

SYNTHESIS OF 2-SUBSTITUTED DERIVATIVES OF DILTIAZEM[†]

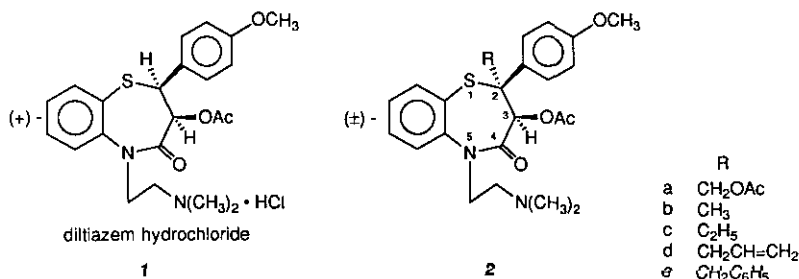
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Abstract — Titled compounds, 2a,b,c,d and e, were efficiently synthesized from 3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (**4**) through alkylation at the C₂-position followed by stereoselective reduction of the C₃-carbonyl group.

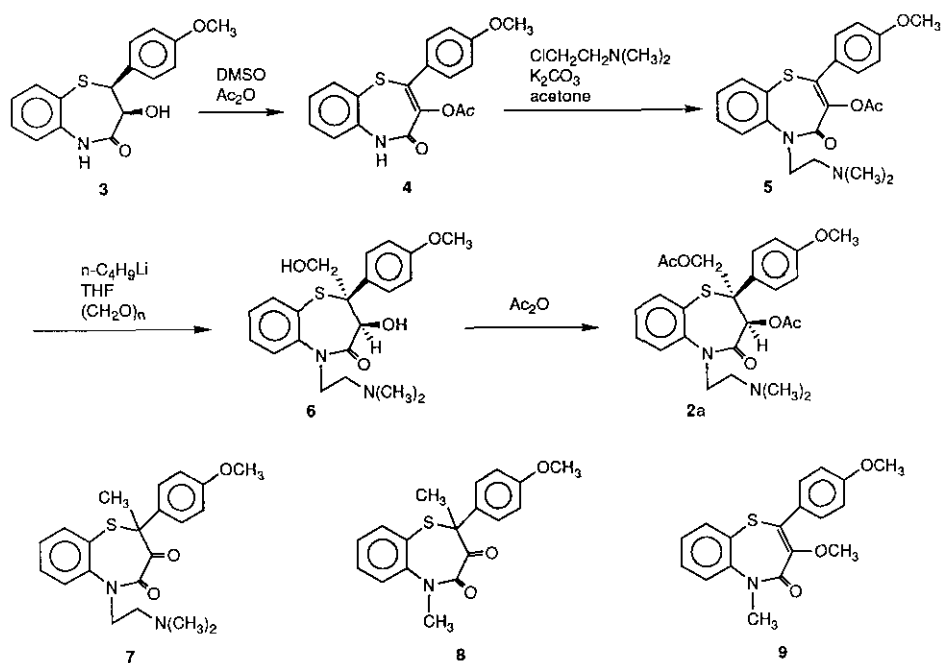
Diltiazem hydrochloride, (+)-(2S,3S)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride (**1**),¹ is a representative calcium antagonist and has been widely used as an effective antianginal and antihypertensive agent all over the world. A number of the congeners have already been synthesized in our laboratory.² In this paper, we wish to describe the synthesis of a new class of derivatives (**2**) with additional substituents at the C₂ position.

cis-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (**3**),^{2a,3} a key intermediate for **1**, was oxidized with dimethyl sulfoxide-acetic anhydride to give the crystalline enol acetate (**4**) in 64% yield.⁴ Reaction of **4**



[†]Dedicated to the memory of Professor Tetsuji Kametani.

with 2-(dimethylamino)ethyl chloride in acetone using potassium carbonate⁵ afforded the corresponding *N*-dimethylaminoethyl compound (5) in 52% yield. When 5 was treated with *n*-butyllithium in tetrahydrofuran (THF) and then with paraformaldehyde, hydroxymethylation and crossed Cannizzaro reduction occurred simultaneously to give the 2-hydroxymethyl-3-hydroxy compound (6) in 78% yield. The stereochemical relation between the C₂-aryl group and the C₃-hydroxyl group of 6 was confirmed to be *cis* by X-ray crystallographic analysis (Figure 1). Hydroxymethylation and crossed Cannizzaro reduction of 5 thus took place from the same direction. Formaldehyde, generated from the paraformaldehyde molecule which reacted at the C₂-position of 5, possibly reduced the C₃-carbonyl group, consequently giving the *cis* isomer. Such a stereocontrolled 1,3-diol synthesis has scarcely been reported⁶ and scope and limitation of this reaction are now in progress. Acetylation of 6 with acetic anhydride afforded the diacetate (2a) in 66% yield (Scheme 1).



Scheme 1

Attempts to synthesize the 2-methyl compound (7) from 5 with iodomethane were unsuccessful, because of the rapid quaternarization of the dimethylamino group. Methylation of 4 with iodomethane to the keto lactam (14b) was also unsuccessful. The products obtained were the *N*-methylated compounds (8 and 9).⁷ In order to

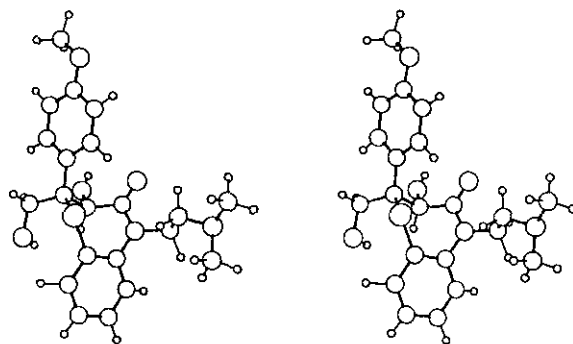
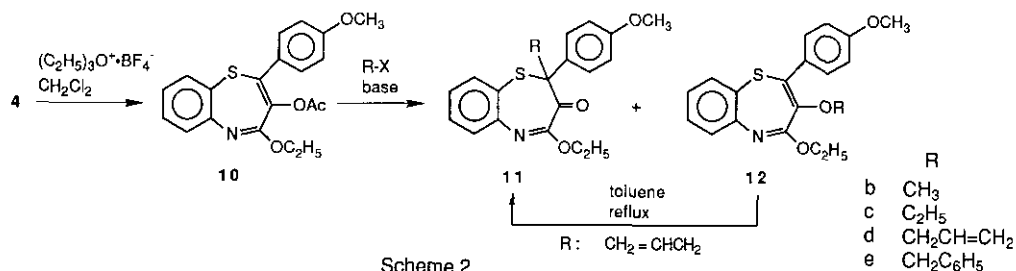


