

Novel 5-Substituted 2,4-Thiazolidinedione and 2,4-Oxazolidinedione Derivatives as Insulin Sensitizers with Antidiabetic Activities

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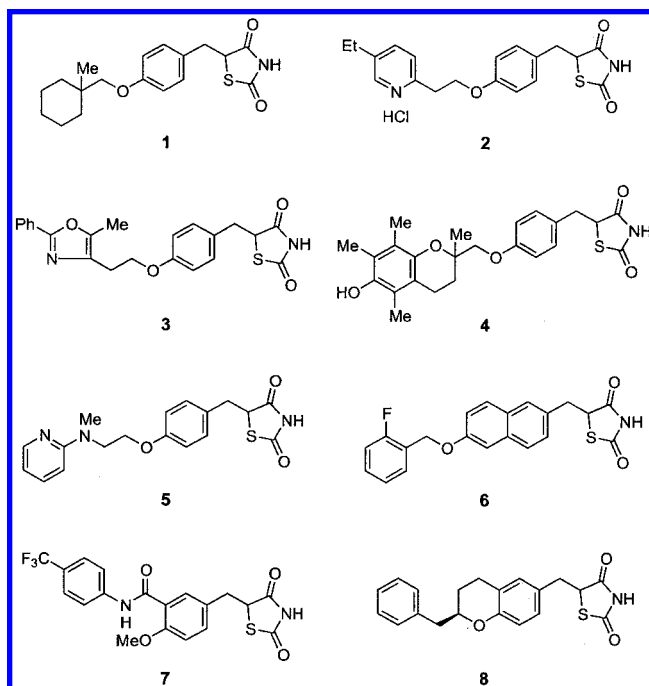
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Two novel classes of 2,4-thiazolidinediones and 2,4-oxazolidinediones with an *ω*-(azolyalkoxy-phenyl)alkyl substituent at the 5-position were prepared and their antidiabetic effects were evaluated in two genetically obese and diabetic animal models, KKA^y mice and Wistar fatty rats. A large number of the 2,4-thia(oxa)zolidinediones showed potent glucose- and lipid-lowering activities. The antidiabetic activities of the 2,4-oxazolidinediones were superior to those of the 2,4-thiazolidinediones. Among the compounds, both enantiomers of 5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione (**64**), one of the most interesting compounds in terms of activity, were synthesized by using an asymmetric *O*-acetylation of the corresponding α -hydroxyvalerate (**26**) with immobilized lipase, followed by cyclization of the oxazolidinedione ring. (*R*)-(+)-**64** showed more potent glucose-lowering activity (effective dose (ED)₂₅ = 0.561 mg/kg/d) than (*S*)-(–)-**64** (ED₂₅ > 1.5 mg/kg/d) or pioglitazone (ED₂₅ = 6 mg/kg/d) in KKA^y mice. It also exhibited a 10-fold more potent antidiabetic activity (ED₂₅ = 0.05 mg/kg/d) than pioglitazone (ED₂₅ = 0.5 mg/kg/d) in Wistar fatty rats. The antidiabetic effects of this compound are considered to be due to its potent agonistic activity for peroxisome proliferator-activated receptor γ (EC₅₀ = 8.87 nM).

Introduction

Diabetes, obesity, and cardiovascular disease are risk factors for mortality and morbidity. The number of people with diabetes is growing rapidly, and it is now estimated that about 5% of the population of developed countries is afflicted. In the U.S., about 90% of the diabetic population is classified as type 2 diabetes or impaired glucose tolerance.¹ Type 2 diabetes is characterized by hyperglycemia, which is mainly due to insulin resistance and impaired insulin secretion and leads to several complications such as neuropathy, nephropathy, retinopathy, and atherosclerosis.² Therefore, it is important to maintain an appropriate blood glucose level, especially during the early stage of the disease.³ The most commonly used oral hypoglycemics for the disease are sulfonylureas. These agents, however, induce serious hypoglycemia and exhibit primary or secondary failure, which is presumably due to their characteristics as insulin secretagogues.⁴ Thus, the use of the nonsulfonylurea class of hypoglycemics, which do not increase insulin secretion but enhance the action of insulin (insulin sensitizers), is required.⁵ In the course of our research directed toward the development of novel therapeutic agents for type 2 diabetes, we discovered the prototypical 2,4-thiazolidinedione ciglitazone **1** (Chart 1),⁶ which has antihyperglycemic activity in insulin

Chart 1



resistant animal models, KKA^y mice⁷ and Wistar fatty rats,⁸ but does not show the effect in type 1 diabetic or nondiabetic animals.⁹ During structure–activity relationship (SAR) studies on the 2,4-thiazolidinediones, we discovered two highly potent compounds, pioglitazone **2**¹⁰ and AD-5061 **3**¹¹ (Chart 1). Since our discovery of ciglitazone **1**, a number of pharmaceutical companies

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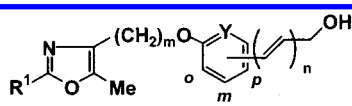
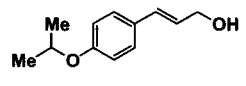
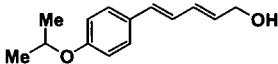
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Table 1. Physical Data and Yields of Unsaturated Alcohol **10**

									
compd	R ¹	Y	m	n	substituted position	yield ^a (%)	mp (°C)	recryst. solvent ^b	empirical formula ^c
10a	Ph	C-OMe	1	1	<i>p</i>	61	137–138	AC–E	C ₂₁ H ₂₁ NO ₄
10b	Ph	C–H	2	1	<i>p</i>	79	127–128	AC	C ₂₁ H ₂₁ NO ₃
10c	Ph	C–H	1	1	<i>p</i>	93	133–134	AC–H	C ₂₀ H ₁₉ NO ₃ ^e
10d	2-furyl	C-OMe	1	1	<i>p</i>	76	128–129	D–E	C ₁₉ H ₁₉ NO ₅
10e	Ph	C–H	1	1	<i>m</i>	75	120–121	AC	C ₂₀ H ₁₉ NO ₃
10f	Ph	C–H	1	1	<i>o</i>	76	128–129	AC–IP	C ₂₀ H ₁₉ NO ₃
10g	Ph	C–H	2	2	<i>p</i>	35	132–133	D–H	C ₂₃ H ₂₃ NO ₃
10h	Ph	N	1	1	<i>p</i>	– ^d	116–117	D–IP	C ₁₉ H ₁₈ N ₂ O ₃
10i						76	oil	–	–
10j						44	91–92	IP	C ₁₄ H ₁₈ O ₂

^a Yield from **9**. ^b See footnote b in Table 2. ^c Analytical results were within 0.4% of the theoretical value. ^d See Experimental Section. ^e •1/4H₂O.

have been evaluating new thiazolidinedione analogues as insulin sensitizers, including troglitazone **4**,¹² BRL-49653 **5**,¹³ MCC-555 **6**,¹⁴ KRP-297 **7**,¹⁵ and englitazone **8**¹⁶ (Chart 1). All, however, have a benzyl type substituent at the 5-position of the thiazolidinedione ring. We recently identified a novel series of 5-substituted-1*H*-tetrazole derivatives as insulin sensitizers and found that the trimethylene and the tetramethylene moieties were the optimal spacers between the central benzene ring and the terminal tetrazole.¹⁷ These findings led us to investigate novel thiazolidinediones and oxazolidinediones with a prolonged alkyl substituent at the 5-position.

We describe in this paper the syntheses and antidiabetic activities of two novel classes of 5-substituted 2,4-thiazolidinediones and 2,4-oxazolidinediones. The results of SAR studies on these compounds, including optically active compounds, are also discussed.

Chemistry

Each 2,4-thia(oxa)zolidinedione, as shown in Tables 4–6, was prepared from an aryl aldehyde **9** according to one of the general methods (A–D) described in the schemes below.

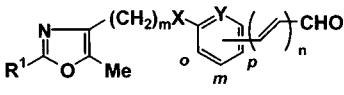
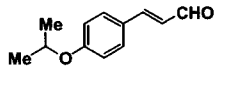
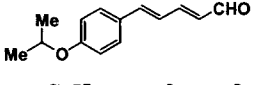
Thia(oxa)zolidinediones with a propyl or a pentyl substituent at the 5-position **12** ($n = 3$ or 5) were synthesized from the aryl aldehyde **9** via a five step process. The Horner–Emmons reaction of **9** yielded unsaturated esters, which were reduced with diisobutylaluminum hydride (DIBAL-H) to provide unsaturated alcohol **10** (Table 1). Oxidation of **10** with activated manganese dioxide yielded the corresponding unsaturated aldehyde **11** (Table 2), which was condensed with 2,4-thia(oxa)zolidinedione followed by catalytic hydro-

genation to obtain the desired product (method A, Scheme 1). Pyridine derivative **10h** was obtained by dehydrobromination of methyl 3-pyridyl-2-bromopropionate followed by DIBAL-H reduction (see Experimental Section). The Wittig reaction of **9** and subsequent catalytic hydrogenation provided the acetal **13**, which was converted into the 5-butyl-2,4-thia(oxa)zolidinedione **12** ($n = 4$) by a procedure similar to that described previously (method B, Scheme 1). For the 5-ethyl-2,4-thia(oxa)zolidinedione **12** ($n = 2$), condensation of the aldehyde **9** with pyruvic acid was employed in the first step. Catalytic hydrogenation of the intermediate **14** and subsequent reduction with sodium borohydride yielded the α -hydroxyester **15**, which was cyclized to the 2,4-oxazolidinediones by reaction with potassium cyanate. Treatment of **15** with thionyl chloride furnished the α -chloroester **16**, which was transformed into the corresponding 2,4-thiazolidinediones by reaction with thio-urea followed by acidic hydrolysis (method C, Scheme 1).

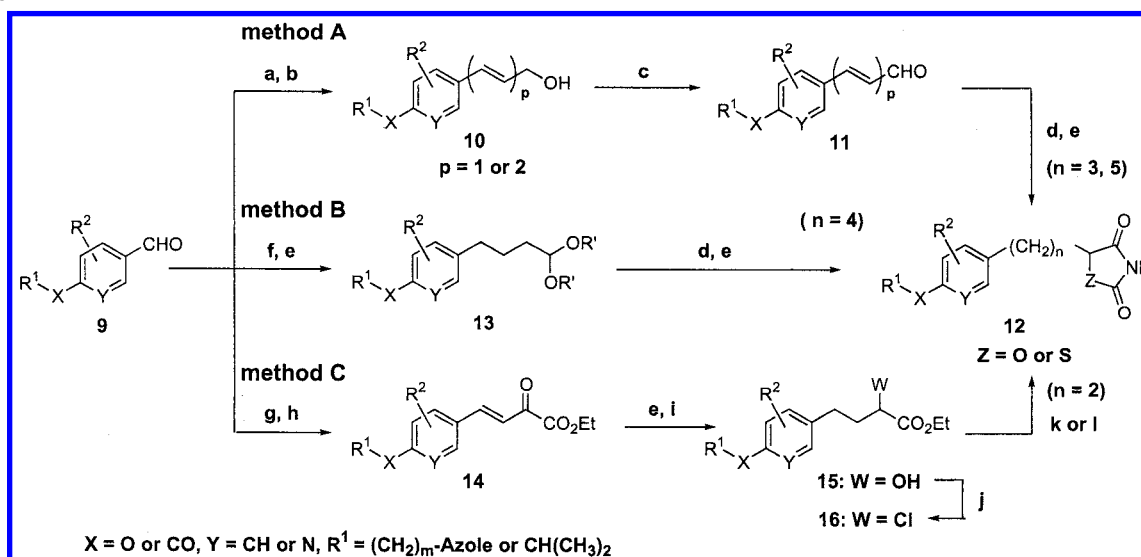
Deprotection of the phenol ether **17** and subsequent *O*-alkylation of the resultant **18** (Table 3) with the appropriate chloromethylazole **19** provided a simple method for the preparation of the azolylmethoxy derivative **12a** (method D, Scheme 2). The requisite ether **17** was synthesized from 4-isopropoxybenzaldehyde using one of the procedures described in Scheme 1.

Each optical isomer of compound **64**, one of the most potent compounds, was obtained by a synthesis involving an asymmetric *O*-acetylation as described in Scheme 3. The Horner–Emmons reaction of the starting aldehyde **20** and subsequent catalytic hydrogenation yielded the 3-arylpropionate **22**. The prolonged chain 4-arylbutyrate **23** was prepared from **22** by a five step process. Reduction of **22** with sodium borohydride in methanol

Table 2. Physical Data and Yields of Unsaturated Aldehyde **11**

										
compd	R ¹	X	Y	m	n	substituted position	yield ^a (%)	mp (°C)	recryst. solvent ^b	empirical formula ^c
11a	Ph	O	C-OMe	1	1	<i>p</i>	92	159–160	AC	C ₂₁ H ₁₉ NO ₄
11b	Ph	O	C-H	2	1	<i>p</i>	94	128–129	AC-H	C ₂₁ H ₁₉ NO ₃
11c	Ph	O	C-H	1	1	<i>p</i>	70	114–115	AC-H	C ₂₀ H ₁₇ NO ₃
11d	2-furyl	O	C-OMe	1	1	<i>p</i>	94	125–126	D-E	C ₁₉ H ₁₇ NO ₅
11e	Ph	O	C-H	1	1	<i>m</i>	96	103–104	AC-H	C ₂₀ H ₁₇ NO ₃
11f	Ph	O	C-H	1	1	<i>o</i>	92	112–113	C-IP	C ₂₀ H ₁₇ NO ₃
11g	Ph	C=O	C-H	2	1	<i>p</i>	— ^d	119–120	D-IP	C ₂₂ H ₁₉ NO ₃
11h	Ph	O	N	1	1	<i>p</i>	92	147–148	D-IP	C ₁₉ H ₁₆ N ₂ O ₃
11i							89	oil	—	—
11j							99	oil	—	—
11k	Ph	O	C-H	2	2	<i>p</i>	82	133–134	D-H	C ₂₃ H ₂₁ NO ₃ ^e

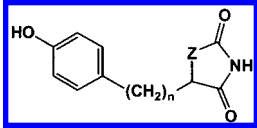
^a Yield from **10**. ^b See footnote b in Table 2. ^c Analytical results were within 0.4% of the theoretical value. ^d See Experimental Section. ^e •1/4H₂O.

Scheme 1^a

^a Key: (a) NaOMe, RO₂C(CH=CH)_{p-1}CH₂CO₂P(O)(OR)₂, DMF. (b) DIBAL-H, CH₂Cl₂. (c) MnO₂, CH₂Cl₂. (d) 2,4-Thia(oxa)zolidinedione, piperidine, EtOH. (e) H₂, Pd-C, 1,4-dioxane, EtOH. (f) NaH, Ph₃P(CH₂)₂CH(OR)₂Br, DMF. (g) Na₂CO₃, pyruvic acid, water, MeOH. (h) HCl-EtOH. (i) NaBH₄, EtOH. (j) SOCl₂. (k) KCNO, *n*-BuOH. (l) Thiourea, NaOAc, EtOH then aqueous HCl.

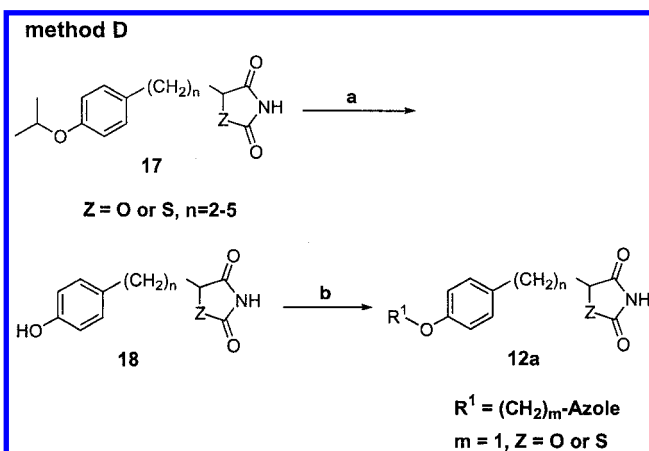
furnished the 3-arylpropanol, which was sequentially treated with methanesulfonyl chloride and sodium cyanide to yield the 4-arylbutyronitrile. Conversion of the nitrile into the butyrate **23** was accomplished by basic hydrolysis followed by esterification. Base-catalyzed condensation of **23** with diisopropyl oxalate gave the β -isopropoxycarbonyl- α -ketoester **24**, which was used for the next reaction without purification. Decarboxylation of **24** and subsequent reduction with sodium borohydride afforded the isopropyl α -hydroxyvalerate **26**. Asymmetric *O*-acetylation of **26** with immobilized lipase

gave (*R*)-acetate **27** and (*S*)-alcohol **26**, which were separated by silica gel column chromatography. Treatment of (*R*)-**27** and (*S*)-**26** with methanolic hydrogen chloride yielded the corresponding methyl α -hydroxyvalerates (*R*)- and (*S*)-**28**, respectively. Conversion of the optically active α -hydroxyesters into the oxazolidinediones was accomplished by a three step procedure without racemization. The reaction of (*R*)- and (*S*)-**28** with *p*-nitrophenyl chloroformate followed by treatment with gaseous ammonia generated carbamoyloxy derivatives, which were cyclized with 1,8-diazabicyclo[5.4.0]-

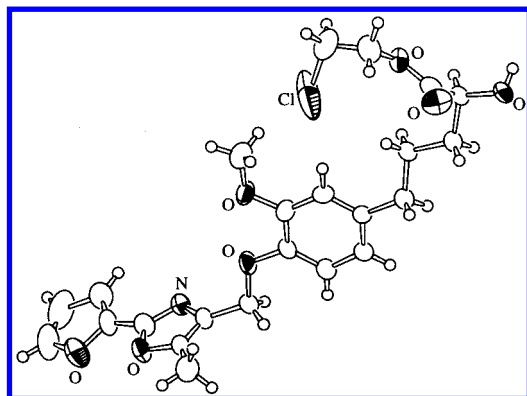
Table 3. Physical Data and Yields of 2,4-Thia(oxa)-zolidinediones


compd	<i>n</i>	Z	yield ^a (%)	mp (°C)	recryst solvent ^b	empirical formula ^c
18a	2	S	63	175–176	A–IP	C ₁₁ H ₁₁ NO ₃ S
18b	3	S	57	129–130	A–IP	C ₁₂ H ₁₃ NO ₃ S
18c	4	S	78	125–126	D–IP	C ₁₃ H ₁₅ NO ₃ S ^d
18d	5	S	49	112–113	A–IP	C ₁₄ H ₁₇ NO ₃ S
18e	3	O	59	132–133	A–H	C ₁₂ H ₁₃ NO ₄
18f	4	O	78	151–152	D–ME	C ₁₃ H ₁₅ NO ₄
18g	5	O	69	96–97	E–IP	C ₁₄ H ₁₇ NO ₄

^a Yield from **17**. ^b See footnote b in Table 2. ^c Analytical results were within 0.4% of the theoretical value. ^d •1/8H₂O.

