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Asymmetric Construction of Two Contiguous Stereocenters by Diastereoface Differentiating Addition Reaction of Thiols to Chiral Imides: Formal Synthesis of (+)-Diltiazem

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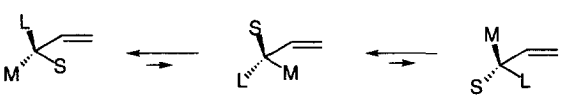
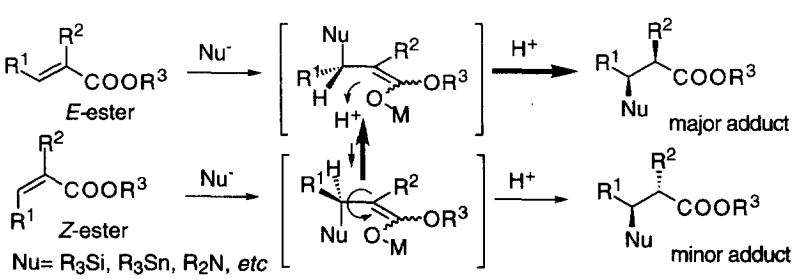
Abstract: A high degree of diastereoselectivity has been achieved on the asymmetric construction of two contiguous stereocenters by the conjugate addition of thiols to α,β-unsaturated imides possessing Evans's chiral auxiliary. Addition reactions of thiophenol to chiral *E*-and *Z*-2-methylcrotonyl imides **4** proceeded with high diastereoface selectivities. Diastereoselectivities were discussed when *E*- and *Z*-imides **4** and **5** were used as the substrates. A successful application was demonstrated by the formal synthesis of a clinically useful cardiac drug, (+)-diltiazem.

INTRODUCTION

Conjugate addition reaction of nucleophiles to electron-withdrawing olefins has emerged as a powerful tool for diastereoselective construction of two contiguous stereogenic centers at α- and β-positions of carboxylic acid derivatives.[1] The highly diastereoselective addition developed has been predicted on the rational analysis of the reaction pathway. Conformational analysis of simple acyclic and allylic systems depicted in Scheme 1 successfully expanded to the enolate system[2] and made prediction of the most energetically favorable conformer in the enolate case. On the basis of the conformational analysis, nucleophiles can induce high levels of diastereoface differentiating approach of electrophiles by their steric hindrances and/or stereoelectronic effect. Therefore, the previously known[2] approach showed that the same adducts were selectively obtained from both *E*-and *Z*-olefins (Scheme 2).

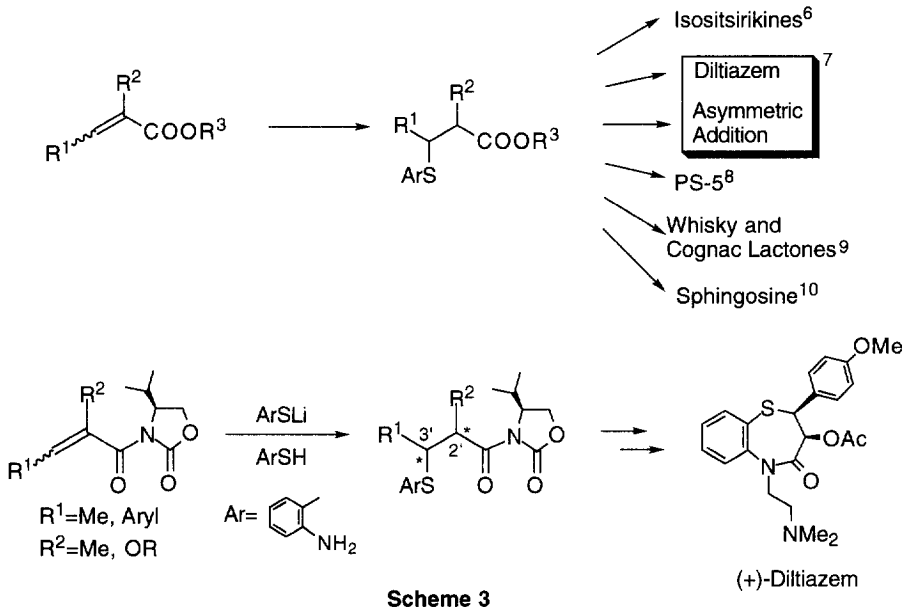


Scheme 1



Scheme 2

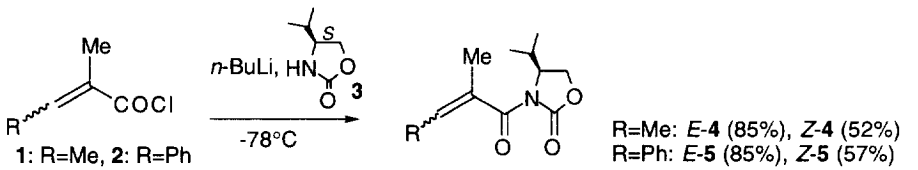
In contrast, we have recently reported an example of stereoselective conjugate addition reaction by the use of thiol as a nucleophile (Scheme 3).[3] The potential synthetic utilities were demonstrated by the total syntheses of *rac*-diltiazem[5] and all of stereoisomers of isositsirikine alkaloids.[6] Furthermore, we have recently shown preliminary studies on asymmetric formal syntheses of (+)-diltiazem[7], (+)-PS-5[8], (+)-whisky lactone[9], (+)-cognac lactone[9], and L-*erythro*-C18-sphingosine[10] on the basis of the successful expansion of this addition reaction to asymmetric version.[3] We enclose herein the full details of the asymmetric diastereoface differentiating additions[11] of thiols[7] by using Evans's oxazolidinone[12] as a chiral auxiliary and formal synthesis of a clinically useful cardiac drug, (+)-diltiazem.[13]



Scheme 3

RESULTS AND DISCUSSION

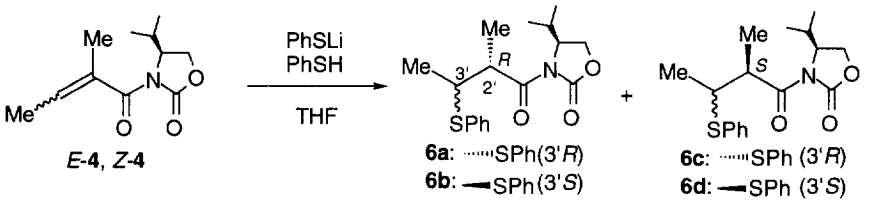
We first examined the addition of thiophenol to the chiral imides *E*-**4**, *Z*-**4**, *E*-**5**, and *Z*-**5**. Unsaturated chiral imides **4** and **5** bearing Evans's chiral oxazolidinone were readily prepared by condensation of **1** and **2** with the lithiated oxazolidinone **3** (Scheme 4) and employed as the substrate to optimize the asymmetric addition reaction. (Scheme 5, Table 1).



Scheme 4

The addition reaction involving the best diastereoselectivity was that treatment of *E*-**4** with 10 equiv. of thiophenol in the presence of a catalytic amount of lithium thiophenoxide at -50°C gave (2'*R*,3'*R*)-**6a** in

high yield (entry 2). Comparison of the results in entries 1 and 2 clearly revealed a pronounced temperature effect for the stereoselectivity, in particular, for the initial diastereoface differentiation. Under the similar condition given for the optimum selectivity, *Z*-imide **4** underwent selective addition reaction to give (2'*S*,3'*S*)-**6d** (entry 5).