Figure 1 Stereoview of the structure of 6

protect the amide hydrogen, **4** was treated with Meerwein reagent in dichloromethane to give the imino ether (**10**) in quantitative yield. Alkylation of **10** was investigated in various conditions to afford the desired product (**11**) together



Scheme 2

Table I. Alkylation of **10** with various alkylating agents (R-X) to **11** and **12**

R-X	base	solvent	yield(%) (11 + 12)	ratio* (11 : 12)	isolated yield(%) 11	12
CH ₃ I	n-C ₄ H ₉ Li	THF-hexane-HMPA	80	3.8 : 1	52	
	KOH	C ₂ H ₅ OH	77	2.4 : 1	50	14
C ₂ H ₅ I	n-C ₄ H ₉ Li	THF-hexane-HMPA	58	1 : 3.5	12	42
	KOH	C ₂ H ₅ OH	86	1 : 1.4	25	
	KOH	DMF	73	1 : 2.8	22	42
	LiOH	DMF	86	1 : 1.4		
(C ₂ H ₅) ₂ SO ₄	n-C ₄ H ₉ Li	THF-hexane		1 : >10**		
CH ₂ =CH-CH ₂ Br	n-C ₄ H ₉ Li	THF-hexane-HMPA	49	1 : 2.1	14	24
	KOH	C ₂ H ₅ OH	88	2.9 : 1		
C ₆ H ₅ CH ₂ Br	n-C ₄ H ₉ Li	THF-hexane-HMPA			33	27
	KOH	C ₂ H ₅ OH	93	12.5 : 1		

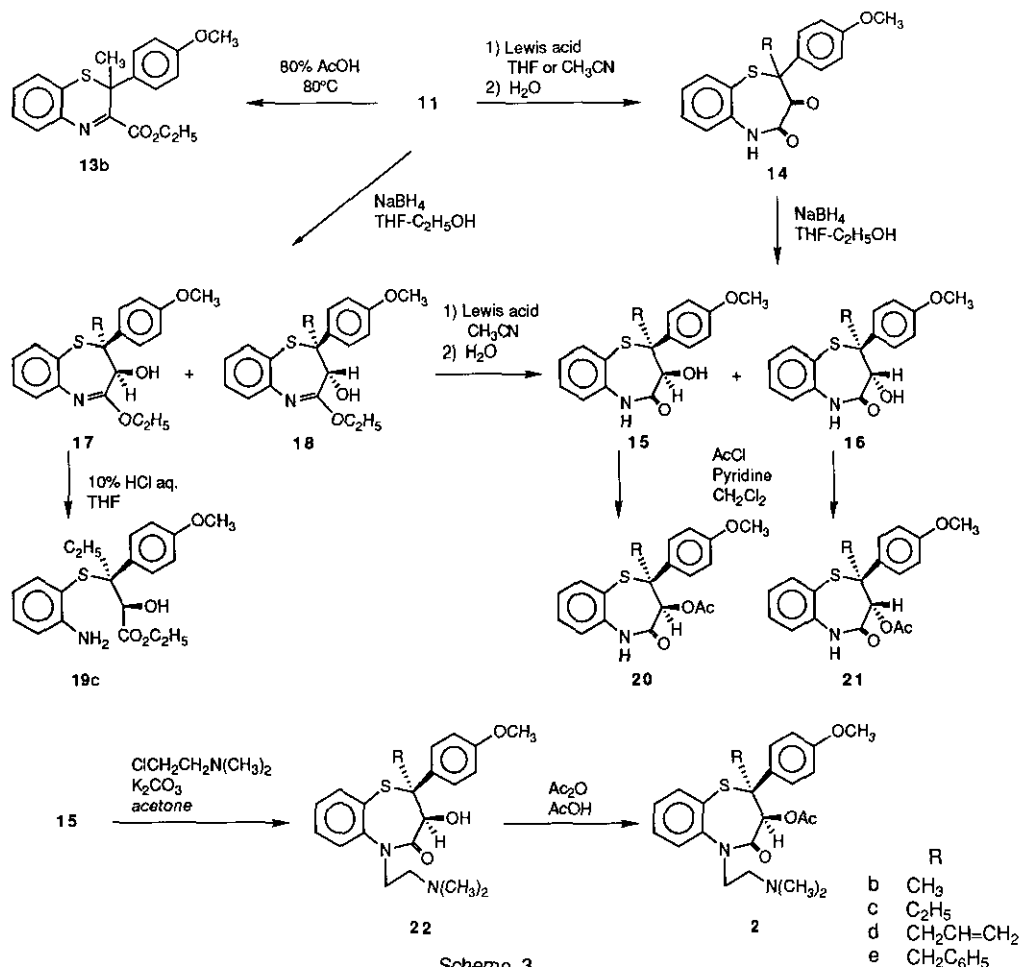
• The ratio was determined by ¹H-nmr.

** Judged from the tlc of the reaction mixture.

with the O-alkylated product (12) as shown in Scheme 2 and Table I.

Methylation of 10 with iodomethane and *n*-butyllithium in THF-hexamethylphosphoramide (HMPA) yielded 11b and 12b in a ratio of 3.8 : 1, whereas ethylation and allylation in the same reaction conditions gave 12c and 12d preferentially. When 10 was alkylated in ethanol using potassium hydroxide, 11b, 11d and 11e were obtained as a major product. It was unexpected that under several conditions examined, 11c couldn't be obtained predominantly. In the case of 12d with an allyl substituent, Claisen rearrangement readily occurred in hot toluene to give the desired compound (11d) in excellent yield.