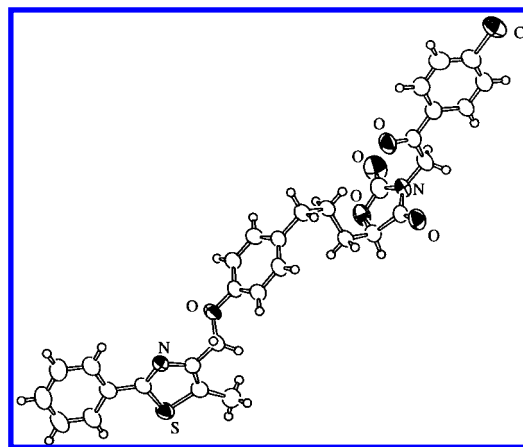
Scheme 2^a

^a Key: (a) TiCl₄, CH₂Cl₂. (b) NaH, azole–CH₂Cl (**19**), DMF.

**Figure 1.** Molecular structure of **29** as determined by X-ray crystal analysis.

undec-7-ene to give the target compounds (*R*)- and (*S*)-**64**, respectively. The absolute configuration of the final compound was determined by X-ray analysis of compound **29** (Figure 1) derived from (*S*)-**26**. This is the first synthesis of both enantiomers of the insulin sensitizer with an asymmetric center at the 5-position of the acidic 2,4-oxazolidinedione.

The absolute configuration of the more active isomer of compound **55**, one of the most interesting compounds in terms of activity and toxicity, was also determined by X-ray analysis of compound **30** (Figure 2) prepared from (*R*)-**55** as shown in Scheme 4. Compound (*R*)-**55**

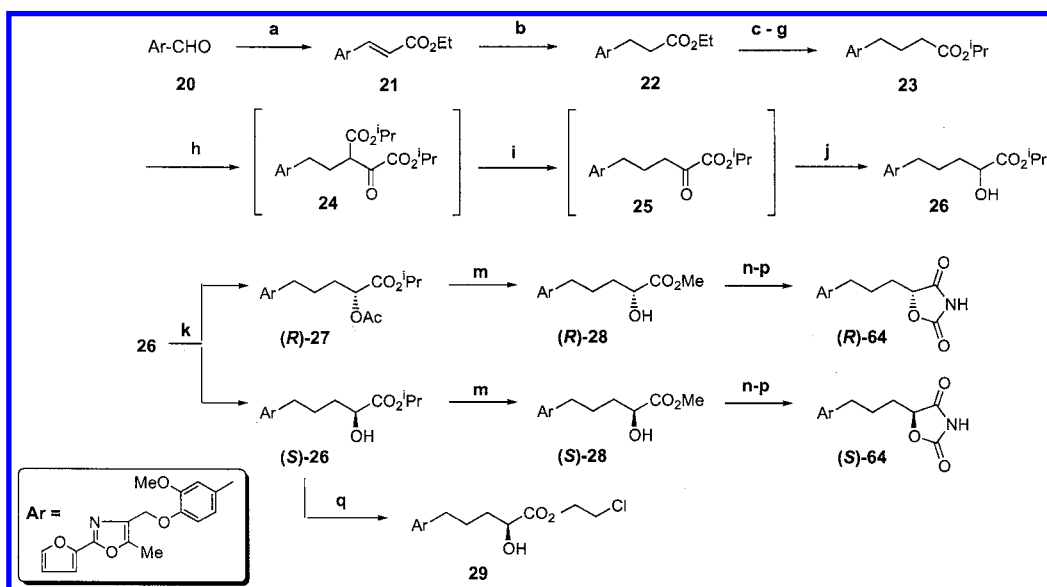
**Figure 2.** Molecular structure of **30** as determined by X-ray crystal analysis.

was obtained by separation of racemic **55** using high-performance liquid chromatography (HPLC; see Experimental Section).

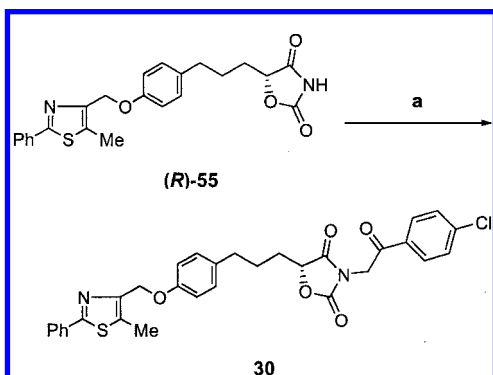
The requisite aldehydes **9** and **20** were readily prepared by the method described in previous papers.^{11,17} The 4-functionalized azoles used above were prepared using the procedure reported by Meguro and co-workers.¹⁸

Results and Discussion

All compounds synthesized were initially evaluated in KKA^y mice to determine their antidiabetic activities (Table 7). We initially examined the 2,4-thiazolidinediones with a prolonged alkyl substituent at the 5-position (**31–36**). These compounds were found to exhibit considerable antidiabetic activity. Specifically, the 3-arylpropyl derivatives (*n* = 3: **32** and **34**) were quite active. Introduction of an electron-donating methoxy group into the 3-position on the central benzene ring produced a more active compound (**37** vs **34**). The effective dose (ED)₂₅ value of 3.17 mg/kg/d for this compound was comparable to that of pioglitazone **2**. The unsaturated analogue had markedly reduced activity (**38** vs **32**). We next directed our attention to a series of 2,4-oxazolidinediones. In the ethoxy spacer-linked analogues (*m* = 2: **39–42**), the 3-arylpropyl derivative **40** was remarkably active. This finding was similar to that for the above-mentioned 2,4-thiazolidinediones. Shortening this spacer from ethoxy (*m* = 2) to methoxy (*m* = 1) resulted in a significant increase in activity (**39–42** vs **44–47**). In particular, the 3-arylpropyl derivative **45** showed significantly potent antidiabetic activity. Compound **45** (ED₂₅ = 0.402 mg/kg/d) exhibited an approximately 10-fold increase in antidiabetic activity over pioglitazone **2** (ED₂₅ = 6.0 mg/kg/d).¹⁰ Exchange of both the alkyl spacers in compound **45** (–CH₂– and –(CH₂)₃–) resulted in compound **48** with less antidiabetic activity. The carbon analogues proved to be less active (**49–51** vs **40**). Unsaturation of the trimethylene spacer on **45** resulted in a reduction of activity (**52** vs **45**), as observed for compounds **38** and **32**. The pattern of substitution of both spacers (alkoxy and alkylene) on the central benzene ring influenced potency. Both meta and ortho isomers were less active than the corresponding para analogue (**53** and **54** vs **45**). These findings suggested

Scheme 3^a

^a Key: (a) NaH, EtO₂CCH₂CO₂P(O)(OEt)₂, DMF. (b) H₂, Pd-C, AcOEt. (c) NaBH₄, MeOH, THF. (d) MsCl, Et₃N, AcOEt. (e) NaCN, DMF. (f) Aqueous KOH, 2-methoxyethanol. (g) K₂CO₃, ^tPr-I, DMF. (h) NaH, (CO₂^tPr)₂, PhMe, DMF. (i) NaCl, DMSO. (j) NaBH₄, THF, ⁱ-PrOH. (k) Immobilized lipase (LIP-301), MS-4A, vinyl acetate, PhMe. (m) HCl-MeOH. (n) ClCO₂C₆H₄(*p*-NO₂), pyridine. (o) NH₃ gas, THF. (p) DBU, CHCl₃. (q) HCl, Cl(CH₂)₂OH.

Scheme 4^a

^a Key: (a) 4-Chlorophenacyl bromide, K₂CO₃, DMF.

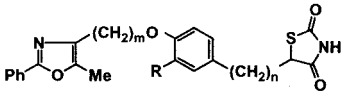
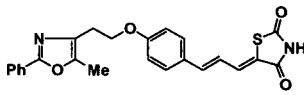
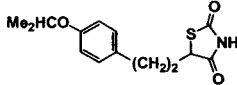
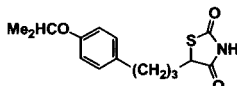
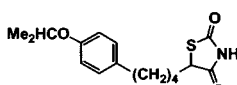
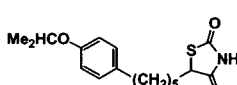
that the spatial configuration of three rings (oxazole, central benzene, and oxazolidinedione ring) connected by two alkyl spacers $-(CH_2)_m$ and $-(CH_2)_n$ plays an important role in increasing activity. Replacement of the oxazole ring of **45** with a thiazole moiety resulted in a decrease of activity (**55** vs **45**). As discussed above, the 5-(3-phenylpropyl)-2,4-oxazolidinedione with an oxazolylmethoxy moiety at the para-position on the 3-phenyl ring appeared to yield the most activity. We therefore explored substituted variations around the oxazole ring and the 3-phenyl ring. The oxazolyl analogue without a 5-methyl group had reduced activity (**56** vs **45**). Substitutions on the oxazole ring at the 2-position favored monocyclic aryl moieties rather than bicyclic aryl moieties (**45** and **59** vs **57**, **58**, **60**, and **61**). Replacement of the central benzene ring with a pyridine ring resulted in an enhancement of activity (**45** vs **62**). Introduction of a methoxy group into the central benzene ring preserved the activity (**45** vs **63** and **59** vs **64**).

A number of potent analogues (**45**, **55**, **58**, **62**, and **64**) were tested for transcriptional activity against peroxisome proliferator-activated receptor γ (PPAR γ) and antidiabetic activity in Wistar fatty rats.⁸ As shown

in Table 8, all compounds exhibited remarkable anti-hyperglycemic activity. Moreover, similar SARs were observed among the in vitro activities for PPAR γ and the in vivo antidiabetic activities in Wistar fatty rats and KKA^y mice as expected.¹⁹ On the other hand, various azolidinedione derivatives were reported as inhibitors of protein tyrosine phosphatase (PTP) 1B with antihyperglycemic properties.²⁰ In particular, oxadiazolidinediones with both the hydrophobic substituents on the benzene ring at the 2-position of the oxazole ring and long and/or bulky lipophilic substituents on the carbon chain between the central benzene ring and the oxadiazolidinedione ring showed potent PTP 1B inhibitory activity, whereas the inhibitory activity of the corresponding oxazolidinedione derivatives was weak. This information suggested that the antidiabetic effects of the novel 5-substituted thiazolidinedione and oxazolidinedione derivatives prepared might be due to their potent agonistic activities for PPAR γ .

The effect of stereochemistry at the 5-position of the 2,4-oxazolidinedione ring of compound **64**, one of the most active compounds, was examined next. (*R*)-(+)-**64** was clearly more potent than its enantiomer, (*S*)-(–)-**64**, in both diabetic models and activity for PPAR γ in vitro (Table 8). Compound **55** also showed a similar tendency, with (*R*)-(+)-**55** having more potent antihyperglycemic activity and transcriptional activity for PPAR γ than (*S*)-(–)-**55** as shown in Table 8. Furthermore, both enantiomers of compound **64** were also evaluated for their racemization in JclSD rats by intravenous administration. After administration of either (*R*)-(+)-**64** or (*S*)-(–)-**64**, the antipode of each enantiomer in plasma was negligible as shown in Table 9. This finding suggested that in vivo racemization, which was observed for the 2,4-thiazolidinedione pioglitazone, would not take place in the 2,4-oxazolidinediones with a prolonged alkyl substituent at the 5-position. It is noteworthy that this is the first example of the chiral

Table 4. Physical Data and Yields of 2,4-Thiazolidinediones

								
compd	R	m	n	prep. method ^a	yield (%)	mp (°C)	recryst. solvent ^b	empirical formula ^c
31	H	2	2	C	56 ^d	151–152	D–ET	C ₂₃ H ₂₂ N ₂ O ₄ S
32	H	2	3	A	13 ^e	151–152	AC–H	C ₂₄ H ₂₄ N ₂ O ₄ S
33	H	1	2	D	58 ^f	146–147	D–IP	C ₂₂ H ₂₀ N ₂ O ₄ S
34	H	1	3	D	65 ^f	165–166	D–ME	C ₂₃ H ₂₂ N ₂ O ₄ S
35	H	1	4	D	26 ^f	184–185	D–ME	C ₂₄ H ₂₄ N ₂ O ₄ S
36	H	1	5	D	49 ^f	107–108	D–ME	C ₂₅ H ₂₆ N ₂ O ₄ S
37	OMe	1	3	A	15 ^e	118–120	AC–E–H	C ₂₄ H ₂₄ N ₂ O ₅ S
38				A	24 ^e	222–223	C–ME	C ₂₄ H ₂₀ N ₂ O ₄ S
17a				C	quant. ^d	oil	–	–
17b				A	39 ^e	oil	–	–
17c				B	68 ^g	72–73	E–H	C ₁₆ H ₂₁ NO ₃ S
17d				A	26 ^e	oil	–	–

^a See schemes in Chemistry section. ^b AC = ethyl acetate, C = chloroform, D = dichloromethane, E = diethyl ether, ET = ethanol, H = hexane, IP = isopropyl ether, ME = methanol. ^c Analytical results were within 0.4% of the theoretical value. ^d Yield from **16**. ^e Yield from **11**. ^f Yield from **18**. ^g Yield from **13**.

insulin sensitizer with an asymmetric center on its five-membered acidic heterocycle and that the more active isomer is the (*R*)-(+)-enantiomer different from a series of antidiabetic α -alkoxy, α -thio, and α -aminopropionic acids.²¹

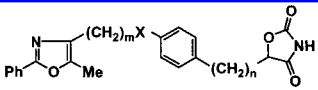
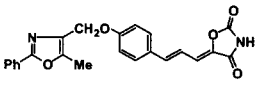
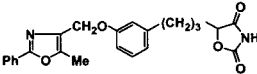
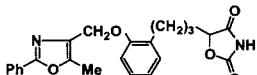
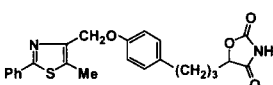
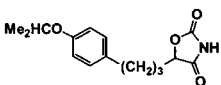
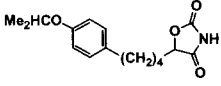
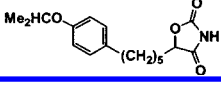
In summary, we showed that a series of 2,4-thia(oxa)-zolidinediones with a prolonged alkyl substituent at the 5-position have potent antidiabetic effects in two genetically obese and diabetic models, KKA^y mice and Wistar fatty rats. The antidiabetic effects of these compounds are considered to be due to potent agonistic activities for PPAR γ . We also succeeded in the enantiospecific synthesis of 5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolyl-methoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione (**64**), one of the most interesting compounds in terms of activity, by asymmetric *O*-acetylation of the corresponding α -hydroxyvalerate (**26**) with immobilized lipase, followed by cyclization of the oxazolidinedione ring. The results of the SAR studies identified that the spatial configuration of the three rings (oxazole, central

benzene, and 2,4-thia(oxa)zolidinedione) connected by two alkyl spacers $-(CH_2)_m-$ and $-(CH_2)_n-$ plays an important role in increasing activity. Furthermore, we found that the (*R*)-(+)-enantiomers of 2,4-oxazolidinediones were more potent than the corresponding (*S*)-(–)-isomers different from a series of antidiabetic α -alkoxy, α -thio, and α -aminopropionic acids.²¹

Experimental Section

Biological Methods. In Vitro. COS-1 cells were seeded at 5×10^6 cells in a 150 cm² tissue culture flask and cultured in 5% CO₂ at 37 °C overnight. Transfection was performed with LipofectAMINE (Life Technologies, Inc., USA) according to the instructions of the manufacturer. Briefly, the transfection mixture contained 125 μ L of LipofectAMINE, 100 μ L of LipofectAMINE Plus, 2.5 μ g of each expression plasmid pMCMVneo-hPPAR γ and pMCMVneo-hRXR α , 5 μ g of reporter plasmid pGL3-PPRE \times 4-tk-luc-neo, and 5 μ g of pRL-tk (Promega, USA). Cells were incubated in 25 mL of transfection mixture for 3 h in 5% CO₂ at 37 °C. After 25 mL of Dulbecco's

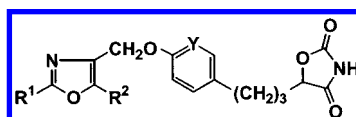
Table 5. Physical Data and Yields of 2,4-Oxazolidinediones

								
compd	X	m	n	prep. method ^a	yield (%)	mp (°C)	recryst. solvent ^b	empirical formula ^c
39	O	2	2	C	63 ^f	193–194	D–ET	C ₂₃ H ₂₂ N ₂ O ₅
40	O	2	3	A	20 ^g	162–163	AC–H	C ₂₄ H ₂₄ N ₂ O ₅
41	O	2	4	B	16 ^h	136–137	D–ME	C ₂₅ H ₂₆ N ₂ O ₅
42	O	2	5	A	24 ^g	157–158	D–ME	C ₂₆ H ₂₈ N ₂ O ₅
43	O	1	1	— ^d	—	—	—	—
44	O	1	2	C	35 ^f	158–159	AC–H	C ₂₂ H ₂₀ N ₂ O ₅
45	O	1	3	A	14 ^g	157–158	AC–H	C ₂₃ H ₂₂ N ₂ O ₅
46	O	1	4	D	32 ⁱ	186–187	D–IP	C ₂₄ H ₂₄ N ₂ O ₅
47	O	1	5	D	58 ⁱ	120–121	D–IP	C ₂₅ H ₂₆ N ₂ O ₅
48	O	3	1	— ^e	16 ^j	150–151	C–E	C ₂₃ H ₂₂ N ₂ O ₅
49	C=O	2	3	A	14 ^g	184–185	D–ME	C ₂₅ H ₂₄ N ₂ O ₅
50	CHOH	2	3	— ^e	64 ^k	150–151	A–IP	C ₂₅ H ₂₆ N ₂ O ₅
51	CH ₂	2	3	— ^e	82 ^l	119–120	ME–ET	C ₂₅ H ₂₆ N ₂ O ₄ ^m
52				A	26 ^g	244–245	C–ME	C ₂₃ H ₁₈ N ₂ O ₅ ⁿ
53				A	14 ^g	134–135	AC–H	C ₂₃ H ₂₂ N ₂ O ₅
54				A	17 ^g	158–159	C–ME–E	C ₂₃ H ₂₂ N ₂ O ₅
55				D	71 ⁱ	104–105	D–IP	C ₂₃ H ₂₂ N ₂ O ₄ S
17e				A	20 ^g	oil	—	—
17f				B	27 ^h	81–82	D–IP	C ₁₆ H ₂₁ NO ₄
17g				A	26 ^j	oil	—	—

