Synthesis of Structural Analogs of Leukotriene B_4 and Their Receptor Binding Activity

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Structural analogs of leukotriene B_4 (LTB_4) were designed using a preferred conformation of LTB_4 (1). Appending an aromatic ring scaffold between LTB_4 carbons 7 and 11 led to quinoline analogs 3 and 15. A similar modification to the LTB_4 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 [^{3}H]LTB_4 and intact human DMSO differentiated U-937 cells. The first analog prepared, quinoline 3, displayed moderate potency in the LTB_4 receptor binding assay (K_i = 0.9 μM). 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 μM); a further improvement in receptor binding was achieved in the pyridine series (e.g., 41; K_i = 0.001 μM). The LTB_4 receptor agonist/antagonist activity of the test compounds was determined using a functional assay that relies upon intracellular calcium mobilization induced by LTB_4. Of the analogs prepared in this report only 47 demonstrated LTB_4 receptor antagonist activity.

Leukotriene B_4 (LTB_4, 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 LTB_4 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 LTB_4 have been demonstrated *in vivo*: topical application of LTB_4 on human skin promotes the infiltration of PMNs and other inflammatory cells,[2] intradermal injection of LTB_4 results in the accumulation of neutrophils at the injection site,[3] and intravenous injection of LTB_4 causes rapid but transient neutropenia.[4] These phenomena coupled with the presence of elevated concentrations of LTB_4 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 effusions[8] support the involvement of LTB_4 in human inflammatory diseases. LTB_4 is produced by mast cells, PMNs, monocytes, alveolar macrophages, peritoneal macrophages, and keratinocytes. The synthesis of LTB_4 can be induced in these cells by the calcium ionophore A23187, opsonized zymosan particles, antigen, the chemotactic peptide formylmethionylleucylphenylalanine (FMLP), aggregated immunoglobins (IgG, IgE, and IgA), and bacterial exotoxins.

The pharmacological effects of LTB_4 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 LTB_4 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 LTB_4 synergizes with other chemotactic factors, such as C5a, to amplify the inflammatory response.[1] Thus, the availability of potent, selective LTB_4 receptor antagonists will be useful in elucidating the role of LTB_4 in human inflammatory diseases.

A number of LTB_4 receptor antagonists have been described (Figure 1). SM-9064[10] and U-75302[11] are structurally related to LTB_4, and both exhibit partial agonist activity; LY-223982[12] and SC-41930[13] are structurally related to the LTD_4 receptor antagonist FPL-55712. Recent reports describe the high affinity, orally active LTB_4 receptor antagonists ONO 4057[14] and RG-14893.[15]

In the present study, we describe the results of our efforts to identify structural leads to unique LTB_4 receptor antagonists. The strategic approach focused on building ring-fused analogs of LTB_4 that would restrict the conformational freedom of the molecule. Thus, a series of quinoline (3 and 15) and pyridine (41 and 46) LTB_4 analogs was synthesized. The receptor binding affinities as well as the functional activity at the human LTB_4 receptor(s) of the analogs were determined. Based on the formative results of this study, high-affinity (e.g., low-nanomolar) LTB_4 receptor antagonist were identified.[16,17]

Chemistry

Our initial strategy focused on the use of LTB_4 (1) as a template to design structurally rigid analogs of LTB_4. To begin this process, it was necessary to select a representative conformation of LTB_4. This was complicated by the conformational flexibility of LTB_4 and by the lack of conformational information related to LTB_4 at the receptor. However, high-field nuclear magnetic resonance studies of an aqueous solution of the potassium salt of LTB_4 support a preferred conformation of LTB_4 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

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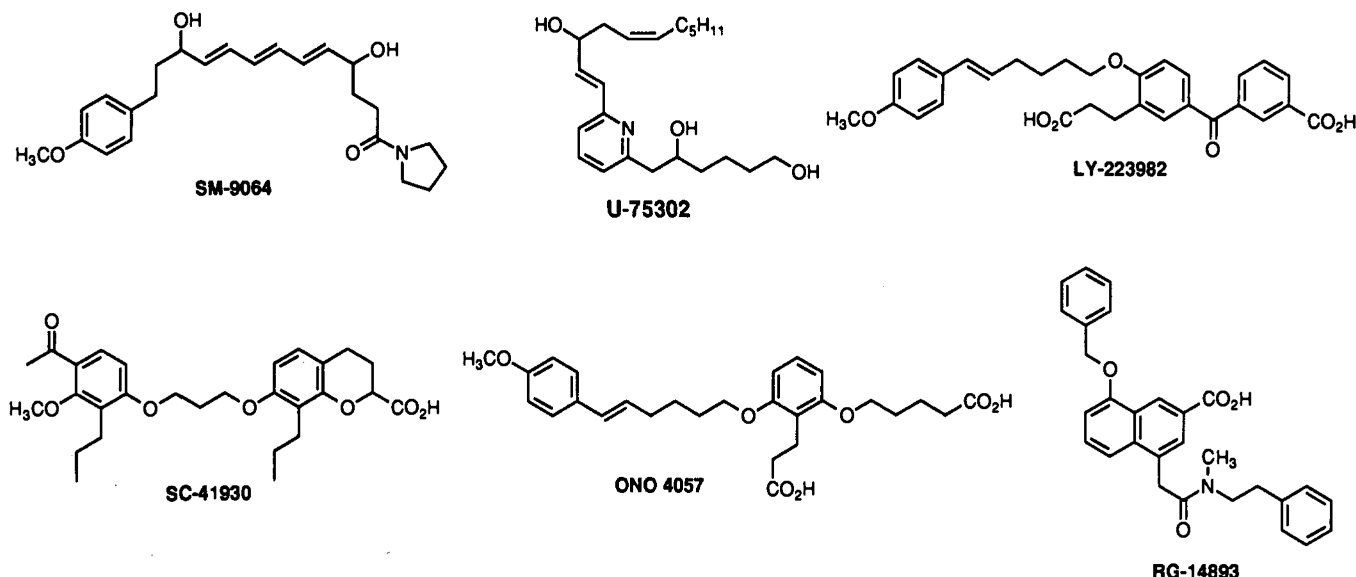


Figure 1.

