 mL) and filtered, and the solid residue was washed with additional Et₂O. The filtrate was concentrated and the residue purified by flash chromatography (0–25% EtOAc–hexanes gradient elution) to afford (R)-7 as an oil (0.64 g, 64%). ¹H NMR was identical to the racemic material 7. Anal. (C₁₈H₂₅NO) C, H, N.

(R)-3-[2-[7-(1-Hydroxynonyl)quinolin-2-yl]ethyl]benzoic Acid, Lithium Salt (R)-19 was prepared by the sequence of reactions used to prepare racemic 19.

7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinoline-2-carbaldehyde (21). A mixture of 17 (1 g, 1.9 mmol), DMSO (6 mL), CH₃OH (4 mL), Et₃N (0.7 mL, 4.8 mmol), Pd(OAc)₂ (0.014 g, 0.06 mmol), and dppp (0.025 g, 0.06 mmol) was purged with carbon monoxide for 5 min, heated to 65 °C, stirred for 3 h, and cooled to room temperature. The reaction mixture was diluted with Et₂O, washed with H₂O, NaHCO₃, and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (5–30% EtOAc–petroleum ether gradient elution) afforded methyl 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinoline-2-carboxylate as a waxy oil (0.7 g, 82%): ¹H NMR δ 8.3–7.7 (m, 5H, aromatic), 4.87 (t, 1H, CHOSi), 4.09 (s, 3H, CH₃O₂C), 1.8–1.65 (br m, 2H, CH₂-aliphatic), 1.23 (br s, 15H, aliphatic), 0.9 (s, 9H, *t*-BuSi), 0.074 (s, 3H, CH₃Si), –0.12 (s, 3H, CH₃Si).

A solution of methyl 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinoline-2-carboxylate (0.7 g, 1.6 mmol) in CH₂Cl₂ (8 mL) at –78 °C was treated with DIBAL (1 M in CH₂Cl₂, 2.7 mL, 2.7 mmol) over a 20-min period. The resulting solution was stirred for 1 h, quenched with aqueous potassium sodium tartrate, and extracted with EtOAc. The organic phase was separated, washed with tartrate solution and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (2–30% EtOAc–petroleum ether gradient elution) afforded aldehyde 21

as an oil (0.6 g, 85%): $^1\text{H NMR}$ δ 10.23 (s, 1H, CHO); MS (DCI, CH_4) 414 ($\text{M} + \text{H}$).

2-(Bromomethyl)-7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinoline (22). A solution of 21 (0.25 g, 0.61 mmol) in CH_3OH (6 mL) at 0°C was treated with NaBH_4 (24 mg, 0.65 mmol), stirred for 15 min, quenched with saturated NH_4Cl , and extracted with EtOAc. The EtOAc fraction was washed with H_2O and saturated NaCl, dried (MgSO_4), and concentrated to afford 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl]methanol (0.25 g, 99%): $^1\text{H NMR}$ δ 8.1–7.23 (m, 5H, aromatic), 4.9 (s, 2H, CH_2 -quinolinyl), 4.85 (t, 1H, CHOSi), 1.81–1.63 (m, 2H, CH_2 -aliphatic), 1.23 (br s, 15H, aliphatic), 0.9 (s, 9H, *t*-BuSi), 0.066 (s, 3H, CH_3Si), -0.125 (s, 3H, CH_3Si).

[7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinolin-2-yl]methanol (0.26 g, 0.62 mmol) in CH_2Cl_2 (3 mL) at 0°C was treated with CBr_4 (0.5 g, 1.5 mmol) and $(\text{Ph})_3\text{P}$ (0.4 g, 1.6 mmol). The reaction mixture was stirred for 2 h, warmed to room temperature, and concentrated. The residue was purified by flash chromatography (3–7% EtOAc–petroleum ether gradient elution) to afford 22 (0.11 g, 37%): $^1\text{H NMR}$ δ 8.15–6.8 (m, 5H, aromatic), 4.82 (t, 1H, CHOSi), 4.71 (s, 2H, CH_2 -quinolinyl), 1.7–1.68 (m, 2H, CH_2 -aliphatic), 1.23 (br s, 15H, aliphatic), 0.89 (s, 9H, *t*-BuSi), 0.055 (s, 3H, CH_3Si), -0.135 (s, 3H, CH_3Si).

2-[[[7-(1-Hydroxynonyl)quinolin-2-yl]methyl]sulfanyl]benzoic Acid, Potassium Salt (23). To a solution of 22 (0.1 g, 0.22 mmol) in DMF (2 mL) at 0°C was added methyl 3-mercaptopropionate (80 mg, 0.5 mmol) and K_2CO_3 (0.07 g, 0.5 mmol). After being stirred for 0.5 h, the reaction mixture was diluted with CH_2Cl_2 , washed with H_2O and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (2–30% EtOAc–petroleum ether gradient elution) afforded the silyl ester as an oil (0.11 g, 95%): $^1\text{H NMR}$ δ 8.08–7.25 (m, 9H, aromatic), 4.81 (t, 1H, CHOSi), 4.47 (s, 2H, CH_2SAr), 3.87 (s, 3H, $\text{CH}_3\text{O}_2\text{C}$), 1.65–1.17 (br m, 17H, aliphatic), 0.88 (s, 9H, *t*-BuSi), 0.049 (3H, CH_3Si), -0.14 (s, 3H, CH_3Si).

The silyl ester (0.1 g, 0.2 mmol) was deprotected and saponified as previously described to afford 23 as an amorphous solid purified by MPLC (0–10% CH_3OH – H_2O gradient elution; 42 mg, 72%): $^1\text{H NMR}$ (CD_3OD) δ 8.35–7.20 (m, 9H, aromatic), 4.95–4.80 (m, 1H, CHOH + CD_3OH), 4.46 (s, 2H, CH_2SAr), 1.90–1.70 (m, 2H, aliphatic), 1.27 (br s, 12H, aliphatic), 0.86 (t, 3H, CH_3 -aliphatic); MS (FAB): 476.1 ($\text{M} + \text{H}$).

2-[[[7-(1-Hydroxynonyl)quinolin-2-yl]methyl]sulfanyl]benzoic Acid, Lithium Salt (24). A solution of the silyl ester prepared above (60 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) at 0°C was treated with MCPBA (20 mg, 0.13 mmol) and stirred for 0.5 h. The reaction mixture was extracted with CH_2Cl_2 (3 mL), and the CH_2Cl_2 fraction was washed with H_2O , NaHCO_3 , and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (10–30% EtOAc–hexane gradient elution) afforded the sulfoxide ester (60 mg, 97%): $^1\text{H NMR}$ δ 8.25–7.80 (m, 9H, aromatic), 4.81 (t, 1H, CHOSi), 4.40 (s, 2H, CH_2SOAr), 3.87 (s, 3H, $\text{CH}_3\text{O}_2\text{C}$), 1.88–1.60 (br m, 2H, CH_2 -aliphatic), 1.25 (br s, 12H, aliphatic), 0.90 (s, 9H, *t*-BuSi), 0.88 (t, 3H, CH_3 -aliphatic), 0.049 (s, 3H, CH_3Si), -0.14 (s, 3H, CH_3Si); MS (DCI, CH_4) 582 ($\text{M} + \text{H}$).

The silyl sulfoxide ester was deprotected as previously described using TBAF. Flash chromatography (60–100% EtOAc–petroleum ether gradient elution) afforded the alcohol ester sulfoxide as an oil (40 mg, 89%): MS (DCI, NH_3) 468 ($\text{M} + \text{H}$). Anal. ($\text{C}_{27}\text{H}_{33}\text{NO}_5\text{S}$): C, H, N.

