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

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Two novel classes of 2,4-thiazolidinediones and 2,4-oxazolidinediones with an ω-(azolylalkoxyphenyl)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** ($ED_{25} > 1.5$ mg/kg/d) or pioglitazone ($ED_{25} = 6$ mg/kg/d) in KKA^y mice. It also exhibited a 10-fold more potent antidiabetic activity ($ED_{25} = 0.05$ mg/kg/d) than pioglitazone ($ED_{25} = 0.5$ 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 ($EC_{50} = 8.87$ 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 resistant animal models, KKA^y mice[7] 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

Chart 1

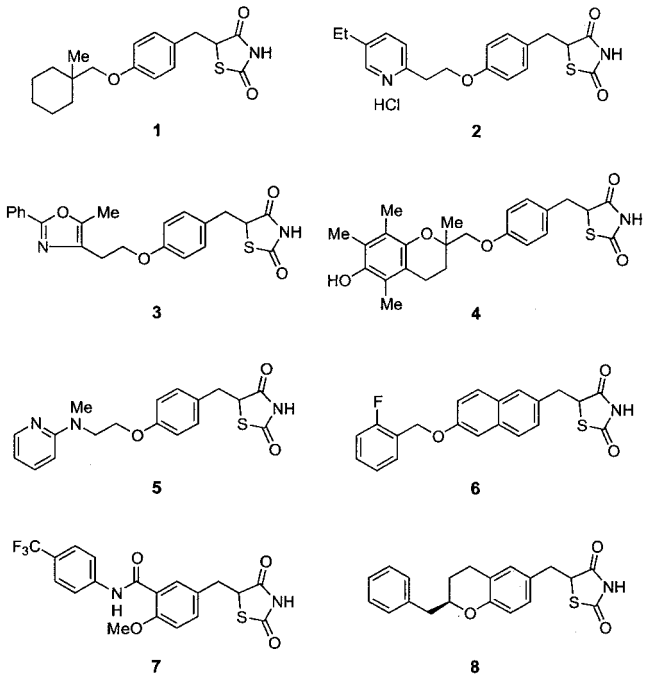

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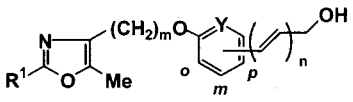
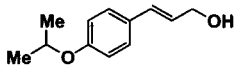
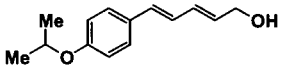
Table 1. Physical Data and Yields of Unsaturated Alcohol **10**



compd	R^1	Y	m	n	substituted position	yield[a] (%)	mp (°C)	recryst. solvent[b]	empirical formula[c]
10a	Ph	C–OMe	1	1	*p*	61	137–138	AC–E	$C_{21}H_{21}NO_4$
10b	Ph	C–H	2	1	*p*	79	127–128	AC	$C_{21}H_{21}NO_3$
10c	Ph	C–H	1	1	*p*	93	133–134	AC–H	$C_{20}H_{19}NO_3$[e]
10d	2-furyl	C–OMe	1	1	*p*	76	128–129	D–E	$C_{19}H_{19}NO_5$
10e	Ph	C–H	1	1	*m*	75	120–121	AC	$C_{20}H_{19}NO_3$
10f	Ph	C–H	1	1	*o*	76	128–129	AC–IP	$C_{20}H_{19}NO_3$
10g	Ph	C–H	2	2	*p*	35	132–133	D–H	$C_{23}H_{23}NO_3$
10h	Ph	N	1	1	*p*	–[d]	116–117	D–IP	$C_{19}H_{18}N_2O_3$
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] •1/4H_2O.

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

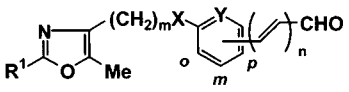
Each 2,4-thia(oxa)zolidinedione, as shown in Tables 4−6, was prepared from an aryl aldehyde **9** according to one of the general methods (A−D) described in the schemes below.

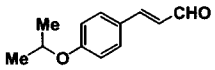
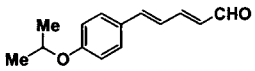
Thia(oxa)zolidinediones with a propyl or a pentyl substituent at the 5-position **12** (n = 3 or 5) were synthesized from the aryl aldehyde **9** via a five step process. The Horner−Emmons reaction of **9** yielded unsaturated esters, which were reduced with diisobutylaluminum hydride (DIBAL-H) to provide 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 hydrogenation 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 thiourea 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