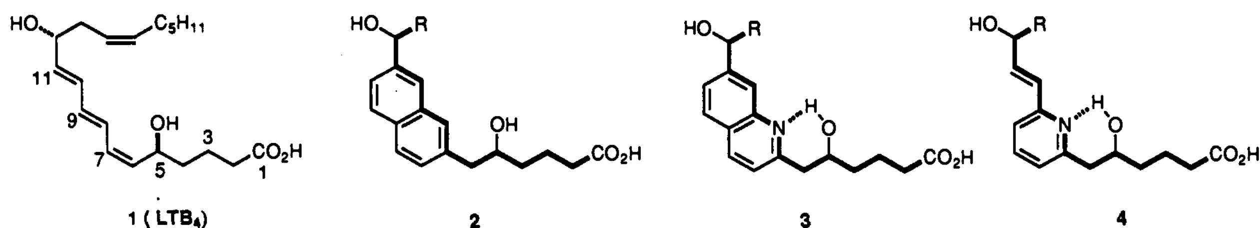


Figure 2.

of LTB_4 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).

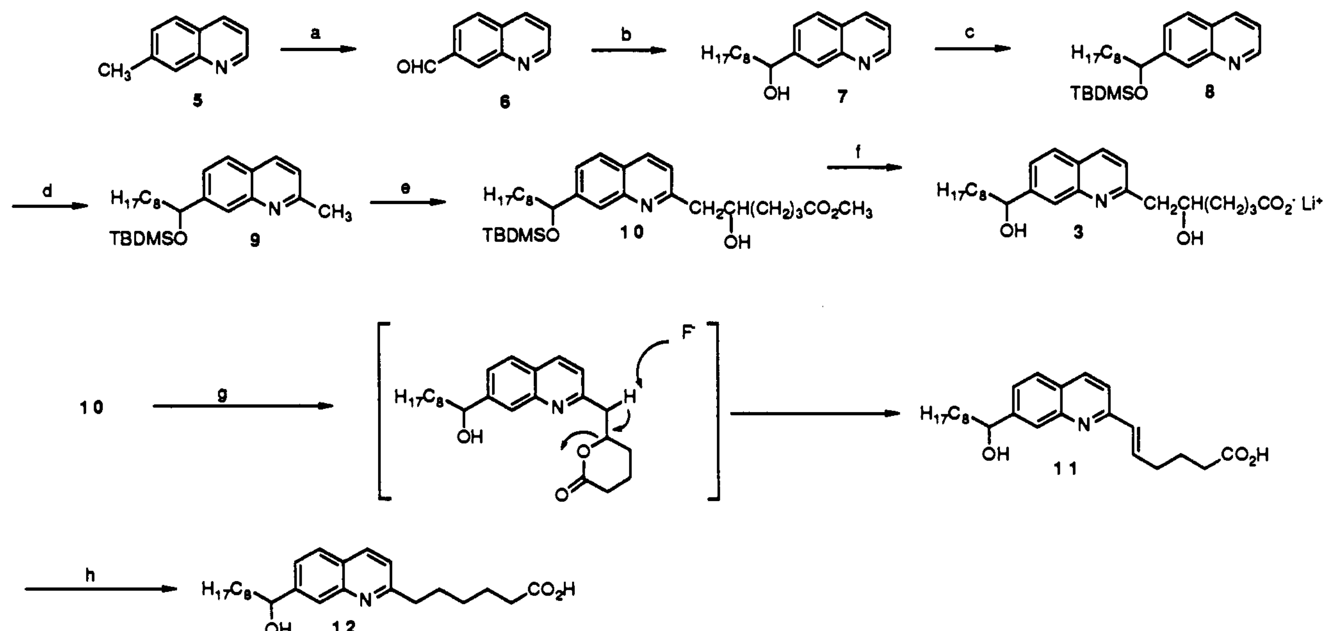
Joining carbon atoms 7–11 into an aromatic ring system led to the initial target structure 2. Although 2 incorporates a rigid mimic of the *trans*-diene backbone of 1, it does not mimic the C-6,7 *cis* olefin geometry present in LTB_4 and thus permits variability with regard to the orientation of the 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 cisoid geometry present in LTB_4. 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 methyllithium 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 carbonylation[20] 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.

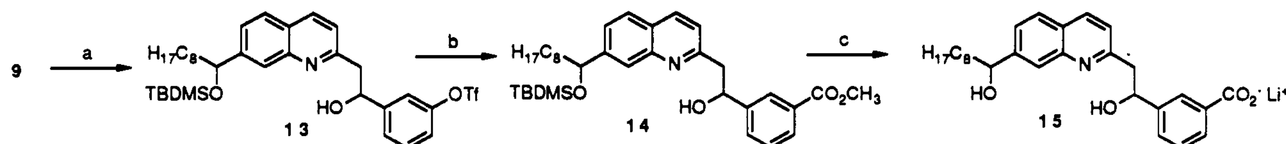
The 12(*R*), 5(*S*) stereochemistry of the LTB_4 hydroxyl groups has been reported to be important in terms of receptor binding potency.[28] Therefore, an effort was made to examine the consequence of the hydroxyl stereochemistry in this series. Preliminary experiments revealed that (***R,S***)-7 could 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 (−)-Ipc_2BCl afforded (***S***)-7, whereas

Scheme I[a]



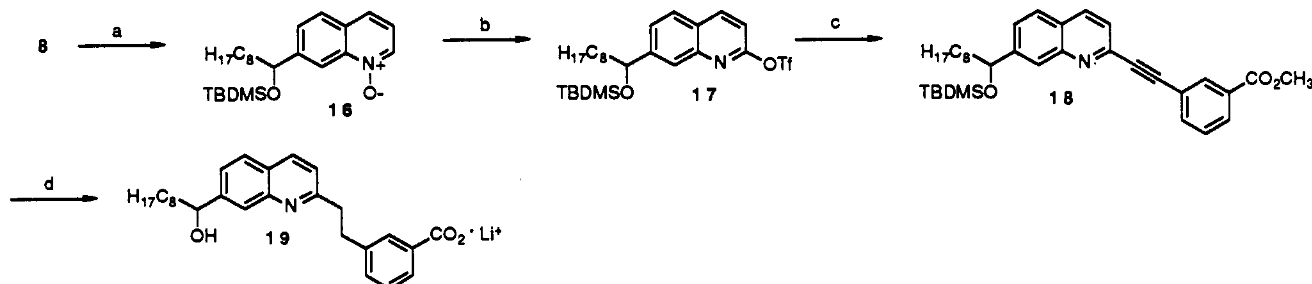
[a] (a) SeO_2, 150 °C; (b) $C_8H_{17}MgBr$, THF; (c) TBDMSOTf, CH_2Cl_2, lutidine; (d) CH_3Li, TMEDA, THF, 0 °C; (e) (1) n-BuLi, THF, (2) (i-PrO)$_3$TiCl, (3) $OHC(CH_2)_3CO_2CH_3$, −78 °C; (f) (1) HF, pyridine, CH_3CN, (2) LiOH, THF, H_2O; (g) TBAF, THF, 0 °C; (h) H_2, Pd/C, EtOH.

