Design, Synthesis, and Evaluation of Substituted Phenylpropanoic Acid Derivatives as Human Peroxisome Proliferator Activated Receptor Activators. Discovery of Potent and Human Peroxisome Proliferator Activated Receptor α Subtype-Selective Activators

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Substituted phenylpropanoic acid derivatives were prepared as part of a search for subtype-selective human peroxisome proliferator activated receptor α (PPARα) activators. Structure−activity relationship studies indicated that the nature and the stereochemistry of the substituent at the α-position of the head part containing the carboxyl group, the distance between the carboxyl group and the central benzene ring, the linking group between the central benzene ring and the distal benzene ring, and the substituent at the distal hydrophobic tail part of the molecule all play key roles in determining the potency and selectivity of PPAR subtype transactivation. This study has led to the identification of potent and human PPARα selective optically active α-alkylphenylpropanoic acid derivatives, which will be useful not only as pharmacological tools to investigate the physiology and pathophysiology of PPARα but also as candidate drugs for the treatment of altered metabolic homeostasis, such as dyslipidemia, obesity, and diabetes.

Introduction

Peroxisome proliferator activated receptors (PPARs) are members of a huge nuclear hormone receptor superfamily, a group of nuclear proteins that mediate the specific effects of small lipophilic compounds, such as steroids, retinoids, and fatty acids, on DNA transcription. PPARs are heterogeneous, and three subtypes have been isolated to date: PPARα [NR1C1], PPARδ [NR1C2] (also known as PPARβ, NUCI, FAAR), and PPARγ [NR1C3].[1] Each PPAR subtype appears to be differentially expressed in a tissue-specific manner and to play a pivotal role in lipid and lipoprotein homeostasis. Upon ligand binding, PPARs heterodimerize with another nuclear receptor partner, retinoid X receptor (RXR), and the heterodimers regulate gene expression by binding to specific consensus DNA sequences, termed PPRE (peroxisome proliferator responsive elements),[2] which are located in the regulatory regions of target genes.[3]

One of the subtypes, PPARα, which was originally cloned as an orphan receptor from a mouse liver cDNA library,[4] has since been cloned from many species, including humans. PPARα is mostly expressed in organs with a high rate of fatty acid catabolism, such as liver, and regulates the expression of the genes encoding for proteins involved in lipid and lipoprotein metabolism.[1] In mice lacking PPARα (PPARα-/-), inhibition of cellular fatty acid flux caused massive hepatic and cardiac lipid accumulation.[5] Detailed mRNA and protein expression analysis of PPARα-/- mice has indicated that the metabolic abnormalities are due to altered expression levels of a range of metabolic enzymes.[6] These results clearly indicate a pivotal role for PPARα in lipid homeostasis in vivo.

The antihyperlipidemic drugs of the fibrate class, such as clofibrate, bezafibrate, and fenofibrate (Chart 1), are widely used clinically as hypolipidemic drugs. These drugs increase HDL cholesterol levels and lower LDL and VLDL cholesterol levels.[7] Fibrates have a stronger triglyceride-lowering effect than statins, which are HMG-CoA reductase inhibitors. These beneficial pharmacological effects of fibrates are thought to be mediated in part by PPARα activation.[8] Although fibrates are ligands of PPARs, their affinity is very weak (high micromolar concentrations are needed to activate PPARα) and the PPAR subtype-selectivity is poor. Consequently, in humans, fibrates must be used at very high doses (about 300−1200 mg/day) to achieve a sufficient lipid-lowering effect. Therefore, the search for more potent and selective activators of PPARα, especially human PPARα, is important. Such activators should be superior to both fibrates and statins for the treatment of altered lipid homeostasis in the target organs, especially liver.

Here, we describe the design and synthesis of novel phenylpropanoic acid derivatives as human PPARα selective activators,[9] leading to the identification of some human PPARα selective α-alkylphenylpropanoic acid derivatives as candidate drugs for the treatment of metabolic disorders such as hyperlipidemia, obesity, and diabetes.

To develop structurally new human PPARα selective activators, we selected KRP-297 (Chart 1) as a lead compound.[10] Although KRP-297 belongs structurally to

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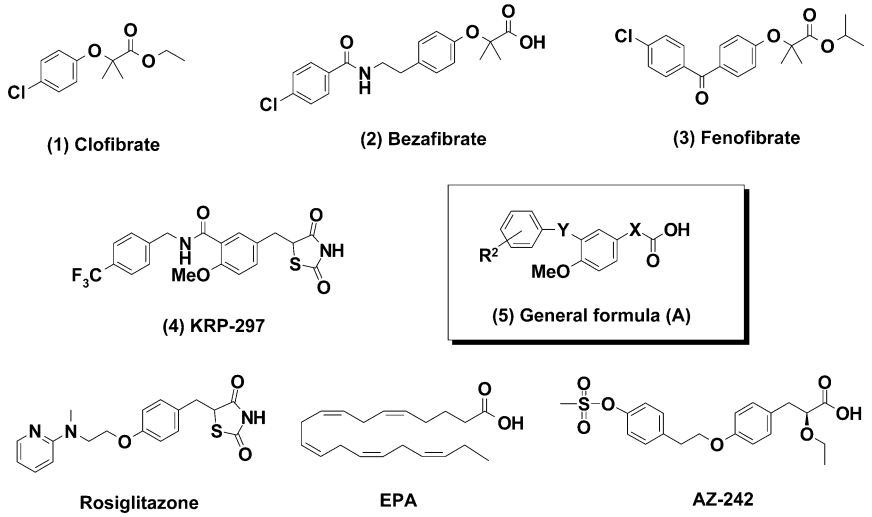
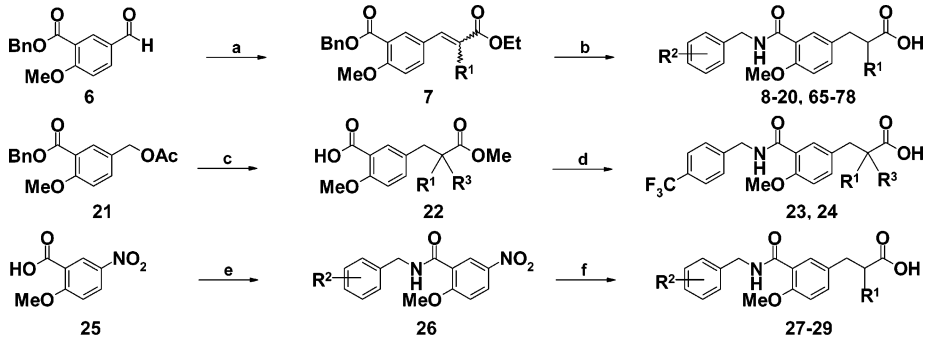
Chart 1. Chemical Structures of the PPAR Agonists



Scheme 1. Synthetic Routes to the Phenylpropanoic Acids and Related Compounds[a]



[a] Reagents: (a) $(EtO)_2POCH(Et)CO_2Et$, NaH, THF; (b) (1) H_2, 10% Pd−C, EtOH, (2) amine, $ClCO_2Et$, TEA, CH_2Cl_2, (3) aqueous NaOH, EtOH; (c) (1) $(R)_2C{=}C(OTMS)OMe$ (R = Me or Et), $Mg(ClO_4)_2$, CH_2Cl_2, (2) H_2, 10% Pd−C, EtOH; (d) (1) 4-$(CF_3)PhCH_2NH_2$, $ClCO_2Et$, triethylamine, CH_2Cl_2, (2) same as in (b); (e) same as in (a2); (f) (1) same as in (b1), (2) $NaNO_2$, HBr, MeOH-acetone, (3) ethyl acrylate, Cu_2O; (4) NaSR (R = alkyl, phenyl, benzyl), EtOH, (5) same as in (b3).

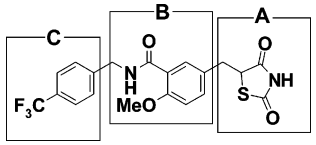


Figure 1. Chemical structure of the lead compound KRP-297 (MK-767).

the glitazones (thiazolidine-2,4-dione class insulin sensitizers), it binds directly to and activates both PPARγ and PPARα isoforms with almost equal affinity.[10] This is characteristic of classical glitazones, such as troglitazone,[11] pioglitazone,[12] and rosiglitazone,[13] which were reported to bind to and selectively activate the PPARγ isoform.[14] The reason KRP-297 exhibits coligand nature is unclear, but we anticipated that the replacement of the thiazolidine-2,4-dione ring of KRP-297 with another acidic functionality, such as a carboxyl group, usually used in fibrates, might favor PPARα selectivity and that further chemical modification might improve the potency and selectivity for the PPARα subtype.

Structurally, KRP-297can be regarded as having three key regions: (A) the acidic head part, (B) the linker part, and (C) the hydrophobic tail part (Figure 1). Therefore, chemical modification of each part of the molecule was performed to understand the structure−activity relationship in detail.

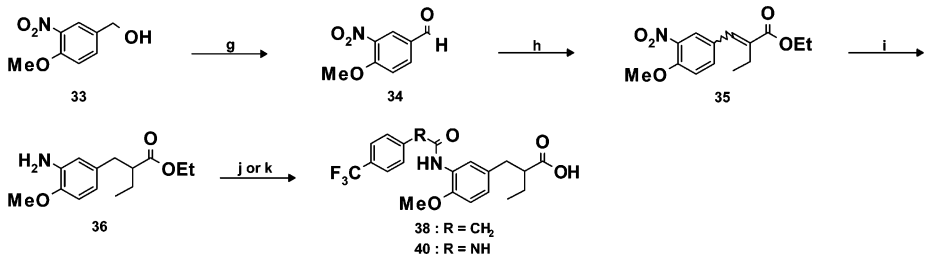
Chemistry

Synthetic routes to the phenylpropanoic acids and related compounds prepared in this study are outlined in Schemes 1−9.

The α-monosubstituted phenylpropanoic acid derivatives (**8**−**20**, **65**−**78**) were prepared from **6** via four steps. Compound **6**, which was prepared from 5-formylsalicilic acid, was treated with Emmons reagents, followed by hydrogenolysis, condensation with various amine derivatives, and alkaline hydrolysis to afford the desired product. The α,α-disubstituted phenylpropanoic acid derivatives (**23**, **24**) were prepared by the reaction of **21** (which was prepared from 5-formyl-2-methoxybenzoic acid by benzyl esterification, reduction, and acylation) with silylketene acetal derivatives,[15] followed by hydrogenation, condensation, and alkaline hydrolysis. Compound **25** was condensed with 4-(trifluoromethyl)benzylamine, followed by reduction. The Meerwein arylation[16] reaction provided the ethyl α-bromophenylpropanoate derivative, which was treated with alkyl- or (aralkyl)mercaptan, followed by alkaline hydrolysis to afford α-alkyl- (or aralkyl)thio-substituted derivatives (**27**−**29**) (Scheme 1).

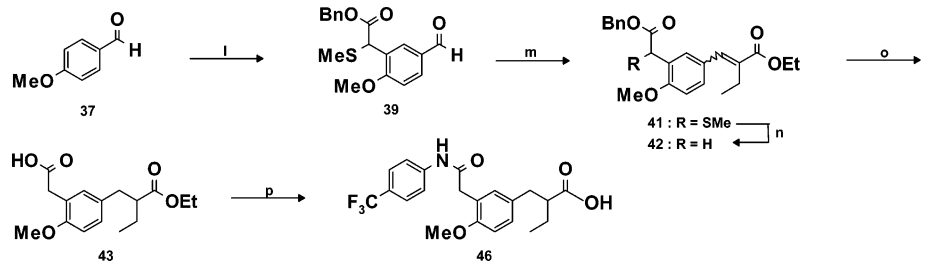
The CH_2CONH linker derivative (**38**) was synthesized from **33**. Oxidation of **33** with activated manganese dioxide yielded the corresponding aldehyde (**34**), which was treated with triethyl 2-phosphonobutyrate followed by reduction to afford **36**. This was converted into the

Scheme 2. Synthetic Routes to the Phenylpropanoic Acids and Related Compounds[a]



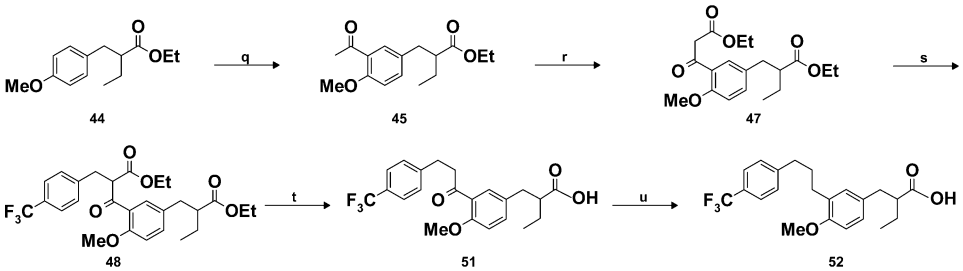
[a] Reagents: (g) MnO_2, CH_2Cl_2; (h) $(EtO)_2POCH(Et)CO_2Et$, NaH, THF; (i) H_2, 10% Pd−C, EtOH; (j) (1) 4-$(CF_3)PhCH_2CO_2H$, EDCI·HCl, CH_2Cl_2, (2) aqueous NaOH, EtOH; (k) (1) 4-$(CF_3)PhNCO$, EtOH, (2) same as in (j2).

Scheme 3. Synthetic Routes to the Phenylpropanoic Acids and the Related Compounds[a]



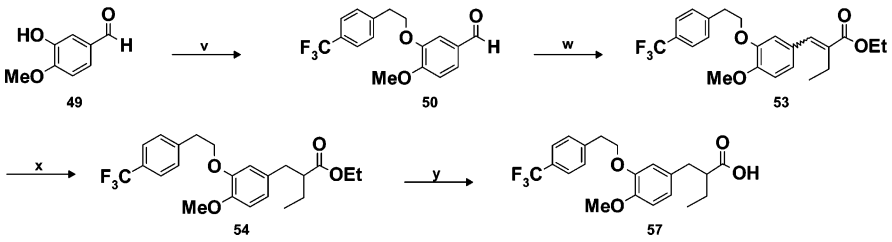
[a] Reagents: (l) (1) $MeSCH(Cl)CO_2Et$, $TiCl_3$, CH_2Cl_2, CCl_4, (2) aqueous NaOH, EtOH, (3) $PhCH_2Br$, K_2CO_3, DMF; (m) $(EtO)_2POCH(Et)CO_2Et$, NaH, THF; (n) Zn, AcOH; (o) H_2, 10% Pd−C, EtOH, (p) (1) 4-$(CF_3)PhNH_2$, $ClCO_2Et$, triethylamine, CH_2Cl_2, (2) same as in (l2).

Scheme 4. Synthetic Routes to the Phenylpropanoic Acids and Related Compounds[a]



[a] Reagents: (q) AcCl, $AlCl_3$, CH_2Cl_2; (r) $(CO_2Et)_2CO$, NaH; (s) 4-$(CF_3)PhCH_2Br$, NaH, THF; (t) AcOH, concentrated HCl; (u) H_2, 10% Pd−C, EtOH.

Scheme 5. Synthetic Routes to the Phenylpropanoic Acids and Related Compounds[a]



[a] Reagents: (v) 4-$(CF_3)PhCH_2CH_2OH$, $P(Ph)_3$, DEAD, THF; (w) $(EtO)_2POCH(Et)CO_2Et$, NaH, THF; (x) H_2, 10% Pd−C, EtOH; (y) aqueous NaOH, EtOH.

desired compound (**38**) by a procedure similar to that described for the synthesis of **8** (Scheme 2).

The NHCONH linker derivative (**40**) was also synthesized from **36** by reaction with 4-(trifluoromethyl)-phenyisocyanate and subsequent alkaline hydrolysis (Scheme 2).

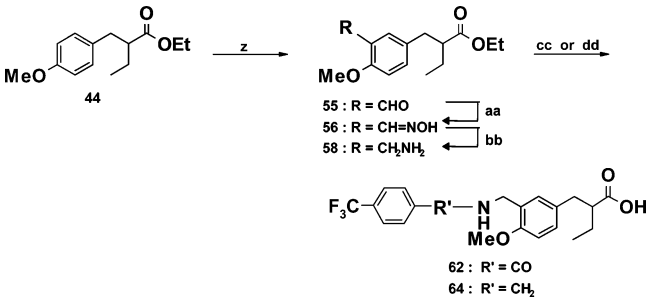
Friedel−Crafts reaction of **37** with ethyl 2-chloromethylthioacetate, followed by ester exchange, afforded the benzyl ester (**39**), which was treated with triethyl 2-phosphonobutyrate. Desulfurization then provided **42**, which was reduced, hydrogenolyzed, and converted into the desired $NHCOCH_2$ linker derivative (**46**) by a procedure similar to that described for the synthesis of **8** (Scheme 3).

The $CH_2CH_2CH_2$ linker derivative (**52**) was synthesized from **44** via five steps. Friedel−Crafts acylation of **44** followed by ethoxycarbonylation and benzylation provided **48**. Acid-catalyzed decarboxylation and dehydroxylation afforded the desired $CH_2CH_2CH_2$ linker derivative (**52**) (Scheme 4).

