Stereospecific High-affinity TRPV1 Antagonists: Chiral *N*-(2-Benzyl-3-pivaloyloxypropyl) 2-[4-(methylsulfonylamino)phenyl]propionamide Analogues

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Previously, we reported the thiourea antagonists **2a** and **2b** as potent and high affinity TRPV1 antagonists. For further optimization of the lead compounds, a series of their amide and α-substituted amide surrogates were investigated and novel chiral *N*-(2-benzyl-3-pivaloyloxypropyl) 2-[4-(methylsulfonylamino)phenyl]-propionamide analogues were characterized as potent and stereospecific rTRPV1 antagonists. In particular, compounds **72** and**73** displayed high binding affinities, with K_i values of 4.12 and 1.83 nM and potent antagonism with K_i values of 0.58 and 5.2 nM, respectively, in rTRPV1/CHO cells. These values are comparable or more potent than those of 5-iodoRTX under the same assay conditions. A distinctive binding model that includes two hydrophobic pockets is proposed for this series of compounds based on docking studies of **57** and **72** with a homology model of the TM3/4 region of TRPV1.

Introduction

The TRPV1 (vanilloid receptor 1 or VR1) is a member of the transient receptor potential (TRP) superfamily.[1] The receptor is activated by protons, heat, endogenous substances, such as anandamide and lipoxygenase products, and by natural ligands such as capsaicin (CAP) and resiniferatoxin (RTX).[2,3] Because TRPV1 functions as a nonselective cation channel with high Ca^{2+} permeability, its activation by these agents leads to an increase in intracellular Ca^{2+} that results in excitation of primary sensory neurons and ultimately in the central perception of pain.[4] The involvement of this receptor in both pathological and physiological conditions suggests that the blocking of this receptor activation, by desensitization or antagonism, would have considerable therapeutic utility.[5,6] TRPV1 antagonists have attracted much attention as promising drug candidates to inhibit the transmission of nociceptive signals from the periphery to the CNS and to block other pathological states associated with this receptor. The therapeutic advantage of TRPV1 antagonism over agonism is that it lacks the initial excitatory effect preceding the desensitization, which represents a limiting toxicity for the systemic application of the agonists.[7] Since the discovery of capsazepine as the first TRPV1 antagonist,[8] multiple classes of antagonists have been described.[9,10]

We have previously reported that isosteric replacement of the phenolic hydroxyl group in potent TRPV1 agonists, for example, **1** (K_i = 6.35 nM, EC_{50} = 2.83 nM in rTRPV1/CHO), with the alkylsulfonamido group provided a series of compounds that were effective antagonists to the action of capsaicin on rat TRPV1 heterologously expressed in Chinese hamster ovary (CHO) cells.[11] Notably, *N*-[2-(4-*t*-butylbenzyl)-3-pivaloyloxypropyl]-*N*′-[3-fluoro-4-(methylsulfonyl amino)benzyl]thiourea (**2**) showed high affinity with a K_i = 22.6 nM for the inhibition of [^{3}H]RTX binding and potent antagonism with a K_i = 52 nM for the inhibition of $^{45}Ca^{2+}$ uptake in response to capsaicin, albeit with a low level of residual agonism.

As a continuation of our effort to optimize the 4-methylsulfonamide TRPV1 antagonists, we explored the amide surrogates of the parent thiourea antagonists (Figure 1). Their receptor activities were moderately reduced. Next, we undertook an extensive SAR investigation of a series of α-substituted analogues of amide antagonists and found that a series of α-methyl amide analogues showed very promising activities. In particular, a diastereomeric mixture (**10**) of the α-methyl amide analogues of **3** displayed high binding affinity and potent antagonism. This finding prompted us to synthesize the optically pure isomers of the α-methyl amide analogues and to evaluate their receptor activities. Here, we demonstrate that the thiourea antagonist is optimized to an α-methyl amide antagonist for receptor activity and that the optical isomers of α-methyl antagonist interact with the receptor and antagonize the effect of capsaicin in a stereospecific manner with high affinities and potent antagonism.

Chemistry. The racemic or diastereomeric α-methyl (**9**−**16**), dimethyl (**20**−**22**), and cyclopropyl amide (**26**−**28**) analogues were prepared by the coupling of the corresponding 2-substituted arylacetic acids[12] and amines,[11] respectively, as shown in Scheme 1.

The syntheses of four different α-methyl amide enantiomers are summarized in Schemes 2−4. For the synthesis of the chiral A-region, we employed a chemical resolution from racemic acids using L-phenylalanol. For a large scale synthesis of acids **6** and **7**, we developed an efficient method, as described in Scheme 2.

Ethyl 2-(4-nitrophenyl)propionates (**31**, **32**) were prepared from the corresponding 2-halonitrobenzenes (**29**, **30**), respectively, by the reaction of Makosza's vicarious nucleophilic substitution.[13] The 4-nitro groups of **31** and **32** were converted to the corresponding 4-methylsulfonylamino groups and then their esters were hydrolyzed to afford the racemic acids, **6** and **7**, respectively. These racemates were chemically

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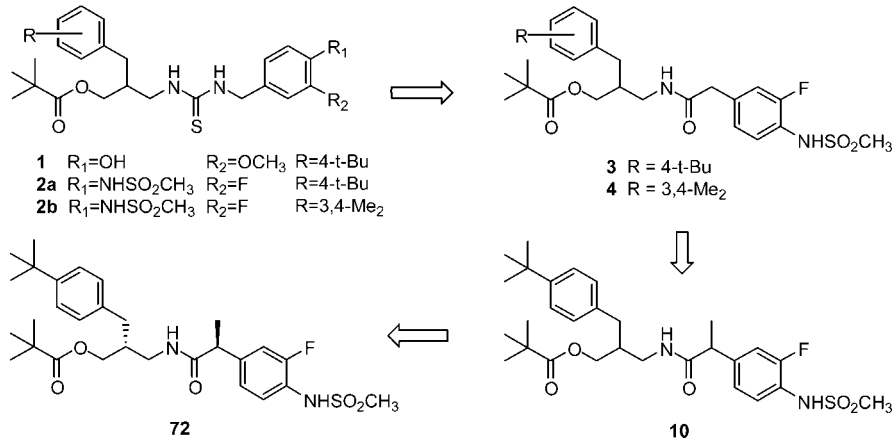
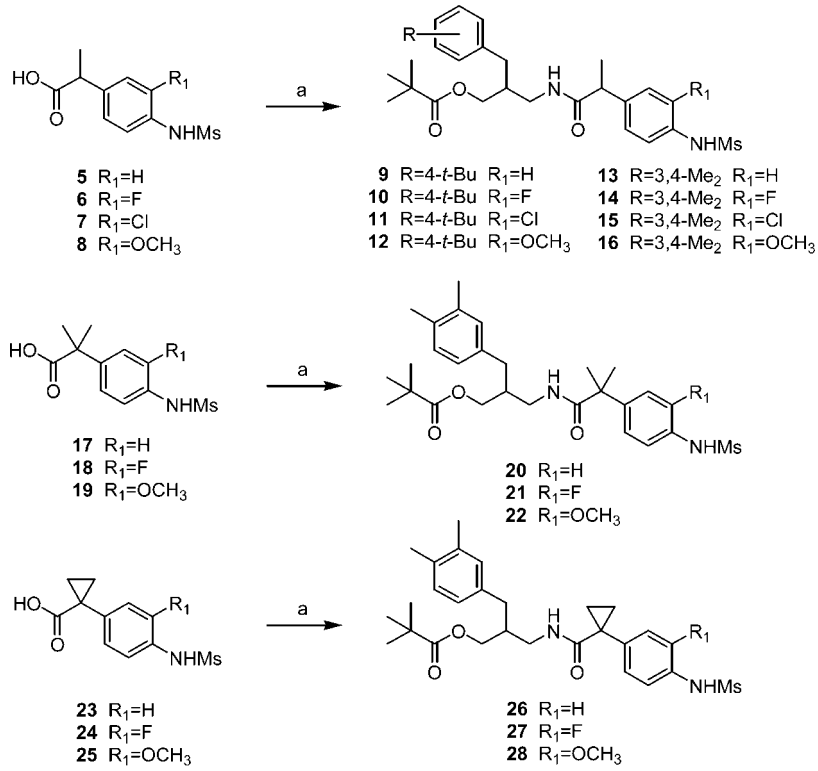


Figure 1

Scheme 1. Synthesis of Racemic and Diastereomeric Analogues[a]



[a] Reagents and conditions: (a) R-NH_2, EDC, CH_2Cl_2.

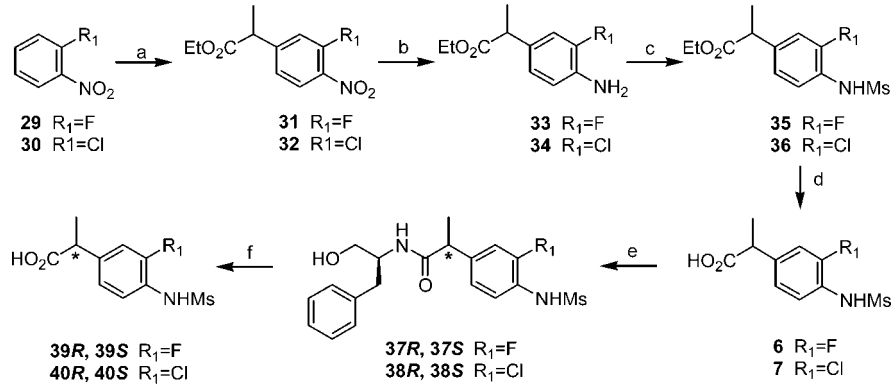
separated utilizing L-phenylalanol as a resolving agent via the diastereomeric mixtures **37** and **38** to provide the optically pure enantiomers, **39*R*/39*S*** and **40*R*/40*S***, respectively. The absolute stereochemistry of each enantiomer was determined based on the spectral comparison of its Evan's oxazolidinone derivative with that prepared from independent synthesis by a different route. The synthesis of the chiral C-region was accomplished by Seebach's diastereoselective alkylation of β-alkoxide enolate as a key reaction.[14] Antiselective alkylations of dibenzyl L-malate (**41**) with benzyl or 4-*t*-butylbenzyl bromides afforded 3*R*-benzyl-2*S*-hydroxysuccinates (**42**, **43**), respectively, which were transformed into the diverging intermediates (**46**, **47**) for the synthesis of chiral 3-pivaloyloxy-2-benzylpropyl azides (*S*-isomers: **54/55**, *R*-isomers: **67/68**). A coupling reaction between the chiral A-region (**39*R*/39*S***, **40*R*/40*S***) and C-region (**54/55**, **67/68**) provided the final α-methyl amide ligands (**56**−**60**, **69**−**73**), respectively.