Scheme II[a]



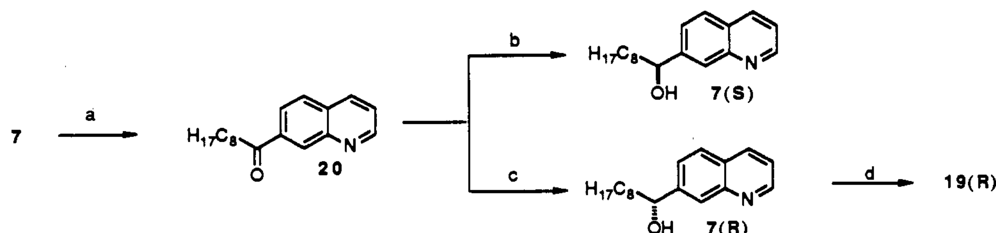
[a] (a) (1) n-BuLi, THF, −78 °C, (2) m-$TfOC_6H_4CHO$; (b) $Pd(OAc)_2$, dppp, TEA, CO, CH_3OH, DMSO, 70 °C; (c) (1) TBAF, THF, (2) LiOH, THF, H_2O.

Scheme III[a]



[a] (a) MCPBA, CH_2Cl_2, 0 °C; (b) (1) TFAA, TEA, THF, 0 °C, (2) Tf_2O, CH_2Cl_2, Et(i-Pr)$_2$N; (c) $(Ph_3P)_2PdCl_2$, CuI, TEA, methyl 3-ethynylbenzoate; (d) (1) H_2, Pd/C, (2) TBAF, (3) LiOH, THF, CH_3OH, H_2O.

Scheme IV[a]

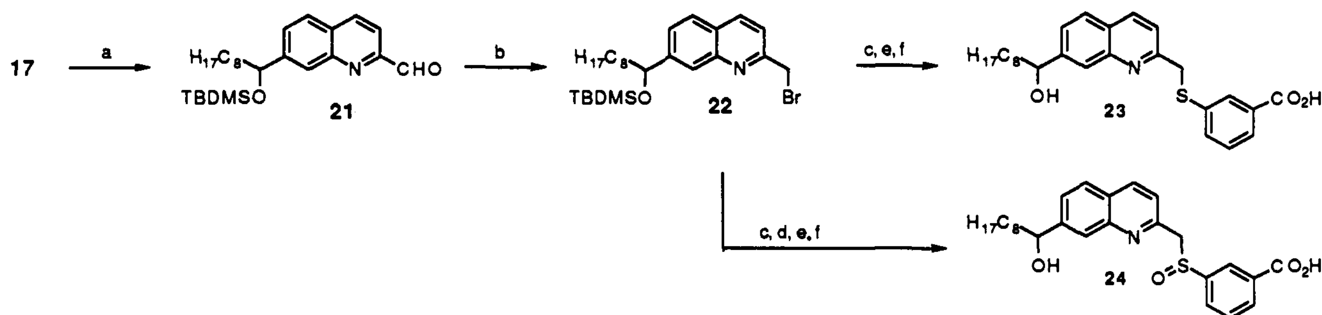


[a] (a) MnO_2, CH_2Cl_2; (b) (−)-Ipc_2BCl, THF, −25 °C; (c) (+)-Ipc_2BCl, THF, −25 °C; (d) (1) TBDMSOTf, CH_2Cl_2, lutidine, (2) as in Scheme III.

reduction of **20** using (+)-Ipc_2BCl afforded **(*R*)-7**.[24] The enantiomeric excess of each was judged to be >98% as measured by NMR–GC analysis of the Mosher esters.[25] **(*R*)-19** was prepared from **(*R*)-7** according to Scheme III via **(*R*)-8** and contained <3% of **(*S*)-19** as determined by Pirkle column HPLC. The stereochemical assignment was based on literature analogy[24] and supported by the receptor binding activity observed for this enantiomer in comparison to **(*R,S*)-19**.

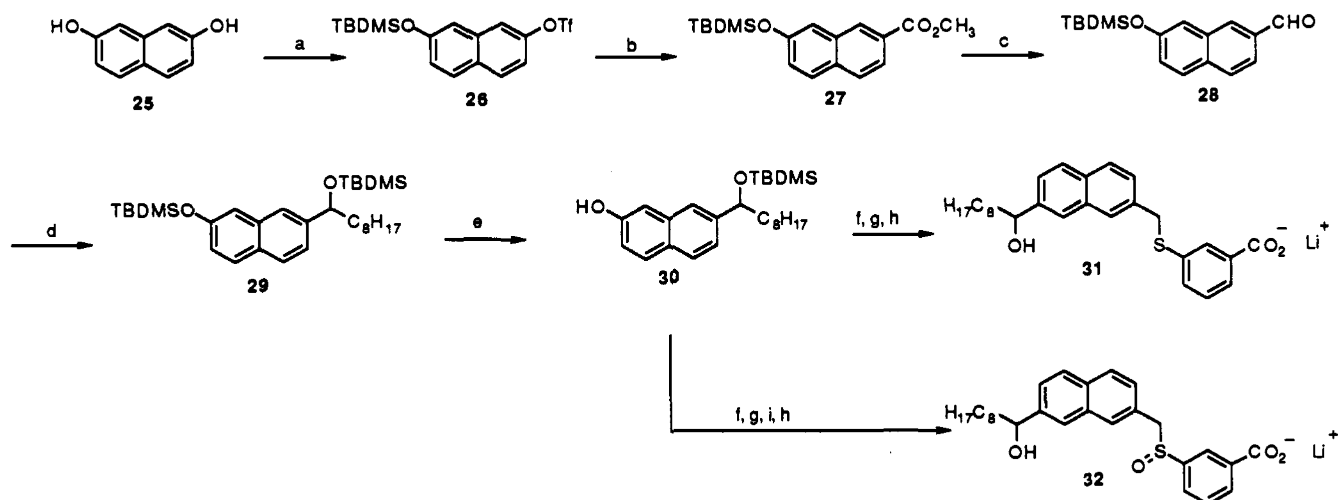
Compounds **23** and **24** represent sulfur analogs of **19** and **15**, respectively, and were prepared as shown in Scheme V. The triflate **17** afforded the corresponding methyl ester

Scheme V[a]



[a] (a) (1) $Pd(OAc)_2$, dppp, TEA, CO, DMSO, CH_3OH, 65 °C, (2) DIBAL, CH_2Cl_2, -78 °C; (b) (1) $NaBH_4$, CH_3OH, 0 °C, (2) Ph_3P, CBr_4, CH_2Cl_2; (c) ArSH, K_2CO_3, DMF; (d) MCPBA, CH_2Cl_2, 0 °C; (e) TBAF, THF; (f) LiOH, THF, H_2O.