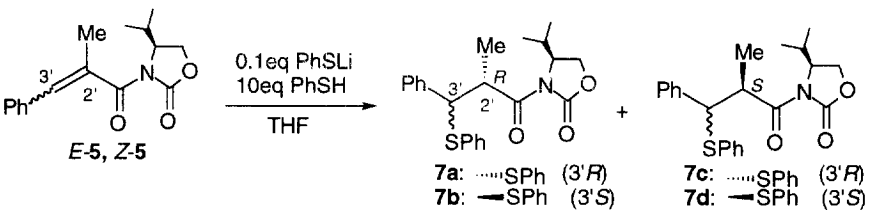
Scheme 5

Table 1. Addition reaction of thiophenol to 2-methylcrotonyl imides **4**

Entry	Substrate	PhSLi (eq)	PhSH (eq)	Temp. (°C)	Time (h)	Yield (%)	Ratio* 6a	6b	6c	6d
1	*E*-**4**	0.1	10	R.T.	1	84	>55	<1	<1	>43
2	*E*-**4**	0.1	10	-50	2	98	>89	<1	4	6
3	*E*-**4**	1.1	10	-50	2	96	>87	<1	4	8
4	*E*-**4**	Et_3N	10	R.T.	24	60	>49	<1	<1	>49
5	*Z*-**4**	0.1	10	-30~-10	2	95	3	4	<1	>92

* Ratios were determined by ^{1}H-NMR.

We next investigated the substituent effect at C-3' position using *E*- and *Z*-cinnamoyl imides **5** (Scheme 6, Table 2). Although both additions proceeded smoothly at 0°C to give adducts **7** in high yields, the diastereoselectivities were lower than the cases of the addition to *E*- and *Z*-olefins **4**. These reactions were very sluggish at lower temperature than 0°C. Of the contiguous stereocenters at C-2' and C-3' of the resulting adducts, the stereocenters at C-2' were selectively constructed, whereas the selectivities at C-3' were moderate.



Scheme 6

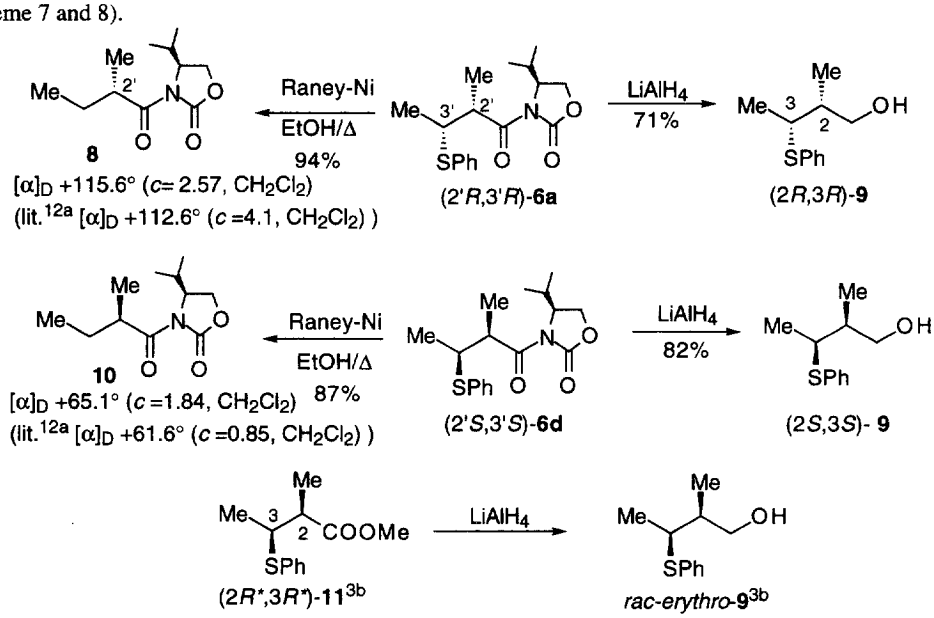
Table 2. Addition reaction of thiophenol to 2-methylcinnamoyl imides **5**

Substrate	Temp. (°C)	Time (h)	Yield (%)	Ratio* 7a	7b	7c	7d
E-**5**	0	5	91	8	2	45	45
Z-**5**	0	5	96	8	1	22	69

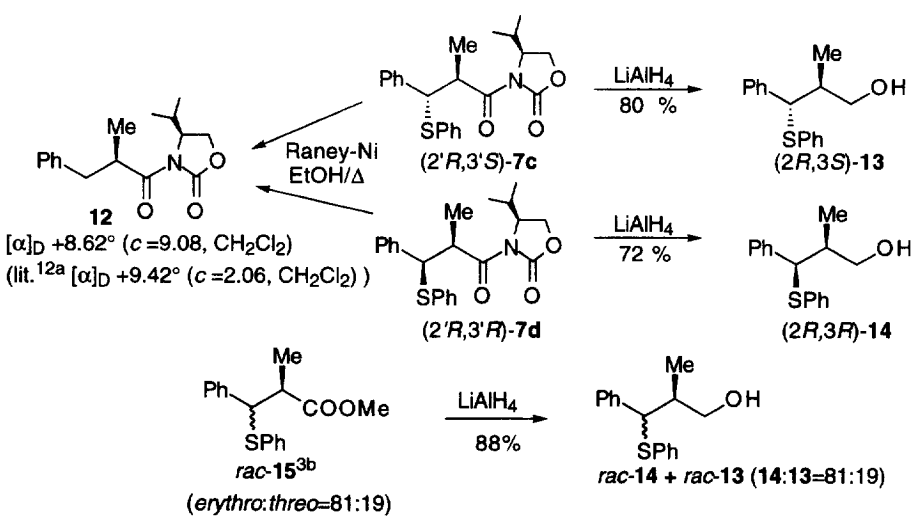
* Ratios were determined by ^{1}H-NMR.

STRUCTURE DETERMINATION OF ADDUCTS

Relative configurations of the adducts **6ad** and **7cd** were confirmed by comparison of the ^{1}H-NMR spectra of the corresponding alcohols (2*R*,3*R*)-and (2*S*,3*S*)-**9**, (2*R*,3*S*)-**13**, and (2*R*,3*R*)-**14** with those of authentic *rac*-alcohols **9**[3b] and **14**. Absolute configurations of the adducts **6ad** and **7cd** were determined by comparison of these optical rotations of the corresponding 2-methylimides **8**, **10**, and **12**, which were provided by desulfurization of the phenylthio groups of **6ad** and **7cd**, with those of the authentic samples[12a] (Scheme 7 and 8).