Results and Discussion

The functional potencies of the synthesized TRPV1 ligands as agonists and antagonists and their receptor binding affinities were assessed in vitro by assay of $^{45}Ca^{2+}$ uptake and by competitive binding with [^{3}H]RTX, respectively, in Chinese hamster ovary cells heterologously expressing rat TRPV1 (CHO/VR1 cells), as previously described.[15] The results are summarized in Tables 1 and 2.

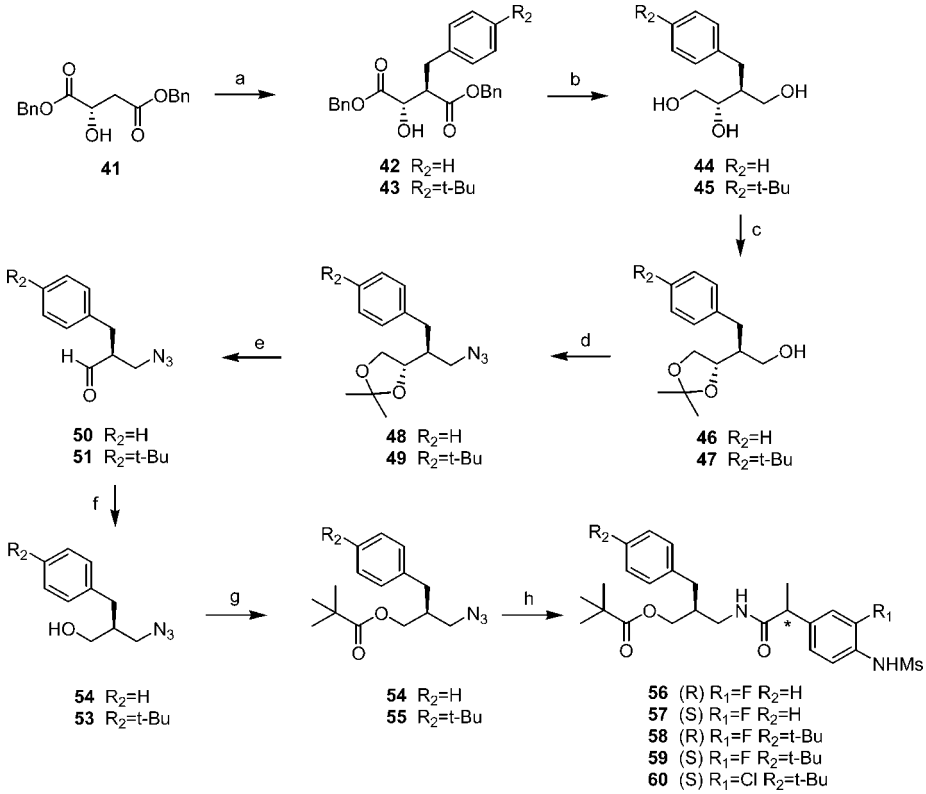
To optimize the receptor activity of the parent 4-methylsulfonamide TRPV1 antagonist (**2**) and avoid the potential toxicity related to the thiourea group, we explored the amide surrogates (**3**, **4**) of the B-region of compounds **2a** and **2b**. We found that their receptor activities were moderately reduced. The binding

Scheme 2. Synthesis of Chiral A-Region[a]



[a] Reagents and conditions: (a) $ClCH(Me)CO_2Et$, *t*-BuOK, DMF; (b) H_2, Pd-C, MeOH for R = F; Fe, AcOH for R = Cl; (c) MsCl, pyridine; (d) LiOH, H_2O−THF; (e) L-phenylalanol, EDC, CH_2Cl_2; (f) 3 N H_2SO_4.

Scheme 3. Synthesis of Target Compounds with (*S*)-C_2 Chirality[a]



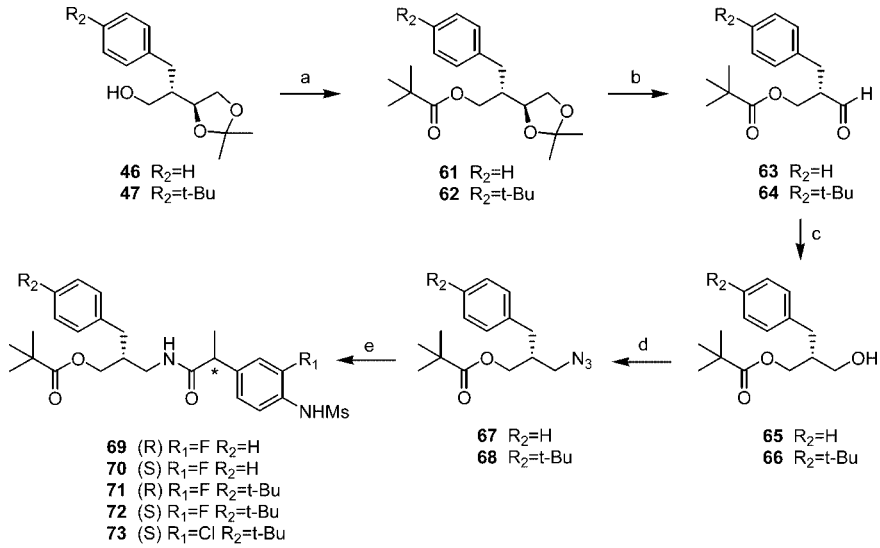
[a] Reagents and conditions: (a) LHMDS, $ArCH_2Br$, HMPA, THF; (b) $LiAlH_4$, THF; (c) pTsOH, acetone; (d) PPh_3, DPPA, DEAD, THF; (e) H_5IO_6, ether; (f) $NaBH_4$, MeOH; (g) Me_3CCOCl, pyridine; (h) (i) Pd-C, MeOH; (ii) **39*R*/*S*** or **40*R*/*S***, EDC, CH_2Cl_2.

affinities of **3** and **4** showed 3-fold reduced potencies compared to **2a** and **2b**, respectively. Their antagonism was also much reduced, but the weak efficacy as an agonist remained similar.

As the next step, we investigated the SAR of an extensive series of α-substituted analogues of the amide antagonists and found that a series of α-methyl amide analogues (**9**−**12**, **13**−**16**) showed very potent activities. In particular, a diastereomeric mixture (**10**) of the α-methyl amide analogue of **3** displayed high binding affinity with a K_i = 13.6 nM and potent antagonism with a K_i = 3.24 nM, showing much greater potency than the corresponding amide (**3**) and thiourea (**2a**) surrogates. The other α-substituted analogues such as the dimethyl (**20**−**22**) and cyclopropyl amides (**26**−**28**), in contrast, showed dramatic loss in receptor activity compared to the corresponding α-methyl amide (**13**, **14**, **16**). These results indicated that the α-methyl in the B-region might constitute an additional pharmacophoric group for the receptor interaction, providing hydrophobic contacts and complementing the previously identified pharmacophores.

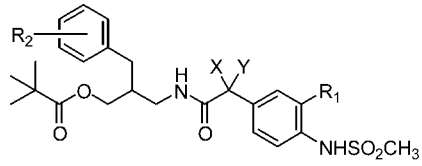
To follow up on the potent receptor binding and antagonism of capsaicin by the diastereomeric mixture of **10**, we next sought to prepare the optically pure isomers of the α-methyl amide analogues and to evaluate their receptor activities. For synthetic convenience and confirmation of the SAR pattern, we initially investigated the benzyl derivatives (R_2 = H, **56**, **57**, **69**, **70**). Their receptor potencies were stereospecific and compound **57** (*S*,*S*) showed the strongest binding affinity with a K_i = 16.5 nM. The analysis indicated that whereas the stereocenter at the α-position was crucial for determining the potencies in binding affinity and antagonism, the chirality of the C-region had little effect. Similarly, the analysis of the enantiomers of **2** and **3** revealed that their receptor potencies were very close (unpublished results).

Scheme 4. Synthesis of Target Compounds with (*R*)-C_2 Chirality[a]



[a] Reagents and conditions: (a) Me_3CCOCl, pyridine; (b) H_5IO_6, ether; (c) $NaBH_4$, MeOH; (d) PPh_3, DPPA, DEAD, THF; (e) (i) Pd-C, MeOH; (ii) **39*R/S*** or **40*R/S***, EDC, CH_2Cl_2.

Table 1. rTRPV1 Activities of Racemic and Diastereomeric Compounds



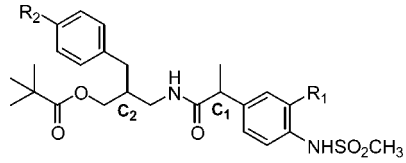
	X, Y	R_1	R_2	K_i[a] (nM) binding affinity	EC_{50}[b,e] (nM) agonism	K_i[c] (nM) antagonism
CPZ[d]				1300 (±150)	NE	520 (±12)
5-I-RTX[d]				0.61 (±0.08)	NE	12.2 (±4.0)
2a				22.6 (±2.7)	WE[b]	52 (±17)
3	H, H	F	4-*t*-Bu	74 (±13)	WE[b]	440 (±190)[c]
9	H, CH_3	H	4-*t*-Bu	55 (±1.0)	NE	52 (±11)
10	H, CH_3	F	4-*t*-Bu	13.6 (±2.4)	WE[b]	3.24 (±0.83)[c]
11	H, CH_3	Cl	4-*t*-Bu	3.6 (±1.2)	WE[b]	12.3 (±4.7)[c]
12	H, CH_3	OMe	4-*t*-Bu	24.0 (±4.9)	WE[b]	NE
2b				54 (±28)	NE	7.8 (±3.0)
4	H, H	F	3,4-Me_2	157 (±37)	WE[b]	151 (±36)[b]
13	H, CH_3	H	3,4-Me_2	119 (±15)	NE	38 (±5.8)
14	H, CH_3	F	3,4-Me_2	33.1 (±8.7)	NE	10.8 (±3.6)
15	H, CH_3	Cl	3,4-Me_2	11.3 (±3.1)	WE[b]	36 (±17)
16	H, CH_3	OMe	3,4-Me_2	71 (±19)	WE[b]	13.6 (±4.4)[c]
20	CH_3, CH_3	H	3,4-Me_2	370 (±100)	NE	104 (±39)
21	CH_3, CH_3	F	3,4-Me_2	280 (±120)	NE	65 (±16)
22	CH_3, CH_3	OCH_3	3,4-Me_2	153 (±50)	NE	133 (±40)
26	$(CH_2)_2$	H	3,4-Me_2	396 (±66)	NE	197 (±81)
27	$(CH_2)_2$	F	3,4-Me_2	1580 (±290)	NE	567 (±84)
28	$(CH_2)_2$	OCH_3	3,4-Me_2	239 (±48)	NE	118 (±32)

[a] K_i values represent mean ± SEM from 3 or more experiments. [b] Only fractional calcium uptake compared to 300 nM capsaicin (**2a**, 5%; **3**, 7%; **10**, 8%; **12**, 40%; **15**, 16%; **16**, 10%). Values from 1 to 5 experiments. [c] Only fractional antagonism to 150 nM capsaicin (**3**, 56%; **4**, 71%; **10**, 95%; **11**, 61%; **16**, 63%). [d] CPZ: capsazepine; 5-I-RTX: 5-iodoresiniferatoxin. [e] NE: not effective; WE: weakly effective at 30 μM. Results from 1–5 experiments.

