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Stereoselective Addition of 2-Aminothiophenol to α-Alkoxycinnamic Acid Derivatives---Alternative Synthesis of (±)-Diltiazem---

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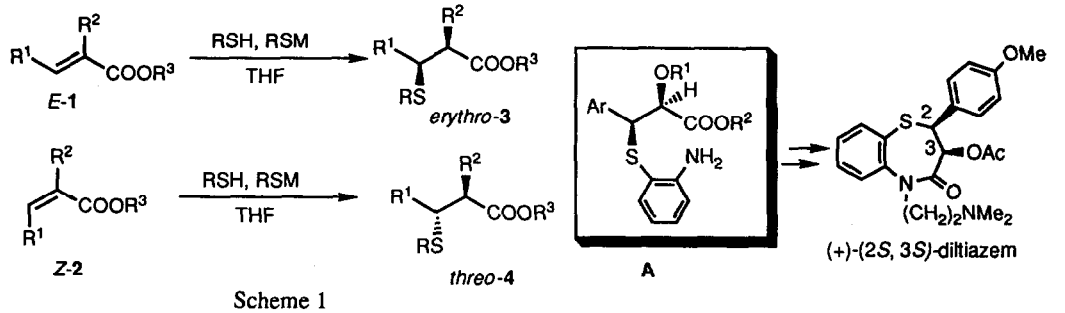
Dedicated with respect and affection to Sir Derek Barton
on the occasion of his seventy-fifth birthday.

Abstract A stereocontrolled synthesis of (±)-diltiazem by applying nucleophilic addition of 2-aminothiophenol to α-alkoxycinnamic acid derivatives is described.

Michael-type addition of nucleophiles to α,β-unsaturated carbonyl compounds has been known as one of the most widely used reactions. However, its stereochemistry has not been well understood. Recently we found that nucleophilic addition[1,2] of thiols to electron-deficient olefins proceeds stereospecifically and with high stereoselectivity in the presence of an electrophile under protic conditions, thus forming new contiguous stereogenic centers with a phenylthio substituent which has high potentiality for further conversion to various types of structures. The addition is thought to proceed *via* the course of rapid protonation of the intermediary enolate formed by the attack of the nucleophile (RSM) (Scheme 1). Thus the *erythro*-adduct **3** was obtained stereoselectively from the *E*-olefin **1** while predominantly *threo*-**4** was obtained from *Z*-**2** under protic conditions.



Scheme 1

We now report further application of this synthetic methodology to (±)-diltiazem,[3] a potent vasodilating drug developed by Tanabe Seiyaku Co. Ltd. With the application of the above addition reaction in mind, our synthetic strategy, based on the synthesis of the key intermediate *threo*-amino ester A by Michael addition of thiol to cinnamate, was planned. Several α-acyloxy and alkoxycinnamic acid derivatives **5** and **6** were prepared and their structures, particularly the geometries were determined mainly by NMR analysis (Table 1 and 2).

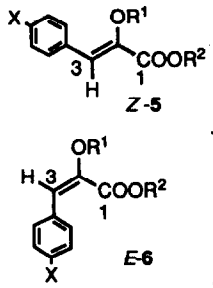


Table 1 Chemical Shifts of 3-H [^{1}H NMR (200 MHz, $CDCl_3$)]

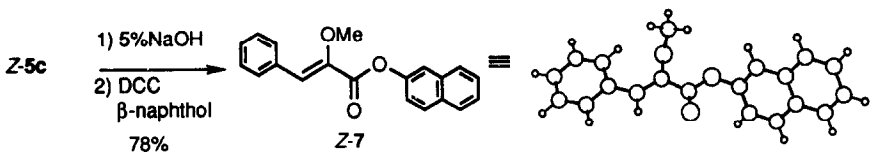
	X	R^1	R^2	*Z*-5 (δ; ppm)	*E*-6 (δ; ppm)
a	H	COOMe	Me	7.06	——
b	H	Ac	Me	7.36	——
c	H	Me	Me	7.02	6.60
d	H	MEM	Et	7.11	6.70
e	Me	MEM	Et	7.09	6.49
f	MeO	MEM	Et	7.07	——

Table 2 Coupling Constants between 3-H and 1-C [^{13}C NMR (125 MHz, $CDCl_3$) (*J* in Hz)]

	X	R^1	R^2	*Z*-5	*E*-6
c	H	Me	Me	3.5	10.5
f	MeO	MEM	Et	3.5	——

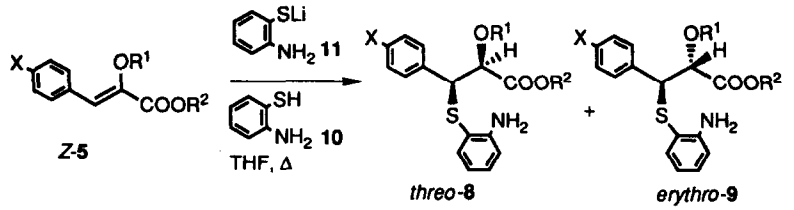
From the above data, it is deduced that the geometry can be assigned from their chemical shifts in ^{1}H NMR spectra and the coupling constants between 1-C and 3-H (^3J values[4]) in ^{13}C NMR spectra. In ^{1}H NMR spectra, the cinnamates which exhibited signals for an olefinic proton at the 3-position at lower field (δ>7 ppm) have *Z*-geometries while those which appeared at higher fields (δ< 6.7 ppm) having *E*-geometries (Table 1). Also, in the ^{13}C NMR spectra of these cinnamates, ^3J values of the *Z*-isomer *Z*-**5** appeared at 3.5 Hz while at 10.5 Hz for the *E*-isomer *E*-**6** as shown in Table 2. These data were perfectly consistent with the empirical rule that ^3J values of the compound having a configuration with an olefinic proton and C_3-carbon on the same side of the molecule show smaller coupling constants (^3J value) than those with the opposite configuration.

α-Alkoxycinnamates **5** and **6** were prepared according to the Wenkert's procedure[5] by the aldol condensation of methyl α-alkoxyacetate with an aromatic aldehyde followed by mesylation and elimination. The cinnamates were obtained as mixtures of *Z*- and *E*-isomers with predominant formation of the more stable *Z*-isomer. The oily compound *Z*-**5c** having *Z*-geometry was determined by X-ray crystallography as its β-naphthyl ester *Z*-**7** (Scheme 2).