Hydrolysis of 11b in aqueous acetic acid gave the undesirable benzothiazine derivative (13b)⁷ in quantitative yield, while Lewis acid treatment of 11 in THF or acetonitrile followed by an addition of water afforded the expected keto-lactam



Scheme 3

(14) in moderate yield. Reduction of 14 with sodium borohydride in THF-ethanol gave the cis⁸ lactam (15) stereoselectively as shown in Table II.

As an alternative route to the cis lactam (15), 11 was reduced with sodium borohydride first to give the cis isomer (17) also stereoselectively (Table III). All the cis (17) and trans⁸ isomers (18) were easily separated by column chromatography. The subsequent hydrolysis of 17 and 18 with Lewis acid⁹ afforded the corresponding cis (15) and trans (16) lactams in good yield (Scheme 3).

Table II. Reduction of 14 with NaBH₄ to 15 and 16

R	conditions	ratio* (15 : 16)	isolated yield(%)	
			15	16
CH ₃	THF-C ₂ H ₅ OH(1:1) -57°~rt, 2 h	32 : 1	93	
C ₂ H ₅	THF-C ₂ H ₅ OH(1:1) -57°~rt, 2 h	11 : 1	75	
CH ₂ =CH-CH ₂	THF-C ₂ H ₅ OH(1:1) -54°~rt, 1 h	10 : 1	82	
CH ₂ =CH-CH ₂	C ₂ H ₅ OH rt, 15 min	6.2 : 1	68	11

* The ratio was determined by ¹H-nmr.

Table III. Reduction of 11 with NaBH₄ in THF-C₂H₅OH to 17 and 18

R	isolated yield(%)	
	17	18
CH ₃	80	4.7
C ₂ H ₅	82	15
CH ₂ =CH-CH ₂	84	11
C ₆ H ₅ CH ₂	79	5.5

The cis configuration of the C₂-aryl group and the C₃-hydroxyl group of 15b was determined also by X-ray crystallographic analysis (Figure 2). The stereochemistry of 15c,d,e and 16c,d,e was presumed on the basis of the following. First, the major products of the sodium borohydride reduction of 11 and 14 should be cis isomers because hydride would attack the C₃-carbonyl group from the opposite side of the bulky C₂-aryl group. Secondly, in the ¹H-nmr spectra, the signal of the C₂-methyl protons (δ: 1.99) of the 3-acetoxy compound (21b) derived

from the trans lactam (**16b**) was observed in lower field (0.18 ppm) than that (δ : 1.81) of **16b**. The C₂-methyl signal (δ : 1.88) of the corresponding cis 3-acetoxy isomer (**20b**), on the contrary, was observed in slightly higher field (0.07 ppm) than that (δ : 1.95) of **15b**. This tendency was invariably observed in the chemical shifts of the methylene protons of the C₂-substituents of **16c,d,e** and **21c,d,e**, and **15c,d,e** and **20c,d,e** (Table IV).

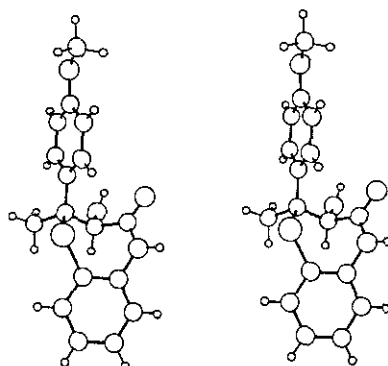


Figure 2 Stereoview of the structure of **15b**

Table IV. The chemical shifts (CDCl₃, δ) of the methyl or methylene protons of C₂-substituents of **15**, **16**, **20** and **21**

R	<u>cis</u>		<u>trans</u>	
	15	20	16	21
CH ₃	1.95	1.88	1.81	1.99
CH ₃ CH ₂	2.02 , 2.56	2.07 , 2.30	2.11 , 2.54	2.34 , 2.76
CH ₂ =CH-CH ₂	2.90 , 3.24	2.91 , 3.06	2.78 , 3.30	3.01 , 3.54
C ₆ H ₅ CH ₂	3.23 , 3.96	3.33 , 3.76	3.33 , 3.73	3.62 , 3.99

Finally, the cis lactam (**15**) was alkylated with 2-(dimethylamino)ethyl chloride and potassium carbonate in acetone,⁵ to give the N-(dimethylamino)ethyl compound (**22**). Heating of **22** with acetic anhydride in acetic acid afforded 2-substituted diltiazem derivatives (**2**) in excellent yield (Scheme 3).

The compounds prepared in the present study were tested for cerebral vasodilating activity by measuring the increase in blood flow in the vertebral artery of anesthetized dogs after intraarterial administration.^{2f,10} The activity of the hydrochlorides of **2b**, **2c**, **22b** and **22c** was comparable to that of racemic diltiazem

hydrochloride. The C_2 -substituents favorable to activity were thus found to be methyl and ethyl groups. Further pharmacological evaluation in detail are now in progress.

EXPERIMENTAL

All the melting points were uncorrected. Infrared spectra were taken with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. Nmr spectra were recorded with a Hitachi R-90H, a JEOL JNM-FX-200 or a JEOL JNM-GSX-400 spectrometer. Chemical shifts are given as δ values from tetramethylsilane as an internal standard. The following abbreviations are used; s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, dq=double quartet, m=multiplet. Mass spectra (EI) were recorded with a Hitachi RMU-6 or a JEOL JMS-HX 100 mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240B C, H, N analyzer and a Yokokawa IC-100 ion chromatographic analyzer. Preparative tlc was carried out on Kieselgel 60 F₂₅₄ (Merck). Kieselgel 60 (230-400 mesh) (Merck) or Silica Gel 60 K-230 (230-400 mesh) (Katayama) was used for flash column chromatography.

3-Acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (4)⁴ : Acetic anhydride (200 ml) was added to a solution of the alcohol (3) (60.2 g, 0.2 mol) in DMSO (400 ml) and toluene (1000 ml). The reaction mixture was stirred for 42 h at room temperature (rt), poured into ice-water and extracted with ethyl acetate. The ethyl acetate layer was thoroughly washed with water, dried over $MgSO_4$ and evaporated to give a yellow solid, which was triturated with ether to give 4 (43.7 g, 64%) as pale yellow crystals. mp 206-207°C. Ir (nujol, cm^{-1}) : 3170, 3080, 3040, 1765, 1650. Nmr (DMSO- d_6 , δ) : 2.03 (3H, s), 3.79 (3H, s). 6.9-7.8 (8H, m), 10.78 (1H, s). Ms (m/z) : 341 (M^+), 299, 238 (base). Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10; S, 9.39. Found : C, 63.38; H, 4.38; N, 4.10; S, 9.21.