The receptor stereospecificity of this template was confirmed with a series of 4-*t*-butylbenzyl analogues (R_2 = 4-*t*-Bu) **58**−**60** and **71**−**73**. The *S*-configuration of 2-phenylpropionate (corresponding to C_1 in Table 2) was critical for high receptor potency. For example, compounds **72** (*S*,*R*) and **59** (*S*,*S*) were 13- and 10-fold more potent in binding affinity and 52- and 13-fold more potent in antagonism compared to compounds **71** (*R*,*R*) and **58** (*R*,*S*), respectively. On the other hand, the stereochemistry of the C-region (corresponding to C_2 in Table 2) modestly favored the *R*-configuration for receptor potency; the difference of potency was small for binding affinity (1.5-fold in **72**(*S*,*R*)/**59**(*S*,*S*); 1.2-fold in **71**(*R*,*R*)/**58**(*R*,*S*)) but larger for antagonism (19-fold in **72**/**59**; 5-fold in **71**/**58**). The stereoselectivity of the 3-chloro derivatives (**60**, **73**) followed that of the corresponding 3-fluoro derivatives. Taken together, the order of receptor potencies in this series can be described as C_1,C_2: *S*,*R* (**70**, **72**) > *S*,*S* (**57**, **59**) >> *R*,*R* (**69**, **71**) > *R*,*S* (**56**, **58**); the binding affinities of **57** and **70** represent the only exception, where *S*,*S* (**57**) binds with 2-fold stronger affinity than does *S*,*R* (**70**).

The optimization of this series led to the two optimized TRPV1 antagonists, **72** and **73**, with an *S*,*R* chirality and high receptor potencies. Under our assay conditions, their functional activities were more potent than that of 5-iodoRTX, one of most potent antagonists so far. Compound **72** with a 3-fluoro

Table 2. rTRPV1 Activities of Chiral Compounds



	R_1	R_2	chirality (C_1,C_2)	K_i[a] (nM) binding affinity	EC_{50}[b,c] (nM) agonism	K_i (nM) antagonism
56	F	H	*R*,*S*	370 (±120)	NE	205 (±42)
57	F	H	*S*,*S*	16.5 (±2.4)	NE	10.0 (±2.5)
69	F	H	*R*,*R*	298 (±58)	NE	98 (±18)
70	F	H	*S*,*R*	43 (±13)	NE	8.56 (±0.94)
58	F	*t*-Bu	*R*,*S*	64 (±9.0)	WE[b]	142 (±35)
59	F	*t*-Bu	*S*,*S*	6.26 (±1.8)	NE	10.9 (±4.8)
60	Cl	*t*-Bu	*S*,*S*	3.29 (±0.67)	NE	12.1 (±3.9)
71	F	*t*-Bu	*R*,*R*	53.0 (±6.9)	NE	30.3 (±8.9)
72	F	*t*-Bu	*S*,*R*	4.12 (±0.54)	NE	0.58 (±0.16)
73	Cl	*t*-Bu	*S*,*R*	1.83 (±0.5)	NE	5.2 (±1.6)

[a] K_i values represent mean ± SEM from 3 or more experiments. [b] Only fractional calcium uptake compared to 300 nM capsaicin (**58**, 9%). Values from 1 to 5 experiments. [c] NE: not effective; WE: weakly effective at 30 μM. Results from 1–5 experiments.

substitution showed high binding affinity with a $K_i = 4.12$ nM and potent antagonism with a $K_i = 0.58$ nM; the antagonism was thus about 900-fold and 21-fold more potent than capsazepine and 5-iodoRTX, respectively. Compound **73** with a 3-chloro substitution exhibited better binding affinity, with a $K_i = 1.83$ nM, and less potent antagonism, with a $K_i = 5.2$ nM, compared to **72**. The antagonism of **73** was approximately 99-fold and 2-fold more potent than capsazepine and 5-iodoRTX, respectively.

Molecular Modeling. Recently, hypothetical models for the vanilloid binding site of TRPV1 and for its molecular determinants were proposed based on species differences in TRPV1 sequence, site-directed mutagenesis, homology modeling of the transmembrane domain of TRPV1, and docking studies of capsaicin or RTX bound to the putative binding site.[16–18] In the model of Jordt and Julius, an aromatic residue, Tyr511, on the intracellular S2/S3 loop was predicted to interact with the vanillyl-moiety of capsaicin. Additional polar residues, such as Ser512 or Arg491, could interact with capsaicin via hydrogen bonds, whereas lipophilic residues in TM3 might contribute to hydrophobic interactions with the aliphatic moiety of capsaicin within the plane of the membrane.[16] In the model of Gavva and co-workers, Tyr511, Met547, and Thr550 were suggested to be present in the binding pocket, because all three residues are important molecular determinants for vanilloid sensitivity. This model proposed the interactions of the vanillyl moiety with Thr550 and the "tail end" hydrophobic group of capsaicin or RTX interacting with Tyr511.[17] In the model of Middleton and co-workers, Met547 and Tyr555 interact with the vanillyl moiety and Tyr511 contacts the orthophenyl group of RTX. That model also shows the additional interactions of the C_3-carbonyl and the C_2-methyl of RTX with Asn551 and Leu515, respectively.[18] The most distinctive difference among the three models is that whereas Tyr 511 interacts with the vanillyl group (A-region) in the model of Jordt and Julius, it contacts the hydrophobic ends of RTX or capsaicin (C-region) in the models of Gavva or Middleton and co-workers.

To investigate the binding mode of a series of the α-methyl TRPV1 antagonists, the potent antagonist **72** ($K_i = 4.12$ nM) was docked into the transmembrane helices TM3 and TM4 of human TRPV1, which was constructed through homology modeling by Gavva and colleagues.[17] Two alternative binding modes are possible in the molecular docking simulation. However, the molecular surface mapping of **72** and of the receptor is able to distinguish their regions of hydrophobic and hydrophilic surface. The calculations indicated that, in **72**, the 4-*t*-butylbenzyl group represents the area of highest lipophilicity (brown) and the sulfonylaminobenzyl segment represents the area of highest hydrophilicity (blue), as shown in Figure 2a. In the receptor, the hydrophobic binding pocket is surrounded by Trp549, Met552, and Leu553, and the hydrophilic pocket is formed by Ser510, Tyr511, and Ser512. On the basis of this mapping, the docking study was conducted such that the nonpolar part of the ligand was fitted to the hydrophobic region of the pocket and the polar subunit was bound to the hydrophilic region. The resultant binding model is displayed as surface-ball and stick and ribbon-stick pictures in Figure 2b,c, respectively. In the proposed model, the oxygen atom of the sulfonamide (A-region) acts as a hydrogen bond acceptor for the phenolic hydroxyl group of Tyr511 (2.1 Å) and the 3-fluoro atom engages in a hydrogen bond to the amide proton of Gly563 (2.0 Å). The N-H of the amide group (B-region) makes a hydrogen bond to the side chain of Gln561 (1.9 Å), and the carbonyl of the ester group (C_2-region) forms a hydrogen bond with Tyr565 (1.7 Å). The hydrophobic 4-*t*-butylbenzyl group (C_1-region) closely contacts Phe517, Trp549, Leu553, and Arg557 in the hydrophobic pocket designated as hole A. Of particular note, the α-methyl next to the amide group closely contacts the hydrophobic side chains of Tyr511, Glu513, Arg557, and Gln560 in hole B. The hydrophobic interactions between the methyl group and these amino acids may contribute to the observed high binding affinity. This finding is more like the model of Jordt and Julius in which Tyr511 interacts with the vanillyl-moiety (A-region) and the hydrophobic tail protrudes into the membrane.

Compound **57** contains an unsubstituted phenyl and an *S*-configuration at C_2 in the C-region compared to compound **72**. Interestingly, the binding affinity of **57** was 2-fold stronger than that of **70**, which has the *R*-configuration at C_2 and, thus, shows somewhat different SAR from that of the series of *t*-butylbenzyl derivatives. We, therefore, examined the docking of compound **57**; the resulting model is shown in Figure 2d. Because only one *t*-butyl group in 3-pivaloyloxypropyl is present in the compound, this group rather than the benzyl group would bind preferentially to hole A to maintain the hydrophobic interaction critical for high affinity. That results in the binding affinity of the *S*-isomer at C_2 (compound **57**) being better than that of the *R*-isomer (compound **70**) in the benzyl series. The interactions in the A- and B-regions of compound **57** were similar to those found for compound **72**.