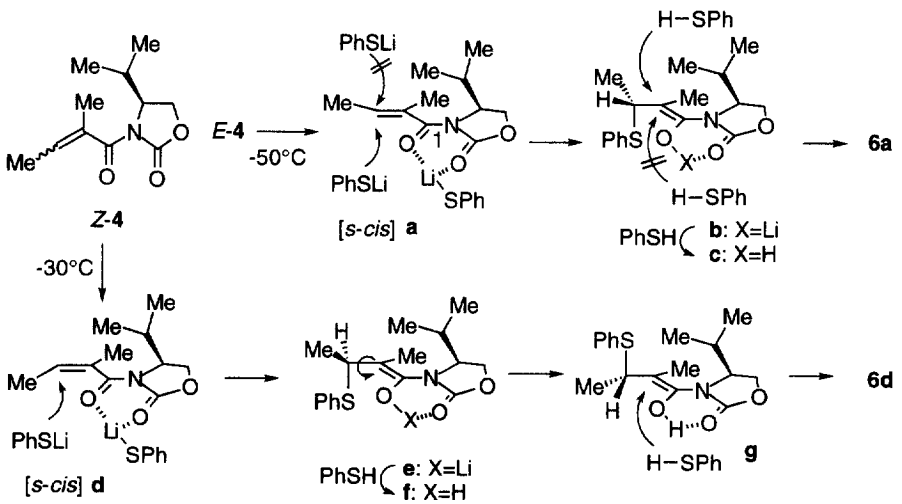
Scheme 7



Scheme 8

REACTION PATHWAY

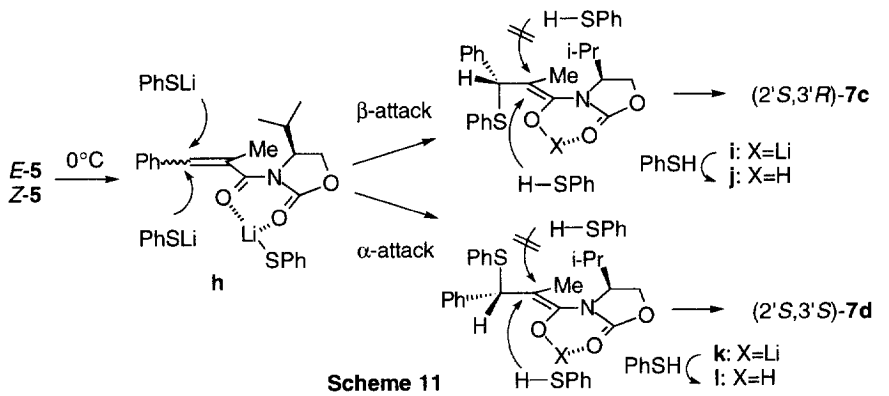
We have previously investigated the addition reaction of thiophenol to *E*- and *Z*-2-methylcrotonyl imides and proposed a rational reaction pathway.[3b] Considering the results obtained in this study, we also propose a stereochemical rationalization as shown in Scheme 9. Conformational analysis of the starting chiral imides *E*-and *Z*-**4**[14] has a key role in the face differentiating addition of lithium thiophenoxide. It is presumed that both carbonyl groups of β-substituted crotonic acid moiety and the chiral auxiliaries would be fixed by a chelation with a lithium thiolate (Scheme 9). The conformation of chiral imides with respect to the rotamers arising from between C-1' and C-2' axis would be in a *s-cis* form as shown in transition models **a** and **d**. Conformational analysis of simple acrylic acid derivatives suggests that these olefins prefer a *s-cis* conformer to its *s-trans* form[15] (Scheme 10). Moreover, the preferential existence of *s-cis* conformer of a chiral imide in the presence of metal salts was proved by its NMR studies[14d] and contributed to the high levels of diastereoface differentiating Diels-Alder reaction using chiral oxazolidinones.[12b] Addition of lithium thiophenoxide to the metal coordinated imides **a** and **d** would occur from the α-face according to the 1,5-asymmetric induction by the isopropyl group on the oxazolidinone ring, giving stable enols **c** and **g**, respectively. It is noteworthy that the following protonation of **c** occurred stereoselectively from the α-face in overcoming the steric hindrance of the methyl and isopropyl groups to give **6a**. This stereoselectivity would be enhanced by the significant stereoelectronic effect of the phenylthio group which can induce the protonation from the *anti*-periplanar face to the phenylthio group. On the other hand, diastereoface differentiating protonation of **g** would take place from the sterically and stereoelectronically favorable α-face to give adduct **6d**.



Scheme 9

Scheme 10

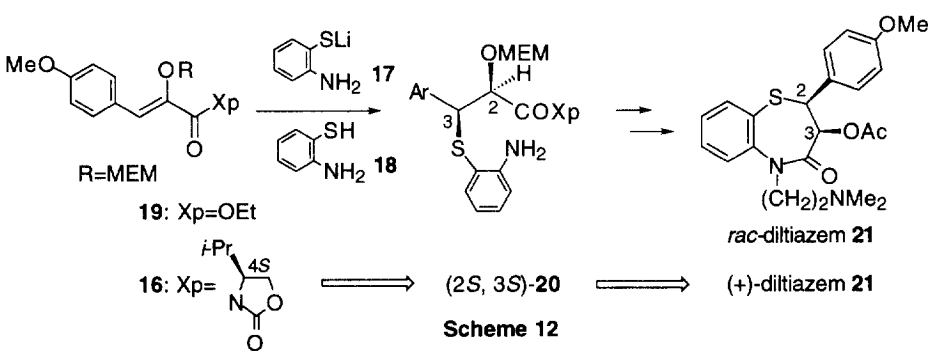
When the substituent at C-3' position was replaced with a phenyl group, different stereoselectivities from the cases of *E*- and *Z*-**4** were observed (Scheme 11). The significantly decreased stereoselectivity at C-3' position is attributable to higher reaction temperature (0°C) required to accelerate the addition reactions. The following stereoselective protonation at C-2' position is explained by the steric bulkiness of the phenyl and isopropyl groups at the β-face of the enol **j** which would exceed the steric and stereoelectronic effects of the phenylthio group.[16]



Scheme 11

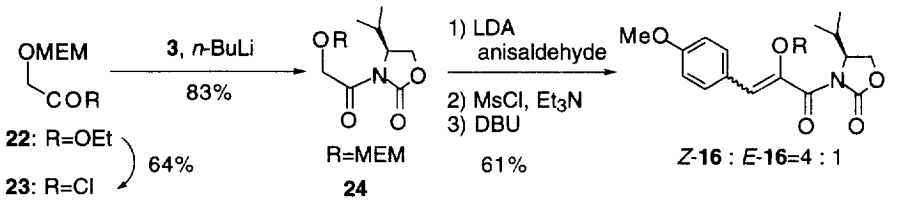
ASYMMETRIC SYNTHESIS OF (+)-DILTIAZEM

We then applied this methodology to the asymmetric synthesis of a clinically useful cardiac drug, (+)-diltiazem **21**. Previously, we furnished formal synthesis of racemic diltiazem **21** *via* the stereoselective addition of 2-aminothiophenol **18** to 2-[(methoxyethoxy)methyloxy]cinnamic acid derivative **19**[5] (Scheme 12). We anticipated that two chiral centers at C-2 and C-3 positions of (+)-diltiazem **21** would be stereoselectively constructed by the addition of **18** to a chiral imide **16**.



Scheme 12

The unsaturated chiral imide **16** was prepared by sequential reactions, condensation of glycolic acid chloride **23** with lithiated **3**, aldol reaction of the resulting imide **24** with anisaldehyde, dehydration *via* the corresponding mesylate (Scheme 13). Stereochemistry of the *Z*-and *E*-unsaturated imides **16** was characterized by comparison of their $^{3}J_{C\text{-}H}$ values[17] with those of the known 2-methoxy esters **25**[5] (Table 3).



Scheme 13

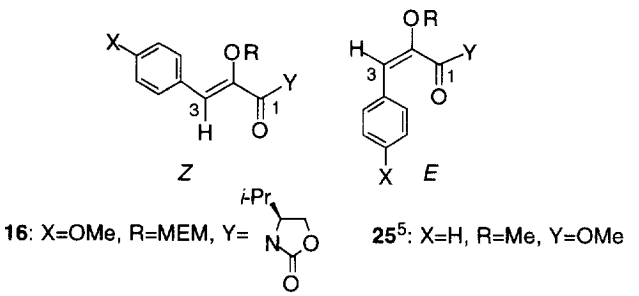
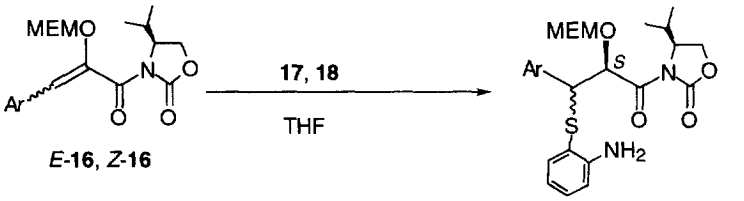


Table 3. Chemical shift * and ^{3}J ** values of *E*- and *Z*-**16** and **25**[5]

Compound	*Z* (δ; ppm)	*E* (δ; ppm)
16	6.33 ($^{3}J_{C\text{-}H}$=4.0)	6.47 ($^{3}J_{C\text{-}H}$=10.6)
25	7.02 ($^{3}J_{C\text{-}H}$=3.5)	6.60 ($^{3}J_{C\text{-}H}$=10.5)

* ^{1}H-NMR (200 MHz, $CDCl_3$); **Between the carbon at C-1 and proton at C-2, ^{13}C-NMR, (125 MHz, $CDCl_3$, *J* in Hz).