Scheme 2

Michael additions of 2-aminothiophenol **10** to cinnamates **5** with α-acyloxy and alkoxy substituents were then investigated (Scheme 3, Table 3). Though the addition of 2-aminothiophenol **10** to the cinnamates *Z*-**5a,b** with acyloxy substitutents did not give any adducts (entries, 1 and 2), the addition to cinnamates **5c-f** with α-alkoxy substituents proceeded differently. When *Z*-cinnamate **5c** with an α-methoxy group was treated at room temperature, only the starting compound was recovered while treatment under refluxing temperature in tetrahydrofuran afforded the desired adduct, *threo*-**8c**, though in a low yield (entry 3). Use of one equivalent amount of lithium thiolate **11** gave no difference (entry 4). Then the addition to the *Z*-cinnamate **5d** with an α-MEM-protected group was carried out in the presence of one equivalent of lithium thiolate **11** and ten equivalents of 2-aminothiophenol **10** under THF-refluxing temperature. The desired *threo*-**8d** was obtained in a good yield with moderate stereoselectivity (entry 6). Then the effect of substituent (X) on the aromatic ring was investigated (entries 7 and 8). The result showed that the presence of an electron-donating group (X), i.e.,



5a ; R^1=COOMe, R^2=Me, X=H
5b ; R^1=Ac, R^2=Me, X=H
5c ; R^1=Me, R^2=Me, X=H
5d ; R^1=MEM, R^2=Et, X=H
5e ; R^1=MEM, R^2=Et, X=Me
5f ; R^1=MEM, R^2=Et, X=OMe

Scheme 3

Table 3 Addition of 2-Aminothiophenol to Cinnamates *Z*-**5**

Entry	Substrate	**11** :**10** (eq.)	Yield (%)	**8** : **9**
1	**5a**	0.1:10	-	-
2	**5b**	0.1:10	-	-
3	**5c**	0.1:10	22	74:26
4	**5c**	1 :10	24	72:28
5	**5d**	0.1:10	23	81:19
6	**5d**	1 :10	78	76:24
7	**5e**	1 :10	80	82:18
8	**5f**	1 :10	82	85:15

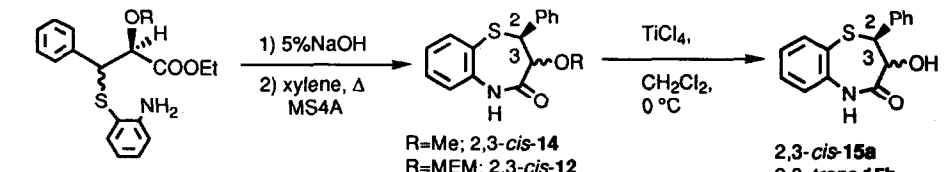
Table 4 Chemical Shifts of 2-H and 3-H in the Cinnamates **8** and **9**

Adducts	2- and 3-H δ;(ppm)	δ;(ppm)	Δδ
threo-**8c**	4.13	4.34	0.20
erythro-**9c**	4.13	4.42	0.29
threo-**8d**	4.49	4.56	0.07
erythro-**9d**	4.40	4.66	0.26
threo-**8e**	4.42	4.50	0.08
erythro-**9e**	4.38	4.60	0.22
threo-**8f**	4.42	4.48	0.06
erythro-**9f**	4.36	4.60	0.24

methyl and methoxy groups, played an important role in yielding the adducts **8e,f** and **9e,f** in good yields with better stereoselectivity.

The structures of the adducts **8** and **9** were determined based on the facts that these adducts showed a molecular ion peak with a greater mass number by m/z 125 than that of the cinnamates, the presence of a primary amino group in the IR spectra and the absence of an olefinic hydrogen and the presence of new signals for 2- and 3-hydrogens in their NMR spectra. Relative configurations at the 2- and 3-positions in the adducts **8** and **9** were deduced as follows. A mixture of *threo*-**8d** and *erythro*-**9d** was hydrolyzed by the treatment with 5% sodium hydroxide to give the aminocarboxylic acids which were heated in the presence of MS4A under reflux in xylene to give a mixture of two lactams, 2,3-*cis*-**12** and 2,3-*trans*-**13** in 30 and 13% yields, respectively, (Scheme 4) both of which showed identical molecular ion peak at m/z 359 and a strong IR absorption band at 1684 cm^{-1} for their lactam structure.

Removal of the MEM group of **12** and **13** with titanium tetrachloride afforded the hydroxylactams **15a,b**, both of which showed a molecular ion peak at m/z 271, and an IR absorption at 3380 cm^{-1} for a hydroxy group. Direct comparison of this compound **15a** with an authentic sample[6] of 2,3-*cis*-benzothiazepinone



R=Me; *threo*-**8c**
R=MEM; *threo*-**8d** :*erythro*-**9d** = 74 : 26

R=Me; 2,3-*cis*-**14**
R=MEM; 2,3-*cis*-**12**
R=MEM; 2,3-*trans*-**13**

2,3-*cis*-**15a**
2,3-*trans*-**15b**

Scheme 4

unambiguously established its structure as depicted. The structure of the trans-lactam **15b** which was also established by direct comparison with a known sample,[7] firmly established the structure of **8d** as *threo*- and **9d** as *erythro* configurations. The structures of the adducts **8f** and **9f** were also established by the conversion to (±)-diltiazem **19**.

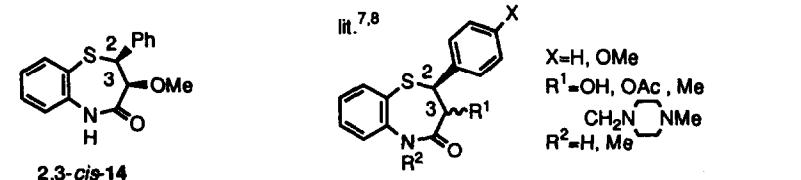
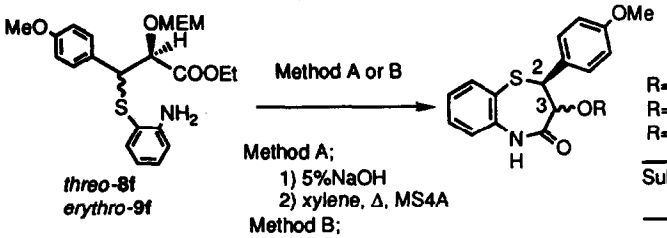


Figure 1 The Coupling Constants Between 2-H and 3-H in the Benzothiazepines

The structures of other adducts, *threo*-**8c, e** and *erythro*-**9c, e**, were confirmed by the comparison of their chemical shifts of 2- and 3-hydrogens in their ^{1}H NMR spectra (Table 4). From their spectra, a practical criterion for the determination of the stereochemistry of *threo*-**8e** and *erythro*-**9e** is established. Previously, it was reported[7,8] that in the series of compounds of benzothiazepine skeleton with two substituents at the 2- and 3-positions, the coupling constants (*J*-value) between 2- and 3-hydrogens are smaller in the 2,3-*cis* series than in the *trans* series. The observation in the present cases showed a *J*-value of 6.5 Hz in compound **14**, prepared from *threo*-**8c**, and was found to be identical with the reported data, thus establishing the 2,3-*cis* relation in compound **14** (Figure 1). As a result, the *threo* configuration in **8c** and *erythro* in **9c** were also established.