3-Acetoxy-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (5)⁵ : A mixture of 4 (5.12 g, 15.0 mmol), 2-(dimethylamino)ethyl chloride (2.42 g, 22.5 mmol) and K_2CO_3 (2.50 g, 18.1 mmol) in acetone (80 ml) was refluxed for 20 h and filtered. The filtrate and washings were concentrated, diluted with ethyl acetate and washed with water. The ethyl acetate layer was then extracted with 10% HCl, which was basified with saturated $NaHCO_3$ solution (satd

NaHCO_3) and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO_4 , concentrated and purified on a silica gel column ($\text{CHCl}_3\text{-C}_2\text{H}_5\text{OH}$ (20:1)) to give **5** (3.22 g, 52%) as an amorphous powder. Ir (CHCl_3 , cm^{-1}) : 1760, 1640. Nmr (CDCl_3 , δ) : 2.03 (3H, s), 2.25 (6H, s), 2.3-2.9 (2H, m), 3.83 (3H, s), 3.5-4.0 (1H, m), 4.2-4.8 (1H, m), 6.8-7.8 (8H, m). Ms (m/z) : 412 (M^+), 72 (base).

(2RS,3SR)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-hydroxymethyl-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (**6**) : A solution of $n\text{-C}_4\text{H}_9\text{Li}$ in hexane (4 ml, 6.4 mmol) was added dropwise to a solution of **5** (1.0 g, 2.42 mmol) in THF (30 ml) at -60°C under an argon atmosphere. After stirring for 30 min at the same temperature, paraformaldehyde (0.74 g) was added and the whole was stirred for 3.5 hr at -60°C rt. The reaction was quenched by addition of brine and the mixture was extracted with CHCl_3 . The organic layer was washed with brine, dried, concentrated and then purified on a silica gel column ($\text{CHCl}_3\text{-C}_2\text{H}_5\text{OH}$ (40:1)) to give **6** (0.76 g, 78%) as colorless crystals. Analytical sample was obtained by recrystallization from $\text{C}_2\text{H}_5\text{OH}$ -ether. mp $132\text{-}133^\circ\text{C}$. Ir (nujol, cm^{-1}) : 3500, 1660. Nmr (CDCl_3 , δ) : 2.27 (6H, s), 2.3-3.0 (4H, m, $\text{OH}\times 2$), 3.4-3.9 (1H, m), 3.82 (3H, s), 3.91 (1H, d, $J=12$ Hz), 3.97 (1H, broad s), 4.24 (1H, d, $J=12$ Hz), 4.3-4.6 (1H, m), 6.8-7.8 (8H, m). Ms (m/z) : 402 (M^+), 72 (base). Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$: C, 62.67; H, 6.51; N, 6.96; S, 7.97. Found : C, 62.63; H, 6.53; N, 7.01; S, 8.25.

(2RS,3SR)-3-Acetoxy-2-acetoxymethyl-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (**2a**) : A solution of **6** (0.35 g, 0.87 mmol) in Ac_2O (10 ml) was heated at 100°C for 2 h and concentrated. Ethyl acetate and satd NaHCO_3 were added to the residue. The ethyl acetate layer was separated, washed with brine, dried over MgSO_4 , concentrated and purified on a silica gel column ($\text{CHCl}_3\text{-C}_2\text{H}_5\text{OH}$ (40:1)) to give **2a** (0.28 g, 66%) as colorless crystals, which was triturated with ether and dried. mp $138\text{-}139^\circ\text{C}$. Ir (nujol, cm^{-1}) : 1740, 1670. Nmr (CDCl_3 , δ) : 1.86 (3H, s), 1.99 (3H, s), 2.30 (6H, s), 2.3-2.9 (2H, m), 3.6-4.0 (1H, m), 3.84 (3H, s), 4.2-4.5 (1H, m), 4.50 (1H, d, $J=12$ Hz), 4.73 (1H, d, $J=12$ Hz), 5.02 (1H, s), 6.8-7.8 (8H, m). Ms (m/z) : 486 (M^+), 71 (base). Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_6\text{S}$: C, 61.71; H, 6.21; N, 5.76; S, 6.59. Found : C, 61.67; H, 6.18; N, 5.76; S, 6.85.

3-Acetoxy-4-ethoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine (**10**) : The enol acetate (**4**) (1.71 g, 5 mmol) was added to a solution of $(\text{C}_2\text{H}_5)_3\text{O}^+\text{BF}_4^-$ (2.30 g, 12.1 mmol) in CH_2Cl_2 (13 ml) and the suspension was stirred at rt overnight. 50% K_2CO_3

solution (2 ml) was added to the reaction mixture under ice-cooling and the organic layer was separated by decantation, dried over MgSO_4 and then evaporated to give **10** (1.90 g, quant.) as a crystalline powder. This was used for the next reaction without further purification. Ir (nujol, cm^{-1}) : 1755, 1625. Nmr (CDCl_3 , δ) : 1.38 (3H, t, $J=7$ Hz), 2.03 (3H, s), 3.80 (3H, s), 4.41 (2H, q, $J=7$ Hz), 6.8-7.6 (8H, m). Ms (m/z) : 369 (M^+), 327, 151 (base).

(RS)-4-Ethoxy-2-(4-methoxyphenyl)-2-methyl-1,5-benzothiazepin-3(2H)-one (11b) and 4-Ethoxy-3-methoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine (12b) : A solution of KOH (0.92 g, 16.4 mmol) in $\text{C}_2\text{H}_5\text{OH}$ (14 ml) was added to a solution of **10** (2.24 g, 6.06 mmol) in $\text{C}_2\text{H}_5\text{OH}$ (10 ml) at 4°C . Iodomethane (6.52 g, 45.9 mmol) was then added and the yellow reaction mixture was stirred for 5 h at rt and concentrated. The residue was partitioned between ethyl acetate and water, and the organic layer separated was washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine, dried over MgSO_4 , concentrated and purified on a silica gel column (hexane-ethyl acetate (15:1)) to give a mixture (1.59 g, 77%) of **11b** and **12b** (**11b**:**12b** = 2.4:1).¹¹ The mixture was recrystallized from hexane to afford **11b** (1.04 g, 50%) as pale yellow prisms. mp $97-98.5^\circ\text{C}$. Ir (nujol, cm^{-1}) : 1710, 1640. Nmr (CDCl_3 , δ) : 1.37 (3H, t, $J=7$ Hz), 1.75 (3H, s), 3.78 (3H, s), 4.42 (2H, q, $J=7$ Hz), 6.7-7.6 (8H, m). Ms (m/z) : 341 (M^+), 313. Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{S}$: C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found : C, 67.10; H, 5.12; N, 4.37; S, 9.48.