The phenolic hydroxyl group of isovaniline (**49**) was alkylated, and the product was treated with triethyl 2-phosphonobutyrate followed by reduction and alkaline hydrolysis to afford the CH_2CH_2O linker derivative (**57**) (Scheme 5).

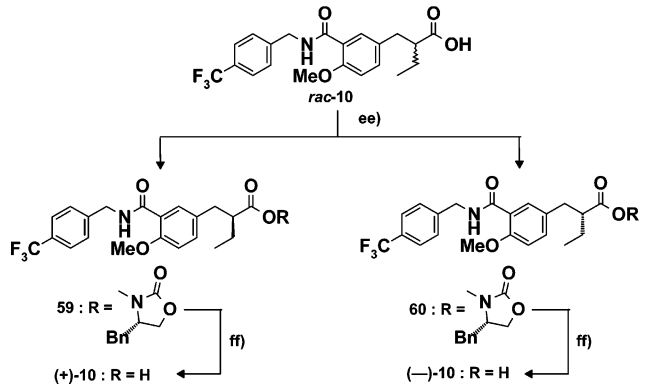
The $CONHCH_2$ linker derivative (**62**) was also synthesized from **44**. Formylation of **44** followed by hydroxylamine·hydrochloride treatment and reduction

Scheme 6. Synthetic Routes to the Phenylpropanoic Acids and Related Compounds[a]



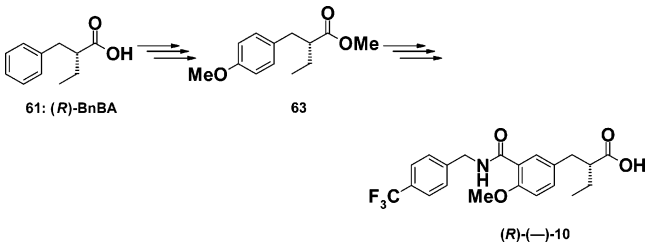
[a] Reagents: (z) $TiCl_4$, $MeOCHCl_2$, CH_2Cl_2; (aa) $NH_2OH{\cdot}HCl$, pyridine, EtOH; (bb) H_2, 10% Pd−C, EtOH; (cc) (1) 4-$(CF_3)PhCO_2H$, $ClCO_2Et$, triethylamine, CH_2Cl_2, (2) aqueous NaOH, EtOH; (dd) (1) 4-$(CF_3)PhCH_2Br$, K_2CO_3, DMF, (2) same as in (cc2).

Scheme 7. Synthetic Routes to Optically Active Phenylpropanoic Acids[a]



[a] Reagents: (ee) (1) pivaloyl chloride, NEt_3, THF, (2) 4-(*S*)-benzyloxazolidinone, *t*-BuOK, THF; (ff) LiOH, 30% H_2O_2, MeOH.

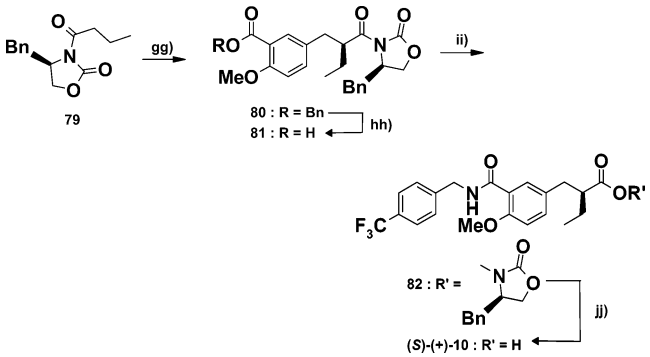
Scheme 8. Synthetic Routes to (*R*)-**10**



afforded **58**. This was converted into the desired compound (**62**) by a procedure similar to that described for the synthesis of **8** (Scheme 6). Furthermore, **58** was alkylated and subjected to alkaline hydrolysis to afford the CH_2NHCH_2 linker derivative (**64**) (Scheme 6).

Each enantiomer of compound **10**, one of the most potent compounds, was obtained according to the procedure reported by Haigh et al.,[17] with slight modifications, i.e., by optical resolution of the corresponding 4-(*S*)-benzyloxazolidinoneimide derivative of **10**, which was prepared by the reaction of racemic **10** and 4-(*S*)-benzyloxazolidinone via the mixed-anhydride method, followed by alkaline removal of the chiral auxiliary (Scheme 7).[9] The optical purity of the enantiomers was estimated to be more than 95%.[18] The absolute configuration of the optically active **10** was determined by the preparation of (*R*)-**10**, starting from the optically active (*R*)-2-benzylbutanoic acid[19] (Scheme 8). The (*R*)-**10** exhibited levo rotation, so the absolute configuration of

Scheme 9. Asymmetric Synthetic Routes to (*S*)-**10**[a]



[a] Reagents: (gg) LiHMDS, benzyl 5-bromomethyl-2-methoxybenzoate, THF; (hh) H_2, 10% Pd−C, EtOH; (ii) 4-$(CF_3)PhCH_2NH_2$, $ClCO_2Et$, TEA, CH_2Cl_2; (jj) $LiOH{\cdot}H_2O$, 30% H_2O_2.

(−)-**10** was deduced to be *R* and that of the antipodal (+)-**10** was deduced to be *S*.[9]

Next, the asymmetric synthesis of α-monosubstituted phenylpropanoic acid derivatives was exploited for the large-scale preparation of the desired enantiomer to provide a sufficient amount for investigation of the in vivo activity (Scheme 9).[20] Acylation of 4-(*R*)-benzyloxazolidinone provided **79**, which was treated with benzyl 5-bromomethyl-2-methoxybenzoate under Evans's asymmetric alkylation protocol,[21] followed by hydrogenolysis to afford the key synthetic intermediate **81**. This was condensed with the appropriate benzylamine derivative, followed by removal of the chiral auxiliary to afford the desired (*S*)-configuration product (Scheme 9). By means of this procedure, kilogram-scale preparation of the key intermediate (**81**) was achieved with high enantiomeric excess.

Biology

The compounds prepared in this study were at first evaluated for in vitro transactivation activity on human PPARs transfected into Chinese hamster ovary (CHO) K1 cells. The compounds that exhibited potent and/or selective PPARα subtype transactivation activity were then evaluated further, in vitro and in vivo. The in vitro activity of the compounds showed some variation from experiment to experiment. However, the order of efficacy of the test compounds was reproducible.

Plasmids

cDNA encoding for the ligand-binding domain (LBD) of human PPAR was cloned by reverse transcriptase polymerase chain reaction (RT-PCR) using total RNA from a human hepatoma cell line, HepG2. GAL4/human PPARLBD receptor plasmid was prepared by inserting the DNA fragment of human PPARLBD into the pM vector containing the DNA-binding domain (DBD) of a yeast transcriptional factor, GAL4. pFR-Luc, firefly luciferase reporter plasmid, was purchased from Stratagene (La Jolla, CA). pRL-TK, renilla luciferase internal standard plasmid, was obtained from Promega (Madison, WI).

Transfection Assay

CHO-K1 cells were seeded at 5×10^4 cells/well in 24-well plates and cultured in Ham's F12 medium containing 10% fetal calf serum for 24 h at 37 °C. Cells

were cotransfected for 2 h with 40 ng of GAL4/human PPAR LBD, 400 ng of pFR-Luc, and 5 ng of pRL-TK per well using lipofectamine (Gibco BRL, Grand Island, NY). Transfected cells were treated with various concentrations of test compounds at 37 °C for 20 h. Cells were washed with phosphate-buffered saline and dissolved in passive lysis buffer (Promega, Madison, WI). Luciferase activity was determined with a microplate luminescence reader, LUCY2 (Anthos, Salzburg, Austria). The EC_{50} values of tested compounds were derived from the curve fitting using the Prism program (GraphPad Software, San Diego, CA).

Animals

Male Sprague−Dawley rats were obtained from Charles River Japan (Yokohama, Japan). All rats were given a standard diet CE-2 (CLEA Japan, Tokyo, Japan) and tap water ad libitum. (*S*)-**10** or vehicle was suspended in 0.5% (w/v) Arabic gum and administered orally to 11-week-old SD rats once a day at 0.3, 3, or 30 mg/kg for 4 days. In the fructose diet study, all rats were given an AIN-93 modified fructose diet (Oriental Yeast, Tokyo, Japan) after having been deprived of food for 2 days, with tap water ad libitum. (*S*)-**10** (10, 30 mg/kg), bezafibrate (30 mg/kg), or vehicle was administered orally to 11-week-old SD rats once a day for 4 days. At the end of the treatment period, plasma samples were obtained.

Determination of Serum Parameters

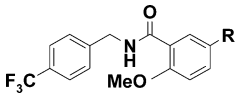
Plasma total cholesterol and free fatty acid levels were determined by means of an enzymatic method using Cholesterol E Test Wako and NEFA C Test Wako (Wako Pure Chemical Industries, Osaka, Japan). Plasma triglyceride levels were determined with a triglyceride assay kit (Roche Diagnostics K. K., Tokyo, Japan). Serum lipoproteins were separated to afford the HDL fraction by using a precipitation reagent (Wako Pure Chemical Industries). The supernatant was used for cholesterol determination of HDL cholesterol. Total cholesterol content of unfractionated whole serum and that of the HDL fraction were determined by an enzymatic method. VLDL and LDL cholesterol levels were calculated as follows: total cholesterol level minus HDL cholesterol level. Hepatic triglyceride content and total cholesterol content were measured by an enzymatic procedure as described for plasma triglyceride and cholesterol after extraction of total tissue lipid with chloroform−methanol. Hepatic triglyceride content and total cholesterol content were expressed as milligrams of triglyceride or total cholesterol per gram of tissue wet weight.

Results and Discussion

The transactivation activity of the present series of compounds toward human PPARs is summarized in Tables 1−3, together with the results for fibrates. The fibrate class of antihyperlipidemic agents, such as bezafibrate and fenofibrate, exhibited weak and nonselective PPARs activation, in accordance with reported data.[22]

Structure−Activity Relationship: Effect of the Acidic Head Part. For activity on the PPARα isoform, the distance between the carboxyl group and the right side benzene ring in the compound is important (Table 1).[9] The benzoic acid and phenylacetic acid derivatives (**30** and **31**) were inactive at 10 μM, but the phenylpropanoic acid derivative (**8**) exhibited transactivation activity, comparable to that of the lead compound (**4**). Further elongation of the methylene chain to give the phenylbutanoic acid derivative (**32**) decreased the activity to some extent.

Table 1. Effect of the Acidic Part of the Present Series of Compounds



compd	R	transactivation EC_{50} (μM)[a] PPARα	PPARγ	PPARδ
4	CH_2TZD[b]	1.0	0.8	ia[c]
8	$(CH_2)_2CO_2H$	1.3	ia[c]	ia[c]
9	$CH_2CH(Me)CO_2H$[d]	0.24	ia[c]	2.8
10	$CH_2CH(Et)CO_2H$[d]	0.040	0.4	3.6
11	$CH_2CH(n\text{-}Pr)CO_2H$[d]	0.36	ia[c]	2.4
12	$CH_2CH(i\text{-}Pr)CO_2H$[d]	0.29	ia[c]	ia[c]
13	$CH_2CH(n\text{-}Bu)CO_2H$[d]	1.0	2.5	ia[c]
14	$CH_2CH(Ph)CO_2H$[d]	ia[c]	ia[c]	ia[c]
15	$CH_2CH(OMe)CO_2H$[d]	0.23	ia[c]	ia[c]
16	$CH_2CH(OEt)CO_2H$[d]	1.6	2.8	3.0
17	$CH_2CH(OPh)CO_2H$[d]	ia[c]	ia[c]	ia[c]
23	$CH_2C(Me)_2CO_2H$	2.9	ia[c]	ia[c]
24	$CH_2C(Et)_2CO_2H$	2.8	ia[c]	ia[c]
27	$CH_2CH(SEt)CO_2H$[d]	1.6	2.8	3.0
28	$CH_2CH(SPh)CO_2H$[d]	ia[c]	ia[c]	ia[c]
29	$CH_2CH(SCH_2Ph)CO_2H$[d]	ia[c]	ia[c]	ia[c]
30	CO_2H	ia[c]	ia[c]	ia[c]
31	CH_2CO_2H	ia[c]	ia[c]	ia[c]
32	$(CH_2)_3CO_2H$	2.2	3.0	ia[c]
bezafibrate		>78	>137	>143

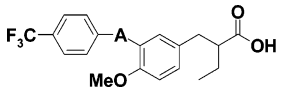
[a] Compounds were screened for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CHO-K1 cells as described. EC_{50} value is the molar concentration of the test compound that causes 50% of the maximal reporter activity. $n = 3$. [b] KRP-297. Data taken from ref 10. [c] "ia" means inactive at a concentration of 10 μM. [d] Assayed as a racemate.

On the other hand, these surrogates (**30**−**32**) were weak activators (**32**) or inactive (**30**, **31**) at 10 μM on PPARγ. These results support the prevailing hypothesis that the thiazolidine-2,4-dione ring structure is a good pharmacophore for potent and selective PPARγ transactivation activity.[23] Furthermore, these surrogates (**8**, **30**, **31**, and **32**) were also inactive at 10 μM on PPAR δ.

Considering that **8** possessed distinct (micromolar order) PPARα transactivation activity and PPARα subtype selectivity, we selected **8** as the next lead compound and performed further chemical modification focused on the α-position of the carboxyl group of **8**. We anticipated that the introduction of certain shapes of substituents at the α-position of the carboxyl group of **8** would enhance the PPARα transactivation activity, based on the results obtained from the X-ray crystallographic analysis of the human PPARγ−rosiglitazone complex.[24]

As also indicated in Table 1, introduction of appropriate alkyl substituents at the α-position of the carboxyl group of **8** strikingly affected PPARα transactivation activity and subtype selectivity. Introduction of a methyl group (**9**) increased the effect on PPARα transactivation activity to some extent, but introduction of an ethyl group (**10**) greatly enhanced the activity. Bulkier substituents generally decreased the activity. These data

Table 2. Effect of the Linker Part of the Present Series of Compounds



		transactivation EC_{50} (μM)[a]		
compd	A	PPARα	PPARγ	PPARδ
10	CH_2NHCO[c]	0.04	0.4	3.6
18	$NHCO$[c]	6.0	ia[b]	ia[b]
19	$(CH_2)_2NHCO$[c]	0.74	ia[b]	1.5
20	$CH_2N(CH_3)CO$[c]	ia[b]	ia[b]	ia[b]
38	CH_2CONH[c]	0.13	ia[b]	ia[b]
40	$NHCONH$[c]	ia[b]	ia[b]	ia[b]
46	$NHCOCH_2$[c]	0.02	ia[b]	ia[b]
51	CH_2CH_2CO[c]	0.32	7.4	ia[b]
52	$CH_2CH_2CH_2$[c]	0.86	ia[b]	0.64
57	CH_2CH_2O[c]	0.68	ia[b]	0.40
62	$CONHCH_2$[c]	0.04	>10	0.12
64	CH_2NHCH_2[c]	4.9	ia[b]	8.0
bezafibrate		>78	>137	>143

[a] Compounds were screened for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CHO-K1 cells as described. EC_{50} value is the molar concentration of the test compound that causes 50% of the maximal reporter activity. $n = 3$. [b] "ia" means inactive at a concentration of 10 μM. [c] Assayed as a racemate.

indicated that there are distinct structural requirements for potent PPARα transactivation activity, and the ethyl group is the most favorable.

On the other hand, as regards the PPARγ and PPARδ isoforms, most of the compounds listed in Table 1 were inactive at 10 μM. Thus, most of these α-alkyl-substituted derivatives have preferentiality on PPARα.

A similar tendency was seen in the case of α-alkoxy- and α-alkylthio-substituted derivatives except for **16** and **27**. Although some other structural types of α-ethoxy- and α-ethylthio-substituted phenylpropanoic acid derivatives were reported to exhibit potent PPAR transactivation activity,[25] compounds bearing these substituents in the present series exhibited weak transactivation activity on all PPAR isoforms. Compounds **16** and **27** showed weak activity and poor subtype selectivity (pan-agonistic activity), although the reason is not known.

Introduction of one more substituent at the α-position of the α-monosubstituted phenylpropanoic acid derivatives is unfavorable for PPARα activity; i.e., the α,α-dimethyl- and the α,α-diethyl-substituted derivatives (**23**, **24**) exhibited decreased PPARα transactivation activity compared to the corresponding α-monosubstituted compounds (**9**, **10**).

Almost all the compounds listed in Table 1 showed no significant PPARδ transactivation activity. These results might indicate that the structural requirements for transactivation of PPARδ are more restrictive, though this isoform is ubiquitously expressed in many organs and tissues[22] (structural requirements for PPARδ agonists will be discussed later).