^a See schemes in Chemistry section. ^b A = acetone, AC = ethyl acetate, C = chloroform, D = dichloromethane, E = diethyl ether, ET = ethanol, H = hexane, IP = isopropyl ether, ME = methanol. ^c Analytical results were within 0.4% of the theoretical value. ^d See ref 16. ^e See Experimental Section. ^f Yield from **15**. ^g Yield from **11**. ^h Yield from **13**. ⁱ Yield from **18**. ^j Yield from benzaldehyde **9**. ^k Yield from **51**. ^l Yield from **52**. ^m •1/2H₂O. ⁿ •1/8H₂O.

modified Eagle's medium (DMEM) (Nikken Bio Medical Lab, Japan) containing 0.1% fatty acid free bovine serum albumin (BSA) was added, the cells were then incubated for 24 h in 5% CO₂ at 37 °C. After transfection, cells were detached by treating with trypsin–ethylenediaminetetraacetic acid (EDTA) (Life Technologies INC., USA) centrifuged, and then suspended in DMEM medium containing 0.1% fatty acid free BSA. The suspended cells were added in an OPAQUE PLATE (white 96 well plate, COSTAR) at the density of 8.8×10^3 cells/well in 80 μ L of DMEM medium containing 0.1% fatty acid free BSA and 20 μ L of test compounds and cultured in 5% CO₂ at 37 °C

for 48 h. After the medium was removed, 40 μ L of PICAGENE 7.5 (Wako Pure Chemical Ind. Ltd.) was added, and after this was stirred, luciferase activity was determined using Lumistar (BMG Labtechnologies GmbH, Germany). The degree of induction was calculated based on the luciferase activity of each test substance with the luciferase activity in the non-treated group regarded as 1. The values of the test substance concentration and the degree of induction were analyzed using PRISM 2.01 (GraphPad Software Inc., USA) to calculate the EC₅₀, the effective concentration of a compound for the

Table 6. Physical Data and Yields of 2,4-Oxazolidinediones

compd	R ¹	R ²	Y	prep method ^a	yield (%)	mp (°C)	recryst solvent ^b	empirical formula ^c
45	Ph	Me	C–H	A	14 ^d	157–158	AC–H	C ₂₃ H ₂₂ N ₂ O ₅
56	Ph	H	C–H	D	72 ^e	167–168	D–ME	C ₂₂ H ₂₀ N ₂ O ₅
57	1-naphthyl	Me	C–H	D	72 ^e	oil		C ₂₇ H ₂₄ N ₂ O ₅
58	2-naphthyl	Me	C–H	D	84 ^e	151–152	D–ME	C ₂₇ H ₂₄ N ₂ O ₅
59	2-furyl	Me	C–H	D	74 ^e	146–147	D–IP	C ₂₁ H ₂₀ N ₂ O ₆
60	2-benzofuranyl	Me	C–H	D	70 ^e	165–166	D–IP	C ₂₅ H ₂₂ N ₂ O ₆
61	2-benzothienyl	Me	C–H	D	76 ^e	154–155	D–IP	C ₂₅ H ₂₂ N ₂ O ₅ S
62	Ph	Me	N	A	22 ^d	oil		C ₂₂ H ₂₁ N ₃ O ₅ ⁱ
63	Ph	Me	C–OMe	A	16 ^d	161–162	AC–H	C ₂₄ H ₂₄ N ₂ O ₆
64	2-furyl	Me	C–OMe	A	14 ^d	127–129	D–E	C ₂₂ H ₂₂ N ₂ O ₇ ⁱ
(+)- 64	2-furyl	Me	C–OMe	– ^f	91 ^g	122–123	A–IP	C ₂₂ H ₂₂ N ₂ O ₇
(–)- 64	2-furyl	Me	C–OMe	– ^f	91 ^h	122–123	A–IP	C ₂₂ H ₂₂ N ₂ O ₇

^a See schemes in Chemistry section. ^b See footnote b in Table 2. ^c Analytical results were within 0.4% of the theoretical value. ^d Yield from **11**. ^e Yield from **18**. ^f See Experimental Section. ^g Yield from (*R*)-**28**. ^h Yield from (*S*)-**28**. ⁱ 1/2H₂O.

Table 7. Glucose- and Lipid-Lowering Activities of 2,4-Thia(Oxa)zolidinediones in KKA^y Mice

compd	glucose-lowering activity ^a				lipid-lowering activity ^a			
	dose (%)			ED ₂₅ ^b	dose (%)			ED ₂₅ ^b
	0.001	0.005	0.01		0.001	0.005	0.01	
31		14				32*		
32		26**	35**			18	42*	
33		24*				15		
34	LA ^d	48**			LA	37*		
35		22*				21		
36		19				LA		
37	12	54**		3.17	24	58**		
38		13				13		
39	18	56**		4.83	15	53**		
40	11	49**		2.91	26	41*		
41		27**				27		
42		23*				17		
43		29*				LA		
44	28**	63**		1.31	13	60**		
45	53**	61**		0.402	55**	83**		
46		43**				51*		
47		45**				59**		
48		30**				25		
49		32*				17		
50		23				22		
51		22*				19		
52		23*				29		
53		32**		45**			24	47**
54		11		LA			30	33
55	15	43**			2.61	17	58**	
56		44**					42**	
57		23**					19*	
58	45**	55**			0.629	40**	72**	
59	38**	61**				38*	58**	
60	27	47**			0.823	12	71**	
61	25**	48**			1.297	24	62**	
62	53**	54**			0.274	69**	82**	
63	48**	61**				29*	75**	
64	39**	58**			0.631	LA	74**	
(+)- 64	45**				0.561	32*		
(–)- 64		LA			>1.5	LA		
1	ciglitazone				31			25
2	pioglitazone·HCl				6.0			6.0

^a Maximum reductions in plasma glucose and plasma triglyceride levels at a dosage of 0.001, 0.005, or 0.01% in the diet were calculated as percent reduction with respect to the control value. ^b ED (mg/kg/d) for 25% reduction, estimated from a dose–response curve for three doses. ^c Statistically significant at (*) $p < 0.05$, (**) $p < 0.01$ by Dunnett's test. ^d Less than 10% reduction at this dosage.

induction of 50% of maximum activity, and the 95% confidence interval.

In Vivo. The glucose- and lipid-lowering activities of the compounds prepared were tested using KKA^y mice⁶ and Wistar fatty rats.⁷

(a) KKA^y Mice (9–13 Weeks Old). (i) First Screening. After they were fed a powdered laboratory chow (CE-2, Clea

Japan Inc., Tokyo, Japan) for 3 d, the mice were divided into experimental groups of five animals each based on their blood glucose levels. The test compounds were given as a dietary admixture at 0.01, 0.005, or 0.001% in the diet. The mice were fed the experimental diet and water ad libitum for 4 d. Blood samples were taken from the orbital vein. The plasma glucose and plasma triglyceride levels were determined by enzyme

Table 8. Glucose-Lowering Activities in KKA γ Mice and Wistar Fatty Rats and Transcriptional Activities for PPAR γ of 2,4-Thia(Oxa)zolidinediones

compd	glucose-lowering activity (ED ₂₅) ^a		transcriptional activity for PPAR γ EC ₅₀ (95% confidence interval) (nM) ^b
	KKA γ mice	Wistar fatty rats	
45	0.402	0.078	119 (66.4–214)
55	2.61	0.50	813 (314–2110)
(+)- 55	1.44	0.23	269 (172–420)
(-)- 55	ND ^c	3.0	>1000
58	0.629	0.178	29.3 (22.0–39.0)
62	0.274	0.048	16.5 (9.67–28.1)
64	0.631	0.069	24.1 (11.3–51.3)
(+)- 64	0.561	0.050	8.87 (4.33–18.1)
(-)- 64	>1.5	0.362	35.4 (20.8–60.3)
2 (pioglitazone·HCl)	6	0.5	490 ^d (400–610)

^a See footnote b in Table 4. ^b Concentration required to induce 50% of the maximum luciferase activity. ^c Not determined. ^d See ref 22.

Table 9. Plasma Concentrations of (*R*)-(+)-**64** and (*S*)-(-)-**64** in JclSD Rats after Intravenous Administration of Each Enantiomer

compd	time (min)	plasma concn (μ g/mL) ^a	
		(<i>R</i>)-(+)- 64	(<i>S</i>)-(-)- 64
(<i>R</i>)-(+)- 64 ^c (1 mg/kg)	pre	nd ^b	nd
	5	6.46 \pm 0.82	0.02 \pm 0.00
	10	6.06 \pm 0.83	0.02 \pm 0.01
	15	5.13 \pm 0.53	0.02 \pm 0.00
	30	4.78 \pm 0.73	0.02 \pm 0.00
	60	3.19 \pm 0.65	0.02 \pm 0.00
	120	1.46 \pm 0.37	nd
(<i>S</i>)-(-)- 64 ^d (1 mg/kg)	pre	nd	nd
	5	0.04 \pm 0.01	4.78 \pm 0.50
	10	0.04 \pm 0.01	4.30 \pm 0.23
	15	0.04 \pm 0.01	3.97 \pm 0.42
	30	0.05 \pm 0.02	3.65 \pm 0.67
	60	0.07 \pm 0.02	2.94 \pm 0.21
	120	0.07 \pm 0.02	1.61 \pm 0.26

^a The results are the mean \pm SD of three male animals in each group. ^b Not detected (below the lower quantitation limit (0.01 mg/mL)). ^c 99%ee by HPLC. ^d 98%ee by HPLC.

methods using the Iatrochem-GLU(A) and Iatro-MA701 TG kits (Iatron Laboratories, Inc., Tokyo, Japan), respectively. The respective values are shown as percent reduction from the control value.

(ii) Determination of the ED₂₅. The ED to reduce plasma glucose and triglyceride levels by 25% (ED₂₅) was determined using results of an experiment in which three different doses were tested as shown above. The doses were selected in accordance with the potency of the compound, which was estimated from the result of the first screening. The dosages of test compounds (mg/kg/d) were calculated using data of total food intake and average body weight. The ED₂₅ (mg/kg/d) was then derived by linear regression analysis.

(b) Wistar Fatty Rats (10–15 Weeks Old). The rats were divided into experimental groups of five animals each based on their plasma glucose and triglyceride levels. They were orally administered the compounds suspended in 0.5% methyl cellulose (Wako Pure Chemicals Ind., Osaka, Japan) at three different concentrations once per day for 6 d via a stomach tube. They were fed a CE-2 pellet diet and water ad libitum. Blood samples were taken from a tail vein. Plasma glucose and triglyceride levels were measured, and the ED₂₅ was estimated in the same fashion as described above.

Plasma Concentration Analysis. (a) Administration. Experiments were carried out in JclSD rats (8 weeks old, male, $n = 3$). The animals were fed laboratory chow (CE-2) and water ad libitum. Compounds were administered intravenously at a dose of 1 mg/kg in a *N,N*-dimethylacetamide–poly(ethylene

glycol) 400 (1:9) solution. Blood samples were collected from a tail vein. The samples were analyzed by HPLC to calculate plasma concentration.

(b) Analysis of Plasma Samples. (i) Sample Preparation. Acetonitrile (300 μ L) was added to each plasma sample (100 μ L). The mixture was vortex-mixed followed by centrifugation at 10 000 rpm for 5 min. The supernatant (300 μ L) was collected and dried up under a nitrogen gas stream. The residue was dissolved in 200 μ L of acetonitrile–0.02 mol/L potassium dihydrogenphosphate (43:57, v/v), and an aliquot of 50 μ L was injected into the HPLC analysis.

(ii) HPLC Assay. CHIRALCEL OJ-R (4.6 mm i.d. \times 150 mm (Daicel Chemical Industries, Ltd., Tokyo, Japan)) was used for HPLC analysis. Analyses of samples were carried out using acetonitrile–0.02 mol/L potassium dihydrogenphosphate (38:62, v/v) as a mobile phase at a flow rate of 0.6 mL/min and 40 $^{\circ}$ C. Detection was carried out at UV 283 nm. Under these conditions, the retention times for (*R*)-(+)-**64** and (*S*)-(-)-**64** were 13.7 and 15.7 min, respectively.

Chemical Methods. All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as an internal standard, and coupling constants (*J*) are given in hertz. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. Elemental analyses were performed by Takeda Analytical Research Laboratories, Ltd., and results obtained were within $\pm 0.4\%$ of the theoretical values. Column chromatography was performed using SiO₂ (Merck Kieselgel 60, 70–230 mesh).

Method A. General Procedure for Unsaturated Alcohols (10). (*E*)-3-[3-Methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]-2-propen-1-ol (**10a**). Sodium methoxide (28% in MeOH, 16.0 g, 82.9 mmol) was added to a stirred solution of 3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)-benzaldehyde (25.5 g, 78.8 mmol) and trimethyl phosphonoacetate (15.1 g, 82.9 mmol) in dimethylformamide (DMF; 120 mL) at 0 $^{\circ}$ C. After the mixture was stirred for 2 h, the reaction mixture was poured into water to give crystals that were collected and recrystallized from AcOEt–CHCl₃–Et₂O to give methyl (*E*)-3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)-cinnamate as colorless needles (21.9 g, 73%). ^1H NMR (CDCl₃): δ 2.43 (3H, s), 3.80 (3H, s), 3.89 (3H, s), 5.10 (2H, s), 6.32 (1H, d, *J* = 16 Hz), 7.0–7.15 (3H, m), 7.35–7.55 (3H, m), 7.63 (1H, d, *J* = 16 Hz), 7.9–8.1 (2H, m). IR (KBr) (cm⁻¹): 1700, 1635, 1505. Anal. Calcd for C₂₂H₂₁NO₅: C, 69.65; H, 5.58; N, 3.69. Found: C, 69.68; H, 5.66; N, 3.50.

Diisobutylaluminum hydride (1.5 M solution in toluene, 79 mL, 119 mmol) was added dropwise to a stirred solution of methyl (*E*)-3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)-cinnamate (21.5 g, 56.7 mmol) in CH₂Cl₂ (120 mL) at 0 $^{\circ}$ C. After the mixture was stirred at room temperature for 1.5 h, MeOH (12 mL) and water (12 mL) were added to the mixture with cooling. The reaction mixture was acidified with concentrated HCl and extracted with CH₂Cl₂. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo to give the title compound as colorless crystals (**10a**, 16.5 g, 83%). Recrystallization from AcOEt–Et₂O gave colorless prisms; mp 137–138 $^{\circ}$ C. ^1H NMR (CDCl₃): δ 2.41 (3H, s), 3.88 (3H, s), 4.25–4.4 (2H, m), 5.06 (2H, s), 6.25 (1H, dt, *J* = 16, 6 Hz), 6.55 (1H, d, *J* = 16 Hz), 6.85–7.05 (3H, m), 7.35–7.55 (3H, m), 7.9–8.1 (2H, m). IR (KBr) (cm⁻¹): 1510. Anal. (C₂₁H₂₁NO₄) C, H, N. Compounds **10b**–**10f** and **10i** were obtained similarly. The yields, recrystallization solvents, melting points, and elemental analyses were listed in Table 1. **10b**: ^1H NMR (CDCl₃): δ 1.42 (1H, t, *J* = 6 Hz), 2.27 (3H, s), 2.98 (2H, t, *J* = 6.5 Hz), 4.25 (2H, t, *J* = 6.5 Hz), 4.25–4.35 (2H, m), 6.22 (1H, dt, *J* = 16, 6 Hz), 6.55 (1H, d, *J* = 16 Hz), 6.86 (2H, d, *J* = 9 Hz), 7.30 (2H, d, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.9–8.05 (2H, m). **10c**: ^1H NMR (CDCl₃): δ 2.44 (3H, s), 4.25–4.35 (2H, m), 5.00 (2H, s), 6.25 (1H, dt, *J* = 16, 6 Hz), 6.57 (1H, d, *J* = 16 Hz), 6.98 (2H, d, *J* = 9 Hz), 7.34 (2H, d, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.95–8.1 (2H, m). **10d**: ^1H NMR (CDCl₃): δ 1.45

(1H, br s), 2.40 (3H, s), 3.88 (3H, s), 4.25–4.35 (2H, m), 5.05 (2H, s), 6.25 (1H, dt, $J = 16$, 6 Hz), 6.5–6.6 (2H, m), 6.85–7.0 (3H, m), 7.5–7.55 (1H, m). IR (KBr) (cm^{-1}): 3380, 1515. **10e**: ^1H NMR (CDCl_3): δ 1.49 (1H, t, $J = 6$ Hz), 2.44 (3H, s), 4.25–4.4 (2H, m), 5.01 (2H, s), 6.37 (1H, dt, $J = 16$, 5.5 Hz), 6.60 (1H, d, $J = 16$ Hz), 6.85–7.1 (3H, m), 7.25 (1H, t, $J = 8$ Hz), 7.4–7.55 (3H, m), 7.95–8.1 (2H, m). **10f**: ^1H NMR (CDCl_3): δ 2.40 (3H, s), 4.25–4.4 (2H, m), 5.02 (2H, s), 6.37 (1H, dt, $J = 16$, 6 Hz), 6.9–7.1 (3H, m), 7.15–7.3 (1H, m), 7.4–7.5 (4H, m), 7.95–8.1 (2H, m). **10i**: ^1H NMR (CDCl_3): δ 1.33 (6H, d, $J = 6$ Hz), 1.38 (1H, t, $J = 6$ Hz), 4.30 (2H, dt, $J = 6$, 1.5 Hz), 4.45–4.65 (1H, m), 6.23 (1H, dt, $J = 16$, 6 Hz), 6.56 (1H, d, $J = 16$ Hz), 6.84 (2H, d, $J = 8.5$ Hz), 7.31 (2H, d, $J = 8.5$ Hz). IR (neat) (cm^{-1}): 3360, 1650, 1605, 1570, 1510.

