Carboxy-Substituted Cinnamides: A Novel Series of Potent, Orally Active LTB_4 Receptor Antagonists

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A series of carboxy-substituted cinnamides were investigated as antagonists of the human cell surface leukotriene B_4 (LTB_4) receptor. Binding was determined through measurement of [^{3}H]-LTB_4 displacement from human neutrophils. Receptor antagonism was confirmed through a functional assay, which measures inhibition of Ca^{2+} release in human neutrophils. Potent antagonists were discovered through optimization of a random screening hit, a *p*-(α-methylbenzyloxy)cinnamide, having low-micromolar activity. Substantial improvement of in vitro potency was realized by the attachment of a carboxylic acid moiety to the cinnamide phenyl ring through a flexible tether, leading to identification of compounds with low-nanomolar potency. Modification of the benzyloxy substituent, either through *ortho*-substitution on the benzyloxy phenyl group or through replacement of the ether oxygen with a methylene or sulfur atom, produced achiral antagonists of equal or greater potency. The most potent compounds in vitro were assayed for oral activity using the arachidonic acid-induced mouse ear edema model of inflammation. Several compounds in this series were found to significantly inhibit edema formation and myeloperoxidase activity in this model up to 17 h after oral administration. Representatives of this series have been shown to be potent and long-acting orally active inhibitors of the LTB_4 receptor.

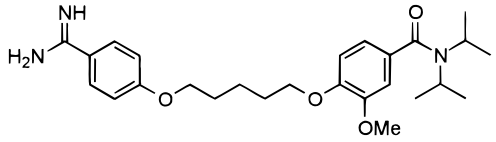
Introduction

Leukotriene B_4 (LTB_4), a product of 5-lipoxygenase-induced arachidonic acid metabolism, has been shown to be a potent mediator of the inflammatory process and has thus been implicated in the progression of a variety of inflammatory diseases.[1] At the cellular level, LTB_4 exerts its effect through recruitment and activation of neutrophils and eosinophils, via binding to a G-protein-coupled cell-surface receptor.[2] More recently, it was reported that LTB_4 can activate the nuclear receptor PPARα, raising the possibility that it may be involved in feedback regulation of lipid metabolism.[3] Clinically, elevated levels of LTB_4 have been observed in patients of a number of inflammatory diseases, including rheumatoid arthritis,[4] ulcerative colitis,[5] asthma,[6] and chronic bronchitis.[7]

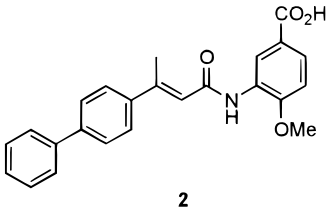
A variety of potent, orally active antagonists of the cell-surface LTB_4 receptor have been reported over recent years.[8] Preclinical pharmacology conducted with these compounds has strengthened the case for LTB_4 receptor antagonism as a viable drug discovery target. Representative antagonists have been found to be effective in the collagen-induced mouse arthritis model,[9] a primate model of inflammatory bowel disease,[10] and a guinea pig model of respiratory inflammation.[11] Several of these compounds have been reported to be undergoing clinical development.

Previously, we reported the discovery of potent LTB_4 antagonists, exemplified by the arylamidine CGS 25019C (**1**)[12] and the phenylcinnamide **2** (Chart 1).[13] As part of our continued effort in this area, we report herein the identification of a novel carboxyphenylcinnamide series of potent, orally active antagonists of the human cell-surface LTB_4 receptor.

Chart 1. Structures of LTB_4 Antagonists Previously Reported by Novartis



1: CGS 25019C



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Chemistry

The compounds discussed in this report contain a cinnamide nucleus, with varying substitution on the aryl moiety (Table 1). Syntheses of the required cinnamides proceeded either through Horner−Emmons coupling of an appropriately substituted methyl ketone or via Heck olefination of the corresponding aryl bromide.[14] In our first series of compounds (Scheme 1), cinnamate ester **3** was prepared through a Heck coupling with an aryl bromide generated from the alkylation of *p*-bromophenol. Compounds with R_2 = Me were prepared stereospecifically from ethyl crotonate. Hydrolysis of the

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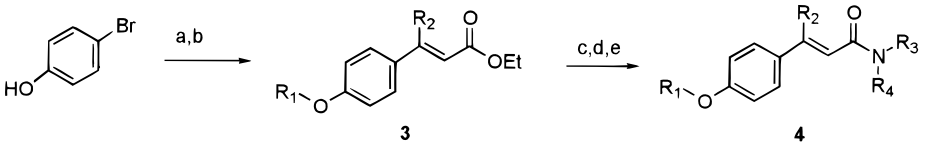
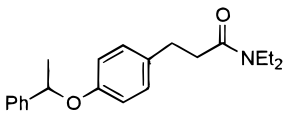
Scheme 1. Synthesis of 4-Alkoxyphenylcinnamides[a]



[a] (a) R_1Br, K_2CO_3; (b) ethyl crotonate (R_2 = Me) or ethyl acrylate (R_2 = H), $Pd(OAc)_2$, P(*o*-tol)$_3$, triethylamine, 80 °C; (c) 1 N NaOH, MeOH, reflux; (d) $(COCl)_2$, DMF, CH_2Cl_2; (e) HNR_3R_4, THF.

Chart 2. Miscellaneous Compounds Prepared Similarly to Scheme 1



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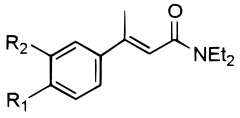


6: R_1 = Ph, R_2 = H
7: R_1 = Ph(Me)CHO-, R_2 = CO_2H

ester and acid chloride formation, followed by coupling with the appropriate amine, yielded products of type **4**. Dihydrocinnamide **5** (Chart 2) was prepared through Pd/C-catalyzed hydrogenation of cinnamide **4** (R_1 = Ph(Me)CHO, R_2 = H). Synthesis of phenylcinnamide **6** proceeded through Horner−Emmons coupling of 4-acetylbiphenyl with triethyl phosphonoacetate, followed by amide formation as described in Scheme 1. Benzoic acid **7** was prepared from methyl 5-bromosalicylate, using a protocol similar to Scheme 1.

Compounds oxygenated in the 3-position of the cinnamide phenyl ring (Scheme 2) were prepared through selective alkylation of 3,4-dihydroxyacetophenone, according to the reported procedure,[15] followed by a second alkylation with the appropriate alkyl halide. Previous SAR studies had identified the *N,N*-diethylamide moiety as being the optimal amide substitution pattern for in vitro potency (see Table 1, compounds **4a**−**e**). Therefore, to improve the efficiency of the syntheses, Horner−Emmons olefinations were carried out with phosphonoamide **8**. This reaction generally provided a ca. 5:1 ratio of *E*/*Z* isomers (determined by ^{1}H NMR), from which the desired *E* isomer could be easily isolated via chromatography. The X group was then appropriately modified to provide the desired targets, as indicated in Scheme 2.

Compounds **14** and **15,** which are 3,5- or 2,4-dioxygenated (respectively)**,** were also prepared via sequential alkylation, although mixtures were obtained in the first alkylation (Chart 3).

Synthesis of phenoxypropionate **13** via an ester intermediate was complicated by the tendency for these compounds to undergo retro-Michael elimination during hydrolysis. For this reason, olefinic **10** (n = 2, X = CH=CH_2, R = Ph(Me)CHO−) was prepared. Oxidative olefin cleavage, followed by immediate oxidation of the unstable aldehyde, yielded the desired product.