Structure−Activity Relationship: Effect of the Linker Part. Interesting subtype-selective PPAR transactivation profiles were obtained by manipulation of the linker part of **10** (Table 2). In the case of the PPARα isoform, the length of the linking group is important for potency. The transactivation activity of **10** (three-atom unit, $-C(H_2)-N(H)-C(O)-$) was very potent, but shortening or lengthening (especially shortening) the linking group (**18**, **19**) considerably decreased the activity. The compounds with a secondary amide bond (−NHCO−) (**10**, **46**) or reversed secondary amide bond (−CONH−) (**38**, **62**) exhibited almost equipotent transactivation activity, whereas other compounds with a three-atom unit as a linking group showed moderate (**51**, **52**, **57**) or weak activity (**64**). The tertiary amide derivative (**20**) and urea-type derivative (**40**) did not show transactivation activity at 10 μM. It is well recognized that the three-dimensional distance and the alignment of the acidic head part and the hydrophobic tail part of the molecule are important for potent PPAR transactivation activity.[26] Therefore, we speculated that the two pharmacophores of molecules with amide-type linkers (**10**, **46**) and reversed amide-type linkers (**38**, **62**) having a three-atom unit are positioned favorably in the large binding pocket of PPARα. In contrast, the two pharmacophores of molecules with other three-atom unit linkers (**51**, **52**, and **57**) are not located at the proper position in the binding pocket probably because of conformational flexibility of the linkers. Further, we thought that the urea-type and the tertiary amide compounds (**40**, **20**) did not form favorable conformations for potent transactivation activity toward PPARα owing to the introduction of the planar ureido bond or the existence of cis/trans isomers (^{1}H NMR study indicated that **20** exists as a 2:1 mixture of regioisomers in $CDCl_3$). The hydrogen-bonding interaction between the linker part and the PPARα backbone might not be crucial because all the secondary amide linker compounds exhibited equipotent transactivation activity, although these compounds have various kinds of amide bonds with respect to position and alignment.

It has been determined on the basis of an X-ray crystallographic study that potent PPARs agonists such as rosiglitazone (PPARγ agonist; Chart 1) and AZ-242 (dual agonist of PPARγ and PPARα; Chart 1)[27] take a "U"-shaped conformation, wrapping around the helix 3 (H3) region of each PPAR with the central benzene ring directly behind H3 and the acidic headgroup and hydrophobic tail group wrapping around H3.[24] Therefore, we speculate that the potent PPARα activators in the present series of compounds, such as **10** and **46**, might form "U"-shaped conformations, while the less potent derivatives, such as **57** and **40**, might not form a proper "U"-shaped conformation probably because of conformational flexibility or conformational restriction. To investigate this point, computer-aided conformational analysis of representative compounds (**10**, **40**, **46**, **57**) was performed using the Insight 2/Discover 3[28] system. The common part of the molecules, the 2-[4-(methoxyphenyl)methyl]butyric acid moiety, was used as an anchor. The anchor part of each molecule was built using the crystal structure of GW 409544 bound to the PPAR ligand binding domain homodimer (PDB code 1k7l) as the reference structure. For the chiral center of the α-position of the carboxyl group, the *S*-form (the binding isomer) was used. The conformations of each molecule were searched by a systematic rotation of torsion angles. During the search, the structure of the anchor moiety was fixed, while the conformation of the rest of the molecule was calculated for each conformer. The energies of conformations were minimized with the cvff force field (conjugate gradient method and

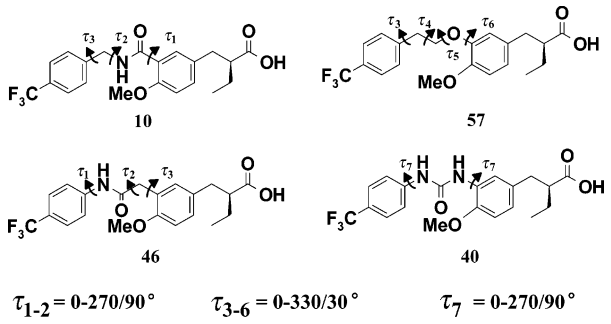


Figure 2. Effect of the stereochemistry of the substituent introduced at the α-position of the carboxylic acid group on transactivation to PPARα.

0.01 kcal/mol energy convergence criterion). Figure 2 shows the rotated bonds and torsion angle values used to generate conformers for each representative compound, and the analytical results are summarized in Figures 3 and 4. In the case of **10** and **46**, which showed potent PPARα transactivation activity, about 70 and 200 conformers, respectively, out of 845 conformers were calculated to form "U"-shaped conformations having an energy of no more than 0.3 kcal/mol above the minimum energy structure (relative existence probability (RE) versus the minimum energy structure was estimated to be 65% and 61% for **10** and **46**, respectively). In the case of **57**, only 10 conformers out of 10 985 conformers was calculated to form "U"-shaped conformations, but these conformers were energetically unfavorable, being about 3.7 kcal/mol above the minimum energy structure of **57** (RE was estimated to be only 0.2%). Moreover, the ureido linker compound (**40**) was proved not to form "U"-shaped conformations (RE was estimated to be 0%) because of the planar and transoid-preferential nature of the ureido linkage. These data clearly support our speculation.

In contrast to the activity toward PPARα, which ranges over more than 2 orders of magnitude, none of the compounds, except **10** and **51**, exhibited significant PPARγ transactivation activity at 10 μM. These results might indicate that the chemical modification of the linker part produced an unfavorable orientation of the two pharmacophores for proper binding to the large binding pocket of PPARγ.

As for PPARδ, the methylene linker compound (**52**) and the ether linker compound (**57**), which showed about 10-fold less potent PPARα transactivation activity compared to **10**, exhibited much more potent PPARδ transactivation activity (about 5- to 9-fold more potent) than **10**. Improvement of PPARδ transactivation activity rendered these compounds moderately potent dual activators of PPARα and PPARδ. Recent X-ray crystallographic studies of PPARδ and a naturally occurring unsaturated fatty acid, eicosapentaenoic acid (EPA) (Chart 1), which is a pan-agonist of PPARs, revealed that EPA occupied the ligand binding pocket of PPARδ in two distinct conformations (tail-up and tail-down conformations).[29] The numerous hydrophobic contacts between the hydrophobic tail part of EPA and the binding pocket of PPARδ are likely to be important for potency. Therefore, we considered that the introduction of flexible linkers, such as the methylene linker and the ether linker, improved the conformational flexibility of the hydrophobic tail part of **52** and **57**, and as a result, these compounds were stabilized through numerous hydrophobic interactions with the PPARδ ligand binding pocket.

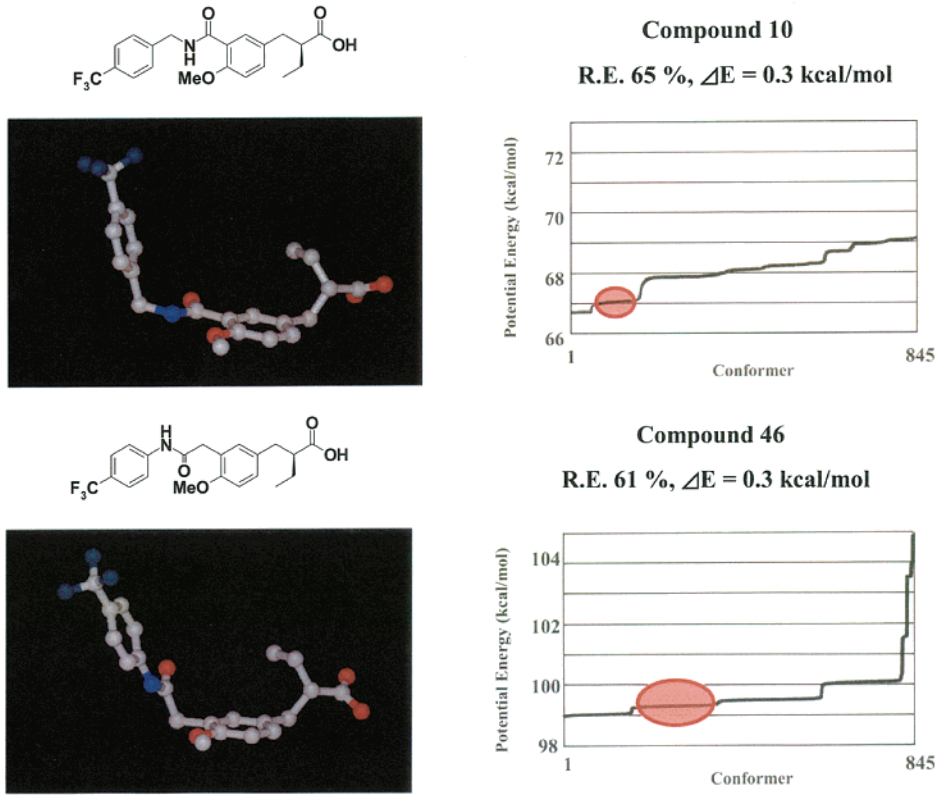


Figure 3. Chemical structures and torsion angle definitions of **10**, **40**, **46**, and **57**, together with values assigned in the systematic search.

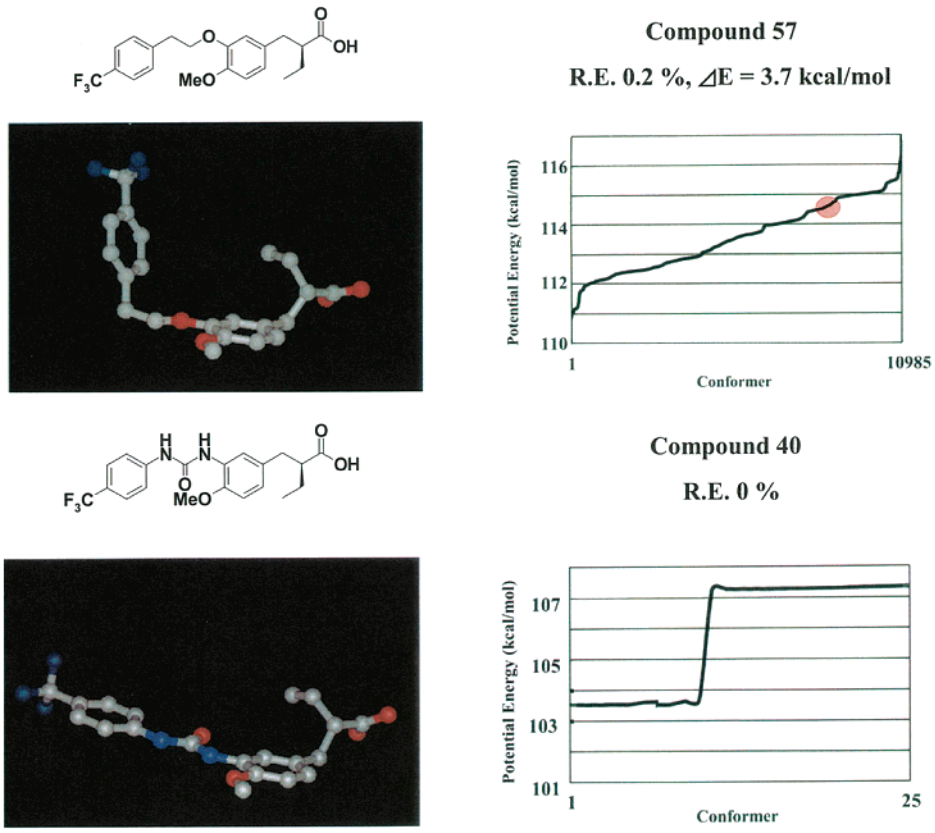


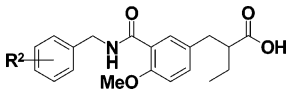
Figure 4. Schematic presentation of a representative "U"-shaped conformation of **10** and **46** together with potential energy results from the systematic search of the generated conformers: RE, relative existence probability versus minimum energy conformer; ΔE, potential energy difference versus minimum energy conformer. Red circle indicates the area of the "U"-shaped conformer.

An exceptionally interesting compound is **62**, which has the $CONHCH_2$ group as a linker. Although almost all amide-containing-linkers are unfavorable for PPARδ activity, **62** exhibited potent PPARδ transactivation activity compared to **10**, with comparably potent PPARα transactivation activity. Therefore, **62** is a dual activator of PPARα and PPARδ, although the reason **62** showed potency against PPARδ is not known.

Although our primary goal in the present study was to discover potent PPARα activators as candidate drugs for the treatment of altered lipid and lipoprotein homeostasis, **62** be of potential value as a dual activator of PPARα and PPARδ, since a recent publication indicated that PPARδ plays a key role in cholesterol metabolism by contributing to reverse cholesterol transport.[30]

Structure−Activity Relationship: Effect of the Substituent at the Hydrophobic Tail Part. The nonsubstituted compound (**65**) exhibited moderate PPARα transactivation activity (Table 3). Introduction of a small substituent such as a chlorine atom or methoxyl group (**66**, **69**−**71**) did not affect the activity, but the introduction of a CF_3 or an OCF_3 group, especially at the 4 position, greatly increased the activity. The increase in activity might be explained by the positive contribution of the steric effect and/or the hydrophobic nature of the fluorine atoms of these groups in binding to the hydrophobic ligand-binding pocket of PPARα. In this case, the position of the substituent introduced at the benzene ring is important because **67**, which has a CF_3 group at the 3 position of the benzene ring, did not show superior PPARα transactivation activity compared with **65**. On the other hand, some compounds in which the benzene ring contains substituents such as phenoxyl (**74**) and phenyl (**75**) also

Table 3. Effect of the Substituents Introduced at the Left Benzene Ring



		transactivation EC_{50} (μM)[a]		
compd	R^2	PPARα	PPARγ	PPARδ
65	H[c]	2.3	10.0	ia[b]
66	4-Cl[c]	3.0	ia[b]	ia[b]
67	3-CF_3[c]	1.8	ia[b]	ia[b]
10	4-CF_3[c]	0.040	0.4	3.6
68	4-OCF_3[c]	0.043	ia[b]	0.90
69	2-OCH_3[c]	9.4	ia[b]	ia[b]
70	3-OCH_3[c]	3.1	nd[d]	ia[b]
71	4-OCH_3[c]	1.2	ia[b]	6.60
72	2-OPh[c]	ia[b]	ia[b]	ia[b]
73	3-OPh[c]	0.40	6.2	ia[b]
74	4-OPh[c]	0.090	2.4	3.0
7/5	4-Ph[c]	0.11	4.0	ia[b]
76	4-OCH_2Ph[c]	1.5	ia[b]	ia[b]
77	4-CH_2CH_2Ph[c]	5.6	5.4	ia[b]
78	4-OCH_2CH_2Ph[c]	2.7	3.0	ia[b]
bezafibrate		>78	>137	>143

[a] Compounds were screened for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CHO-K1 cells as described. EC_{50} value is the molar concentration of the test compound that causes 50% of the maximal reporter activity. $n = 3$. [b] "ia" means inactive at a concentration of 10 μM. [c] Assayed as a racemate. [d] nd means not determined.

exhibited potent PPARα transactivation activity. In this case, the position of the introduced substituent is also important, since the introduction of the phenoxyl group at the 2 or 3 position of the benzene ring (**72**, **73**) decreased PPARα transactivation activity, especially in the case of the 2-phenoxyl group. The distance between the two phenyl groups is also important. Simple phenoxyl and phenyl groups are preferable, and benxyloxyl (**76**), phenetyl (**77**), and phenetyloxyl (**78**) groups decreased the activity considerably.

As regards PPARγ and PPARδ transactivation activity, all compounds except **10** and **68** are weak activators. Compound **68**, which exhibited potent PPARα transactivation activity comparable to that of **10**, exhibited very weak PPARγ transactivation activity but significant PPARδ transactivation activity. Therefore, **10** exhibited a much higher α/δ selectivity ratio compared to that of **68**, while the α/γ selectivity ratio is reversed between the two compounds. It is of interest to note that the subtype-selectivity ratio can be dramatically changed by a small manipulation of the substituents at the peripheral benzene ring. These results might indicate that the shape and environment of the hydrophobic cavity hosting the 4-substituted benzene ring differ somewhat among the three PPAR isoforms.

Structure−Activity Relationship: Effect of the Stereochemistry of the α-Position of the Carboxyl Group. The compounds that have substituents at the α-position of the carboxyl group discussed above were assayed as racemates. It has already been reported that the in vitro and in vivo pharmacological properties of other structural series of α-alkoxyphenylpropanoic acid derivatives differ between the enantiomers.[31] Therefore, we decided to investigate the enantio-dependent transactivation activity of a representative compound, optically active **10**, on PPARα isoform. Compound **10** has an asymmetric center at the α-position of the carboxylic acid functionality, and it is important to determine which enantiomer is the true eutomer.[9]

Optically active **10** ((+)-**10** and (−)-**10**) was obtained by optical resolution (Scheme 7), and the absolute configuration was determined by the preparation of the (*R*)-form of **10** starting from optically active (*R*)-2-benzylbutanoic acid (Scheme 8).[9]

As can be seen from Figure 5, a clear enantio dependence of the transactivation activity toward the PPARα isoform was found. (*S*)-**10** exhibited much more potent transactivation activity, while the antipodal (*R*)-**10** exhibited less potency. Therefore, we concluded that the activity was found to reside almost exclusively in the (*S*)-enantiomer.

In the case of rosiglitazone, a potent and selective PPARγ agonist used for the treatment of non-insulin-dependent diabetes mellitus (type 2 diabetes), enantio dependency was also noted and (*S*)-rosiglitazone exhibited much more potent binding to PPARγ than (*R*)-rosiglitazone.[32] However, the enantio dependency of (*S*)-rosiglitazone decreased time-dependently probably because of rapid racemization at the C-5 position of the thiazolidine-2,4-dione ring at physiological pH.[33] Therefore, rosiglitazone is optically labile and was launched as a racemate. However, unlike rosiglitazone, (*S*)-**10** is expected to be a potent and optically stable agent for the treatment of metabolic disorders.