The alcohol ester sulfoxide prepared above (36 mg, 0.077 mmol) was dissolved in CH_3OH (0.25 mL) and THF (0.7 mL), degassed with Ar, and treated with aqueous LiOH (1 M, 0.2 mL, 0.2 mmol). The reaction mixture was stirred for 1 h and concentrated, and the residue was purified by MPLC as previously described to give sulfoxide 24 (20 mg, 57%): $^1\text{H NMR}$ (CD_3OD) δ 8.25–7.25 (m, 9H, aromatic), 5.0–4.8 (m, 1H, CHOH + CD_3OH), 4.55 (s, 2H, CH_2SOAr), 1.88–1.75 (br m, 2H, CH_2 -aliphatic), 1.3 (br s, 12H, aliphatic), 0.88 (t, 3H, CH_3 -aliphatic); MS (FAB) 460.2 ($\text{M} + \text{H}$) $^+$.

Trifluoromethanesulfonic Acid 7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-yl Ester (26). To a solution of 2,7-naphthalenediol (10 g, 62.5 mmol, Aldrich), imidazole (4.3 g, 63.0 mmol), and DMF (60 mL), under Ar at 0°C ,

$^\circ\text{C}$, was added *tert*-butyldimethylsilyl chloride (8.4 g, 56.2 mmol) in two equal portions. The reaction solution was maintained at 0°C for 2 h and extracted with Et_2O , and the Et_2O fraction was washed with H_2O and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (10% EtOAc–hexane) afforded 7-[[dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-ol (8.3 g, 48%) as a colorless solid: $^1\text{H NMR}$ δ 7.65 and 7.60 (doublets, $J = 8.4$ Hz, 2H total, 4,5-naphthyl), 7.02 and 6.98 (doublets, $J = 1.6$ Hz, 2H total, 1,8-naphthyl), 6.90 (m, 2H, 3,6-naphthyl), 5.05 (dd, 1H, OH), 1.0 (s, 9H, *tert*-butyl), 0.20 (s, 6H, Me_2).

To 7-[[dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-ol (8.3 g, 30 mmol) in CH_2Cl_2 (60 mL) under Ar at 0°C was added pyridine (4 mL, 45.7 mmol) and trifluoromethanesulfonic anhydride (10 g, 35.4 mmol). The reaction solution was stirred at 0°C for 1 h, diluted with Et_2O , washed with H_2O , 5% HCl, aqueous NaHCO_3 , and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (2% EtOAc–hexane) gave 26 (11.6 g, 95%) as a pale yellow oil: $^1\text{H NMR}$ δ 7.85 and 7.75 (doublets, $J = 8.4$ Hz, 2H total, 4,5-naphthyl), 7.58 (d, $J = 1.6$ Hz, 1H, 1-naphthyl), 7.20 (m, 3H, 3,6,8-naphthyl), 1.02 (s, 9H, *tert*-butyl), 0.28 (s, 6H, Me_2).

Methyl 7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalene-2-carboxylate (27). A mixture of 26 (813 mg, 2 mmol), DMSO (6 mL), anhydrous MeOH (4 mL), Et_3N (0.6 mL, 4.4 mmol), $\text{Pd}(\text{OAc})_2$ (13.4 mg, 0.06 mmol), and 1,3-bis(diphenylphosphino)propane (25 mg, 0.06 mmol) was purged with carbon monoxide for 4 min, and the mixture was heated at 75°C under a carbon monoxide atmosphere (balloon pressure) for 1 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and concentrated. The residue was diluted with Et_2O , washed with H_2O , 5% HCl, aqueous NaHCO_3 , and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) afforded 27 (0.46 g, 73%) as a colorless oil: $^1\text{H NMR}$ δ 8.49 (s, 1H, 8-naphthyl), 7.90 (d, $J = 8.4$ Hz, 1H, 6-naphthyl), 7.85 and 7.75 (doublets, $J = 8.4$ Hz, 2H total, 4,5-naphthyl), 7.30 (d, $J = 1.6$ Hz, 1H, 1-naphthyl), 7.15 (dd, $J = 8.4$, 1.6 Hz, 1H, 3-naphthyl), 3.95 (s, 3H, methyl ester), 1.05 (s, 9H, *tert*-butyl), 0.28 (s, 6H, Me_2); MS (CI) 317 ($\text{M} + \text{H}$).

7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalene-2-carbaldehyde (28). To a solution of 27 (0.46 g, 1.45 mmol) in CH_2Cl_2 (5 mL) under Ar at -78°C was added DIBAL (4.5 mL, 4.5 mmol; 1.0 M solution in CH_2Cl_2). The reaction solution was stirred for 15 min at -78°C , treated with EtOAc (5 mL), warmed to room temperature, diluted with Et_2O , washed with 2% HCl, H_2O , aqueous potassium sodium tartrate, and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (10% EtOAc–hexane) gave 7-[[dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-yl]methanol (0.4 g, 95%): $^1\text{H NMR}$ δ 7.76 (d, $J = 8.4$ Hz, 1H, 5-naphthyl), 7.71 (d, $J = 8.4$ Hz, 1H, 4-naphthyl), 7.67 (d, $J = 1.6$ Hz, 1H, 8-naphthyl), 7.33 (dd, $J = 8.4$, 1.6 Hz, 1H, 6-naphthyl), 7.18 (d, $J = 1.6$ Hz, 1H, 1-naphthyl), 7.07 (dd, $J = 8.4$, 1.6 Hz, 1H, 3-naphthyl), 4.83 (d, $J = 5.9$ Hz, 2H, CH_2O), 1.75 (t, $J = 5.9$ Hz, 1H, OH), 1.02 (s, 9H, *tert*-butyl), 0.24 (s, 6H, Me_2).

[7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-yl]methanol (0.4 g, 1.4 mmol), CH_2Cl_2 (3 mL), and MnO_2 (1.2 g, 14 mmol) were stirred at room temperature for 18 h under Ar, filtered through Celite, and concentrated. Flash chromatography (3% EtOAc–hexane) gave 28 (0.3 g, 84%) as an oil: $^1\text{H NMR}$ δ 10.15 (s, 1H, aldehyde), 8.20 (s, 1H, 8-naphthyl), 7.80 (m, 3H, 4,5,6-naphthyl), 7.32 (d, $J = 1.6$ Hz, 1H, 1-naphthyl), 7.22 (dd, $J = 8.4$, 1.6 Hz, 1H, 3-naphthyl), 1.02 (s, 9H, *tert*-butyl), 0.30 (s, 6H, Me_2).

7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-2-[1-[[1,1-dimethylethyl)silyl]oxy]nonyl]naphthalene (29). A solution of *n*-octylmagnesium bromide was prepared from 1-bromooctane (2.7 mL, 15.6 mmol) and Mg (0.45 g, 18.5 mmol) in dry THF (40 mL) under Ar. The solution of the Grignard reagent at 0°C was transferred via canula to a -25°C solution of 28 (2.6 g, 9 mmol) in THF (10 mL). After stirring at -25°C for 10 min, H_2O and aqueous NH_4Cl were added. The reaction mixture was diluted with Et_2O , washed with H_2O and saturated NaCl, dried (MgSO_4), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) gave 1-[7-[[dimethyl(1,1-dimethylethyl)silyl]oxy]naph-

thalen-2-yl]nonan-1-ol (3.1 g, 84%): ¹H NMR δ 7.80 (d, *J* = 8.4 Hz, 1H, 5-naphthyl), 7.75 (d, *J* = 8.4 Hz, 1H, 4-naphthyl), 7.65 (d, *J* = 1.6 Hz, 1H, 8-naphthyl), 7.33 (d, *J* = 8.4, 1.6 Hz, 1H, 6-naphthyl), 7.18 (d, *J* = 1.6 Hz, 1H, 1-naphthyl), 7.07 (dd, *J* = 8.4, 1.6 Hz, 1H, 3-naphthyl), 4.82 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 1.95 (br s, 1H, OH), 1.88 (m, 2H, CH₂), 1.30 (m, 12H, aliphatic), 1.02 (s, 9H, *tert*-butyl), 0.90 (t, *J* = 6.8 Hz, 3H, CH₃), 0.24 (s, 6H, Me₂); MS (CI) 401 (M + H).