To prepare **17**, phenol **10** (n = 0, X = H, R = $PhCH_2$) was converted to aryl triflate **16** and then subjected to Pd(0)-catalyzed acetylene coupling.[16] After acetylene hydrogenation, the synthesis was completed as described previously (Scheme 3).

Sulfide **20** was prepared via methoxy thiol **18**. This intermediate was obtained through thermal rearrangement of a thiocarbamate (Scheme 4).[17] The synthesis was completed as shown.

Compounds **23** and **24** were prepared from 2-hydroxyphenylacetic acid (Scheme 5). Bromination in alcohol solvent effected simultaneous esterification, providing **21**, which was carried on as before. Enantiomers of **23** were prepared via Mitsunobu alkylation of intermediate **22**,[18] using either enantiomer of 1-methylbenzyl alcohol as the nucleophile (Scheme 6). Alkylation is known to proceed with inversion of stereochemistry at the methylbenzyl position,[18] and ee values for the alkylation, which were determined using ^{1}H NMR,[19] were found to be 93% and 97%, respectively, for the *R* and *S* isomers.

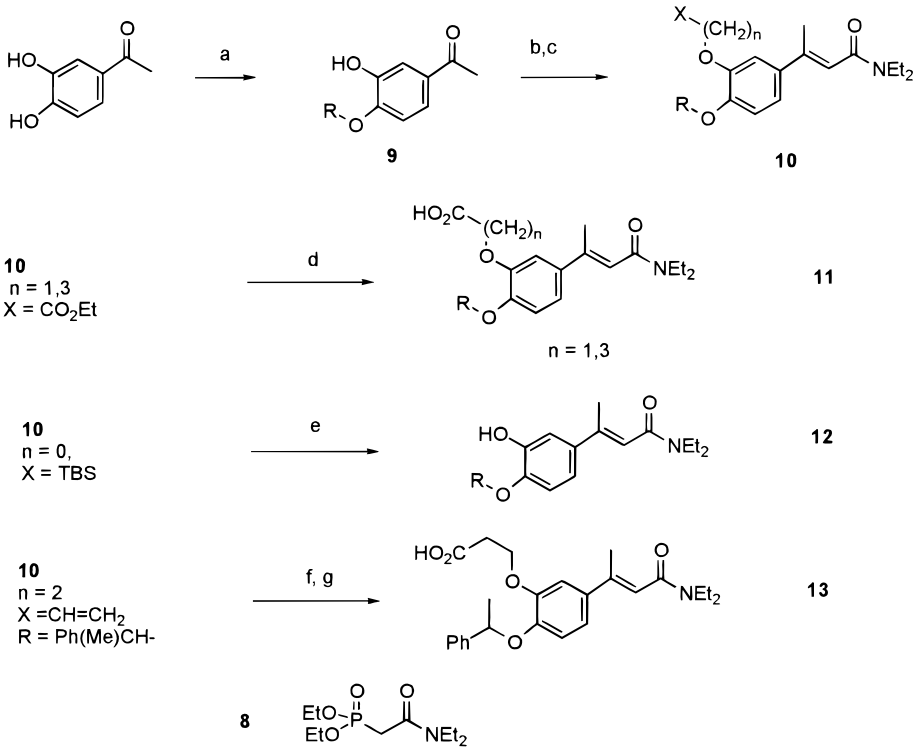
The synthesis of phenylpropionate **27** is shown in Scheme 7. The carbon side chain was incorporated via a Claisen rearrangement. Rhodium-catalyzed hydroboration[20] and oxidation provided the desired compound.

Results

In Vitro Activity. LTB_4 receptor binding potency was determined through the measurement of [^{3}H]LTB_4 displacement from human neutrophils (PMNs). Our early lead compound **4a**, identified from random screening, displayed modest LTB_4 receptor binding potency (see Table 1). Removal of the α-methyl group (**4h**) caused a substantial drop in potency. Modification the amide substitution pattern, through variation of alkyl chain length or acylation of a cyclic amine (**4b**−**e**), also reduced potency. Replacing the pendant α-methylbenzyl ether with an isopropyl ether resulted in complete loss of activity (**4i**). A tertiary amide was found to be important, as demonstrated by the drop in potency observed with secondary amide **4f**. Olefin reduction (**5**) and removal of the β-methyl group (**4g**) both resulted in loss of potency. In addition, compounds **4j** and **6,** which incorporated elements of an *N*-arylcinnamide series previously reported by our group (exemplified by compound **2**, Chart 1),[13] were prepared but found to be inactive.

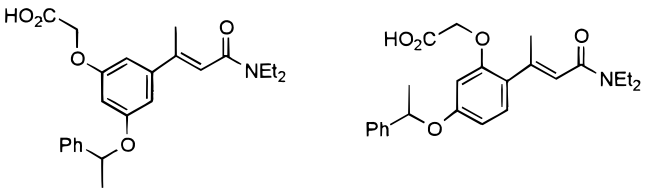
A feature common to many potent LTB_4 receptor antagonists is the presence of a carboxylic acid or carboxylate isostere tethered to a hydrophobic nucleus.[8] With this in mind, we set out to incorporate a carboxylate moiety on the template. Since the benzyloxycinnamide template **4a** already demonstrated submicromolar activity, it was hoped that an additional electrostatic interaction would be sufficient to yield more potent derivatives. Incorporation of a carboxylic acid group at the R_2 position had no effect on potency (**7**). However, a simple hydroxy substituent at this position resulted in a 2-fold improvement (**12**). Having determined that acidic substitution at this position would not interfere with receptor binding, carboxylate groups were then tethered to the aromatic ring using the phenol as a linker, as shown in compounds **11a**−**20**. Compound **11a** was found to be 15-fold more potent than the lead compound **4a**.

Scheme 2. Synthesis of Dialkoxyphenylcinnamides[a]



[a] (a) Li_2CO_3, DMF, RBr; (b) ethyl bromoacetate, K_2CO_3, acetone, reflux; (c) **8**, NaH, THF, reflux; (d) 1 N NaOH, MeOH; (e) tetrabutylammonium fluoride, THF; (f) OsO_4, $NaIO_4$, THF, H_2O; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O.

Chart 3. Regioisomers of Compound **4**



14 **15**

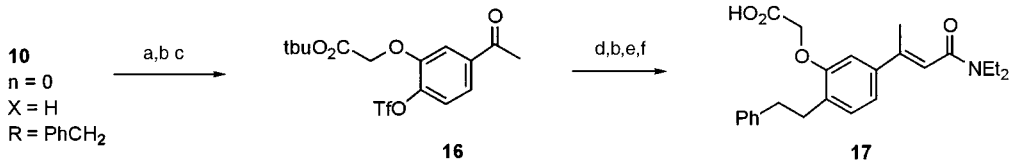
Substantial efforts were then undertaken to define the binding requirements of this carboxylate. Changes in the tether length (**11b**, **13**) resulted in reduced potency. Replacement of the oxygen in the tether with a methylene group had no effect on in vitro activity (**27**), while reducing the tether length to one carbon resulted in only a modest decrease in potency (**23**). Moving the carboxylate attachment point from the 3- to the 2-position of the core aromatic ring drastically reduced activity (**15**). Relocation of the benzyloxy substituent from the 4- to the 5-position resulted in a modest drop in potency (**14**). From this study, it was clearly established that a one- or two-atom carboxylate tether to the 3-position of the cinnamide phenyl group was optimal for in vitro activity.