We next examined the addition reaction of 2-aminothiophenol **18** to the *E*- and *Z*-**16** (Scheme 14, Table 4). *Z*-**16** was treated with 10 equiv. of 2-aminothiophenol **18** in the presence of 0.1 equiv. of lithium 2-aminothiophenoxide **17** to give a mixture of two adducts **20** and **26** with a ratio of 63 : 37 (entry 1). At low temperature (-40°C) in the presence of 3 equiv. of **17** and 1.5 equiv. of **18**, *Z*-**16** afforded the desired product **20** with higher diastereoselectivity (entry 3). **20** was also obtained from the corresponding *E*-isomer **16** with the almost same diastereoselectivity (entry 4).



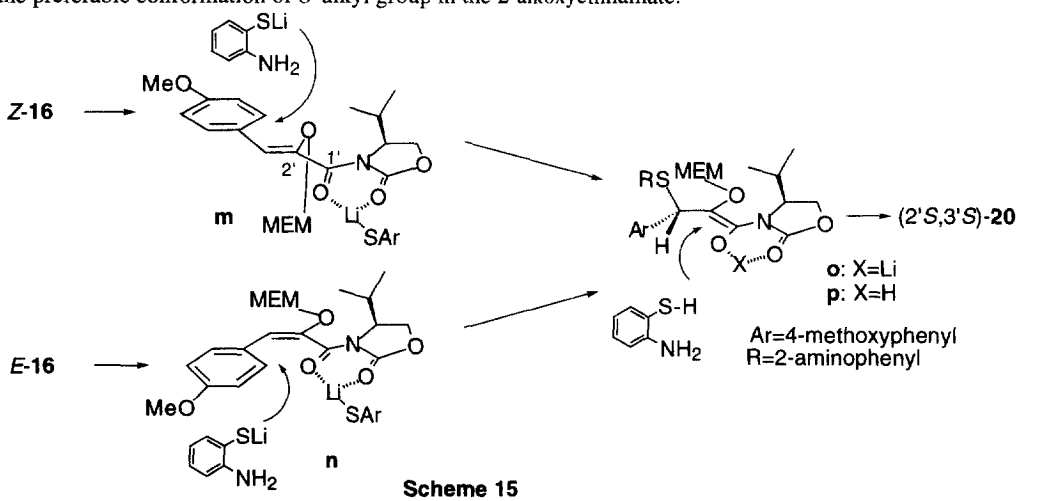
Scheme 14

Table 4. Addition reaction of **17** to *E*- and *Z*-**16**

Entry	Substrate	**17** : **18** (eq)	Temp. (°C)	Time (h)	Yield (%)	Ratio* **20** : **26**
1	*Z*-**16**	0.1 : 10	0	1.5	84	63 : 37
2	*Z*-**16**	0.1 : 10	-20	6	92	70 : 30
3	*Z*-**16**	3 : 1.5	-40	3	97	82 : 18
4	*E*-**16**	3 : 1.5	-40	3	89	70 : 30

* Ratios were determined by ^{1}H-NMR

These stereoselectivities were explained as follows (Scheme 15). In the case of *Z*-imide **16**, the MEM group would lie perpendicular to the olefin to avoid steric repulsion due to the isopropyl and aryl groups to shield the α-face. A crystal structure of 2-methoxycinnamate[5] provides an additional evidence for the preferable conformation of *O*-alkyl group in the 2-alkoxycinnamate.

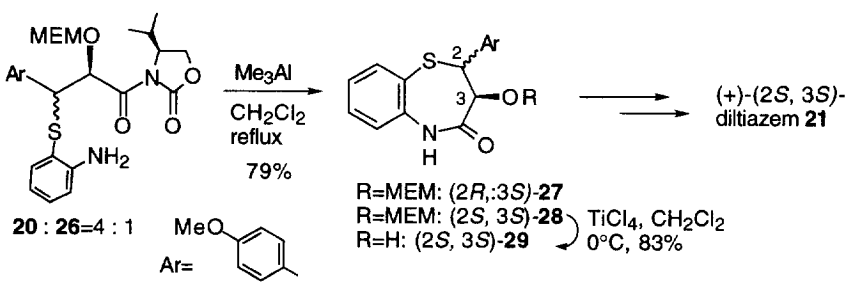


Scheme 15

Thus, addition of lithium 2-aminothiophenoxide **17** to *Z*-**16** occurs preferentially from the β-face of **m** due to steric hindrance of the MEM group, leading to enol **p**. In the case of *E*-**16**, the MEM group is probably situated at the same plane to the olefin as shown in the transition model **n**. Lithium 2-aminothiophenoxide **17** approached from the α-face due to steric hindrance of the isopropyl group in the β-face on the chiral

auxiliary to provide the same enol **p**. The enol **p** would be protonated from the α-face in the similar manner to the precedent results depicted in Scheme 11 which showed the route for the selective formation of the chiral center at C-2' position.

We next attempted conversion of the chiral adduct **20** to (+)-diltiazem **21** (Scheme 16). Unfortunately, the known methods for removal of the chiral oxazolidinone were not effective to the adducts **20** and **26**.[18] We assumed that the removal would be achieved by the use of trimethylaluminum which had been successfully utilized for the lactam cyclization in the synthesis of racemic diltiazem **21**.[5] As expected, removal of the chiral auxiliary by treatment with trimethylaluminum was smoothly achieved along with the concomitant lactam formation in one-pot, without any racemization, to give the desired lactams **27** and **28** from an inseparable mixture of **20** and **26**. Deprotection of the MEM group in **28** with titanium (IV) chloride afforded the known hydroxylactam **29**[13d, o] which had been transformed into (+)-diltiazem **21**. **29** was determined to be formed in nearly 100 % enantiomeric excess by ^{1}H NMR (500 MHz) stereoscopic analysis of the corresponding (+)-MTPA ester (MTPA = α-methyl-α-(trifluoromethyl)phenylacetic acid) which was derived from **29** by esterification using (+)-α-methyl-α-(trifluoromethyl)phenylacetyl chloride.



Scheme 16

ACKNOWLEDGEMENTS

We are grateful to the Ministry of Education, Science, Sports and Culture of Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants and Misses T. Inoue and Y. Ueda for technical assistance.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were measured with Varian XL-200 (200 MHz) and VXR-500 (500 MHz) instruments for solution in deuteriochloroform unless otherwise stated (trimethylsilane as internal reference), ^{13}C-NMR spectra with VXR-500 (125 MHz) instruments for solution in deuteriochloroform, mass spectra with Hitachi M-80 instruments, specific rotation with JEOL DIP-181, and IR spectra for solutions in chloroform on a Hitachi 270-30 spectrophotometer. Melting points were determined with a Kofler-type hot stage apparatus and uncorrected. The extracts from the reaction mixture were dried over anhydrous sodium sulfate. Unless otherwise noted, all nonaqueous reactions were carried out under a nitrogen atmosphere. Thin layer chromatography (tlc) was performed on pre-coated Silicagel 60F-254 (0.25 mm thick, Merck). Medium-pressure column chromatography (mcc) was undertaken on a 530-4-10V apparatus (Yamazen) using Lobar größe B (310-25, Lichroprep Si60, Merck) as a column. Ether refers to diethy ether.

Acylation of the Oxazolidinone 3: General procedure

According to the literature,[12b] **3** (3 mmol) was lithiated with *n*-butyllithium ((1.60 M in hexane) 1.88 ml (3 mmol)) in THF (25 ml) at -78°C, followed by treatment with the corresponding acid chloride[19, 20] (3.3 mmol) to afford the imide.