To 1-[7-[[dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-yl]nonan-1-ol (3 g, 7.5 mmol) in CH₂Cl₂ (20 mL) under Ar at 0 °C were sequentially added 2,6-lutidine (2.6 mL, 22.3 mmol) and *tert*-butyldimethylsilyl triflate (2.6 mL, 11.3 mmol). The temperature was maintained at 0 °C for 30 min, the reaction mixture was extracted with Et₂O, and the Et₂O fraction was washed with H₂O, 5% HCl, aqueous NaHCO₃, and saturated NaCl, dried (MgSO₄), filtered, and concentrated to afford 29 which was used in the next step without further purification: ¹H NMR δ 7.72 (d, *J* = 8.4 Hz, 1H, 5-naphthyl), 7.68 (d, *J* = 8.4 Hz, 1H, 4-naphthyl), 7.55 (d, *J* = 1.6 Hz, 1H, 8-naphthyl), 7.31 (dd, *J* = 8.4, 1.6 Hz, 1H, 6-naphthyl), 7.15 (d, *J* = 1.6 Hz, 1H, 1-naphthyl), 7.02 (dd, *J* = 8.4, 1.6 Hz, 1H, 3-naphthyl), 4.72 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 1.70 (m, 2H, CH₂), 1.28 (m, 12H, aliphatic), 1.02 (s, 9H, *tert*-butyl), 0.91 (s, 9H, *tert*-butyl), 0.89 (t, *J* = 6.8 Hz, 3H, CH₃), 0.28 (s, 6H, Me₂), 0.040 and -0.13 (singlets, 6H total, Me₂).

7-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-ol (30). A mixture of 29, MeOH (20 mL), THF (10 mL), and excess anhydrous K₂CO₃ was vigorously stirred for 1 h under Ar. The reaction mixture was treated with aqueous NH₄Cl and extracted with Et₂O. The Et₂O phase was washed with H₂O and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (7% EtOAc-hexane) afforded 30 as a waxy solid (2.9 g, 96%): ¹H NMR δ 7.71 (m, 2H, 4,5-naphthyl), 7.54 (d, *J* = 1.6 Hz, 1H, 8-naphthyl), 7.30 (dd, *J* = 8.4, 1.6 Hz, 1H, 6-naphthyl), 7.12 (d, *J* = 1.6 Hz, 1H, 1-naphthyl), 7.06 (dd, *J* = 8.4, 1.6 Hz, 1H, 3-naphthyl), 5.07 (s, 1H, OH), 4.76 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 1.71 (m, 2H, CH₂), 1.24 (m, 12H, aliphatic), 0.89 (s, 9H, *tert*-butyl), 0.86 (t, *J* = 6.8 Hz, 3H, CH₃), 0.040 and -0.13 (singlets, 6H total, Me₂).

2-[[7-(1-Hydroxynonyl)naphthalen-2-yl]methyl]sulfanyl]benzoic Acid, Lithium Salt (31). A solution of 30 (3 g, 7.5 mmol) in CH₂Cl₂ (20 mL) under Ar at 0 °C was treated sequentially with pyridine (2.5 mL, 31.0 mmol) and Tf₂O (2.5 mL, 15.5 mmol). The solution was stirred for 30 min, diluted with Et₂O, washed with H₂O, 5% HCl, aqueous NaHCO₃, and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (1% Et₂O-hexane) afforded trifluoromethanesulfonic acid 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-yl ester (3.6 g, 90%) as a pale yellow oil: ¹H NMR δ 7.89 (d, *J* = 8.4 Hz, 1H, 4-naphthyl), 7.84 (d, *J* = 8.4 Hz, 1H, 5-naphthyl), 7.71 (m, 2H, 1,8-naphthyl), 7.56 (dd, *J* = 8.4, 1.6 Hz, 1H, 6-naphthyl), 7.32 (dd, *J* = 8.4, 1.6 Hz, 1H, 3-naphthyl), 4.80 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 1.70 (m, 2H, CH₂), 1.27 (m, 12H, aliphatic), 0.90 (s, 9H, *tert*-butyl), 0.86 (t, *J* = 6.8 Hz, 3H, CH₃), 0.058 and -0.13 (singlets, 6H total, Me₂).

A mixture containing 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-yl ester (0.53 g, 1 mmol), DMSO (3 mL), anhydrous MeOH (2 mL), Et₃N (0.3 mL, 2.2 mmol), Pd(OAc)₂ (6.7 mg, 0.03 mmol), and 1,3-bis(diphenylphosphino)propane (12.5 mg, 0.03 mmol) was purged with carbon monoxide for 4 min, heated to 75 °C under a carbon monoxide atmosphere (balloon pressure), and stirred for 1 h. After cooling to room temperature, the reaction mixture was filtered through Celite, concentrated, and extracted with Et₂O. The Et₂O fraction was washed with H₂O, 5% HCl, aqueous NaHCO₃, and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (3% Et₂O-hexane) gave methyl 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-carboxylate (0.4 g, 98%): ¹H NMR δ 8.58 (d, *J* = 1.6 Hz, 1H, 1-naphthyl), 8.02 (dd, *J* = 8.4, 1.6 Hz, 1H, 3-naphthyl), 7.83 (m, 3H, 4,5,8-naphthyl), 7.57 (dd, *J* = 8.4, 1.6 Hz, 1H, 6-naphthyl), 4.80 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 3.98 (s, 3H, methyl ester), 1.70 (m, 2H, CH₂), 1.24 (m, 12H, aliphatic), 0.90 (s, 9H, *tert*-butyl), 0.86 (t, *J* = 6.8 Hz, 3H, CH₃), 0.051 and -0.14 (singlets, 6H total, Me₂); MS (CI) 443 (M + H).

Methyl 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-carboxylate (0.4 g, 0.98 mmol) in CH₂Cl₂ (2 mL) under Ar at -78 °C was treated with DIBAL (3 mL, 3 mmol; 1 M solution in CH₂Cl₂) and stirred for 20 min. EtOAc (2 mL) was added, and the reaction solution was warmed to room temperature, diluted with Et₂O, and vigorously shaken with aqueous potassium sodium tartrate. The organic layer was separated, washed with saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (10% EtOAc-hexane) afforded 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-yl]methanol (0.4 g, 100%): ¹H NMR δ 7.78 (m, 3H, 1,4,5-naphthyl), 7.69 (s, 1H, 8-naphthyl), 7.46 (m, 2H, 3,6-naphthyl), 4.85 (d, *J* = 6 Hz, 2H, CH₂-O), 4.78 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 1.74 (t, *J* = 6 Hz, 1H, OH), 1.70 (m, 2H, CH₂), 1.23 (m, 12H, aliphatic), 0.90 (s, 9H, *tert*-butyl), 0.86 (t, *J* = 6.8 Hz, 3H, CH₃), 0.041 and -0.14 (singlets, 6H total, Me₂); MS (CI) 413 (M - H).

[7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-yl]methanol (0.23 g, 0.56 mmol) in CH₂Cl₂ (1 mL) under Ar at 0 °C was sequentially treated with CBr₄ (0.28 g, 0.85 mmol) and (Ph)₃P (0.2 g, 0.8 mmol). After the mixture was stirred for 1 h, the solvent was concentrated and the resulting residue purified by flash chromatography (2% Et₂O-hexane) to afford 7-(bromomethyl)-2-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalene (0.24 g, 91%) as a colorless oil: ¹H NMR δ 7.79 (m, 3H, 1,4,5-naphthyl), 7.67 (s, 1H, 8-naphthyl), 7.47 (m, 2H, 3,6-naphthyl), 4.78 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 4.67 (s, 2H, CH₂-Br), 1.70 (m, 2H, CH₂), 1.23 (m, 12H, aliphatic), 0.88 (s, 9H, *tert*-butyl), 0.87 (t, *J* = 6.8 Hz, 3H, CH₃), 0.044 and -0.14 (singlets, 6H total, Me₂).

