SYNTHESIS OF 2-SUBSTITUTED DERIVATIVES OF DILTIAZEM†

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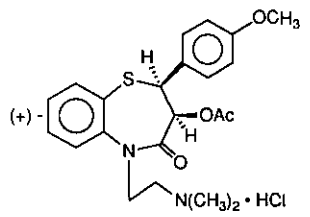
Abstract ——— Titled compounds, **2**a,b,c,d and e, were efficiently synthesized from 3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (**4**) through alkylation at the C_2-position followed by stereoselective reduction of the C_3-carbonyl group.

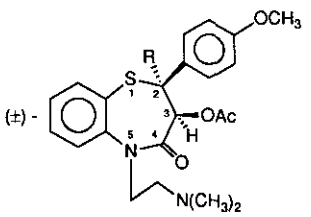
Diltiazem hydrochloride, (+)-(2S,3S)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride (**1**),[1] is a representative calcium antagonist and has been widely used as an effective antianginal and antihypertensive agent all over the world. A 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 C_2 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**



diltiazem hydrochloride

1



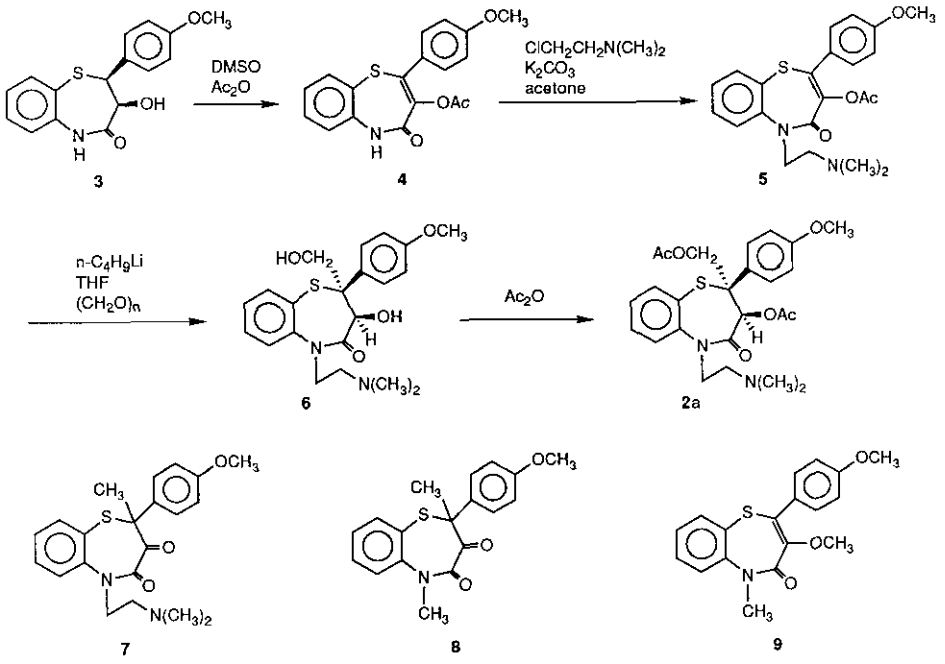
2

R	
a	CH_2OAc
b	CH_3
c	C_2H_5
d	$CH_2CH{=}CH_2$
e	$CH_2C_6H_5$

†Dedicated to the memory of Professor Tetsuji Kametani.

with 2-(dimethylamino)ethyl chloride in acetone using potassium carbonate[5] 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 C_2-aryl group and the C_3-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 C_2-position of **5**, possibly reduced the C_3-carbonyl group, consequently giving the cis isomer. Such a stereocontrolled 1,3-diol synthesis has scarcely been reported[6] 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