Scheme VI[a]



[a] (a) (1) TBDMSCl, DMF, imidazole, 0 °C, (2) Tf_2O, pyridine, 0 °C; (b) $Pd(OAc)_2$, dppp, TEA, CO, DMSO, CH_3OH, 65 °C; (c) (1) DIBAL, CH_2Cl_2, -78 °C, (2) MnO_2, CH_2Cl_2; (d) $C_8H_{17}MgBr$, THF, -25 °C, (2) TBDMSOTf, lutidine, CH_2Cl_2, 0 °C; (e) K_2CO_3, CH_3OH, THF; (f) (1) Tf_2O, pyridine, (2) $Pd(OAc)_2$, dppp, TEA, CO, DMSO, CH_3OH, 65 °C, (3) DIBAL, CH_2Cl_2, -78 °C, (4) Ph_3P, CBr_4, CH_2Cl_2, (5) ArSH, K_2CO_3, DMF; (g) TBAF, THF; (h) LiOH, THF, CH_3OH, H_2; (i) MCPBA, CH_2Cl_2, 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-mercaptobenzoate followed by desilylation and hydrolysis afforded sulfide **23**. Sulfoxide **24** was prepared from **22** by a similar process.

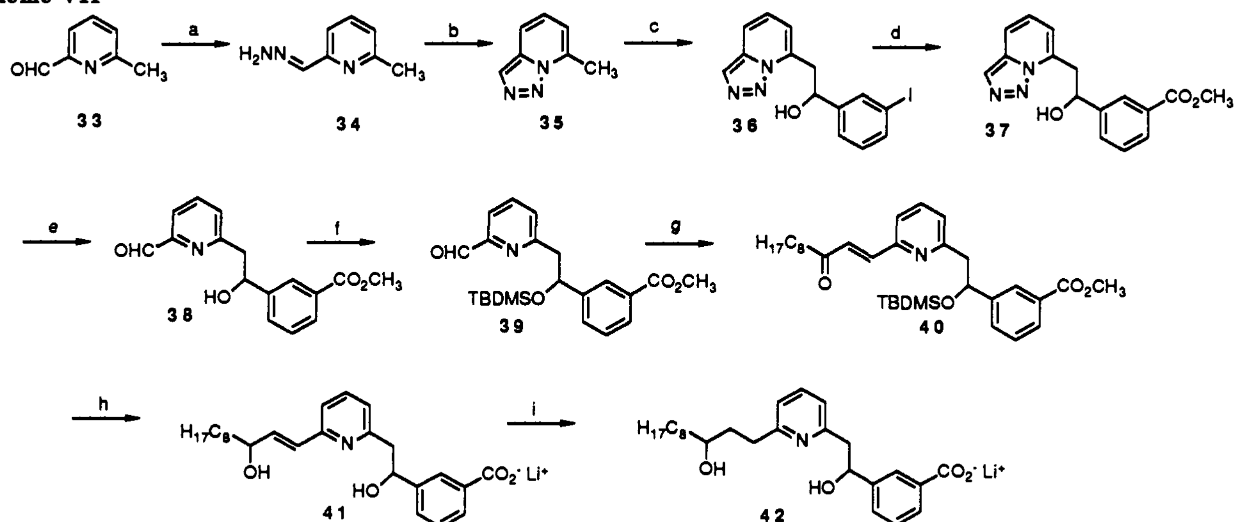
The naphthalene analogs **31** and **32** were prepared as shown in Scheme VI. Dihydroxynaphthalene **25** was converted to the silyl triflate **26**. Palladium-catalyzed carbonylation afforded the ester **27** which was converted to the aldehyde **28**. Reaction of **28** with octylmagnesium bromide 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 Sliskovic[26] 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

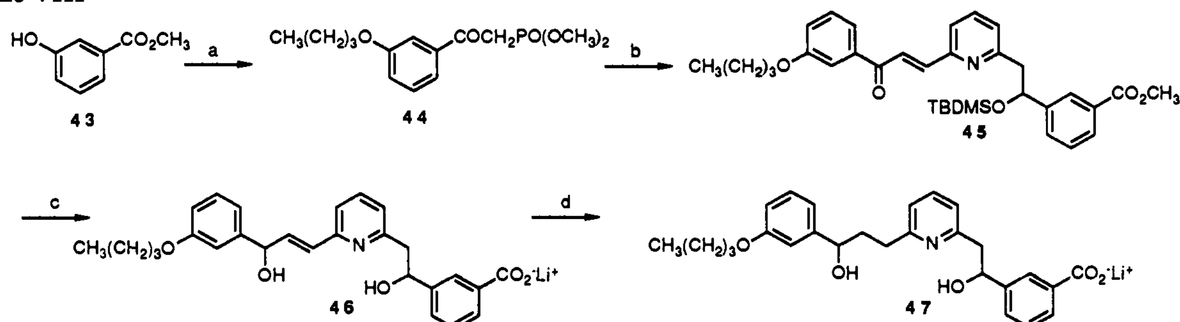
The LTB_4 receptor binding and functional cellular assay data for the test compounds are shown in Tables I and II. Although human polymorphonuclear leukocytes (PMNs) are considered to be the primary target inflammatory cells, they represent a potential biological hazard, and their use was reserved to 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 LTB_4 receptors which appear identical in binding assays to the LTB_4 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 $[^3H]LTB_4$ for binding to the receptor. All compounds that demonstrated reproducible high affinity ($K_i \leq 0.1\ \mu M$) 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) $K_3Fe(CN)_6$, $NaHCO_3$, H_2O, 90 °C; (c) LDA, 3-iodobenzaldehyde, Et_2O; (d) $Pd(OAc)_2$, dppp, TEA, CO, DMSO, CH_3OH, 75 °C; (e) (1) Br_2, CH_2Cl_2, 0 °C, (2) $AgNO_3$, EtOH, H_2O; (f) TBDMSOTf, lutidine, CH_2Cl_2, 0 °C; (g) $H_{17}C_8COCH_2PO(OEt)_2$, 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, C_4H_9I, DMF, 90 °C, (2) $LiCH_2PO(OCH_3)_2$, 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_2O; (d) H_2, Pd/C, EtOH.