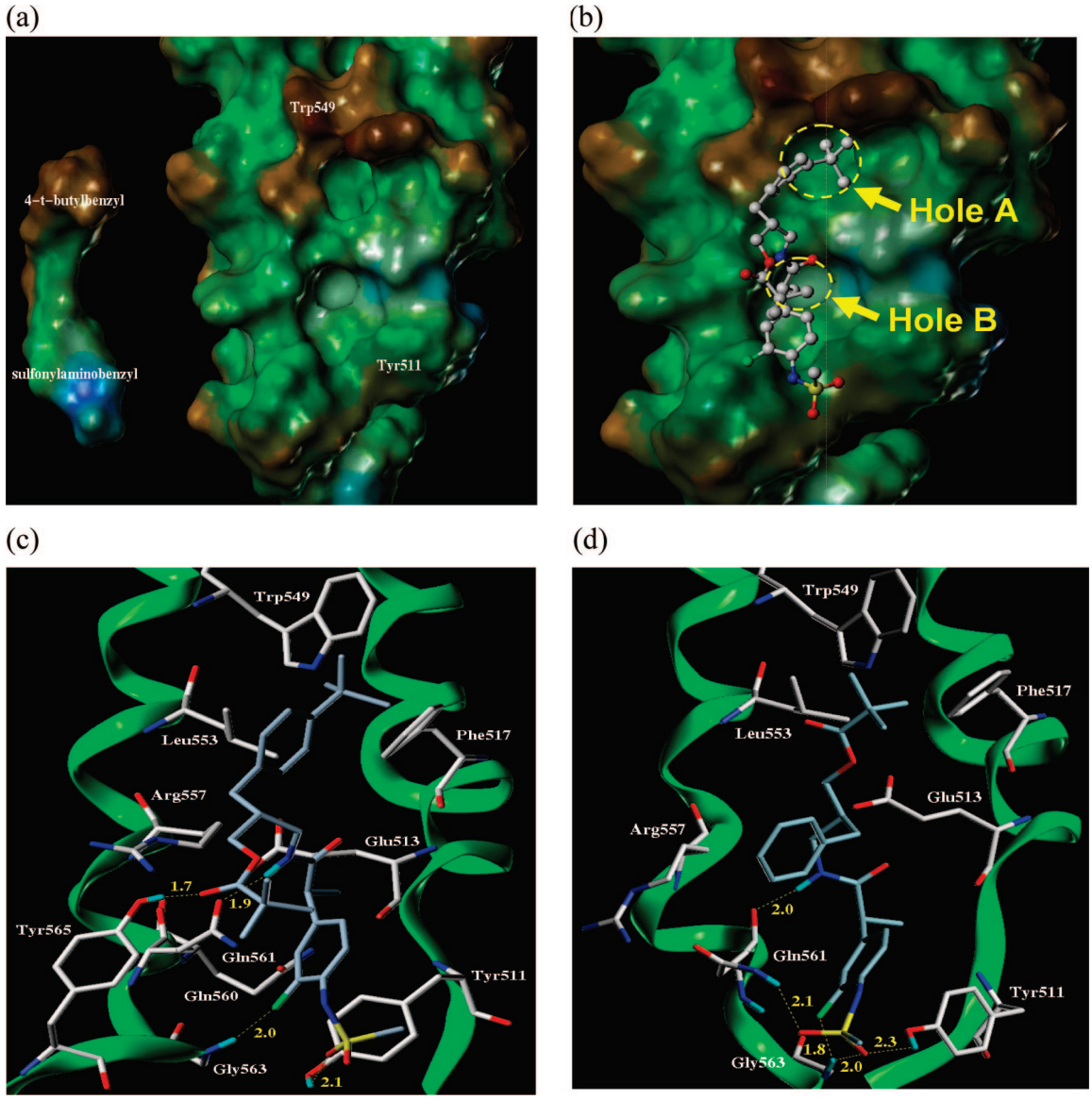


Figure 2. (a) Surface maps color-coded by lipophilic potential (LP) of antagonist **72** and TM3/4 region of human TRPV1. The color for LP ranges from brown (highest lipophilic area of the molecule) to blue (highest hydrophilic area). (b) Proposed models of **72** bound to TRPV1 binding site. (c) and (d) Molecular interactions of **72** and **57** with the TRPV1 binding site, respectively.

The volumes of holes A and B were calculated using the castP program based on the pocket algorithm of the alpha shape theory to calculate quantitative fitting. The analysis revealed that the holes A (147 Å^3) and B (19 Å^3) are suitable to accommodate a 4-*t*-butylphenyl group (138 Å^3) or a pivaloyloxymethyl group (111 Å^3) and an α-methyl group (19 Å^3), respectively. For compound **72**, hole A was better fitted by the 4-*t*-butylphenyl group than by the pivaloyloxymethyl group because of its larger size. However, the relative preference for *t*-butylphenyl would be modest because of the small volume difference between the two groups. The result reflects the small differences in binding affinities between stereoisomers of C_2; for example, **72** (*S*,*R*: K_i = 4.12 nM) compared to **59** (*S*,*S*: K_i = 6.26 nM) and **71** (*R*,*R*: K_i = 53 nM) compared to **58** (*R*,*S*: K_i = 64 nM). On the other hand, for compound **57**, hole A is better fit by the pivaloyloxymethyl group rather than by the smaller phenyl group (68 Å^3), resulting in a reverse chiral preference at C_2. Hole B is almost perfect for the volume of the methyl group. Therefore, unsubstitution or the substitution of other alkyl groups led to a dramatic loss in binding affinities and antagonism in our SAR investigation. These docking analyses thus propose a plausible binding mode for this series in which the α-methyl group of the antagonists occupies hole B with a preferred *S*-configuration and then the relevant group, *t*-butylphenyl or pivaloyloxymethyl, fits hole A for the second crucial hydrophobic interaction.

Conclusion

In conclusion, we have described the optimization of the lead thiourea **2** to afford a novel series of chiral *N*-(2-benzyl-3-pivaloyloxypropyl) 2-[4-(methylsulfonylamino)phenyl] propionamide analogues as rTRPV1 antagonists. The two α-methyl amide antagonists, **72** and **73**, with an *S*,*R*-stereochemistry, displayed high binding affinity and potent antagonism and were more potent antagonists than 5-iodoRTX under the same assay conditions. A docking study of **57** and **72** using a homology model of the TM3/4 region of TRPV1 demonstrated two stereospecific hydrophobic interactions, of the α-methyl (hole B) and 4-*t*-butylphenyl (or pivaloyloxymethyl) groups (hole A), and hydrophilic interactions of the 4-(methylsulfonylamino)-3-

fluorophenyl group (A-region) and the amide (B-region), consistent with the SAR relations for receptor binding and for antagonism.

Experimental Section

General. All chemical reagents were commercially available. Melting points were determined on a Büchi Melting Point B-540 apparatus and are uncorrected. Silica gel column chromatography was performed on silica gel 60, 230–400 mesh, Merck. Proton NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz. Chemical shifts are reported in ppm units with Me_4Si as a reference standard. Infrared spectra were recorded on a Perkin-Elmer 1710 series FTIR. Mass spectra were recorded on a VG Trio-2 GC-MS. Elemental analyses were performed with an EA 1110 Automatic Elemental Analyzer, CE Instruments.

General Procedure for Coupling. A mixture of acid (10 mmol), the corresponding amine (11 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (11 mmol) in CH_2Cl_2 (20 mL) was stirred overnight at room temperature. The reaction mixture was filtered off and the filtrate was concentrated. the residue was purified by flash column chromatography on silica gel using EtOAc/hexanes as eluent.

***N*-[2-(3,4-Dimethylbenzyl)-3-pivaloyloxypropyl]-2-[4-(methylsulfonylamino)phenyl]-2-methylpropionamide (20).** Yield 89%, yellow solid, mp = 126–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (dd, 2 H, J = 8.3, 1 Hz, Ar), 7.18 (d, 2 H, J = 8.3, 1 Hz, Ar), 6.8–7.05 (m, 3 H, Ar), 6.44 (bs, 1 H, $NHSO_2$), 5.60 (t, 1 H, NH), 3.95 (dt, 1 H, CH_2OCO), 3.76 (ddd, 1 H, CH_2OCO), 3.27 (m, 1 H, CH_2NH), 3.08 (m, 1 H, CH_2NH), 3.00 (d, 3 H, SO_2CH_3), 2.45–2.65 (m, 2 H, CH_2Ar), 2.15–2.3 (m, 6 H, 2 × CH_3), 2.05 (m, 1 H, CH), 1.53 (s, 6 H, CH_3CCH_3), 1.19 (d, 9 H, $COC(CH_3)_3$); IR (KBr) 2971, 1725, 1646, 1512, 1457, 1336, 1285, 1155 cm^{-1}; MS (FAB) *m*/*z* 517 (MH^+); Anal. ($C_{28}H_{40}N_2O_5S$) C, H, N, S.

***N*-[2-(3,4-Dimethylbenzyl)-3-pivaloyloxypropyl]-2-[3-fluoro-4-(methylsulfonylamino)phenyl]-2-methylpropionamide (21).** Yield 82%, white solid, mp = 63–65 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (dt, 1 H, H-5), 6.8–7.2 (m, 5 H, Ar), 5.74 (t, 1 H, NH), 4.01 (dt, 1 H, CH_2OCO), 3.77 (ddd, 1 H, CH_2OCO), 3.28 (m, 1 H, CH_2NH), 2.95–3.15 (m, 4 H, CH_2NH and SO_2CH_3), 2.45–2.65 (m, 2 H, CH_2Ar), 2.15–2.3 (m, 6 H, 2 × CH_3), 2.05 (m, 1 H, CH), 1.52 (s, 6 H, CH_3CCH_3), 1.20 (d, 9 H, $COC(CH_3)_3$); IR (KBr) 2972, 1721, 1652, 1584, 1511, 1456, 1336, 1285, 1159 cm^{-1}; MS (FAB) *m*/*z* 535 (MH^+); Anal. ($C_{28}H_{39}FN_2O_5S$) C, H, N, S.

***N*-[2-(3,4-Dimethylbenzyl)-3-pivaloyloxypropyl]-2-[3-methoxy-4-(methylsulfonylamino)phenyl]-2-methylpropionamide (22).** Yield 84%, white solid, mp = 100–103 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (dd, 1 H, J = 8.3, 2 Hz, H-5), 6.8–7.05 (m, 5 H, Ar), 6.74 (bs, 1 H, $NHSO_2$), 5.61 (t, 1 H, NH), 3.95 (ddd, 1 H, CH_2OCO), 3.86 (s, 3 H, OCH_3), 3.75 (ddd, 1 H, CH_2OCO), 3.26 (m, 1 H, CH_2NH), 3.06 (m, 1 H, CH_2NH), 2.96 (d, 3 H, SO_2CH_3), 2.45–2.65 (m, 2 H, CH_2Ar), 2.15–2.3 (m, 6 H, 2 × CH_3), 2.05 (m, 1 H, CH), 1.54 (s, 6 H, CH_3CCH_3), 1.19 (d, 9 H, $COC(CH_3)_3$); IR (KBr) 2969, 1722, 1653, 1512, 1458, 1336, 1285, 1158, 1033 cm^{-1}; MS (FAB) *m*/*z* 547 (MH^+); Anal. ($C_{29}H_{42}N_2O_6S$) C, H, N, S.