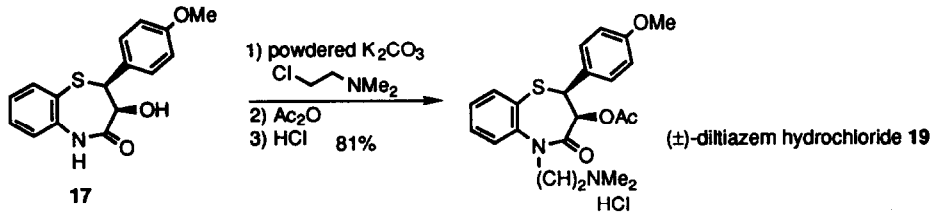


Substrate	Method	16	17	18
		Yield (%)		
8f	A	50	7	-
8f	B	90	-	-
9f	B	-	-	88

Scheme 5

Finally, the above result that established a new synthetic route to diltiazem on the model compounds **15a** and **b** has been successfully applied to the total synthesis of (±)-diltizem **19** (Scheme 5 and 6). The cyclization of the key intermediate, the amino ester **8f** was carried out to afford the lactam **16** as the major product (50% yield) together with the hydroxylactam **17** in 7 % yield as a result of cleavage of the protective MEM group (Method A). The poor yield and slow reaction under this reaction condition pushed us to modify the reaction condition by changing the condensation agent to trimethylaluminum[9] (Method B). Thus the cyclization with 90% yield and in one step from the amino ester **8f** was achieved. Similarly, the 2,3-*trans*-lactam **18** was obtained from the *erythro*-amino ester **9f** in good yield.

The structures of the cyclization products were established as follows. Hydroxylactam **17**, obtained as a byproduct, was found to be identical with a known sample[6] upon comparison of various spectra. The structure of 2,3-*cis*-lactam **16** was established from its mass spectrum which shows a molecular ion peak at m/z 389 and and IR absorption at 3388 cm^{-1} due to NH-absorption and 1686 cm^{-1} for a lactam carbonyl group. Cleavage of the MEM group of **16** was smoothly carried out by treating with titanium tetrachloride. The structure of isomeric lactam **18** was deduced from its spectra.



mp 186-187 °C (Et_2O-EtOH)
(lit.[11] 187-188°C (Et_2O-EtOH))

Scheme 6

Finally the conversion of the 2,3-*cis*-hydroxylactam **17** into (±)-diltiazem **19** was carried out by the route developed previously.[10,11] The hydroxylactam **17** was treated with dimethylaminoethyl chloride in the presence of 2.5 equivalents of powdered potassium carbonate for N-alkylation. Acetylation and subsequent salt formation by using anhydrous hydrogen chloride gas afforded (±)-diltiazem hydrochloride **19**[11] in 81 % yield, which was spectrally identical with an authentic specimen provided by Tanabe Seiyaku Co. Ltd.

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EXPERIMENTAL

The ^1H, ^{13}C NMR, and ^{19}F NMR spectra were measured with Varian XL-200 or Varian VXR-500 instrument for solutions in deuteriochloroform (with tetramethylsilane (^1H and ^{13}C NMR) or fluorobenzene (^{19}F NMR)as an internal reference). The IR spectra were measured with a Hitachi 215 machine for solutions in chloroform. MS were taken with a Hitachi M-80 spectrometer. All melting points were determined with a Kofler-type hot-stage apparatus. Extracts from reaction mixture were washed with water and dried over anhydrous sodium sulfate. All reactions were carried out under a N_2 atmosphere unless otherwise stated. Medium-pressure column chromatography (MCC) was undertaken on a Yamazen 530-4-10V chromatography apparatus using a Lobar grösse B column (310-25, Lichroprep Si60, Merck).

Preparation of the α-acyloxycinnamates 5a and 5b

According to the literature,[12,13] the cinnamates **5a** and **b** were prepared from pyruvic acid and methyl pyruvate, respectively. Methyl (Z)-2-Methoxycarbonyloxy-3-phenyl-2-propenoate **5a** (65 %) was a colorless oil; IR: 1768 (OCOOMe), 1728 (COOMe) cm^{-1}. ^1H-NMR δ: 7.82 (2H, br d, *J*=7 Hz, ArH), 7.50-7.30 (3H, m, ArH), 7.06 (1H, s, 3-H), 3.91 (3H, s, COOMe), 3.84 (3H, s, COOMe). HRMS *m/z*: Calcd for $C_{12}H_{12}O_5$ (M^+): 236.0684. Found: 236.0687. Methyl (Z)-2-Acetyloxy-3-phenyl-2-propenoate **5b** (84 %) was a colorless oil; IR: 1768 (OCOMe), 1728 (COOMe) cm^{-1}. ^1H-NMR δ: 7.62 (2H, m, ArH), 7.41 (3H, m, ArH), 7.36 (1H, s, 3-H), 3.87 (3H, s, COOMe), 2.35 (3H, s, Ac). HRMS *m/z*: Calcd for $C_{12}H_{12}O_4$ (M^+): 220.0734. Found: 220.0734.

Aldol reaction between methyl methoxyacetate and benzaldehyde

A solution of methyl methoxyacetate (1.04 g, 10 mmol) in THF (10 ml) was added with stirring at -78 °C to an LDA solution, prepared from diisopropylamine (1.54 ml, 11 mmol) and butyllithium (1.60 M solution in hexane) (6.9 ml, 11 mmol) at -78 °C. After being stirred at -78 °C for 15 min, benzaldehyde (1.23 g, 11 mmol) was added and the resulting solution was stirred at -78 °C for 1 h. After addition of saturated aqueous ammonium chloride, the reaction mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give a residue which was purified by MCC (hexane:Et_2O=1:4) to afford a 1:2 (or 2:1) diastereomeric mixture of methyl *erythro*- and *threo*-3-hydroxy-2-methoxy-3-phenylpropionate (1.54 g, 73 %) as colorless oil. IR: 3572 (OH), 1740 (COOMe) cm^{-1}. ^{1}H-NMR δ: 7.50 (5H, m, ArH), 5.00 (2/3H), 4.95 (1/3H), 4.00 (2/3H), 3.92 (1/3H) (each d, *J*=6 Hz, 2- and 3-H), 3.68 (2H, s, COOMe), 3.66 (3H, s, COOMe), 3.43 (3H, s, OMe), 3.38 (2H, s, OMe). HRMS (CI, isobutane) *m/z*: Calcd for $C_{11}H_{13}O_3$+H (QM^+-H_2O): 193.0863. Found: 193.0853.