A mixture containing 7-(bromomethyl)-2-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalene (0.14 g, 0.29 mmol), methyl 3-mercaptopropionate (55 mg, 0.33 mmol), DMF (1.5 mL), and anhydrous K₂CO₃ (85 mg, 0.62 mmol) was vigorously stirred under Ar for 30 min, diluted with Et₂O, washed with H₂O and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (2% EtOAc-hexane) gave methyl 2-[[7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-yl]methyl]sulfanyl]benzoate (0.16 g, 95%): ¹H NMR δ 8.04 (dd, *J* = 1.6 Hz, 1H, 2-phenyl), 7.84 (ddd, *J* = 7.8, 1.6 Hz, 1H, 6-phenyl), 7.75 (m, 2H, 4,5-naphthyl), 7.65 and 7.60 (singlets, 2H total, 1,8-naphthyl), 7.42 (m, 3H, 4-phenyl, 3,6-naphthyl), 7.28 (dd, *J* = 7.8 Hz, 1H, 5-phenyl), 4.76 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 4.30 (s, 2H, CH₂S), 3.88 (s, 3H, methyl ester), 1.70 (m, 2H, CH₂), 1.24 (m, 12H, aliphatic), 0.89 (s, 9H, *tert*-butyl), 0.88 (t, *J* = 6.8 Hz, 3H, CH₃), 0.037 and -0.15 (singlets, 6H total, Me₂).

Methyl 2-[[[7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalen-2-yl]methyl]sulfanyl]benzoate (0.16 g, 0.28 mmol) was deprotected and saponified as described previously to give 31 (32 mg, 86%) as a colorless amorphous solid after lyophilization: ¹H NMR (CD₃OD) δ 8.03 (dd, *J* = 1.6 Hz, 1H, 2-phenyl), 7.75 (m, 3H, 6-phenyl, 4,5-naphthyl), 7.71 (m, 2H, 1,8-naphthyl), 7.44 (m, 2H, 3,6-naphthyl), 7.33 (ddd, *J* = 7.8, 1.6 Hz, 1H, 4-phenyl), 7.19 (dd, *J* = 7.8 Hz, 1H, 5-phenyl), 4.72 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 4.33 (s, 2H, CH₂S), 1.78 (m, 2H, CH₂), 1.25 (m, 12H, aliphatic), 0.87 (t, *J* = 6.8 Hz, 3H, CH₃); MS (FAB): 435.2 (M - H, free acid).

3-[[[7-(1-Hydroxynonyl)naphthalen-2-yl]methyl]sulfanyl]benzoic Acid, Lithium Salt (32). Methyl 2-[[[7-(1-hydroxynonyl)naphthalen-2-yl]methyl]sulfanyl]benzoate (30 mg, 0.067 mmol) in CH₂Cl₂ (1 mL) under Ar at 0 °C was treated with 80% MCPBA (16 mg, 0.074 mmol), and the solution was stirred for 30 min, poured into aqueous NaHCO₃, extracted with CH₂Cl₂, washed with saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (40% EtOAc-hexane) gave methyl 3-[[[7-(1-hydroxynonyl)naphthalen-2-yl]methyl]sulfanyl]benzoate (22 mg, 72%) as a colorless solid: ¹H NMR δ 8.12 (dd, *J* = 7.8, 1.6 Hz, 1H, 4-phenyl), 7.96 (dd, *J* = 1.6 Hz, 1H, 2-phenyl), 7.77 (d, *J* = 8.4 Hz, 1H, 4-naphthyl), 7.70 (d, *J* = 8.4 Hz, 1H, 5-naphthyl), 7.62 (s, 1H, 8-naphthyl), 7.50 (m, 3H, 5,6-phenyl, 6-naphthyl), 7.36 (s, 1H, 1-naphthyl), 7.06 (d, *J* = 8.4 Hz, 1H, 3-naphthyl), 4.80 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 4.19 (q, *J* = 13 Hz, 2H, CH₂S), 3.80 (s, 3H, methyl ester), 2.20 (broad singlet, 1H, OH), 1.84 (m, 2H, CH₂), 1.25 (m, 12H, aliphatic), 0.86 (t, *J* = 6.8 Hz, 3H, CH₃).

A mixture of methyl 3-[[[7-(1-hydroxynonyl)naphthalen-2-yl]methyl]sulfinyl]benzoate (22 mg, 0.05 mmol), THF (0.3 mL), MeOH (0.2 mL), and LiOH (1 M, 0.2 mL, 0.2 mmol) was stirred under Ar for 4 h. The solvents were concentrated and the product was purified by MPLC (H₂O–MeOH gradient elution) to give **32** (21 mg, 100%) as a colorless amorphous solid after lyophilization: ¹H NMR (CD₃OD) δ 8.20 (dd, *J* = 1.6 Hz, 1H, 2-phenyl), 8.10 (ddd, *J* = 7.8, 1.6 Hz, 1H, 4-phenyl), 7.80 (d, *J* = 8.4 Hz, 1H, 4-naphthyl), 7.72 (d, *J* = 8.4 Hz, 1H, 5-naphthyl), 7.67 (s, 1H, 8-naphthyl), 7.57 (s, 1H, 1-naphthyl), 7.42 (m, 3H, 5,6-phenyl, 6-naphthyl), 7.15 (d, *J* = 8.4 Hz, 1H, 3-naphthyl), 4.73 (dd, *J* = 6.8, 5.4 Hz, 1H, CHO), 4.35 (q, *J* = 13 Hz, 2H, CH₂S), 1.78 (m, 2H, CH₂), 1.26 (m, 12H, aliphatic), 0.87 (t, *J* = 6.8 Hz, 3H, CH₃); MS (FAB): 451.2 (M – H, free acid).

7-Methyl-1,2,3-triazolo[1,5-*a*]pyridine (35). A mixture of **33** (20 g, 0.17 mol) and hydrazine hydrate (40 mL, 99%) under Ar was heated at 95–100 °C for 1 h, cooled to room temperature, treated with NaOH (40 mL, 25%), and extracted with Et₂O. The Et₂O fraction was washed with H₂O and saturated NaCl and dried (Na₂SO₄). Concentration followed by recrystallization from hexane gave **34** (14.4 g, 65%), mp 178–180 °C.

A mixture of hydrazone **34** (9.2 g, 0.06 mol), 420 mL of H₂O, potassium ferricyanide (49.5 g, 0.15 mol), and NaHCO₃ (12.7 g, 0.15 mol) was heated at 90 °C for 1 h, cooled to room temperature, and treated with NaOH (50 mL, 30%). The mixture was extracted with CH₂Cl₂, washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. The residue was treated with hot hexane, cooled, and filtered to remove the unreacted hydrazone **34**. The hexane solution was concentrated to give the triazopyridine **35** (3.5 g, 45%), mp 48 °C (lit.⁴ mp 42 °C).