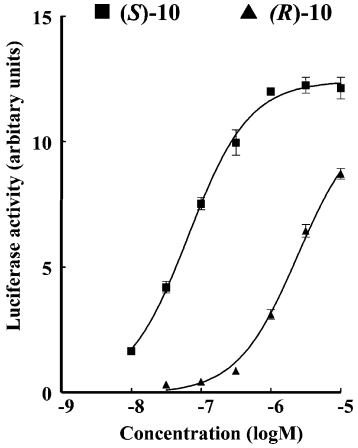


Figure 5. Schematic presentation of a representative "U"-shaped conformation of **40** and **57** together with potential energy results from the systematic search of the generated conformers: RE, relative existence probability versus minimum energy conformer; Δ*E*, potential energy difference versus minimum energy conformer. Red circle indicates the area of the "U"-shaped conformer.

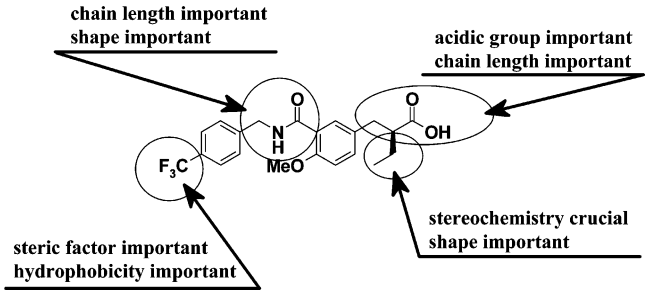


Figure 6. Summary of the SAR of the present series of compounds.

The X-ray crystallographic analysis of the ligand binding domain in the complex with the dual PPARα and PPARγ agonist AZ 242 (an α-ethoxyphenylpropanoic acid derivative) indicated that the side chain ethoxyl group of AZ 242 is positioned in a hydrophobic region of the PPARα ligand binding pocket, surrounded by the side chains of the amino acids Phe273, Cys276, Ile354, and Met355.[27] Because the three-dimensional structure of the acidic head part of (*S*)-**10** appears to be quite similar to that of AZ 242, we speculated that the side chain ethyl group of (*S*)-**10** interacts hydrophobically with the same region of the PPARα ligand-binding pocket. In contrast to AZ 242 (having an ethoxyl group (three-atom unit) as a substituent at the α-position of the carboxylic acid), the two-carbon ethyl group was the most potent α-substituent in the present series of compounds. This difference in length may indicate that the ethyl group of (*S*)-**10** is located deeper in the hydrophobic pocket formed by the side chains of Phe273, Cys276, Ile354, and Met355.

Figure 6 summarizes the structure−activity relationships of the present series of compounds.

Species-Dependent PPARα Transactivation by the Present Series of Compounds. Some peroxisome proliferators show species-dependent transactivation characteristics for PPARα.[34] The classical PPARα agonist WY-14643 is more effective on rodent PPARα than on human PPARα. Moreover, GW-9578, a recently disclosed ureidothioisobutyric acid derivative with potent PPARα activity, also transactivates rodent PPARα

Table 4. Species Differences in the Transactivation of PPARα Isoform

compd	transactivation EC_{50} (μM)[a] human	dog	rat
(*S*)-**10**	0.06	0.16	5.2
fenofibrate	41	50	49

[a] Compounds were screened for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CHO-K1 cells as described. EC_{50} value is the molar concentration of the test compound that causes 50% of the maximal reporter activity. $n = 3$.

preferentially over human PPARα.[35] 5,8,11,14-Eicosatetraynoic acid (ETYA) showed the reverse preference; i.e., it is 10-fold more effective on human PPARα than rodent PPARα. On the other hand, clofibric acid and fenofibric acid, which are active metabolites of the fibrate class antihyperlipidemic agents clofibrate and fenofibrate, respectively, did not show clear species differences. Therefore, three types of PPARα activators have been identified to date, i.e., rodent-selective, human-selective, and non-species-selective PPARα activators. For clinical application, the human PPARα selective nature would be preferred, so we evaluated the species-selective PPARα transactivation profile of (*S*)-**10**.

As can be seen from Table 4, (*S*)-**10** activated human, dog, and rat PPARα with EC_{50} values of 0.06, 0.16, and 5.2 μM, respectively. Thus, to our surprise, (*S*)-**10** showed species preference for humans and the transactivation activity of (*S*)-**10** for PPARα was approximately 100-fold and 30-fold less potent in rats than in humans and dogs, respectively.

The (*S*)-**10** was thus proved to be a highly potent, subtype-selective, and species-selective PPARα activator. It exhibited potent activity on human PPARα, with a higher species selectivity over rats than ETYA.

Although the reason (*S*)-**10** exhibits human selectivity is not yet known, we speculate that the species-dependent differences in activation by (*S*)-**10** may be related to different affinities of (*S*)-**10** for the three different PPARα receptors. To understand the situation at the molecular level, mutational studies using chimeric PPARα are in progress.

In Vivo Pharmacology. To determine the ability of (*S*)-**10** to impact lipid/cholesterol homeostasis, normal rats were used to investigate the effects of (*S*)-**10** on the serum levels of triglyceride, free fatty acid, total cholesterol, and the sum of LDL and VLDL cholesterol. When administered orally to normal rats ($N = 5$) once a day for 5 days, (*S*)-**10** (0.3, 3, and 30 mg/kg) lowered the serum levels of triglyceride (−1%, 26%, and 33%), free fatty acid (11%, 27%, and 72%), total cholesterol (19%, 26%, and 32%), and the sum of LDL and VLDL cholesterol (46%, 56%, and 58%) in a dose-dependent fashion (Table 5). Upon withdrawal of (*S*)-**10**, the serum levels of all parameters recovered to the pretreatment levels (data not shown). The finding that (*S*)-**10** effectively lowered both triglyceride and total cholesterol indicates that (*S*)-**10** might have therapeutic advantages over statins in the treatment of hyperlipidemia and atherosclerosis, since currently marketed statins do not effectively lower serum triglyceride.

Since PPARα is highly expressed in the liver[1] and is a potent activator of hepatic fatty acid oxidation, we investigated whether activation of PPARα by (*S*)-**10** might be a possible option to treat obesity-related steatosis and associated complications. As can be seen from Table 6, oral dosing of (*S*)-**10** (30 mg/kg) for 5 days to fructose-fed fatty-liver rats effectively lowered the hepatic levels of both triglyceride (by 80%) and total cholesterol (by 50%). The effect was much more potent than that of a representative fibrate, bezafibrate (30 mg/kg).

Table 5. Influence of (*S*)-**10** on Serum Lipid Parameters in Rats

treatment	% reduction after 5 days of oral dosing[a] TG	FFA	total cholesterol	LDL, VLDL cholesterol
0.3 mg/kg	15	12	22	29
3 mg/kg	25	28	29	58
30 mg/kg	56	69	35	60
bezafibrate, 30 mg/kg	41	46	27	22

[a] Data represent the mean of the percent reduction. $N = 5$ or 6. Normal SD rats were treated as descried in the text. Blood samples from animals in the fed state were analyzed for triglycerides (TG), free fatty acids (FFA), total cholesterol, and LDL, VLDL cholesterol.

In summary, we have developed the potent human PPARα selective activator (*S*)-**10**, which possesses much more potent PPARα transactivation activity with higher selectivity for PPARα over other PPAR isoforms compared to those of classical fibrates. Further in vivo pharmacological evaluation of (*S*)-**10** and related compounds is underway.

Experimental Section

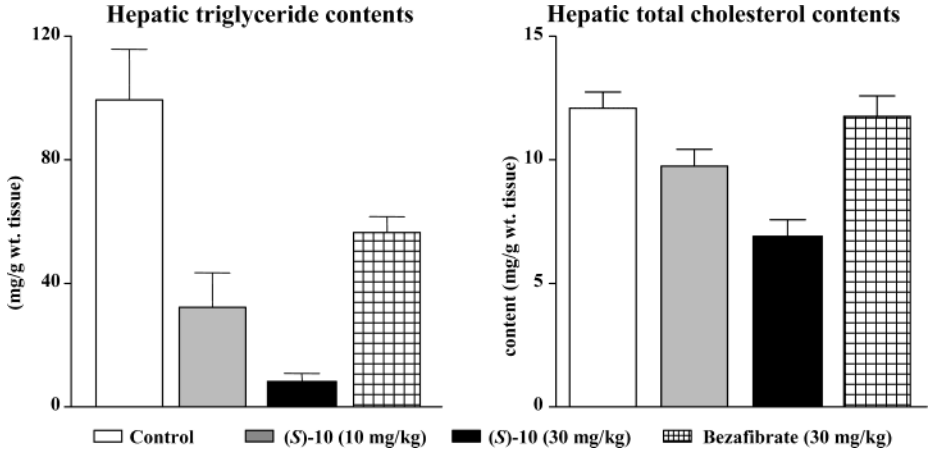
General. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS and the solvent peak as internal standards, on a JEOL JMN-A400 spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-HX110 spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel $60F_{254}$ plates, and the compounds were visualized by UV illumination (254 nm) or by heating after spraying with phosphomolybdic acid in ethanol. Elemental analysis was performed in the microanalytical laboratory of Kyorin Pharmaceutical Co., Ltd.

Chemicals. Syntheses and physicochemical properties of **30**−**32** were described previously.[9]

Ethyl (3-Benzyloxycarbonyl-4-methoxyphenyl)-2-ethylacrylate (7). Sodium hydride (214 mg, 5.35 mmol; 60% oil dispersion) was suspended in 10 mL of dehydrated tetrahydrofuran under argon and cooled with ice. Triethyl 2-phosphonobutyrate (1.34 g, 5.31 mmol) dissolved in 20 mL of dehydrated tetrahydrofuran was added dropwise. When the addition was completed, the mixture was stirred for 1 h, and then benzyl 5-formyl-2-methoxybenzoate (1.44 g, 5.33 mmol) dissolved in 25 mL of dehydrated tetrahydrofuran was added dropwise. When the addition was completed, the mixture was stirred for a further 4.5 h at room temperature and then poured into ice/water. The whole was extracted with ethyl acetate, and the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 5:1 v/v) to afford 1.45 g (74%) of the title compound as a yellow oil.

This product (4.00 g, 10.9 mmol) was dissolved in 200 mL of ethanol, 10% palladium on carbon (1.10 g) was added, and hydrogenation was carried out for 3 h at an initial pressure of 353 kPa. After completion of the reaction, the catalyst was removed by filtration and the filtrate was concentrated to

Table 6. Influence of(*S*)-**10** on Serum Total Cholesterol and Triglyceride Levels in Rats[a]



[a] Data represent the mean ± SE. $N = 5$. Fructose diet fed SD rats were treated as described in the text. Heparic triglycerides and total cholesterol accumulation were measured in rats given the fructose diet with or without the indicated treatment.

afford 3.0 g (98%) of ethyl 3-(3-carboxy-4-methoxyphenyl)-2-ethylpropionate as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.3$ Hz), 1.18 (3H, t, $J = 7.3$ Hz), 1.52−1.59 (1H, m), 1.59−1.70 (1H, m), 2.55−2.61 (1H, m), 2.76 (1H, dd, $J = 14.2$, 6.4 Hz), 2.92 (1H, dd, $J = 14.2$, 6.4 Hz), 4.03−4.12 (2H, m), 4.06 (3H, s), 6.97 (1H, d, $J = 8.8$ Hz), 7.38 (1H, dd, $J = 8.8$, 2.4 Hz), 8.00 (1H, d, $J = 2.4$ Hz); low-resolution MS (EI$^+$) *m/e* 280 (M^+).

Ethyl 3-(3-carboxy-4-methoxyphenyl)-2-ethylpropionate (5.00 g, 17.8 mmol) was dissolved in 80 mL of dehydrated dichloromethane, and the solution was cooled to −10 to −15 °C. Triethylamine (6.21 mL, 44.5 mmol) was added under stirring, followed by the addition of ethyl chlorocarbonate (1.86 mL, 19.5 mmol) dissolved in 10 mL of dehydrated dichloromethane. The mixture was stirred for 10 min at −10 °C, and then 4-(trifluoromethyl)benzylamine (2.51 mL, 17.8 mmol) dissolved in 10 mL of dehydrated dichloromethane was added dropwise. Stirring was continued for 30 min at −10 °C and then for 7 h at room temperature, and finally, the mixture was left to stand overnight. It was washed with aqueous citric acid, aqueous sodium hydrogen carbonate and brine and then dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from a mixed solvent of *n*-hexane and ethyl acetate to afford 7.20 g (93%) of ethyl 2-ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-propionate as colorless crystals: mp 77.5−79.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, $J = 7.3$ Hz), 1.18 (3H, t, $J = 7.3$ Hz), 1.51−1.69 (2H, m), 2.54−2.61 (1H, m), 2.75 (1H, dd, $J = 13.7$, 6.8 Hz), 2.92 (1H, dd, $J = 13.7$, 8.8 Hz), 3.92 (3H, s), 4.04−4.12 (2H, m), 4.73 (2H, d, $J = 5.9$ Hz), 6.89 (1H, d, $J = 8.8$ Hz), 7.25−7.28 (1H, m), 7.47 (2H, d, $J = 7.8$ Hz), 7.59 (2H, d, $J = 8.3$ Hz), 8.06 (1H, d, $J = 2.4$ Hz), 8.30 (1H, t, $J = 5.4$ Hz); low-resolution MS (EI+) *m/z* 437 (M^+).

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]-methyl]carbamoyl]phenyl]propanoic Acid (10). Ethyl 2-ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]-carbamoyl]phenyl]propionate (1.26 g, 2.88 mmol), 15 mL of ethanol, and 15 mL of 1 M aqueous solution of sodium hydroxide were stirred for 4 h at 50 °C, and then the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water and acidified with diluted HCl. The precipitate formed was collected by filtration, dried, and recrystallized from ethyl acetate to afford 1.26 g (95%) of the title compound as colorless prisms: mp 144.5−146.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, $J = 7.3$ Hz), 1.53−1.72 (2H, m), 2.59−2.66 (1H, m), 2.77 (1H, dd, $J = 13.7$, 6.8 Hz), 2.96 (1H, dd, $J = 13.7$, 8.3 Hz), 3.92 (3H, s), 4.73 (2H, d, $J = 5.9$ Hz), 6.90 (1H, d, $J = 8.3$ Hz), 7.29 (1H, dd, $J = 8.3$, 2.4 Hz), 7.47 (2H, d, $J = 8.3$ Hz), 7.59 (2H, d, $J = 7.8$ Hz), 8.08 (1H, d, $J = 2.4$ Hz), 8.32 (1H, t, $J = 5.9$ Hz); low-resolution MS (EI$^+$) *m/e* 409 (M^+). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]propanoic Acid (8). This compound was prepared using the same procedures as described for the preparation of **10**: mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (2H, t, $J = 7.8$ Hz), 2.96 (2H, t, $J = 7.8$ Hz), 3.93 (3H, s), 4.74 (2H, d, $J = 5.9$ Hz), 6.92 (1H, d, $J = 8.8$ Hz), 7.33 (1H, dd, $J = 8.3$, 2.4 Hz), 7.47 (2H, d, $J = 7.8$ Hz), 7.59 (2H, d, $J = 7.8$ Hz), 8.09 (1H, d, $J = 2.4$ Hz), 8.33 (1H, t, $J = 5.9$ Hz); low-resolution MS (EI$^+$) *m/e* 381 (M^+). Anal. ($C_{19}H_{18}F_3NO_4$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-2-methylpropanoic Acid (9). This compound was prepared using the same procedures as described for the preparation of **10**: mp 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, $J = 6.9$ Hz), 2.67−2.83 (2H, m), 3.05 (1H, dd, $J = 6.4$, 13.2 Hz), 3.93 (3H, s), 4.73 (2H, d, $J = 5.9$ Hz), 6.92 (1H, d, $J = 8.3$ Hz), 7.30 (1H, dd, $J = 2.4$, 8.3 Hz), 7.47 (2H, d, $J = 8.3$ Hz), 7.59 (2H, d, $J = 8.3$ Hz), 8.08 (1H, d, $J = 2.4$ Hz), 8.32 (1H, t, $J = 5.9$ Hz); low-resolution MS (EI$^+$) *m/e* 395 (M^+). Anal. ($C_{20}H_{20}F_3NO_4$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-2-*n*-propylpropanoic Acid (11). This compound was prepared using the same procedures as described for the preparation of **10**: mp 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28−1.53 (3H, m), 1.60−1.69 (1H, m), 2.66−2.73 (1H, m), 2.77 (1H, dd, $J = 13.7$, 6.4 Hz), 2.95 (1H, dd, $J = 13.7$, 8.3 Hz), 3.92 (3H, s), 4.73 (2H, d, $J = 5.9$ Hz), 6.90 (1H, d, $J = 8.8$ Hz), 7.29 (1H, dd, $J = 8.3$, 2.4 Hz), 7.47 (2H, d, $J = 7.8$ Hz), 7.59 (2H, d, $J = 7.8$ Hz), 8.08 (1H, d, $J = 2.4$ Hz), 8.32 (1H, t, $J = 5.9$ Hz); low-resolution MS (EI$^+$) *m/e* 423 (M^+). Anal. ($C_{22}H_{24}F_3NO_4$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-2-isopropylpropanoic Acid (12). This compound was prepared using the same procedures as described for the preparation of **10**: mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, $J = 6.4$ Hz), 1.05 (3H, d, $J = 6.9$ Hz), 1.92−2.01 (1H, m), 2.51 (1H, q, $J = 7.3$ Hz), 2.86 (2H, d, $J = 7.3$ Hz), 3.91 (3H, s), 4.72 (2H, d, $J = 5.9$ Hz), 6.88 (1H, d, $J = 8.3$ Hz), 7.29 (1H, dd, $J = 8.3$, 2.4 Hz), 7.46 (2H, d, $J = 8.3$ Hz), 7.59 (2H, d, $J = 7.8$ Hz), 8.07 (1H, d, $J = 2.4$ Hz), 8.31 (1H, t, $J = 5.9$ Hz); low-resolution MS (EI$^+$) *m/e* 423 (M^+). Anal. ($C_{22}H_{24}F_3NO_4$) C, H, N.