The residue obtained from the mother liquor was purified on preparative tlc (hexane- CHCl_3 (1:1)) to give **12b** (0.28 g, 14%) as a yellow oil. Ir (liquid, cm^{-1}) : 1625. Nmr (CDCl_3 , δ) : 1.48 (3H, t, $J=7$ Hz), 3.45 (3H, s), 3.80 (3H, s), 4.50 (2H, q, $J=7$ Hz), 6.7-7.8 (8H, m). Ms (m/z) : 341 (M^+), 326, 312, 151 (base).

(RS)-2-Ethyl-4-ethoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-3(2H)-one (11c) and 3,4-Diethoxy-2-(4-methoxyphenyl)-1,5-benzothiazepine(12c) : A solution of $n\text{-C}_4\text{H}_9\text{Li}$ in hexane (1.06 ml, 1.66 mmol) was added dropwise to a solution of **10** (278 mg, 0.75 mmol) in THF (1.5 ml) - HMPA (0.16 ml) at -50°C under an argon atmosphere and the reddish brown solution was stirred for 30 min at the same temperature. $\text{C}_2\text{H}_5\text{I}$ (0.42 ml, 5.27 mmol) was added to the solution and the whole was stirred for 6 days at rt. Saturated NH_4Cl solution was added and the mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine, dried over MgSO_4 , concentrated and then chromatographed to give a yellow oil (155 mg, 58%. **11c**:**12c** = 1:3.5).¹¹ The oil was purified on preparative

tlc (hexane- CHCl_3 (2:1)) to afford **11c** (32 mg, 12%) as colorless crystals and **12c** (112 mg, 42%) as a pale yellow oil. **11c**; mp 118.5–119°C (hexane). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3\text{S}$: C, 67.58; H, 5.95; N, 3.94; S, 9.02. Found : C, 67.65; H, 5.94; N, 3.86; S, 8.99. **12c**; Ir (liquid, cm^{-1}) : 1630. Ms (m/z) : 355 (M^+), 151 (base). Compounds **11d** and **12d**, and **11e** and **12e** were prepared similarly, and the yields and ratios are summarized in Table I. **11d**; mp 79–80°C (hexane). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_3\text{S}$: C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found : C, 68.70; H, 5.74; N, 3.81; S, 8.72. **12d**; a yellow oil. Ir (liquid, cm^{-1}) : 1625. Ms (m/z) : 367 (M^+). **11e**; mp 91.5–93.5°C (ether-hexane). Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_3\text{S}$: C, 71.92; H, 5.55; N, 3.35; S, 7.68. Found : C, 71.99; H, 5.60; N, 3.32; S, 7.88. **12e**; a pale yellow oil. Ir (liquid, cm^{-1}) : 1635. Ms (m/z) : 417 (M^+), 326 (base).

Preparation of **11d** through Claisen rearrangement of **12d** : A solution of KOH (3.86 g, 68.8 mmol) in $\text{C}_2\text{H}_5\text{OH}$ (50 ml) was added dropwise to a cooled solution of **10** (10.2 g, 27.5 mmol) in $\text{C}_2\text{H}_5\text{OH}$ (50 ml) and the yellow solution was stirred for 30 min under ice-cooling. Allyl bromide (4.76 ml, 55.1 mmol) was then added and the reaction mixture was stirred for 4 h at rt, worked up as usual and chromatographed on a silica gel column (hexane-ethyl acetate (20:1~10:1)) to give a yellow oil (8.92 g, 88%. **11d**:**12d** = 2.9:1).¹¹ The oil was dissolved in toluene (90 ml), refluxed for 3 h and evaporated to give yellow crystals. Recrystallization from hexane afforded **11d** (8.02 g, 90%) as pale yellow prisms. mp 79–80°C. All spectral data of **11d** thus obtained were identical with those of an authentic sample.

(**RS**)-2-(4-Methoxyphenyl)-2-methyl-1,5-benzothiazepine-3,4(2H,5H)-dione (**14b**) : A pale yellow solution of **11b** (1.71 g, 5 mmol) in CH_2Cl_2 (5 ml) and $(\text{CH}_3)_2\text{S}$ (5 ml) was added dropwise to a solution of AlCl_3 (2.0 g, 15 mmol) in CH_2Cl_2 (5 ml) and $(\text{CH}_3)_2\text{S}$ (5 ml) under ice-cooling. The reaction mixture was stirred for 2 h at 0–2°C, poured into ice-water and extracted with CH_2Cl_2 . The organic layer was washed with satd NaHCO_3 and brine, dried over MgSO_4 and evaporated to give a solid. Recrystallization from ethyl acetate-hexane afforded **14b** (1.30 g, 83%) as colorless crystals. mp 191.5–192°C. Ir (nujol, cm^{-1}) : 3180, 1710, 1650. Nmr (CDCl_3 , δ) : 1.81 (3H, s), 3.79 (3H, s), 6.8–7.7 (8H, m), 8.64 (1H, broad s). Ms (m/z) : 313 (M^+), 285, 134 (base). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$: C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found : C, 65.07; H, 4.86; N, 4.43; S, 10.33.

Compound **14e** was prepared similarly, y. 22%. mp 192–193°C (ethyl acetate-hexane). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_3\text{S}$: C, 70.93; H, 4.92; N, 3.60; S, 8.23. Found : C,

70.72; H, 4.71; N, 3.52; S, 8.23.

