Notes

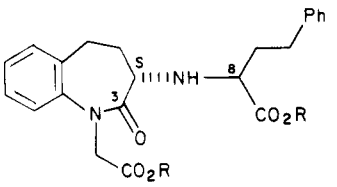
Angiotensin Converting Enzyme Inhibitors: 1,5-Benzothiazepine Derivatives†

Joel Slade,* James L. Stanton, Daniel Ben-David, and Gerard C. Mazzenga

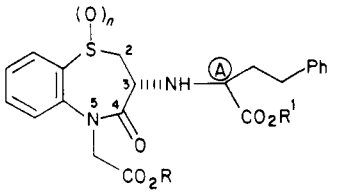
Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Ardsley, New York 10502.
Received January 7, 1985

The synthesis of chiral 1,5-benzothiazepines **2a–c**, **14a–c**, **15c**, and **16a** prepared from cysteine is described. In vitro inhibition of angiotensin converting enzyme (ACE) is reported for each compound. Compound **2c** was the most potent in vitro having an IC_{50} of 2.95 nM. The ester of **2c**, i.e. **14c**, was found to inhibit the AI pressor response by 75% at a dose of 0.05 mg/kg iv and by 39% at 1.0 mg/kg po. Additionally, **14c** lowered blood pressure in the spontaneous hypertensive rat (SHR) by 35 mmHg, at a dose of 10 mg/kg po.

The discovery of captopril [1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline][1a,b] as the first potent, orally effective inhibitor of angiotensin converting enzyme (ACE) has touched off the search for related compounds with improved pharmacological profiles.[2-8] Over the past few years considerable effort has been expended by several groups in designing more conformationally rigid analogues to serve as better substrates for the active site of the enzyme.[9a-c,10] One structural modification that has resulted in improved biological activity has been alteration of the five-membered ring at the carboxyl terminus of the proline-derived ACE inhibitors.[9-11] This improvement is exemplified by the significant activity exhibited by the benzazepines **1a,b** recently reported by Watthey[9a-c] and



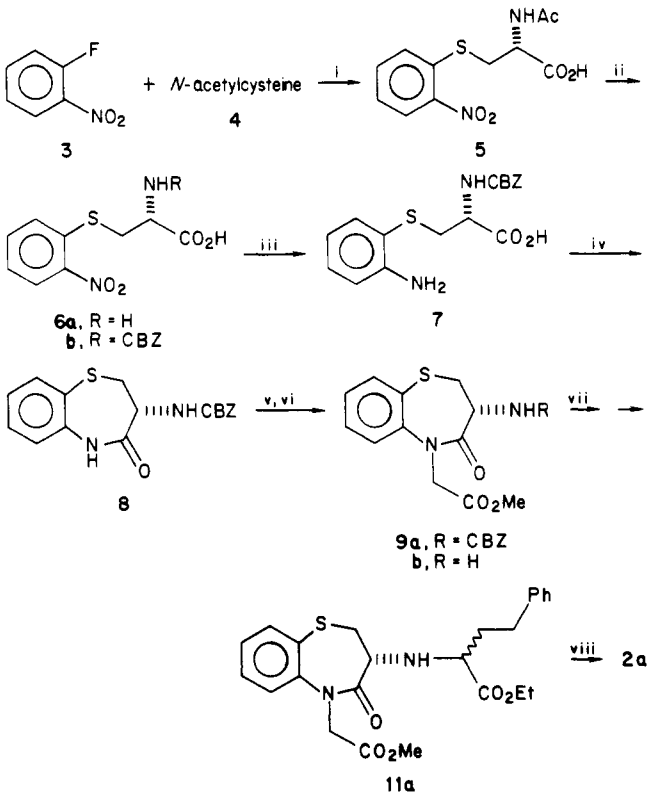
1a, R = H
b, R = Et



2a: R = H, R' = H, *n* = 0 (mixture of diastereomers at A)
b: R = H, R' = H, *n* = 0 (R,R isomer)
c: R = H, R' = H, *n* = 0 (R,S isomer)
14a: R = H, R' = Et, *n* = 0 (mixture of diastereomers at A)
b: R = H, R' = Et, *n* = 0 (R,R isomer)
c: R = H, R' = Et, *n* = 0 (R,S isomer)
15c: R = H, R' = H, *n* = 1 (R,S isomer)
16a: R = H, R' = H, *n* = 2 (mixture of diastereomers at A)