1-(3-Iodophenyl)-2-[1,2,3]triazolo[1,5-*a*]pyridin-7-ylethanol (36). Diisopropylamine (3.9 mL, 27 mmol) dissolved in Et₂O (35 mL) was added to a flame-dried flask under Ar and cooled to –40 °C. *n*-BuLi (11 mL, 2.5 M in hexane) was added, and the solution was stirred for 5 min. To this was added dropwise over a period of 15 min a solution containing **35** (3.4 g, 25 mmol) in Et₂O (100 mL). The resulting deep brown-red solution was stirred at –40 °C for 6 h, followed by the rapid addition of a solution containing 3-iodobenzaldehyde (6.3 g, 27 mmol) in Et₂O (90 mL). The resulting reaction mixture was allowed to warm to room temperature, stirred overnight, and diluted with EtOAc, and the EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (10–40% EtOAc–hexane) afforded **36** as an amorphous solid (6.1 g, 65%): ¹H NMR δ 8.12 (s, 1H, CHN), 7.8 (s, 1H, aromatic), 7.7 (m, 2H, 5-pyridyl; aromatic), 7.4 (d, 1H, aromatic), 7.2 (m, 2H, 4-pyridyl; aromatic), 7.1 (t, 1H, aromatic), 6.8 (d, 1H, 3-pyridyl), 5.49 (m, 1H, CHOH), 3.7 (dd, 1H, CH-pyridyl), 3.6 (dd, 1H, CH-pyridyl), 3.3 (d, 1H, CHOH).

Methyl 3-(1-Hydroxy-2-[1,2,3]triazolo[1,5-*a*]pyridin-7-ylethyl)benzoate (37). A mixture containing **36** (4 g, 11 mmol), DMSO (29 mL), anhydrous MeOH (19 mL), Et₃N (3 mL), Pd(OAc)₂ (65 mg, 0.4 mmol), and 1,3-bis(diphenylphosphino)propane (120 mg, 0.8 mmol) was purged with carbon monoxide for 4 min, heated to 75 °C under a carbon monoxide atmosphere (balloon pressure), and stirred for 1 h. After cooling to room temperature, the reaction mixture was filtered through Celite and concentrated. The residue was diluted with Et₂O, washed with H₂O, 5% HCl, aqueous NaHCO₃, and saturated NaCl, dried (MgSO₄), filtered, and concentrated. Flash chromatography (10–50% EtOAc–hexane gradient elution) afforded **37** (1.4 g, 43%) as an oil: ¹H NMR δ 8.15 (s, 1H, aromatic), 8.12 (s, 1H, CHN), 7.98 (d, 1H, aromatic), 7.7 (m, 2H, 5-pyridyl; aromatic), 7.4 (t, 1H, aromatic), 7.2 (t, 1H, 4-pyridyl), 6.8 (s, 1H, 3-pyridyl), 5.55 (m, 1H, CHOH), 4.0 (s, 3H, CO₂CH₃), 3.9 (dd, 1H, CH-pyridyl), 3.7 (dd, 1H, CH-pyridyl), 3.55 (d, 1H, CHOH).

Methyl 3-[2-(6-Formylpyridin-2-yl)-1-hydroxyethyl]benzoate (38). A solution of **37** (1.4 g, 4.7 mmol) in CH₂Cl₂ (25 mL) at 0 °C was treated dropwise with a solution of bromine (0.75 g, 0.24 mL, 4.7 mmol) in CH₂Cl₂ (15 mL). Gas was evolved; the reaction mixture was stirred at 0 °C for 1 h, washed with NaHCO₃, H₂O, and saturated NaCl, dried (Na₂SO₄), and concentrated to give 1.8 g of an oil. The oil was dissolved in EtOH (40 mL) and treated with a solution of AgNO₃ (1.6 g, 9 mmol) in hot H₂O (14 mL). This mixture was heated to boiling, stirred for 1 h, cooled,

and treated with HCl (c, 11 mL). Filtration removed the silver salts. The filtrate was concentrated, the residue treated with saturated NaHCO₃, and the resulting solution was extracted with CH₂Cl₂, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (10–30% EtOAc–hexane gradient elution) gave **38** as an oil (0.6 g, 45%): ¹H NMR δ 10.1 (s, 1H, CHO), 8.1 (s, 1H, aromatic), 8.0 (d, 1H, aromatic), 7.8 (m, 2H, 5-pyridyl, aromatic), 7.6 (d, 1H, aromatic), 7.4 (m, 2H, 3-pyridyl, aromatic), 5.3 (t, 1H, CHOH), 3.9 (s, 3H, CO₂CH₃), 3.3 (d, 2H, CH₂-pyridyl).

(*E*)-Methyl {1-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-2-[6-(3-oxoundec-1-enyl)pyridin-2-yl]ethyl]benzoate (40). A solution of **38** (0.55 g, 1.9 mmol), CH₂Cl₂ (10 mL), and lutidine (0.45 g, 0.48 mL, 4.2 mmol) at 0 °C was treated dropwise (approximately 20 min) with *tert*-butyldimethylsilyl triflate (0.55 g, 0.48 mL, 2.1 mmol). The solution was allowed to warm to room temperature, diluted with CH₂Cl₂, washed with NaHCO₃, H₂O, and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (10% EtOAc–hexane) afforded **39** (0.6 g, 75%) as an oil: ¹H NMR δ 10.1 (s, 1H, CHO), 8.12 (s, 1H, aromatic), 8.0 (d, 1H, aromatic), 7.8 (m, 2H, 3,4-pyridyl), 7.6 (d, 1H, aromatic), 7.4 (m, 2H, 5-pyridyl, aromatic), 5.3 (m, 1H, CHOH), 4.0 (s, 3H, CO₂CH₃), 3.2 (d, 2H, CH₂-pyridyl), 0.8 (s, 9H, *t*-BuSi), –0.2 (s, 3H, CH₃Si), –0.3 (s, 3H, CH₃Si).

To a mixture of 1-(diethylphosphono)decane-2-one (0.2 g, 0.73 mmol), NaH (30 mg, 0.73 mmol), and THF (3 mL) was added a solution of **39** (0.26 g, 0.66 mmol) in THF (3 mL). The resulting mixture was stirred at room temperature for 1 h and diluted with EtOAc, and the EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and evaporated. Flash chromatography (10–20% EtOAc–hexane gradient elution) afforded **40** (0.14 g, 40%) as a yellow oil: ¹H NMR δ 8.05 (s, 1H, aromatic), 7.95 (d, 1H, aromatic), 7.55 (m, 2H, 3,4-pyridyl), 7.5 (d, 1H, *J* = 15.9 Hz, olefinic), 7.35 (t, 1H, aromatic), 7.25 (d, 1H, aromatic), 7.15 (d, 1H, *J* = 15.9 Hz, olefinic), 7.05 (d, 1H, 5-pyridyl), 5.15 (m, 1H, CHOH), 3.95 (s, 3H, CO₂CH₃), 3.05 (d, 2H, CH₂-pyridyl), 2.6 (t, 2H, CH₂CO), 1.4–1.0 (m, 15H, aliphatic), 0.9 (s, 9H, *t*-BuSi), –0.1 (s, 3H, CH₃Si), –0.3 (s, 3H, CH₃Si).

(*E*)-3-[1-Hydroxy-2-[6-(3-hydroxyundec-1-enyl)pyridin-2-yl]ethyl]benzoic Acid, Lithium Salt (41). A solution of **40** (0.13 g, 0.24 mmol) in CH₃OH (2 mL) at –10 °C was treated with NaBH₄ (0.0045 g, 0.12 mmol). The mixture was stirred at 0 °C for 1 h and extracted with EtOAc, and the EtOAc fraction was washed with H₂O, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (10–20% EtOAc–hexane gradient elution) afforded the corresponding alcohol (0.12 g, 91%) as a colorless oil: ¹H NMR δ 8.07 (s, 1H, aromatic), 7.96 (d, 1H, aromatic), 7.6 (d, 1H, aromatic), 7.5 (t, 1H, aromatic), 7.4 (t, 1H, 4-pyridyl), 7.1 (d, 1H, 5-pyridyl), 6.9 (d, 1H, 3-pyridyl), 6.7 (m, 2H, olefin), 5.25 (m, 1H, CHOH), 4.4 (m, 1H, CHOH), 3.9 (s, 3H, CO₂CH₃), 3.0 (d, 2H, CH₂-pyridyl), 1.7–0.9 (m, 17H, aliphatic), 0.8 (s, 9H, *t*-BuSi), –0.3 (s, 3H, CH₃Si), –0.4 (s, 3H, CH₃Si).