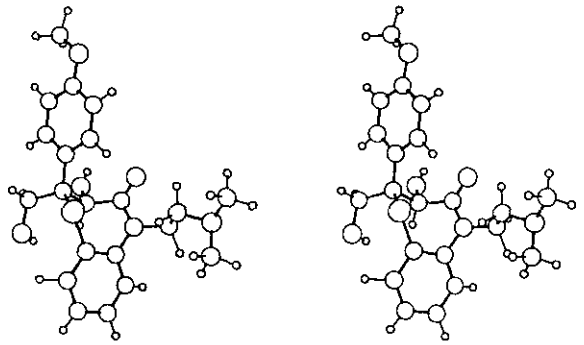
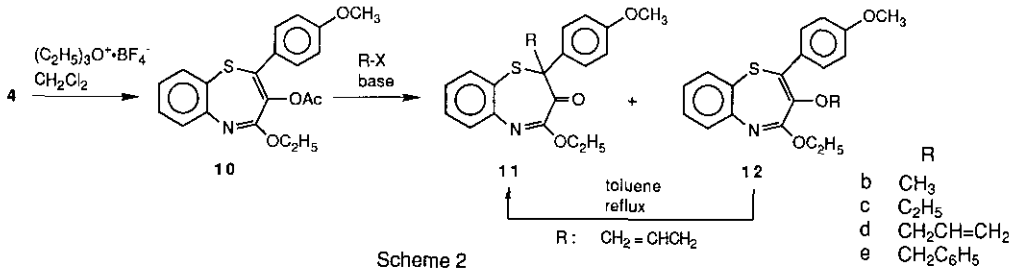


Figure 1 Stereoview of the structure of **6**

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_3I	n-C_4H_9Li	THF-hexane-HMPA	80	3.8 : 1	52	
	KOH	C_2H_5OH	77	2.4 : 1	50	14
C_2H_5I	n-C_4H_9Li	THF-hexane-HMPA	58	1 : 3.5	12	42
	KOH	C_2H_5OH	86	1 : 1.4	25	
	KOH	DMF	73	1 : 2.8	22	42
	LiOH	DMF	86	1 : 1.4		
$(C_2H_5)_2SO_4$	n-C_4H_9Li	THF-hexane		1 : >10**		
CH_2=CH-CH_2Br	n-C_4H_9Li	THF-hexane-HMPA	49	1 : 2.1	14	24
	KOH	C_2H_5OH	88	2.9 : 1		
$C_6H_5CH_2Br$	n-C_4H_9Li	THF-hexane-HMPA			33	27
	KOH	C_2H_5OH	93	12.5 : 1		

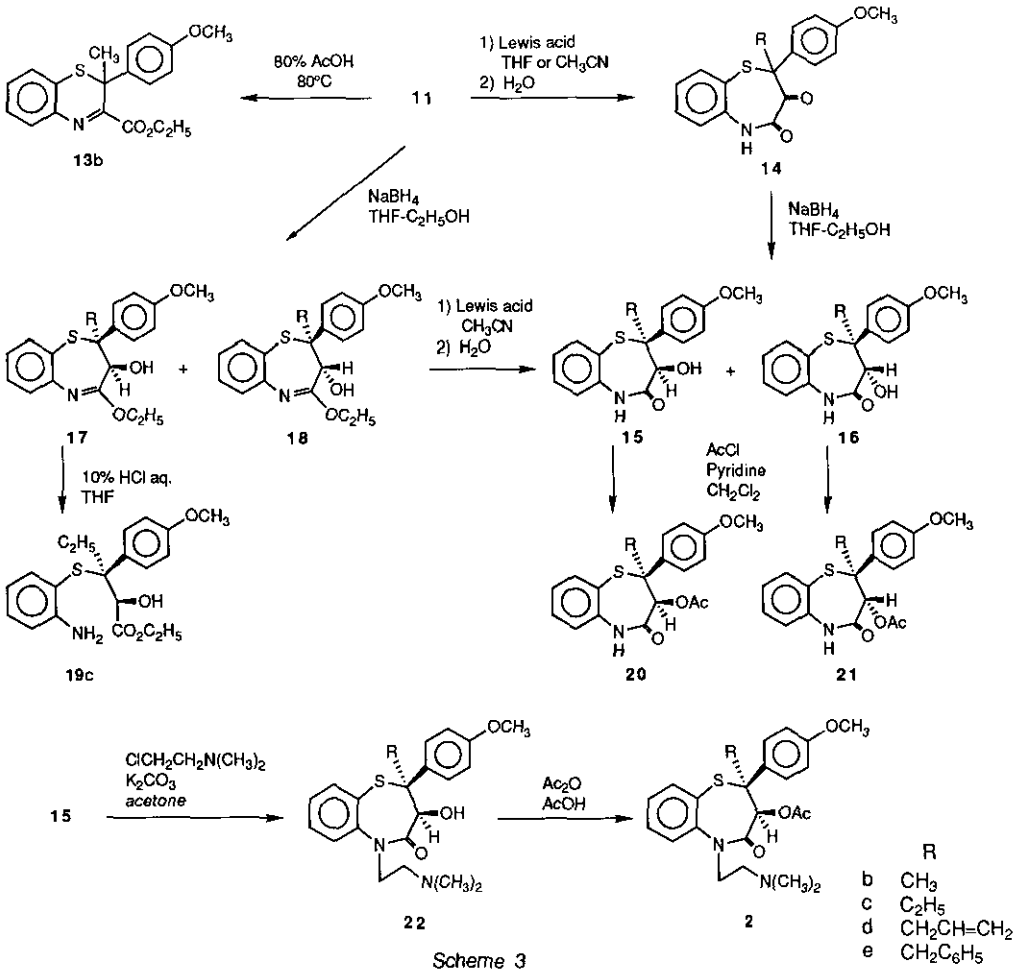
* The ratio was determined by ^{1}H-nmr.