2-*n*-Butyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]methyl]carbamoyl]phenyl]propanoic Acid (13). This compound was prepared using the same procedures as described for the preparation of **10**: mp 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25−1.39 (4H, m), 1.47−1.56 (1H, m), 1.61−1.72 (1H, m), 2.64−2.71 (1H, m), 2.78 (1H, dd, $J = 13.7$, 6.4 Hz), 2.95 (1H, dd, $J = 13.7$, 8.3 Hz), 3.92 (3H, s), 4.73 (2H, d, $J = 5.9$ Hz), 6.90 (1H, d, $J = 8.3$ Hz), 7.29 (1H, dd, $J = 8.3$, 2.5 Hz), 7.47 (2H, d, $J = 8.3$ Hz), 7.59 (2H, d, $J = 8.3$ Hz),

8.07 (1H, d, J = 2.5 Hz), 8.32 (1H, t, J = 5.9 Hz); low-resolution MS (EI^+) *m/e* 437 (M^+). Anal. ($C_{23}H_{26}F_3NO_4$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-2-phenylpropanoic Acid (14). This compound was prepared using the same procedures as described for the preparation of **10**: mp 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (1H, dd, J = 13.7, 6.8 Hz), 3.39 (1H, dd, J = 13.7, 8.8 Hz), 3.87−3.90 (1H, m), 3.88 (3H, s), 4.71 (2H, d, J = 5.9 Hz), 6.81 (1H, d, J = 8.3 Hz), 7.16 (1H, dd, J = 8.3, 2.5 Hz), 7.23−7.32 (5H, m), 7.45 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz), 8.09 (1H, d, J = 2.5 Hz), 8.29 (1H, t, J = 5.9 Hz); low-resolution MS (EI^+) *m/e* 457 (M^+). Anal. ($C_{25}H_{22}F_3NO_4$) C, H, N.

2-Methoxy-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]methyl]carbamoyl]phenyl]propanoic Acid (15). This compound was prepared using the same procedures as described for the preparation of **10**: mp 161−163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.84 (1H, dd, J = 14.2, 7.8 Hz), 2.95 (1H, dd, J = 14.2, 4.9 Hz), 3.23 (3H, s), 3.89 (3H, s), 3.88−3.92 (1H, m), 4.57 (2H, d, J = 6.4 Hz), 7.07 (1H, d, J = 8.3 Hz), 7.33 (1H, dd, J = 8.3, 2.4 Hz), 7.54 (2H, d, J = 8.3 Hz), 7.61 (1H, d, J = 2.4 Hz), 7.70 (2H, d, J = 7.8 Hz), 8.81 (1H, t, J = 6.4 Hz), 12.74 (1H, br); low-resolution MS (EI^+) *m/e* 411 (M^+). Anal. ($C_{20}H_{20}F_3NO_5$) C, H, N.

2-Ethoxy-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]methyl]carbamoyl]phenyl]propanoic Acid (16). This compound was prepared using the same procedures as described for the preparation of **10**: mp 146−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (3H, t, J = 6.8 Hz), 2.82 (1H, dd, J = 14.2, 7.8 Hz), 2.93 (1H, dd, J = 14.2, 4.9 Hz), 3.26−3.33 (1H, s), 3.52 (1H, dq, J = 9.3, 6.8 Hz), 3.88 (3H, s), 3.96 (1H, dd, J = 7.8, 4.9 Hz), 4.57 (2H, d, J = 5.9 Hz), 7.07 (1H, d, J = 8.8 Hz), 7.34 (1H, dd, J = 8.8, 2.4 Hz), 7.54 (2H, d, J = 7.8 Hz), 7.63 (1H, d, J = 2.4 Hz), 7.70 (2H, d, J = 8.3 Hz), 8.81 (1H, t, J = 5.9 Hz), 12.67 (1H, br); low-resolution MS (EI^+) *m/e* 425 (M^+). Anal. ($C_{21}H_{22}F_3NO_5$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-2-phenoxypropanoic Acid (17). This compound was prepared using the same procedures as described for the preparation of **10**: mp 142−143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.12 (1H, dd, J = 14.2, 7.8 Hz), 3.18 (1H, dd, J = 14.2, 4.9 Hz), 3.88 (3H, s), 4.57 (2H, d, J = 6.4 Hz), 4.89 (1H, dd, J = 5.8, 4.9 Hz), 6.83 (2H, d, J = 8.8 Hz), 6.92 (1H, t, J = 7.3 Hz), 7.09 (1H, d, J = 8.3 Hz), 7.24 (1H, dd, J = 8.8, 7.3 Hz), 7.44 (1H, dd, J = 8.8, 2.4 Hz), 7.54 (2H, d, J = 8.3 Hz), 7.69 (2H, d, J = 8.3 Hz), 7.72 (1H, d, J = 2.4 Hz), 8.81 (1H, t, J = 6.4 Hz), 13.12 (1H, br); low-resolution MS (FAB$^+$) *m/e* 474 $(M + H)^+$. Anal. ($C_{25}H_{22}F_3NO_5$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[4-(trifluoromethyl)phenyl]-carbamoyl]phenyl]propanoic Acid (18). This compound was prepared using the same procedures as described for the preparation of **10**: mp 141−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.56−1.72 (2H, m), 2.60−2.67 (1H, m), 2.80 (1H, dd, J = 14.2, 8.3 Hz), 2.98 (1H, dd, J = 14.2, 8.3 Hz), 4.05 (3H, s), 6.96 (1H, d, J = 8.3 Hz), 7.34 (1H, dd, J = 8.3, 2.4 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.79 (2H, d, J = 8.8 Hz), 8.10 (1H, d, J = 2.0 Hz), 10.0 (1H, s); low-resolution MS (EI^+) *m/e* 395(M^+). Anal. ($C_{20}H_{20}F_3NO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[2-[4-(trifluoromethyl)-phenyl]ethyl]carbamoyl]phenyl]propanoic Acid (19). This compound was prepared using the same procedures as described for the preparation of **10**: mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.8 Hz), 1.54−1.70 (2H, m), 2.58−2.65 (1H, m), 2.76 (1H, dd, J = 13.7, 8.3 Hz), 2.94 (1H, dd, J = 13.7, 8.3 Hz), 2.99 (2H, t, J = 6.8 Hz), 3.72 (3H, s), 3.73 (2H, m), 6.83 (1H, d, J = 8.3 Hz), 7.24 (1H, d, J = 2.4 Hz), 7.37 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz), 7.89 (1H, t, J = 4.9 Hz), 8.04 (1H, d, J = 2.4 Hz); low-resolution MS (EI^+) *m/e* 423 (M^+). Anal. ($C_{22}H_{24}F_3NO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-methyl-*N*-[[4-(trifluoro-methyl)phenyl]methyl]carbamoyl]phenyl]propanoic Acid (20). This compound (2:1 mixture of the geometric isomers) was prepared using the same procedures as described for the preparation of **10**: foam; low-resolution MS (EI^+) *m/e* 423 (M^+). Anal. ($C_{22}H_{24}F_3NO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-(benzyl)carbamoyl]phenyl]-propanoic Acid (65). This compound was prepared using the same procedures as described for the preparation of **10**: mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.55−1.70 (2H, m), 2.59−2.67 (1H, m), 2.77 (1H, dd, J = 13.7, 6.8 Hz), 2.96 (1H, dd, J = 13.7, 6.8 Hz), 3.88 (3H, s), 4.69 (2H, d, J = 5.4 Hz), 6.88 (1H, d, J = 8.8 Hz), 7.27−7.29 (2H, m), 7.32−7.37 (4H, m), 8.09 (1H, d, J = 2.4 Hz), 8.23 (1H, br); low-resolution MS (EI^+) *m/e* 341 (M^+). Anal. ($C_{20}H_{23}NO_4 \cdot {}^1/_2H_2O$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[(4-chlorophenyl)methyl]-carbamoyl]phenyl]propanoic Acid (66). This compound was prepared using the same procedures as described for the preparation of **10**: mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.56−1.69 (2H, m), 2.61−2.64 (1H, m), 2.77 (1H, dd, J = 13.7, 8.3 Hz), 2.95 (1H, dd, J = 13.7, 8.3 Hz), 3.90 (3H, s), 4.63 (2H, d, J = 5.9 Hz), 7.27−7.32 (5H, m), 8.06 (1H, d, J = 2.4 Hz), 8.23 (1H, t, J = 5.9 Hz); low-resolution MS (EI^+) *m/e* 375 (M^+). Anal. ($C_{20}H_{22}ClNO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[3-(trifluoromethyl)phenyl]-methyl]carbamoyl]phenyl]propanoic Acid (67). This compound was prepared using the same procedures as described for the preparation of **10**: mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.6 Hz), 1.55−1.721 (2H, m), 2.62−2.67 (1H, m), 2.78 (1H, dd, J = 13.7, 6.3 Hz), 2.96 (1H, dd, J = 13.7, 7.8 Hz), 3.92 (3H, s), 4.73 (2H, d, J = 5.9 Hz), 6.90 (1H, d, J = 8.8 Hz), 7.29 (1H, m), 7.46 (1H, t, J = 7.8 Hz), 7.55 (2H, t, J = 7.8 Hz), 7.61 (1H, s), 8.07 (1H, d, J = 2.4 Hz), 8.28 (1H, br); low-resolution MS (EI^+) *m/e* 409 (M^+). Anal. ($C_{21}H_{22}F_3NO_4 \cdot {}^1/_3H_2O$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethoxy)-phenyl]methyl]carbamoyl]phenyl]propanoic Acid (68). This compound was prepared using the same procedures as described for the preparation of **10**: mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.55−1.70 (2H, m), 2.59−2.66 (1H, m), 2.77 (1H, dd, J = 13.7, 6.3 Hz), 2.96 (1H, dd, J = 13.8, 7.8 Hz), 3.91 (3H, s), 4.67 (2H, d, J = 5.9 Hz), 6.89 (1H, d, J = 8.3 Hz), 7.18 (1H, d, J = 8.3 Hz), 7.27−7.30 (1H, m), 7.38 (2H, d, J = 8.8 Hz), 8.08 (1H, d, J = 2.4 Hz), 8.27 (1H, t, J = 5.4 Hz); low-resolution MS (EI^+) *m/e* 425 (M^+). Anal. ($C_{21}H_{22}F_3NO_5$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[(2-methoxyphenyl)methyl]-carbamoyl]phenyl]propanoic Acid (69). This compound was prepared using the same procedures as described for the preparation of **10**: mp 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.3 Hz), 1.56−1.67 (2H, m), 2.60−2.63 (1H, m), 2.75 (1H, dd, J = 14.2, 6.8 Hz), 2.94 (1H, dd, J = 13.7, 8.3 Hz), 3.90 (6H, s), 4.66 (2H, d, J = 5.9 Hz), 6.85−6.94 (3H, m), 7.22−7.28 (2H, m), 7.34 (1H, dd, J = 7.3, 1.5 Hz), 8.06 (1H, d, J = 2.4 Hz), 8.42 (1H, br); low-resolution MS (EI^+) *m/e* 371 (M^+). Anal. ($C_{21}H_{25}NO_5 \cdot {}^1/_{10}H_2O$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[(3-methoxyphenyl)methyl]-carbamoyl]phenyl]propanoic Acid (70). This compound was prepared using the same procedures as described for the preparation of **10**: mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.57−1.69 (2H, m), 2.62−2.67 (1H, m), 2.77 (1H, dd, J = 13.7, 6.8 Hz), 2.96 (1H, dd, J = 13.7, 7.8 Hz), 3.80 (3H, s), 3.89 (3H, s), 4.66 (2H, d, J = 5.4 Hz), 6.81 (1H, dd, J = 8.3, 2.4 Hz), 6.90 (2H, d, J = 3.9 Hz), 6.94 (1H, d, J = 7.3 Hz), 7.24−7.28 (2H, m), 8.08 (1H, d, J = 2.4 Hz), 8.21 (1H, br); low-resolution MS (EI^+) *m/e* 371 (M^+). Anal. ($C_{21}H_{25}NO_5 \cdot {}^1/_2H_2O$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[(4-methoxyphenyl)methyl]-carbamoyl]phenyl]propanoic Acid (71). This compound was prepared using the same procedures as described for the preparation of **10**: mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.55−1.70 (2H, m), 2.61−2.67 (1H, m), 2.77 (1H, dd, J = 14.2, 6.8 Hz), 2.96 (1H, dd, J = 13.7, 8.3 Hz), 3.80 (3H, s), 3.87 (3H, s), 4.60 (2H, d, J = 5.4 Hz), 6.86−6.90 (3H, m), 7.25−7.30 (3H, m), 8.08 (1H, d, J = 2.4 Hz), 8.15 (1H, t, J = 5.9 Hz); low-resolution MS (EI^+) *m/e* 371 (M^+). Anal. ($C_{21}H_{25}NO_5 \cdot {}^1/_3H_2O$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[2-(phenoxy)phenyl]methyl]carbamoyl]phenyl]propanoic Acid (72). This compound was prepared using the same procedures as described for the preparation of **10**: mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.51−1.71 (2H, m), 2.57−2.64 (1H, m), 2.75 (1H, dd, J = 13.7, 6.8 Hz), 2.93 (1H, dd, J = 13.7, 8.3 Hz), 3.72 (3H, s), 4.70 (2H, d, J = 6.4 Hz), 6.82 (1H, d, J = 8.8 Hz), 6.88 (1H, dd, J = 8.3, 1.0 Hz), 6.97−7.00 (2H, m), 7.07−7.12 (2H, m), 7.22 (2H, dt, J = 8.3, 2.0 Hz), 7.29−7.34 (2H, m), 7.50 (2H, dd, J = 7.8, 2.0 Hz), 8.06 (1H, d, J = 2.5 Hz), 8.47 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) *m/e* 433 (M$^+$). Anal. ($C_{26}H_{27}NO_5$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[3-(phenoxy)phenyl]methyl]carbamoyl]phenyl]propanoic Acid (73). This compound was prepared using the same procedures as described for the preparation of **10**: mp 91−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.52−1.72 (2H, m), 2.58−2.65 (1H, m), 2.77 (1H, dd, J = 13.7, 6.8 Hz), 2.95 (1H, dd, J = 13.7, 8.3 Hz), 3.87 (3H, s), 4.66 (2H, d, J = 5.9 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.89−6.91 (1H, m), 6.99−7.02 (3H, m), 7.08−7.12 (2H, m), 7.26−7.35 (4H, m), 8.06 (1H, d, J = 2.4 Hz), 8.23 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) *m/e* 433 (M$^+$). Anal. ($C_{26}H_{27}NO_5$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(phenoxy)phenyl]methyl]carbamoyl]phenyl]propanoic Acid (74). This compound was prepared using the same procedures as described for the preparation of **10**: mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.55−1.71 (2H, m), 2.60−2.67 (1H, m), 2.78 (1H, dd, J = 13.7, 6.4 Hz), 2.96 (1H, dd, J = 13.7, 7.8 Hz), 3.90 (3H, s), 4.65 (2H, d, J = 5.4 Hz), 6.88 (1H, d, J = 8.3 Hz), 6.96−7.01 (4H, m), 7.08−7.11 (1H, m), 7.26−7.29 (1H, m), 7.31−7.35 (4H, m), 8.08 (1H, d, J = 2.5 Hz), 8.22 (1H, t, J = 5.4 Hz); low-resolution MS (EI$^+$) *m/e* 433 (M$^+$). Anal. ($C_{26}H_{27}NO_5$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(biphenylyl)]methyl]carbamoyl]phenyl]propanoic Acid (75). This compound was prepared using the same procedures as described for the preparation of **10**: mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.53−1.73 (2H, m), 2.60−2.68 (1H, m), 2.78 (1H, dd, J = 13.7, 6.9 Hz), 2.97 (1H, dd, J = 13.7, 7.8 Hz), 3.90 (3H, s), 4.72 (2H, d, J = 5.9 Hz), 6.89 (1H, d, J = 8.8 Hz), 7.28 (1H, dd, J = 8.3, 2.4 Hz), 7.32−7.36 (4H, m), 7.41−7.45 (4H, m), 7.56−7.59 (4H, m), 8.11 (1H, d, J = 2.4 Hz), 8.28 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) *m/e* 417 (M$^+$). Anal. ($C_{26}H_{27}NO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(benzyloxy)phenyl]-methyl]carbamoyl]phenyl]propanoic Acid (76). This compound was prepared using the same procedures as described for the preparation of **10**: mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.55−1.72 (2H, m), 2.59−2.67 (1H, m), 2.77 (1H, dd, J = 13.7, 6.9 Hz), 2.96 (1H, dd, J = 13.7, 8.3 Hz), 3.87 (3H, s), 4.60 (2H, d, J = 5.4 Hz), 5.06 (2H, s), 6.87 (1H, d, J = 8.3 Hz), 6.95 (2H, d, J = 8.3 Hz), 7.24−7.44 (8H, m), 8.08 (1H, d, J = 2.4 Hz), 8.16 (1H, t, J = 5.4 Hz); low-resolution MS (EI$^+$) *m/e* 447 (M$^+$). Anal. ($C_{27}H_{29}NO_5$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-[2-(phenyl)ethyl]phenyl]-methyl]carbamoyl]phenyl]propanoic Acid (77). This compound was prepared using the same procedures as described for the preparation of **10**: mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.53−1.73 (2H, m), 2.59−2.66 (1H, m), 2.78 (1H, dd, J = 13.7, 6.8 Hz), 2.91 (4H, s), 2.96 (1H, dd, J = 13.7, 8.3 Hz), 3.88 (3H, s), 4.65 (2H, d, J = 5.9 Hz), 6.88 (1H, d, J = 8.8 Hz), 7.15−7.21 (5H, m), 7.26−7.30 (5H, m), 8.09 (1H, d, J = 2.4 Hz), 8.21 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) *m/e* 445 (M$^+$). Anal. ($C_{28}H_{31}F_3NO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[*N*-[[4-[2-(phenyl)ethoxy]-phenyl]methyl]carbamoyl]phenyl]propanoic Acid (78). This compound was prepared using the same procedures as described for the preparation of **10**: mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.52−1.72 (2H, m), 2.58−2.66 (1H, m), 2.77 (1H, dd, J = 13.7, 6.8 Hz), 2.95 (1H, dd, J = 13.7, 8.3 Hz), 3.09 (2H, t, J = 7.3 Hz), 3.86 (3H, s), 4.16 (2H, t, J = 7.3 Hz), 4.59 (2H, d, J = 5.4 Hz), 6.85−6.89 (3H, m), 7.21−7.34 (8H, m), 8.07 (1H, d, J = 2.4 Hz), 8.15 (1H, t, J = 5.4 Hz); low-resolution MS (EI$^+$) *m/e* 461 (M$^+$). Anal. ($C_{28}H_{31}NO_5$) C, H, N.