Table I. Quinoline and Naphthalene Analogs: Inhibition of [^{3}H]LTB_4 Binding on Human U-937 cells and LTB_4-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
(*R*,*S*)-19	0.1	66
(*R*)-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 LTB_4, 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 LTB_4-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 [^{3}H]LTB_4 Binding on Human U-937 Cells and LTB_4-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 μM) 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 LTB_4 receptor antagonists, structural modifications of **3** were made in an attempt to eliminate the LTB_4 receptor agonist activity while maintaining or enhancing the LTB_4 receptor binding affinity.

The "C-5" deoxy analog of LTB_4 has been reported to retain high affinity LTB_4 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 LTB_4 analogs; the "C-5" hydroxyl group is not a requirement for receptor binding, although the "C-5" deoxy analog of LTB_4 is slightly less potent than

LTB_4. Both derivatives **11** and **12** demonstrated agonist activity in the human PMN LTB_4 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 LTB_4 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 LTB_4 is 10 times less potent than LTB_4, the 12-deoxy LTB_4 analog is 300 times less potent than LTB_4.[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 LTB_4. **(*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 LTB_4 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 LTB_4.

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 LTB_4 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 LTB_4 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 LTB_4 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 LTB_4 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 LTB_4 receptor agonist activity in the human PMN functional assay at concentrations up to 100 μM. Thus, **47** represents the first LTB_4 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 LTB_4 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, LTB_4. As such, they bind to the receptor in a manner similar to that of LTB_4 and therefore result in similar cellular responses. Since our goal is to identify novel LTB_4 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 (^{1}H NMR) spectra were recorded on a Brucker AM-250 instrument using $CDCl_3$ unless otherwise indicated. All ^{1}H 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 chromatography[29] 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 CH_2Cl_2, 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; ^{1}H 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 H_2O, and extracted with EtOAc. The EtOAc fraction was washed with H_2O and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography (5% EtOAc–hexane) afforded **7** (4.2 g, 61%): mp >250 °C; ^{1}H 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. ($C_{18}H_{25}NO$) C, H, N.

7-[1-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]-quinoline (8). A solution of **7** (4 g, 14.8 mmol) in CH_2Cl_2 (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 $NaHCO_3$, H_2O, and saturated NaCl, dried (Na_2SO_4), 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 methyllithium (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 H_2O, extracted with EtOAc, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (2% EtOAc–hexane) afforded **9** as an amorphous solid (1.6 g, 40%): ^{1}H 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, 6-quinolinyl), 7.35 (dd, 1H, 5-quinolinyl), 4.8 (t, 1H, CHOSi), 2.7 (s, 3H, CH_3), 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, CH_3Si), −0.2 (s, 3H, CH_3Si).

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 1h at −78 °C, and the mixture was warmed to room temperature, stirred for 12 h, quenched with H_2O, extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (1–10% EtOAc–hexane gradient elution) afforded **10** as an oil (40 mg, 30%): ^{1}H 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, CH_3CO_2), 3.28 (d, 1H,), 3.15 (m, 2H, CH_2-quinolinyl), 2.56 (m, 2H, $CH_2CO_2CH_3$), 1.15 (s, 9H, t-BuSi), 0.85–2.2 (m, 21H, aliphatic), 0.25 (s, 6H, CH_3Si); 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 CH_3CN (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% CH_3OH–CH_2Cl_2) afforded the corresponding dihydroxy methyl ester (60 mg, 75%) as a yellow oil: ^{1}H 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, CH_3O_2C), 3.08 (br dd, 1H, CH-quinolinyl), 2.97 (dd, 1H, CH-quinolinyl), 2.48 (t, 2H, $CH_2CO_2CH_3$), 1.1–1.95 (m, 18H, aliphatic), 0.82 (t, 3H, CH_3-aliphatic). Anal. ($C_{25}H_{37}NO_4 \cdot {}^1/_8H_2O$) C, H, N.

To a solution of the dihydroxy methyl ester (60 mg, 0.14 mmol) in 1:1 THF–H_2O (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% CH_3OH–H_2O gradient elution) afforded **3** (30 mg, 53%) as a lyophilized solid: ^{1}H NMR (CD_3OD) 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, CH_2CO_2 Li), 1.15–1.95 (m, 18H, aliphatic), 0.85 (t, 3H, CH_3-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 H_2O, extracted with EtOAc, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (SiO_2, 5% CH_3OH–CH_2Cl_2) afforded **11** (60 mg, 78%) as a white crystalline solid: MS (CI) 384 (M + H). Anal. ($C_{24}H_{33}NO_3 \cdot {}^1/_2$ H_2O) 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, H_2) for 2 h, filtered, and concentrated to afford **12** as a solid (15 mg, 83%): ^{1}H NMR (CD_3OD) 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, CH_2-quinolinyl), 2.25 (t, 2H, CH_2CO_2H), 1.55–1.95 (m, 4H, aliphatic), 1.15–1.55 (m, 14H, aliphatic), 1.02 (t, 2H, aliphatic), 0.87 (br t, 3H, CH_3-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*-phenyltrifluoromethanesulfonimide (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 H_2O and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) afforded 3-[(trifluoromethyl)sulfonyl]benzaldehyde as an oil (0.3 g, 33%): ^{1}H 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 H_2O, and extracted with EtOAc. The EtOAc layer was washed with H_2O and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (5% EtOAc–hexane) afforded **13** as an oil (0.18 g, 46%): ^{1}H 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, CH_2-quinolinyl), 1.8–1.3 (m, 17 H, aliphatic), 0.9 (m, 9H, *tert*-butyl), 0.1(s, 3H, CH_3Si), –0.1 (s, 3H, CH_3Si).

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), Et_3N (8.4 μL, 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 H_2O, saturated NaCl, dried (Na_2SO_4), 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 afforded 15 (11 mg, 65%) as a lyophilized solid: ^1H NMR (CD_3OD) 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, CH_2-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 CH_2Cl_2 (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 CH_2Cl_2 (50 mL), washed with $NaHCO_3$, H_2O, and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (0–1% CH_3OH–CH_2Cl_2 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 Et_3N (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% $NaHCO_3$, ice, and EtOAc, and the organic phase was separated, dried (Na_2SO_4), 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, 17 H, aliphatic), 0.86 (s, 9H, t-BuSi), 0.00 (s, 3H, CH_3Si), –0.17 (s, 1H, CH_3Si).