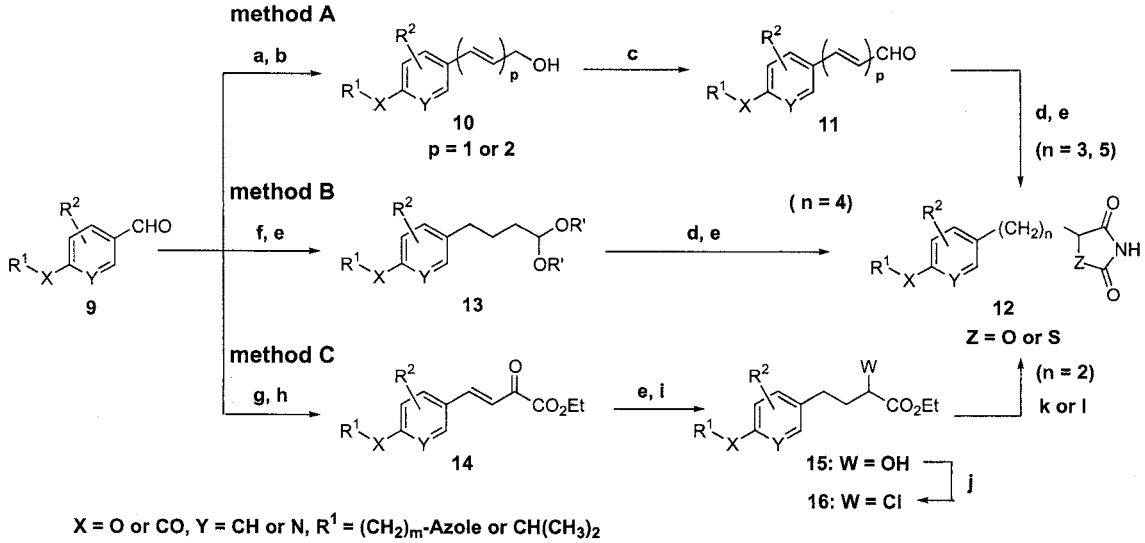
Table 2. Physical Data and Yields of Unsaturated Aldehyde **11**



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	*p*	92	159–160	AC	$C_{21}H_{19}NO_4$
11b	Ph	O	C–H	2	1	*p*	94	128–129	AC–H	$C_{21}H_{19}NO_3$
11c	Ph	O	C–H	1	1	*p*	70	114–115	AC–H	$C_{20}H_{17}NO_3$
11d	2-furyl	O	C–OMe	1	1	*p*	94	125–126	D–E	$C_{19}H_{17}NO_5$
11e	Ph	O	C–H	1	1	*m*	96	103–104	AC–H	$C_{20}H_{17}NO_3$
11f	Ph	O	C–H	1	1	*o*	92	112–113	C–IP	$C_{20}H_{17}NO_3$
11g	Ph	C=O	C–H	2	1	*p*	–[d]	119–120	D–IP	$C_{22}H_{19}NO_3$
11h	Ph	O	N	1	1	*p*	92	147–148	D–IP	$C_{19}H_{16}N_2O_3$
11i							89	oil	–	–
11j							99	oil	–	–
11k	Ph	O	C–H	2	2	*p*	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] •1/4H_2O.

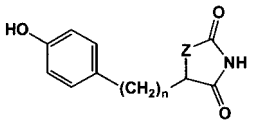
Scheme 1[a]



[a] Key: (a) NaOMe, $RO_2C(CH{=}CH)_{p-1}CH_2CO_2P(O)(OR)_2$, DMF. (b) DIBAL-H, CH_2Cl_2. (c) MnO_2, CH_2Cl_2. (d) 2,4-Thia(oxa)zolidinedione, piperidine, EtOH. (e) H_2, Pd–C, 1,4-dioxane, EtOH. (f) NaH, $Ph_3P(CH_2)_2CH(OR')_2Br$, DMF. (g) Na_2CO_3, pyruvic acid, water, MeOH. (h) HCl–EtOH. (i) $NaBH_4$, EtOH. (j) $SOCl_2$. (k) KCNO, *n*-BuOH. (l) Thiourea, NaOAc, EtOH then aqueous HCl.

furnished the 3-arylpropanol, which was sequentially treated with methanesufonyl 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]-

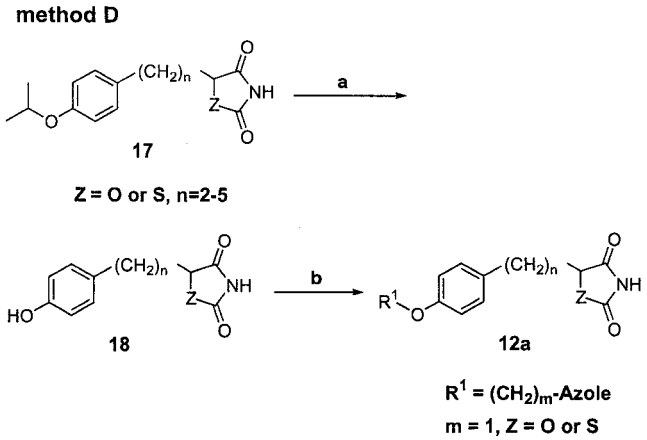
Table 3. Physical Data and Yields of 2,4-Thia(oxa)-zolidinediones



compd	*n*	Z	yield[a] (%)	mp (°C)	recryst solvent[b]	empirical formula[c]
18a	2	S	63	175−176	A−IP	$C_{11}H_{11}NO_3S$
18b	3	S	57	129−130	A−IP	$C_{12}H_{13}NO_3S$
18c	4	S	78	125−126	D−IP	$C_{13}H_{15}NO_3S$[d]
18d	5	S	49	112−113	A−IP	$C_{14}H_{17}NO_3S$
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] •1/8H_2O.