[*S*-(*E*)]-4-(1-Methylethyl)-3-(2-methyl-1-oxo-2-butenyl)-2-oxazolidinone *E*-(4)

Colorless crystals. mp. 61-62°C (ether-hexane); IR ν_{max} cm^{-1}: 1784, 1676; ^{1}H-NMR (200 MHz) δ: 6.32 (1H, qq, *J*=7, 1.5 Hz), 4.33 (1H, ddd, *J*=8, 6, 4 Hz), 4.24 (1H, t, *J*=8 Hz), 4.18 (1H, dd, *J*=8, 6 Hz), 2.36 (1H, sept. d, *J*=7, 4 Hz), 1.91 (3H, quint., *J*=1.5 Hz), 1.81 (3H, dquint., *J*=7, 1.5 Hz), 0.92, 0.90 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{11}H_{17}NO_3$ (M^+) 211.1207. Found: 211.1199. *Anal.* Calcd $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.24; H, 8.35; N, 6.58. $[\alpha]_D^{22}$ +111.3° (*c*=1.30, chloroform).

[*S*-(*Z*)]-4-(1-Methylethyl)-3-(2-methyl-1-oxo-2-butenyl)-2-oxazolidinone *Z*-(4)

Colorless crystals. mp. 60-61°C (ether-hexane); IR ν_{max} cm^{-1}: 1788, 1689; ^{1}H-NMR (200 MHz) δ: 5.62 (1H, qq, *J*=7, 1.5 Hz), 4.53 (1H, dt, *J*=8, 4 Hz), 4.34 (1H, t, *J*=8 Hz), 4.23 (1H, dd, *J*=8, 4 Hz), 2.48 (1H, sept. d, *J*=7, 4 Hz), 1.95 (3H, quint., *J*=1.5 Hz), 1.66 (3H, dq, *J*=7, 1.5 Hz), 0.96, 0.92 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{11}H_{17}NO_3$ (M^+) 211.1207. Found: 211.1198. *Anal.* Calcd $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.42; H, 8.40; N, 6.38. $[\alpha]_D^{22}$ +86.7° (*c*=0.6, chloroform).

[*S*-(*E*)]-4-(1-Methylethyl)-3-(2-methyl-1-oxo-3-phenyl -2-propenyl)-2-oxazolidinone *E*-(5)

Colorless crystals. mp. 98-99°C (methanol); IR ν_{max} cm^{-1}: 1786, 1678; ^{1}H-NMR (200 MHz) δ: 7.50-7.20 (5H, m), 6.99 (1H, br q, *J*=1.5 Hz), 4.60 (1H, ddd, *J*=8, 6, 4 Hz), 4.40 (1H, t, *J*=8 Hz), 4.25 (1H, dd, *J*=8, 4 Hz), 2.46 (1H, sept. d, *J*=7, 4 Hz), 2.20 (3H, d, *J*=1.5 Hz), 0.96 (6H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{16}H_{19}NO_3$ (M^+) 273.1364. Found: 273.1369. *Anal.* Calcd $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.16; H, 7.11; N, 4.92. $[\alpha]_D^{22}$ +114.0° (*c*=2.43, chloroform).

[*S*-(*Z*)]-4-(1-Methylethyl)-3-(2-methyl-1-oxo-3-phenyl -2-propenyl)-2-oxazolidinone *Z*-(5)

Colorless crystals. mp. 142-143°C (methanol); IR ν_{max} cm^{-1}: 1786, 1684; ^{1}H-NMR (200 MHz) δ: 7.40-7.20 (5H, m), 6.94 (1H, br q, *J*=1.5 Hz), 4.28 (1H, m), 4.09 (1H, dd, *J*=8, 4 Hz), 3.90 (1H, m), 2.35 (1H, sept. d, *J*=7, 4 Hz), 2.15 (3H, m), 0.88 and 0.70 (each 3H, d, *J*=7 Hz); *Anal.* Calcd $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.95; H, 7.04; N, 5.13. $[\alpha]_D^{22}$ +113.7° (*c*=2.04, chloroform).

Addition of thiophenol to chiral imides: General procedure.

Thiophenol (10 mmol) was added with stirring at 0°C to a solution of *n*-butyllithium ((1.6M in hexane) 0.1 mmol) in THF (5 ml) to give a solution of 100:1 mixture of thiophenol and lithium thiophenoxide. To the resulting solution was added a solution of chiral imide (1 mmol) in THF (5 ml) under the conditions as depicted in Tables 1 and 2. The mixture was made alkaline by addition of 5% aqueous sodium hydroxide and extracted with dichloromethane. The extract was dried and condensed to give a residue which was purified by mcc.

Addition of thiophenol to *E*-(4)

According to the general procedure described above, the addition to *E*-**4** (211 mg, 1 mmol) was carried out at -50°C. The mixture of adducts was separated by mcc (hexane-dichloromethane, 1:1) to give inseparable mixtures of **6ab** (282 mg, 88%) and **6cd** (31 mg, 10%). Ratios of the adducts were deduced from the highest peak of ^{1}H-NMR spectra.

[**6a**:**6b**=>89:<1]: colorless oil; IR ν_{max}cm^{-1}: 1782, 1694; ^{1}H-NMR (200 MHz) **6a** δ: 7.64-7.20 (5H, m), 4.30-4.10 (3H, m), 4.00 (1H, quint., *J*=7 Hz), 3.56 (1H, quint., *J*=7Hz), 2.37 (1H, sept. d, *J*=7, 3.5 Hz), 1.40 (3H, d, *J*=7 Hz), 1.37 (3H, d, *J*=7 Hz), 0.90 and 0.86 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{23}NO_3S$ (M^+) 321.1396. Found: 321.1377. $[\alpha]_D^{22}$ +94.4° (*c*=3.64, dichloromethane).

[**6c**:**6d**=4:6]: colorless oil; ^{1}H-NMR (200 MHz) δ: 7.60-7.20 (5H, m), 4.50 (1H, m), 4.30-4.10 (2H, m), 4.05 (1H, quint., *J*=7 Hz), 3.64 (1H, quint., *J*=7Hz), 2.40-2.20 (1H, m), 1.39 (9/5H), 1.33 (9/5H), 1.28 (6/5H), 1.21 (6/5H), (each d, *J*=7 Hz), 0.91 (12/5H), 0.90 (9/5H), 0.81 (9/5H), 0.81 (9/5H), (each d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{23}NO_3S$ (M^+) 321.1396. Found: 321.1387.

Addition of thiophenol to *Z*-(4)

According to the general procedure described above, the addition to *Z*-**4** (105 mg, 0.5 mmol) was carried out at -30°C. The mixture of adducts was separated by mcc (hexane-dichloromethane, 1:1) to give inseparable mixtures of **6ab** (11 mg, 7%) and **6cd** (141 mg, 88%). Ratios of the adducts were deduced from the highest peak of ^{1}H-NMR spectra.

[**6a**:**6b**=3:4]: colorless oil;^{1}H-NMR (200 MHz) δ: 7.64-7.20 (5H, m), 4.44-4.00 (3H, m), 4.00 (1H, quint., *J*=7 Hz), 3.56 (1H, quint., *J*=7Hz), 2.34 (1H, m), 1.40 (9/7H), 1.37 (9/7H), 1.30 (12/7H), 1.25 (12/7H), (each d, *J*=7 Hz), 0.90 (9/7H), 0.86 (9/7H), 0.85 (24/7H), (each d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{23}NO_3S$ (M^+) 321.1396. Found: 321.1387.