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 H_2O and saturated NaCl, dried (Na_2SO_4), 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, CH_3Si), –0.12 (s, 3H, CH_3Si).

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 Et_3N (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 CH_2Cl_2 (50 mL), washed with H_2O, and saturated NaCl, dried (Na_2SO_4), 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, CH_3O_2C), 1.9–1.6 (br s, 2H, CH_2CHSi), 1.3–1.2 (br s, 15H, aliphatic), 0.9 (s, 9H, t-BuSi), 0.07 (s, 3H, CH_3Si), –0.11 (s, 3H, CH_3Si).

3-{2-[7-(1-Hydroxynonyl)quinolin-2-yl]ethyl}benzoic Acid, Lithium Salt (19). Compound 18 (0.15 g, 0.3 mmol), CH_3OH (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 afforded 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, CH_3O_2C), 3.27 (m, 4H, ethylene), 1.8–1.6 (br s, 2H, CH_2CHSi), 1.4–1.2 (br s, 15H, aliphatic), 0.9 (s, 9H, t-BuSi), 0.1 (s, 3H, CH_3Si), –0.1 (s, 3H, CH_3Si).

The silyl ester (0.2 g, 0.36 mmol) was deprotected and saponified as previously described to afford, after chromatography (HP-20, H_2O, 50% CH_3OH, 100% CH_3OH), 19 (20 mg): ^1H NMR (free acid) δ 8.22–7.26 (m, 9H, aromatic), 4.89 (t, CHOH), 3.37 (m, 2H, CH_2Ar), 3.23 (m, 2H, CH_2Ar), 1.86 (m, 2H, CH_2 CHOH), 1.6–1.2 (br s, 12H, aliphatic), 0.85 (t, 3H, CH_3-aliphatic). Anal. ($C_{27}H_{32}LiNO_3$) C, H, N.

1-Quinolin-7-ylnonan-1-one (20). A mixture of 7 (4.5 g, 17 mmol), MnO_2 (4.5 g), and CH_2Cl_2 (225 mL) was stirred overnight. The reaction was incomplete (TLC), so therefore an additional 2.3 g of MnO_2 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 Et_2O (4 mL). Diethanolamine (0.2 mL, 0.2 mmol) was added to the Et_2O 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 Et_2O (3 mL), filtered and washed again with additional Et_2O (2 × 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. ($C_{18}H_{25}NO$) 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 Et_2O (30 mL). Diethanolamine (2 mL, 2 mmol) was added to the Et_2O solution, and the mixture was allowed to stand at room temperature for 4 h. The resulting mixture was triturated with Et_2O (30 mL) and filtered, and the solid residue was washed with additional Et_2O. 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. ($C_{18}H_{25}NO$) 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), CH_3OH with (4 mL), Et_3N (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 Et_2O, washed with H_2O, $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$), 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, CH_3O_2C), 1.8–1.65 (br m, 2H, CH_2-aliphatic), 1.23 (br s, 15H, aliphatic), 0.9 (s, 9H, t-BuSi), 0.074 (s, 3H, CH_3Si), –0.12 (s, 3H, CH_3Si).

A solution of methyl 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]quinoline-2-carboxylate (0.7 g, 1.6 mmol) in CH_2Cl_2 (8 mL) at –78 °C was treated with DIBAL (1 M in CH_2Cl_2, 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 ($MgSO_4$), filtered, and concentrated. Flash chromatography (2–30% EtOAc–petroleum ether gradient elution) afforded aldehyde 21

as an oil (0.6 g, 85%): ^{1}H NMR δ 10.23 (s, 1H, CHO); MS (DCI, CH_4) 414 (M + 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}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 $(Ph)_3P$ (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 (0.11g, 37%): ^{1}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). Toa solution of 22 (0.1 g, 0.22 mmol) in DMF (2 mL) at 0 °C was added methyl 3-mercaptobenzoate (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}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, CH_3O_2C), 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}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 (M + H).

2-[[[7-(1-Hydroxynonyl)quinolin-2-yl]methyl]sulfinyl]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}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, CH_3O_2C), 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 (M + 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 (M + H). Anal. ($C_{27}H_{33}NO_4S$): 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}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 $(M + H)^+$.

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, 63.0mmol), and DMF (60 mL), under Ar at 0 °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}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}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), $Pd(OAc)_2$ (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}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 (M + 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}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}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%): ^{1}H 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, CH_2), 1.30 (m, 12H, aliphatic), 1.02 (s, 9H, *tert*-butyl), 0.90 (t, J = 6.8 Hz, 3H, CH_3), 0.24 (s, 6H, Me_2); 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 CH_2Cl_2 (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 Et_2O, and the Et_2O fraction was washed with H_2O, 5% HCl, aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to afford **29** which was used in the next step without further purification: ^{1}H 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, CH_2), 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, CH_3), 0.28 (s, 6H, Me_2), 0.040 and -0.13 (singlets, 6H total, Me_2).

7-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]naphthalen-2-ol (30). A mixture of **29**, MeOH (20 mL), THF (10 mL), and excess anhydrous K_2CO_3 was vigorously stirred for 1 h under Ar. The reaction mixture was treated with aqueous NH_4Cl and extracted with Et_2O. The Et_2O phase was washed with H_2O and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (7% EtOAc–hexane) afforded **30** as a waxy solid (2.9 g, 96%): ^{1}H 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, CH_2), 1.24 (m, 12H, aliphatic), 0.89 (s, 9H, *tert*-butyl), 0.86 (t, J = 6.8 Hz, 3H, CH_3), 0.040 and -0.13 (singlets, 6H total, Me_2).

2-[[7-(1-Hydroxynonyl)naphthalen-2-yl]methyl]sulfanyl]-benzoic Acid, Lithium Salt (31). A solution of **30** (3 g, 7.5 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C was treated sequentially with pyridine (2.5 mL, 31.0 mmol) and Tf_2O (2.5 mL, 15.5 mmol). The solution was stirred for 30 min, diluted with Et_2O, washed with H_2O, 5% HCl, aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (1% Et_2O–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: ^{1}H 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, CH_2), 1.27 (m, 12H, aliphatic), 0.90 (s, 9H, *tert*-butyl), 0.86 (t, J = 6.8 Hz, 3H, CH_3), 0.058 and -0.13 (singlets, 6H total, Me_2).