A solution of the alcohol prepared above (0.11 g, 0.2 mmol) was deprotected and saponified as described previously to afford **41** (0.04 g, 65%) as a lyophilized white solid: ¹H NMR (CD₃OD) δ 7.9 (s, 1H, aromatic), 7.7 (d, 1H, aromatic), 7.45 (t, 1H, aromatic), 7.3 (d, 1H, aromatic), 7.15 (m, 2H, 3,4-pyridyl), 6.9 (d, 1H, 5-pyridyl), 6.5 (m, 2H, olefin), 5.0 (t, 1H, CHOH), 4.15 (m, 1H, CHOH), 3.0 (d, 2H, CH₂-pyridyl), 1.6–0.7 (m, 17H, aliphatic); MS (FAB) 418.6 (M + H)⁺.

3-[1-Hydroxy-2-[6-(3-hydroxyundecyl)pyridin-2-yl]ethyl]benzoic Acid, Lithium Salt (42). A mixture of **41** (7 mg, 0.0018 mmol), EtOH (2 mL), and 5% Pd/C (2 mg) was treated with H₂ under 30 psi for 2 h. The reaction mixture was filtered through Celite and the solvent concentrated to afford **42** as an amorphous solid (4.6 mg): ¹H NMR (CD₃OD) δ 8.05 (s, 1H, aromatic), 7.9 (d, 1H, aromatic), 7.8 (t, 1H, aromatic), 7.65 (d, 1H, aromatic), 7.4 (t, 1H, 5-pyridyl), 7.3 (d, 1H, 4-pyridyl), 7.25 (d, 1H, 3-pyridyl), 5.2 (t, 1H, CHOH), 3.6 (t, 1H, CHOH), 3.3 (d, 2H, CH₂-pyridyl), 3.0 (m, 2H, CH₂-pyridyl), 2.0 (m, 2H, CHCHOH), 1.5–1.0 (m, 17H, aliphatic).

Dimethyl [2-(3-Butoxyphenyl)-2-oxoethyl]phosphonate (44). Methyl 3-hydroxybenzoate (10 g, 0.065 mol, Aldrich), DMF (200 mL), iodobutane (13.3 g, 0.072 mol), and K₂CO₃ (10 g, 0.072 mol) were combined and heated to 90 °C for 2 h. After cooling, the mixture was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (5%

EtOAc-hexane) afforded methyl 3-*n*-butoxybenzoate as an oil (9.7 g, 69%).

A solution of dimethyl methylphosphonate (1.5 g, 0.012 mol) in THF was added to a flame-dried flask and cooled to -78 °C. *n*-BuLi (4.8 mL, 2.5 M in hexane) was added, and the solution was stirred for 20 min and then treated dropwise with a solution of methyl 3-*n*-butoxybenzoate (1 g, 0.005 mol) in THF (20 mL). The reaction mixture was warmed to room temperature, diluted with H₂O, and extracted with EtOAc. The EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), and concentrated to afford 44 as an amorphous solid (1.6 g, 98%).

Methyl (E)-3-[2-[6-[3-(3-Butoxyphenyl)-3-oxopropenyl]pyridin-2-yl]-1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]benzoate (45). A mixture of 44 (0.14 g, 0.46 mmol), THF (6 mL), and NaH (60% dispersion, 18.5 mg, 1.1 equiv) was heated to 45 °C under Ar, stirred for 20 min, and cooled to room temperature. To this was added dropwise a solution of 39 (0.17 g, 0.42 mmol) in THF (4 mL), the mixture was stirred at room temperature for 1 h and extracted with EtOAc, and the EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (10% EtOAc-hexane) gave ketone 45 as an oily solid (0.13 g, 55%): ¹H NMR δ 8.1 (s, 1H, aromatic), 8.0 (d, 1H, *J* = 15.8, olefin), 7.9 (d, 1H, aromatic), 7.75 (d, 1H, *J* = 15.8 Hz, olefin), 7.7-7.5 (m, 5H, 3,4-pyridyl, aromatic), 7.5-7.1 (m, 4H, 5-pyridyl, aromatic), 5.3 (t, 1H, CHOSi), 4.1 (t, 2H, CH₂OPh), 3.9 (s, 3H, CO₂CH₃), 3.15 (m, 2H, CH₂-pyridyl), 1.8-1.5 (m, 4H, aliphatic), 1.0 (m, 3H, aliphatic), 0.9 (s, 9H, *t*-BuSi), -0.3 (s, 3H, CH₃Si), -0.4 (s, 3H, CH₃Si).

(E)-3-[2-[6-[3-(3-Butoxyphenyl)-3-hydroxypropenyl]pyridin-2-yl]-1-hydroxyethyl]benzoatebenzoic Acid, Lithium Salt (46). A solution of 45 (0.1 g, 0.2 mmol) in CH₃OH (2 mL) at -10 °C was treated with NaBH₄ (4 mg, 0.5 equiv) and stirred for 1 h. The reaction mixture was diluted with H₂O, concentrated, and extracted with EtOAc, and the EtOAc fraction was washed with H₂O and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (10-20% EtOAc-hexane gradient elution) afforded methyl (E)-3-[2-[6-[3-(3-butoxyphenyl)-3-hydroxypropenyl]pyridin-2-yl]-1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]benzoate as a gummy solid (88 mg, 74%): ¹H NMR δ 8.15 (s, 1H, aromatic), 7.9 (d, 1H, aromatic), 7.6 (d, 1H, aromatic), 7.5 (m, 2H, 3,4-pyridyl), 7.4 (m, 2H, 5-pyridyl, aromatic), 7.3 (d, 1H, aromatic), 7.2 (d, 1H, aromatic), 7.1-7.0 (m, 2H, aromatic), 6.9 (m, 2H, olefin), 5.4 (t, 1H, CHOH), 5.2 (t, 1H, CHOH), 4.1 (t, 2H, CH₂OPh), 3.9 (s, 3H, CO₂CH₃), 3.12 (m, 2H, CH₂-pyridyl), 1.9-1.5 (m, 4H, aliphatic), 1.0 (t, 3H, aliphatic), 0.85 (s, 9H, *t*-BuSi), -0.3 (s, 3H, CH₃Si), -0.4 (s, 3H, CH₃Si).

Methyl (E)-3-[2-[6-[3-(3-butoxyphenyl)-3-hydroxypropenyl]pyridin-2-yl]-1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]benzoate (78 mg, 0.13 mmol) was deprotected and saponified as described previously to give 46 (30 mg, 69%) as a lyophilized solid: ¹H NMR (CD₃OD) δ 8.0 (s, 1H, aromatic), 7.8 (d, 1H, aromatic), 7.6 (t, 1H, aromatic), 7.4-7.2 (m, 4H, 3,4-pyridyl, aromatic), 7.0 (m, 3H, 5-pyridyl, aromatic), 6.8 (m, 3H, olefin, aromatic), 5.3 (t, 1H, CHOH), 5.15 (t, 1H, CHOH), 4.0 (t, 2H, CH₂OPh), 3.12 (m, 2H, CH₂-pyridyl), 1.8-1.4 (m, 4H, aliphatic), 1.0 (t, 3H, aliphatic); MS (FAB) 454.1 (M + H).