** 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 cis[8] 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 trans[8] isomers (**18**) were easily separated by column chromatography. The subsequent hydrolysis of **17** and **18** with Lewis acid[9] afforded the corresponding cis (**15**) and trans (**16**) lactams in good yield (Scheme 3).

Table II. Reduction of **14** with $NaBH_4$ to **15** and **16**

R	conditions	ratio* (**15** : **16**)	isolated yield(%) **15**	**16**
CH_3	THF-C_2H_5OH(1:1) -57°∿rt, 2 h	32 : 1	93	
C_2H_5	THF-C_2H_5OH(1:1) -57°∿rt, 2 h	11 : 1	75	
CH_2=CH-CH_2	THF-C_2H_5OH(1:1) -54°∿rt, 1 h	10 : 1	82	
CH_2=CH-CH_2	C_2H_5OH rt, 15 min	6.2 : 1	68	11

* The ratio was determined by ^{1}H-nmr.

Table III. Reduction of **11** with $NaBH_4$ in THF-C_2H_5OH to **17** and **18**

R	isolated yield(%) **17**	**18**
CH_3	80	4.7
C_2H_5	82	15
CH_2=CH-CH_2	84	11
$C_6H_5CH_2$	79	5.5

The cis configuration of the C_2-aryl group and the C_3-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 C_3-carbonyl group from the opposite side of the bulky C_2-aryl group. Secondly, in the ^{1}H-nmr spectra, the signal of the C_2-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 C_2-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 C_2-substituents of **16c,d,e** and **21c,d,e**, and **15c,d,e** and **20c,d,e** (Table IV).

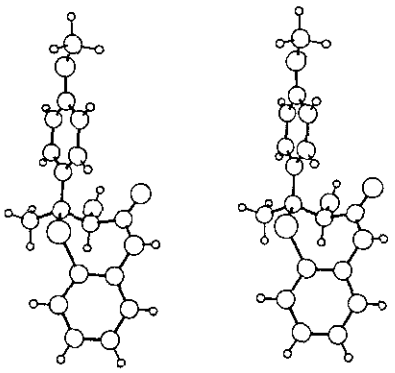


Figure 2 Stereoview of the structure of **15b**

Table IV. The chemical shifts ($CDCl_3$, δ) of the methyl or methylene protons of C_2-substituents of **15**, **16**, **20** and **21**