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), Et_3N (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 Et_2O. The Et_2O fraction was washed with H_2O, 5% HCl, aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (3% Et_2O–hexane) gave methyl 7-[1-[[dimethyl-(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalene-2-carboxylate (0.4 g, 98%): ^{1}H 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, CH_2), 1.24 (m, 12H, aliphatic), 0.90 (s, 9H, *tert*-butyl), 0.86 (t, J = 6.8 Hz, 3H, CH_3), 0.051 and -0.14 (singlets, 6H total, Me_2); MS (CI) 443 (M + H).

Methyl 7-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]-naphthalene-2-carboxylate (0.4 g, 0.98 mmol) in CH_2Cl_2 (2 mL) under Ar at −78 °C was treated with DIBAL (3 mL, 3 mmol; 1 M solution in CH_2Cl_2) and stirred for 20 min. EtOAc (2 mL) was added, and the reaction solution was warmed to room temperature, diluted with Et_2O, and vigorously shaken with aqueous potassium sodium tartrate. The organic layer was separated, washed with saturated NaCl, dried ($MgSO_4$), 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%): ^{1}H 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, CH_2-O), 4.78 (dd, J = 6.8, 5.4 Hz, 1H, CHO), 1.74 (t, J = 6 Hz, 1H, OH), 1.70 (m, 2H, CH_2), 1.23 (m, 12H, aliphatic), 0.90 (s, 9H, *tert*-butyl), 0.86 (t, J = 6.8 Hz, 3H, CH_3), 0.041 and -0.14 (singlets, 6H total, Me_2); 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 CH_2Cl_2 (1 mL) under Ar at 0 °C was sequentially treated with CBr_4 (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% Et_2O–hexane) to afford 7-(bromomethyl)-2-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]-naphthalene (0.24 g, 91%) as a colorless oil: ^{1}H 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, CH_2-Br), 1.70 (m, 2H, CH_2), 1.23 (m, 12H, aliphatic), 0.88 (s, 9H, *tert*-butyl), 0.87 (t, J = 6.8 Hz, 3H, CH_3), 0.044 and −0.14 (singlets, 6H total, Me_2).

A mixture containing 7-(bromomethyl)-2-[1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]nonyl]naphthalene (0.14 g, 0.29 mmol), methyl 3-mercaptobenzoate (55 mg, 0.33 mmol), DMF (1.5 mL), and anhydrous K_2CO_3 (85 mg, 0.62 mmol) was vigorously stirred under Ar for 30 min, diluted with Et_2O, washed with H_2O and saturated NaCl, dried ($MgSO_4$), 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%): ^{1}H 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, CH_2S), 3.88 (s, 3H, methyl ester), 1.70 (m, 2H, CH_2), 1.24 (m, 12H, aliphatic), 0.89 (s, 9H, *tert*-butyl), 0.88 (t, J = 6.8 Hz, 3H, CH_3), 0.037 and −0.15 (singlets, 6H total, Me_2).

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: ^{1}H NMR (CD_3OD) 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, CH_2S), 1.78 (m, 2H, CH_2), 1.25 (m, 12H, aliphatic), 0.87 (t, J = 6.8 Hz, 3H, CH_3); MS (FAB): 435.2 (M − H, free acid).

3-[[[7-(1-Hydroxynonyl)naphthalen-2-yl]methyl]sulfinyl]-benzoic Acid, Lithium Salt (32). Methyl 2-[[[7-(1-hydroxynonyl)naphthalen-2-yl]methyl]sulfonyl]benzoate (30 mg, 0.067 mmol) in CH_2Cl_2 (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 $NaHCO_3$, extracted with CH_2Cl_2, washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (40% EtOAc–hexane) gave methyl 3-[[[7-(1-hydroxynonyl)naphthalen-2-yl]methyl]sulfinyl]benzoate (22 mg, 72%) as a colorless solid: ^{1}H 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, CH_2S), 3.80 (s, 3H, methyl ester), 2.20 (broad singlet, 1H, OH), 1.84 (m, 2H, CH_2), 1.25 (m, 12H, aliphatic), 0.86 (t, J = 6.8 Hz, 3H, CH_3).

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 (H_2O–MeOH gradient elution) to give **32** (21 mg, 100%) as a colorless amorphous solid after lyophilization: ^{1}H NMR (CD_3OD) 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, CH_2S), 1.78 (m, 2H, CH_2), 1.26 (m, 12H, aliphatic), 0.87 (t, J = 6.8 Hz, 3H, CH_3); 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 Et_2O. The Et_2O fraction was washed with H_2O and saturated NaCl and dried (Na_2SO_4). 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 H_2O, potassium ferricyanide (49.5 g, 0.15 mol), and $NaHCO_3$ (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 CH_2Cl_2, washed with H_2O and saturated NaCl, dried (Na_2SO_4), 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 Et_2O (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 Et_2O (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 Et_2O (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 H_2O and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (10–40% EtOAc–hexane) afforded **36** as an amorphous solid (6.1 g, 65%): ^{1}H 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), Et_3N (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 Et_2O , washed with H_2O, 5% HCl, aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (10–50% EtOAc–hexane gradient elution) afforded **37** (1.4 g, 43%) as an oil: ^{1}H 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, CO_2CH_3), 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 CH_2Cl_2 (25 mL) at 0 °C was treated dropwise with a solution of bromine (0.75 g, 0.24 mL, 4.7 mmol) in CH_2Cl_2 (15 mL). Gas was evolved; the reaction mixture was stirred at 0 °C for 1 h, washed with $NaHCO_3$, H_2O, and saturated NaCl, dried (Na_2SO_4), and concentrated to give 1.8 g of an oil. The oil was dissolved in EtOH (40 mL) and treated with a solution of $AgNO_3$ (1.6 g, 9 mmol) in hot H_2O (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 $NaHCO_3$,and the resulting solution was extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated. Fash chromatography (10–30% EtOAc–hexane gradient elution) gave **38** as an oil (0.6 g, 45%): ^{1}H 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, CO_2CH_3), 3.3 (d, 2H, CH_2-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), CH_2Cl_2 (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 CH_2Cl_2, washed with $NaHCO_3$, H_2O, and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (10% EtOAc–hexane) afforded **39** (0.6 g, 75%) as an oil: ^{1}H 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, CO_2CH_3), 3.2 (d, 2H, CH_2-pyridyl), 0.8 (s, 9H, t-BuSi), –0.2 (s, 3H, CH_3Si), –0.3 (s, 3H, CH_3Si).