Methanesulfonyl chloride (504 mg, 4.4 mmol) was added to a solution of the β-hydroxy ester (840 mg, 4 mmol) and Et_3N (0.61 ml, 4.4 mmol) in CH_2Cl_2 (40 ml) at 0 °C. After being stirred at 0 °C for 1 h, 5% HCl was added. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give the mesylate, which without purification was heated with DBU (1 ml) at 100 °C for 2 h. After being cooled, 5% HCl was added and the reaction mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give a residue which was purified by MCC (Et_2O:hexane=1:2) to afford methyl (*Z*)-2-methoxy-3-phenyl-2-propenoate *Z*-**5c** (510 mg, 66 %) as colorless oil and the *E*-isomer *E*-**6c** (56 mg, 7 %) as colorless oil.

Z-**5c**: IR: 1716 (conj. COOMe) cm^{-1}. ^{1}H-NMR δ: 7.88 (2H, br dd, *J*=7, 2 Hz, ArH), 7.64 (3H, m, ArH), 7.02 (1H, s, 3-H), 3.89 (3H, s, COOMe), 3.76 (3H, s, OMe). ^{13}C NMR δ: 164.98 (1-C), 145.59, 133.46 (2- and 1'-C), 130.20, 129.05, 128.63, 124.13 (ArCx5 and 3-C), 59.25, 52.17 (COOMe and OMe). The coupling constant between 1-C and 3-H: ^3J=3.5 Hz. HRMS *m/z*: Calcd for $C_{11}H_{12}O_3$ (M^+): 192.0784. Found 192.0781.

E-**6c**: IR: 1732 (conj. COOMe) cm^{-1}. ^{1}H-NMR δ: 7.30 (5H, m, ArH), 6.60 (1H, s, 3-H), 3.78 (3H, s, COOMe), 3.70 (3H, s, OMe). ^{13}C-NMR δ: 164.59 (1-C), 147.64, 134.69 (2- and 1'-C), 128.50, 128.14, 126.98, 109.40 (ArCx5 and 3-C), 56.00, 52.11 (COOMe and OMe). The coupling constant between 1-C and 3-H: ^3J=10.5 Hz HRMS *m/z*: Calcd for $C_{11}H_{12}O_3$ (M^+): 192.0784. Found: 192.0779.

Ethyl (2-Methoxyethoxy)methoxyacetate 20

A solution of methoxyethoxymethyl chloride (1.36 g, 11 mmol) in CH_2Cl_2 (20 ml) was added with stirring at room temperature to a solution of ethyl glycolate (1.04 g, 10 mmol) and *N,N*-diisopropylethylamine (1.92 ml, 11 mmol) in CH_2Cl_2 (70 ml). After being stirred for 12 h, the reaction mixture was made acidic by addition of 5% HCl and then extracted with CH_2Cl_2. The extract was dried and evaporated to give a crude product, which was distilled to afford the ester **20** (1.65 g, 86 %) as colorless oil. bp. 103 °C (3 mmHg). IR: 1746 (COOEt) cm^{-1}. ^{1}H-NMR δ: 4.87 (2H, s, OCH_2O), 4,26 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 4.24 (2H, s, OCH_2COOEt), 3.76, 3.59 (each 2H, m, OCH_2CH_2O), 3.42 (3H, s, OMe), 1.31 (3H, t, *J*=7 Hz, $COOCH_2CH_3$).

MS (CI, isobutane) *m/z* : Calcd for $C_8H_{17}O_5$+H (QM^+): 193. Found: 193.

Preparation of the α-alkoxycinnamates 5de and 6de

According to the procedure given for **5c**, aldol reaction between the α-alkoxy ester **20** (768 mg, 4 mmol) and benzaldehyde or *p*-tolualdehyde (4.1 mmol) followed by dehydration *via* the mesylate of the resulting hydroxy ester gave the α-alkoxycinnamates **5de** and **6de**. Ethyl (*Z*)-2-(2-Methoxyethoxy)methoxy-3-phenyl-2-propenoate *Z*-**5d** (324 mg, 58 %): IR: 1712 (conj. COOEt) cm^{-1}. ^{1}H-NMR δ: 7.81 (2H, br d, *J*=7 Hz, ArH), 7.50-7.30 (3H, m, ArH), 7.11 (1H, s, 3-H), 5.25 (2H, s, OCH_2O), 4.34 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.64, 3.40 (each 2H, m, OCH_2CH_2O), 3.32 (3H, s, OMe), 1.40 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z:* Calcd for $C_{15}H_{21}O_5$ (M^+): 280.1309. Found: 280.1310. (*E*)-isomer *E*-**6d** (62 mg, 11 %): IR: 1728 (conj. COOEt) cm^{-1}. ^{1}H-NMR δ: 7.20-7.40 (5H, m, ArH), 6.70 (1H, s, 3-H), 5.25 (2H, s, OCH_2O), 4.16 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.89, 3.63 (each 2H, m, OCH_2CH_2O), 3.42 (3H, s, OMe), 1.10 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS (CI, isobutane) *m/z*: Calcd for $C_{15}H_{21}O_5$+H (QM^+): 281.1386. Found: 281.1363.

Ethyl (*Z*)-2-(2-Methoxyethoxy)methoxy-3-(4-methylphenyl)-2-propenoate *Z*-**5e** (378 mg, 53 %). *Z*-**5e**: IR: 1710 (conj. COOEt) cm^{-1}. ^{1}H-NMR δ: 7.71 (2H, d-like, *J*=7 Hz, ArH), 7.21 (2H, d-like, *J*=7 Hz, ArH), 7.09 (1H, s, 3-H), 5.23 (2H, s, OCH_2O), 4.32 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.76, 3.42 (each 2H, m, OCH_2CH_2O), 3.32(3H, s, OMe), 2.39 (3H, s, Ar-Me), 1.38 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{16}H_{22}O_5$ (M^+): 294.1466. Found: 294.1479. (*E*)-isomer *E*-**6e** (86 mg, 12 %): IR: 1730 (conj. COOEt). cm^{-1}. ^{1}H-NMR δ: 6.99 (2H, d-like, *J*=7 Hz, ArH), 6.96 (2H, d-like, *J*=7 Hz, ArH), 6.49 (1H, s, 3-H), 5.08 (2H, s, OCH_2O), 4.05 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.78, 3.68 (each 2H, m, OCH_2CH_2O), 3.30 (3H, s, OMe), 2.26 (3H, s, Ar-Me), 1.06 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{16}H_{22}O_5$ (M^+): 294.1466. Found: 294.1488.