One obvious point of concern with this series was its chirality. To determine if a stereochemical binding preference existed within the series, both enantiomers of **23** were prepared. Indeed, the *S* isomer **(*S*)-23** was found to be substantially more potent than the *R* isomer **(*R*)-23**. Since the need for an enantiomerically pure synthesis was viewed as a disadvantage for this series, attention was turned to modification of the benzyloxy group, to determine if the chiral center was necessary. Simple removal of the methyl substituent from **11a** caused a 2−3-fold loss in potency, as observed in **11c**. However, potency could be regained by replacement of the oxygen in the aryl tether with either a sulfur or a methylene group (**20**, **17**). It was also observed that *o*-halo substitution on the benzylic phenyl ring of the benzyloxy moiety provided a binding enhancement similar in magnitude to that observed with the 2-phenylethyl group (**11d**,**e**). This effect was even more pronounced for 2,6-disubstituted benzyl groups (**11f**,**g**) and was found to carry over to compounds with the shortened carboxylate tether (**24**). Replacement of the benzyloxy group with a phenyl ether was ineffective (**11i**). As an alternative means of removing chirality, the methylbenzyloxy group was replaced with a diphenylmethoxy substituent. This achiral compound was found to be reasonably potent (**11h**), although lack of activity in the ear edema model precluded further exploration of this approach (vide infra).

To confirm that these compounds were indeed antagonists (not agonists) of the LTB_4 receptor, several of the most potent inhibitors were tested in a functional assay which measures the inhibition of LTB_4-induced Ca^{2+} release from human PMNs. As can be seen from Table 1, these compounds are indeed potent receptor antagonists. To confirm that the compounds were not inhibiting LTB_4 production, compound **11a** was tested for 5-lipoxygenase activity.[21] The compound displayed no enzyme inhibition at 100 μM.

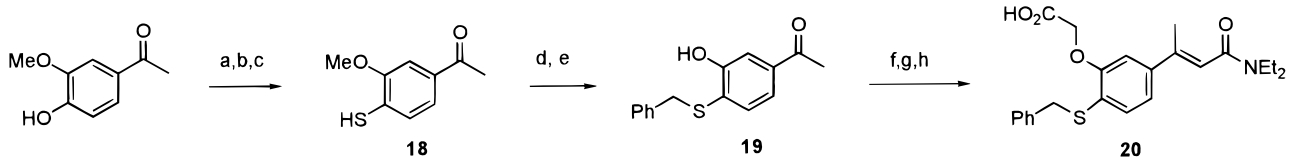
In Vivo Activity. To determine the in vivo potency of our inhibitors, we utilized the arachidonic acid-induced mouse ear edema model. In this model, inhibitors were administered orally. After a set time period (see Table 2), the left ear was treated with an acetone solution of arachidonic acid. (The right ear was treated with acetone alone.) After 1 h, punches were taken from

Scheme 3. Synthesis of Cinnamide with 4′-Carbon Tether[a]



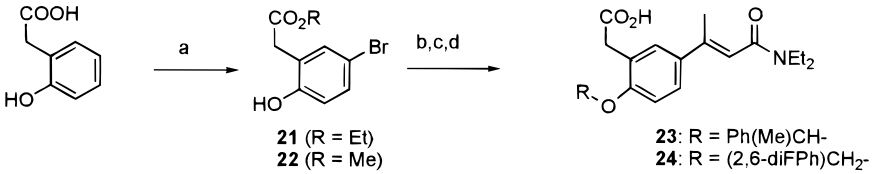
[a] (a) *tert*-Butyl bromoacetate, K_2CO_3, acetone, reflux; (b) 10% Pd/C, H_2, EtOH; (c) Tf_2O, pyr, CH_2Cl_2, −30 °C; (d) phenylacetylene, TEA, $(Ph_3)_2PdCl_2$, CuI, 60 °C; (e) **8**, NaH, THF, reflux; (f) HCl, EtOAc.

Scheme 4. Synthesis of Sulfur-Tethered Phenylcinnamides[a]



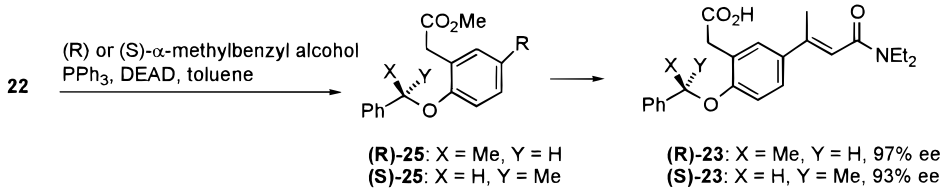
[a] (a) Me_2NCSCl, KOH; (b) 250 °C, neat; (c) $HO(CH_2)_2OH$, KOH, H_2O; (d) BBr_3, CH_2Cl_2, −78 °C; (e) BnBr, K_2CO_3, acetone, reflux; (f) ethyl bromoacetate, K_2CO_3, acetone, reflux; (g) **8**, NaH, THF; (h) 1 N NaOH, MeOH.

Scheme 5. Synthesis of Phenylacetate Derivatives[a]

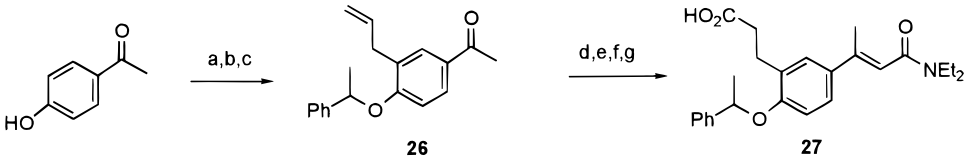


[a] (a) $Bu_4N^+Br_3^-$, ROH; (b) RBr, K_2CO_3, acetone, reflux; (c) diethyl crotonamide, $Pd(OAc)_2$, P(*o*-tol)$_3$, triethylamine, 80 °C; (d) 1 N NaOH, MeOH.

Scheme 6. Synthesis of Optically Enriched **23**



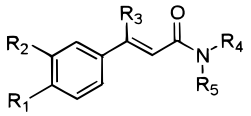
Scheme 7. Synthesis of Phenylpropionate Derivatives[a]



[a] (a) Allyl bromide, K_2CO_3, acetone, reflux; (b) 230 °C; (c) K_2CO_3, Ph(Me)CHBr, acetone, reflux; (d) **8**, NaH, THF, reflux; (e) catecholborane, Wilkinson cat., THF, 0 °C; (f) $(COCl)_2$, DMSO, −78 °C; (g) $NaClO_2$, 2-methyl-2-butene, Na_2HPO_4, *t*-BuOH, H_2O.

both ears, and they were measured for myeloperoxidase (MPO) activity (a marker of neutrophil influx and activation) and punch weight (edema). Results are shown in Table 2. In general, inhibition of both measurements was dose-dependent, although a maximal inhibition of 60−70% was normally observed for both parameters. The reason for this plateau effect is not known, although one might surmise that other arachidonic acid metabolites might be responsible for the remainder of the observed inflammatory response. As an initial study, compounds were dosed 0.5 h prior to arachidonic acid challenge. At this time point, **11a** was found to be extremely potent in vivo, demonstrating significant inhibition at doses as low as 0.1 mg/kg. Indeed, this compound was the most potent compound tested in this model at this time point, with several other compounds showing appreciable activity at 1 mg/kg. To gauge the duration of action of these compounds, animals were dosed 17 h prior to arachidonic acid challenge. Under these conditions, **11a** displayed only modest inhibition even at 10 mg/kg. On the other hand, compounds with an altered carboxylate tether (**23**, **13**) and 2,6-difluorobenzyloxy substitution (**11g**) were found to have excellent duration of action, demonstrating good inhibition at the 17-h time point, despite lower inhibition levels than **11a** at the shorter time point. The best potency at the longer time point was observed with 2,6-difluorobenzyloxy-substituted cinnamide **24**, for which excellent inhibition was observed at doses as low as 3 mg/kg. This result indicates that **24** maintains a level of potency at 18 h virtually identical to that observed at the 0.5-h time point. As a general trend, it appears