a Merck group.[10] Although the pyrrolidine moiety is lacking, the presence of the seven-membered ring in **1a,b**[9a] helps to maintain the spatial orientation of atoms necessary for activity as dictated by the active site model of the enzyme.[1a,b] Initially, the most straightforward synthesis of optically active **1a,b**[9a,c] required a resolution of the racemic 3-amino-1-benzazepin-2-one precursor. Since a classical resolution can be a somewhat inefficient procedure, it was felt advantageous to prepare analogues of **1a,b** that could be obtained from readily available chiral pre-

Scheme I[a]



[a] Key: (i) $NaHCO_3$, EtOH-H_2O; (ii) (a) H_2SO_4, NH_4OH, (b) $ClCO_2CH_2Ph$, NaOH; (iii) Zn, NH_4Cl, MeOH-H_2O; (iv) $Me_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, DMF; (v) $BrCH_2CO_2Me$, KOH, *n*-Bu_4NBr, THF; (vi) HBr/HOAc; (vii) BF_3Et_2O, ethyl 4-phenyl-2-ketobutyrate, $NaBH_3CN$; (viii) NaOH, HCl.

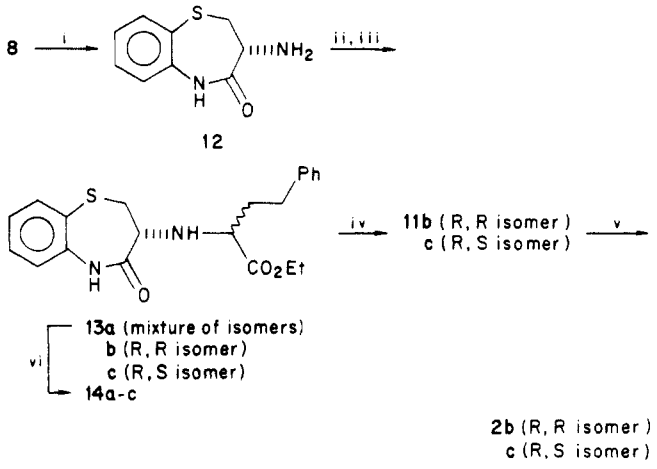
† See ref 9d and 12a,b.

(1) (a) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science (Washington, D.C.)* **1977**, *No. 196*, 441. (b) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16*, 5484.

(2) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvrett, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature (London)* **1980**, *288*, 280.

0022-2623/85/1828-1517$01.50/0

Scheme II[a]



[a] Key: (i) HBr–HOAc; (ii) ethyl4-phenyl-2-ketobutyrate, $BF_3{\cdot}Et_2O$, $NaBH_3CN$; (iii) HPLC separation; (iv) $BrCH_2CO_2Me$, KOH, n-Bu_4NBr, THF; (v) NaOH, HCl; (vi) $BrCH_2CO_2H$, KOH, n-Bu_4NBr, THF.

cursors. Therefore, the preparation of the benzothiazepine ring system **2a** and derivatives, which could be obtained from L-cysteine, was undertaken. The results of this investigation are described below.