Scheme 2[a]



[a] Key: (a) $TiCl_4$, CH_2Cl_2. (b) NaH, azole−CH_2Cl (19), DMF.

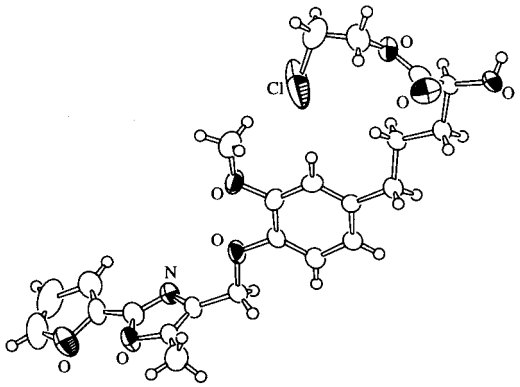


Figure 1. Molecular structure of **29** as determined by X-ray crystal analysis.

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

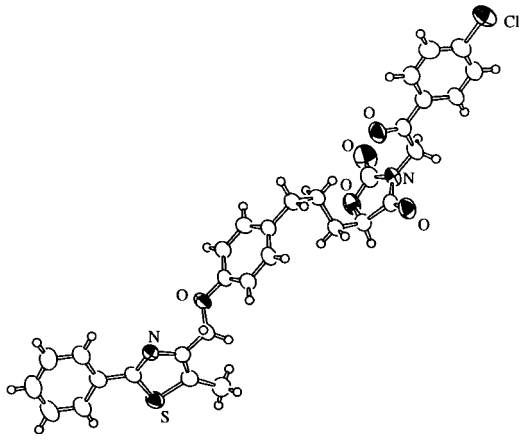


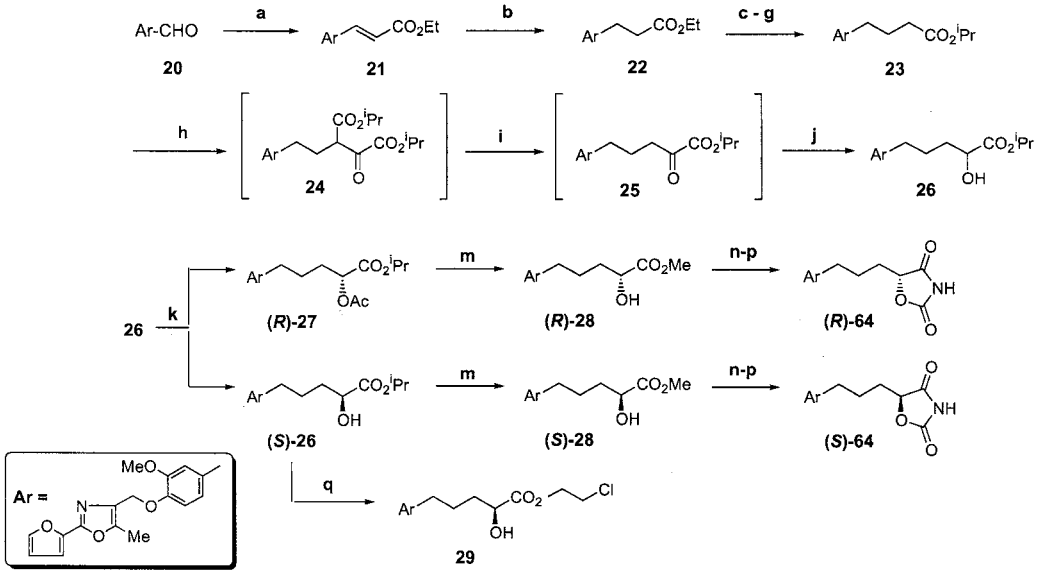
Figure 2. Molecular structure of **30** as determined by X-ray crystal analysis.