Aldol reaction between the α-alkoxy ester 20 and anisaldehyde

According to the procedure given for **5c**, aldol reaction between the α-alkoxy ester **20** (2.88 g, 15 mmol) and anisaldehyde (2.18 g, 16 mmol) followed by purification of the crude product by MCC (Et_2O:hexane=1:1) gave a diastereomeric mixture of the β-hydroxy esters (3.45 g, 72 %) as a colorless oil. The less polar product (2.36 g, 48 %): IR: 3460 (OH), 1736 (COOEt) cm^{-1}. ^{1}H-NMR δ: 7.34 (2H, d-like, *J*=7 Hz, ArH), 6.88 (2H, d-like, *J*=7 Hz, ArH), 5.00 (1H, d, *J*=5.5 Hz, 2- or 3-H), 4.71, 4.70 (2H, ABq, *J*=7 Hz, OCH_2O), 4.20 (1H, d, *J*=5.5 Hz, 2- or 3-H), 4.15 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.81 (3H, s, Ar-OMe), 3.70-3.30 (4H, m, OCH_2CH_2O), 3.38, (3H, s, OMe), 1.20 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{16}H_{25}O_6$ (M^+-(H_2O+OCH_2CH_2OMe)) : 235.0970. Found: 235.0974. The polar product (1.09 g, 24 %): IR: 3576 (OH), 1736 (COOEt) cm^{-1} ^{1}H-NMR δ: 7.35 (2H, d-like, *J*=7 Hz, ArH), 6.91 (2H, d-like, *J*=7 Hz, ArH), 5.00 (1H, d, *J*=5 Hz, 2- or 3-H), 4.82, 4.79 (2H, ABq, *J*=7 Hz, OCH_2O), 4.29 (1H, d, *J*=5 Hz, 2- or 3-H), 4.10 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.83 (3H, s, Ar-OMe), 3.70-3.30 (4H, m, OCH_2CH_2O), 3.36 (3H, s, OMe), 1.14 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{16}H_{25}O_6$ (M^+-(H_2O+OCH_2CH_2OMe)): 235.0970. Found: 235.0943.

According to the literature,[14] Et_3N (10 ml, 72 mmol) and 2-fluoro-1-methylpyridinium *p*-toluenesulfonate (10.2 g, 36 mmol) were added with stirring at room temperature to a solution of a mixture of the β-hydroxyesters (7.9 g, 24 mmol) in CH_2Cl_2 (200 ml). After being stirred for 2 h, 5% HCl was added. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give a residue which was purified by MCC (Et_2O:hexane=3:7) to afford ethyl (*Z*)-2-(2-methoxyethoxy)methoxy-3-(4-methoxyphenyl)-2-propenoate *Z*-**5f** (3.64 g, 49 %) as colorless oil and a 5:1 (or 1:5) mixture of ethyl *erythro*- and *threo*-3-fluoro-2-[(2-methoxyethoxy)methoxy]-3-(4-methoxyphenyl)propionate **21** (1.42 g, 18 %) as colorless oil.
Z-**5f**: IR: 1708 (conj. COOEt) cm^{-1}. ^{1}H-NMR δ: 7.78 (2H, d-like, *J*=7 Hz, ArH), 6.92 (2H, d-like, *J*=7 Hz, ArH), 7.07 (1H, s, 3-H), 5.22 (2H, s, OCH_2O), 4.30 (2H, q, *J*=7 Hz, $COOCH_2CH_3$), 3.85 (3H, s, Ar-OMe), 3.77, 3.43 (each 2H, m, OCH_2CH_2O), 3.38 (3H, s, OMe), 1.36 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). ^{13}C-NMR δ: 164.56 (1-C), 160.20, 140.59, 126.13 (1'-C, 4'-C, and 2-C), 131.88, 124.84, 113.99 (ArCx4 and 3-C), 96.09 (OCH_2O), 71.06, 69.13, 61.20 [(OCH_2CH_2O) and (OCH_2CH_3)], 58.95, 55.30 (Ar-OMe and OMe), 14.33 (OCH_2CH_3). The coupling constant between 1-C and 3-H: ^3J=3.5 Hz. HRMS *m/z*: Calcd for $C_{16}H_{22}O_6$ (M^+) : 310.1414. Found: 310.1411. **21**: IR: 1712 (COOEt) cm^{-1}. ^{1}H-NMR δ:7.55, 6.91 (each 2H, d-like, *J*=7 Hz, ArH_4), 5.75 (1/6H, dd, *J*=45, 4 Hz, 3-H), 5.63 (5/6H, dd, *J*=44, 6 Hz, 3-H), 4.70-4.60 (2H, m, OCH_2O), 4.57 (5/6H, dd, *J*=8, 6 Hz, 2-H), 4.46 (1/6H, dd, *J*=23, 4 Hz, 2-H), 4.23 (5/3H), 4.14 (1/3H), (each q, *J*=7 Hz, $COOCH_2CH_3$), 3.81 (3H, s, Ar-OMe), 3.70-3.40 (4H, m, OCH_2CH_2O), 3.36 (1/2H), 3.32 (5/2H), (each s, OMe), 1.26 (5/2H), 1.15 (1/2H), (each t, *J*=7 Hz, $COOCH_2CH_3$). ^{19}F-NMR (fluorobenzene) δ: -67.0 (5/6F, dd, *J*=44, 8 Hz), -73.7 (1/6F, dd, *J*=45, 23 Hz). HRMS *m/z*: Calcd for $C_{16}H_{23}O_6F$ (M^+): 330.1473. Found: 330.1476.

Dehydrofluorination of the β-fluoro ester 21

A mixture of the β-fluoro ester **21** (1 g, 3 mmol) and DBU (5 ml) was heated at 150 °C for 9 h. After being cooled, 5% HCl was added. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give a residue which was purified by MCC (Et_2O:hexane=3:7) to afford the *Z*-ester **5f** (550 mg, 59 %). The *Z*-**5f** was identical with the sample prepared above.

2-Naphthyl (*Z*)-2-Methoxy-3-phenyl-2-propenoate *Z*-7

Hydrolysis of the *Z*-ester **5c** (96 mg, 0.5 mmol) with 5% aqueous NaOH followed by esterification of the resulting carboxylic acid using β-naphthol (75 mg, 0.5 mmol), DCC (109 mg, 0.53 mmol), and DMAP (5 mg) gave the 2-naphthyl ester *Z*-**7** (130 mg, 85 %) as colorless crystals, mp 107-108 °C ($CHCl_3$-pentane). IR:1730 (conj. COOAr) cm^{-1}. ^{1}H-NMR δ: 8.00-7.80 (5H, m, ArH), 7.70 (1H, m, ArH), 7.64-7.30 (6H, m, ArH), 7.32 (1H, s, 3-H), 3.40 (3H, s, OMe). HRMS *m/z*: Calcd for $C_{20}H_{16}O_3$ (M^+): 304.1098. Found: 304.1094. *Anal.* Calcd for $C_{20}H_{16}O_3$: C, 78.92; H, 5.30. Found: C, 78.76; H, 5.21. X ray crystallographic data: $C_{20}H_{16}O_3$, *Mr*=304.10, monoclinic; *a*=32.303(6), *b*=6.284(1), *c*=7.855(1)Å, β=94.80 (2)°, Z=4, *D*x=1.272 gcm^{-3}, *R* value 0.057 for 2349 reflections, μ(Cu Kα, 2θmax<120°), space group $P2_1/C$.