***N*-[2-(3,4-Dimethylbenzyl)-3-pivaloyloxypropyl]-1-[4-(methylsulfonylamino)phenyl]cyclopropanecarboxamide (26).** Yield 80%, white solid, mp = 54–56 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2 H, J = 8.3 Hz, Ar), 7.21 (d, 2 H, J = 8.3 Hz, Ar), 6.75–7.05 (m, 3 H, Ar), 6.37 (bs, 1 H, $NHSO_2$), 5.56 (bs, 1 H, NH), 3.93 (m, 1 H, CH_2OCO), 3.76 (m, 1 H, CH_2OCO), 3.27 (m, 1 H, CH_2NH), 2.95–3.1 (m, 4 H, SO_2CH_3 and CH_2NH), 2.4–2.6 (m, 2 H, CH_2Ar), 2.15–2.3 (m, 6 H, 2 × CH_3), 2.05 (m, 1 H, CH), 1.58 (m, 2 H, CH_2CCH_2), 1.17 (s, 9 H, $COC(CH_3)_3$), 1.00 (m, 2 H, CH_2CCH_2); IR (KBr) 2969, 1723, 1644, 1517, 1333, 1286, 1156 cm^{-1}; MS (FAB) *m*/*z* 515 (MH^+); Anal. ($C_{28}H_{38}N_2O_5S$) C, H, N, S.

***N*-[2-(3,4-Dimethylbenzyl)-3-pivaloyloxypropyl]-1-[3-fluoro-4-(methylsulfonylamino)phenyl]cyclopropanecarboxamide (27).** Yield 82%, white solid, mp = 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (dt, 1 H, H-5), 6.8–7.2 (m, 5 H, Ar), 6.38 (bs, 1 H, $NHSO_2$), 5.57 (bs, 1 H, NH), 3.95 (m, 1 H, CH_2OCO), 3.76 (m, 1 H, CH_2OCO), 3.28 (m, 1 H, CH_2NH), 2.95–3.1 (m, 4 H, SO_2CH_3 and CH_2NH), 2.4–2.6 (m, 2 H, CH_2Ar), 2.15–2.3 (m, 6 H, 2 × CH_3), 2.05 (m, 1 H, CH), 1.58 (m, 2 H, CH_2CCH_2), 1.17 (s, 9 H, $COC(CH_3)_3$), 1.00 (m, 2 H, CH_2CCH_2); IR (KBr) 2972, 1721, 1652, 1584, 1511, 1336, 1285, 1159 cm^{-1}; MS (FAB) *m*/*z* 533 (MH^+); Anal. ($C_{28}H_{37}FN_2O_5S$) C, H, N, S.

***N*-[2-(3,4-Dimethylbenzyl)-3-pivaloyloxypropyl]-1-[3-methoxy-4-(methylsulfonylamino)phenyl]cyclopropanecarboxamide (28).** Yield 82%, white solid, mp = 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (dd, 1 H, J = 8.3, 1.3 Hz, Ar), 6.75–7.05 (m, 6 H, Ar and $NHSO_2$), 5.65 (bt, 1 H, NH), 3.94 (m, 1 H, CH_2OCO), 3.90 (s, 3 H, OCH_3), 3.76 (m, 1 H, CH_2OCO), 3.29 (m, 1 H, CH_2NH), 2.9–3.1 (m, 4 H, SO_2CH_3 and CH_2NH), 2.4–2.6 (m, 2 H, CH_2Ar), 2.15–2.3 (m, 6 H, 2 × CH_3), 2.05 (m, 1 H, CH), 1.58 (m, 2 H, CH_2CCH_2), 1.16 (d, 9 H, $COC(CH_3)_3$), 1.02 (m, 2 H, CH_2CCH_2); IR (KBr) 2969, 1722, 1657, 1514, 1340, 1286, 1246, 1158, 1033 cm^{-1}; MS (FAB) *m*/*z* 545 (MH^+); Anal. ($C_{29}H_{40}N_2O_6S$) C, H, N, S.

General Procedure for Vicarious Nucleophilic Substitution. To a stirred solution of potassium *t*-butoxide (20 mmol) in DMF (20 mL) was added a mixture of **29** (or **30**; 10 mmol) and ethyl 2-chloropropionate (10 mmol) dropwise at 0 °C. After being stirred for 10 min at 0 °C, the mixture was quenched with 1 N HCl solution, diluted with water and extracted with diethyl ether several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:10) as eluent.

Ethyl 2-(3-Fluoro-4-nitrophenyl)propionate (31). Yield 68%, yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.02 (dd, 1 H, J = 7.8, 8.0 Hz, H-5), 7.2–7.3 (m, 2 H, H-2,6), 4.14 (m, 2 H, $CO_2CH_2CH_3$), 3.78 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 1.52 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 1.22 (t, 3 H, J = 7.08 Hz, $CO_2CH_2CH_3$).

Ethyl 2-(3-Chloro-4-nitrophenyl)propionate (32). Yield 64%, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 1 H, J = 8.4 Hz, H-5), 7.51 (d, 1 H, J = 1.8 Hz, H-2), 7.36 (dd, 1 H, J = 8.4, 1.8 Hz, H-6), 4.15 (m, 2 H, $CO_2CH_2CH_3$), 3.77 (q, 1 H, J = 7.2 Hz, $CHCH_3$), 1.53 (d, 3 H, J = 7.2 Hz, $CHCH_3$), 1.24 (t, 3 H, J = 7.08 Hz, $CO_2CH_2CH_3$).

General Procedure for Nitro Reduction. Method A: A suspension of **31** (5 mmol) and 10% Pd-C (500 mg) in EtOH (30 mL) was hydrogenated under a balloon of hydrogen for 1 h and filtered through celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:4) as eluent to afford **33**.

Method B: A suspension of **32** (5 mmol) and activated iron (0.28 g, 5 mmol) in acetic acid (30 mL) was heated at 90 °C for 1 min. After being cooled at room temperature, the mixture was diluted with EtOH and filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:4) as eluent to afford **34**.

Ethyl 2-(4-Amino-3-fluorophenyl)propionate (33). Yield 94%, a colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, 1 H, J = 1.7, 11.9 Hz, H-2), 6.87 (dd, 1 H, J = 1.7, 8.3 Hz, H-6), 6.71 (dd, 1 H, J = 8.3, 11.9 Hz, H-5), 4.11 (m, 2 H, $CO_2CH_2CH_3$), 3.58 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 3.45 (bs, 2 H, NH_2), 1.43 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 1.20 (t, 3 H, J = 7.05 Hz, $CO_2CH_2CH_3$).

Ethyl 2-(4-Amino-3-chlorophenyl)propionate (34). Yield 88%, yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, 1 H, J = 2 Hz, H-2), 7.00 (dd, 1 H, J = 2, 8.1 Hz, H-6), 6.71 (d, 1 H, J = 8.1 Hz, H-5), 4.11 (m, 2 H, $CO_2CH_2CH_3$), 4.00 (bs, 2 H, NH_2), 3.56 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 1.44 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 1.21 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$).

General Procedure for Mesylation. A cooled solution of **33** (or **34**; 4 mmol) in pyridine (10 mL) at 0 °C was treated dropwise with methanesulfonyl chloride (6 mmol) over 10 min and stirred for 1 h at room temperature. After aqueous workup, the residue was purified by flash column chromatography on silica gel using EtOAc/hexanes (1:2) as eluent.

Ethyl 2-[3-Fluoro-4-(methylsulfonylamino)phenyl]propionate (35). Yield 91%, white solid, mp = 81 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (t, 1 H, J = 8.3 Hz, H-5), 7.0–7.1 (m, 2 H, H-2,6), 6.55 (bs,

1 H, $NHSO_2$), 4.12 (m, 2 H, $CO_2CH_2CH_3$), 3.68 (q, 1 H, $J = 7.1$ Hz, $CHCH_3$), 3.02 (s, 3 H, SO_2CH_3), 1.48 (d, 3 H, $J = 7.1$ Hz, $CHCH_3$), 1.22 (t, 3 H, $J = 7.1$ Hz, $CO_2CH_2CH_3$).

Ethyl 2-[3-Chloro-4-(methylsulfonylamino)phenyl]propionate (36). Yield 90%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1 H, $J = 8.4$ Hz, H-5), 7.40 (d, 1 H, $J = 2$ Hz, H-2), 7.25 (dd, 1 H, $J = 8.4$, 2 Hz, H-6), 6.78 (bs, 1 H, $NHSO_2$), 4.14 (m, 2 H, $CO_2CH_2CH_3$), 3.67 (q, 1 H, $J = 7.1$ Hz, $CHCH_3$), 3.02 (s, 3 H, SO_2CH_3), 1.49 (d, 3 H, $J = 7.1$ Hz, $CHCH_3$), 1.23 (t, 3 H, $J = 7.1$ Hz, $CO_2CH_2CH_3$).

General Procedure for Ester Hydrolysis. A solution of **35** (or **36**; 2 mmol) in H_2O and THF (1:2, 30 mL) was treated with lithium hydroxide (6 mmol) and stirred for 4 h at room temperature. The mixture was diluted with H_2O and CH_2Cl_2, acidified with 1 N HCl solution, and extracted with CH_2Cl_2 several times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was crystallized from diethyl ether and *n*-hexane.

2-[3-Fluoro-4-(methylsulfonylamino)phenyl]propionic Acid (6). Yield 97%, white solid, mp = 120 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1 H, $J = 8.04$ Hz, H-5), 7.1–7.15 (m, 2 H, H-2,6), 6.60 (bs, 1 H, $NHSO_2$), 3.73 (q, 1 H, $J = 7.1$ Hz, $CHCH_3$), 3.03 (s, 3 H, SO_2CH_3), 1.51 (d, 3 H, $J = 7.1$ Hz, $CHCH_3$).

2-[3-Chloro-4-(methylsulfonylamino)phenyl]propionic Acid (7). Yield 92%, pink solid, mp = 133–135 °C; ^{1}H NMR ($CDCl_3$) δ 10.19 (bs, 1 H, CO_2H), 7.60 (d, 1 H, $J = 8.4$ Hz, H-5), 7.41 (d, 1 H, $J = 1.8$ Hz, H-2), 7.26 (dd, 1 H, $J = 8.4$, 1.8 Hz, H-6), 6.91 (bs, 1 H, $NHSO_2$), 3.72 (q, 1 H, $J = 7.1$ Hz, $CHCH_3$), 3.02 (s, 3 H, SO_2CH_3), 1.51 (d, 3 H, $J = 7.1$ Hz, $CHCH_3$).

General Procedure for Coupling with L-Phenylalaniol. A cooled solution of **6** (or **7**; 1 mmol) and L-phenyl alaninol (1.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.5 mmol) followed by 1-hydroxybenzotriazole (1.5 mmol) and triethylamine (1.5 mmol). After being stirred for 6 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAc as eluent to afford **37** (or **38**) in 95–98% yield.