Table 1. Substituted Cinnamides and Their Antagonism of the LTB_4 Receptor



compd	R_1	R_2	R_3	R_4	R_5	LTB_4 IC_{50}[a]	Ca^{2+} inhibn K_i[b]
4a	Ph(Me)CHO−	H	Me	Et	Et	744 ± 27	
4b	Ph(Me)CHO−	H	Me	$-(CH_2)_5-$		5800[c]	
4c	Ph(Me)CHO−	H	Me	*i*-Pr	*i*-Pr	1100[c]	
4d	Ph(Me)CHO−	H	Me	Me	Me	2100 ± 43	
4e	Ph(Me)CHO−	H	Me	*n*-Pr	*n*-Pr	1400 ± 60	
4f	Ph(Me)CHO−	H	Me	Et	H	2000 ± 43	
4g	Ph(Me)CHO−	H	H	Et	Et	1600[c]	
4h	$PhCH_2O$−	H	Me	Et	Et	7900 ± 900	
4i	*i*-PrO−	H	Me	Et	Et	>10000[c]	
4j	Ph(Me)CHO−	H	Me	2-(MeO)-5-(CO_2H)Ph	H	>10000	
5[d]	Ph(Me)CHO−	H	Me	Et	Et	4300[c]	
6	Ph−	H	Me	Et	Et	>10000[c]	
7	Ph(Me)CHO−	COOH	Me	Et	Et	884 ± 54	
11a	Ph(Me)CHO−	OCH_2COOH	Me	Et	Et	50 ± 2	9.1
11b	Ph(Me)CHO−	$O(CH_2)_3COOH$	Me	Et	Et	216 ± 18	
11c	$PhCH_2O$−	OCH_2COOH	Me	Et	Et	182 ± 6	82
11d	(2-ClPh)CH_2O−	OCH_2COOH	Me	Et	Et	67[c]	16
11e	(2-FPh)CH_2O−	OCH_2COOH	Me	Et	Et	119[c]	27
11f	(2,6-di-ClPh)CH_2O−	OCH_2COOH	Me	Et	Et	31 ± 4	14
11g	(2,6-di-FPh)CH_2O−	OCH_2COOH	Me	Et	Et	56 ± 6	18
11h	Ph_2CHO−	OCH_2COOH	Me	Et	Et	64 ± 4	5.2
11i	PhO−	OCH_2COOH	Me	Et	Et	2400[c]	
12	Ph(Me)CHO−	OH	Me	Et	Et	420 ± 32	
13	Ph(Me)CHO−	$O(CH_2)_2COOH$	Me	Et	Et	128 ± 7	81
14[e]	Ph(Me)CHO−	OCH_2CO_2H	Me	Et	Et	84 ± 4	11.2
15[f]	Ph(Me)CHO−	OCH_2CO_2H	Me	Et	Et	2225 ± 819	
17	$PhCH_2CH_2$−	OCH_2COOH	Me	Et	Et	56 ± 9	7.7
20	$PhCH_2S$−	OCH_2COOH	Me	Et	Et	34 ± 6	26
23	Ph(Me)CHO−	CH_2COOH	Me	Et	Et	81 ± 4	9.5
(*S*)-23	(*S*)-Ph(Me)CHO−	CH_2COOH	Me	Et	Et	39 ± 9	
(*R*)-23	(*R*)- Ph(Me)CHO−	CH_2COOH	Me	Et	Et	536 ± 22	
24	(2,6-di-FPh)CH_2O−	CH_2COOH	Me	Et	Et	87[c]	22
27	Ph(Me)CHO−	CH_2CH_2COOH	Me	Et	Et	48 ± 3	9.5

[a] Inhibition of [^{3}H]LTB_4 binding to human PMNs. IC_{50}'s reported in nM; $n = 3$ except where stated. [b] Inhibition of Ca^{2+} release from human PMNs. K_i's reported in nM; $n = 1$ for all compounds. [c] $n = 1$ for this compound. [d] Dihydrocinnamide. [e] Ph(Me)CHO substituent at 5-position of aryl ring. [f] OCH_2CO_2H substituent at 2-positon of aryl ring.

Table 2. Inhibition of Arachidonic Acid (AA)-Induced Ear Edema[a]

	dosing 0.5 h prior to AA challenge			dosing 17 h prior to AA challenge	
compd	0.1 mg/kg	1 mg/kg	3 mg/kg	3 mg/kg	10 mg/kg
11a	41**/49**	50**/67**	56**/71**	nt	27/31*
13	21/15	24**/24*	39**/58**	25*/12	40**/55**
23	nt	41**/41**		29*/26	55**/55**
11g	nt	26**/32**	52**58**	34*15	46**/54**
24	nt	32*/38**	45**/53**	44**/53**	59**/67**
11d	nt	nt	nt	nt	33**/2
11e	nt	nt	nt	nt	19/30*
11f	nt	nt	nt		0/0
11h	nt	14/0	nt	nt	nt
20	nt	nt	nt	nt	1/1
17	nt	nt	nt	nt	27/0

[a] Compounds were dosed orally to mice in suspension. One ear was then challenged with AA. Animals were sacrificed 2 h after AA challenge. Values are percent inhibition relative to control ear (reported as punch wt/MPO activity). nt, not tested; *$p < 0.05$; **$p < 0.01$.

that many of the more lipophilic compounds, even those with good in vitro potency, displayed only minimal in vivo activity. Examples of these compounds include **11d**,**f**,**h**, **17**, and **20**, which all either possess additional hydrophobic substituents on the pendent phenyl ring or have the oxygen of the phenyl ring replaced with a sulfur or methylene group.[22] The 2,6-difluorobenzyloxy group found in **11g** and **24** appears to be the optimal substituent in terms of balancing in vivo and in vitro potency. The lack of in vivo potency for the monofluoro compound **11e** may be due to its lower in vitro potency.

Conclusion

Reported herein is a novel series of LTB_4 receptor antagonists. Although initial members of the series were found to have only moderate potency, identification of a site for carboxylate binding resulted in preparation of nanomolar antagonists. The compounds containing the chiral 1-phenylethoxy substituent exhibited enantiomeric binding selectivities, with the *S* isomer some 12-fold more potent than the *R* isomer. In addition, potent achiral antagonists were also identified, either

by replacement of the oxygen in the phenyl tether with a carbon or sulfur atom or by *ortho*-substitution on the benzylic aromatic ring. Subsequent in vivo studies led to the discovery of several members of this series which possess excellent oral activity as long as 17 h after dosing.

Experimental Section

Preparation of Compound for in Vitro Analysis. Identical procedures were used to prepare and dilute compounds for all in vitro studies. LTB_4 was purchased as a solution in either ethanol or dimethyl sulfoxide (DMSO) (Biomol, Plymouth Meeting, PA) and diluted into Hank's balanced salt solution (HBSS) before use. Test compounds were dissolved in DMSO to produce stock solution of 10 mM. Dilutions were made so that the final concentration of DMSO was 0.35%.

Antagonism of [^{3}H]LTB_4 Binding to Intact Human Neutrophils. Neutrophils were prepared from citrated venous blood. Blood (25 mL) was mixed with HESPAN (15 mL) (DuPont, Wilmington, DE) and allowed to stand at room temperature for 40 min. The supernatant was removed and centrifuged for 10 min at 400*g*. The resulting pellet was resuspended in phosphate-buffered saline without calcium and magnesium (GIBCO, Grand Island, NY); 35 mL of the resuspended cells was layered over 15 mL of Ficoll-Paque (Sigma, St. Louis, MO) and then centrifuged for 15 min at 420*g*. The resulting cell pellet was resuspended in 10 mL of phosphate-buffered saline without calcium and magnesium; 25 mL of deionized water was added to the suspension for 20 s followed by the same volume of buffer at twice the normal concentration. The suspension was centrifuged for 5 min at 200*g*, and the pellet resuspended in HBSS.