Addition of 2-aminothiophenol to the (*Z*)-α-alkoxycinnamates 5c-f

2-Aminothiophenol **10** (1.17 ml, 11 mmol) was added with stirring at 0 °C to a solution of butyllithium (1.60 M solution) (0.63 ml, 1 mmol) in THF (5 ml) to give a solution of a 10:1 mixture of the thiol and lithium thiolate. To the resulting solution was added a solution of the (*Z*)-α-alkoxycinnamates **5c-f** (1 mmol) in THF (5 ml). After stirring at 70 °C for 5 h, the mixture was made alkaline by addition of 5% aqueous NaOH and

extracted with CH_2Cl_2. The extract was dried and evaporated to give a residue, which was purified by MCC to afford a diastereomeric mixture of adducts **8** and **9** in the yield as shown in the Table 3. The ratio of *erythro* to *threo* was determined by 200 MHz ^1H NMR.

Methyl *threo*- and *erythro*-3-(2-Aminophenylthio)-2-methoxy-3-phenylpropanoates **8c** and **9c**:
The major diastereomer **8c** was isolated by repeated MCC (Et_2O:hexane=1:1). **8c**; pale yellow oil: IR: 3438, 3380 (NH_2), 1742 (COOMe) cm^{-1}. ^1H-NMR δ:7.40-7.10 (7H, m, ArH), 6.80-6.66 (2H, m, ArH), 4.34 (1H, d, *J*=5 Hz, 2- or 3-H), 4.13 (1H, d, *J*=5 Hz, 2- or 3-H), 3.64 (3H, s, COOMe), 3.42 (3H, s, OMe). HRMS *m/z*: Calcd for $C_{17}H_{19}NO_3S$ (M^+): 317.1083. Found: 317.1072. **9c**; ^1H-NMR δ: 4.42 (1H, d, *J*=6 Hz, 2- or 3-H), 4.13 (1H, d, *J*=5 Hz, 2- or 3-H), 3.59 (3H, s, COOMe), 3.48 (3H, s, OMe).

Ethyl *threo*- and *erythro*-3-(2-Aminophenylthio)-2-[(2-methoxyethoxy)methoxy]-3-phenylpropanoates **8d** and **9d**:
[*threo*-**8d**:*erythro*-**9d**=76:24]; pale yellow oil: IR: 3484, 3372 (NH_2), 1740 (COOEt) cm^{-1}. ^1H-NMR δ: 7.46-7.00 (7H, m, ArH), 6.72 (1H, dd, *J*=7, 2 Hz, ArH), 6.58 (1H, td, *J*=7, 2 Hz, ArH), 4.90, 4.80 (2H, ABq, *J*=7 Hz, OCH_2O), 4.66 (ca. 1/4H, d, *J*=7 Hz, 2- or 3-H), 4.56, 4.49 (ca. 3/2H, ABq, *J*=6 Hz, 2- and 3-H), 4.40 (ca. 1/4H, d, *J*=7 Hz, 2- or 3-H), 4.10-3.90 (2H, m, $COOCH_2CH_3$), 3.66-3.30 (4H, m, OCH_2CH_2O), 3.41 (ca. 3/4H), 3.34 (ca. 9/4H), (each s, OMe), 1.21 (ca. 3/4H), 1.06 (ca. 9/4H), (each t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{21}H_{27}NO_5S$ (M^+): 405.1607. Found: 405.1602.

Ethyl *threo*- and *erythro*-3-(2-Aminophenylthio)-2-[(2-methoxyethoxy)methoxy]-3-(4-methylphenyl)-propanoates **8e** and **9e**:
threo-**8e** and *erythro*-**9e** were separated by MCC (Et_2O:hexane=1:1).
threo-**8e**; pale yellow oil: IR: 3488, 3368 (NH_2), 1736 (COOEt). cm^{-1} ^1H-NMR δ 7.24 (2H, d-like, *J*=7 Hz, ArH), 7.20-7.10 (2H, m, ArH), 7.10 (2H, d-like, *J*=7 Hz, ArH), 6.74 (1H, br d, *J*=7 Hz, ArH), 6.58 (1H, br t, *J*=7 Hz, ArH), 4.85, 4.77 (2H, ABq, *J*=7 Hz, OCH_2O), 4.42, 4.50 (2H, ABq, *J*=6 Hz, 2- and 3-H), 4.05-3.95 (2H, $COOCH_2CH_3$), 3.70-3.30 (4H, m, OCH_2CH_2O), 3.32 (3H, s, OMe), 2.32 (3H, s, Ar-Me), 1.06 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{22}H_{29}NO_5S$ (M^+): 419.1763. Found: 419.1760. *erythro*-**9e**; pale yellow oil: IR: 3468, 3370 (NH_2), 1730 (COOEt) cm^{-1}. ^1H-NMR δ: 7.30-7.10 (2H, m, ArH), 7.16 (2H, d-like, *J*=7 Hz, ArH), 7.06 (2H, d-like, *J*=7 Hz, ArH), 6.96 (1H, br d, *J*=7 Hz, ArH), 6.73 (1H, br t, *J*=7 Hz, ArH), 4.79 (2H, s, OCH_2O), 4.60 (1H, d, *J*=7.5 Hz, 2- or 3-H), 4.38 (1H, d, *J*=7.5 Hz, 2- or 3-H), 4.16-4.08 (2H, m, $COOCH_2CH_3$), 3.66, 3.50 (each 2H, m, OCH_2CH_2O), 2.32 (3H, s, Ar-Me), 1.19 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{22}H_{29}NO_5S$ (M^+): 419.1763. Found: 419.1760.