Benzyl 5-Acetoxymethyl-2-methoxybenzoate (21). 5-Formyl-2-methoxybenzoic acid (1.76 g, 9.77 mmol), benzyl bromide (1.26 mL, 10.3 mmol), potassium hydrogen carbonate (2.94 g, 29.3 mmol), and 40 mL of *N*,*N*-dimethylformamide were mixed and stirred for 4 h at room temperature. Then the insolubles were removed by filteration. Ethyl acetate was added to the filtrate. It was washed with water and brine and then dried over anhydrous sodium sulfate and concentrated to afford benzyl 5-formyl-2-methoxybenzoate: mp 58.5−59.5 °C; low-resolution MS (EI$^+$) *m/e* 270 (M$^+$). This product (1.10 g, 4.07 mmol) and 30 mL of methanol were mixed and stirred under ice-cooling, and then sodium borohydride (155 mg, 4.10 mmol) was added potionwise. After being stirred for 2 h, the mixture was poured into ice−water and acidified with 1 M HCl. The whole was extracted with ethyl acetate. The extract was washed with water and brine and then dried over anhydrous sodium sulfate and concentrated to afford 1.11 g (99%) of benzyl 5-hydroxymethyl-2-methoxybenzoate. This compound and 100 mL of methylene chloride were mixed, followed by the addition of pyridine (660 μL, 8.16 mmol), acetic anhydride (460 μL, 4.88 mmol), and *N*,*N*-(dimethylamino)-pyridine (25 mg, 0.205 mmol) under stirring and ice-cooling. The mixture was stirred overnight. The mixture was washed with 1 M HCl, aqueous solution of sodium hydrogen carbonate, and brine, dried over anhydrous sodium sulfate, and concentrated to afford 1.27 g (99%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (3H, s), 3.91 (3H, s), 5.03 (2H, s), 5.35 (2H, s), 6.97 (1H, d, J = 8.3 Hz), 7.31−7.50 (6H, m), 7.83 (1H, d, J = 2.4 Hz); low-resolution MS (EI$^+$) *m/e* 314 (M$^+$).

Methyl 3-(3-Benzyloxycarbonyl-4-methoxyphenyl)-2,2-dimethylpropanoate. To a solution of **21** (630 mg, 2.00 mmol), methyl trimethylsilyldimethylketeneacetal (730 mg, 4.02 mmol), and 25 mL of methylene chloride was added magnesium perchlorate (45.0 mg, 0.202 mmol) under argon, and the mixture was stirred for 6 h at room temperature. The mixture was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 8:1 v/v) to afford 131 mg (18%) of the title compound as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (6H, s), 2.79 (2H, s), 3.56 (3H, s), 3.88 (3H, s), 5.33 (2H, s), 6.88 (1H, d, J = 8.8 Hz), 7.20 (1H, dd, J = 8.3, 2.4 Hz), 7.30−7.47 (5H, m), 7.56 (1H, d, J = 2.4 Hz); low-resolution MS (EI$^+$) *m/e* 356 (M$^+$).

Methyl 3-(3-Carboxy-4-methoxyphenyl)-2,2-dimethylpropanoate (22). To a solution of methyl 3-(3-benzyloxycarbonyl-4-methoxyphenyl)-2,2-dimethylpropionate (310 mg, 0.870 mmol) in 7 mL of a mixed solvent of ethanol and tetrahydrofuran at a ratio of 1:1 was added 10% palladium on carbon (20 mg), and hydrogenation was carried out for 5 h. After completion of the reaction, the catalyst was removed by filtration and the filtrate was concentrated to afford 290 mg (90%) of the title compound as a colorless oily product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (6H, s), 2.85 (2H, s), 3.68 (3H, s), 4.06 (3H, s), 6.96 (1H, d, J = 8.3 Hz), 7.31 (1H, dd, J = 8.3, 2.0 Hz), 7.94 (1H, d, J = 2.0 Hz), 10.46−11.00 (1H, br s); low-resolution MS (EI$^+$) *m/e* 266 (M$^+$).

Methyl 3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]-methyl]carbamoyl]phenyl]-2,2-dimethylpropanoate. By use of **22** (204 mg, 0.766 mmol), triethylamine (135 μL, 0.969 mmol), ethyl chlorocarbonate (82.0 μL, 0.843 mmol), 4-(trifluoromethyl)benzylamine (120 μL, 0.842 mmol), and 8 mL of dehydrated dichloromethane, 309 mg (95%) of the title compound was afforded as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (6H, s), 2.85 (2H, s), 3.69 (3H, s), 3.92 (3H, s), 4.73 (2H, d, J = 5.9 Hz), 6.89 (1H, d, J = 8.3 Hz), 7.20 (1H, dd, J = 8.3, 2.4 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.59 (2H, d, J = 7.8 Hz), 7.99 (1H, d, J = 2.4 Hz), 8.29 (1H, brs); low-resolution MS (EI$^+$) *m/e* 266(M$^+$).

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]-2,2-dimethylpropanoic Acid (23). By use of methyl 3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]-methyl]carbamoyl]phenyl]-2,2-dimethylpropionate (300 mg, 0.708 mmol), 5 mL of ethanol, and 2 mL of 10% aqueous solution of sodium hydroxide, 206 mg (90%) of the title compound was afforded as colorless crystals: mp 151.0−152.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06 (6H, s), 2.96 (2H, s), 3.88 (3H, s), 4.56 (2H, d, J = 6.4 Hz), 7.06 (1H, d, J = 8.8 Hz), 7.25 (1H, dd, J = 8.8, 2.4 Hz), 7.51−7.58 (2H, m), 7.70 (1H, d, J = 7.8 Hz), 8.80 (1H, t, J = 5.9 Hz), 12.24 (1H, s); low-resolution MS (EI$^+$) *m/e* 409 (M$^+$). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

2,2-Diethyl-3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]methyl]carbamoyl]phenyl]propaonic Acid (24). This compound was prepared using the same procedures as described for the preparation of **23**: mp 156−157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (6H, t, J = 7.3 Hz), 1.32−1.53 (4H, m), 2.75 (2H, s), 3.88 (3H, s), 4.56 (2H, d, J = 5.9 Hz), 7.06 (1H, d, J = 8.3 Hz), 7.22 (1H, dd, J = 8.3, 2.4 Hz), 7.52−7.56 (3H, m), 7.70 (2H, d, J = 8.3 Hz), 8.80 (1H, t, J = 5.9 Hz), 12.28 (1H, br); low-resolution MS (EI$^+$) *m/e* 437 (M$^+$). Anal. ($C_{23}H_{26}F_3NO_4$) C, H, N.

2-Methoxy-5-nitro-*N*-[[4-(trifluoromethyl)phenyl]-methyl]benzamide (26). This compound was prepared from **25**, using the same procedures as described for the preparation of **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (3H, s), 4.75 (2H, d, J = 5.9 Hz), 7.11 (1H, d, J = 8.8 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.61 (2H, d, J = 7.8 Hz), 8.05 (1H, br s), 8.36 (1H, dd, J = 8.8, 3.0 Hz), 9.12 (1H, t, J = 3.0 Hz); low-resolution MS (EI$^+$) *m/e* 354 (M$^+$).

5-Amino-2-methoxy-*N*-[[4-(trifluoromethyl)phenyl]-methyl]benzamide. This compound was prepared from 2-methoxy-5-nitro-*N*-[[4-(trifluoromethyl)phenyl]methyl]-benzamide, using the same procedures as described for the preparation of **36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 4.72 (2H, d, J = 5.9 Hz), 6.80 (1H, dd, J = 8.8, 3.0 Hz), 6.83 (1H, d, J = 8.8 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.59 (3H, m), 8.43 (1H, br s); low-resolution MS (EI$^+$) *m/e* 324 (M$^+$).

Ethyl 2-Bromo-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]propanoate. To a solution of 5-amino-2-methoxy-*N*-[[4-(trifluoromethyl)phenyl]methyl]-benzamide (7.00 g, 21.6 mmol), 85 mL of acetone, and 34 mL of methanol was added 17.5 mL of 47% hydrobromic acid, sodium nitrite (1.65 g, 23.9 mmol), and 6.2 mL of water with ice-cooling. The mixture was stirred for 10 min. To the solution was added ethyl acrylate (13.4 mL, 128 mmol) and CuO (416 mg, 2.91 mmol) at room temperature. After being stirred for 30 min, the mixture was poured into a saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The mixture was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was recrystallized to afford 683 mg (71%) of the title compound as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.26 (6H, m), 2.61−2.67 (2H, m), 2.96 (1H, dd, J = 14.2, 6.8 Hz), 3.18 (1H, dd, J = 14.2, 9.3 Hz), 3.53 (1H, dd, J = 9.3, 6.8 Hz), 3.93 (3H, s), 4.10−4.19 (2H, m), 4.73 (2H, d, J = 5.9 Hz), 6.91 (1H, d, J = 8.3 Hz), 7.32 (1H, dd, J = 8.3, 2.4 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.59 (2H, d, J = 7.8 Hz), 8.11 (1H, d, J = 2.4 Hz), 8.30 (1H, br s); low-resolution MS (EI$^+$) *m/e* 469 (M$^+$).

Ethyl 2-Ethylthio-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamyl]phenyl]propanoate. To a solution of ethyl 2-bromo-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamyl]propanoate (1.00 g, 2.05 mmol) and 56 mL of ethanol was added sodium thioethoxide (268 mg, 2.55 mmol), and the mixture was refluxed for 1.5 h. The mixture was concentrated, and water was added. The whole was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 2:1 v/v) to afford 3.40 g (43%) of the title compound as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s), 4.72 (2H, d, J = 5.9 Hz), 6.80 (1H, dd, J = 8.8, 3.0 Hz), 6.83 (1H, d, J = 8.8 Hz), 7.46 (2H, d, J = 7.8 Hz), 7.59 (3H, m), 8.43 (1H, br s); low-resolution MS (EI$^+$) *m/e* 324 (M$^+$).

2-Ethylthio-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]methyl]carbamyl]phenyl]propanoic Acid (27). This compound was prepared from ethyl 2-ethylthio-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamyl]-phenyl]propanoate, using the same procedures as described for the preparation of **10**: mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.3 Hz), 2.69 (2H, q, J = 7.3 Hz), 2.99 (1H, dd, J = 14.2, 6.3 Hz), 3.20 (1H, dd, J = 14.2, 9.3 Hz), 3.56 (1H, dd, J = 9.3, 6.3 Hz), 3.93 (3H, s), 4.73 (2H, d, J = 5.9 Hz), 6.92 (1H, d, J = 8.3 Hz), 7.35 (1H, dd, J = 8.3, 2.4 Hz), 7.46 (2H, d, J = 7.8 Hz), 7.59 (2H, d, J = 7.8 Hz), 8.12 (1H, d, J = 2.4 Hz), 8.32 (1H, br s); low-resolution MS (CI$^+$) *m/e* 442 (M + H)$^+$. Anal. ($C_{21}H_{22}F_3NO_4S$) C, H, N.

3-[4-Methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamyl]phenyl]-2-phenylthiopropanoic Acid (28). This compound was prepared using the same procedures as described for the preparation of **27**: mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (1H, dd, J = 14.2, 6.3 Hz), 3.18 (1H, dd, J = 14.2, 9.3 Hz), 3.89−3.93 (4H, m), 4.71 (2H, d, J = 5.9 Hz), 6.91 (1H, d, J = 8.3 Hz), 7.27−7.34 (4H, m), 7.44−7.46 (4H, m), 7.58 (2H, d, J = 7.8 Hz), 8.10 (1H, d, J = 2.4 Hz), 8.32 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) *m/e* 489 (M$^+$). Anal. ($C_{25}H_{22}F_3NO_4S$) C, H, N.

2-Benzylthio-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)-phenyl]methyl]carbamyl]phenyl]propanoic Acid (29). This compound was prepared using the same procedures as described for the preparation of **27**: foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (1H, dd, J = 14.2, 6.8 Hz), 3.16 (1H, dd, J = 14.2, 8.8 Hz), 3.44 (1H, dd, J = 8.8, 6.8 Hz), 3.82 (1H, d, J = 13.2 Hz), 3.86 (1H, d, J = 13.2 Hz), 3.91 (3H, s), 4.72 (2H, d, J = 5.9 Hz), 6.87 (1H, d, J = 8.8 Hz), 7.20−7.28 (6H, m), 7.46 (2H, d, J = 7.8 Hz), 7.59 (2H, d, J = 7.8 Hz), 8.03 (1H, d, J = 2.4 Hz), 8.31 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) *m/e* 503 (M$^+$). Anal. ($C_{26}H_{24}F_3NO_4S$) C, H, N.

Ethyl 3-(4-Methoxy-3-nitrophenyl)-2-ethylpropenoate (35). Sodium hydride (795 mg, 19.9 mmol) was suspended in 120 mL of dehydrated tetrahydrofuran under argon and cooled with ice. Triethyl 2-phosphonobutyrate (5.00 g, 19.8 mmol) dissolved in 30 mL of dehydrated tetrahydrofuran was added dropwise. When the addition was completed, the mixture was stirred for 1 h. Then 4-methoxy-3-nitrobenzaldehyde (3.26 g, 18.0 mmol) dissolved in 50 mL of dehydrated tetrahydrofuran was added dropwise. The mixture was stirred for 1 h at 0 °C and then for 3 h at room temperature. The reaction mixture was concentrated and mixed with ice−water. The whole was extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 8:1 and then 2:1 v/v) to afford 4.69 g (93%) of the title compound as colorless crystals (6:1 mixture of the geometric isomers): low- resolution MS (EI$^+$) *m/e* 279 (M$^+$).

Ethyl 3-(3-Amino-4-methoxyphenyl)-2-ethylpropanoate (36). Compound **35** (4.68 g, 16.8 mmol) was dissolved in a mixed solvent of 150 mL of tetrahydrofuran and ethanol (1:1 v/v), 10% palladium on carbon (1.50 g) was added, and hydrogenation was carried out at an initial pressure of 294.3 kPa. After completion of the reaction, the catalyst was removed by filtration and the filtrate was concentrated to afford 3.96 g (94%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.3 Hz), 1.19 (3H, t, J = 7.3 Hz), 1.48−1.67 (2H, m), 2.47−2.55 (1H, m), 2.59 (1H, dd, J = 13.2, 6.8 Hz), 2.81 (1H, dd, J = 13.7, 7.8 Hz), 3.72 (2H, br), 3.82 (3H, s), 4.04−4.12 (2H, m), 6.51 (1H, dd, J = 7.8, 2.9 Hz), 6.53 (1H, d, J = 2.0 Hz), 6.68 (1H, d, J = 7.8 Hz); low-resolution MS (EI$^+$) *m/e* 251 (M$^+$).