(RS)-2-Allyl-2-(4-methoxyphenyl)-1,5-benzothiazepine-3,4(2H,5H)-dione (14d) : Tri-methylsilyl chloride (0.55 ml, 4.3 mmol) was added dropwise to a mixture of 11d (0.79 g, 2.15 mmol) and NaI (0.64 g, 4.3 mmol) in CH_3CN (15 ml) and the yellow suspension was stirred for 20 min at rt, poured into ice-water and extracted with ethyl acetate. The ethyl acetate layer was washed with satd NaHCO_3 and brine, dried over MgSO_4 , concentrated and purified on a silica gel column (hexane-ethyl acetate (4:1)) to give 14d (0.58 g, 80%) as colorless needles. mp 175-176°C (ethyl acetate-hexane). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3\text{S}$: C, 67.24; H, 5.05; N, 4.13; S, 9.45. Found : C, 67.12; H, 4.97; N, 4.07; S, 9.63.

Compound 14c was prepared similarly, y. 71%. mp 213.5-214.5°C (ethyl acetate). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{S}$: C, 66.03; H, 5.23; N, 4.28; S, 9.79. Found : C, 66.20; H, 5.18; N, 4.60; S, 9.97.

(2RS,3RS)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-2-methyl-1,5-benzothiazepin-4(5H)-one (15b) : A solution of 14b (213 mg, 0.68 mmol) in THF (2.5 ml) and $\text{C}_2\text{H}_5\text{OH}$ (2.5 ml) was cooled to -57°C. NaBH_4 (51 mg, 1.36 mmol) was added portionwise and the mixture was stirred for 2 h at -57°C_{rt}. Brine (10 ml) and ethyl acetate (20 ml) were added to the reaction mixture and separated. The aqueous layer was extracted with ethyl acetate and the ethyl acetate layers were combined, washed with water and brine, dried over MgSO_4 and evaporated to give colorless crystals (quantitative, 15b:16b = 32:1).¹¹ Recrystallization from $\text{C}_2\text{H}_5\text{OH}$ afforded 15b (199 mg, 93%) as colorless prisms, mp 190-191°C. Ir (nujol, cm^{-1}) : 3330, 1680, 1640 (sh). Nmr (CDCl_3 , δ) : 1.95 (3H, s), 2.78 (1H, d, $J=9.7$ Hz, OH), 3.78 (3H, s), 3.98 (1H, d, $J=9.7$ Hz), 6.6-7.7 (8H, m), 8.70 (1H, broad s). Ms (m/z) : 315 (M^+), 297. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3\text{S}$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found : C, 64.71; H, 5.58; N, 4.61; S, 10.33.

Compounds 15c, 15d and 16d were prepared similarly and the isolated yields of these compounds are summarized in Table II. 15c; mp 197.5-198.5°C (toluene). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{S}$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found : C, 65.37; H, 5.79; N, 4.29; S, 9.93. 15d; mp 172-174.5°C ($\text{C}_2\text{H}_5\text{OH}$). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{S}$: C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found : C, 66.71; H, 5.55; N, 4.17; S, 9.55. 16d; mp 133-134°C (toluene-hexane). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{S} \cdot 1/3\text{C}_6\text{H}_5\text{CH}_3$: C, 68.85; H, 5.87; N, 3.76; S, 8.62. Found : C, 69.02; H, 5.82; N, 3.62; S, 8.55.

Reduction of 11b with NaBH₄ to 17b and 18b : A solution of 11b (0.75 g, 2.2 mmol) in THF (16 ml) and C₂H₅OH (4 ml) was cooled to -58°C. NaBH₄ (83 mg, 2.2 mmol) was added and the pale yellow solution was stirred for 19 h at -58~-27°C. The reaction solution was worked up in a similar manner described above and purified on a silica gel column (hexane-ethyl acetate (10:1)) to give 17b (0.61 g, 80%) as colorless needles and 18b (36 mg, 4.7%) as a colorless viscous oil. 17b; mp 95-96°C (isopropyl ether-hexane). Ir (nujol, cm⁻¹) : 3600-3100, 1635, 1615. Nmr (CDCl₃, δ) : 1.30 (3H, t, J=7 Hz), 1.91 (3H, s), 1.92 (1H, d, J=11.6 Hz, OH), 3.82 (3H, s), 4.07 (1H, d, J=11.6 Hz), 4.37, 4.39 (2H, dq, J=7 Hz), 6.8-7.8 (8H, m). Ms (m/z) : 343 (M⁺), 314, 299, 164 (base). Anal. Calcd for C₁₉H₂₁NO₃S : C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found : C, 65.99; H, 6.19; N, 4.21; S, 9.37. 18b; Ir (liquid, cm⁻¹) : 3600-3100, 1635. Nmr (CDCl₃, δ) : 1.46 (3H, t, J=7 Hz), 1.82 (3H, s), 1.95 (3H, s), 2.70 (1H, broad s, OH), 3.75 (3H, s), 4.3-4.7 (3H, m), 6.6-7.8 (8H, m). Ms (m/z) : 343 (M⁺), 180, 164 (base).

Compounds 17c and 18c, 17d and 18d, and 17e and 18e were prepared similarly and the isolated yields of these compounds are summarized in Table III. 17c; mp 106-107°C (hexane). Anal. Calcd for C₂₀H₂₃NO₃S : C, 67.20; H, 6.48; N, 3.92; S, 8.97. Found : C, 67.43; H, 6.35; N, 3.91; S, 9.01. 18c; an oil. Ir (liquid, cm⁻¹) : 3600-3100, 1640. Ms (m/z) : 358 (M⁺+1), 178 (base). 17d; mp 96.5-97.5°C (hexane). Anal. Calcd for C₂₁H₂₃NO₃S : C, 68.27; H, 6.27; N, 3.79; S, 8.68. Found : C, 68.17; H, 6.25; N, 3.67; S, 8.66. 18d; an oil. Ir (liquid, cm⁻¹) : 3600-3100, 1640. Ms (m/z) : 369 (M⁺), 180 (base). 17e; mp 140.5-141°C (hexane). Anal. Calcd for C₂₅H₂₅NO₃S : C, 71.57; H, 6.01; N, 3.34; S, 7.64. Found : C, 71.66; H, 5.89; N, 3.25; S, 7.64. 18e; mp 158-158.5°C (toluene-hexane). Anal. Calcd for C₂₅H₂₅NO₃S : C, 71.57; H, 6.01; N, 3.34; S, 7.64. Found : C, 71.52; H, 5.96; N, 3.21; S, 7.83.