3-[2-[6-[3-(3-Butoxyphenyl)-3-hydroxypropyl]pyridin-2-yl]-1-hydroxyethyl]benzoic Acid, Lithium Salt (47). A mixture of 46 (10 mg, 0.02 mmol), EtOH (2 mL), and 5% Pd/C (10 mg) was treated with H₂ for 2 h at 22 psi. The reaction mixture was filtered and the solvent concentrated to afford 47 as a lyophilized solid (10 mg, 90%): ¹H NMR (CD₃OD) δ 7.97 (s, 1H, aromatic), 7.83 (d, 1H, aromatic), 7.53 (t, 1H, aromatic), 7.4 (d, 1H, aromatic), 7.2 (m, 2H, 4-pyridyl, aromatic), 7.08 (d, 1H, aromatic), 7.0 (d, 1H, aromatic), 6.9 (m, 2H, 3,5-pyridyl), 6.8 (dd, 1H, aromatic), 5.11 (t, 1H, CHOH), 4.65 (t, 1H, CHOH), 4.0 (t, 2H, CH₂OPh), 3.2 (m, 2H, CH₂-pyridyl), 2.85 (m, 2H, CH₂-pyridyl), 2.1 (m, 2H, HOCHCH₂), 1.8-1.5 (m, 4H, aliphatic), 1.0 (t, 3H, aliphatic).

Biological Evaluation. [³H]LTB₄ Binding Assays. [³H]-LTB₄ with specific activity of 140-210 Ci/mmol was obtained from New England Nuclear (Boston, MA). Unlabeled LTB₄ was synthesized by the Medicinal Chemistry Prep Group at Smith-Kline Beecham. U-937 cells were obtained from American Type

Culture Collection and grown in RPMI-1640 media supplemented with 10% (v/v) heat-inactivated fetal calf serum in spinner culture in a humidified environment of 5% CO₂, 95% air at 37 °C. U-937 cells were differentiated with 1.3% DMSO for 3-4 days, grown to a density of 10⁶ cells/mL, and then harvested by centrifugation. Cells were washed with 50 mM Tris, pH 7.4, containing 1 mM EDTA. Washed U-937 cells were utilized for whole-cell binding assays.

Human peripheral blood from healthy aspirin-free donors was phlebotomized into sterile heparinized syringes. PMNs were isolated by the standard Ficoll-Hypaque centrifugation, dextran 70 sedimentation, and hypotonic lysis procedure.³⁰ Cell preparations used for calcium mobilization studies were >90% neutrophils and >95% viable.

Test compounds were evaluated for the ability to compete with [³H]LTB₄ for receptors on intact differentiated U-937 cells and human PMNs utilizing methods described previously.^{31,32} Washed cells (10⁶ cells) were incubated in Hanks balanced salt solution (HBSS) with 0.1% ovalbumin and 0.2 nM [³H]LTB₄ for 20 min at 0 °C in a total volume of 500 μL. Total and nonspecific binding of [³H]LTB₄ were determined in the absence and presence of 1 μM unlabeled LTB₄, respectively. For radioligand competition experiments, increasing concentrations of LTB₄ (0.1-10 nM) or test compound (0.1 nM-10 μM) were included. Unbound radioligand and competing compounds were separated from cell-bound ligand by vacuum filtration through Whatman GF/C filters. Cell-bound radioactivity was determined by liquid scintillation spectrometry. The percent inhibition of specific [³H]LTB₄ binding was determined for each concentration, and the IC₅₀ is defined as the concentration of test compound required to inhibit 50% of the specific [³H]LTB₄ binding. There were five to eight concentrations tested for a curve where each concentration of test compound was run in duplicate, and all compounds were tested in at least two separate assays. Values presented are the mean K_i which was determined from the IC₅₀ values as described by Cheng and Prusoff.³³ An estimate of the precision of the measurements can be assessed from the data obtained with other LTB₄ receptor antagonists. LY-223982 in four different assays had a K_i of 3.3 ± 0.8 nM for the mean and standard error while similar data for U-75302 showed a K_i of 709 ± 123 nM.

LTB₄-Induced Calcium Mobilization. The functional assay used to determine agonist activity of test compounds was LTB₄-induced Ca²⁺ mobilization in human PMNs.³⁴ The [Ca²⁺]_i was estimated with the calcium fluorescent probe fura 2.³⁵ Isolated PMNs were suspended in Krebs Ringer Henselet buffer at 2 × 10⁶ cells/mL containing 0.1% BSA, 1.1 mM MgCl₂, and 5 mM HEPES, pH 7.4 (buffer A). The diacetoxymethoxy ester of fura 2 (fura 2/AM) was added at a concentration of 2 μM and incubated for 45 min at 37 °C. Cells were centrifuged at 225g for 5 min and resuspended at 2 × 10⁶ cells/mL in buffer A and incubated an additional 20 min to allow complete hydrolysis of the entrapped ester. Cells were centrifuged as above and resuspended at 10⁶ cells/mL in buffer A containing 1 mM CaCl₂ and maintained at room temperature until used in the fluorescent assay which was performed within 3 h.

The fluorescence of fura 2 containing PMNs was measured with a fluorometer designed by the Johnson Foundation Biomedical Instrumentation Group. The fluorometer was equipped with a temperature control and a magnetic stirrer under the cuvette holder. Wavelengths were set at 340 nm (10-nm band width) for excitation and 510 nm (20-nm band width) for emission. All experiments were performed at 37 °C with constant stirring. For compound studies fura 2 loaded cells were centrifuged and resuspended in buffer A containing 1 mM CaCl₂ minus BSA at 10⁶ cells/mL. Aliquots (2 mL) were transferred into a cuvette and warmed in a water bath to 37 °C. The 1-cm² cuvette was transferred to the fluorometer, and fluorescence was recorded for 15 s to ensure a stable baseline before addition of compound. Fluorescence was recorded continuously for up to 3 min after addition of vehicle or compounds to monitor agonist activity. The maximal calcium/fura 2 fluorescence was determined for each concentration of compound. The standard, LTB₄ (100 nM), was added to the vehicle-treated samples, and the maximal [Ca²⁺]_i/fura 2 fluorescence was determined. The maximal [Ca²⁺]_i achieved with each sample was calculated using the following

formula as previously described.³¹

$$[\text{Ca}^{2+}]_i = 224 \text{ (nM)} \frac{F - F_{\min}}{F_{\max} - F}$$

The percent of maximal LTB₄ (100 nM) induced [Ca²⁺]_i was determined for each concentration of compound and the maximal percent agonist activity of the compound relative to LTB₄ was determined. All compounds showing agonist activity were run in concentration response curves (5–8 points) to its maximal [Ca²⁺]_i. Maximal [Ca²⁺]_i was generally seen between 0.1 and 10 μM. The data reported is the mean maximal [Ca²⁺]_i achieved relative to 100 nM LTB₄ from two agonist curves run on different days. The difference in the maximum response was not greater than 8%. Compound 47 showed no significant agonist activity at concentrations up to 100 μM in four experiments.