Binding of [^{3}H]LTB_4 to neutrophils was measured as described previously.[23,24] Intact human neutrophils (3×10^6) were added to HBSS containing 0.5 nM [^{3}H]LTB_4 (specific activity 32 Ci/mmol; DuPont-NEN, Boston, MA) and compound (final volume 0.5 mL). After incubating for 20 min at 0 °C, the bound radioactivity was collected on Whatman GF/C filters by vacuum filtration using a Brandel harvester. The filters were washed twice with ice-cold HBSS. Filters were counted using Formula-989 scintillation cocktail (DuPont-NEN, Boston, MA). Nonspecific binding was determined in the presence of 300 nM LTB_4 (Biomol, Plymouth Meeting, PA).

Inhibition of the LTB_4-Induced Intracellular Calcium Rise in Human Neutrophils. Increases in intracellular Ca^{2+} were measured as described previously.[25] Neutrophils were purified from citrated human venous blood by sedimentation in HESPAN as described above. Neutrophils were isolated from the resulting pellet by centrifugal elutriation.[26] The neutrophils (2×10^6/mL) were incubated with acetoxymethyl ester of Fura-2 (0.2 μM) (Molecular Probes Inc.) for 30 min at 37 °C in HEPES-buffered Hank's solution containing Ca^{2+} and Mg^{2+}. The Fura-2-loaded cells were washed and stored on ice at a concentration of 2×10^6 cells/mL in 10 mM HEPES-buffered HBSS without Ca^{2+} and Mg^{2+}. Fifteen minutes before assay, 1.5 mL of the cell suspension was mixed with 10 μL of 0.15 M Ca^{2+} and 0.15 M Mg^{2+} by stirring at 37 °C. Compounds were added 40 s before the addition of 1 nM LTB_4. The change in fluorescence was followed using a DMX 1000 spectrofluorometer (SLM-Aminco Instruments, Urbana, IL). The K_i was determined assuming simple competitive inhibition: $K_i = IC_{50}/(1 + [LTB_4]/EC_{50}$ of $LTB_4)$.

Inhibition of Mouse Ear Inflammation. The methodology used was essentially that described previously.[27] Female mice (A/J, Jackson Labs., Bar Harbor, ME) weighing 20 g were divided into groups consisting of six mice per treatment group. They were fasted overnight. Compounds were orally administered a set time before the application of arachidonic acid using 3% fortified cornstarch, 5% poly(ethylene glycol) 400, and 0.34% Tween 80 as the vehicle. Arachidonic acid (2 mg in 15 μL of acetone) (Sigma, St. Louis, MO) was applied to the inner surface of the right ear. The left ear received 15 μL of acetone. The animals were sacrificed 1 h later. Edema was determined by subtracting the weight of the left ear punch from that of the right ear. As the marker for neutrophil infiltration, myeloperoxidase activity was measured.[28] The right ear punches from the both the vehicle- and compound-treated groups were used. The percentage of inhibition was calculated by comparing the myeloperoxidase activity of the compound-treated groups with those of the vehicle-treated group. Statistical significance was determined using a 2-tail *T*-test.

Chemistry. Melting points (mp) were determined on either a Thomas-Hoover or a Mel-Temp II melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Bruker AC-250, a Bruker AC-300, or a Bruker AC-400 spectrometer using $CDCl_3$ or DMSO-d_6 as internal standard. Chemical ionization MS (CI) were perfomed on an HP 5985 mass spectrometer, using CH_4 as the reagent gas. Microanalyses were performed at Robertson Laboratory, Inc., Madison, NJ. All organic solvents used were of anhydrous grade. All reactions were run under a positive pressure of nitrogen unless otherwise stated. Chromatographic separations were performed with silica gel 60. Compounds were dried by suspension of anhydrous $MgSO_4$, followed by vacuum filtration.

Compounds **4a**−**j** were prepared using the same synthetic sequence. Compound **4h** is representative.

(*R,S*)-(*E*)-Ethyl 3-(4-Benzyloxyphenyl)-2-butenoate (3h). To a solution of *p*-bromophenol (9.51 g, 55 mmol) and benzyl bromide (5.95 mL, 50 mmol) in acetone (250 mL) was added K_2CO_3, and the mixture was heated overnight to reflux. After cooling, the solvent was evaporated, and the residue was dissolved in ethyl acetate (EtOAc) (400 mL), washed with NaOH (1 N, 3 × 200 mL) and brine (200 mL), dried, evaporated, chromatographed (10% EtOAc/hexane) to yield 1-benzyloxy-4-bromobenzene as a clear oil (12.12 g). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.45 (7H, m); 6.83 (2H, d, J = 8.1 Hz); 5.01 (s, 2H). A 5.26-g portion of this compound (20 mmol) was taken up in triethylamine (12 mL), and ethyl crotonate (5.0 mL, 40 mmol) was added to the solution. After the mixture was purged with nitrogen for 5 min, tri-*o*-tolylphosphine ((*o*-tol)$_3$P) (0.61 g, 2.0 mmol) and palladium acetate ($Pd(OAc)_2$) (224 mg, 1.0 mmol) were added, the mixture was deoxygenated for another 5 min, and then the tube was sealed and heated to 100 °C for 5 h. The mixture was then cooled to room temperature, diluted with EtOAc (300 mL), and filtered through Celite. The filtrate was then washed with 1 N HCl (2 × 200 mL) and brine (100 mL), dried, evaporated, and chromatographed (5% EtOAc/hexane, then 7% EtOAc/hexane) to yield **3h** (2.15 g, 30% for 2 steps) as a white solid, mp 67−68 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32−7.53 (7H, m); 7.47 (2H, d, J = 8.1 Hz); 6.11 (1H, s); 5.09 (2H, s); 4.20 (1H, q, J = 7.2 Hz); 1.58 (3H, s); 1.32 (3H, t, J = 7.2 Hz).

(*R,S*)-(*E*)-Diethyl 3-(4-Benzyloxyphenyl)-2-butenamide (4a). To a solution of **3a** (1.6 g, 5.4 mmol) in methanol (MeOH) (30 mL) and tetrahydrofuran (THF) (50 mL) was added 1 N NaOH (21.6 mL), and the solution was stirred at room temperature for 1 h. The organic solvents were evaporated, and the aqueous residue was acidified with 1 N HCl (150 mL) and extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with brine, dried, and evaporated. The residue was then dissolved in methylene chloride (CH_2Cl_2) (90 mL). The solution was cooled to 0 °C, and *N*,*N*-dimethylformamide (DMF) (50 μL) followed by oxalyl chloride (1.7 mL, 19.4 mmol) were then added. The mixture was then warmed to room temperature over 30 min. Evaporation yielded 1.4 g of a yellow solid, of which 0.7 g (ca. 2.44 mmol) was dissolved in THF (50 mL), followed by addition of diethylamine (1.01 mL, 9.77 mmol). The now cloudy mixture was stirred at room temperature for 2 h, during which time a white precipitate formed. The solvent was evaporated, and the residue was dissolved in EtOAc (100 mL), washed with 1 N HCl (2 × 200 mL) and brine, dried, evaporated, and chromatographed (35% EtOAc/hexane) to yield **4a** as a white solid (0.62 g, 71%), mp 39−40 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28−7.48 (7H, m); 6.96 (2H, d, J = 8.1 Hz); 6.24 (1H, s); 5.09 (2H, s); 3.47 (2H, q,

J = 7.3 Hz); 3.38 (2H, q, J = 7.4 Hz); 2.29 (3H, s); 1.17 (6H, q, J = 7.4 Hz). MS (CI): m/z 324 (M + H). Anal. ($C_{21}H_{25}NO_2$) C, H, N.