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

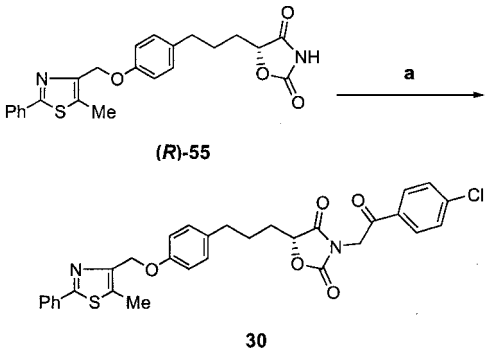
All compounds synthesized were initially evaluated in KKA^y mice to determine their antidiabetic activities (Table 7). We initially examined the 2,4-thiazolidinediones with a prolonged alkyl substituent at the 5-position (**31**−**36**). These compounds were found to exhibit considerable antidiabetic 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** ($ED_{25} = 0.402$ mg/kg/d) exhibited an approximately 10-fold increase in antidiabetic activity over pioglitazone **2** ($ED_{25} = 6.0$ mg/kg/d).[10] Exchange of both the alkyl spacers in compound **45** (-CH_2- and -$(CH_2)_3$-) 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, $EtO_2CCH_2CO_2P(O)(OEt)_2$, DMF. (b) H_2, Pd−C, AcOEt. (c) $NaBH_4$, MeOH, THF. (d) MsCl, Et_3N, AcOEt. (e) NaCN, DMF. (f) Aqueous KOH, 2-methoxyethanol. (g) K_2CO_3, ^{i}Pr−I, DMF. (h) NaH, $(CO_2{}^iPr)_2$, PhMe, DMF. (i) NaCl, DMSO. (j) $NaBH_4$, THF, *i*-PrOH. (k) Immobilized lipase (LIP-301), MS-4A, vinyl acetae, PhMe. (m) HCl−MeOH. (n) $ClCO_2C_6H_4(p\text{-}NO_2)$, pyridine. (o) NH_3 gas, THF. (p) DBU, $CHCl_3$. (q) HCl, $Cl(CH_2)_2OH$.

Scheme 4[a]



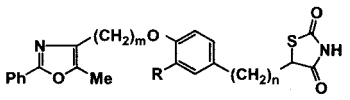
[a] Key: (a) 4-Chlorophenacyl bromide, K_2CO_3, DMF.

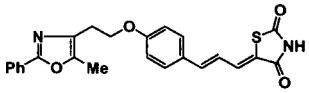
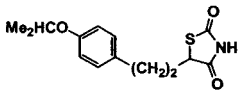
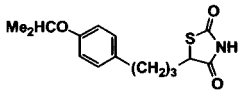
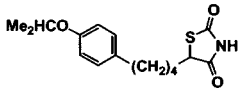
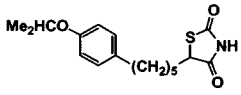
that the spatial configuration of three rings (oxazole, central benzene, and oxazolidinedione ring) connected by two alkyl spacers (-$(CH_2)_m$- and -$(CH_2)_n$-) plays an important role in increasing activity. Replacement of the oxazole ring of **45** with a thiazole moiety resulted in a decrease of 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 (PPARγ) and antidiabetic activity in Wistar fatty rats.[8] As shown in Table 8, all compounds exhibited remarkable antihyperglycemic activity. Moreover, similar SARs were observed among the in vitro activities for PPARγ 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 PPARγ in vitro (Table 8). Compound **55** also showed a similar tendency, with (*R*)-(+)-**55** having more potent antihyperglycemic activity and transcriptional activity for PPARγ 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	$C_{23}H_{22}N_2O_4S$
32	H	2	3	A	13[e]	151–152	AC–H	$C_{24}H_{24}N_2O_4S$
33	H	1	2	D	58[f]	146–147	D–IP	$C_{22}H_{20}N_2O_4S$
34	H	1	3	D	65[f]	165–166	D–ME	$C_{23}H_{22}N_2O_4S$
35	H	1	4	D	26[f]	184–185	D–ME	$C_{24}H_{24}N_2O_4S$
36	H	1	5	D	49[f]	107–108	D–ME	$C_{25}H_{26}N_2O_4S$
37	OMe	1	3	A	15[e]	118–120	AC–E–H	$C_{24}H_{24}N_2O_5S$
38				A	24[e]	222–223	C–ME	$C_{24}H_{20}N_2O_4S$
17a				C	quant.[d]	oil	–	–
17b				A	39[e]	oil	–	–
17c				B	68[g]	72–73	E–H	$C_{16}H_{21}NO_3S$
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**.