(2RS,3RS)-2-Ethyl-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (15c) : Trimethylsilyl chloride (2.17 ml, 17.1 mmol) was added dropwise to a mixture of 17c (3.05 g, 8.53 mmol) and NaI (2.56 g, 17.1 mmol) in CH₃CN (70 ml) under ice-cooling and the suspension was stirred for 16 h at rt. The reaction mixture was diluted with ethyl acetate (300 ml), washed successively with water, satd NaHCO₃, diluted Na₂S₂O₃ solution and brine, dried over MgSO₄ and then evaporated to give colorless crystals, which were triturated with toluene-hexane to give pure 15c (2.76 g, 98%), mp 197.5-198.5°C. Compounds 15b (87%), 15d (92%), 15e (95%), 16b (75%), 16c (94%), and 16e (95%) were prepared similarly. 15e; mp

224-224.5°C (C_2H_5OH). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 70.56; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.31; H, 5.29; N, 3.75; S, 8.22. 16b; mp 191.5-192°C (ethyl acetate-hexane). Ir (nujol, cm^{-1}): 3400-3000, 1650. Nmr ($CDCl_3$, δ): 1.81 (3H, s), 3.77 (3H, s), 3.77 (1H, d, $J=7$ Hz), 4.53 (1H, d, $J=7$ Hz), 6.7-7.7 (8H, m), 8.92 (1H, broad s). Ms (m/z): 315 (M^+), 164, 135 (base). 16c; mp 151-151.5°C (ethyl acetate-hexane). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found: C, 65.54; H, 5.80; N, 4.15; S, 9.84. 16e; mp 189.5-190°C (toluene-hexane). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 70.56; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.36; H, 5.32; N, 3.70; S, 8.27.

(2RS,3RS)-3-Acetoxy-2-(4-methoxyphenyl)-2-methyl-1,5-benzothiazepin-4(5H)-one (20b): A solution of acetyl chloride (0.43 ml, 0.34 mmol) in CH_2Cl_2 (10 ml) was added to a mixture of 15b (97 mg, 0.31 mmol) in pyridine (0.5 ml) under ice-cooling. The pale yellow reaction mixture was stirred for 23 h at rt, diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated to give colorless crystals. Recrystallization from ethyl acetate-hexane afforded pure 20b (94 mg, 85%) as colorless needles, mp 190.5-191.5°C. Ir (nujol, cm^{-1}): 3220, 3140, 3080, 1750, 1685. Nmr ($CDCl_3$, δ): 1.88 (3H, s), 1.95 (3H, s), 3.82 (3H, s), 4.89 (1H, s), 6.8-7.7 (8H, m), 7.80 (1H, broad s). Ms (m/z): 357 (M^+), 164 (base). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 63.85; H, 5.36; N, 3.92; S, 8.97. Found: C, 63.74; H, 5.21; N, 3.86; S, 8.88.

Compounds 20c (89%), 20d (90%), 20e (84%), 21b (70%), 21c (83%), 21d (73%), and 21e (84%) were prepared similarly, and recrystallized from ethyl acetate-hexane. 20c; mp 218.5-220°C. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.31; H, 5.82; N, 3.47; S, 8.74. 20d; mp 127.5-130°C. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 65.78; H, 5.52; N, 3.65; S, 8.36. Found: C, 65.99; H, 5.65; N, 3.59; S, 8.19. 20e; mp 192.5-194.0°C. Anal. Calcd for $C_{25}H_{23}NO_4 \cdot 1/3 CH_3CO_2C_2H_5$: C, 68.33; H, 5.59; N, 3.03; S, 6.93. Found: C, 68.10; H, 5.57; N, 3.09; S, 7.14. 21b; mp 207.5-210°C. Ir (KBr, cm^{-1}): 3440, 3260, 1745, 1690. Nmr ($CDCl_3$, δ): 1.99 (6H, s), 3.79 (3H, s), 5.35 (1H, s), 6.7-7.4 (9H, m). Ms (m/z): 357 (M^+), 298, 164 (base). 21c; mp 234.5-248.5°C (decomp). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.44; H, 5.69; N, 3.67; S, 8.48. 21d; mp 238-238.5°C. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 65.78; H, 5.52; N, 3.65; S, 8.36. Found: C, 65.55; H, 5.59; N, 3.63; S, 8.43. 21e; mp 251.5-253°C. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 69.26; H, 5.35; N, 3.23; S, 7.40. Found: C, 69.09; H,

5.31; N, 3.00; S, 7.20.

(2RS,3RS)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-2-methyl-1,5-benzothiazepin-4(5H)-one hydrochloride (22b.HCl)⁵ : A suspension of 15b (2.60 g, 8.24 mmol), ClCH₂CH₂N(CH₃)₂.HCl (1.42 g, 9.89 mmol) and K₂CO₃ (3.42 g, 24.7 mmol) in acetone (70 ml) was refluxed for 22 h under vigorous stirring. The reaction mixture was concentrated, dissolved in ethyl acetate and water and then separated. The organic layer was washed with brine, dried over MgSO₄ and evaporated to give an oily residue, which was dissolved in ethyl acetate (30 ml). A solution of 2.3 N dry HCl in ethyl acetate (7 ml) was added dropwise to the solution under ice-cooling and colorless crystals separated were collected by filtration. Recrystallization from C₂H₅OH afforded pure 22b.HCl (3.10 g, 86%), mp 251-252.5°C (decomp). Ir (nujol, cm⁻¹) : 3200-2400, 1645. Nmr (DMSO-d₆, δ) : 1.70 (3H, s), 2.79 (6H, s), 2.9-4.7 (6H, m), 3.77 (3H, s), 6.89 (2H, d, J=9 Hz), 7.2-7.8 (6H, m), 10.95 (1H, broad s). Ms (m/z): 386 (M⁺-HCl), 316, 164, 71, 58 (base). Anal. Calcd for C₂₁H₂₇ClN₂O₃S : C, 59.63; H, 6.43; Cl, 8.38; N, 6.62; S, 7.58. Found : C, 59.51; H, 6.37; Cl, 8.48; N, 6.60; S, 7.53.