Intermediates of type **10** were all prepared using the same general protocol. The following compound is provided as an example.

3′-Hydroxy-4′-(2,6-difluorobenzyloxy)acetophenone (9, R = 2,6-difluorobenzyl). A mixture of 3′,4′-dihydroxyacetophenone (25.0 g, 164.3 mmol), lithium carbonate (12.1 g, 164.3 mmol), and α-bromo-2,6-difluorotoluene (34.0 g, 164.3 mmol) in DMF (400 mL) was stirred at room temperature for 2 days. The mixture was then filtered through Celite, and the filtrate was evaporated. The residue was diluted with water (200 mL), and the mixture was filtered. The collected solid was recrystallized from ethanol to give **9** (R = 2,6-difluorobenzyl) (17.9 g, 38%). ^{1}H NMR (DMSO-d_6, 250 MHz): δ 9.46 (1H, br s); 7.10−7.56 (6H, m); 5.16 (2H, s); 2.50 (6H, s).

(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-(2,6-difluorobenzyloxy)phenoxy]acetate (10, R = 2,6-difluorobenzyl, X = COOEt, *n* = 1). A mixture of **9** (R = 2,6-difluorobenzyl) (15.0 g, 53.96 mmol), ethyl bromoacetate (7.2 mL, 64.75 mmol), and K_2CO_3 (14.9 g, 107.92 mmol) in acetone (350 mL) was heated to reflux for 18 h. After cooling, the mixture was filtered, and the filtrate was concentrated in vacuo. Recrystallization from EtOAc yielded ethyl [5-acetyl-2-(2,6-difluorobenzyloxy)phenoxy]acetate (13.35 g, 68%). To a solution of diethyl [2-(diethylamino)-2-oxoethyl]phosphonate (**8**)[29] (6.9 g, 27.45 mmol) in THF (150 mL) was added sodium hydride (1.1 g, 27.45 mmol, 60% in mineral oil) in one portion. The solution was then stirred at room temperature until it became clear. A solution of the product from the previous step (8.0 g, 21.96 mmol) in THF (50 mL) was added, and the mixture was heated to reflux for 18 h. After cooling, the mixture was then quenched with saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (2 × 150 mL). The combined organic phase was washed with water (1 × 100 mL) and brine (1 × 100 mL), dried, evaporated, and chromatographed (diethyl ether), providing a ca. 7:1 ratio of *E*/*Z* isomers of the product. Recrystallization from diethyl ether provided **10** (R = 2,6-difluorobenzyl, X = COOEt, n = 1) (2.11 g, 20%), mp 73−76 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 6.90−7.42 (6H, m); 6.20 (1H, s); 5.19 (2H, s); 4.65 (2H, s); 4.17 (2H, q, J = 7.1 Hz); 3.47 (2H, q, J = 7.4 Hz); 3.38 (2H, q, J = 7.4 Hz); 2.25 (3H, s); 1.26 (3H, t, J = 7.1 Hz); 1.18 (3H, t, J = 7.4 Hz); 1.15 (3H, t, J = 7.4 Hz).

Compounds of type **11** were all prepared from their precursors **10** using the same protocol. Compound **11g** is representative.

(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-(2,6-difluorobenzyloxy)phenoxy]acetic Acid (11g). To a solution of **10** (R = 2,6-difluorobenzyl, X = COOEt, n = 1) (2.1 g, 4.55 mmol) in methanol (30 mL) was added 1 N NaOH (13.7 mL, 13.7 mmol), and the mixture was stirred at room temperature for 2 h. The solution was then acidified to pH 1 with 1 N HCl, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic phase was washed with water (1 × 100 mL) and brine (1 × 100 mL), dried, and evaporated. The resulting solid was triturated from diethyl ether, giving **11g** (1.94 g, 98%), mp 120−122 °C. ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.90−7.42 (6H, m); 6.20 (s, 1H); 5.21 (2H, s); 4.65 (2H, s); 3.50 (2H, q, J = 7.4 Hz); 3.40 (2H, q, J = 7.4 Hz); 2.25 (3H, s); 1.21 (3H, t, J = 7.4 Hz); 1.18 (3H, t, J = 7.4 Hz). Anal. ($C_{23}H_{25}F_2N_2O_5$) C, H, N.

(*R,S*)-(*E*)-Diethyl 3-(3-Hydroxy-4-benzyloxyphenyl)-2-butenamide (12). To **10** (n = 0, R = Ph(Me)CHO, X = TMS) (0.93 g, 2.05 mmol) in THF (40 mL) at 0 °C was added 1 M tetrabutylammonium fluoride (TBAF) in THF (2.25 mL, 2.25 mmol) slowly, via syringe. The solution was then warmed to room temperature over 1.5 h. The solution was quenched with 1 N HCl (20 mL), and THF was evaporated. The residue was dissolved in EtOAc (100 mL), washed with water and brine, dried, and evaporated. The residue was chromatographed (45% EtOAc/hexane) to yield **12** as a thick oil (0.353 g, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25−7.40 (5H, m); 7.04 (1H, d, J = 3.5 Hz); 6.78 (1H, dd, J = 9.7, 3.5 Hz); 6.65 (1H, d, J = 9.7 Hz); 6.19 (1H, s); 5.77 (1H, s); 5.33 (1H, q, J = 8.6 Hz); 3.43 (2H, q, J = 7.4 Hz); 3.37 (2H, q, J = 7.4 Hz); 2.21 (3H, s); 1.68 (3H, d, J = 8.6 Hz); 1.07−1.23 (6H, m). MS (CI): m/z 354 (M + H). Anal. ($C_{24}H_{29}N_5O_3$) H, N; C: calcd, 74.76; found, 74.10.

(*E*)-3-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-(2,6-difluorobenzyloxy)phenoxy]propionic Acid (13). To a solution of **10** (R = Ph(Me)CH−, X = CH=CH_2, n = 2) (1.7 g, 4.35 mmol) in THF/water (100 mL:100 mL) was added OsO_4 solution (4% solution in water, 2.42 mL, 0.22 mmol). After 10 min, sodium periodate (4.65 g, 21.74 mmol) was added, and the resulting mixture was stirred at room temperature for 5 h. The organic layer was separated, and the aqueous layer was washed with EtOAc (50 mL). The combined organic layers were washed with brine, dried, and evaporated. The resulting residue was taken up in *tert*-butyl alcohol (60 mL), and 2.0 M 2-methyl-2-butene in THF (26 mL, 52.2 mmol) was added to the solution. A freshly made solution of sodium chlorite (1.17 g, 13.05 mmol) and sodium dihyodrogen phosphate (1.44 g, 10.44 mmol) in water (12 mL) was then added. The reaction mixture was stirred at room temperature for 6 h, after which time it was diluted with 1 N NaOH (50 mL), extracted with diethyl ether, dried, and evaporated. The product was chromatographed (75% EtOAc/hexane, 0.7% AcOH) to yield **13** as a white solid (160 mg, 8.6%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16−7.38 (5H, m); 7.02 (1H, d, J = 2.2 Hz); 7.85 (1H, dd, J = 8.5, 2.2 Hz); 6.68 (1H, d, J = 8.5 Hz); 6.16 (1H, d, J = 1.1 Hz); 5.23 (1, q, J = 7.2 Hz); 4.31 (1H, t, J = 6.4 Hz); 3.26−3.50 (4H, m); 2.86 (2H, t, J = 6.3 Hz); 2.17 (3H, d, J = 1.1 Hz); 1.62 (3H, d, J = 7.2 Hz); 1.05−1.21 (6H, m). MS (CI): m/z 426 (M + H). Anal. ($C_{25}H_{31}NO_5$) C, H, N.