[**6c**:**6d**=<1:>92]: colorless oil; IR ν_{max}cm^{-1}: 1782, 1694; ^{1}H-NMR (200 MHz) **6d** δ: 7.60-7.18 (5H, m), 4.51 (1H, dt, *J*=9, 4 Hz), 4.31 (1H, t, *J*=9 Hz), 4.22 (1H, dd, *J*=9, 4 Hz), 4.05 (1H, quint. *J*=7 Hz), 3.64 (1H, quint., *J*=7Hz), 2.33 (1H, m), 1.39 (3H, d, *J*=7 Hz), 1.33 (3H, d, *J*=7 Hz), 0.90 and 0.81 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{23}NO_3S$ (M^+) 321.1396. Found: 321.1387. $[\alpha]_D^{23}$ +12.8° (*c*=3.20, dichloromethane).

Addition of thiophenol to *E*-(5)

According to the general procedure described above, the addition to *E*-**5** (546 mg, 2 mmol) was carried out at 0°C to give a mixture of adducts, which was separated by mcc (hexane-dichloromethane, 1:2) to give a 8:2 mixture of **7a**:**7b** (69 mg, 9%) and a 1:1 mixture of **7c**:**7d** (628 mg, 82%). Ratios of the adducts were deduced from the highest peak of ^{1}H-NMR spectra. The mixture of **7c** and **7d** was separated by mcc (hexane-dichloromethane, 4:1).

[**7a**:**7b**=8:2]: colorless oil; ^{1}H-NMR (200 MHz) δ: 7.40-7.10 (10H, m), 4.58-4.40 (2H, m), 4.03 (1H, dd, *J*=9, 2 Hz), 3.93 (1H, ddd, *J*=9, 4, 2 Hz), 3.48 (1H, br t, *J*=9, 8 Hz), 2.25 (1H, m), 1.58 (12/5H), 1.03 (3/5H), (each d, *J*=7 Hz), 0.96 (3/5H), 0.91 (3/5H), 0.83 (12/5H), 0.81 (12/5H), (each d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{22}H_{25}NO_3S$ (M^+) 383.1553. Found: 383.1533.

[**7c**]: colorless oil; IR ν_{max} cm^{-1}: 1776, 1694; ^{1}H-NMR (200 MHz) δ: 7.83-7.16 (10H, m), 4.63 (1H, dq, *J*=12, 7 Hz), 4.61 (1H, dt, *J*=8, 4 Hz), 4.38 (1H, d, *J*=12 Hz), 4.36 (2H, m), 2.57 (1H, m), 1.05 (3H, d, *J*=7 Hz), 1.01, 1.00, (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{22}H_{25}NO_3S$ (M^+) 383.1553. Found: 383.1533. $[\alpha]_D^{23}$ -152.9° (*c*=1.66, dichloromethane).

[**7d**]: colorless crystals mp 117-118 °C (hexane-ether); IR ν_{max} cm^{-1}: 1776, 1692; ^{1}H-NMR (200 MHz) δ: 7.34-7.14 (10H, m), 4.64 (1H, dq, *J*=9, 7 Hz), 4.55 (1H, d, *J*=9 Hz), 4.35 (1H, dt, *J*=8, 3 Hz), 4.22 (1H, t, *J*=8 Hz), 4.08 (1H, dd, *J*=8, 3 Hz), 1.75 (1H, m), 1.50 (3H, d, *J*=7 Hz), 0.68, 0.30, (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{22}H_{25}NO_3S$ (M^+) 383.1553. Found: 383.1564. *Anal.* Calcd $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.57; N, 3.65. Found: C, 68.73; H, 6.63; N, 3.67. $[\alpha]_D^{23}$ +160.2° (*c*=1.89, dichloromethane).

Addition of thiophenol to *Z*-(5)

According to the general procedure described above, the addition to *Z*-**5** (55 mg, 0.2 mmol) was carried out at 0°C.The mixture was separated by mcc (hexane-dichloromethane, 1:1) to give a 98:1 mixture of **7a**:**7b** (7 mg, 9%) and a 22:69 mixture of **7c**:**7d** (67 mg, 87%). Ratios of the adducts were deduced from the highest peak of ^{1}H-NMR spectra The mixture of **7c** and **7d** was separated by mcc (hexane-dichloromethane, 4:1).

Desulfurization of adducts (6a), (6d), (7c), and (7d): General procedure.

Suspension of Raney-Ni, W-2 and an adduct (0.08~0.40 mmol) in EtOH was vigorously stirred under reflux until spots due to the starting sulfides disappeared on tlc. The mixture was cooled at room temperature, filtered, and the filtrate was condensed in *vacuo*. The residue was purified by mcc (ether-hexane, 1:2).

[*S*-(*R,*R**)-4-(1-Methylethyl)-3-(2-methyl-1-oxobutyl)-2-oxazolidinone (8)**

According to the general procedure described above, imide **6a** (**6a**:**6d**=>89:<1) (80 mg, 0.25 mmol) was desulfurizated to give **8** (50 mg, 94%) as a colorless oil. IR ν_{max} cm^{-1}: 1776, 1696; ^{1}H-NMR (200 MHz) δ: 4.94 (1H, dt, *J*=8, 4 Hz), 4.32 (1H, t, *J*=8 Hz), 4.23 (1H, dd, *J*=8, 4 Hz), 3.89 (1H, sext., *J*=7 Hz), 2.38 (1H, sept.d, *J*=7, 4 Hz), 1.77, 1.44 (each 1H, dquint., *J*=14, 7 Hz), 1.22 (3H, d, *J*=7 Hz), 0.96 (3H, t, *J*=7 Hz), 0.94, 0.90, (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{11}H_{19}NO_3$ (M^+) 213.1364. Found: 213.1369. $[\alpha]_D^{24}$ +115.6° (*c*=2.57, dichloromethane), (lit.[12a] $[\alpha]_D$+112.6° (*c*=4.1, dichloromethane)).

[*S*-(*R,*S**)-4-(1-Methylethyl)-3-(2-methyl-1-oxobutyl)-2-oxazolidinone (10)**

According to the general procedure described above, imide **6d** (**6c**:**6d**=<1:>92) (120 mg, 0.37 mmol) was desulfurizated to give **10** (68 mg, 87%) as a colorless oil. IR ν_{max} cm^{-1}: 1776, 1694; ^{1}H-NMR (200 MHz) δ: 4.50 (1H, dt, *J*=8, 4 Hz), 4.31 (1H, t, *J*=8 Hz), 4.22 (1H, dd, *J*=8, 4 Hz), 3.63 (1H, sext., *J*=7 Hz), 2.35 (1H, sept. d, *J*=7, 4 Hz), 1.79, 1.52 (each 1H, dquint., *J*=14.5, 7 Hz), 1.15 (3H, d, *J*=7 Hz), 0.97 (3H, t, *J*=7 Hz), 0.92, 0.88, (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{11}H_{19}NO_3$ (M^+) 213.1364. Found: 213.1362. $[\alpha]_D^{22}$ +65.1° (*c*=1.84, dichloromethane), (lit.[12a] $[\alpha]_D$+61.6° (*c*=0.85, dichloromethane)).

[*S*-(*R,*R**)-4-(1-Methylethyl)-3-(2-methyl-1-oxo-3-phenylpropyl)-2-oxazolidinone (12)**

According to the general procedure described above, imide **7c** (32 mg, 0.084 mmol) was desulfurizated to give **12** (21 mg, 90%) as a colorless oil. Similarly, **7d** (33 mg, 0.086 mg) was desulfurizated to give **12** (20 mg, 86%). IR ν_{max} cm^{-1}: 1776, 1694; ^{1}H-NMR (200 MHz) δ: 7.38-7.14 (5H, m), 4.46 (1H, dt, *J*=8, 4 Hz), 4.28 (1H, t, *J*=8 Hz), 4.20 (2H, m), 3.12, 2.66 (each 1H, dd, *J*=13, 7 Hz), 2.17 (1H, m), 1.16 (3H, d, *J*=7 Hz), 0.84, 0.60, (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{16}H_{21}NO_3$ (M^+) 275.1520. Found: 275.1523. $[\alpha]_D^{23}$ +8.62° (*c*=9.08, dichloromethane), (lit.[12a] $[\alpha]_D$+9.42° (*c*=2.06, dichloromethane)).