R	cis		trans	
	15	**20**	**16**	**21**
CH_3	1.95	1.88	1.81	1.99
CH_3CH_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
$C_6H_5CH_2$	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 F_{254} (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 ($CHCl_3$-C_2H_5OH (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-C_4H_9Li 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 ($CHCl_3$-C_2H_5OH (40:1)) to give **6** (0.76 g, 78%) as colorless crystals. Analytical sample was obtained by recrystallization from C_2H_5OH-ether. mp 132-133°C. Ir (nujol, cm^{-1}) : 3500, 1660. Nmr ($CDCl_3$, δ) : 2.27 (6H, s), 2.3-3.0 (4H, m, OH×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 $C_{21}H_{26}N_2O_4S$: 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 ($CHCl_3$-C_2H_5OH (40:1)) to give 2a (0.28 g, 66%) as colorless crystals, which was triturated with ether and dried. mp 138-139°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 $C_{25}H_{30}N_2O_6S$: 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 $(C_2H_5)_3O^+ \cdot BF_4^-$ (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 C_2H_5OH (14 ml) was added to a solution of **10** (2.24 g, 6.06 mmol) in C_2H_5OH (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 $Na_2S_2O_3$ 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°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 $C_{19}H_{19}NO_3S$: 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-C_4H_9Li 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. C_2H_5I (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 $Na_2S_2O_3$ 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 $C_{20}H_{21}NO_3S$: 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 $C_{21}H_{21}NO_3S$: 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 $C_{25}H_{23}NO_3S$: 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 C_2H_5OH (50 ml) was added dropwise to a cooled solution of **10** (10.2 g, 27.5 mmol) in C_2H_5OH (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 $(CH_3)_2S$ (5 ml) was added dropwise to a solution of $AlCl_3$ (2.0 g, 15 mmol) in CH_2Cl_2 (5 ml) and $(CH_3)_2S$ (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 $C_{17}H_{15}NO_3S$: 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 $C_{23}H_{19}NO_3S$: 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**) : Trimethylsilyl 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 $C_{19}H_{17}NO_3S$: 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 $C_{18}H_{17}NO_3S$: 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 C_2H_5OH (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 C_2H_5OH 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 $C_{17}H_{17}NO_3S$: 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 $C_{18}H_{19}NO_3S$: 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 (C_2H_5OH). Anal. Calcd for $C_{19}H_{19}NO_3S$: 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 $C_{19}H_{19}NO_3S \cdot 1/3C_6H_5CH_3$: 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 $NaBH_4$ to **17b** and **18b** : A solution of **11b** (0.75 g, 2.2 mmol) in THF (16 ml) and C_2H_5OH (4 ml) was cooled to -58°C. $NaBH_4$ (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 ($CDCl_3$, 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 $C_{19}H_{21}NO_3S$: 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 ($CDCl_3$, 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 $C_{20}H_{23}NO_3S$: 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 $C_{21}H_{23}NO_3S$: 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 $C_{25}H_{25}NO_3S$: 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 $C_{25}H_{25}NO_3S$: 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 CH_3CN (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 $NaHCO_3$, diluted $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$ 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 $C_{23}H_{21}NO_3S$: 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 $C_{18}H_{19}NO_3S$: 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 $C_{23}H_{21}NO_3S$: 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-2,3-dihydro-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 $C_{19}H_{19}NO_4S$: 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 $C_{20}H_{21}NO_4S$: 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 $C_{21}H_{21}NO_4S$: 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 $C_{25}H_{23}NO_4S \cdot 1/3CH_3CO_2C_2H_5$: 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 $C_{20}H_{21}NO_4S$: 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 $C_{21}H_{21}NO_4S$: 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 $C_{25}H_{23}NO_4S$: 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), $ClCH_2CH_2N(CH_3)_2$·HCl (1.42 g, 9.89 mmol) and K_2CO_3 (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 $MgSO_4$ 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 C_2H_5OH afforded pure 22b·HCl (3.10 g, 86%), mp 251-252.5°C (decomp). Ir (nujol, cm^{-1}) : 3200-2400, 1645. Nmr (DMSO-d_6, 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 $C_{21}H_{27}ClN_2O_3S$: 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 C_2H_5OH. 22c·HCl; mp 242.5-243°C (decomp). Anal. Calcd for $C_{22}H_{29}ClN_2O_3S$: 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 $C_{23}H_{29}ClN_2O_3S$·1/4H_2O : 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 $C_{27}H_{31}ClN_2O_3S$: 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 Ac_2O (20 ml) was refluxed for 2 h and evaporated to dryness to give a crystalline residue. Recrystallization from C_2H_5OH - 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-d_6, 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 $C_{23}H_{29}ClN_2O_4S$: 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 C_2H_5OH-isopropyl ether. 2c·HCl; mp 211-212°C. Anal. Calcd for $C_{24}H_{31}ClN_2O_4S$: 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 $C_{25}H_{31}ClN_2O_4S$: 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 $C_{29}H_{33}ClN_2O_4S$: 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 $C_{21}H_{26}N_2O_4S$, 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) $Å^3$, Z=2, Space group $P2_1$, Dcalc.=1.314 kg/m^3, 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 20 reflections in the range of $30° < 2\theta < 60°$. Intensity data were collected in the range of $2\theta < 130°$ using $\omega/2\theta$ 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 ($\sqrt{W} = 1/\sigma(Fobs)$).

X-Ray Crystallographic Analysis of Compound 15b : Crystal data $C_{17}H_{17}NO_3S$, 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) $Å^3$, Z=2, Space group $P2_1/c$, Dcalc.=1.356 kg/m^3, 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 ($\sqrt{W} = 1/\sigma(Fobs)$).

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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 ^{1}H-nmr.

Received 27th July, 1989