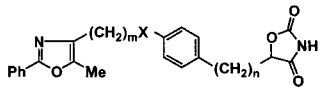
insulin sensitizer with an asymmetric center on its five-membered acidic heterocycle and that the more active isomer is the (*R*)-(+)-enantiomer different from a series of antidiabetic α-alkoxy, α-thio, and α-aminopropionic acids.[21]

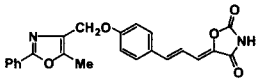
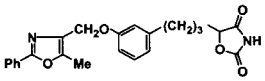
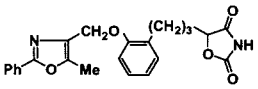
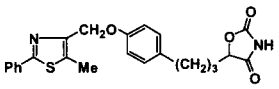
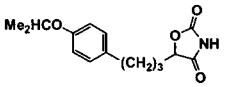
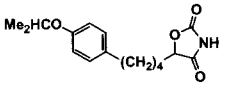
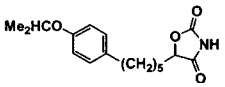
In summary, we showed that a series of 2,4-thia(oxa)-zolidinediones with a prolonged alkyl substituent at the 5-position have potent antidiabetic effects in two genetically obese and diabetic models, KKA^y mice and Wistar fatty rats. The antidiabetic effects of these compounds are considered to be due to potent agonistic activities for PPARγ. 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 cm^2 tissue culture flask and cultured in 5% CO_2 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 μL of LipofectAMINE, 100 μL of LipofectAMINE Plus, 2.5 μg of each expression plasmid pMCMVneo-hPPARγ and pMCMVneo-hRXRα, 5 μg of reporter plasmid pGL3-PPRE × 4-tk-luc-neo, and 5 μg of pRL-tk (Promega, USA). Cells were incubated in 25 mL of transfection mixture for 3 h in 5% CO_2 at 37 °C. After 25 mL of Dulbecco's

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

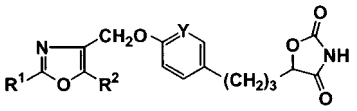


compd	X	m	n	prep. method[a]	yield (%)	mp (°C)	recryst. solvent[b]	empirical formula[c]
39	O	2	2	C	63[f]	193–194	D–ET	$C_{23}H_{22}N_2O_5$
40	O	2	3	A	20[g]	162–163	AC–H	$C_{24}H_{24}N_2O_5$
41	O	2	4	B	16[h]	136–137	D–ME	$C_{25}H_{26}N_2O_5$
42	O	2	5	A	24[g]	157–158	D–ME	$C_{26}H_{28}N_2O_5$
43	O	1	1	–[d]				
44	O	1	2	C	35[f]	158–159	AC–H	$C_{22}H_{20}N_2O_5$
45	O	1	3	A	14[g]	157–158	AC–H	$C_{23}H_{22}N_2O_5$
46	O	1	4	D	32[i]	186–187	D–IP	$C_{24}H_{24}N_2O_5$
47	O	1	5	D	58[i]	120–121	D–IP	$C_{25}H_{26}N_2O_5$
48	O	3	1	–[e]	16[j]	150–151	C–E	$C_{23}H_{22}N_2O_5$
49	C=O	2	3	A	14[g]	184–185	D–ME	$C_{25}H_{24}N_2O_5$
50	CHOH	2	3	–[e]	64[k]	150–151	A–IP	$C_{25}H_{26}N_2O_5$
51	CH_2	2	3	–[e]	82[l]	119–120	ME–ET	$C_{25}H_{26}N_2O_4$[m]
52				A	26[g]	244–245	C–ME	$C_{23}H_{18}N_2O_5$[n]
53				A	14[g]	134–135	AC–H	$C_{23}H_{22}N_2O_5$
54				A	17[g]	158–159	C–ME–E	$C_{23}H_{22}N_2O_5$
55				D	71[i]	104–105	D–IP	$C_{23}H_{22}N_2O_4S$
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] $\bullet 1/2H_2O$. [n] $\bullet 1/8H_2O$.

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% CO_2 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 μL of DMEM medium containing 0.1% fatty acid free BSA and 20 μL of test compounds and cultured in 5% CO_2 at 37 °C for 48 h. After the medium was removed, 40 μL 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 EC_{50}, 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	$C_{23}H_{22}N_2O_5$
56	Ph	H	C−H	D	72[e]	167−168	D−ME	$C_{22}H_{20}N_2O_5$
57	1-naphthyl	Me	C−H	D	72[e]	oil		$C_{27}H_{24}N_2O_5$
58	2-naphthyl	Me	C−H	D	84[e]	151−152	D−ME	$C_{27}H_{24}N_2O_5$
59	2-furyl	Me	C−H	D	74[e]	146−147	D−IP	$C_{21}H_{20}N_2O_6$
60	2-benzofuranyl	Me	C−H	D	70[e]	165−166	D−IP	$C_{25}H_{22}N_2O_6$
61	2-benzothienyl	Me	C−H	D	76[e]	154−155	D−IP	$C_{25}H_{22}N_2O_5S$
62	Ph	Me	N	A	22[d]	oil		$C_{22}H_{21}N_3O_5$[i]
63	Ph	Me	C−OMe	A	16[d]	161−162	AC−H	$C_{24}H_{24}N_2O_6$
64	2-furyl	Me	C−OMe	A	14[d]	127−129	D−E	$C_{22}H_{22}N_2O_7$[i]
(+)-64	2-furyl	Me	C−OMe	-[f]	91[g]	122−123	A−IP	$C_{22}H_{22}N_2O_7$
(−)-64	2-furyl	Me	C−OMe	-[f]	91[h]	122−123	A−IP	$C_{22}H_{22}N_2O_7$

[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] •1/2H_2O.