[*R*-(*R,*R**)]-2-Methyl-3-(phenylthio)butan-1-ol (2*R*,3*R*)-(9)**

According to the literature[3b], imide **6a** (**6a**:**6d**=>89:<1) (200 mg, 0.62 mmol) was reduced with lithium aluminum hydride in ether. Alcohol (2*R*,3*R*)-**9** (86 mg, 88%) was obtained after purification by mcc (hexane-ether, 2:1). The ^{1}H-NMR and IR spectra of (2*R*,3*R*)-**9** were identified with those of *rac*-**9**.[3b] $[\alpha]_D^{23}$ -36.1° (*c*=1.03, dichloromethane).

[*S*-(*R,*R**)]-2-Methyl-3-(phenylthio)butan-1-ol (2*S*,3*S*)-(9)**

According to the known procedure[3b], imide **6d** (**6c**:**6d**=<1:>92) (128 mg, 0.4 mmol) was reduced with lithium aluminum hydride in ether. The products were purified by by mcc (hexane-ether, 2:1) to give (2*S*,3*S*)-**9** (64 mg, 82%) as a colorless oil. The ^{1}H-NMR and IR spectra of (2*S*,3*S*)-**9** were identified with those of *rac*-**9**.[3b] $[\alpha]_D^{24}$ +40.1° (*c*=1.12, dichloromethane).

(2*R,3*R**/2*R**,3*S**)-2-Methyl-3-phenyl-3-(phenylthio)propan-1-ol *rac*-(14) and *rac*-(13)**

According to the procedure given for **9**, a 81:19 mixture of *rac*-**15**[3b] (*erythro*:*threo*=81:19) (30 mg, 0.1 mmol) was reduced with lithium aluminum hydride in ether. The crude products were purified by mcc (hexane-ether, 2:1) to give a mixture of *rac*-**14** and *rac*-**13** (23 mg, 88%, [**14**:**13**=81:19]) as a colorless oil. IR ν_{max} cm^{-1}: 3626, 3476; ^{1}H-NMR (200 MHz) δ: 7.50-7.10 (10H, m), 4.38 (4/5H, d, *J*=7 Hz), 4.32 (1/5H, d, *J*=7 Hz), 3.80 (1/5H, dd, *J*=11, 5 Hz), 3.71 (4/5H, dd, *J*=11, 6 Hz), 3.65 (4/5H, dd, *J*=11, 6 Hz), 3.48 (4/5H, dd, *J*=11, 5 Hz), 2.23 (1H, m), 1.25 (4/5H), 0.90 (1/5H), (each d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{16}H_{18}OS$ (M^+) 258.1077. Found: 258.1056.

[*S*-(2*R,3*S**)]-2-Methyl-3-phenyl-3-(phenylthio)propan-1-ol (2*R*,3*S*)-(13)**

According to the procedure given for **9**, **7c** (20 mg, 0.05 mmol) was reduced with lithium aluminum hydride in ether. The crude product was purified by by mcc (hexane-ether, 2:1) to give (2*R*,3*S*)-**13** (10 mg, 80%) as a colorless oil. The ^{1}H-NMR spectra of (2*R*,3*S*)-**13** was identified with that of *threo*-alcohol **14**.

[*S*-(2*R,3*R**)]-2-methyl-3-phenyl-3-(phenylthio)propan-1-ol (2*R*,3*R*)-(14)**

According to the procedure given for **9**, **7d** (20 mg, 0.05 mmol) was reduced with lithium aluminum hydride in ether. The crude products was purified by mcc (hexane-ether, 2:1) to give (2*R*,3*R*)-**14** (9 mg, 72%) as a colorless oil. The ^{1}H-NMR spectra of (2*R*,3*R*)-**14** was identified with that of *erythro*-alcohol **14**.

(2-Methoxyethoxy)methyloxyacetyl Chloride (23)

To a solution of **22** (5.7 g, 30 mmol) in methanol (50 ml) was added dropwise a solution of KOH (86%) 1.95 g (30 mmol) in methanol (20 ml) with stirring. The mixture was stirred for 12 h, then condensed and dried in *vacuo*. To a suspension of the residue in absolute ether (50 ml) was added dropwise oxalyl chloride 2.76 ml (31.6 mmol) at 0°C. The suspension was stirred at 0°C for 2h and filtrated to remove the resulting potassium chloride. The filtrate was concentrated in *vacuo* and distillated to give **23** (3.34 g, 64%) as a colorless oil. bp. 73°C (4 mHg); ^{1}H-NMR (200 MHz) δ: 4.85 (2H, s), 4.59 (2H, s), 3.78, 3.60 (each 2H, m), 3.42 (3H, s).

(*S*)-3-(2-Methoxyethoxy)methyloxyacetyl-4-(1-methylethyl)-2-oxzolidinone (24)

According to the procedure given for **4**, oxazolidinone **3** (890 mg, 6.9 mmol) was acylated with **23** (1.38g, 7.59 mmol). The imide **24** (1.57 g, 83%) was obtained as a colorless oil after purification by mcc (ether). IR ν_{max}cm^{-1}:1786, 1720; ^{1}H-NMR (200 MHz) δ: 4.86 (2H, s), 4.82 (2H, s), 4.78, 4.52 (each, 2H, m), 4.50-4.20 (3H, m), 4.38 (3H, s), 2.20 (1H, m), 0.91, 0.86 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_9H_{14}NO_4$ (M^+-OCH_2CH_2OMe) 200.0921. Found: 200.0893. $[\alpha]_D^{23}$ +68.9° (*c*=3.81, chloroform).

Aldol reaction of 24 with anisaldehyde.

According to the procedure given for **19**[5], imide **24** (1.1g, 4 mmol) underwent aldol reaction with anisaldehyde (1.09g, 8 mmol). Three aldol isomers [A: 785 mg (48%), B: 471 mg (29%), C: 175 mg (10%)] were isolated after separation by mcc (hexane-ether, 2:1).

Isomer A: IR ν_{max}cm^{-1}: 3464, 1780, 1706; ^{1}H-NMR (200 MHz) δ: 7.40 (2H, br d, *J*=7 Hz), 6.90 (2H, br d, *J*=7 Hz), 5.82 (1H, d, *J*=7 Hz), 4.84 (1H, d, *J*=7 Hz), 4.65 (2H, s), 4.50-4.10 (3H, m), 3.81 (3H, s), 3.60-3.30 (4H, m), 3.32 (3H, s), 2.30 (1H, m), 0.92, 0.88 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{20}NO_5$ (M^+-(H_2O+OCH_2CH_2OMe) 318.1339. Found: 318.1309.

Isomer B: IR ν_{max}cm^{-1}: 3484, 1776, 1710; ^{1}H-NMR (200 MHz) δ: 7.43 (2H, br d, *J*=7 Hz), 6.90 (2H, br d, *J*=7 Hz), 5.79 (1H, d, *J*=7 Hz), 4.84 (1H, d, *J*=7 Hz), 4.62, 4.60 (2H, ABq, *J*=7 Hz), 4.48-4.26 (3H, m), 3.81 (3H, s), 3.70-3.30 (4H, m), 3.32 (3H, s), 2.36 (1H, m), 0.92, 0.82 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{20}NO_5$ (M^+-(H_2O+OCH_2CH_2OMe) 318.1339. Found: 318.1365.