(E)-3-[6-(5-Methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]-2-propen-1-ol (10h). An ice-cooled solution of 5-methyl-2-phenyl-4-oxazolylmethanol (8.00 g, 42.3 mmol) and 2-chloro-5-nitropyridine (7.04 g, 44.4 mmol) in DMF (150 mL) was treated with sodium hydride (60% in oil, 1.78 g, 44.5 mmol) for 3 h, poured onto ice-water, and neutralized with 2 N HCl to give 2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-nitropyridine (11.0 g, 84%); mp 142–143 °C (CH_2Cl_2 –isoPr₂O). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4$: C, 68.31; H, 5.37; N, 14.94. Found: C, 67.98; H, 5.35; N, 15.10.

A mixture of 2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-nitropyridine (6.00 g, 19.3 mmol), 5% Pd–C (50% wet, 4.00 g), tetrahydrofuran (THF) (80 mL), and EtOH (80 mL) was hydrogenated at 1 atm. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo to give 5-amino-2-(5-methyl-2-phenyl-4-oxazolylmethoxy)pyridine (4.83 g, 81%); mp 106–107 °C (MeOH –isoPr₂O). ^1H NMR (CDCl_3): δ 2.46 (3H, s), 3.39 (2H, br s), 5.21 (2H, s), 6.68 (1H, d, $J = 9$ Hz), 7.04 (1H, dd, $J = 9$, 3 Hz), 7.35–7.5 (3H, m), 7.67 (1H, d, $J = 3$ Hz), 7.95–8.1 (2H, m). Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.39; H, 4.18; N, 13.57.

A solution of sodium nitrite (1.08 g, 15.7 mmol) in water (2 mL) was added dropwise to a stirred and ice-cooled mixture of 5-amino-2-(5-methyl-2-phenyl-4-oxazolylmethoxy)pyridine (4.00 g, 14.2 mmol), aqueous hydrogen bromide (47%, 12.2 g, 70.9 mmol), and acetone (80 mL) below 5 °C. After the solution was stirred for 30 min, methyl acrylate (6.12 g, 71.1 mmol) was added and the temperature was raised to 20 °C. Powdered copper(I) oxide (200 mg) was added gradually to the vigorously stirred mixture. After a nitrogen gas evolution had ceased, the reaction mixture was concentrated in vacuo. The residue was diluted with water, made alkaline with concentrated ammonium hydroxide, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated to leave an oil that was purified by column chromatography on SiO_2 (80 g) with AcOEt–hexane (1:5, v/v) to give methyl 2-bromo-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propionate as a colorless oil (2.27 g, 37%). ^1H NMR (CDCl_3): δ 2.48 (3H, s), 3.18 (1H, dd, $J = 14.5$, 7 Hz), 3.39 (1H, dd, $J = 14.5$, 8 Hz), 3.76 (3H, s), 4.34 (1H, dd, $J = 8$, 7 Hz), 5.28 (2H, s), 6.78 (1H, d, $J = 8.5$ Hz), 7.35–7.5 (4H, m), 7.95–8.1 (3H, m).

A mixture of methyl 2-bromo-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propionate (4.00 g, 9.27 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.41 g, 9.26 mmol), and toluene (60 mL) was stirred at 90–100 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated to leave an oil that was purified by column chromatography on SiO_2 (60 g) with AcOEt–hexane (1:3, v/v) to give methyl (E)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]acrylate (2.71 g, 83%); mp 116–117 °C (Et_2O –isoPr₂O). ^1H NMR (CDCl_3): δ 2.40 (3H, s), 3.81 (3H, s), 5.33 (2H, s), 6.34 (1H, d, $J = 16$ Hz), 6.84 (1H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.65 (1H, d, $J = 16$ Hz), 7.78 (1H, dd, $J = 8.5$, 2.5 Hz), 7.95–8.1 (2H, m), 8.29 (1H, d, $J = 2.5$ Hz). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.41; H, 5.09; N, 8.06.

DIBAL-H (1.03 M in hexane, 17.3 mL, 17.8 mmol) was added dropwise to a stirred and ice-cooled solution of methyl (E)-3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]acry-

late (2.50 g, 7.14 mmol) in CH_2Cl_2 (100 mL). After the mixture was stirred for 2 h, the reaction mixture was quenched with MeOH (1 mL)–water (2 mL) at 0 °C. The insoluble material was removed by filtration, and then, the filtrate was concentrated to leave an oil that was purified by column chromatography on SiO_2 (60 g) with AcOEt–hexane (1:1, v/v) to give the title compound (**10h**, 1.75 g, 76%); mp 116–117 °C (CH_2Cl_2 –isoPr₂O). ^1H NMR (CDCl_3): δ 1.65 (1H, br s), 2.48 (3H, s), 4.32 (2H, br t, $J = 5$ Hz), 5.29 (2H, s), 6.26 (1H, dt, $J = 16$, 5.5 Hz), 6.56 (1H, d, $J = 16$ Hz), 6.78 (1H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.66 (1H, dd, $J = 8.5$, 2.5 Hz), 7.95–8.1 (2H, m), 8.12 (1H, d, $J = 2.5$ Hz). Anal. ($\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$) C, H, N.

(2E,4E)-5-(4-Isopropoxyphenyl)-2,4-pentadien-1-ol (10j). To an ice-cooled solution of 4-isopropoxybenzaldehyde (15.00 g, 91.4 mmol) and triethyl phosphonocrotonate (27.3 g, 109 mmol) in DMF (100 mL) was added gradually sodium hydride (60% in oil, 4.38 g, 110 mmol) followed by stirring at room temperature for 16 h. The reaction mixture was poured into ice-water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo to give an oil that was purified by column chromatography on SiO_2 (300 g). Elution with Et_2O –hexane (1:5, v/v) gave ethyl (2E,4E)-5-(4-isopropoxyphenyl)-2,4-pentadienoate (13.7 g, 58%). Recrystallization from Et_2O –hexane gave colorless prisms; mp 64–65 °C. ^1H NMR (CDCl_3): δ 1.31 (3H, t, $J = 7$ Hz), 1.35 (6H, d, $J = 6$ Hz), 4.23 (2H, q, $J = 7$ Hz), 4.5–4.7 (1H, m), 5.93 (1H, d, $J = 15$ Hz), 6.65–6.9 (4H, m), 7.35–7.6 (3H, m). IR (KBr) (cm^{-1}): 1700, 1620, 1595, 1565, 1505. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$: C, 73.82; H, 7.74. Found: C, 73.70; H, 7.77.

DIBAL-H (1.5 M in toluene, 76 mL, 114 mmol) was added dropwise to a stirred and ice-cooled solution of ethyl (2E,4E)-5-(4-isopropoxyphenyl)-2,4-pentadienoate (13.5 g, 51.9 mmol) in CH_2Cl_2 (250 mL). After the mixture was stirred at room temperature for 16 h, the reaction mixture was quenched with MeOH (15 mL)–water (30 mL) at 0 °C. The insoluble material was removed by filtration, and then, the filtrate was concentrated to leave an oil that was purified by column chromatography on SiO_2 (150 g) with AcOEt–hexane (1:2, v/v) to give the title compound (**10j**, 8.60 g, 76%). Recrystallization from isoPr₂O gave colorless needles; mp 91–92 °C. ^1H NMR (CDCl_3): δ 1.33 (6H, d, $J = 6$ Hz), 4.2–4.3 (2H, m), 4.45–4.65 (1H, m), 5.90 (1H, dt, $J = 15$, 6 Hz), 6.40 (1H, ddt, $J = 15$, 10, 1.5 Hz), 6.50 (1H, d, $J = 15.5$ Hz), 6.67 (1H, dd, $J = 15.5$, 10 Hz), 6.83 (2H, d, $J = 9$ Hz), 7.32 (2H, d, $J = 9$ Hz). IR (KBr) (cm^{-1}): 3320, 1600, 1505. Anal. ($\text{C}_{14}\text{H}_{18}\text{O}_2$) C, H. Compound **10g** was obtained similarly. The yield, recrystallization solvent, melting point, and elemental analysis were listed in Table 1. **10g**: ^1H NMR (CDCl_3): δ 1.39 (1H, br s), 2.37 (3H, s), 2.98 (2H, t, $J = 7$ Hz), 4.15–4.3 (4H, m), 5.90 (1H, dt, $J = 15.5$, 6 Hz), 6.3–6.75 (3H, m), 6.85 (2H, d, $J = 9$ Hz), 7.31 (2H, d, $J = 9$ Hz), 7.35–7.5 (3H, m), 7.9–8.05 (2H, m). IR (neat) (cm^{-1}): 3340, 1645, 1600, 1555, 1505.

General Procedure for Unsaturated Aldehydes 11. (E)-3-Methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)cinnamaldehyde (11a). A mixture of **10a** (16.0 g, 45.5 mmol), activated manganese dioxide (30.0 g, 345 mmol), and CH_2Cl_2 (250 mL) was stirred at room temperature for 14 h. After the insoluble material was removed by filtration, the filtrate was concentrated in vacuo to give the title compound (**11a**, 14.6 g, 92%). Recrystallization from AcOEt gave pale yellow prisms; mp 159–160 °C. ^1H NMR (CDCl_3): δ 2.45 (3H, s), 3.91 (3H, s), 5.11 (2H, s), 6.62 (1H, dd, $J = 16$, 7.5 Hz), 7.0–7.2 (3H, m), 7.35–7.55 (3H, m), 7.9–8.1 (2H, m), 9.66 (1H, d, $J = 8$ Hz). IR (KBr) (cm^{-1}): 1670, 1620, 1595, 1510. Anal. ($\text{C}_{21}\text{H}_{19}\text{NO}_4$) C, H, N. Compounds **11b–11f** and **11h–11k** were obtained similarly. The yields, recrystallization solvents, melting points, and elemental analyses were listed in Table 2. **11b**: ^1H NMR (CDCl_3): δ 2.38 (3H, s), 3.00 (2H, t, $J = 6.5$ Hz), 4.31 (2H, t, $J = 6.5$ Hz), 6.60 (1H, dd, $J = 16$, 8 Hz), 6.94 (2H, d, $J = 9$ Hz), 7.35–7.6 (6H, m), 7.9–8.05 (2H, m), 9.64 (1H, d, $J = 8$ Hz). **11c**: ^1H NMR (CDCl_3): δ 2.45 (3H, s), 5.05 (2H, s), 6.62 (1H, dd, $J = 16$, 8 Hz), 7.07 (2H, d, $J = 9$ Hz), 7.35–7.55 (4H, m), 7.54 (2H, d, $J = 9$ Hz), 7.95–8.1 (2H, m), 9.66 (1H, d, $J =$

8 Hz). **11d**: ^1H NMR (CDCl_3): δ 2.43 (3H, s), 3.91 (3H, s), 5.11 (2H, s), 6.5–6.7 (2H, m), 6.97 (1H, d, J = 3 Hz), 7.05–7.2 (3H, m), 7.42 (1H, d, J = 16 Hz), 7.5–7.6 (1H, m), 9.67 (1H, d, J = 8 Hz). IR (KBr) (cm^{-1}): 1670, 1620, 1595, 1510. **11e**: ^1H NMR (CDCl_3): δ 2.45 (3H, s), 5.04 (2H, s), 6.72 (1H, dd, J = 16, 7.5 Hz), 7.05–7.5 (8H, m), 7.95–8.1 (2H, m), 9.71 (1H, d, J = 7.5 Hz). **11f**: ^1H NMR (CDCl_3): δ 2.43 (3H, s), 5.10 (2H, s), 6.76 (1H, dd, J = 16, 8 Hz), 7.04 (1H, t, J = 7.5 Hz), 7.15 (1H, d, J = 8 Hz), 7.35–7.5 (4H, m), 7.58 (1H, dd, J = 8, 1.5 Hz), 7.88 (1H, d, J = 16 Hz), 7.95–8.1 (2H, m), 9.66 (1H, d, J = 8 Hz). IR (KBr) (cm^{-1}): 1665, 1615, 1595, 1555. **11h**: ^1H NMR (CDCl_3): δ 2.50 (3H, s), 5.36 (2H, s), 6.64 (1H, dd, J = 16, 7.5 Hz), 6.89 (1H, d, J = 9 Hz), 7.35–7.5 (4H, m), 7.82 (1H, dd, J = 9, 2.5 Hz), 7.95–8.1 (2H, m), 8.35 (1H, d, J = 2.5 Hz), 9.68 (1H, d, J = 7.5 Hz). IR (KBr) (cm^{-1}): 1680, 1640, 1620, 1595, 1555. **11i**: ^1H NMR (CDCl_3): δ 1.37 (6H, d, J = 6 Hz), 4.5–4.7 (1H, m), 6.61 (1H, dd, J = 16, 8 Hz), 6.92 (2H, d, J = 9 Hz), 7.42 (1H, d, J = 16 Hz), 7.51 (2H, d, J = 9 Hz), 9.65 (1H, d, J = 8 Hz). IR (neat) (cm^{-1}): 1670, 1620, 1600, 1565, 1505. **11j**: ^1H NMR (CDCl_3): δ 1.36 (6H, d, J = 6 Hz), 4.5–4.7 (1H, m), 6.22 (1H, dd, J = 15, 8 Hz), 6.8–7.05 (4H, m), 7.26 (1H, dd, J = 15, 10 Hz), 7.44 (2H, d, J = 9 Hz), 9.59 (1H, d, J = 8 Hz). IR (neat) (cm^{-1}): 1670, 1615, 1590, 1565, 1505. **11k**: ^1H NMR (CDCl_3): δ 2.38 (3H, s), 3.00 (2H, t, J = 7 Hz), 4.28 (2H, t, J = 7 Hz), 6.22 (1H, dd, J = 15, 8 Hz), 6.75–7.05 (4H, m), 7.15–7.5 (4H, m), 7.9–8.05 (2H, m), 9.59 (1H, d, J = 8 Hz). IR (KBr) (cm^{-1}): 1670, 1645, 1615, 1590, 1550, 1505.

4-(5-Methyl-2-phenyl-4-oxazolepropionyl)cinnamaldehyde (11g). A mixture of 4-(5-methyl-2-phenyl-4-oxazolepropionyl)benzaldehyde (6.00 g, 18.8 mmol), formylmethylene triphenylphosphorane (6.29 g, 20.7 mmol), and benzene (100 mL) was refluxed for 24 h. After the solvent was removed, the residue was purified by column chromatography on SiO_2 (200 g). Elution with AcOEt–hexane (1:2, v/v) gave the title compound as crystals (**11g**, 4.08 g, 63%). Recrystallization from CH_2Cl_2 –isoPr $_2\text{O}$ gave colorless prisms; mp 119–120 °C. ^1H NMR (CDCl_3): δ 2.38 (3H, s), 2.95 (2H, t, J = 7 Hz), 3.42 (2H, t, J = 7 Hz), 6.77 (1H, dd, J = 16, 7.5 Hz), 7.35–7.5 (3H, m), 7.5 (1H, d, J = 16 Hz), 7.64 (2H, d, J = 8.5 Hz), 7.9–8.0 (2H, m), 8.04 (2H, d, J = 8.5 Hz). IR (KBr) (cm^{-1}): 1675, 1640, 1620, 1600, 1550. Anal. ($\text{C}_{22}\text{H}_{19}\text{NO}_3$) C, H, N.

General Procedure for 5-Propyl- or 5-Pentyl-2,4-thiazolidinediones 12 (n = 3 or 5 in Tables 4–6). **5-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-2,4-thiazolidinedione (32)**. A mixture of **11b** (2.50 g, 7.50 mmol), 2,4-thiazolidinedione (878 mg, 7.50 mmol), piperidine (192 mg, 2.25 mmol), and EtOH (50 mL) was refluxed for 3 h. The reaction mixture was poured into water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (60 g). Elution with AcOEt– CHCl_3 (1:10, v/v) gave 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propylidene]-2,4-thiazolidinedione as crystals (**38**, 780 mg, 24%). Recrystallization from CHCl_3 –MeOH gave yellow needles; mp 222–223 °C. ^1H NMR (dimethyl sulfoxide (DMSO)– d_6): δ 2.37 (3H, s), 2.95 (2H, t, J = 6.5 Hz), 4.27 (2H, t, J = 6.5 Hz), 6.76 (1H, dd, J = 7.5, 5.5 Hz), 6.98 (2H, d, J = 8.5 Hz), 7.22 (1H, d, J = 7.5 Hz), 7.4–7.55 (4H, m), 7.60 (2H, d, J = 8.5 Hz), 7.85–8.0 (2H, m). Anal. ($\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$) C, H, N.