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

	glucose-lowering activity[a]				lipid-lowering activity[a]			
	dose (%)				dose (%)			
compd	0.001	0.005	0.01	ED_{25}[b]	0.001	0.005	0.01	ED_{25}[b]
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 mice[6] 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^y Mice and Wistar Fatty Rats and Transcriptional Activities for PPARγ of 2,4-Thia(Oxa)zolidinediones

compd	glucose-lowering activity (ED_{25})[a]		transcriptional activity for PPARγ
	KKA^y mice	Wistar fatty rats	EC_{50} (95% confidence interval) (nM)[b]
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 (μg/mL)[a]	
		(*R*)-(+)-**64**	(*S*)-(−)-**64**
(*R*)-(+)-**64**[c] (1 mg/kg)	pre	nd[b]	nd
	5	6.46 ± 0.82	0.02 ± 0.00
	10	6.06 ± 0.83	0.02 ± 0.01
	15	5.13 ± 0.53	0.02 ± 0.00
	30	4.78 ± 0.73	0.02 ± 0.00
	60	3.19 ± 0.65	0.02 ± 0.00
	120	1.46 ± 0.37	nd
(*S*)-(−)-**64**[d] (1 mg/kg)	pre	nd	nd
	5	0.04 ± 0.01	4.78 ± 0.50
	10	0.04 ± 0.01	4.30 ± 0.23
	15	0.04 ± 0.01	3.97 ± 0.42
	30	0.05 ± 0.02	3.65 ± 0.67
	60	0.07± 0.02	2.94 ± 0.21
	120	0.07± 0.02	1.61 ± 0.26

[a] The results are the mean ± 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 ED_{25}. The ED to reduce plasma glucose and triglyceride levels by 25% (ED_{25}) 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 ED_{25} (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 ED_{25} 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 μL) was added to each plasma sample (100 μL). The mixture was vortex-mixed followed by centrifugation at 10 000 rpm for 5 min. The supernatant (300 μL) was collected and dried up under a nitrogen gas stream. The residue was dissolved in 200 μL of acetonitrile−0.02 mol/L potassium dihydrogenphosphate (43:57, v/v), and an aliquot of 50 μL was injected into the HPLC analysis.

(ii) HPLC Assay. CHIRALCEL OJ-R (4.6 mm i.d. × 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 °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 ^{1}H 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 ±0.4% of the theoretical values. Column chromatography was performed using SiO_2 (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 °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−$CHCl_3$−Et_2O to give methyl (*E*)-3-methoxy-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)-cinnamate as colorless needles (21.9 g, 73%). ^{1}H NMR ($CDCl_3$): 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 $C_{22}H_{21}NO_5$: 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 CH_2Cl_2 (120 mL) at 0 °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 CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give the title compound as colorless crystals (**10a**, 16.5 g, 83%). Recrystallization from AcOEt−Et_2O gave colorless prisms; mp 137−138 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{21}H_{21}NO_4$) 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**: ^{1}H NMR ($CDCl_3$): 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**: ^{1}H NMR ($CDCl_3$): 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**: ^{1}H NMR ($CDCl_3$): 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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-oxazolemethanol (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−$isoPr_2O$). Anal. Calcd for $C_{16}H_{13}N_3O_4$: 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−$isoPr_2O$). ^{1}H 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 $C_{16}H_{15}N_3O_2$: 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%). ^{1}H 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−$isoPr_2O$). ^{1}H 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 $C_{20}H_{18}N_2O_4$: 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]acrylate (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−$isoPr_2O$). ^{1}H 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. ($C_{19}H_{18}N_2O_3$) C, H, N.

(2*E*,4*E*)-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 (2*E*,4*E*)-5-(4-isopropoxyphenyl)-2,4-pentadienoate (13.7 g, 58%). Recrystallization from Et_2O−hexane gave colorless prisms; mp 64−65 °C. ^{1}H 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 $C_{16}H_{20}O_3$: 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 (2*E*,4*E*)-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 $isoPr_2O$ gave colorless needles; mp 91−92 °C. ^{1}H 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. ($C_{14}H_{18}O_2$) C, H. Compound **10g** was obtained similarly. The yield, recrystallization solvent, melting point, and elemental analysis were listed in Table 1. **10g**: ^{1}H 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. ^{1}H 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. ($C_{21}H_{19}NO_4$) 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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$_2$O gave colorless prisms; mp 119−120 °C. ^{1}H 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. ($C_{22}H_{19}NO_3$) C, H, N.