***tert*-Butyl {5-Acetyl-2-[(trifluoromethyl)sulfonyloxy]-phenoxy}acetate (16).** To a solution of **10** (X = CO_2t-Bu, R = Bn, n = 1) (2.0 g, 5.6 mmol) in EtOH (25 mL) was added 10% Pd/C (0.10 g), and the mixture was hydrogenated at 1 atm for 1.25 h. The solution was filtered, evaporated, and dissolved in CH_2Cl_2. To this solution at −30 °C was added pyridine (1.2 mL, 15.0 mmol), followed by triflic anhydride (1.5 g, 5.6 mmol) via syringe over 2 min. After stirring 10 min, water (20 mL) was added; the solution was warmed to room temperature, washed with 1 N HCl (1 × 50 mL) and brine (1 × 50 mL), dried, and concentrated in vacuo. The residue was chromatographed (silica, 15% EtOAc/hexane) to yield **16** (1.3 g, 60% for 2 steps). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61 (1H, dd, J = 9.5, 1.2 Hz); 7.52 (1H, d, J = 1.2 Hz); 7.35 (1H, d, J = 9.5 Hz); 7.27 (1H, s); 4.66 (2H, s); 2.0.53 (3H, s); 1.49 (9H, s).

(*R,S*)-(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-phenethylphenoxy]acetic Acid (17). A solution of **16** (0.50 g, 1.3 mmol) and phenylacetylene (0.33 mL, 3.0 mmol) in 20 mL of triethylamine in a thick walled Pyrex tube was degassed with nitrogen for 15 min. Bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and copper(I) iodide (10 mg, 0.05 mmol) were added, and the vessel was sealed and heated to 60 °C for 18 h. After cooling, the triethylamine was removed in vacuo, and the residue was dissolved in diethyl ether (100 mL), washed with 1 N HCl (1 × 100 mL) and brine (1 × 50 mL), dried, and evaporated. The product was chromatographed (15% EtOAc/hexane), dissolved in 5 mL of THF, and diluted with ethanol (15 mL). 10% Palladium on activated carbon (0.10 g) was added, and the mixture was hydrogenated at 1 atm until the theoretical amount of hydrogen was consumed. Filtration through Celite, followed by solvent removal in vacuo, yielded *tert*-butyl (*E*)-(5-acetyl-2-phenethylphenoxy)acetate (0.20 g, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14−7.41 (6H, m); 6.78 (2H, s); 4.61 (2H, s); 2.53 (3H, s); 1.50 (9H, s). This material was then subjected to Horner−Emmons olefination as described for **10**, directly affording **17** after chromatography (5% MeOH/CH_2Cl_2) as a clear oil (0.14 g, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13−7.42 (5H, m); 7.09 (d, 1H, J = 8.0 Hz); 6.94 (1H, d, J = 8.0 Hz); 6.83 (1H, s); 6.23 (1H, s); 4.65 (2H, s); 3.50 (2H, q, J = 7.2 Hz); 3.38 (2H. q, J = 7.2 Hz); 2.70−3.15 (4H, m); 2.19 (3H, s); 1.10−1.31 (6H, m). MS: m/z 396 (M + H). Anal. ($C_{24}H_{29}NO_4 \cdot H_2O$) C, H, N.

4′-Mercapto-3′-methoxyacetophenone (18). To a solution of 3-hydroxy-4-methoxyacetophenone (8.31 g, 50 mmol) and 2.81 g of potassium hydroxide (50 mmol) in water (34 mL), at 0 °C, was added a solution of dimethylthiocarbamoyl chloride (8.28 g, 67 mmol) in THF (14 mL), dropwise, at such a rate as to keep the reaction temperature below 12 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. It was then diluted with 1 N NaOH (100 mL) and extracted with EtOAc (3 × 80 mL). The combined organic phase was washed with water (1 × 100 mL) and brine (1 × 50 mL), dried, concentrated in vacuo, and then added to a thick walled Pyrex tube. The tube was flushed with nitrogen, sealed, and then heated to 250 °C for 1 h. After cooling, the residue was chromatographed (silica gel, 50% EtOAc/hexane), and the product was dissolved in ethylene glycol (50 mL). Potassium hydroxide (1.0 g, 17.8 mmol) in water (5 mL) was added, and this mixture was heated to reflux for 1 h. After cooling, this mixture was poured into 250 mL of ice and then washed with diethyl ether (3 × 75 mL). The aqueous phase was then acidified to pH 1 with concentrated HCl, and the solution was filtered to remove the precipitate. The aqueous layer was then extracted with EtOAc (3 × 75 mL), and the combined organic phase was washed with water (1 × 50 mL) and brine (1 × 50 mL), dried, and evaporated to yield **18** (3.59 g, 42% for 3 steps). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.42 (1H, s); 7.41 (1H, d, J = 8.1 Hz); 7.28 (1H, d, J = 8.1 Hz); 3.93 (3H, s); 2.60 (1H, s).

4′-Benzylthio-3′-hydroxyacetophenone (19). To a solution of **18** (3.59 g, 19.73 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added BBr_3 (3.73 mL, 39.46 mmol) dropwise via syringe, and the resulting solution was stirred for 2 h. The solution was then poured into ice water (300 mL), and the organic layer was collected and evaporated. The residue was dissolved in EtOAc (140 mL), washed with water and brine, dried, and evaporated to yield 2.51 g of crude phenol, of which 0.84 g (ca. 5 mmol) was dissolved in acetone (30 mL). To this solution were added benzyl bromide (0.60 mL, 5 mmol) and K_2CO_3 (0.69 g, 5 mmol), and the mixture was heated to reflux for 2 h. After cooling, the solvent was evaporated, and the residue was dissolved in EtOAc (400 mL), washed with HCl (1 N, 3 × 200 mL) and brine (200 mL), dried, evaporated, and chromatographed (35% EtOAc/hexane). The lower, minor spot was isolated as **19** (0.38 g, 20% for 2 steps). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 702−7.43 (8H, m); 6.51 (1H, s); 4.90 (2H, s); 2.04 (3H, s).

(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-(1-benzylthio)phenyl]acetic Acid (20). Phenol **19** (1.16 g, 4.5 mmol) was carried on as described for compounds **10** and **11** to yield **20** as a white solid, mp 132−134 °C (0.35 g, 19% for 3 steps). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17−7.34 (5H, m); 7.15 (1H, d, J = 8.0 Hz); 6.91 (1H, dd, J = 8.0, 1.8 Hz); 6.81 (1H, d, J = 1.8 Hz); 6.20 (1H, d, J = 1.0 Hz); 4.67 (2H, s); 4.11 (2H, s); 3.45 (1H, q, J = 7.1 Hz); 3.33 (1H, q, J = 7.1 Hz); 2.13 (3H, d, J = 1.0 Hz); 1.16 (3H, t, J = 7.1 Hz); 1.13 (3H, t, J = 7.1 Hz). MS (CI): m/z 414 (M + H). Anal. ($C_{23}H_{27}NO_4S$) C, H, N.