A solution of **38** (433 mg, 1.0 mmol) in 1,4-dioxane (40 mL)–EtOH (40 mL) was hydrogenated on 5% Pd–C (50% wet, 1.50 g) under atmospheric pressure. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo to give the title compound as crystals (**32**, 235 mg, 54%). Recrystallization from AcOEt–hexane gave colorless prisms; mp 151–152 °C. ^1H NMR (CDCl_3): δ 1.06–2.3 (4H, m), 2.38 (3H, s), 2.61 (2H, t, J = 7 Hz), 2.97 (2H, t, J = 6.5 Hz), 4.15–4.3 (3H, m), 6.83 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.35–7.5 (3H, m), 7.9–8.0 (2H, m), 8.18 (1H, br s). Anal. ($\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$) C, H, N. Compounds **17b**, **17d**, and **37** were obtained similarly. Compounds **17e**, **17g**, **40**, **42**, **45**, **49**, **52**–**54**, and **62**–**64** were also prepared similarly by treatment with 2,4-oxazolidinedione instead of 2,4-thiazolidinedione. The yields, recrystallization

solvents, melting points, and elemental analyses were listed in Tables 4–6. **17b**: ^1H NMR (CDCl_3): δ 1.32 (6H, d, J = 6 Hz), 1.6–2.3 (4H, m), 2.61 (2H, t, J = 7.5 Hz), 4.28 (1H, dd, J = 8.5, 4.5 Hz), 4.4–4.65 (1H, m), 6.82 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 8.34 (1H, br s). IR (neat) (cm^{-1}): 3200, 3060, 1750, 1700, 1690, 1605, 1575, 1505. **17d**: ^1H NMR (CDCl_3): δ 1.2–1.75 (6H, m), 1.32 (6H, d, J = 6 Hz), 1.8–2.3 (2H, m), 2.54 (2H, t, J = 7.5 Hz), 4.26 (1H, dd, J = 9, 4.5 Hz), 4.4–4.6 (1H, m), 6.80 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 8.06 (1H, br s). IR (neat) (cm^{-1}): 3200, 1750, 1700, 1690, 1605, 1505. **17e**: ^1H NMR (CDCl_3): δ 1.32 (6H, d, J = 6 Hz), 1.65–2.15 (4H, m), 2.62 (2H, t, J = 7 Hz), 4.4–4.6 (1H, m), 4.84 (1H, dd, J = 7, 4.5 Hz), 6.81 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 8.00 (1H, br s). IR (neat) (cm^{-1}): 3210, 3050, 1820, 1750, 1605, 1505. **17g**: ^1H NMR (CDCl_3): δ 1.32 (6H, d, J = 6 Hz), 1.3–2.1 (8H, m), 2.54 (2H, t, J = 7.5 Hz), 4.4–4.6 (1H, m), 4.84 (1H, dd, J = 7.5, 4.5 Hz), 6.80 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.98 (1H, br s). IR (neat) (cm^{-1}): 3230, 1825, 1750, 1610, 1505. **37**: ^1H NMR (CDCl_3): δ 1.55–2.3 (4H, m), 2.41 (3H, s), 2.63 (2H, t, J = 7 Hz), 3.86 (3H, s), 4.27 (1H, dd, J = 8, 4.5 Hz), 5.03 (2H, s), 6.6–6.75 (2H, m), 6.97 (1H, d, J = 8.5 Hz), 7.35–7.5 (3H, m), 7.95–8.05 (2H, m), 8.14 (1H, br s). IR (KBr) (cm^{-1}): 3160, 3050, 1745, 1690, 1510. **40**: ^1H NMR (CDCl_3): δ 1.6–2.1 (4H, m), 2.37 (3H, s), 2.60 (2H, t, J = 7 Hz), 2.97 (2H, t, J = 6.5 Hz), 4.21 (2H, t, J = 6.5 Hz), 4.81 (1H, dd, J = 7, 4.5 Hz), 6.82 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.3–7.5 (3H, m), 7.9–8.05 (2H, m), 8.40 (1H, br s). **42**: ^1H NMR (CDCl_3): δ 1.25–2.1 (8H, m), 2.38 (3H, s), 2.54 (2H, t, J = 7.5 Hz), 2.97 (2H, t, J = 6.5 Hz), 4.22 (2H, t, J = 6.5 Hz), 4.81 (1H, dd, J = 7, 4.5 Hz), 6.82 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.35–7.5 (3H, m), 7.9–8.0 (2H, m), 8.14 (1H, br s). IR (KBr) (cm^{-1}): 1820, 1745, 1645, 1605, 1545, 1510. **45**: ^1H NMR (CDCl_3): δ 1.6–2.1 (4H, m), 2.43 (3H, s), 2.62 (2H, t, J = 7 Hz), 4.80 (1H, dd, J = 7, 4.5 Hz), 4.97 (2H, s), 6.94 (2H, d, J = 8.5 Hz), 7.09 (2H, d, J = 8.5 Hz), 7.35–7.5 (3H, m), 7.9–8.05 (2H, m), 8.55 (1H, br s). **49**: ^1H NMR (CDCl_3): δ 1.75–2.1 (4H, m), 2.38 (3H, s), 2.73 (2H, t, J = 7 Hz), 2.93 (2H, t, J = 7 Hz), 3.39 (2H, t, J = 7 Hz), 4.85 (1H, dd, J = 6.5, 4.5 Hz), 7.25 (2H, d, J = 8 Hz), 7.35–7.5 (3H, m), 7.9–8.1 (5H, m). IR (KBr) (cm^{-1}): 1820, 1740, 1685, 1655, 1605, 1550. **52**: ^1H NMR ($\text{DMSO}-d_6$): δ 2.47 (3H, s), 5.06 (2H, s), 6.55–7.2 (5H, m), 7.45–7.6 (3H, m), 7.60 (2H, d, J = 9 Hz), 7.9–8.0 (2H, m), 12.26 (1H, br s). **53**: ^1H NMR (CDCl_3): δ 1.6–2.1 (4H, m), 2.45 (3H, s), 2.66 (2H, t, J = 7 Hz), 4.79 (1H, dd, J = 6.5, 4.5 Hz), 4.99 (2H, s), 6.7–6.9 (3H, m), 7.15–7.3 (1H, m), 7.4–7.5 (3H, m), 7.95–8.1 (2H, m), 8.46 (1H, br s). **54**: ^1H NMR ($\text{DMSO}-d_6$): δ 1.5–1.9 (4H, m), 2.44 (3H, s), 2.60 (2H, t, J = 7 Hz), 4.96 (1H, dd, J = 6.5, 4.5 Hz), 5.03 (2H, s), 6.85–6.95 (1H, m), 7.1–7.25 (3H, m), 7.45–7.6 (3H, m), 7.9–8.0 (2H, m), 11.81 (1H, br s). IR (KBr) (cm^{-1}): 3420, 1820, 1745. **62**: ^1H NMR (CDCl_3): δ 1.7–2.15 (4H, m), 2.48 (3H, s), 2.61 (2H, t, J = 7 Hz), 4.84 (1H, dd, J = 6.5, 4.5 Hz), 5.27 (2H, s), 6.76 (1H, d, J = 8.5 Hz), 7.3–7.5 (4H, m), 7.95–8.1 (3H, m), 8.84 (1H, br s). IR (KBr) (cm^{-1}): 1820, 1745, 1600, 1565, 1550. **63**: ^1H NMR (CDCl_3): δ 1.7–2.1 (4H, m), 2.41 (3H, s), 2.63 (2H, t, J = 7 Hz), 3.86 (3H, s), 4.82 (1H, dd, J = 7, 4.5 Hz), 5.03 (2H, s), 6.65–6.75 (2H, m), 6.96 (1H, d, J = 9 Hz), 7.35–7.5 (3H, m), 7.95–8.1 (2H, m), 8.11 (1H, br s). IR (KBr) (cm^{-1}): 3050, 1815, 1745, 1515. **64**: ^1H NMR (CDCl_3): δ 1.7–2.15 (4H, m), 2.40 (3H, s), 2.62 (2H, t, J = 7 Hz), 3.85 (3H, s), 4.82 (1H, dd, J = 7, 4.5 Hz), 5.03 (2H, s), 6.51 (1H, dd, J = 3.5, 2 Hz), 6.65–6.75 (2H, m), 6.85–7.05 (2H, m), 7.5–7.6 (1H, m), 8.53 (1H, br s). IR (KBr) (cm^{-1}): 3000, 1820, 1745, 1515.

Method B. 4-[2-[4-[3-(1,3-Dioxan-2-yl)propyl]phenoxy]ethyl]-5-methyl-2-phenyloxazole (13a). Sodium hydride (60% in oil, 780 mg, 19.5 mmol) was added gradually to a stirred solution of [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide (8.93 g, 19.5 mmol) in DMF (100 mL) at room temperature. After the mixture was stirred for 30 min, 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (5.00 g) was added to the mixture. The resultant was stirred at room temperature for 15 h and at 70 °C for 5 h. The reaction mixture was poured into water, acidified with 2 N HCl, and extracted

with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (120 g). Elution with AcOEt–hexane (1:3, v/v) gave (Z)-4-[2-[4-[3-(1,3-dioxan-2-yl)-1-propenyl]phenoxy]ethyl]-5-methyl-2-phenyloxazole as an oil (5.05 g, 77%). ¹H NMR (CDCl₃): δ 1.25–1.4 (1H, m), 1.95–2.25 (1H, m), 2.37 (3H, s), 2.66 (1H, ddd, *J* = 7, 5, 2 Hz), 2.98 (2H, t, *J* = 6.5 Hz), 3.7–3.85 (2H, m), 4.05–4.3 (4H, m), 4.63 (1H, t, *J* = 5 Hz), 5.64 (1H, dt, *J* = 11.5, 7 Hz), 6.48 (1H, br d, *J* = 11.5 Hz), 6.85 (2H, d, *J* = 9 Hz), 7.22 (2H, d, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.9–8.0 (2H, m). IR (neat) (cm⁻¹): 1690, 1635, 1605, 1570, 1550, 1505.

A solution of (Z)-4-[2-[4-[3-(1,3-dioxan-2-yl)-1-propenyl]phenoxy]ethyl]-5-methyl-2-phenyloxazole (5.00 g, 12.3 mmol) in EtOH (100 mL) was hydrogenated on 5% Pd–C (1.00 g) under atmospheric pressure. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (100 g). Elution with AcOEt–hexane (1:3, v/v) gave the title compound as an oil (**13a**, 4.83 g, 96%). ¹H NMR (CDCl₃): δ 1.25–1.4 (1H, m), 1.5–1.8 (4H, m), 1.9–2.2 (1H, m), 2.37 (3H, s), 2.54 (2H, t, *J* = 7 Hz), 2.98 (2H, t, *J* = 6.5 Hz), 3.65–3.85 (2H, m), 4.0–4.15 (2H, m), 4.21 (2H, t, *J* = 6.5 Hz), 4.50 (1H, t, *J* = 5 Hz), 6.80 (2H, d, *J* = 9 Hz), 7.06 (2H, d, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.9–8.0 (2H, m). IR (neat) (cm⁻¹): 1635, 1605, 1580, 1550, 1505. 2-[3-(4-isopropoxyphenyl)propyl]-1,3-dioxolane (**13b**) was obtained similarly. Yield: 24% (a colorless oil). ¹H NMR (CDCl₃): δ 1.32 (6H, d, *J* = 6 Hz), 1.6–1.8 (4H, m), 2.5–2.65 (2H, m), 3.8–4.0 (4H, m), 4.4–4.6 (1H, m), 4.8–4.9 (1H, m), 6.80 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.5 Hz). IR (neat) (cm⁻¹): 1610, 1580, 1505.

5-[4-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butylidene]-2,4-oxazolidinedione (41). A mixture of **13a** (2.00 g, 4.91 mmol), 2,4-oxazolidinedione (990 mg, 9.80 mmol), piperidine (210 mg, 2.47 mmol), and acetic acid (50 mL) was refluxed for 24 h. After the solvent was removed, the residue was diluted with AcOEt and washed successively with saturated aqueous sodium bicarbonate, 2 N HCl, and water. The organic layer was separated, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (60 g). Elution with AcOEt–CHCl₃ (1:5, v/v) gave 5-[4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butylidene]-2,4-oxazolidinedione as crystals (550 mg, 26%, *E:Z* = ca. 6:1 mixture). Collection by filtration with Et₂O–isoPr₂O gave pure (*E*)-isomer as crystals (450 mg, 21%). Recrystallization from Et₂O–MeOH gave colorless needles; mp 152–153 °C. ¹H NMR (CDCl₃): δ 1.75–1.95 (2H, m), 2.25–2.4 (2H, m), 2.38 (3H, s), 2.63 (2H, t, *J* = 7 Hz), 2.97 (2H, t, *J* = 6.5 Hz), 4.22 (2H, t, *J* = 6.5 Hz), 5.80 (1H, t, *J* = 8 Hz), 6.81 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.5 Hz), 7.35–7.5 (3H, m), 7.9–8.0 (2H, m), 9.43 (1H, br s). IR (KBr) (cm⁻¹): 1815, 1745, 1695, 1645, 1610, 1550, 1510. Anal. Calcd for C₂₅H₂₄N₂O₅: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.67; H, 5.59; N, 6.18.

A solution of 5-[4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butylidene]-2,4-oxazolidinedione (380 mg) in THF (40 mL) was hydrogenated on 10% Pd–C (200 mg) at 3 kgf/cm² for 24 h. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (40 g). Elution with 3% MeOH–CHCl₃ gave the title compound as crystals (**41**, 250 mg, 65%). Recrystallization from CH₂Cl₂–MeOH gave colorless prisms; mp 136–137 °C. ¹H NMR (CDCl₃): δ 1.4–2.1 (6H, m), 2.38 (3H, s), 2.55 (2H, t, *J* = 7.5 Hz), 2.97 (2H, t, *J* = 7 Hz), 4.21 (2H, t, *J* = 7 Hz), 4.81 (1H, dd, *J* = 7.5, 4.5 Hz), 6.82 (2H, d, *J* = 8.5 Hz), 7.05 (2H, d, *J* = 8.5 Hz), 7.35–7.5 (3H, m), 7.9–8.0 (2H, m), 8.41 (1H, br s). IR (KBr) (cm⁻¹): 1815, 1740, 1650, 1610, 1580, 1550, 1510. Anal. (C₂₅H₂₆N₂O₅) C, H, N. Compound **17f** was obtained similarly. Compound **17c** was also prepared similarly by treatment with 2,4-thiazolidinedione instead of 2,4-oxazolidinedione. The yields, recrystallization solvents, melting points, and elemental analyses were listed in Tables 4 and 5. **17c**: ¹H NMR (CDCl₃): δ 1.32 (6H, d, *J* = 6 Hz), 1.3–1.75 (4H, m), 1.85–2.3 (2H, m), 2.57 (2H, t, *J* = 7.5 Hz), 4.27 (1H, dd, *J* = 9, 4.5 Hz), 4.4–4.6 (1H, m), 6.81

(2H, d, *J* = 8.5 Hz), 7.05 (2H, d, *J* = 8.5 Hz), 8.02 (1H, br s). IR (KBr) (cm⁻¹): 3120, 3050, 1780, 1750, 1720, 1690, 1610, 1510. **17f**: ¹H NMR (CDCl₃): δ 1.32 (6H, d, *J* = 6 Hz), 1.45–2.15 (6H, m), 2.57 (2H, t, *J* = 7.5 Hz), 4.4–4.6 (1H, m), 4.84 (1H, dd, *J* = 7.5, 4.5 Hz), 6.81 (2H, d, *J* = 9 Hz), 7.06 (2H, d, *J* = 9 Hz), 7.73 (1H, br s). IR (KBr) (cm⁻¹): 3220, 1825, 1745, 1610, 1505.

Method C. General Procedure for (*E*)-Benzylidenepyruvates 14. Ethyl (*E*)-4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidenepyruvate (**14a**). A solution of sodium carbonate (4.14 g, 39.1 mmol) in water (80 mL) was added to a stirred solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde (3.00 g, 9.76 mmol) and pyruvic acid (3.44 g, 39.1 mmol) in MeOH (80 mL) at room temperature. After this was refluxed for 24 h, the reaction mixture was poured into water and extracted with AcOEt. The aqueous layer was separated and acidified with 2 N HCl to give the crystals (ca. 1.2 g). The crystals were dissolved in 5% HCl–EtOH (15 mL) and gently refluxed for 30 min. After the solvent was removed, the residue was dissolved in CHCl₃. The organic layer was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (60 g). Elution with AcOEt–CHCl₃ (1:9, v/v) gave the title compound as crystals (**14a**, 1.00 g, 25%). Recrystallization from CH₂Cl₂–EtOH gave pale yellow needles; mp 99–100 °C. ¹H NMR (CDCl₃): δ 1.41 (3H, t, *J* = 7 Hz), 2.38 (3H, s), 3.01 (2H, t, *J* = 6.5 Hz), 4.31 (2H, t, *J* = 6.5 Hz), 4.38 (2H, q, *J* = 7 Hz), 6.93 (2H, d, *J* = 8.5 Hz), 7.22 (1H, d, *J* = 16 Hz), 7.35–7.5 (3H, m), 7.57 (2H, d, *J* = 8.5 Hz), 7.82 (1H, d, *J* = 16 Hz), 7.9–8.05 (2H, m). IR (KBr) (cm⁻¹): 1685, 1650, 1640, 1590, 1565, 1505. Anal. (C₂₄H₂₃NO₅·1/2H₂O) C, H, N. Ethyl (*E*)-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzylidenepyruvate (**14b**) and ethyl (*E*)-4-isopropoxybenzylidenepyruvate (**14c**) were obtained similarly. **14b**: Yield, 38%; mp 110–111 °C (AcOEt–hexane). ¹H NMR (CDCl₃): δ 1.41 (3H, t, *J* = 7 Hz), 2.45 (3H, s), 4.39 (2H, q, *J* = 7 Hz), 5.05 (2H, s), 7.06 (2H, d, *J* = 9 Hz), 7.26 (1H, d, *J* = 16 Hz), 7.35–7.5 (3H, m), 7.62 (2H, d, *J* = 9 Hz), 7.84 (1H, d, *J* = 16 Hz), 7.95–8.05 (2H, m). Anal. (C₂₃H₂₁NO₅) C, H, N. **14c**: Yield, 38% (a colorless oil). ¹H NMR (CDCl₃): δ 1.37 (6H, d, *J* = 6 Hz), 1.41 (3H, t, *J* = 7 Hz), 4.39 (2H, q, *J* = 7 Hz), 4.55–4.75 (1H, m), 6.91 (2H, d, *J* = 9 Hz), 7.23 (1H, d, *J* = 16 Hz), 7.58 (2H, d, *J* = 9 Hz), 7.83 (1H, d, *J* = 16 Hz). IR (KBr) (cm⁻¹): 1725, 1685, 1660, 1590, 1565, 1510.