General Procedure for 5-Propyl- or 5-Pentyl-2,4-thia(oxa)zolidinediones 12 (n = 3 or 5 in Tables 4−6). 5-[3-[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-[3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propenylidene]-2,4-thiazolidinedione as crystals (**38**, 780 mg, 24%). Recrystallization from $CHCl_3$−MeOH gave yellow needles; mp 222−223 °C. ^{1}H 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. ($C_{24}H_{20}N_2O_4S$) 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. ^{1}H 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. ($C_{24}H_{24}N_2O_4S$) 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H NMR (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**: ^{1}H 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**: ^{1}H NMR (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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (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%). ^{1}H NMR ($CDCl_3$): 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 SiO_2 (100 g). Elution with AcOEt−hexane (1:3, v/v) gave the title compound as an oil (**13a**, 4.83 g, 96%). ^{1}H NMR ($CDCl_3$): 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). ^{1}H NMR ($CDCl_3$): 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]-butyl]-2,4-oxazolidinedione (41). A mixture of **13a** (2.00 g, 4.91 mmol), 2,4-oxazolidinedione (990 mg, 9.80 mg), 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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (60 g). Elution with AcOEt−$CHCl_3$ (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 Et_2O−$isoPr_2O$ gave pure (*E*)-isomer as crystals (450 mg, 21%). Recrystallization from Et_2O−MeOH gave colorless needles; mp 152−153 °C. ^{1}H NMR ($CDCl_3$): 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 $C_{25}H_{24}N_2O_5$: 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/cm^2 for 24 h. After the catalyst was removed by filtration, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (40 g). Elution with 3% MeOH−$CHCl_3$ gave the title compound as crystals (**41**, 250 mg, 65%). Recrystallization from CH_2Cl_2−MeOH gave colorless prisms; mp 136−137 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{25}H_{26}N_2O_5$) 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**: ^{1}H NMR ($CDCl_3$): 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**: ^{1}H NMR ($CDCl_3$): 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 $CHCl_3$. The organic layer 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 (**14a**, 1.00 g, 25%). Recrystallization from CH_2Cl_2−EtOH gave pale yellow needles; mp 99−100 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{24}H_{23}NO_5 \cdot 1/2H_2O$) 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). ^{1}H NMR ($CDCl_3$): 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. ($C_{23}H_{21}NO_5$) C, H, N. **14c**: Yield, 38% (a colorless oil). ^{1}H NMR ($CDCl_3$): 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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (50 g). Elution with AcOEt−$CHCl_3$ (1:9, v/v) gave the title compound as crystals (**15a**, 550 mg, 64%). Recrystallization from Et_2O−hexane gave colorless needles; mp 67−68 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{24}H_{27}NO_5$) 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). ^{1}H NMR ($CDCl_3$): 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). ^{1}H NMR ($CDCl_3$): 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%). ^{1}H 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). ^{1}H 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. ^{1}H NMR (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. ($C_{23}H_{22}N_2O_5$) C, H, N. 5-[2-[4-(5-Methyl-2-phenyl-4-oxazolylmethoxy)phenyl]ethyl]-2,4-oxazolidinedione (**44**) was similarly prepared. Yield, 35%; mp 158−159 °C (AcOEt−hexane). ^{1}H 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. ($C_{22}H_{20}N_2O_5$) 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. ^{1}H 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. ($C_{23}H_{22}N_2O_4S$) C, H, N. 5-[2-(4-Isopropoxyphenyl)ethyl]-2,4-thiazolidinedione (**17a**) was obtained similarly. Yield, quant. (a colorless oil). ^{1}H 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. ^{1}H NMR (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. ($C_{11}H_{11}NO_3S$) C, H, N. Compounds **18b**−**18g** were obtained similarly. The yields, recrystallization solvents, melting points, and elemental analyses were listed in Table 3. **18b**: ^{1}H NMR (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**: ^{1}H 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**: ^{1}H 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**: ^{1}H NMR (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**: ^{1}H NMR (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**: ^{1}H 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. ^{1}H 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. ($C_{22}H_{20}N_2O_4S$) 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**: ^{1}H 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**: ^{1}H 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**: ^{1}H 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 (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 $C_{23}H_{20}N_2O_5$: 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 (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. ($C_{23}H_{22}N_2O_5$) 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−isoPr$_2$O gave colorless needles; mp 150−151 °C. ^1H NMR (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. ($C_{25}H_{26}N_2O_5$) 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. ($C_{25}H_{26}N_2O_4$¥1/2H_2O) C, H, N.