2-Ethyl-3-[4-methoxy-3-[2-[4-(trifluoromethyl)phenyl]-acetylamino]phenyl]propanoic Acid (38). 4-(Trifluoromethyl)phenylacetic acid (188 mg, 0.893 mmol) and compound **36** (224 mg, 0.891 mmol) were dissolved in 10 mL of dichloromethane. 1-[3-(Dimethylaminopropyl)]-3-ethylcarbodiimide hydrochloride (171 mg, 0.892 mmol) was added, and

the mixture stood overnight at room temperature. The mixture was washed with diluted HCl, saturated $NaHCO_3$ solution, water, and brine, dried over anhydrous sodium sulfate, and concentrated to afford ethyl 2-ethyl-3-[4-methoxy-3-[2-[4-(trifluoromethyl)phenyl]acetylamino]phenyl]propanoate as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.3 Hz), 1.17 (3H, t, J = 6.8 Hz), 1.46−1.67 (2H, m), 2.50−2.57 (1H, m), 2.66 (1H, dd, J = 13.7, 6.8 Hz), 2.86 (1H, dd, J = 13.7, 8.3 Hz), 3.75 (3H, s), 3.79 (2H, s), 4.02−4.13 (2H, m), 6.71 (1H, d, J = 8.3 Hz), 6.81 (1H, dd, J = 8.3, 2.0 Hz), 7.48 (2H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.3 Hz), 7.74 (1H, br), 8.19 (1H, d, J = 2.0 Hz); low-resolution MS (EI$^+$) *m/e* 437 (M$^+$).

This compound was hydrolyzed using the same procedures as described for the preparation of **10** to afford the title compound as a foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.50−1.69 (2H, m), 2.55−2.62 (1H, m), 2.69 (1H, dd, J = 13.7, 6.8 Hz), 2.89 (1H, dd, J = 13.7, 8.3 Hz), 3.74 (3H, s), 3.79 (2H, s), 6.92 (1H, d, J = 8.3 Hz), 6.84 (1H, dd, J = 8.3, 2.0 Hz), 7.47 (2H, d, J = 7.8 Hz), 7.64 (2H, d, J = 7.8 Hz), 7.74 (1H, br), 8.21 (1H, d, J = 2.0 Hz); low-resolution MS (EI$^+$) *m/e* 409 (M$^+$). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

2-Ethyl-3-[4-methoxy-3-[2-[4-(trifluoromethyl)phenyl]-ureido]phenyl]propanoic Acid (40). This compound was prepared from **36**, using the same procedures as described for the preparation of **38**: mp 205−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (3H, t, J = 7.3 Hz), 1.46−1.55 (2H, m), 2.37−2.44 (1H, m), 2.60 (1H, dd, J = 13.2, 6.8 Hz), 2.75 (1H, dd, J = 13.2, 8.3, Hz), 3.85 (3H, s), 6.78 (1H, dd, J = 8.3, 2.0 Hz), 6.92 (1H, d, J = 8.3 Hz), 7.63 (2H, d, J = 9.3 Hz), 7.66 (2H, d, J = 9.3 Hz), 8.01 (1H, d, J = 2.0 Hz), 8.29 (1H, s), 9.70 (1H, s), 12.07 (1H, br); low-resolution MS (EI$^+$) *m/e* 410 (M$^+$). Anal. ($C_{20}H_{21}F_3N_2O_4$) C, H, N.

Benzyl 2-Methylthio-2-(5-formyl-2-methoxyphenyl)-acetate (39). To a solution of 4-methoxybenzaldehyde (7.46 g, 57.3 mmol) and 250 mL of dichloromethane was added dropwise anhydrous tin chloride (6.49 mL, 57.3 mmol) in 100 mL of dichloromethane under argon atmosphere. When the addition was completed, the mixture was stirred for 15 min at room temperature. A mixture of ethyl 2-chloro-2-methylthioacetate (9.24 g, 54. 8 mmol) and 50 mL of 1:1 v/v mixture of dichloromethane and carbon tetrachloride was added to the mixture and refluxed for 24 h. The mixture was poured into ice−water, and the whole was extracted with dichloromethane. The extract was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 5:1 v/v) to afford 7.59 g (52%) of ethyl 2-methylthio-2-(5-formyl-2-methoxyphenyl)acetate as a yellowish oil: low-resolution MS (EI$^+$) *m/e* 268 (M$^+$). A mixture of this product (4.80 g, 17.9 mmol), 30 mL of ethanol, and 20 mL of 10% sodium hydroxide was stirred for 3 h at room temperature. The mixture was poured into ice−water, acidified with concentrated HCl, and extracted with ethyl acetate. The extract was washed with water and then dried over anhydrous sodium sulfate and concentrated to afford 4.00 g of crude 2-methylthio-2-(5-formyl-2-methoxyphenyl)acetic acid as a yellow crystal. A mixture of this product (4.00 g, 16.4 mmol), anhydrous potassium carbonate (3.71 g, 26.8 mmol), benzyl bromide (3.06 g, 17.9 mmol), and 50 mL of *N*,*N*-dimethyformamide was stirred for 5 h at room temperature. The mixture was poured into ice−water and extracted with ether. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 6:1 v/v) to afford 4.50 g (76%) of the title compound as a pale-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (3H, s), 3.82 (3H, s), 4.92 (1H, s), 5.20 (2H, s), 6.98 (1H, d, J = 8.8 Hz), 7.26−7.36 (5H, m), 7.85 (1H, dd, J = 8.8, 2.0 Hz), 8.06 (1H, d, J = 2.0 Hz), 9.88 (1H, s); low-resolution MS (EI$^+$) *m/e* 330 (M$^+$).

Benzyl 2-Methylthio-2-[5-[1-(2-ethoxycarbonyl)butenyl]-2-methoxyphenyl]acetate (41). This compound (mixture of the geometric isomers) was prepared from **39**, using the same procedures as described for the preparation of **35**: low-resolution MS (EI$^+$) *m/e* 428 (M$^+$).

Benzyl 2-[5-[1-(2-Ethoxycarbonyl)butenyl]-2-methoxyphenyl]acetate (42). To a mixture of **41** (2.14 g, 4.99 mmol) and 100 mL of acetic acid was added zinc powder (13.0 g, 199 mmol) at room temperature. The mixture was stirred for 6 h at room temperature. The insolubles were removed by filtration, and the filtrate was concentrated. The residue was redissolved in 50 mL of ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to afford 1.86 g (97%) of the title compound (mixture of the geometric isomers) as a yellow oil: low-resolution MS (EI$^+$) *m/e* 382 (M$^+$).

Ethyl 2-Ethyl-3-[4-methoxy-3-[[*N*-[4-(trifluoromethyl)-phenyl]carbamoyl]methyl]phenyl]propanoate. This compound was prepared from **42** by hydrogenolysis and amidation with 4-(trifluoromethyl)aniline using the same procedures as described for the preparation of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 1.15 (3H, t, J = 7.3 Hz), 1.50−1.72 (2H, m), 2.50−2.58 (1H, m), 2.72 (1H, dd, J = 13.7, 6.3 Hz), 2.86 (1H, dd, J = 13.7, 8.8 Hz), 3.69 (2H, s), 3.93 (3H, s), 3.99−4.11 (2H, m), 6.87 (1H, d, J = 9.3 Hz), 7.08−7.12 (1H, m), 7.52 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.89 (1H, s); low-resolution MS (EI$^+$) *m/e* 437 (M$^+$).

2-Ethyl-3-[4-methoxy-3-[[*N*-[4-(trifluoromethyl)phenyl]-carbamoyl]methyl]phenyl]propanoic Acid (46). This compound was prepared from ethyl 2-ethyl-3-[4-methoxy-3-[[*N*-[4-(trifluoromethyl)phenyl]carbamoyl]methyl]phenyl]-propanoate, using the same procedures as described for the preparation of **10**: mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.3 Hz), 1.54−1.73 (2H, m), 2.55−2.62 (1H, m), 2.74 (1H, dd, J = 14.2, 5.9 Hz), 2.88 (1H, dd, J = 14.2, 5.9 Hz), 3.68 (3H, s), 3.91 (3H, s), 6.87 (1H, d, J = 9.3 Hz), 7.11−7.14 (2H, m), 7.51 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.90 (1H, s); low-resolution MS (EI$^+$) *m/z* 409 (M$^+$). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

Ethyl 2-Ethyl-3-(4-methoxyphenyl)acrylate. This compound (mixture of the geometrical isomers) was prepared from 4-methoxybenzaldehyde, using the same procedures as described for the preparation of **36**: low-resolution MS (EI$^+$) *m/e* 234 (M$^+$).

Ethyl 2-Ethyl-3-(4-methoxyphenyl)propanoate (44). This compound was prepared from ethyl 2-ethyl-3-(4-methoxyphenyl)acrylate, using the same procedures as described for the preparation of **36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.17 (3H, t, J = 7.3 Hz), 1.49−1.69 (2H, m), 2.49−2.56 (1H, m), 2.69 (1H, dd, J = 13.7, 6.8 Hz), 2.86 (1H, dd, J = 13.7, 8.3 Hz), 3.78 (3H, s), 4.07 (1H, dq, J = 7.8, 2.0 Hz), 6.81 (2H, d, J = 8.8 Hz), 7.08 (2H, d, J = 8.3 Hz); low-resolution MS (EI$^+$) *m/e* 236 (M$^+$).

Ethyl 3-(3-Acetyl-4-methoxyphenyl)-2-ethylpropanoate (45). To a suspension of anhydrous $AlCl_3$ and 30 mL of dichloromethane was added acetyl chloride (1.00 mL, 14.1 mmol) under ice-cooling. The mixture was stirred for 30 min at ambient temperature. A mixture of **44** (2.10 g, 8.89 mmol) and 10 mL of dichloromethane was added. The mixture was stirred for 1 h at 0 °C and then for overnight at room temperature. The mixture was poured into ice−water and extracted with dichloromethane. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 6:1 v/v) to afford 1.21 g (49%) of the title compound as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.18 (3H, t, J = 7.3 Hz), 1.49−1.70 (2H, m), 2.51−2.58 (1H, m), 2.60 (3H, s), 2.71 (1H, dd, J = 13.7, 6.3 Hz), 2.88 (1H, dd, J = 13.7, 8.8 Hz), 3.89 (3H, s), 4.02−4.13 (2H, m), 6.87 (1H, d, J = 8.3 Hz), 7.26 (1H, dd, J = 8.3, 2.4 Hz), 7.54 (1H, d, J = 2.4 Hz); low-resolution MS (EI$^+$) *m/e* 278 (M$^+$).

Ethyl 3-[3-(2-Ethoxycarbonylacetyl)-4-methoxyphenyl]-2-ethylpropanoate (47). Sodium hydride (1.27 g, 52.9 mmol; 60% oil dispersion) was suspended in 20 mL of anhydrous ether at 0 °C. Then diethyl carbonate (2.25 g, 19.0 mmol) was added and the mixture was stirred for 30 min at room

temperature. A mixture of **45** (3.53 g, 12.7 mmol), 10 mL of anhydrous ether, and 0.24 mL of anhydrous ethanol was added dropwise for 20 min and refluxed for 6 h. After cooling to room temperature, the mixture was poured into a mixed solvent of 45 mL of 2 M HCl and 80 mL of ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The extract was mixed and washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 9:1 v/v) to afford 2.59 g (58%) of the title compound (mixture of the geometrical isomer) as a yellow oil: low-resolution MS (EI^+) *m/e* 350 (M^+).

Ethyl 3-[3-[2-Ethoxycarbonylacetyl-3-[4-(trifluoromethyl)phenyl]proionyl]-4-methoxyphenyl]-2-ethylpropanoate (48). To a solution of **47** (2.59 g, 7.39 mmol) and 30 mL of anhydrous tetrahydrofuran was added sodium hydride (296 mg, 7.40 mmol; 60% oil dispersion) portionwise under ice cooling and an argon atmosphere. The mixture was stirred for 20 min under ice-cooling and then for 30 min at room temperature. A mixture of 4-(trifluoromethyl)benzyl bromide (1.77 g, 7.40 mmol) and 10 mL of anhydrous tetrahydrofuran was added dropwise, and the whole was refluxed for 6 h. After the mixture was cooled to room temperature, 15 mL of 1 M HCl and 100 mL of ice−water were added, and the whole was extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 8:1 v/v) to afford 3.70 g (98%) of the title compound as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (3H, t, J = 7.3 Hz), 0.98−1.08 (6H, m), 1.45−1.55 (2H, m), 2.68−2.77 (2H, m), 3.15 (1H, dd, J = 14.2, 7.3 Hz), 3.25 (1H, dd, J = 14.2, 6.8 Hz), 3.79 (3H, s), 3.91−4.16 (2H, m), 4.68 (1H, dt, J = 7.8, 2.4 Hz), 7.07 (1H, d, J = 8.3 Hz), 7.34−7.38 (2H, m), 7.42 (2H, d, J = 7.3 Hz), 7.61 (2H, d, J = 8.3 Hz); low-resolution MS (EI^+) *m/e* 508 (M^+).

2-Ethyl-3-[3-[3-[4-(trifluoromethyl)phenyl]proionyl]-4-methoxyphenyl]propanoic acid (51). A mixture of **50** (2.62 g, 5.15 mmol), 10 mL of glacial acetic acid, and 5 mL of concentrated HCl was refluxed for 5 h. After cooling to room temperature, the mixture was poured into ice−water and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate/acetic acid = 400:100:1.5 v/v/v) to afford 1.47 g (70%) of the title compound as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.54−1.69 (2H, m), 2.54−2.61 (1H, m), 2.73 (1H, dd, J = 13.7, 6.8 Hz), 2.92 (1H, dd, J = 13.7, 7.8 Hz), 3.06 (2H, t, J = 7.3 Hz), 3.31 (2H, t, J = 7.3 Hz), 3.85 (3H, s), 6.87 (1H, d, J = 8.8 Hz), 7.28 (1H, dd, J = 8.3, 2.4 Hz), 7.34 (2H, d, J = 7.8 Hz), 7.52−7.54 (2H, m); low-resolution MS (EI^+) *m/z* 408 (M^+). Anal. ($C_{22}H_{23}F_3O_4$) C, H.

2-Ethyl-3-[3-[3-[4-(trifluoromethyl)phenyl]propyl]-4-methoxyphenyl]propanoic Acid (52). 51 (224 mg, 0.548 mmol), 30 mL of ethanol, and 250 mg of palladium on carbon was mixed, and hydrogenation was carried out at an initial hydrogen pressure of 392 kPa at room temperature for 7 h. The catalyst was removed by filtration, and the filtrate was evaporated off. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate/acetic acid = 200:100:2 v/v/v) to afford 185 mg (86%) of the title compound as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.3 Hz), 1.52−1.67 (2H, m), 1.52−1.67 (2H, m), 1.87−1.94 (2H, m), 2.53−2.71 (6H, m), 2.88 (1H, dd, J = 13.7, 7.8 Hz), 3.78 (3H, s), 6.74 (1H, d, J = 8.3 Hz), 6.92 (1H, d, J = 2.4 Hz), 6.98 (1H, dd, J = 8.3, 2.4 Hz), 7.29 (2H, d, J = 8.3 Hz), 7.52 (2H, d, J = 8.3 Hz); low-resolution MS (EI^+) *m/z* 394 (M^+). Anal. ($C_{22}H_{25}F_3O_3$) C, H.

4-Methoxy-3-[2-[4-(trifluoromethyl)phenyl]ethoxy]-benzaldehyde (50). To a solution of 2-[4-(trifluoromethyl)-phenyl]ethanol (1.59 g, 8.36 mmol), isovaniline (1.28 g, 8.41 mmol), triphenylphosphin (2.20 g, 8.39 mmol), and 50 mL of anhydrous tetrahydrofuran was added a 40% toluene solution of diethyl azodicarboxylate (3.80 mL, 8.38 mmol) under ice-cooling and an argon atmosphere. The mixture was stirred for 1 h under ice-cooling and stood overnight at room temperature. The mixture was evaporated off, and the residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 6:1 v/v) to afford 1.96 g (72%) of the title compound as a colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (2H, t, J = 6.8 Hz), 3.95 (3H, s), 4.30 (2H, t, J = 6.8 Hz), 6.99 (1H, d, J = 8.3 Hz), 7.39 (1H, d, J = 2.0 Hz), 7.43 (2H, d, J = 7.8 Hz), 7.47 (1H, dd, J = 8.3, 2.0 Hz), 7.58 (2H, d, J = 8.3 Hz), 9.83 (1H, s); low-resolution MS (EI^+) *m/e* 324 (M^+).

Ethyl 2-Ethyl-3-[4-methoxy-3-[2-[4-(trifluoromethyl)-phenyl]ethoxy]phenyl]acrylate (53). This compound (mixture of the geometrical isomer) was prepared from **50**, using the same procedures as described for the preparation of **35**: low-resolution MS (EI^+) *m/e* 422 (M^+).