General Procedure for 2-Hydroxy-4-phenylbutyrates 15. Ethyl 2-Hydroxy-4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butyrate (**15a**). A solution of **14a** (850 mg, 2.10 mmol) in 1,4-dioxane (80 mL) was hydrogenated on 10% Pd–C (100 mg) under atmospheric pressure. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was dissolved in EtOH (20 mL), and sodium borohydride (80 mg, 2.11 mmol) was added to the solution at room temperature. After it was stirred for 1 h, the reaction mixture was quenched with 1 N HCl and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (50 g). Elution with AcOEt–CHCl₃ (1:9, v/v) gave the title compound as crystals (**15a**, 550 mg, 64%). Recrystallization from Et₂O–hexane gave colorless needles; mp 67–68 °C. ¹H NMR (CDCl₃): δ 1.28 (3H, t, *J* = 7 Hz), 1.75–2.2 (2H, m), 2.38 (3H, s), 2.6–2.75 (2H, m), 2.79 (1H, br d, *J* = 5.5 Hz), 2.97 (2H, t, *J* = 7 Hz), 4.1–4.3 (5H, m), 6.83 (2H, d, *J* = 8.5 Hz), 7.10 (2H, d, *J* = 8.5 Hz), 7.35–7.5 (3H, m), 7.9–8.05 (2H, m). IR (KBr) (cm⁻¹): 3350, 1745, 1650, 1610, 1555, 1510. Anal. (C₂₄H₂₇NO₅) C, H, N. Ethyl 2-hydroxy-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]butyrate (**15b**) and ethyl 2-hydroxy-4-(4-isopropoxyphenyl)butyrate (**15c**) were similarly prepared. **15b**: Yield, 89% (a colorless oil). ¹H NMR (CDCl₃): δ 1.28 (3H, t, *J* = 7 Hz), 1.8–2.2 (2H, m), 2.43 (3H, s), 2.6–2.8 (2H, m), 2.84 (1H, d, *J* = 5 Hz), 4.1–4.3 (3H, m), 4.97 (2H, s), 6.94 (2H, d, *J* = 8.5 Hz), 7.14 (2H, d, *J* = 8.5 Hz), 7.35–7.5 (3H, m), 7.95–8.1 (2H, m). **15c**: Yield, 58% (a colorless oil). ¹H NMR (CDCl₃): δ 1.29 (3H, t, *J* = 7 Hz), 1.32 (6H, d, *J* = 6 Hz), 1.8–2.2 (2H, m), 2.65–2.75 (2H, m), 2.80

(1H, d, $J = 5.5$ Hz), 4.1–4.25 (3H, m), 4.4–4.6 (1H, m), 6.81 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz). IR (neat) (cm^{-1}): 3440, 1725, 1635, 1610, 1580, 1505.

General Procedure for 2-Chloro-4-phenylbutyrate 16. Ethyl 2-Chloro-4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]phenyl]butyrate (**16a**). A mixture of **15a** (320 mg, 0.781 mmol) and thionyl chloride (3 mL, excess) was gently refluxed for 2 h. After the reagent was removed, the residue was purified by column chromatography on SiO_2 (50 g). Elution with AcOEt–hexane (1:4, v/v) gave the title compound as an oil (**16a**, 210 mg, 63%). ^1H NMR (CDCl_3): δ 1.29 (3H, t, $J = 7$ Hz), 2.05–2.45 (2H, m), 2.38 (3H, s), 2.6–2.85 (2H, m), 2.97 (2H, t, $J = 6.5$ Hz), 4.15–4.3 (5H, m), 6.84 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.9–8.05 (2H, m). IR (neat) (cm^{-1}): 1740, 1640, 1610, 1580, 1550, 1510. Ethyl 2-chloro-4-(4-isopropoxyphenyl)butyrate (**16b**) was similarly prepared. Yield, 27% (a colorless oil). ^1H NMR (CDCl_3): δ 1.29 (3H, t, $J = 7$ Hz), 1.32 (6H, d, $J = 6$ Hz), 2.1–2.35 (2H, m), 2.6–2.9 (2H, m), 4.15–4.3 (3H, m), 4.4–4.6 (1H, m), 6.82 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz). IR (neat) (cm^{-1}): 1740, 1610, 1505.

General Procedure for 5-Ethyl-2,4-thia(oxa)zolidinediones 12 ($n = 2$). 5-[2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)-ethoxy]phenyl]ethyl]-2,4-oxazolidinedione (**39**). A mixture of **15a** (450 mg, 1.10 mmol), powdered potassium cyanate (240 mg, 2.96 mmol), and *n*-butanol (20 mL) was refluxed for 4 d. After the solvent was removed, the residue was treated with 2 N HCl and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (40 g). Elution with 2% MeOH– CHCl_3 gave the title compound as crystals (**39**, 280 mg, 63%). Recrystallization from CH_2Cl_2 –EtOH gave colorless prisms; mp 193–194 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 1.95–2.2 (2H, m), 2.36 (3H, s), 2.63 (2H, t, $J = 7.5$ Hz), 2.92 (2H, t, $J = 6.5$ Hz), 4.19 (2H, t, $J = 6.5$ Hz), 4.87 (1H, dd, $J = 7.5$, 5 Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz), 7.45–7.6 (3H, m), 7.85–8.0 (2H, m), 11.82 (1H, br s). IR (KBr) (cm^{-1}): 1820, 1740, 1650, 1610, 1550, 1510. Anal. ($\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_5$) C, H, N. 5-[2-[4-(5-Methyl-2-phenyl-4-oxazolyl)-methoxy]phenyl]ethyl]-2,4-oxazolidinedione (**44**) was similarly prepared. Yield, 35%; mp 158–159 °C (AcOEt–hexane). ^1H NMR (CDCl_3): δ 1.95–2.3 (2H, m), 2.44 (3H, s), 2.63 (2H, t, $J = 7.5$ Hz), 4.76 (1H, dd, $J = 7.5$, 5 Hz), 4.97 (2H, s), 6.93 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.9–8.05 (2H, m), 9.53 (1H, br s). Anal. ($\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5$) C, H, N.

5-[2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]ethyl]-2,4-thiazolidinedione (**31**). A mixture of **16a** (200 mg, 0.467 mmol), thiourea (145 mg, 1.90 mmol), sodium acetate (155 mg, 1.89 mmol), and EtOH (15 mL) was refluxed for 30 h. A 6 N HCl (15 mL) amount was added to the mixture, and then the refluxing was continued for 15 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (50 g). Elution with 2% MeOH– CHCl_3 gave the title compound as crystals (**31**, 110 mg, 56%). Recrystallization from CH_2Cl_2 –EtOH gave colorless prisms; mp 151–152 °C. ^1H NMR (CDCl_3): δ 2.05–2.9 (4H, m), 2.38 (3H, s), 2.97 (2H, t, $J = 7$ Hz), 4.17 (1H, dd, $J = 9$, 4.5 Hz), 4.23 (2H, t, $J = 7$ Hz), 6.84 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.8–8.0 (2H, m), 8.22 (1H, br s). IR (KBr) (cm^{-1}): 1775, 1705, 1645, 1605, 1550, 1510. Anal. ($\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$) C, H, N. 5-[2-[4-(Isopropoxyphenyl)ethyl]-2,4-thiazolidinedione (**17a**) was obtained similarly. Yield, quant. (a colorless oil). ^1H NMR (CDCl_3): δ 1.32 (6H, d, $J = 6$ Hz), 2.05–2.90 (4H, m), 4.19 (1H, dd, $J = 9.5$, 4 Hz), 4.4–4.6 (1H, m), 6.83 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 8.29 (1H, br s). IR (neat) (cm^{-1}): 3200, 1735, 1700, 1690, 1610, 1510.

Method D. Deprotection Reaction of 5-[ω -(4-Isopropoxyphenyl)alkyl]-2,4-thia(oxa)zolidinediones 17. 5-[2-(4-Hydroxyphenyl)ethyl]-2,4-thiazolidinedione (**18a**). Titanium tetrachloride (3.67 g, 19.3 mmol) was added dropwise to a stirred solution of **17a** (1.35 g, 4.83 mmol) in CH_2Cl_2 (70 mL) at 0 °C. After the mixture was stirred for 2 h, the reaction

mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (50 g). Elution with AcOEt–hexane (1:3, v/v) gave the title compound as crystals (**18a**, 720 mg, 63%). Recrystallization from acetone–isoPr $_2$ O gave colorless prisms; mp 175–176 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 1.90–2.7 (4H, m), 4.41 (1H, dd, $J = 9$, 4 Hz), 6.68 (2H, d, $J = 8.5$ Hz), 6.99 (2H, d, $J = 8.5$ Hz), 9.19 (1H, s), 12.02 (1H, br s). IR (KBr) (cm^{-1}): 3380, 3200, 3060, 1730, 1680, 1595, 1510. Anal. ($\text{C}_{11}\text{H}_{11}\text{NO}_3\text{S}$) C, H, N. Compounds **18b–18g** were obtained similarly. The yields, recrystallization solvents, melting points, and elemental analyses were listed in Table 3. **18b**: ^1H NMR ($\text{DMSO}-d_6$): δ 1.4–2.15 (4H, m), 2.49 (2H, t, $J = 7$ Hz), 4.55 (1H, dd, $J = 8.5$, 4.5 Hz), 6.66 (2H, d, $J = 8.5$ Hz), 6.96 (2H, d, $J = 8.5$ Hz), 9.12 (1H, s), 12.01 (1H, br s). IR (KBr) (cm^{-1}): 3400, 3220, 3050, 1750, 1700, 1675, 1605, 1590, 1510. **18c**: ^1H NMR (CDCl_3): δ 1.3–1.75 (4H, m), 1.85–2.3 (2H, m), 2.57 (2H, t, $J = 7.5$ Hz), 4.27 (1H, dd, $J = 9$, 4.5 Hz), 4.68 (1H, s), 6.76 (2H, d, $J = 8.5$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 8.07 (1H, br s). IR (KBr) (cm^{-1}): 3400, 3150, 3050, 1750, 1720, 1695, 1615, 1515. **18d**: ^1H NMR (CDCl_3): δ 1.25–1.7 (6H, m), 1.8–2.3 (2H, m), 2.54 (2H, t, $J = 7.5$ Hz), 4.25 (1H, dd, $J = 9$, 4 Hz), 4.75 (1H, br s), 6.74 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz), 8.20 (1H, br s). IR (KBr) (cm^{-1}): 3450, 3160, 3050, 1740, 1675, 1605, 1505. **18e**: ^1H NMR ($\text{DMSO}-d_6$): δ 1.45–1.9 (4H, m), 2.50 (2H, t, $J = 6$ Hz), 4.97 (1H, dd, $J = 6.5$, 4.5 Hz), 6.67 (2H, d, $J = 8.5$ Hz), 6.97 (2H, d, $J = 8.5$ Hz), 9.12 (1H, s), 11.83 (1H, br s). IR (KBr) (cm^{-1}): 3420, 3180, 3080, 1810, 1740, 1730, 1610, 1515. **18f**: ^1H NMR ($\text{DMSO}-d_6$): δ 1.2–2.0 (6H, m), 2.46 (2H, t, $J = 7.5$ Hz), 4.95 (1H, dd, $J = 7$, 5 Hz), 6.65 (2H, d, $J = 8.5$ Hz), 6.96 (2H, d, $J = 8.5$ Hz), 9.09 (1H, s), 11.81 (1H, br s). IR (KBr) (cm^{-1}): 3310, 3180, 3100, 1790, 1755, 1740, 1615, 1600, 1515. **18g**: ^1H NMR (CDCl_3): δ 1.2–2.1 (8H, m), 2.54 (2H, t, $J = 7.5$ Hz), 4.80 (1H, br s), 4.83 (1H, dd, $J = 7$, 4.5 Hz), 6.75 (2H, d, $J = 8.5$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 8.15 (1H, br s). IR (KBr) (cm^{-1}): 3400, 3200, 1800, 1745, 1610, 1510.

General Procedure for 2,4-Thia(oxa)zolidinediones (12) from Phenols (18). 5-[2-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]ethyl]-2,4-thiazolidinedione (**33**). Sodium hydride (60% in oil, 100 mg, 2.50 mmol) was added gradually to a stirred solution of **18a** (300 mg, 1.26 mmol) in DMF (20 mL) at room temperature. After the mixture was stirred for 15 min, 4-chloromethyl-5-methyl-2-phenyloxazole (290 mg, 1.40 mmol) was added to the mixture, and then, the resultant was stirred at 90–100 °C for 2 h. The reaction mixture was poured into water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (60 g). Elution with AcOEt– CHCl_3 (1:9, v/v) gave the title compound as crystals (**33**, 300 mg, 58%). Recrystallization from CH_2Cl_2 –isoPr $_2$ O gave colorless needles; mp 146–147 °C. ^1H NMR (CDCl_3): δ 2.1–2.85 (4H, m), 2.44 (3H, s), 4.19 (1H, dd, $J = 9$, 4 Hz), 4.98 (2H, s), 6.96 (2H, d, $J = 8.5$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 7.4–7.5 (3H, m), 7.95–8.05 (2H, m), 8.18 (1H, br s). IR (KBr) (cm^{-1}): 3430, 1750, 1695, 1645, 1605, 1555, 1510. Anal. ($\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$) C, H, N. Compounds **34–36**, **46**, **47**, and **55–61** were obtained similarly by treatment with the corresponding 2,4-thia(oxa)zolidinediones (**18b–g**). The yields, recrystallization solvents, melting points, and elemental analyses were listed in Tables 4–6. **34**: ^1H NMR (CDCl_3): δ 1.6–2.3 (4H, m), 2.44 (3H, s), 2.63 (2H, t, $J = 7$ Hz), 4.26 (1H, dd, $J = 8.5$, 4.5 Hz), 4.98 (2H, s), 6.95 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.4–7.55 (3H, m), 7.95–8.1 (2H, m), 8.27 (1H, br s). IR (KBr) (cm^{-1}): 3110, 1750, 1700, 1645, 1600, 1580, 1555, 1505. **35**: ^1H NMR (CDCl_3): δ 1.3–2.3 (6H, m), 2.43 (3H, s), 2.58 (2H, t, $J = 7.5$ Hz), 4.26 (1H, dd, $J = 9$, 4.5 Hz), 4.98 (2H, s), 6.94 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.95–8.1 (3H, m). IR (KBr) (cm^{-1}): 1750, 1700, 1650, 1605, 1580, 1555, 1505. **36**: ^1H NMR (CDCl_3): δ 1.3–2.3 (8H, m), 2.43 (3H, s), 2.56 (2H, t, $J = 7$ Hz), 4.24 (1H, dd, $J = 9$, 4.5 Hz), 4.98 (2H, s), 6.93 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.95–8.05 (2H, m), 8.22 (1H, br s). IR

(KBr) (cm^{-1}): 3180, 3050, 1745, 1715, 1665, 1505. **46**: ^1H NMR (CDCl_3): δ 1.4–2.1 (6H, m), 2.44 (3H, s), 2.56 (2H, t, $J = 7.5$ Hz), 4.81 (1H, dd, $J = 7.5, 4.5$ Hz), 4.98 (2H, s), 6.94 (2H, d, $J = 9$ Hz), 7.09 (2H, d, $J = 9$ Hz), 7.4–7.5 (3H, m), 7.95–8.1 (2H, m), 8.31 (1H, br s). IR (KBr) (cm^{-1}): 1815, 1750, 1650, 1610, 1580, 1555, 1510. **47**: ^1H NMR (CDCl_3): δ 1.25–2.05 (8H, m), 2.44 (3H, s), 2.5–2.65 (2H, m), 4.80 (1H, dd, $J = 7, 4.5$ Hz), 4.99 (2H, s), 6.93 (2H, d, $J = 9$ Hz), 7.09 (2H, d, $J = 9$ Hz), 7.4–7.5 (3H, m), 7.95–8.1 (2H, m), 8.53 (1H, br s). IR (KBr) (cm^{-1}): 3220, 1825, 1745, 1635, 1605, 1505. **55**: ^1H NMR (CDCl_3): δ 1.7–2.1 (4H, m), 2.53 (3H, s), 2.63 (2H, t, $J = 7$ Hz), 4.82 (1H, dd, $J = 6.5, 4.5$ Hz), 5.15 (2H, s), 6.97 (2H, d, $J = 9$ Hz), 7.10 (2H, d, $J = 9$ Hz), 7.35–7.5 (3H, m), 7.8–8.0 (3H, m). IR (KBr) (cm^{-1}): 3150, 3060, 1840, 1745, 1605, 1505. **56**: ^1H NMR (CDCl_3): δ 1.65–2.15 (4H, m), 2.63 (2H, t, $J = 7$ Hz), 4.83 (1H, dd, $J = 7, 4.5$ Hz), 5.07 (2H, d, $J = 1$ Hz), 6.94 (2H, d, $J = 9$ Hz), 7.10 (2H, d, $J = 9$ Hz), 7.4–7.55 (3H, m), 7.74 (1H, t, $J = 1$ Hz), 8.05–8.15 (2H, m), 8.20 (1H, br s). IR (KBr) (cm^{-1}): 3170, 3040, 1820, 1750, 1610, 1545, 1510. **57**: ^1H NMR (CDCl_3): δ 1.7–2.1 (4H, m), 2.50 (3H, s), 2.62 (2H, t, $J = 7$ Hz), 4.79 (1H, dd, $J = 6.5, 4.5$ Hz), 5.07 (2H, s), 6.99 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.45–7.7 (3H, m), 7.85–8.0 (2H, m), 8.15 (2H, dd, $J = 7, 1$ Hz), 9.21 (1H, d, $J = 8.5$ Hz). IR (KBr) (cm^{-1}): 1820, 1745, 1635, 1605, 1580, 1540, 1505. **58**: ^1H NMR (CDCl_3): δ 1.7–2.1 (4H, m), 2.48 (3H, s), 2.64 (2H, t, $J = 7$ Hz), 4.83 (1H, dd, $J = 6.5, 4.5$ Hz), 5.01 (2H, s), 6.96 (2H, d, $J = 9$ Hz), 7.10 (2H, d, $J = 9$ Hz), 7.45–7.6 (2H, m), 7.8–8.0 (3H, m), 8.11 (1H, dd, $J = 8.5, 2$ Hz), 8.52 (1H, br s). **59**: ^1H NMR (CDCl_3): δ 1.7–2.15 (4H, m), 2.42 (3H, s), 2.62 (2H, t, $J = 7$ Hz), 4.82 (1H, dd, $J = 7, 4.5$ Hz), 4.97 (2H, s), 6.52 (1H, dd, $J = 3.5, 2$ Hz), 6.92 (2H, d, $J = 9$ Hz), 6.95–7.0 (1H, m), 7.08 (2H, d, $J = 9$ Hz), 7.53 (1H, dd, $J = 2, 1$ Hz), 8.23 (1H, br s). IR (KBr) (cm^{-1}): 1815, 1745, 1630, 1605, 1525, 1505. **60**: ^1H NMR (CDCl_3): δ 1.7–2.1 (4H, m), 2.47 (3H, s), 2.63 (2H, t, $J = 7$ Hz), 4.84 (1H, dd, $J = 7, 4.5$ Hz), 5.02 (2H, s), 6.94 (2H, d, $J = 9$ Hz), 7.09 (2H, d, $J = 9$ Hz), 7.2–7.45 (3H, m), 7.55–7.7 (2H, m), 7.97 (1H, br s). IR (KBr) (cm^{-1}): 3200, 3100, 1830, 1725, 1635, 1605, 1580, 1510. **61**: ^1H NMR (CDCl_3): δ 1.7–2.15 (4H, m), 2.45 (3H, s), 2.63 (2H, t, $J = 7$ Hz), 4.83 (1H, dd, $J = 7, 4.5$ Hz), 4.99 (2H, s), 6.94 (2H, d, $J = 9$ Hz), 7.10 (2H, d, $J = 9$ Hz), 7.35–7.45 (2H, m), 7.75–7.9 (3H, m), 8.11 (1H, br s). IR (KBr) (cm^{-1}): 3100, 3030, 1815, 1745, 1605, 1510.