Synthesis of Optically Active 5-[3-[4-[2-(2-Furyl)-5-methyl-4-oxazolyl-methoxy]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. ($C_{21}H_{21}NO_6$) 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. ($C_{21}H_{23}NO_6$) 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 $C_{19}H_{21}NO_5$: 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 ($MgSO_4$), 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 $C_{20}H_{23}NO_7S$: 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 $C_{20}H_{20}N_2O_4$: 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 $C_{20}H_{21}NO_6$: 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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (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. ^{1}H NMR ($CDCl_3$): 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. ($C_{23}H_{27}NO_6$) 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 ($MgSO_4$), 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 ($MgSO_4$), 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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (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. ^{1}H NMR ($CDCl_3$): 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. ($C_{24}H_{29}NO_7$) C, H, N.

Asymmetric *O*-Acetylation of 26. Synthesis of Isopropyl (*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 SiO_2. Elution with isoPr$_2$O gave (*R*)-**27** as an oil (15.9 g, 96%ee, 44%). ^{1}H NMR ($CDCl_3$): 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); $[\alpha]_D$ +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 SiO_2. Elution with isoPr$_2$O gave (*S*)-**26** as an oil (13.9 g, 98%ee, 42%). ^{1}H NMR ($CDCl_3$): 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); $[\alpha]_D$ −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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (50 g). Elution with AcOEt−hexane (1:1, v/v) gave the title compound as crystals. Recrystallization from AcOEt−isoPr$_2$O gave colorless prisms ((*R*)-**28**, 3.20 g, 96%ee (HPLC), 77%); mp 83−84 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{22}H_{25}NO_7$) C, H, N; $[\alpha]_D$ −3.08° (c = 1.0, $CHCl_3$).

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). ^{1}H NMR ($CDCl_3$): 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. ($C_{22}H_{25}NO_7$) C, H, N; $[\alpha]_D$ +3.03° (c = 1.0, $CHCl_3$); 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-oxazolidinedione ((*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 ($MgSO_4$), and concentrated in

vacuo. The residue was purified by column chromatography on SiO_2 (80 g). Elution with AcOEt−hexane (1:2, v/v) gave methyl (*R*)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolyl-methoxy]-3-methoxyphenyl]-2-(4-nitrophenoxycarbonyloxy)valerate as an oil (5.30 g, 98%). ^{1}H NMR ($CDCl_3$): 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; $[\alpha]_D$ +8.06° (c = 1.0, $CHCl_3$).

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-nitrophenoxycarbonyloxy)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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (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−isoPr$_2$O gave colorless needles; mp 110−111 °C. ^{1}H NMR ($CDCl_3$): 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 $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.05; H, 5.92; N, 5.87; $[\alpha]_D$ +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 $CHCl_3$ (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 ($MgSO_4$), and concentrated in vacuo to give the title compound as crystals ((*R*)-**64**, 2.25 g, 98%ee (HPLC), 91%). Recrystallization from acetone−isoPr$_2$O gave colorless needles; mp 122−123 °C. ^{1}H 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 = 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. ($C_{22}H_{22}N_2O_7$) C, H, N; $[\alpha]_D$ +39.4° (c = 0.495, $CHCl_3$).

(*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). ^{1}H NMR ($CDCl_3$): 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. ($C_{22}H_{22}N_2O_7$) C, H, N; $[\alpha]_D$ −39.8° (c = 0.500, $CHCl_3$); 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−isoPr$_2$O (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 SiO_2 (30 g). Elution with isoPrOH−hexane (1:1, v/v) gave the title compound as crystals (**29**, 153 mg, 29%). Recrystallization from EtOH−isoPr$_2$O gave colorless prisms; mp 88−91 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{23}H_{26}ClNO_7$) 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), K_2CO_3 (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 ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (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. ^{1}H NMR ($CDCl_3$): 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. ($C_{31}H_{27}ClN_2O_5S$) C, H, N; $[\alpha]_D$ +35.7° (c = 0.497, $CHCl_3$).

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 ($MgSO_4$), 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−isoPr$_2$O gave colorless prisms; mp 113−114 °C. ^{1}H NMR ($CDCl_3$): 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. ($C_{23}H_{22}N_2O_4S$) C, H, N; $[\alpha]_D$ +38.0° (c = 0.397, $CHCl_3$). Subsequent elution gave (*S*)-**55** as colorless crystals (407 mg, 99.9%ee). Recrystallization from acetone−isoPr$_2$O gave colorless prisms; mp 113−114 °C. ^{1}H 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). Anal. ($C_{23}H_{22}N_2O_4S$) C, H, N; $[\alpha]_D$ −37.3° (c = 0.505, $CHCl_3$).

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 teXsan[23] system. The structure was refined by SHELXL-97.[24] Hydrogen atoms were included using a riding model. At convergence, $wR2$ = 0.1659 and GOF = 1.029 for 289 variables refined against all 3296 unique data. The absolute configuration was reliably determined from the refined Flack[25] 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, $wR2$ = 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.

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