Ethyl 2-Ethyl-3-[4-methoxy-3-[2-[4-(trifluoromethyl)-phenyl]ethoxy]phenyl]propanoate (54). This compound was prepared from **53**, using the same procedures as described for the preparation of **36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.3 Hz), 1.14 (3H, t, J = 7.3 Hz), 1.48−1.68 (2H, m), 2.45−2.55 (1H, m), 2.65 (1H, dd, J = 13.7, 6.8 Hz), 2.84 (1H, dd, J = 13.7, 8.8 Hz), 3.19 (2H, t, J = 6.8 Hz), 3.82 (3H, s), 3.99−4.11 (2H, m), 4.20 (2H, t, J = 6.8 Hz), 6.67 (1H, d, J = 2.0 Hz), 6.72 (1H, dd, J = 8.3, 2.0 Hz), 6.78 (1H, d, J = 7.8 Hz), 7.43 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz); low-resolution MS (EI^+) *m/e* 424 (M^+).

2-Ethyl-3-[4-methoxy-3-[2-[4-(trifluoromethyl)phenyl]-ethoxy]phenyl]propanoic Acid (57). This compound was prepared from **54**, using the same procedures as described for the preparation of **10**: mp 64−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.51−1.68 (2H, m), 2.51−2.58 (1H, m), 2.66 (1H, dd, J = 13.7, 6.8 Hz), 2.87 (1H, dd, J = 13.7, 7.8 Hz), 3.18 (2H, t, J = 7.3 Hz), 3.82 (3H, s), 4.20 (2H, t, J = 7.3 Hz), 6.68 (1H, d, J = 2.0 Hz), 6.73 (1H, dd, J = 7.8, 2.0 Hz), 6.79 (1H, d, J = 8.3 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.56 (2H, d, J = 8.3 Hz); low-resolution MS (EI^+) *m/z* 396 (M^+). Anal. ($C_{21}H_{23}F_3O_4$) C, H.

Ethyl 2-Ethyl-3-(3-formyl-4-methoxyphenyl)propanoate (55). To a solution of **44** (10.0 g, 42.3 mmol) and 500 mL of anhydrous dichloromethane was added titanium tetrachloride (35.0 mL, 318 mmol), followed by dichloromethyl methyl ether (13.4 mL, 148 mmol) at −20 °C, under an argon atmosphere. The mixture was stirred for 6 h at −20 °C. The mixture was poured into a dilute HCl solution and separated from the dichloromethane layer. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 4:1 v/v) to afford 10.9 g (97%) of the title compound as a pale-brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 1.17 (3H, t, J = 7.3 Hz), 1.49−1.71 (2H, m), 2.51−2.55 (1H, m), 2.73 (1H, dd, J = 13.7, 6.3 Hz), 2.89 (1H, dd, J = 13.7, 8.8 Hz), 3.91 (3H, s), 4.03−4.11 (2H, m), 6.90 (1H, d, J = 8.3 Hz), 7.36 (1H, dd, J = 8.3, 2.4 Hz), 7.63 (1H, d, J = 2.4 Hz), 10.44 (1H, s); low-resolution MS (EI^+) *m/e* 264 (M^+).

Ethyl 2-Ethyl-3-[3-(hydroxyimino)-4-methoxyphenyl]-propanoate (56). A mixture of **55** (1.06 g, 4.01 mmol), hydroxylamine hydrochloride (293 mg, 4.22 mmol), 1 mL of pyridine, and 20 mL of ethanol was refluxed for 6 h. After cooling to room temperature, the mixture was concentrated and redissolved in ethyl acetate, washed with 1 M HCl, saturated sodium hydrogen carbonate, and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 6:1 v/v) to afford 1.00 g (89%) of the title compound as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.17 (3H, t, J = 7.3 Hz), 1.51−1.68 (2H, m), 2.51−2.58 (1H, m), 2.69 (1H, dd, J = 13.7, 6.8 Hz), 2.87 (1H, dd, J = 13.7, 8.3 Hz), 3.83 (3H, s), 4.04−4.11 (2H, m), 6.81 (1H, d, J = 8.3 Hz), 7.15 (1H, dd, J = 8.3, 2.4 Hz), 7.51 (1H, s), 8.46 (1H, s); low-resolution MS (EI^+) *m/e* 279 (M^+).

Ethyl 3-[3-(Aminomethyl)-4-methoxyphenyl]-2-ethyl-propanoate Hydrochloride (58). This compound was pre-

pared from **56**, using the same procedures as described for the preparation of **36**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (3H, t, J = 7.3 Hz), 1.12 (3H, t, J = 7.3 Hz), 1.47−1.54 (2H, m), 2.50−2.57 (1H, m), 2.64 (1H, dd, J = 13.7, 6.3 Hz), 2.78 (1H, dd, J = 13.7, 8.3 Hz), 3.80 (3H, s), 3.91 (2H, s), 3.97−4.09 (2H, m), 6.97 (1H, d, J = 8.8 Hz), 7.17 (1H, d, J = 8.3 Hz), 7.21 (1H, s), 8.22 (2H, br s); low-resolution MS (EI$^+$) m/e 265 (M$^+$).

3-[3-[4-(Trifluoromethyl)benzoylaminomethyl]-4-methoxyphenyl]-2-ethylpropanoic Acid (62). This compound was prepared from **58**, using the same procedures as described for the preparation of **10**: mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.54−1.70 (2H, m), 2.51−2.59 (1H, m), 2.71 (1H, dd, J = 13.7, 6.3 Hz), 2.88 (1H, dd, J = 13.7, 8.3 Hz), 3.85 (3H, s), 4.58 (2H, d, J = 5.9 Hz), 6.78−6.82 (2H, m), 7.10 (1H, dd, J = 8.3, 2.4 Hz), 7.16 (2H, d, J = 2.4 Hz), 7.56 (2H, d, J = 8.3 Hz), 7.85 (2H, d, J = 8.3 Hz); low-resolution MS (EI$^+$) m/z 409 (M$^+$). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

Ethyl 2-Ethyl-3-[3-[4-(trifluoromethyl)benzylaminomethyl]-4-methoxyphenyl]propanoate. To a solution of **58** (203 mg, 0.673 mmol) and 4 mL of *N*,*N*-dimethyformamide was added potassium carbonate (232 mg, 1.68 mmol) and 4-(trifluoromethyl)benzyl bromide (169 mg, 0.707 mmol). The mixture was stirred for 3 h at room temperature and then for 4 h at 60 °C. After cooling to room temperature, the mixture was poured into ice−water and the whole was extracted with ether. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 2:1 v/v) to afford 92.3 mg (32%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.17 (3H, t, J = 7.3 Hz), 1.50−1.70 (2H, m), 2.50−2.57 (1H, m), 2.68 (1H, dd, J = 13.7, 6.8 Hz), 2.87 (1H, dd, J = 13.1, 8.3 Hz), 3.76 (2H, s), 3.80 (3H, s), 3.81 (2H, s), 4.01−4.13 (2H, m), 6.77 (1H, d, J = 8.3 Hz), 7.01−7.05 (2H, m), 7.47 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 8.3 Hz); low-resolution MS (EI$^+$) m/e 424 (M$^+$).

2-Ethyl-3-[3-[4-(trifluoromethyl)benzylaminomethyl]-4-methoxyphenyl]propanoic Acid (64). This compound, obtained as an oil, was prepared from ethyl 2-ethyl-3-[3-[4-(trifluoromethyl)benzylaminomethyl]-4-methoxyphenyl]propanoate, using the same procedures as described for the preparation of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.3 Hz), 1.54−1.61 (1H, m), 1.71−1.78 (1H, m), 2.52−2.57 (1H, m), 2.71−2.83 (2H, m), 3.72 (3H, s), 3.88−3.98 (4H, m), 6.67 (1H, d, J = 8.8 Hz), 7.10 (1H, dd, J = 8.8, 2.0 Hz), 7.30 (1H, d, J = 2.0 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.71 (2H, d, J = 8.3 Hz); low-resolution MS (EI$^+$) m/z 394 (M$^+$). Anal. ($C_{21}H_{24}F_3NO_3$ HCl) C, H, N.

[3(2*S*),4*S*]-3-[2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]propionyl]-4-benzyloxazolidin-2-one (59). Racemic **10** (26.8 g, 65.6 mmol) and 34 mL of dehydrated tetrahydrofuran were mixed under an argon atmosphere, and triethylamine (9.14 mL, 65.8 mmol) and pivaloyl chloride (8.07 mL, 65.6 mmol) were added dropwise with ice-cooling. The mixture was stirred for 1.5 h at room temperature to afford the mixed acid anhydride derivative. In another vessel, potassium *tert*-butoxide (8.83 g, 78.7 mmol) and 88 mL of dehydrated tetrahydrofuran were mixed under an argon atmosphere and (*S*)-4-benzyloxazolidin-2-one (13.9 g, 78.7 mmol) dissolved in 70 mL of dehydrated tetrahydrofuran was added dropwise. The mixture was stirred for 45 min. Then, the suspension of the mixed acid anhydride derivative described above was added dropwise. The reaction mixture was concentrated, poured into water, and extracted with ethyl acetate. The extract was washed with 5% HCl, saturated sodium hydrogen carbonate, and brine and then dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluant, *n*-hexane/ethyl acetate = 3:2 v/v and then methylene chloride/methanol = 15:1 v/v) and recrystallized from diisopropyl ether and ether to afford 5.62 g (15%) of the title compound as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.56−1.67 (1H, m), 1.78−1.87 (1H, m), 2.70 (1H, dd, J = 13.2, 9.8 Hz), 2.78 (1H, dd, J = 13.7, 6.4 Hz), 3.00 (1H, dd, J = 13.7, 8.3 Hz), 3.29 (1H, dd, J = 13.2, 2.9 Hz), 3.92 (3H, s), 3.98−4.07 (3H, m), 4.61−4.67 (1H, m), 4.71 (2H, d, J = 5.9 Hz), 6.91 (1H, d, J = 8.8 Hz), 7.20−7.38 (6H, m), 7.44 (2H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.3 Hz), 8.00 (1H, d, J = 2.4 Hz), 8.24 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) m/z 568 (M$^+$).

(+)-2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]propanoic Acid ((+)-10). 59 (90.9 g, 0.160 mol) was dissolved in 802 mL of a mixed solvent of tetrahydrofuran and water (4:1 v/v) under an argon atmosphere with ice-cooling. To this solution was added 30% aqueous hydrogen peroxide (63.7 mL, 0.630 mol). Then lithium hydroxide monohydrate (10.7 g, 0.256 mol) dissolved in 267 mL of water was added, and the mixture was stirred further for 1 h under ice-cooling. Sodium hydrogen sulfite (64%, 102 g, 0.627 mol) dissolved in 401 mL of water was added dropwise. The reaction mixture was concentrated, poured into ice−water, acidified with 5% HCl, and then extracted with methylene chloride. The extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was dissolved in ethyl acetate and *n*-hexane and allowed to stand. The precipitated crystals were collected by filtration and dried. A second crop of crystals was obtained from the filtrate. The first and second crops were combined, washed with a mixed solvent of *n*-hexane and ethyl acetate (4:1 v/v), and dried to afford 52.4 g (80%) of the title compound as a colorless crystalline powder: mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, dd, J = 7.3, 7.3 Hz), 1.54−1.70 (2H, m), 2.58−2.65 (1H, m), 2.77 (1H, dd, J = 13.7, 6.3 Hz), 2.96 (1H, dd, J = 13.7, 8.3 Hz), 3.92 (3H, s), 4.38 (1H, br s), 4.72 (2H, d, J = 5.9 Hz), 6.90 (1H, d, J = 8.3 Hz), 7.29 (1H, dd, J = 8.3, 2.4 Hz), 7.46 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz), 8.07 (1H, d, J = 2.4 Hz), 8.34 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) m/z 409 (M$^+$); $[\alpha]_D$ +24° (*c* 0.8, MeOH). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

(−)-2-Ethyl-3-[4-methoxy-3-[*N*-[[4-(trifluoromethyl)phenyl]methyl]carbamoyl]phenyl]propanoic Acid ((−)-10). This compound was prepared from racemic **10**, using the same procedures as described for the preparation of (+)-**10**: mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, dd, J = 7.3, 7.3 Hz), 1.54−1.70 (2H, m), 2.58−2.65 (1H, m), 2.77 (1H, dd, J = 13.7, 6.3 Hz), 2.96 (1H, dd, J = 13.7, 8.3 Hz), 3.92 (3H, s), 4.38 (1H, br s), 4.72 (2H, d, J = 5.9 Hz), 6.90 (1H, d, J = 8.3 Hz), 7.29 (1H, dd, J = 8.3, 2.4 Hz), 7.46 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz), 8.07 (1H, d, J = 2.4 Hz), 8.34 (1H, t, J = 5.9 Hz); low-resolution MS (EI$^+$) m/z 409 (M$^+$); $[\alpha]_D$ −24° (*c* 0.8, MeOH). Anal. ($C_{21}H_{22}F_3NO_4$) C, H, N.

(*R*)-3-(1-Butyryl)-4-benzyloxazolidin-2-one (79). Potassium *tert*-butoxide (6.18 g, 55.1 mmol) and 100 mL of dehydrated tetrahydrofuran were mixed under an argon atmosphere, and (*R*)-4-benzyloxazolidin-2-one (8.86 g, 50.0 mmol) dissolved in 100 mL of dehydrated tetrahydrofuran was added dropwise under stirring and cooling with ice. The mixture was stirred for 30 min under cooling with ice, and then *n*-butyryl chloride (5.20 mL, 50.1 mmol) dissolved in 40 mL of dehydrated tetrahydrofuran was added dropwise. After completion of the addition, the mixture was stirred for 1 h and a saturated aqueous solution of ammonium chloride was added. The whole was extracted with ethyl acetate. The organic solution was washed with water, saturated sodium hydrogen carbonate, and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (eluant, *n*-hexane/ethyl acetate = 5:1 v/v) to afford 9.63 g (78%) of the title compound as a pale-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.3 Hz), 1.73 (2H, m), 2.77 (1H, dd, J = 13.9, 9.8 Hz), 2.84−3.00 (2H, m), 3.30 (1H, dd, J = 13.2, 3.4 Hz), 4.15−4.22 (2H, m), 4.68 (1H, m), 7.20−7.36 (2H, m); low-resolution MS (EI$^+$) m/z 247 (M$^+$).

[3(2*S*),4*R*]-3-[2-Ethyl-3-[4-methoxy-3-(benzyloxycarbonyl)phenyl]propionyl]-4-benzyloxazolidin-2-one (80). (*R*)-3-(1-Butyryl)-4-benzyloxazolidin-2-one (3.37 g, 13.6 mmol) and 70 mL of dehydrated tetrahydrofuran were mixed under an argon atmosphere and cooled to −78 °C. Under stirring, a 1

M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (15.0 mL, 15.0 mmol) was added dropwise. After completion of the addition, the mixture was stirred for 1 h at −78 °C and then a solution of benzyl 5-bromomethyl-2-methoxybenzoate (5.04 g, 15.0 mmol) in tetrahydrofuran (20 mL) was added dropwise. After completion of the addition, the mixture was further stirred for 6 h at −78 °C. A saturated aqueous solution of ammonium chloride was added to the reaction mixture, and the whole was extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (eluant, *n*-hexane/ethyl acetate = 4:1 v/v) to afford 4.38 g (64%) of the desired compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.51−1.63 (1H, m), 1.71−1.82 (1H, m), 2.43 (1H, dd, J = 13.2, 9.8 Hz), 2.75 (1H, dd, J = 13.7, 6.3 Hz), 2.99−3.08 (2H, m), 3.86 (3H, s), 4.03−4.15 (3H, m), 4.64 (1H, m), 5.27 (1H, d, J = 12.2 Hz), 5.31 (1H, d, J = 12.7 Hz), 6.91 (1H, d, J = 8.8 Hz), 7.03 (2H, dd, J = 7.8, 2.0 Hz), 7.20−7.42 (9H, m), 7.72 (1H, d, J = 2.0 Hz); low-resolution MS (EI$^+$) m/z 501 (M$^+$).

[5(2*S*,4*R*)]-2-Methoxy-5-[[2-(2-oxo-4-benzyloxazolidin-3-yl)carbonyl]pentyl]benzoic Acid (81). [3(2*S*),4*R*]-3-[2-Ethyl-3-[4-methoxy-3-(benzyloxycarbonyl)phenyl]propionyl]-4-benzyloxazolidin-2-one (4.38 g, 8.73 mmol), 400 mg of 10% palladium on carbon, and 100 mL of ethyl acetate were mixed, and catalytic hydrogenation was carried out at an initial hydrogen pressure of 294 kPa. After completion of the reaction, the catalyst was removed by filtration and the filtrate was washed with ethyl acetate. The reaction mixture and the washings were combined and concentrated to afford 3.45 g (96%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.49−1.59 (1H, m), 1.78 (1H, m), 2.58 (1H, dd, J = 13.2, 9.8 Hz), 2.78 (1H, dd, J = 13.7, 6.8 Hz), 3.09 (1H, dd, J = 13.7, 7.3 Hz), 3.15 (1H, dd, J = 13.2, 3.4 Hz), 3.99−4.05 (1H, m), 4.05 (3H, m), 4.10−4.19 (2H, m), 4.68 (1H, m), 7.00 (1H, d, J = 8.3 Hz), 7.09 (2H, dd, J = 7.8, 2.0 Hz), 7.23−7.31 (9H, m), 7.55 (1H, dd, J = 8.8, 2.4 Hz), 8.06 (1H, d, J = 2.4 Hz), 10.70 (1H, br s); low-resolution MS (EI$^+$) m/z 411 (M$^+$).

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