Ethyl (5-Bromo-2-hydroxyphenyl)acetate (21). 2′-Hydroxyphenylacetic acid (25.0 g, 164 mmol) was dissolved in ethanol (400 mL). Tetrabutylammonium tribromide (79.23 g, 164 mmol) was added to the solution, and the resulting mixture was stirred at room temperature for 18 h. After evaporation of solvent, the residue was dissolved in diethyl ether (300 mL), washed with 1 N HCl (100 mL), 2 M sodium bisulfate (50 mL), water (50 mL), and brine (50 mL), dried, and evaporated to yield **21** (38.25 g, 90%) which was carried on directly. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.75 (1H, br s); 7.28 (1H, d, J = 1.1 Hz); 7.24 (1H, s); 7.20 (1H, d, J = 1.1 Hz); 6.82 (1H, d, J = 7.5 Hz); 4.20 (2H, q, J = 7.1 Hz); 3.16 (3H, s); 1.30 (3H, t, J = 7.1 Hz).

(*R,S*)-(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-(1-phenylethoxy)phenyl]acetic Acid (23). 21 (3.7 g, 14 mmol) was alkylated with 1-bromoethylbenzene and subjected to Heck arylation with diethyl crotonamide using the procedure described for compound **3a**. This product was then subjected to ester hydrolysis as described for compound **11d**, yielding **23** as a clear oil (1.2 g, 21% for 3 steps). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16−7.40 (7H, m); 6.65 (1H, d, J = 8.2 Hz); 6.17 (1H, s); 5.32 (1H, q, J = 7.1 Hz); 3.74 (2H, s); 3.47 (q, 2H, J = 7.4 Hz); 3.36 (2H, q, J = 7.4 Hz); 2.21 (3H, s); 1.60 (3H, d, J = 7.1 Hz); 1.20 (3H, t, J = 7.4 Hz); 1.14 (3H, t, J = 7.4 Hz). MS (CI): m/z 396 (M + H). Anal. ($C_{24}H_{29}NO_4$) C, H, N.

(*R*)-Methyl [5-Bromo-2-(1-phenylethoxy)phenyl]acetate ((*R*)-25). To a solution of **22** (1.0 g, 4.1 mmol), (*S*)-(−)-phenethyl alcohol (0.49 mL, 4.1 mmol), and triphenylphosphine (1.07 g, 4.1 mmol) in toluene (15 mL) at 0 °C was added diethyl azodicarboxylate (0.64 mL, 4.1 mmol) in toluene (5 mL), dropwise, over 15 min, and the solution was warmed to room temperature overnight. The solution was then diluted with 20 mL of toluene, stirred with 10 g of bentonite, filtered, evaporated, and chormatographed to yield **(*R*)-25**. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.09−7.39 (7H, m); 6.51 (1H, d, J = 7.2 Hz); 5.23 (1H, q, J = 6.3 Hz); 3.78 (3H, s); 3.62 (2H, s); 1.57 (3H, d, J = 6.3 Hz).

(*R*)-(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-((*R*)-1-phenylethoxy)phenyl]acetic Acid ((*R*)-23). Compound **(*R*)-25** was carried on to product using the same protocol as described for compound **23** to provide **(*R*)-23**. Optical purity was determined via ^{1}H NMR analysis of a solution of **(R)-23** (11 mg) with (*R*)-naphthylethylamine (6.7 μL) in 0.5 mL of $CDCl_3$. This solution produced a doubling of most ^{1}H signals when racemic **23** was used. With **(*R*)-23**, comparison of signal intensities for methyl singlets at δ 2.15 and 2.17 gave an ee of 97%.

(*S*)-(*E*)-[5-(2-Diethylcarbamoyl-1-methylvinyl)-2-((*S*)-1-phenylethoxy)phenyl]acetic Acid ((*S*)-23). (*S*)-23 was prepared exactly as was **(*R*)-23**, except that (*R*)-(−)-phenethyl alcohol was employed in the Mitsunobu reaction. Optical purity determination as described above gave an ee of 93%.

3′-Allyl-4′-(1-phenylethoxy)acetophenone (26). A solution of 4-hydroxyacetophenone (9.53 g, 70 mmol), allyl bromide (6.66 mL, 77 mmol), and K_2CO_3 (14.51 g, 105 mmol) in acetone (150 mL) was heated to reflux for 6 h. The mixture was then filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (100 mL), then washed with water (1 × 100 mL) and brine (1 × 100 mL), dried, and evaporated. The residue was dissolved in 10 mL of xylene and was introduced into a thick walled Pyrex tube, which was sealed with a Teflon cap. After heating to 230 °C for 5 h, the solution was cooled to 0 °C. The precipitated white solid was filtered and washed with toluene. Half of this material, along with 1-bromoethylbenzene (3.05 mL, 21.63 mmol) and K_2CO_3 (4.07 g, 29.49 mmol), were dissolved in acetone (100 mL) and heated to reflux for 20 h. The mixture was then filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (100 mL), then washed with water (1 × 100 mL) and brine (1 × 100 mL), dried, and evaporated. Chromatography (15% EtOAc/hexane) yielded **26** as a clear oil (4.28 g, 39% for 3 steps). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.91 (2H, d, J = 9.4 Hz); 6.91 (2H, d, J = 9.4 Hz); 5.95−6.14 (1H, m); 5.41 (1H, dq, J = 19.4, 1.1 Hz); 5.29 (1H, dq, J = 11.8, 1.1 Hz); 4.58 (2H, dt, J = 6.8 Hz, 1.1 Hz); 2.52 (3H, s).

(*R,S*)-(*E*)-3-[3-(3-Hydroxypropyl)-4-(1-phenylethoxy)-phenyl]but-2-enamide (27). 26 (2.91 g, 10.4 mmol) was subjected to Horner−Emmons olefinations with phosphonate **8** as described for compound **10**. This material was then dissolved in THF (40 mL), and Wilkinson's catalyst (64 mg, 0.069 mmol) was added to the solution, followed by a 1.0 M solution of catecholborane in THF (7.62 mL, 7.62 mmol), via syringe. After stirring for 3 h at 0 °C, the solution was quenched with methanol (15 mL), followed by addition of a solution 30% hydrogen peroxide (1.94 mL) in 3 M NaOH (18 mL). The solution was then warmed to room temperature over 3 h. The solution was concentrated to 25 mL in vacuo, and the residue was taken up in water (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with water (1 × 50 mL) and brine (1 × 50 mL), dried, evaporated, and chromatographed (20% EtOAc/hexane) to yield 0.25 g of product. A solution of oxalyl chloride (60 μL, 0.696 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C, and DMSO (98 μL, 1.39 mmol) was added dropwise via syringe.

After 5 min, a solution of the product from the previous step was added to this solution. After 15 min, triethylamine (0.40 mL, 2.85 mmol) was added, and the solution was warmed to room temperature over 15 min. The mixture was then quenched with water (50 mL) and extracted with CH_2Cl_2 (25 mL), and the organic phase was washed with water and brine, and dried. This material was then subjected to sodium chlorite oxidation as described for compound **13** to yield **27** as a thick oil (0.10 g, 3% yield for 3 steps). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20−7.40 (6H, m); 7.10 (1H, dd, J = 7.5, 1.1 Hz); 6.62 (1H, d, J = 7.5 Hz); 6.16 (1H, s); 5.81 (1H, q, J = 7.3 Hz); 3.31−3.47 (4H, m); 3.04 (t, 2H, J = 7.7 Hz); 2.75 (2H, t, J = 7.5 Hz); 2.21 (3H, s); 1.63 (3H, d, J = 7.3 Hz); 1.15 (6H, t, J = 7.3 Hz). MS (CI): m/z 410 (M^+ + H). Anal. ($C_{25}H_{29}NO_4 \cdot H_2O$) C, H, N.

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