***N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (37*R*).** White solid, mp = 164∼166 °C, $[\alpha] = -25.48$ (*c* 1.00, MeOH); ^{1}H NMR (CD_3OD) δ 7.33 (t, 1 H, $J = 8.5$ Hz, H-5), 6.9–7.12 (m, 7 H, H-2,6 and Ph), 4.12 (m, 1 H, $CHNH$), 3.5–3.6 (m, 3 H, $CHCH_3$ and CH_2OH), 2.98 (s, 3 H, SO_2CH_3), 2.88 (dd, 1 H, $J = 5.1$, 14 Hz, CH_2Ph), 2.71 (dd, 1 H, $J = 9.3$, 14 Hz, CH_2Ph), 1.36 (d, 3 H, $J = 7.05$ Hz, $CHCH_3$).

***N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (37*S*).** White solid, mp = 150–153 °C, $[\alpha] = -20.36$ (*c* 1.00, MeOH); ^{1}H NMR (CD_3OD) δ 7.36 (t, 1 H, $J = 8.5$ Hz, H-5), 7.0–7.28 (m, 7 H, H-2,6 and Ph), 4.07 (m, 1 H, $CHNH$), 3.56 (q, 1 H, $J = 7.3$ Hz, $CHCH_3$), 3.48 (dd, 2 H, $J = 1.2$, 5.1 Hz, CH_2OH), 2.9–3.0 (m, 4 H, SO_2CH_3 and CH_2Ph), 2.71 (dd, 1 H, $J = 9$, 14 Hz, CH_2Ph), 1.27 (d, 3 H, $J = 7.05$ Hz, $CHCH_3$).

***N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-(2*R*)-2-[3-chloro-4-(methylsulfonylamino)phenyl]propionamide (38*R*).** White solid, mp = 167–169 °C, $[\alpha] = +39.5$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 1 H, $J = 8.4$ Hz, H-5), 7.2–7.3 (m, 4 H), 7.0–7.06 (m, 3 H), 6.76 (bs, 1 H, $NHSO_2$), 5.55 (d, 1 H, $J = 7.7$ Hz, $CHNH$), 4.16 (m, 1 H, $CHNH$), 3.55–3.75 (m, 2 H, CH_2OH), 3.43 (q, 1 H, $J = 7.1$ Hz, $CHCH_3$), 3.02 (s, 3 H, SO_2CH_3), 2.85 (dd of AB, 1 H, $J = 6.4$, 13.7 Hz, CH_2Ph), 2.72 (dd of AB, 1 H, $J = 8.1$, 13.7 Hz, CH_2Ph), 2.43 (t, 1 H, $J = 5.3$ Hz, OH), 1.43 (d, 3 H, $J = 7.1$ Hz, $CHCH_3$).

***N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-(2*S*)-2-[3-chloro-4-(methylsulfonylamino)phenyl]propionamide (38*S*).** White solid, mp = 149–151 °C, $[\alpha] = -43.8$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1 H, $J = 8.4$ Hz, H-5), 7.34 (d, 1 H, $J = 2$ Hz, H-2), 7.22–7.3 (m, 3 H), 7.1–7.15 (m, 3 H), 6.76 (bs, 1 H, $NHSO_2$), 5.64 (d, 1 H, $J = 6.8$ Hz, $CHNH$), 4.12 (m, 1 H, $CHNH$), 3.55–3.7 (m, 2 H, CH_2OH), 3.43 (q, 1 H, $J = 7.1$ Hz, $CHCH_3$), 3.02 (s, 3 H, SO_2CH_3), 2.88 (dd of AB, 1 H, $J = 6.8$, 13.7 Hz, CH_2Ph), 2.80 (dd of AB, 1 H, $J = 7.9$, 13.7 Hz, CH_2Ph), 2.47 (t, 1 H, $J = 5.1$ Hz, OH), 1.43 (d, 3 H, $J = 7.1$ Hz, $CHCH_3$).

General Procedure for Amide Hydrolysis. A solution of **37** (or **38**; 1 mmol) in 3 N H_2SO_4 (4 mL) and 1,4-dioxane (4 mL) was heated to 100 °C for 5 h and cooled to room temperature. The solution was diluted with water and extracted with CH_2Cl_2 several times. The combined organic layers were washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford **39** (or **40**) in 75–90% yields.

(2*R*)-[3-Fluoro-4-(methylsulfonylamino)phenyl]propionic Acid (39*R*). $[\alpha] = -29.25$ (*c* 1.00, $CHCl_3$). The spectra are identical to those of **35**.

(2*S*)-[3-Fluoro-4-(methylsulfonylamino)phenyl]propionic Acid (39*S*). $[\alpha] = +29.76$ (*c* 1.00, $CHCl_3$). The spectra are identical to those of **35**.

(2*R*)-[3-Chloro-4-(methylsulfonylamino)phenyl]propionic Acid (40*R*). $[\alpha] = +14.80$ (*c* 1.00, $CHCl_3$). The spectra are identical to those of **36**.

(2*S*)-[3-Chloro-4-(methylsulfonylamino)phenyl]propionic Acid (40*S*). $[\alpha] = +19.62$ (*c* 1.00, $CHCl_3$). The spectra are identical to those of **36**.

Dibenzyl (2*S*)-2-Hydroxybutanedioate (41). A mixture of L-malic acid (6.7 g, 50 mmol), benzyl alcohol (10.34 mL, 100 mmol), and a few crystals of *p*-toluenesulfonic acid in toluene (50 mL) under a Dean–Stark trap was refluxed overnight. After cooling to ambient temperature, the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluent to give **41** as an oil (13.83 g, 88%); ^{1}H NMR ($CDCl_3$) δ 7.25–7.35 (m, 10 H, 2 × Ph), 5.17 (s, 2 H, CH_2Ph), 5.10 (s, 2 H, CH_2Ph), 4.54 (m, 1 H, CHOH), 3.30 (d, 1 H, $J = 5.4$ Hz, OH), 2.87 (m, 2 H, CH_2CO_2Bn).

General Procedure for Alkylation. A stirred solution of **41** (15 mmol) in THF (20 mL) was cooled to −78 °C and treated dropwise with LiHMDS (1 M in THF, 30 mmol) and HMPA (30 mmol). After being stirred for 30 min at −78 °C, the mixture was treated with benzyl halide (15 mmol) in THF (10 mL) and stirred for 30 min at the same temperature. The reaction mixture was quenched by the slow addition of a saturated aqueous solution of ammonium chloride and extracted with ether several times. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:10) as eluent.

Dibenzyl (2*R*,3*S*)-2-Benzyl-3-hydroxybutanedioate (42). Yield 55%, white solid, mp = 65–66 °C; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 15 H, 3 × Ph), 5.00 (dd of AB, 4 H, 2 × CH_2Ph), 4.13 (d, 1 H, $J = 2.5$ Hz, CHOH), 3.15–3.25 (m, 2 H, CH_2Ph), 3.00 (m, 1 H, $CHCO_2Bn$).

Dibenzyl (2*R*,3*S*)-2-(4-*t*-Butylbenzyl)-3-hydroxybutanedioate (43). Yield 68%, white solid, mp = 37–38 °C; ^{1}H NMR ($CDCl_3$) δ 7.12–7.35 (m, 14 H, 2 × Ph and Ar), 5.02 (s, 4 H, 2 × CH_2Ph), 4.17 (dd, 1 H, $J = 2.9$, 7.1 Hz, CHOH), 3.12–3.28 (m, 3 H, CH_2Ph and OH), 2.97 (dd, 1 H, $J = 9$, 13.2 Hz $CHCO_2Bn$), 1.29 (s, 9 H, $C(CH_3)_3$).

General Procedure for Ester Reduction. To a suspension of lithium aluminum hydride (20 mmol) in THF (10 mL) was added dropwise a solution of **42** (or **43**; 5 mmol) in THF (20 mL). After being stirred for 3 h at room temperature, the reaction mixture was cooled in an ice-bath, quenched with H_2O, 15% NaOH (aq), and H_2O, successively, and stirred for 1 h. The suspension was filtered by washing with EtOAc and the combined filtrates were concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc as eluent.

(2*S*,3*S*)-3-Benzyl-1,2,4-butanetriol (44). Yield 56%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 3.6–3.8 (m, 5 H, 2 × CH_2OH and CHOH), 2.73 (ddd of AB, 2 H, CH_2Ar), 2.46 (bs, 3 H, OH), 1.93 (m, 1 H, CH).

(2*S*,3*S*)-3-(4-*t*-Butylbenzyl)-1,2,4-butanetriol (45). Yield 55%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.31 (bd, 2 H, Ar), 7.12 (bd, 2 H, Ar), 3.6–3.8 (m, 5 H, 2 × CH_2OH and CHOH), 3.19 (bs, 1 H,

OH), 2.76 (dd of AB, 1 H, CH_2Ar), 2.70 (bs, 2 H, OH), 2.62 (dd of AB, 1 H, CH_2Ar), 1.92 (m, 1 H, CH), 1.30 (s, 9 H, $C(CH_3)_3$).

General Procedure for Acetonidation. A mixture of **44** (or **45**; 4 mmol) and *p*-toluenesulfonic acid (10 wt%) in acetone (10 mL) was stirred for 3 h at room temperature. The mixture was neutralized with solid sodium bicarbonate and filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:2) as eluent.

(2*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-phenyl-1-propanol (46). Yield 76%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 4.10 (m, 1 H, CHO), 3.95 (dd, 1 H, CH_2O), 3.74 (dd, 1 H, CH_2O), 3.64 (m, 2 H, CH_2OH), 2.5–2.7 (m, 2 H, CH_2Ar), 1.98 (m, 1 H, CH), 1.42 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3).

(2*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(4-*t*-butylphenyl)-1-propanol (47). Yield 82%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.25 (bd, 2 H, Ar), 7.06 (bd, 2 H, Ar), 4.06 (m, 1 H, CHO), 3.89 (dd, 1 H, CH_2O), 3.52–3.7 (m, 2 H, CH_2O and CH_2OH), 2.43–2.58 (m, 2 H, CH_2Ar), 1.94 (m, 1 H, CH), 1.37 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.26 (s, 9 H, $C(CH_3)_3$).

General Procedure for Azide Formation. To a stirred solution of **46** (or **47**; 3 mmol), triphenylphosphine (6 mmol), and diethyl azodicarboxylate (6 mmol) in THF (10 mL) was added a solution of diphenylphosphoryl azide (6 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 2 h, and the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/heaxanes (1:10) as eluent.