5-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)propoxy]benzyl-2,4-oxazolidinedione (48). A mixture of 4-[3-(5-methyl-2-phenyl-4-oxazolyl)propoxy]benzaldehyde (550 mg, 1.71 mmol), 2,4-oxazolidinedione (364 mg, 3.42 mmol), pyrrolidine (60 mg, 0.84 mmol), and EtOH (12 mL) was refluxed for 10 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (15 g). Elution with AcOEt–hexane (2:1, v/v) gave the corresponding benzylidene-2,4-oxazolidinedione as pale yellow crystals (250 mg, 36%). Recrystallization from CHCl_3 – Et_2O gave pale yellow needles; mp 190–191 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 1.95–2.15 (2H, m), 2.29 (3H, s), 2.64 (2H, t, $J = 7$ Hz), 4.06 (2H, t, $J = 6$ Hz), 6.70 (1H, s), 7.06 (2H, d, $J = 9$ Hz), 7.45–7.6 (3H, m), 7.73 (2H, d, $J = 9$ Hz), 7.85–7.95 (2H, m), 12.33 (1H, br s). IR (KBr) (cm^{-1}): 1810, 1740, 1600. Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_5$: C, 66.82; H, 5.12; N, 6.78. Found: C, 66.50; H, 4.81; N, 7.00.

The crystals (220 mg) were dissolved in THF (20 mL), and then, the solution was hydrogenated on 5% Pd–C (100 mg) under atmospheric pressure. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (25 g). Elution with AcOEt–hexane (2:1, v/v) gave crystals. Recrystallization from CHCl_3 – Et_2O gave the title compound as colorless prisms (**48**, 34.4 mg, 16%); mp 150–151 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 1.9–2.15 (2H, m), 2.28 (3H, s), 2.62 (2H, t, $J = 7$ Hz), 3.00 (1H, dd, $J = 15, 6$ Hz), 3.13 (1H, dd, $J = 15, 4.5$ Hz), 3.96 (2H, t, $J = 6$ Hz), 5.20 (1H, dd, $J = 6, 4.5$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.12 (2H, d, $J = 8.5$ Hz), 7.45–7.55 (3H,

m), 7.8–7.95 (2H, m), 11.71 (1H, br s). IR (KBr) (cm^{-1}): 1820, 1745, 1515. Anal. ($\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_5$) C, H, N.

5-[3-[4-[1-Hydroxy-3-(5-methyl-2-phenyl-4-oxazolyl)propyl]phenyl]propyl]-2,4-oxazolidinedione (50). Sodium borohydride (50 mg, 1.32 mmol) was added gradually to a stirred solution of **49** (250 mg, 0.578 mmol) in THF–EtOH (1:1, 20 mL) at room temperature. After the mixture was stirred for 2 h, the reaction mixture was poured into water, neutralized with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (50 g). Elution with AcOEt– CHCl_3 (1:1, v/v) gave the title compound as crystals (**50**, 160 mg, 64%). Recrystallization from acetone–isoPr₂O gave colorless needles; mp 150–151 °C. ^1H NMR ($\text{DMSO}-d_6$): δ 1.55–2.0 (6H, m), 2.28 (3H, s), 2.4–2.65 (4H, m), 4.45–4.6 (1H, m), 4.98 (1H, dd, $J = 6.5, 4.5$ Hz), 5.20 (1H, d, $J = 4.5$ Hz), 7.13 (2H, d, $J = 8$ Hz), 7.25 (2H, d, $J = 8$ Hz), 7.4–7.55 (3H, m), 7.85–7.95 (2H, m), 11.85 (1H, br s). IR (KBr) (cm^{-1}): 3550, 1820, 1740, 1640, 1545. Anal. ($\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$) C, H, N.

5-[3-[4-[3-(5-Methyl-2-phenyl-4-oxazolyl)propyl]phenyl]propyl]-2,4-oxazolidinedione (51). A mixture of **50** (140 mg, 0.322 mmol), triethylsilane (75 mg, 0.644 mmol), and trifluoroacetic acid (2 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into water, neutralized with saturated aqueous sodium bicarbonate, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (50 g). Elution with 3% MeOH– CHCl_3 gave the title compound as crystals (**51**, 110 mg, 82%). Recrystallization from MeOH– Et_2O gave colorless needles; mp 119–120 °C. ^1H NMR (CDCl_3): δ 1.7–2.15 (6H, m), 2.30 (3H, s), 2.52 (2H, t, $J = 7.5$ Hz), 2.64 (4H, t, $J = 7.5$ Hz), 4.84 (1H, dd, $J = 6.5, 4.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.14 (2H, d, $J = 8.5$ Hz), 7.35–7.5 (3H, m), 7.95–8.1 (3H, m). IR (KBr) (cm^{-1}): 1820, 1740, 1640, 1550. Anal. ($\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_4 \cdot 1/2\text{H}_2\text{O}$) C, H, N.

Synthesis of Optically Active 5-[3-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinediones ((R)- and (S)-64). Ethyl (E)-4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxycinnamate (21). Sodium hydride (60% in oil, 10.8 g, 0.271 mol) was added gradually to a stirred solution of **20** (70.7 g, 0.226 mol) and triethyl phosphonoacetate (55.6 g, 0.248 mol) in DMF (400 mL) at 0 °C. After the mixture was stirred at ambient temperature for 1 h, the reaction mixture was poured onto ice-water to give the title compound as crystals (**21**, 84.5 g, 98%). Recrystallization from AcOEt gave colorless needles; mp 142–143 °C. Anal. ($\text{C}_{21}\text{H}_{21}\text{NO}_6$) C, H, N.

Ethyl 3-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propionate (22). A solution of **21** (119 g, 0.31 mol) in AcOEt (1000 mL) was hydrogenated on 5% Pd–C (50% wet, 10.0 g) under atmospheric pressure. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo to give the title compound as crystals (**22**, 111.5 g, 93%). Recrystallization from AcOEt–hexane gave colorless needles; mp 88–89 °C. Anal. ($\text{C}_{21}\text{H}_{23}\text{NO}_6$) C, H, N.

Isopropyl 4-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]butyrate (23). MeOH (200 mL) was added dropwise to a stirred mixture of **22** (110 g, 0.285 mol), sodium borohydride (53.9 g, 1.43 mol), and THF (800 mL) with continuous reflux over 3 h. The reaction mixture was concentrated in vacuo to half of the original volume, poured into water, and extracted with AcOEt. The extract was washed with water, dried (MgSO_4), and concentrated in vacuo to give 3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propan-1-ol as crystals (81.0 g, 83%). Recrystallization from AcOEt–hexane gave colorless prisms; mp 99–100 °C. Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.37; H, 6.09; N, 3.87.

Methanesulfonyl chloride (31.6 g, 0.276 mol) was added dropwise to a stirred mixture of 3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propan-1-ol (80.0 g, 0.233 mol), triethylamine (27.9 g, 0.276 mol), and AcOEt (800 mL) at 0 °C. After the mixture was stirred at room temperature

for 30 min, the organic layer was separated, dried (MgSO₄), and concentrated in vacuo to give 3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl methanesulfonate as crystals (97.0 g, 99%). Recrystallization from AcOEt–hexane gave colorless prisms; mp 100–101 °C. Anal. Calcd for C₂₀H₂₃NO₇S: C, 57.00; H, 5.50; N, 3.32. Found: C, 56.80; H, 5.38; N, 3.09.

A mixture of 3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl methanesulfonate (97.0 g, 0.230 mol), powdered sodium cyanide (16.9 g, 0.345 mol), and DMF (400 mL) was stirred at 80 °C for 2 h. The reaction mixture was poured into water to give 4-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]butyronitrile as crystals (77.0 g, 95%). Recrystallization from AcOEt–hexane gave colorless needles; mp 94–95 °C. Anal. Calcd for C₂₀H₂₀N₂O₄: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.96; H, 5.74; N, 7.69.

A mixture of 4-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]butyronitrile (75.0 g, 0.213 mol), 4 N potassium hydroxide (300 mL), and 2-methoxyethanol (300 mL) was refluxed for 2 h. The reaction mixture was diluted with water and acidified with concentrated HCl to give 4-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]butyric acid as crystals (74.0 g, 94%). Recrystallization from AcOEt gave colorless prisms; mp 129–130 °C. Anal. Calcd for C₂₀H₂₁NO₆: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.48; H, 5.62; N, 3.55.

A mixture of 4-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]butyric acid (106 g, 0.285 mol), 2-iodopropane (58.2 g, 0.342 mol), potassium carbonate (47.3 g, 0.342 mol), and DMF (500 mL) was stirred at 65–70 °C for 4 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (700 g). Elution with AcOEt–hexane (1:2, v/v) gave the title compound as crystals (**23**, 107 g, 91%). Recrystallization from acetone–hexane gave colorless needles; mp 45–46 °C. ¹H NMR (CDCl₃): δ 1.23 (6H, d, *J* = 6 Hz), 1.8–2.0 (2H, m), 2.29 (2H, t, *J* = 7.5 Hz), 2.39 (3H, s), 2.59 (2H, t, *J* = 7.5 Hz), 3.86 (3H, s), 4.9–5.1 (1H, m), 5.03 (2H, s), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.6–6.75 (2H, m), 6.9–7.0 (2H, m), 7.53 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 1730, 1635, 1615, 1585, 1540, 1515. Anal. (C₂₃H₂₇NO₆) C, H, N.

Isopropyl 5-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-hydroxyvalerate (26**).** A solution of **23** (100 g, 0.242 mol) in toluene (300 mL)–DMF (30 mL) was added dropwise to a stirred mixture of diisopropyl oxalate (84.3 g, 0.484 mol), sodium hydride (60% in oil, 11.6 g, 0.290), and DMF (30 mL) in toluene (300 mL) at 100 °C. After the mixture was stirred for 1 h, the reaction mixture was poured into cooled 2 N HCl and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residual oil and sodium chloride (14.1 g, 0.241 mol) were dissolved in DMSO (400 mL)–water (40 mL), and then, the resultant was stirred at 120 °C for 10 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was dissolved in THF (100 mL)–2-propanol (200 mL), and then, sodium borohydride (1.83 g, 48.4 mmol) was added gradually to the solution at 0 °C. After the mixture was stirred for 90 min, the reaction mixture was poured onto ice-water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (1 kg). Elution with AcOEt–hexane (1:1, v/v) gave the title compound as crystals (**26**, 35.1 g, 33%). Recrystallization from AcOEt–hexane gave colorless prisms; mp 75–76 °C. ¹H NMR (CDCl₃): δ 1.25 (3H, d, *J* = 6 Hz), 1.27 (3H, d, *J* = 6 Hz), 1.55–1.9 (4H, m), 2.39 (3H, s), 2.5–2.7 (2H, m), 2.78 (1H, d, *J* = 5.5 Hz), 3.85 (3H, s), 4.1–4.2 (1H, m), 5.03 (2H, s), 5.0–5.2 (1H, m), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.6–6.75 (2H, m), 6.9–7.0 (2H, m), 7.54 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 3450, 1735, 1725, 1640, 1615, 1585, 1540, 1515. Anal. (C₂₄H₂₉NO₇) C, H, N.

Asymmetric O-Acetylation of **26. Synthesis of Iso-**

propyl (*R*)-(+)-2-Acetoxy-5-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]valerate ((*R*)-27**) and Isopropyl (*S*)-(–)-5-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-hydroxyvalerate ((*S*)-**26**).** A mixture of **26** (33.0 g, 0.0744 mmol), LIP-301 (immobilized lipase derived from *Pseudomonas* sp., TOYOBO Co., Ltd, 16.5 g), molecular sieves 4A (33.0 g), vinyl acetate (158 mL, 1.71 mol), and toluene (1650 mL) was stirred at 23 °C for 4 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on SiO₂. Elution with isoPr₂O gave (*R*)-**27** as an oil (15.9 g, 96%ee, 44%). ¹H NMR (CDCl₃): δ 1.22 (3H, d, *J* = 6 Hz), 1.26 (3H, d, *J* = 6 Hz), 1.6–1.95 (4H, m), 2.13 (3H, s), 2.40 (3H, s), 2.59 (2H, t, *J* = 8 Hz), 3.86 (3H, s), 4.95 (1H, t, *J* = 6 Hz), 4.95–5.15 (1H, m), 5.03 (2H, s), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.65–6.75 (2H, m), 6.9–7.0 (2H, m), 7.53 (1H, dd, *J* = 2, 1 Hz); [α]_D +12.4° (*c* = 2.0, isoPrOH). Subsequent elution gave (*S*)-**26** as an oil (19.7 g, 89%ee). The oil (19.7 g) was mixed with LIP-301 (16.5 g), molecular sieves 4A (33.0 g), vinyl acetate (158 mL, 1.71 mol), and toluene (1650 mL). The resultant was stirred at 23 °C for 4 h and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on SiO₂. Elution with isoPr₂O gave (*S*)-**26** as an oil (13.9 g, 98%ee, 42%). ¹H NMR (CDCl₃): δ 1.25 (3H, d, *J* = 6 Hz), 1.27 (3H, d, *J* = 6 Hz), 1.55–1.90 (4H, m), 2.39 (3H, s), 2.5–2.7 (2H, m), 2.78 (1H, d, *J* = 5.5 Hz), 3.85 (3H, s), 4.1–4.2 (1H, m), 5.03 (2H, s), 5.0–5.2 (1H, m), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.6–6.75 (2H, m), 6.9–7.0 (2H, m), 7.54 (1H, dd, *J* = 2, 1 Hz); [α]_D –2.35° (*c* = 2.0, isoPrOH).

Methyl (*R*)-5-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-hydroxyvalerate ((*R*)-28**).** A mixture of (*R*)-**27** (4.87 g, 10 mmol) and 5% HCl–MeOH (100 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (50 g). Elution with AcOEt–hexane (1:1, v/v) gave the title compound as crystals. Recrystallization from AcOEt–isoPr₂O gave colorless prisms ((*R*)-**28**, 3.20 g, 96%ee (HPLC), 77%); mp 83–84 °C. ¹H NMR (CDCl₃): δ 1.6–1.9 (4H, m), 2.40 (3H, s), 2.59 (2H, t, *J* = 7 Hz), 2.72 (1H, d, *J* = 6.5 Hz), 3.78 (3H, s), 3.86 (3H, s), 4.15–4.3 (1H, m), 5.03 (2H, s), 6.53 (1H, dd, *J* = 3.5, 2 Hz), 6.65–6.75 (2H, m), 6.93 (1H, d, *J* = 8 Hz), 6.97 (1H, dd, *J* = 3.5, 1 Hz), 7.54 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 3430, 1730, 1645, 1635, 1620, 1590, 1510. Anal. (C₂₂H₂₅NO₇) C, H, N; [α]_D –3.08° (*c* = 1.0, CHCl₃).

Methyl (*S*)-5-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-hydroxyvalerate ((*S*)-28**).** Compound (*S*)-**28** was similarly prepared from (*S*)-**26**. Yield, 91%; mp 80–81 °C (AcOEt–hexane). ¹H NMR (CDCl₃): δ 1.55–1.9 (4H, m), 2.39 (3H, s), 2.59 (2H, t, *J* = 7 Hz), 2.72 (1H, d, *J* = 6 Hz), 3.78 (3H, s), 3.86 (3H, s), 4.15–4.3 (1H, m), 5.03 (2H, s), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.65–6.75 (2H, m), 6.9–7.0 (2H, m), 7.53 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 3300, 1755, 1730, 1645, 1635, 1615, 1590, 1540, 1510. Anal. (C₂₂H₂₅NO₇) C, H, N; [α]_D +3.03° (*c* = 1.0, CHCl₃); 98%ee (HPLC).

HPLC Analyses of **28 ((*R*)-**28** and (*S*)-**28**).** CHIRALCEL AD (4.6 mm i.d. × 250 mm (Daicel Chemical Industries, Ltd., Tokyo, Japan)) was used for HPLC analyses. Analyses of samples were carried out using *n*-hexane–2-propanol (8:2, v/v) as a mobile phase at a flow rate of 0.5 mL/min and room temperature. Detection was carried out at UV 254 nm. Under these conditions, the retention times for (*R*)-**28** and (*S*)-**28** were 34.5 and 32.0 min, respectively.

(*R*)-(+)-5-[3-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinone ((*R*)-64**).** To a stirred solution of (*R*)-**28** (3.15 g, 7.58 mmol) in pyridine (50 mL) was added gradually 4-nitrophenyl chloroformate (2.30 g, 11.4 mmol) at room temperature. After the mixture was stirred for 1 h, the reaction mixture was poured into water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in

vacuo. The residue was purified by column chromatography on SiO₂ (80 g). Elution with AcOEt–hexane (1:2, v/v) gave methyl (*R*)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-(4-nitrophenoxy)valerate as an oil (5.30 g, 98%). ¹H NMR (CDCl₃): δ 1.7–2.05 (4H, m), 2.41 (3H, s), 2.63 (2H, t, *J* = 7 Hz), 3.81 (3H, s), 3.87 (3H, s), 5.03 (2H, s), 5.06 (1H, t, *J* = 6 Hz), 6.53 (1H, dd, *J* = 3.5, 2 Hz), 6.65–6.75 (2H, m), 6.9–7.0 (2H, m), 7.41 (2H, d, *J* = 9 Hz), 7.54 (1H, dd, *J* = 2, 1 Hz), 8.29 (2H, d, *J* = 9.0 Hz). IR (neat) (cm⁻¹): 1770, 1750, 1635, 1615, 1590, 1520; [α]_D +8.06° (*c* = 1.0, CHCl₃).