To a mixture of 1-(diethylphosphono)decan-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 H_2O and saturated NaCl, dried (Na_2SO_4), filtered, and evaporated. Flash chromatography (10–20% EtOAc–hexane gradient elution) afforded **40** (0.14 g, 40%) as a yellow oil: ^{1}H 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, CO_2CH_3), 3.05 (d, 2H, CH_2-pyridyl), 2.6 (t, 2H, CH_2CO), 1.4–1.0 (m, 15H, aliphatic), 0.9 (s, 9H, t-BuSi), –0.1 (s, 3H, CH_3Si), –0.3 (s, 3H, CH_3Si).

(*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 CH_3OH (2 mL) at –10 °C was treated with $NaBH_4$ (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 H_2O, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (10–20% EtOAc–hexane gradient elution) afforded the corresponding alcohol (0.12 g, 91%) as a colorless oil: ^{1}H 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, CO_2CH_3), 3.0 (d, 2H, CH_2-pyridyl), 1.7–0.9 (m, 17H, aliphatic), 0.8 (s, 9H, t-BuSi), –0.3 (s, 3H, CH_3Si), –0.4 (s, 3H, CH_3Si).

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: ^{1}H NMR (CD_3OD) 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, CH_2-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 H_2 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): ^{1}H NMR (CD_3OD) 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, CH_2-pyridyl), 3.0 (m, 2H, CH_2-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 K_2CO_3 (10 g, 0.072 mol) were combined and heated to 90 °C for 2 h. After cooling, the mixture was washed with H_2O and saturated NaCl, dried (Na_2SO_4), 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 H_2O, and extracted with EtOAc. The EtOAc fraction was washed with H_2O and saturated NaCl, dried (Na_2SO_4), 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 H_2O and saturated NaCl, dried (Na_2SO_4), 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, CH_2OPh), 3.9 (s, 3H, CO_2CH_3), 3.15 (m, 2H, CH_2-pyridyl), 1.8–1.5 (m, 4H, aliphatic), 1.0 (m, 3H, aliphatic), 0.9 (s, 9H, t-BuSi), –0.3 (s, 3H, CH_3Si), –0.4 (s, 3H, CH_3Si).

(*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 CH_3OH (2 mL) at –10 °C was treated with $NaBH_4$ (4 mg, 0.5 equiv) and stirred for 1 h. The reaction mixture was diluted with H_2O, concentrated, and extracted with EtOAc, and the EtOAc fraction was washed with H_2O and saturated NaCl, dried (Na_2SO_4), 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, CH_2OPh), 3.9 (s, 3H, CO_2CH_3), 3.12 (m, 2H, CH_2-pyridyl), 1.9–1.5 (m, 4H, aliphatic), 1.0 (t, 3H, aliphatic), 0.85 (s, 9H, t-BuSi), –0.3 (s, 3H, CH_3Si), –0.4 (s, 3H, CH_3Si).

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 (CD_3OD) 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, CH_2OPh), 3.12 (m, 2H, CH_2-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 H_2 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 (CD_3OD) 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, CH_2OPh), 3.2 (m, 2H, CH_2-pyridyl), 2.85 (m, 2H, CH_2-pyridyl), 2.1 (m, 2H, $HOCHCH_2$), 1.8–1.5 (m, 4H, aliphatic), 1.0 (t, 3H, aliphatic).

Biological Evaluation. [^{3}H]LTB$_4$ Binding Assays. [^{3}H]-LTB$_4$ with specific activity of 140–210 Ci/mmol was obtained from New England Nuclear (Boston, MA). Unlabeled LTB$_4$ was synthesized by the Medicinal Chemistry Prep Group at SmithKline 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% CO_2, 95% air at 37 °C. U-937 cells were differentiated with 1.3% DMSO for 3–4 days, grown to a density of 10^6 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 phlebotimized 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 [^{3}H]LTB$_4$ for receptors on intact differentiated U-937 cells and human PMNs utilizing methods described previously.[31,32] Washed cells (10^6 cells) were incubated in Hanks balanced salt solution (HBSS) with 0.1% ovalbumin and 0.2 nM [^{3}H]LTB$_4$ for 20 min at 0 °C in a total volume of 500 μL. Total and nonspecific binding of [^{3}H]LTB$_4$ were determined in the absence and presence of 1 μM unlabeled LTB$_4$, respectively. For radioligand competition experiments, increasing concentrations of LTB$_4$ (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 [^{3}H]LTB$_4$ binding was determined for each concentration, and the IC_{50} is defined as the concentration of test compound required to inhibit 50% of the specific [^{3}H]LTB$_4$ 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 IC_{50} 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 LTB$_4$ 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.

LTB$_4$-Induced Calcium Mobilization. The functional assay used to determine agonist activity of test compounds was LTB$_4$-induced Ca^{2+} mobilization in human PMNs.[34] The $[Ca^{2+}]_i$ was estimated with the calcium fluorescent probe fura 2.[35] Isolated PMNs were suspended in Krebs Ringer Hensilet buffer at 2 × 10^6 cells/mL containing 0.1% BSA, 1.1 mM $MgCl_2$, 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 225*g* for 5 min and resuspended at 2 × 10^6 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 10^6 cells/mL in buffer A containing 1 mM $CaCl_2$ 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 $CaCl_2$ minus BSA at 10^6 cells/ mL. Aliquots (2 mL) were transferred into a cuvette and warmed in a water bath to 37 °C. The 1-cm^2 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, LTB$_4$ (100 nM), was added to the vehicle-treated samples, and the maximal $[Ca^{2+}]$/fura 2 fluorescence was determined. The maximal $[Ca^{2+}]_i$ achieved with each sample was calculated using the following

formula as previously described.[31]

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

The percent of maximal LTB_4 (100 nM) induced $[Ca^{2+}]_i$ was determined for each concentration of compound and the maximal percent agonist activity of the compound relative to LTB_4 was determined. All compounds showing agonist activity were run in concentration response curves (5–8 points) to its maximal $[Ca^{2+}]_i$. Maximal $[Ca^{2+}]_i$ was generally seen between 0.1 and 10 μM. The data reported is the mean maximal $[Ca^{2+}]_i$ achieved relative to 100 nM LTB_4 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.

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