(4*S*)-4-[(1*S*)-2-Azido-1-benzylethyl]-2,2-dimethyl-1,3-dioxolane (48). Yield 88%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 3.95–4.16 (m, 2 H, CHO and CH_2O), 3.60 (dd, 1 H, CH_2O), 3.50 (dd, 1 H, CH_2N_3), 3.30 (dd, 1 H, CH_2N_3), 2.53–2.70 (ddd of AB, 2 H, CH_2Ar), 1.97 (m, 1 H, CH), 1.40 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3).

(4*S*)-4-[(1*S*)-2-Azido-1-(4-t-butylbenzyl)ethyl]-2,2-dimethyl-1,3-dioxolane (49). Yield 90%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (bd, 2 H, Ar), 7.09 (bd, 2 H, Ar), 4.06 (dd, 1 H, CHO), 3.97 (dd, 1 H, CH_2O), 3.60 (dd, 1 H, CH_2O), 3.51 (dd, 1 H, CH_2N_3), 3.32 (dd, 1 H, CH_2N_3), 2.5–2.70 (ddd of AB, 2 H, CH_2Ar), 1.96 (m, 1 H, CH), 1.40 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.31 (s, 9 H, $C(CH_3)_3$).

General Procedure for Aldehyde Formation. A solution of **48** (or **49**; 2 mmol) in ether and THF (5:3, 20 mL) was treated with periodic acid (10 mmol). After being stirred for 5 h, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluent.

(2*S*)-3-Azido-2-benzyl-propanal (50). Yield 98%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H, CHO), 7.15–7.35 (m, 5 H, Ph), 3.54 (m, 2 H, CH_2N_3), 3.08 (m, 1 H, C*H*CHO), 2.75–2.88 (m, 2 H, CH_2Ar).

(2*S*)-3-Azido-2-(4-t-butylbenzyl)propanal (51). Yield 98%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.77 (d, 1 H, J = 0.7 Hz, CHO), 7.32 (bd, 2 H, Ar), 7.11 (bd, 2 H, Ar), 3.54 (d, 2 H, J = 4.9 Hz, CH_2N_3), 3.05 (m, 1 H, C*H*CHO), 2.75–2.85 (m, 2 H, CH_2Ar), 1.30 (s, 9 H, $C(CH_3)_3$).

General Procedure for Aldehyde Reduction. A cooled solution of **50** (or **51**; 2 mmol) in MeOH (15 mL) at 0 °C was treated with sodium borohydride (4 mmol) and stirred for 30 min. The reaction mixture was concentrated in vacuo. The residue was treated with H_2O (30 mL) and extracted with CH_2Cl_2 several times. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/heaxanes (1:2) as eluent.

(2*S*)-3-Azido-2-benzyl-1-propanol (52). Yield 72%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 3.55–3.72 (m, 2 H, CH_2OH), 3.33–3.47 (ddd of AB, 2 H, CH_2N_3), 2.60–2.74 (ddd of AB, 2 H, CH_2Ar), 2.00 (m, 1 H, CH).

(2*S*)-3-Azido-2-(4-t-butylbenzyl)-1-propanol (53). Yield 89%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (bd, 2 H, Ar), 7.11 (bd, 2 H, Ar), 3.56–3.73 (m, 2 H, CH_2OH), 3.33–3.48 (ddd of AB, 2 H, CH_2N_3), 2.56–2.7 (ddd of AB, 2 H, CH_2Ar), 2.04 (m, 1 H, CH), 1.31 (s, 9 H, $C(CH_3)_3$).

General Procedure for Pivaloylation. A cooled solution of **52** (or **53**; 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with pyridine (4 mmol) and pivaloyl chloride (2 mmol) and stirred for 30 min at room temperature. The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (1:4) as eluent.

(2*S*)-3-Azido-2-benzylpropyl Pivalate (54). Yield 80%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 4.09 (dd of AB, 1 H, CH_2OCO), 3.99 (dd of AB, 1 H, CH_2OCO), 3.28–3.40 (septet, 2 H, CH_2N_3), 2.68 (d, 2 H, J = 7.3 Hz, CH_2Ar), 2.18 (m, 1 H, CH), 1.23 (s, 9 H, $COC(CH_3)_3$).

(2*S*)-3-Azido-2-(4-t-butylbenzyl)propyl Pivalate (55). Yield 82%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (bd, 2 H, Ar), 7.08 (bd, 2 H Ar), 4.08 (dd of AB, 1 H, CH_2OCO), 3.99 (dd of AB, 1 H, CH_2OCO), 3.28–3.40 (septet, 2 H, CH_2N_3), 2.65 (d, 2 H, J = 7.3 Hz, CH_2Ar), 2.20 (m, 1 H, CH), 1.31 (s, 9 H, $C(CH_3)_3$), 1.23 (s, 9 H, $COC(CH_3)_3$).

(2*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-phenylpropyl Pivalate (61). The compound was prepared from **46** by following the general procedure for pivaloylation. Yield 85%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 4.05–4.16 (m, 3 H, CH_2OCO and CHO), 3.96 (dd, 1 H, CH_2O), 3.68 (t, 1 H, J = 7.5 Hz, CH_2O), 2.68 (d, 2 H, J = 7.3 Hz, CH_2Ar), 2.15 (m, 1 H, CH), 1.41 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.23 (s, 9 H, $C(CH_3)_3$).

(2*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(4-t-butylphenyl)propyl Pivalate (62). The compound was prepared from **47** by following the general procedure for pivaloylation. Yield 92%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.30 (bd, 2 H, Ar), 7.07 (bd, 2 H, Ar), 4.04–4.15 (m, 3 H, CH_2OCO and CHO), 3.96 (dd, 1 H, CH_2O), 3.65 (t, 1 H, J = 7.5 Hz, CH_2O), 2.64 (d, 2 H, J = 7.3 Hz, CH_2Ar), 2.07 (m, 1 H, CH), 1.41 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $COC(CH_3)_3$).

(2*S*)-2-Benzyl-3-oxopropyl Pivalate (63). The compound was prepared from **61** by following the general procedure for adehyde formation. Yield 98%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.76 (d, 1 H, J = 1.2 Hz, CHO), 7.15–7.35 (m, 5 H, Ph), 4.34 (dd, 1 H, CH_2OCO), 4.20 (dd, 1 H, CH_2OCO), 3.10 (dd, 1 H, CH_2Ar), 2.92 (m, 1 H, CH), 2.79 (dd, 1 H, CH_2Ar), 1.19 (s, 9 H, $C(CH_3)_3$).

(2*S*)-2-(4-t-Butylbenzyl)-3-oxopropyl Pivalate (64). The compound was prepared from **62** by following the general procedure for adehyde formation. Yield 98%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H, CHO), 7.32 (bs, 2 H, Ar), 7.10 (bs, 2 H, Ar), 4.32 (dd, 1 H, CH_2OCO), 4.22 (dd, 1 H, CH_2OCO), 3.06 (dd, 1 H, CH_2Ar), 2.90 (m, 1 H, CH), 2.78 (dd, 1 H, CH_2Ar), 1.30 (s, 9 H, $C(CH_3)_3$), 1.19 (s, 9 H, $COC(CH_3)_3$).

(2*R*)-2-Benzyl-3-hydroxypropyl Pivalate (65). The compound was prepared from **63** by following the general procedure for adehyde reduction. Yield 80%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 4.22 (dd, 1 H, CH_2OCO), 4.04 (dd, 1 H, CH_2OCO), 3.4–3.63 (m, 2 H, CH_2OH), 2.58–2.74 (ddd of AB, 2 H, CH_2Ar), 2.14 (m, 1 H, CH), 1.23 (s, 9 H, $C(CH_3)_3$).

(2*R*)-2-(4-t-Butylbenzyl)-3-hydroxypropyl Pivalate (66). The compound was prepared from **64** by following the general procedure for adehyde reduction. Yield 90%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.31 (bd, 2 H, Ar), 7.11 (bd, 2 H, Ar), 4.22 (dd, 1 H, CH_2OCO), 4.05 (dd, 1 H, CH_2OCO), 3.4–3.64 (m, 2 H, CH_2OH), 2.55–2.7 (ddd of AB, 2 H, CH_2Ar), 2.14 (m, 1 H, CH), 1.31 (s, 9 H, $C(CH_3)_3$), 1.23 (s, 9 H, $COC(CH_3)_3$).

(2*R*)-3-Azido-2-benzylpropyl Pivalate (67). The compound was prepared from **65** by following the general procedure for azido formation. Yield 87%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.15–7.35 (m, 5 H, Ph), 4.09 (dd, 1 H, CH_2OCO), 3.99 (dd, 1 H, CH_2OCO), 3.34 (septet, 2 H, CH_2N_3), 2.68 (d, 2 H, J = 7.3 Hz, CH_2Ar), 2.21 (m, 1 H, CH), 1.23 (s, 9 H, $C(CH_3)_3$).

(2*R*)-3-Azido-2-(4-t-butylbenzyl)propyl Pivalate (68). The compound was prepared from **66** by following the general procedure for azide formation. Yield 84%, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32 (bd, 2 H, Ar), 7.08 (bd, 2 H, Ar), 4.09 (dd, 1 H, CH_2OCO), 3.99 (dd, 1 H, CH_2OCO), 3.34 (septet, 2 H, CH_2N_3), 2.65 (d, 2 H,

J = 7.3 Hz, CH_2Ar), 2.20 (m, 1 H, CH), 1.31 (s, 9 H, $C(CH_3)_3$), 1.23 (s, 9 H, $COC(CH_3)_3$)

General Procedure for Coupling. A suspension of azide (1 mmol) and 10% palladium on carbon (100 mg) in MeOH (5 mL) was hydrogenated under a balloon of hydrogen for 2 h. The mixture was filtered through celite and the filtrate was concentrated in vacuo to give the corresponding amine. The amine was dissolved in CH_2Cl_2 (5 mL) and treated with chiral acid (1 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.1 mmol). After being stirred for 12 h at room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using EtOAc/hexanes as eluent.

***N*-[(2*S*)-2-Benzyl-3-(pivaloyloxy)propyl]-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (56).** Yield 88%, white solid, mp = 40–42 °C, [α] = −10.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1 H, J = 8.25 Hz, H-5), 7.06–7.32 (m, 7 H), 6.50 (bs, 1 H, $NHSO_2$), 5.93 (bt, 1 H, NHCO), 4.05 (dd, 1 H, J = 4, 11.5 Hz, CH_2OCO), 3.76 (dd, 1 H, J = 5, 11.5 Hz, CH_2OCO), 3.45 (q, 1 H, J = 7.1 Hz, CHMe), 3.36 (dt, 1 H, CH_2NH), 2.9–3.05 (m, 4 H, CH_2NH and SO_2CH_3), 2.58 (d, 2 H, J = 7.5 Hz, CH_2Ph), 2.09 (m, 1 H, CH), 1.47 (d, 3 H, J = 7.1 Hz, CH_3), 1.22 (s, 9 H, $C(CH_3)_3$); IR (KBr) 3287, 2972, 1723, 1654, 1511, 1333, 1284, 1157 cm^{-1}; MS (FAB) *m*/*z* 493 (MH^+); Anal. ($C_{25}H_{33}FN_2O_5S$) C, H, N, S.