References

- Bray, M. A. Leukotrienes in inflammation. *Agents Actions* 1986, 19, 87–99. Brain, S. D.; Williams, T. J. Leukotrienes and Inflammation. *Pharmac. Ther.* 1990, 46, 57–66.
- Camp, R.; Jones, S.; Brain, P.; Woolard, P.; Greaves, M. Production of Intraepidermal Microabscesses by Topical Application of Leukotriene B₄. *J. Invest. Dermatol.* 1984, 82, 202–207.
- Movat, H. Z.; Rettl, C.; Burrows, C. E.; Johnston, M. G. The in vivo Effect of Leukotriene B₄ on Polymorphonuclear Leukocytes and the Microcirculation. *Am. J. Pathol.* 1984, 115, 233–244.
- Bray, M. A.; Ford-Hutchinson, A. W.; Smith, J. H. Leukotriene B₄: An Inflammatory Mediator in vivo. *Prostaglandins* 1981, 22, 213–222.
- Thorsen, S.; Fogh, K.; Broby-Johansen, U.; Sondergaard, J. Leukotriene B₄ in Atopic Dermatitis: Increased Skin Levels and Altered Sensitivity of Peripheral Blood T-cells. *Allergy* 1990, 45, 457–463.
- Fretland, D. J.; Widomski, D. L.; Levin, S.; Gaginella, T. S. Colonic Inflammation in the Rabbit Induced by Phorbol-12-Myristate-13-Acetate. *Inflammation* 1990, 14, 143–150.
- Klickstein, L. B.; Shapleigh, C.; Goetzl, E. J. Lipoxygenation of Arachidonic Acid as a Source of Polymorphonuclear Leukocyte Chemotactic Factors in Synovial Fluid and Tissue in Rheumatoid Arthritis and Spondyloarthritis. *J. Clin. Invest.* 1980, 66, 1166–1170.
- Rae, S. A.; Davidson, E. M.; Smith, M. J. H. Leukotriene B₄: An Inflammatory Mediator in Gout. *Lancet* 1982, 1122–1124.
- Ford-Hutchinson, A. W. Leukotriene B₄ in Inflammation. *Crit. Rev. Immunol.* 1990, 10, 1–12.
- Namiki, M.; Iganashi, Y.; Sakamoto, K.; Koga, Y. Pharmacological Profiles of Potential LTB₄-Antagonists, SM9064. *Biochem. Biophys. Res. Commun.* 1986, 138, 540–546.
- Morris, J.; Wishka, D. G. Synthesis of Novel Antagonists of Leukotriene B₄. *Tetrahedron Lett.* 1988, 29, 143–146.
- Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T.; Benzophenone Dicarboxylic Acid Antagonists of Leukotriene B₄. 1. Structure-Activity Relationships of the Benzophenone Nucleus. *J. Med. Chem.* 1990, 33, 2798–2807 (and following paper).
- Djuric, S. W.; Collins, P. W.; Jones, P. H.; Shone, R. L.; Tsai, B. S.; Fretland, D. J.; Butchko, G. M.; Villani-Price, D.; Keith, R. H.; Zemaitis, J. M.; Metcalf, L.; Bauer, R. F. 7-[3-(4-Acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid: an Orally Active Selective Leukotriene B₄ Receptor Antagonist. *J. Med. Chem.* 1989, 32, 1145–1147.
- (a) Konno, M.; Sakuyama, S.; Nakae, T.; Hamanaka, N.; Miyamoto, T.; Kawasaki, A.; Synthesis and Structure-Activity Relationships of a Series of Substituted Phenylpropionic Acids as a Novel Class of Leukotriene B₄ Antagonists. *Adv. Prostaglandin, Thromboxane Leukotriene Res.* 1991, 21, 411–414. (b) Kashikawa, K.; Tateishi, T.; Maruyama, T.; Seo, R.; Toda, M.; Miyamoto, T.; Ono-4057, A Novel, Orally Active Leukotriene B₄ Antagonist: Effects on LTB₄-Induced Neutrophil Functions. *Prostaglandins* 1992, 44, 261–275.
- Huang, F.; Chan, W.; Warus, J. D.; Morrisette, M. M.; Moriarty, K. J.; Chang, M. N.; Travis, J. J.; Mitchell, L. S.; Nuss, G. W.; Sutherland, C. A. 4-[2-[Methyl(2-phenethylamino)-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid: A High Affinity, Competitive, Orally Active Leukotriene B₄ Receptor Antagonist. *J. Med. Chem.* 1992, 35, 4253–4255.
- Daines, R. A.; Chambers, P. A.; Pendrak, I.; Jakas, D. R.; Sarau, H. M.; Foley, J. J.; Schmidt, D. B.; Kingsbury, W. D. Trisubstituted Pyridine Leukotriene B₄ Receptor Antagonists. Synthesis and Structure-Activity Relationships. *J. Med. Chem.*, following paper in this issue.
- Daines, R. A.; Chambers, P. A.; Pendrak, I.; Jakas, D. R.; Sarau, H. M.; Foley, J. J.; Schmidt, D. B.; Griswold, D. E.; Martin, L. D.; Kingsbury, W. D. (E)-3-[[[6-(2-Carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]benzoic Acid: A Novel High Affinity Leukotriene B₄ Receptor Antagonist. *J. Med. Chem.*, in press.
- Sugiura, M.; Beierbeck, H.; Belanger, P. C.; Kotovych, G. Conformational Analysis of Leukotriene B₄ in Solution Based on High-Field Nuclear Magnetic Resonance Measurements. *J. Am. Chem. Soc.* 1984, 106, 4021–4025.
- Weidmann, B.; Seebach, D. Organometallic Compounds of Titanium and Zirconium as Selective Nucleophilic Reagents in Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* 1983, 22, 31–33.
- Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortari, G. Palladium-Catalyzed Carbonylation of Aryl Triflates. *Tetrahedron Lett.* 1986, 27, 3931–3934.
- Konno, K.; Hashimoto, K.; Shirahama, H. Improved Procedures for Preparation of 2-Pyridones and 2-Hydroxymethylpyridines from Pyridine N-Oxides. *Heterocycles* 1986, 24, 2169–2172.
- Echavarren, A.; Stille, J. K. Palladium-Catalyzed Coupling of Aryl Triflates with Organostannanes. *J. Am. Chem. Soc.* 1987, 109, 5478–5486.
- Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Schreiner, J.; Pribish, J. R. *Asymmetric Reactions and Processes in Chemistry*; ACS Symposium Series 185; American Chemical Society: Washington, DC, 1982; Chapter 18.
- Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. Chiral Synthesis via Organoboranes. Selective Reductions. 41. Diisopinocampheylchloroborane, an Exceptionally Efficient Chiral Reducing Agent. *J. Am. Chem. Soc.* 1988, 110, 1539–1546.
- Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines. *J. Org. Chem.* 1969, 34, 2543–2549.
- Jones, G.; Sliskovic, D. R. Triazolopyridines. Part 2. Preparation of 7-Substituted Triazolo[1,5-a]pyridines by Directed Lithiation. *J. Chem. Soc., Perkin Trans. I* 1982, 967–971.
- Sarau, H. M.; Mong, S. Co-Expression of Leukotriene B₄ and Leukotriene D₄ Receptors on Human Monocytic Leukemia U-937 Cells. In *Adv. Prostaglandin, Thromboxane, Leukotriene Res.*, 1989, 19, 180–186.
- LeBlanc, Y.; Fitzsimmons, B. J.; Charleston, S.; Alexander, P.; Evans, J. F.; Rokach, J. Analogs of Leukotriene B₄: Effects of Modification of the Hydroxyl Groups on Leukocyte Aggregation and Binding to Leukocyte Leukotriene B₄ Receptors. *Prostaglandins* 1987, 33, 617–625.
- Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* 1978, 43, 2923–2925.
- Boyum, A. Isolation of Mononuclear Cells and Granulocytes from Human Blood. *Scan. J. Clin. Lab. Invest.* 1968, 21 (Supp 97), 77–89.
- Winkler, J. D.; Sarau, H. M.; Foley, J. J.; Mong, S.; Crooke, S. Leukotriene B₄-Induced Homologous Desensitization of Calcium Mobilization and Phosphoinositide Metabolism in U-937 Cells. *J. Pharm. Exp. Ther.* 1988, 246, 204–210.
- Goldman, D. W.; Goetzl, E. J. Specific Binding of Leukotriene B₄ to Receptors on Human Polymorphonuclear Leukocytes. *J. Immunol.* 1982, 129, 1600–1604.
- Cheng, Y.-C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Cause 50 Percent Inhibition (IC₅₀) of an Enzymatic Reaction. *Biochem. Pharmacol.* 1973, 22, 3099–3108.
- Goldman, D. W.; Gifford, L. A.; Olson, D. M.; Goetzl, E. J. Transduction by Leukotriene B₄ Receptors of Increases in Cytosolic Calcium in Human Polymorphonuclear Leukocytes. *J. Immunol.* 1985, 135, 525–530.
- Gryniewicz, G.; Poenie, M.; Tsien, R. Y. A New Generation of Ca²⁺ Indicators with Greatly Improved Fluorescence Properties. *J. Biol. Chem.* 1985, 260, 3440–3450.