Ethyl *threo*- and *erythro*-3-(2-Aminophenylthio)-2-[(2-methoxyethoxy)methoxy]-3-(4-methoxylphenyl) propanoates **8f** and **9f**:
threo-**8f** and *erythro*-**9f** were separated by MCC (Et_2O:hexane=2:1).
threo-**8f**; pale yellow oil IR: 3484, 3372 (NH_2), 1738 (COOEt) cm^{-1}. ^1H-NMR δ: 7.26 (2H, d-like, *J*=7 Hz, ArH), 7.16-7.10 (2H, m, ArH), 6.79 (2H, d-like, *J*=7 Hz, ArH), 6.70 (1H, br d, *J*=7 Hz, ArH), 6.56 (1H, td, *J*=7, 2 Hz, ArH), 4.86, 4.79 (2H, ABq, *J*=7 Hz, OCH_2O), 4.48, 4.42 (2H, ABq, *J*=6 Hz, 2- and 3-H), 4.05-3.96 (2H, m, $COOCH_2CH_3$), 3.77 (3H, s, Ar-OMe), 3.66-3.30 (4H, m, OCH_2CH_2O), 3.30 (3H, s, OMe), 1.05 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{22}H_{29}NO_6S$ (M^+): 435.1713. Found: 435.1694. *erythro*-**9f**; pale yellow oil: IR: 3484, 3380 (NH_2), 1740 (COOEt) cm^{-1}. ^1H-NMR δ:7.21 (2H, d-like, *J*=7 Hz, ArH), 7.20-7.08 (2H, m, ArH), 6.79 (2H, d-like, *J*=7 Hz, ArH), 6.71 (1H, br d, *J*=7 Hz, ArH), 6.60 (1H, td, *J*=7, 2 Hz, ArH), 4.81, 4.79 (2H, ABq, *J*=7 Hz, OCH_2O), 4.60 (1H, d, *J*=7.5 Hz, 2- or 3-H), 4.36 (1H, d, *J*=7.5 Hz, 2- or 3-H), 4.16-4.10 (2H, m, $COOCH_2CH_3$), 3.79 (3H, s, Ar-OMe), 3.70, 3.50 (each 2H, m, OCH_2CH_2O), 3.40 (3H, s, OMe), 1.20 (3H, t, *J*=7 Hz, $COOCH_2CH_3$). HRMS *m/z*: Calcd for $C_{22}H_{29}NO_6S$ (M^+): 435.1713. Found: 435.1691.

Ring closure of the amino esters 8d and 9d

According to the literature,[6] 5% aqueous NaOH was added to a solution of a 74:26 mixture of the *threo*-**8d** and *erythro*-**9d** (120 mg, 0.3 mmol) in EtOH (2 ml). After being stirred at room temperature for 1 h, the reaction mixture was made acidic by addition of 5% HCl and extracted with CH_2Cl_2. The extract was dried and evaporated to give a crude carboxylic acid, which without purification was dissolved in xylene (10 ml). The mixture was heated under reflux in the presence of molecular sieves 4A for 20 h. After evaporation of the solvent, a residue was purified by MCC (AcOEt) to give *cis*-(±)-2,3-dihydro-3-[(2-methoxyethoxy)methoxy]-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **12** (32 mg, 30%) as colorless crystals, mp 109-110 °C (hexane-Et_2O) and *trans*-(±)-2,3-dihydro-3-[(2-methoxyethoxy)methoxy]-2-phenyl-1,5-benzothiazepin-4(5*H*)-one **13** (14 mg, 13%) as colorless crystals, mp 132-133 °C (hexane-Et_2O). 2,3-*cis*-**12**; IR: 3384 (NH), 1684 (CON) cm^{-1}. ^1H-NMR δ: 8.39 (1H, br s, NH), 7.75 (1H, br t, *J*=7 Hz, ArH), 7.74 (1H, dd, *J*=7, 2 Hz, ArH), 7.44 (1H, td, *J*=7, 2 Hz, ArH), 7.40-7.30 (4H, m, ArH), 7.28 (1H, dd, *J*=7, 2 Hz, ArH), 7.20 (1H, br t, *J*=7 Hz, ArH), 5.20 (1H, d,

J=7 Hz, 2- or 3-H), 4.68 (1H, d, *J*=7 Hz, 2- or 3-H), 4.61, 4.59 (2H, ABq, *J*=7 Hz, OCH_2O), 3.52, 3.42 (each 2H, m, OCH_2CH_2O), 3.30 (3H, s, OMe). HRMS *m/z*: Calcd for $C_{19}H_{21}NO_4S$ (M^+): 359.1189. Found: 359.1190. *Anal.* Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.28; H, 5.96; N, 3.77. 2,3-*trans*-**13**; IR: 3380 (NH), 1684 (NCO) cm^{-1}. ^{1}H-NMR δ: 8.20 (1H, br s, NH), 7.72 (1H, dd, *J*=7, 2 Hz, ArH), 7.53 (1H, td, *J*=7, 2 Hz, ArH), 7.40-7.20 (7H, m, ArH), 4.56 (1H, d, *J*=7.5 Hz, 2- or 3-H), 4.54 (2H, s, OCH_2O), 4.40 (1H, d, *J*=7.5 Hz, 2- or 3-H), 3.24 (3H, s, OMe), 3.24-3.16 (4H, m, OCH_2CH_2O). HRMS *m/z*: Calcd for $C_{19}H_{21}NO_4S$ (M^+) 359.1189. Found: 359.1171.

cis-(±)-2,3-Dihydro-3-hydroxy-2-phenyl-1,5-benzothiazepin-4(5*H*)-one 15a

A solution of the 2,3-*cis*-lactam **12** (36 mg, 0.1 mmol) and $TiCl_4$ (0.03 ml, 0.3 mmol) in CH_2Cl_2 (3 ml) was stirred at 0°C for 30 min. After addition of 5% HCl, the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give a residue which was recrystallized from EtOH to afford the 2,3-*cis* -**15a** (26 mg, 97 %) as colorless crystals, mp 211-212 °C (lit.[6] 194-197 °C), which was identical with the authentic sample of **15a** provided by H. Inoue of Tanabe Seiyaku Co. Ltd. IR: 3380, 3188 (OH, NH), 1684 (NCO) cm^{-1}. ^{1}H-NMR [$CDCl_3$+CD_3OD] δ: 7.71 (1H, dd, *J*=7, 2 Hz, ArH), 7.60 (2H, m, ArH), 7.50-7.30 (4H, m, ArH), 7.26 (1H, td, *J*=7, 2 Hz, ArH), 7.18 (1H, dd, *J*=7, 2 Hz, ArH), 5.16 (1H, d, *J*=7 Hz, 2- or 3-H), 4.52 (1H, d, *J*=7 Hz, 2- or 3-H). HRMS *m/z*: Calcd for $C_{15}H_{13}NO_2S$ (M^+): 271.0666. Found: 271.0665.

trans-(±)-2,3-Dihydro-3-hydroxy-2-phenyl-1,5-benzothiazepin-4(5*H*)-one 15b

According to the procedure given for the *cis*-lactam **15a**, demethoxyethoxymethylation of the 2,3-*trans*-lactam **13** (18 mg, 0.05 mmol) with $TiCl_4$ followed by recrystallization of the crude solid from EtOH gave the 2,3-*trans*-**15b** (12 mg, 89 %) as colorless crystals, mp 204-205 °C (lit.[7] 202-202.5 °C), which was identical with the authentic sample of **15b** provided by H. Inoue of Tanabe Seiyaku Co. Ltd.. IR: 3476, 3188 (OH, NH), 1672 (NCO) cm^{-1}. ^{1}H-NMR [$CDCl_3$+CD_3OD] δ: 7.71 (1H, br d, *J*=7 Hz, ArH), 7.49 (1H, br t, *J*=7 Hz, ArH), 7.40-7.20 (7H, m, ArH), 4.40 (1H, d, *J*=10 Hz, 2- or 3-H), 4.30 (1H, d, *J*=10 Hz, 2- or 3-H). HRMS *m/z*: Calcd for $C_{15}H_{13}NO_2S$ (M^+): 271.0666. Found: 271.0656.