Compounds 22c.HCl (93%), 22d.HCl (83%) and 22e.HCl (91%) were prepared similarly, and recrystallized from C₂H₅OH. 22c.HCl; mp 242.5-243°C (decomp). Anal. Calcd for C₂₂H₂₉ClN₂O₃S : C, 60.47; H, 6.69; Cl, 8.11; N, 6.41; S, 7.34. Found : C, 60.37; H, 6.71; Cl, 8.28; N, 6.30; S, 7.53. 22d.HCl; mp 171.5-172.5°C (melt), 212-215°C (decomp). Anal. Calcd for C₂₃H₂₉ClN₂O₃S·1/4H₂O : C, 60.91; H, 6.56; Cl, 7.82; N, 6.18; S, 7.07. Found : C, 60.70; H, 6.77; Cl, 7.89; N, 6.21; S, 7.10. 22e.HCl; mp 217.5-218.5°C. Anal. Calcd for C₂₇H₃₁ClN₂O₃S : C, 64.98; H, 6.26; Cl, 7.10; N, 5.61; S, 6.43. Found : C, 64.73; H, 6.27; Cl, 7.06; N, 5.61; S, 6.42.

(2RS,3RS)-3-Acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-2-methyl-1,5-benzothiazepin-4(5H)-one hydrochloride (2b.HCl) : A mixture of 22b.HCl (2.00 g, 4.73 mmol) in AcOH (20 ml) and Ac₂O (20 ml) was refluxed for 2 h and evaporated to dryness to give a crystalline residue. Recrystallization from C₂H₅OH - isopropyl ether afforded colorless crystals (2.00 g, 91%), mp 218.5-219.5°C. Ir (nujol, cm⁻¹) : 2560, 2500, 2440, 1735, 1670. Nmr (DMSO-d₆, δ) : 1.78 (3H, s), 1.94 (3H, s), 2.87 (6H, s), 3.1-3.7 (2H, m), 3.83 (3H, s), 4.4-4.6 (2H, m), 4.63 (1H, s), 6.8-7.0 (2H, d-like, J=10 Hz), 7.2-7.8 (6H, m), 12.88 (1H, broad s). Ms (m/z) : 428 (M⁺-HCl), 175, 164, 135, 71, 58 (base). Anal. Calcd for C₂₃H₂₉ClN₂O₄S : C, 59.41; H, 6.29; Cl, 7.62; N, 6.02; S, 6.89. Found : C, 59.30; H,

6.38; Cl, 7.80; N, 5.94; S, 7.03.

Compounds 2c·HCl (91%), 2d·HCl (82%) and 2e·HCl (92%) were prepared similarly and recrystallized from C₂H₅OH-isopropyl ether. 2c·HCl; mp 211-212°C. Anal. Calcd for C₂₄H₃₁ClN₂O₄S : C, 60.18; H, 6.52; Cl, 7.40; N, 5.85; S, 6.69. Found : C, 59.89; H, 6.62; Cl, 7.41; N, 5.86; S, 6.86. 2d·HCl; mp 212-212.5°C. Anal. Calcd for C₂₅H₃₁ClN₂O₄S : C, 61.15; H, 6.36; Cl, 7.22; N, 5.70; S, 6.53. Found : C, 60.90; H, 6.59; Cl, 7.15; N, 5.63; S, 6.47. 2e·HCl; mp 231-234°C (decomp). Anal. Calcd for C₂₉H₃₃ClN₂O₄S : C, 64.37; H, 6.15; Cl, 6.55; N, 5.18; S, 5.93. Found : C, 64.49; H, 6.31; Cl, 6.45; N, 5.10; S, 5.96.

X-Ray Crystallographic Analysis of Compound 6 : Crystal data C₂₁H₂₆N₂O₄S, M=402.513, monoclinic, a=8.598 (1), b=15.543 (2), c=8.452 (1) Å, β=115.77 (5)°, V=1017.0 (2) Å³, Z=2, Space group P2₁, Dcalc.=1.314 kg/m³, μ=16.25 cm⁻¹, CuKα radiation λ=1.5418 Å. Diffraction experiments were performed on a diffractometer (AFC5/RIGAKU). Cell parameters were refined using setting angles of 2θ reflections in the range of 30° < 2θ < 60°. Intensity data were collected in the range of 2θ < 130° using ω/2θ scan technique. The structure was solved by the direct method using MULTAN, and refined by the block-diagonal matrix least square's method using anisotropic temperature factors for all non-hydrogen atoms and isotropic ones for all hydrogen atoms, which were located on a difference Fourier map. The final R and W_R values are 0.057 and 0.063 (√W = 1/σ(Fobs)).

X-Ray Crystallographic Analysis of Compound 15b : Crystal data C₁₇H₁₇NO₃S, M=315.391, monoclinic, a=10.857 (1), b=8.176 (1), c=17.798 (1) Å, β=102.17 (1)°, V=1544.37 (2) Å³, Z=2, Space group P2₁/c, Dcalc.=1.356 kg/m³, μ=19.18 cm⁻¹, CuKα radiation λ=1.5418 Å. Diffraction experiments and structure analysis were carried out by the same procedure described above. The final R and W_R values are 0.063 and 0.061 (√W = 1/σ(Fobs)).

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 7. **8**; mp 151-152°C. Ms (m/z) : 327 (M^+), 134 (base). **9**; mp 115-116°C. Ms (m/z) : 327 (M^+), 151 (base). **13b**; an oil. Ir (liquid, cm^{-1}) : 1720. Ms (m/z) : 341 (M^+), 268 (base).
 8. In this paper, the term "cis or trans" represents the stereochemical relation between the C_2 -aryl group and the C_3 -hydroxyl group. The importance of the 2,3-cis stereochemistry of diltiazem for pharmacological activity has already been established : T. Nagao, M. Sato, H. Nakajima, and A. Kiyomoto, Chem. Pharm. Bull., 1973, **21**, 92.
 9. Hydrolysis of **17c** with aqueous HCl in THF at rt afforded **19c** in 89% yield. mp 125-126°C. Ms (m/z) : 375 (M^+), 177 (base).
 10. The pharmacological tests were performed by Dr. T. Nagao and his co-workers in the Biological Research Laboratory of our company.
 11. The ratio was determined by 1H -nmr.

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