Gaseous ammonia was passed through a stirred solution of methyl (*R*)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-(4-nitrophenoxy)valerate (4.25 g, 7.82 mmol) in THF (80 mL) at -65 °C for 10 min. The reaction mixture was poured into cooled 6 N HCl and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (70 g). Elution with AcOEt–hexane (1:1, v/v) gave methyl (*R*)-(+)-2-carbamoyloxy-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]valerate as crystals (3.00 g, 89%). Recrystallization from acetone–isoPr₂O gave colorless needles; mp 110–111 °C. ¹H NMR (CDCl₃): δ 1.6–1.95 (4H, m), 2.40 (3H, s), 2.59 (2H, t, *J* = 7 Hz), 3.75 (3H, s), 3.86 (3H, s), 4.78 (2H, br s), 4.95–5.05 (1H, m), 5.03 (2H, s), 6.53 (1H, dd, *J* = 3.5, 2 Hz), 6.65–6.75 (2H, m), 6.9–7.0 (2H, m), 7.54 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 3430, 3340, 3300, 1760, 1710, 1635, 1605, 1585, 1510. Anal. Calcd for C₂₃H₂₆N₂O₈: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.05; H, 5.92; N, 5.87; [α]_D +5.30° (*c* = 1.0, MeOH).

1,8-Diazabicyclo[5.4.0]undec-7-ene (1.54 g, 10.1 mmol) was added dropwise to a stirred solution of methyl (*R*)-(+)-2-carbamoyloxy-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]valerate (2.92 g) in CHCl₃ (100 mL) at 0 °C. After the mixture was stirred for 1 h, the reaction mixture was washed with 2 N HCl and water. The organic layer was separated, dried (MgSO₄), and concentrated in vacuo to give the title compound as crystals ((*R*)-**64**, 2.25 g, 98% ee (HPLC), 91%). Recrystallization from acetone–isoPr₂O gave colorless needles; mp 122–123 °C. ¹H NMR (CDCl₃): δ 1.7–2.15 (4H, m), 2.40 (3H, s), 2.62 (2H, t, *J* = 7 Hz), 3.85 (3H, s), 4.82 (1H, dd, *J* = 6.5, 4.5 Hz), 5.03 (2H, s), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.6–6.75 (2H, m), 6.9–7.0 (2H, m), 7.53 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 3110, 1815, 1740, 1615, 1590, 1535, 1520. Anal. (C₂₂H₂₂N₂O₇) C, H, N; [α]_D +39.4° (*c* = 0.495, CHCl₃).

(*S*)-(-)-5-[3-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione ((*S*)-**64**). Compound (*S*)-**64** was similarly prepared from (*S*)-**28**. Yield, 79%; mp 122–123 °C (acetone–hexane). ¹H NMR (CDCl₃): δ 1.7–2.15 (4H, m), 2.40 (3H, s), 2.63 (2H, t, *J* = 7 Hz), 3.86 (3H, s), 4.83 (1H, dd, *J* = 6.5, 4.5 Hz), 5.03 (2H, s), 6.52 (1H, dd, *J* = 3.5, 2 Hz), 6.6–6.75 (2H, m), 6.9–7.0 (2H, m), 7.54 (1H, dd, *J* = 2, 1 Hz). IR (KBr) (cm⁻¹): 3110, 1815, 1740, 1615, 1590, 1535, 1520. Anal. (C₂₂H₂₂N₂O₇) C, H, N; [α]_D -39.8° (*c* = 0.500, CHCl₃); 99% ee (HPLC).

HPLC Analyses of 64 ((*R*)-64** and (*S*)-**64**).** CHIRALCEL AD (4.6 mm i.d. × 250 mm (Daicel Chemical Industries, Ltd., Tokyo, Japan)) was used for HPLC analyses. Analyses of samples were carried out using *n*-hexane–2-propanol–ethanol–acetic acid (700:150:150:1, v/v) as a mobile phase at a flow rate of 1.2 mL/min and room temperature. Detection was carried out at UV 290 nm. Under these conditions, the retention times for (*R*)-**64** and (*S*)-**64** were 19.8 and 26.5 min, respectively.

2-Chloroethyl (*S*)-(-)-5-[4-[2-(2-Furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]-2-hydroxyvalerate (29**).** A mixture of (*S*)-**26** (500 mg), 2-chloroethanol (5.0 mL), and ca. 20% HCl–isoPr₂O (1.0 mL) was stirred at room temperature for 24 h. After it was concentrated in vacuo, the residue was purified by column chromatography on SiO₂ (30 g). Elution with isoPrOH–hexane (1:1, v/v) gave the title compound as crystals (**29**, 153 mg, 29%). Recrystallization from EtOH–isoPr₂O gave colorless prisms; mp 88–91 °C. ¹H NMR (CDCl₃): δ 1.55–1.95 (4H, m), 2.39 (3H, s), 2.55–2.80 (3H,

m), 3.70 (2H, t, *J* = 5.6 Hz), 3.85 (3H, s), 4.18–4.55 (3H, m), 5.02 (2H, s), 6.52 (1H, dd, *J* = 3.6, 1.8 Hz), 6.64–6.75 (2H, m), 6.88–6.99 (2H, m), 7.51–7.56 (1H, m). IR (KBr) (cm⁻¹): 3430, 2940, 1720, 1640, 1585, 1520, 1460. Anal. (C₂₃H₂₆ClNO₇) C, H, N.

(*R*)-(+)-3-[2-(4-Chlorophenyl)-2-oxoethyl]-5-[3-[4-(5-methyl-2-phenyl-4-thiazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione (**30**). A mixture of (*R*)-**55** (200 mg, 0.473 mmol), 4-chlorophenacyl bromide (133 mg, 0.570 mmol), K₂CO₃ (80 mg, 0.579 mmol), and DMF (5 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into water, acidified with 2 N HCl, and extracted with AcOEt. The extract was washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (20 g) with AcOEt–hexane (1:2, v/v) to give the title compound (**30**, 245 mg, 86%, >99% ee). Recrystallization from EtOH gave colorless prisms; mp 164–165 °C. ¹H NMR (CDCl₃): δ 1.8–2.1 (4H, m), 2.54 (3H, s), 2.67 (2H, t, *J* = 7 Hz), 4.91 (2H, s), 4.95 (1H, dd, *J* = 7, 4.5 Hz), 5.16 (2H, s), 6.98 (2H, d, *J* = 9 Hz), 7.12 (2H, t, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.50 (2H, d, *J* = 9 Hz), 7.85–7.95 (4H, m). Anal. (C₃₁H₂₇ClN₂O₅S) C, H, N; [α]_D +35.7° (*c* = 0.497, CHCl₃).

Separation of (*R*)-(+)-5-[3-[4-(5-Methyl-2-phenyl-4-thiazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione ((*R*)-55**) and (*S*)-(-)-5-[3-[4-(5-Methyl-2-phenyl-4-thiazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione ((*S*)-**55**) by HPLC.** Racemic mixture (**55**, 1002 mg) was subjected to preparative HPLC [column, CHIRALPAK AD (i.d. 10 mm × 250 mm, Daicel Chemical Industries, Ltd.); mobile phase, hexane/EtOH/AcOH = 200/800/1; flow rate, 3.5 mL/min; column temperature, 50 °C]. Each fraction was concentrated in vacuo to give a solid, which was dissolved in AcOEt. The solution was washed successively with aqueous sodium bicarbonate and water. After it was dried (MgSO₄), the solution was passed through 0.000 45 mm membrane filter and concentrated in vacuo to afford optically pure material as colorless crystals ((*R*)-**55**, 412 mg, 99.9% ee). Recrystallization from acetone–isoPr₂O gave colorless prisms; mp 113–114 °C. ¹H NMR (CDCl₃): δ 1.7–2.1 (4H, m), 2.53 (3H, s), 2.65 (2H, t, *J* = 7 Hz), 4.82 (1H, dd, *J* = 6.5, 4.5 Hz), 5.15 (2H, s), 6.97 (2H, d, *J* = 9 Hz), 7.10 (2H, d, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.8–8.0 (3H, m). Anal. (C₂₃H₂₂N₂O₄S) C, H, N; [α]_D +38.0° (*c* = 0.397, CHCl₃). Subsequent elution gave (*S*)-**55** as colorless crystals (407 mg, 99.9% ee). Recrystallization from acetone–isoPr₂O gave colorless prisms; mp 113–114 °C. ¹H NMR (CDCl₃): δ 1.7–2.1 (4H, m), 2.53 (3H, s), 2.63 (2H, t, *J* = 7 Hz), 4.82 (1H, dd, *J* = 6.5, 4.5 Hz), 5.15 (2H, s), 6.97 (2H, d, *J* = 9 Hz), 7.10 (2H, d, *J* = 9 Hz), 7.35–7.5 (3H, m), 7.8–8.0 (3H, m). Anal. (C₂₃H₂₂N₂O₄S) C, H, N; [α]_D -37.3° (*c* = 0.505, CHCl₃).

X-ray Crystal Analysis. Compound **29**. A colorless thin needle crystal of approximate dimensions 0.90 mm × 0.03 mm × 0.03 mm was mounted on a glass fiber and transferred to a Rigaku AFC5R diffractometer. The intensity data were collected at room temperature with Cu Kα radiation. The structure was solved by direct methods and refined on F² by full-matrix least-squares techniques. Data processing and initial phase determination were carried out using the teXsan²³ system. The structure was refined by SHELXL-97.²⁴ Hydrogen atoms were included using a riding model. At convergence, *w*R² = 0.1659 and GOF = 1.029 for 289 variables refined against all 3296 unique data. The absolute configuration was reliably determined from the refined Flack²⁵ parameter [-0.04(6)]. Compound **30**: A colorless crystal of approximate dimensions 0.30 mm × 0.26 mm × 0.14 mm was analyzed. Methods of data collection, structure solution, and refinement were the same as compound **29**. At convergence, *w*R² = 0.1080 and GOF = 1.025 for 722 variables refined against all 9722 unique data. The absolute configuration was unambiguously determined from the Flack parameter [-0.017(13)].

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Supporting Information Available: X-ray crystal data and details of structure refinement for compounds **29** and **30**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) American Diabetes Association. *Diabetes Care* **1999**, *22* (Suppl. 1), S27.
- (2) Porte, D., Jr.; Schwartz, M. W. Diabetes Complications: Why Is Glucose Potentially Toxic? *Science* **1996**, *272*, 699–700.
- (3) The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N. Engl. J. Med.* **1993**, *329*, 977–986.
- (4) Gerich, J. E. Oral Hypoglycemic Agents. *N. Engl. J. Med.* **1989**, *321*, 1231–1245.
- (5) (a) Hulin, B. New Hypoglycemic Agents. *Prog. Med. Chem.* **1994**, *31*, 1–58. (b) Hulin, B.; McCarthy, P. A.; Gibbs, E. M. The Glitazone Family of Antidiabetic Agents. *Curr. Pharm. Des.* **1996**, *2*, 85–102.
- (6) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexyl-methoxy)benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives. *Chem. Pharm. Bull.* **1982**, *30*, 3580–3600.
- (7) Iwatsuka, H.; Shino, A.; Suzuoki, Z. General Survey of Diabetic Features of Yellow KK Mice. *Endocrinol. Jpn.* **1970**, *17*, 23–35.
- (8) Ikeda, H.; Shino, A.; Matsuo, T.; Iwatsuka, H.; Suzuoki, Z. A New Genetically Obese-Hyperglycemic Rat (Wistar Fatty). *Diabetes* **1981**, *30*, 1045–1050.
- (9) (a) Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamatsu, Y.; Iwatsuka, H.; Suzuoki, Z. Reduction of Insulin Resistance in Obese and/or Diabetic Animals by 5-[4-(1-Methylcyclohexyl-methoxy)benzyl]thiazolidine-2,4-dione (ADD-3878, U-63, 287, Ciglitazone), a New Antidiabetic Agent. *Diabetes* **1983**, *32*, 804–810. (b) Chang, A. Y.; Wyse, B. M.; Gilchrist, B. J.; Peterson, T.; Diani, A. R. Ciglitazone, a New Hypoglycemic Agent. I. Studies in ob/ob and db/db Mice, Diabetic Chinese Hamsters, and Normal and Streptozotocin-Diabetic Rats. *Diabetes* **1983**, *32*, 830–838.
- (10) Sohda, T.; Momose, Y.; Meguro, K.; Kawamatsu, Y.; Sugiyama, Y.; Ikeda, H. Studies on Antidiabetic Agents. Synthesis and Hypoglycemic Activity of 5-[4-(Pyridylalkoxy)benzyl]-2,4-thiazolidinediones. *Arzneim.-Forsch./Drug Res.* **1990**, *40*, 37–42.
- (11) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita, T.; Meguro, K. Studies on Antidiabetic Agents. 11. Novel Thiazolidinedione Derivatives as Potent Hypoglycemic and Hypolipidemic Agents. *J. Med. Chem.* **1992**, *35*, 2617–2626.
- (12) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. Studies on Hindered Phenols and Analogues. 1. Hypolipidemic and Hypoglycemic Agents with Ability to Inhibit Lipid Peroxidation. *J. Med. Chem.* **1989**, *32*, 421–428.
- (13) Cantello, B. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. [[ω -(Hetero-cyclalamino)alkoxy]benzyl]-2,4-thiazolidinedione as Potent Antihyperglycemic Agents. *J. Med. Chem.* **1994**, *37*, 3977–3985.
- (14) Pickavance, L.; Widdowson, P. S.; King, P.; Ishii, S.; Tanaka, H.; Williams, G. The development of overt diabetes in young Zucker Diabetes Fatty (ZDF) rats and the effects of chronic MCC-555 treatment. *Br. J. Pharmacol.* **1998**, *125*, 767–770.
- (15) Nomura, M.; Kinoshita, S.; Satoh, H.; Maeda, T.; Murakami, K.; Tsunoda, M.; Miyachi, H.; Awano, K. 3-(Substituted Benzyl)-thiazolidine-2,4-diones as Structurally New Antihyperglycemic Agents. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 533–538.
- (16) Clark, D. A.; Goldstein, S. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.; Hulin, B.; Stevenson, R. W.; Kreutter, D. K.; Gibbs, E. M.; Krupp, M. N.; Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tickner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajekas, F. J.; Kaooeler, W. H.; McDermott, R. E.; Hutson, N. J.; Johnson, M. R. Substituted Dihydrobenzopyran and Dihydrobenzofuran Thiazolidine-2,4-diones as Hypoglycemic Agents. *J. Med. Chem.* **1991**, *34*, 319–325.
- (17) Momose, Y.; Maekawa, T.; Odaka, H.; Ikeda, H.; Sohda, T. Novel 5-Substituted-1*H*-tetrazole Derivatives as Potent Glucose and Lipid Lowering Agents. *Chem. Pharm. Bull.* **2002**, *50*, 100–111.
- (18) Meguro, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on Antidiabetic Agents. VII. Synthesis and Hypoglycemic Activity of 4-Oxazole-acetic Acid Derivatives. *Chem. Pharm. Bull.* **1986**, *34*, 2840–2851.
- (19) Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliewer, S. A.; Lehmann, J. M. The Structure–Activity Relationship between Peroxisome Proliferator-Activated Receptor γ . Agonism and the Anti-Hyperglycemic Activity of Thiazolidinediones. *J. Med. Chem.* **1996**, *39*, 665–668.
- (20) Malamas, M. S.; Sredy, J.; Gunawan, I.; Mihan, B.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Flam, B. R. New Azolidinediones as Inhibitors of Protein Tyrosine Phosphatase 1B with Anti-hyperglycemic Properties. *J. Med. Chem.* **2000**, *43*, 995–1010.
- (21) (a) Hulin, B.; Newton, L. S.; Lewis, D. M.; Genereux, P. E.; Gibbs, E. M.; Clark, D. A. Hypoglycemic Activity of a Series of α -Alkylthio and α -Alkoxy Carboxylic Acids Related to Ciglitazone. *J. Med. Chem.* **1996**, *39*, 3897–3907. (b) Young, P. W.; Buckle, D. R.; Cantello, B. C. C.; Chapman, H.; Clapham, J. C.; Coyle, P. J.; Haigh, D.; Hindley, R. M.; Holder, J. C.; Kallender, H.; Latter, A. J.; Lawrie, K. W. M.; Mossakowska, D.; Murphy, G. J.; Cox, L. R.; Smith, S. A. Identification of high-affinity binding sites for the insulin sensitizer Rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for Peroxisomal Proliferator-Activated Receptor γ . *J. Pharmacol. Exp. Ther.* **1998**, *284*, 751–759. (c) Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W., Jr.; Hashim, M. A.; Hull-Ryde, E. A.; Kaldor, I.; Kliewer, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Lenhard, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A., Jr.; Noble, S. A.; Oliver, W., Jr.; Parks, D. J.; Plunket, K. D.; Szewczyk, J. R.; Willson, T. M. N-(2-Benzoylphenyl)-L-tyrosine PPAR γ Agonists. 1. Discovery of a Novel Series of Potent Antihyperglycemic and Antihyperlipidemic Agents. *J. Med. Chem.* **1998**, *41*, 5020–5036.
- (22) Sakamoto, J.; Kimura, H.; Moriyama, S.; Odaka, H.; Momose, Y.; Sugiyama, Y.; Sawada, H. Activation of Human Peroxisome Proliferator-Activated Receptor (PPAR) Subtypes by Pioglitazone. *Biochem. Biophys. Res. Commun.* **2000**, *278*, 704–711.
- (23) teXsan: a single-crystal structure analysis software, version 1.9; Molecular Structure Corporation: The Woodlands, TX, 1998.
- (24) Sheldrick, G. M. SHELX-97: a program for crystal structure refinement; University of Göttingen, Germany, 1997.
- (25) Flack, H. D. On enantiomorph-polarity estimation. *Acta Crystallogr.* **1983**, *A39*, 876–881.

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