cis-(±)-2,3-Dihydro-3-methoxy-2-phenyl-1,5-benzothiazepin-4(5*H*)-one 14

According to the procedure given for **8d** and **9d**, hydrolysis of the amino ester **8c** (50 mg, 0.16 mmol) with 5% aqueous NaOH followed by ring closure of the resulting carboxylic acid yielded the 2,3-*cis*-lactam **14** (16 mg, 36 %) as colorless oil. IR: 3384 (NH), 1692 (NCO) cm^{-1}. ^{1}H-NMR δ: 9.22 (1H, br s, NH), 7.73 (1H, m, ArH), 7.56 (2H, m, ArH), 7.50-7.20 (6H, m, ArH), 5.21 (1H, d, *J*=6.5 Hz, 2- or 3-H), 4.21 (1H, d, *J*=6.5 Hz, 2- or 3-H), 3.24 (3H, s, OMe). HRMS *m/z*: Calcd for $C_{16}H_{15}NO_2S$ (M^+): 285.0822. Found: 285.0805.

Ring closure of the *threo*-amino ester 8f

Method A According to the procedure given for **8d** and **9d**, hydrolysis of **8f** (1.8 g, 4.14 mmol) with 5% aqueous NaOH followed by ring closure of the resulting carboxylic acid afforded *cis*-(±)-2,3-dihydro-3-[(2-methoxyethoxy)methoxy]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one **16** (800 mg, 50%) as colorless crystals, mp 136.6-137.5 °C (MeOH) and *cis*-(±)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one **17** (112 mg, 7%) as colorless crystals, mp 178.5-179.5 °C (EtOH) (lit.[6] 166-167 °C) after purification of the crude products by MCC (Et_2O, then AcOEt). **16**; IR: 3388 (NH), 1686 (CON) cm^{-1}. ^{1}H-NMR δ: 8.68 (1H, br s, NH), 7.70 (1H, br dd, *J*=7, 2 Hz, ArH), 7.45 (2H, d-like, *J*=7 Hz, ArH), 7.41 (1H, br d, *J*=7 Hz, ArH), 7.23 (1H, br td, *J*=7, 2 Hz, ArH), 7.18 (1H, br d, *J*=7 Hz, ArH), 6.84 (2H, d-like, *J*=7 Hz, ArH), 5.15 (1H, d, *J*=7 Hz, 2-or 3-H), 4.63 (1H, d, *J*=7 Hz, 2- or 3-H), 4.61 (2H, s, OCH_2O), 3.78 (3H, s, Ar-OMe), 3.55, 3.41 (each 2H, m, OCH_2CH_2O), 3.28 (3H, s, OMe). HRMS *m/z*: Calcd for $C_{20}H_{23}NO_5S$ (M^+) : 389.1296. Found: 389.1314. *Anal.* Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.96; N, 3.60. Found: C, 61.41; H, 5.94; N, 3.58. **17**; IR: 3512, 3388 (OH, NH), 1680 (CON) cm^{-1}. ^{1}H-NMR δ: 8.12 (1H, br s, NH), 7.74 (1H, br d, *J*=7 Hz, ArH), 7.53 (2H, d-like, *J*=7 Hz, ArH), 7.46 (1H, br t, *J*=7 Hz, ArH), 7.29 (1H, br t, *J*=7 Hz, ArH), 7.15 (1H, br d, *J*=7 Hz, ArH), 6.92 (2H, d-like, *J*=7 Hz, ArH), 5.13 (1H, d, *J*=7 Hz, 2- or 3-H), 4.52 (1H, d, *J*=7 Hz, 2- or 3-H), 3.84 (3H, s, Ar-OMe). HRMS *m/z*: Calcd for $C_{16}H_{15}NO_3S$ (M^+): 301.0771. Found: 301.0764. *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.53; H, 4.94; N, 4.53.

Method B Trimethylaluminum (15 % solution in hexane) (0.96 ml, 2 mmol) was added with stirring at 0 °C to a solution of the *threo*-amino ester **8f** (400 mg, 0.92 mmol) in CH_2Cl_2 (5 ml). After being stirred at room temperature for 1 h, 5% HCl was added. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated to give a solid which was purified by MCC (AcOEt) to afford **16** (322 mg 90 %). The product **16** was identical with the sample obtained by method A.

trans-(±)-2,3-Dihydro-3-[(2-methoxyethoxy)methoxy]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one 18

According to the procedure (method B) given for **8f**, ring closure of the *erythro*-**9f** (22 mg, 0.05 mmol) with trimethylaluminum followed by purification of the crude product by MCC (AcOEt) gave the *trans*-lactam **18** (17 mg, 88 %) as pale yellow oil. IR: 3388 (NH), 1690 (NCO) cm^{-1}. ^{1}H-NMR δ: 8.63 (1H, br s, NH), 7.71 (1H, br d, *J*=7 Hz, ArH), 7.58 (1H, br t, *J*=7 Hz, ArH), 7.40-7.30 (2H, m, ArH), 7.21 (2H, d-like, *J*=7 Hz, ArH), 6.46 (2H, d-like, *J*=7 Hz, ArH), 4.55 (1H, d, *J*=7 Hz, 2- or 3-H), 4.51, 4.48 (2H, ABq, *J*=11 Hz, OCH_2O), 4.20 (1H, d, *J*=7 Hz, 2- or 3-H), 3.81 (3H, s, Ar-OMe), 3.30-3.10 (4H, m, OCH_2CH_2O), 3.24 (3H, s, OMe). HRMS *m/z*: Calcd for $C_{16}H_{14}NO_3S$ (M^+-$CH_2OCH_2CH_2OCH_3$): 300.9833. Found: 300.9826.

Demethoxyethoxymethylation of the 2,3-*cis*-lactam 16

According to the procedure given for the lactam **12**, treatment of the *cis*-lactam **16** (544 mg, 1.4 mmol) with $TiCl_4$ (0.46 ml, 0.42 mmol) gave the hydroxylactam **17** (387 mg, 92 %), which was identical with the sample obtained by ring closure of the *threo*-amino ester **8f**.

(±)-Diltiazem hydrochloride 19

According to the literature,[10,11] N-alkylation of the lactam **17** followed by O-acetylation of the resulting hydroxylactam gave *cis*-(±)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [(±)-diltiazem] as pale yellow oil, which was treated with HCl to afford (±)-Diltiazem hydrochloride **19** as colorless crystals, mp 186-187 °C (lit.[11] 187-188 °C). **19** was identical with the authentic sample.[11]

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