***N*-[(2*S*)-2-Benzyl-3-(pivaloyloxy)propyl]-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (57).** Yield 86%, white solid, mp = 92∼94 °C, [α] = +6.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1 H, J = 8.25 Hz, H-5), 7.06–7.32 (m, 7 H), 6.52 (bs, 1 H, $NHSO_2$), 5.92 (bt, 1 H, NHCO), 4.08 (dd, 1 H, J = 4, 11.5 Hz, CH_2OCO), 3.79 (dd, 1 H, J = 5, 11.5 Hz, CH_2OCO), 3.46 (q, 1 H, J = 7.1 Hz, CHMe), 3.33 (dt, 1 H, CH_2NH), 3.03 (dt, 1 H, CH_2NH), 3.00 (s, 3 H, SO_2CH_3), 2.48–2.62 (m, 2 H, CH_2Ph), 2.13 (m, 1 H, CH), 1.47 (d, 3 H, J = 7.1 Hz, CH_3), 1.22 (s, 9 H, $C(CH_3)_3$); IR (KBr) 3287, 2972, 1718, 1658, 1508, 1330, 1283, 1158 cm^{-1}; MS (FAB) *m*/*z* 493 (MH^+); Anal. ($C_{25}H_{33}FN_2O_5S$) C, H, N, S.

***N*-[(2*S*)-2-(4-*t*-Butylbenzyl)-3-(pivaloyloxy)propyl]-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (58).** Yield 87%, white solid, mp = 44–46 °C, [α] = −8.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.51 (t, 1 H, J = 8.25 Hz, H-5), 7.31 (d, 2 H, Ar), 7.16 (dd, 1 H, J = 11.2, 1.8 Hz, H-2), 7.03–7.1 (m, 3 H, Ar and H-6), 6.41 (bs, 1 H, $NHSO_2$), 5.91 (bt, 1 H, NHCO), 4.06 (dd, 1 H, J = 4, 11.5 Hz, CH_2OCO), 3.78 (dd, 1 H, J = 5, 11.5 Hz, CH_2OCO), 3.43 (q, 1 H, J = 7 Hz, C*H*CH_3), 3.36 (ddd, 1 H, C*H*$_2$NH), 2.9–3.05 (m, 4 H, C*H*$_2$NH and SO_2CH_3), 2.55 (d, 2 H, J = 7.5 Hz, CH_2Ar), 2.08 (m, 1 H, CH), 1.46 (d, 3 H, J = 7 Hz, CHC*H*$_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $COC(CH_3)_3$); IR (KBr) 3298, 2964, 1724, 1654, 1512, 1457, 1335, 1284, 1159 cm^{-1}; MS (FAB) *m*/*z* 549 (MH^+); Anal. ($C_{29}H_{41}FN_2O_5S$) C, H, N, S.

***N*-[(2*S*)-2-(4-*t*-Butylbenzyl)-3-(pivaloyloxy)propyl]-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (59).** Yield 92%, white solid, mp = 43–45 °C, [α] = +11.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.52 (t, 1 H, J = 8.25 Hz, H-5), 7.30 (d, 2 H, Ar), 7.17 (dd, 1 H, J = 11.2, 1.8 Hz, H-2), 7.0–7.1 (m, 3 H, Ar and H-6), 6.50 (bs, 1 H, $NHSO_2$), 5.90 (bt, 1 H, NHCO), 4.08 (dd, 1 H, J = 4, 11.5 Hz, CH_2OCO), 3.81 (dd, 1 H, J = 5, 11.5 Hz, CH_2OCO), 3.45 (q, 1 H, J = 7 Hz, C*H*CH_3), 3.34 (ddd, 1 H, C*H*$_2$NH), 2.9–3.1 (m, 4 H, C*H*$_2$NH and SO_2CH_3), 2.53 (ddd of AB, 2 H, CH_2Ar), 2.12 (m, 1 H, CH), 1.47 (d, 3 H, J = 7 Hz, CHC*H*$_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $COC(CH_3)_3$); IR (KBr) 3299, 2963, 1724, 1653, 1512, 1457, 1335, 1284, 1159 cm^{-1}; MS (FAB) *m*/*z* 549 (MH^+); Anal. ($C_{29}H_{41}FN_2O_5S$) C, H, N, S.

***N*-[(2*S*)-2-(4-*t*-Butylbenzyl)-3-(pivaloyloxy)propyl]-(2*S*)-2-[3-chloro-4-(methylsulfonylamino)phenyl]propionamide (60).** Yield 90%, white solid, mp = 55–57 °C, [α] = +3.24 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1 H, J = 8.4 Hz, H-5), 7.42 (d, 1 H, J = 2 Hz, H-2), 7.30 (d, 2 H, Ar), 7.23 (dd, 1 H, J = 8.4, 2 Hz, H-6), 7.05 (d, 2 H, Ar), 6.72 (bs, 1 H, $NHSO_2$), 5.91 (bt, 1 H, NHCO), 4.09 (dd, 1 H, J = 4, 11.3 Hz, CH_2OCO), 3.81 (dd, 1 H, J = 5, 11.3 Hz, CH_2OCO), 3.43 (q, 1 H, J = 7.1 Hz, C*H*CH_3), 3.34 (ddd, 1 H, C*H*$_2$NH), 2.95–3.08 (m, 4 H, C*H*$_2$NH and SO_2CH_3), 2.53 (ddd of AB, 2 H, CH_2Ar), 2.12 (m, 1 H, CH), 1.47 (d, 3 H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $COC(CH_3)_3$); IR (KBr) 3296, 2964, 1722, 1652, 1498, 1333, 1263, 1159, 1027 cm^{-1}; MS (FAB) *m*/*z* 566 (MH^+); Anal. ($C_{29}H_{41}ClN_2O_5S$) C, H, N, S.

***N*-[(2*R*)-2-Benzyl-3-(pivaloyloxy)propyl]-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (69).** Yield 89%, white solid, mp = 92∼94 °C, [α] = −8.5 (*c* 0.5, $CHCl_3$). The spectra are identical to those of **57**. MS (FAB) *m*/*z* 493 (MH^+); Anal. ($C_{25}H_{33}FN_2O_5S$) C, H, N, S.

***N*-[(2*R*)-2-Benzyl-3-(pivaloyloxy)propyl]-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (70).** Yield 87%, white solid, mp = 40–42 °C, [α] = +8.2 (*c* 0.5, $CHCl_3$). The spectra are identical to those of **56**. MS (FAB) *m*/*z* 493 (MH^+); Anal. ($C_{25}H_{33}FN_2O_5S$) C, H, N, S.

***N*-[(2*R*)-2-(4-*t*-Butylbenzyl)-3-(pivaloyloxy)propyl]-(2*R*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (71).** Yield 90%, white solid, mp = 43–45 °C, [α] = −6.7 (*c* 1.0, $CHCl_3$). The spectra are identical to those of **59**. MS (FAB) *m*/*z* 549 (MH^+); Anal. ($C_{29}H_{41}FN_2O_5S$) C, H, N, S.

***N*-[(2*R*)-2-(4-*t*-Butylbenzyl)-3-(pivaloyloxy)propyl]-(2*S*)-2-[3-fluoro-4-(methylsulfonylamino)phenyl]propionamide (72).** Yield 90%, white solid, mp = 44–46 °C, [α] = +6.6 (*c* 1.0, $CHCl_3$). The spectra are identical to those of **58**. MS (FAB) *m*/*z* 549 (MH^+); Anal. ($C_{29}H_{41}FN_2O_5S$) C, H, N, S.

***N*-[(2*R*)-2-(4-*t*-Butylbenzyl)-3-(pivaloyloxy)propyl]-(2*S*)-2-[3-chloro-4-(methylsulfonylamino)phenyl]propionamide (73).** Yield 92%, white solid, mp = 61–63 °C, [α] = −3.18 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 1 H, J = 8.4 Hz, H-5), 7.41 (d, 1 H, J = 2 Hz, H-2), 7.31 (d, 2 H, Ar), 7.22 (dd, 1 H, J = 8.4, 2 Hz, H-6), 7.07 (d, 2 H, Ar), 6.74 (bs, 1 H, $NHSO_2$), 5.93 (bt, 1 H, NHCO), 4.06 (dd, 1 H, J = 4, 11.3 Hz, CH_2OCO), 3.79 (dd, 1 H, J = 4.8, 11.3 Hz, CH_2OCO), 3.41 (q, 1 H, J = 7.1 Hz, C*H*CH_3), 3.35 (ddd, 1 H, C*H*$_2$NH), 2.95–3.05 (m, 4 H, C*H*$_2$NH and SO_2CH_3), 2.55 (d, 2 H, J = 7.5 Hz, CH_2Ar), 2.09 (m, 1 H, CH), 1.46 (d, 3 H, J = 7.1 Hz, CHC*H*$_3$), 1.30 (s, 9 H, $C(CH_3)_3$), 1.22 (s, 9 H, $COC(CH_3)_3$); IR (KBr) 3298, 2965, 1723, 1654, 1499, 1393, 1333, 1285, 1159, 1055 cm^{-1}; MS (FAB) *m*/*z* 566 (MH^+); Anal. ($C_{29}H_{41}ClN_2O_5S$) C, H, N, S.

Molecular Modeling. The structure of compound **72** was built using the Sybyl molecular modeling program (Tripos, Inc.), and then the geometry was fully optimized using the Tripos force field with the following nondefault options: (method) conjugate gradient; (termination) gradient 0.01 kcal mol^{-1} Å^{-1}; (max iterations) 10000. The partial atomic charges were calculated by the Gasteiger−Hückel method in the Sybyl program. The molecular surface maps color-coded by lipophilic potential of the binding site of TRPV1 and compound **72** were calculated using the MOLCAD program implemented in Sybyl 6.9 prior to the docking study. The docking study was conducted using the program DOCK implemented in Sybyl 6.9. The initial receptor–ligand complex was determined using graphical manipulations with continuous energy monitoring. And then the obtained complex was fully optimized by energy minimization using the Tripos force field. All computational work was done on a Silicon Graphics O2 R10000 workstation.

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Supporting Information Available: Elemental analyses data for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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