Isomer C: IR ν_{max}cm^{-1}: 3572, 1776, 1708; ^{1}H-NMR (200 MHz) δ: 7.32 (2H, br d, *J*=7 Hz), 6.83 (2H, br d, *J*=7 Hz), 5.48 (1H, d, *J*=7 Hz), 4.92 (1H, d, *J*=7 Hz), 4.74 (2H, s), 4.50-4.10 (3H, m), 3.80 (3H, s), 3.70-3.30 (4H, m), 3.31 (3H, s), 2.17 (1H, m), 0.86, 0.63 (each 3H, d, *J*=7 Hz); HRMS (EI) *m/z*: Calcd $C_{17}H_{20}NO_5$ (M^+-(H_2O+OCH_2CH_2OMe) 318.1339. Found: 318.1329.

Successive dehydration of a mixture of three isomers A, B, and C (444 mg, 1.08 mmol) *via* the corresponding mesylates to give a 1:4 mixture of *E*- and *Z*-**16** which was separated by mcc (ether).

Z-**16**: colorless crystals mp 87.5-88.5 °C (hexane-ether); IR ν_{max}cm^{-1}: 1786, 1676; ^{1}H-NMR (200 MHz) δ: 7.75 (2H, br d, *J*=7 Hz), 6.92 (2H, br d, *J*=7 Hz), 6.33 (1H, s), 5.31, 5.15 (2H, ABq, *J*=6 Hz), 4.60 (1H, dt, *J*=8, 5 Hz), 4.40 (1H, t, *J*=8 Hz), 4.24 (1H, dd, *J*=8, 5 Hz), 3.86 (3H, s), 3.80, 3.60 (each 2H, m), 3.35 (3H, s), 2.25 (1H, m), 0.96 (6H, d, *J*=7 Hz); ^{13}C-NMR (125 MHz) δ: 165.69, 159.97, 153.30, 141.90, 126.23, 131.67, 121.75, 113.99, 94.42, 71.48, 68.74, 63.57, 58.93, 55.30, 58.65, 28.67, 17.99, 15.30. HRMS (EI) *m/z*: Calcd $C_{20}H_{27}NO_7$ (M^+) 393.1786. Found: 393.1790. *Anal.* Calcd $C_{20}H_{27}NO_7$ 1/4H_2O: C, 60.37; H, 6.97;

N, 3.52. Found: C, 60.56; H, 6.89; N, 3.68. $[\alpha]_D^{23}$ +32.3° (*c*=1.30, chloroform).

E-**16**: pale yellow oil; IR $\nu_{max}cm^{-1}$: 1788, 1694; ^{1}H-NMR (200 MHz) δ: 7.17 (2H, br d, *J*=7 Hz), 6.83 (2H, br d, *J*=7 Hz), 6.47 (1H, s), 5.29 (2H, s), 4.35-4.17 (3H, m), 3.88 (2H, m), 3.82 (3H, s), 3.63 (2H, m), 3.44 (3H, s), 2.40 (1H, m), 0.91, 0.82 (each 3H, d, *J*=7 Hz); ^{13}C-NMR (125 MHz) δ: 164.49, 158.87, 152.48, 146.75, 126.60, 129.47, 113.89, 109.42, 95.62, 71.63, 68.11, 63.63, 59.04, 58.67, 55.27, 28.37, 17.96, 14.62. HRMS (EI) *m/z*: Calcd $C_{20}H_{27}NO_7$ (M^+) 393.1786. Found: 393.1780. $[\alpha]_D^{23}$ -6.52° (*c*=0.92, chloroform).

Addition of 2-aminothiophenol to *Z*-16

To a solution of 2-aminothiophenol (0.48 ml, 4.5 mmol) in THF (10 ml) was added *n*-butyllithium ((1.6M in hexane) 1.88 ml, 3 mmol) with stirring at -40°C. To the mixture was added dropwise a solution of *Z*-**16** (393 mg, 1 mmol) in THF (5 ml) at -40°C. The mixture was stirred for 3 h, poured into ice and made alkaline with 5% aquenous sodium hydroxide. The mixture was extracted with dichloromethane. The extract was dried and condensed. The residue was purified by mcc (ether) to give an inseparable 82:18 mixtuer of adducts **20** and **26** (510 mg, 97%) as a pale yellow oil. Ratios of the adducts were deduced from the highest peak of ^{1}H-NMR spectra.

IR $\nu_{max}cm^{-1}$: 3488, 3372, 1778, 1702; ^{1}H-NMR (200 MHz) δ: 7.28 (2H, br d, *J*=7 Hz), 7.20-7.00 (2H, m), 6.76 (2H, br d, *J*=7 Hz), 6.76 (1H, m), 6.60 (1H, br t, *J*=7 Hz), 5.95 (4/5H, s), 5.88 (1/5H), (each, d, *J*=7 Hz), 4.95 (8/5H), 4.85 (8/5H), 4.75 (2/5H), 4.70 (2/5H), (each, d, *J*=7 Hz), 4.50-4.05 (4H, m), 3.78 (3/5H), 3.75 (12/5H), (each, s), 3.75-3.35 (4H, m), 3.38 (3/5H), 3.35 (12/5H), (each s), 2.20 (1/5H), 1.80 (4/5H), (each m), 0.88 (3/5H), 0.84 (3/5H), 0.67 (12/5H), 0.27 (12/5H), (each d, *J*=7 Hz). HRMS (CI, isobutane) *m/z*: Calcd $C_{26}H_{34}N_2O_7S$+H (QM^+) 519.2163. Found: 519.2192.

Addition of 2-aminothiophenol to *E*-16

According to the procedure given for *Z*-**16**, *E*-**16** (39 mg) (0.1 mmol) was treated with lithium 2-aminothiophenoxide in the presence of 2-aminothiophenol in THF (3 ml) at -40 °C. The products were purified by mcc (ether) to give a 70:30 mixture of adducts **20** and **26** (46 mg, 89%) as a pale yellow oil. Ratios of the adducts were deduced from the highest peak of ^{1}H-NMR spectra.

Cyclization of adducts 20 and 26

To a solution of a 82:18 mixture of adducts **20** and **26** (466 mg, 0.9 mmol) in dichloromethane (25 ml) was added dropwise trimethylaluminum ((15% in hexane) 0.86 ml, 1.8 mmol). The mixture was refluxed with stirring for 18 h and allowed to cool at 0°C. The mixture was acidified with 10% hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water, dried, condensed, and purified by mcc (ethyl acetate) to give **27** (52 mg, 15%) and **28** (224 mg, 63%), respectively. These ^{1}H-NMR and IR spectra were identified with those of racemic lactams.[5]

27: colorless crystals, mp 95-96 °C (hexane-dichloromethane); *Anal.* Calcd $C_{20}H_{23}NO_5S$ 1/4H_2O: C, 60.97; H, 6.01; N, 3.56. Found: C, 60.88; H, 5.93; N, 3.68. $[\alpha]_D^{22}$ +624° (*c*=1.72, chloroform).

28: colorless oil; HRMS (EI) *m/z*: Calcd $C_{20}H_{23}NO_5S$ (M^+) 389.1295. Found: 389.1304. $[\alpha]_D^{22}$ +66.4° (*c*=2.73, chloroform).

(2*S*-*cis*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (29)

To a solution of lactam **28** (60 mg, 0.15 mmol) in dichloromethane (2 ml) was added titanium (IV) chloride (0.05 ml, 0.46 mmol) at 0°C. The mixtrue was stirred for 30 minutes, acidified with 5% hydrochloric acid, and extracted with dichloromethane. The organic layer was washed with water, dried, and condensed. The residue was purified by mcc (ethyl acetate-dichloromethane, 2:1) and recrystallized from ethanol to give **29** (38 mg, 83%, mp 211-212°C, lit. [13d] 196-198°C, lit. [13o] 207-210°C) as colorless crystals. The ^{1}H-NMR and IR spectra were identified with those of racemic lactams.[5] The optical rotation was identified with the authentic data.[13d] $[\alpha]_D^{23}$ +127° (*c*=0.35, EtOH), (lit.[13d] $[\alpha]_D^{24}$ +129° (*c*=0.486, EtOH)).

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