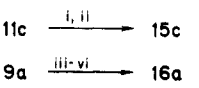
Chemistry. A first consideration was to devise a synthetic strategy that would allow for the preparation of **2a** in useful quantities and yet encompass the greatest flexibility in terms of substitution pattern. Scheme I depicts a solution to this problem. The synthesis begins with the aromatic nucleophilic substitution of *o*-fluoronitrobenzene (**3**) with *N*-acetylcysteine (**4**) according to conditions found in the literature for the substitution of *p*-bromonitrobenzene.[13a] The resulting *S*-(*o*-nitrophenyl)-*N*-acetylcysteine (**5**) is deacetylated[13b] to **6a** and converted to the CBZ derivative **6b**.[14] Nitro group reduction to **7** is then followed by ring closure to lactam **8** using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride[15] in DMF. Alkylation of the lactam nitrogen with methyl bromoacetate[16] gives **9a**, which is deprotected[17] to give **9b**. Whereas standard reductive amination conditions[9c,18] with ethyl 4-phenyl-2-ketobutyrate (**10**)[19] fail, a two-step procedure utilizing $BF_3{\cdot}Et_2O$-catalyzed imine formation[20] between **9b** and **10** followed by sodium cyanoborohydride reduction[21] affords a 2:1 mixture (by HPLC) of diastereomeric esters **11a**. The esters are then hydrolyzed to the corresponding mixture of diastereomeric diacids **2a**.

The diastereomerically pure diacids **2b** and **2c** can be obtained from **8** as shown in Scheme II. Thus, deprotection of **8** with HBr/HOAc[17] gives lactam **12**, which is condensed with ethyl 4-phenyl-2-ketobutyrate, furnishing a 1:1 mixture (by HPLC) of diastereomers **13a** that can be separated by preparative HPLC into the R,R (**13b**) and R,S (**13c**) components (these stereochemical assignments will be discussed in Biological Results). Alkylation and hydrolysis give the diastereomerically pure diesters (**11b** and **11c**) and diacids (**2b** and **2c**), respectively.

The diastereomeric mixture of half-acid esters **14a** is obtained by alkylation of **13a** with bromoacetic acid, and the optically pure components **14b** and **14c** are prepared similarly from **13b** and **13c**, respectively (see Scheme II).

Sulfoxide **15c**[22] results from sodium periodate oxidation of **11c** followed by ester hydrolysis, while sulfone **16a** is prepared from **9a** via MCPBA oxidation, deprotection, reductive amination, and hydrolysis as described previously for **2a** (Scheme III).

Scheme III[a]



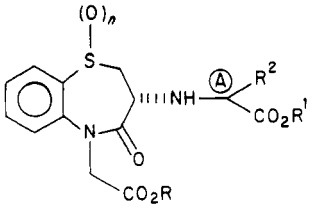
[a] Key: (i) $NaIO_4$; (ii) NaOH, HCl; (iii) MCPBA, $NaHCO_3$; (iv) HBr–HOAc; (v) $BF_3{\cdot}Et_2O$, **10**, $NaBH_3CN$; (vi) NaOH, HCl.

Biological Results

Compounds **2a–c**, **14a–c**, **15c**, and **16a** were evaluated for in vitro inhibition of angiotensin converting enzyme, and the results are included in Table I. Comparison of **2b** with **2c** shows the latter to be approximately 100 times

(3) Almquist, R. G.; Chao, W.-R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.
(4) Klutchko, S.; Hoefle, M. L.; Smith, R. D.; Parker, R. B.; Nemeth, V. L.; Ryan, M. J.; Dugan, D. H.; Kaplan, H. R. *J. Med. Chem.* **1981**, *24*, 104.
(5) Petrillo, E. W.; Spitzmiller, E. R. *Tetrahedron Lett.* **1979**, 4929.
(6) Sugie, A.; Katsube, J. *Chem. Pharm. Bull.* **1979**, *27*, 1708.
(7) McEvoy, F. J.; Lai, F. M.; Albright, J. D. *J. Med. Chem.* **1983**, *26*, 381.
(8) Kim, D. H.; Guinosso, C. J.; Buzby, G. C.; Herbst, D. R.; McCaully, R. J.; Wicks, T. C.; Wendt, R. L. *J. Med. Chem.* **1983**, *26*, 394.
(9) (a) Watthey, J. W. H. U.S. Patent 4 410 520, 1983. (b) Watthey, J. W. H.; Desai, M.; Babiarz, J. E.; Gavin, T.; Finn, B.; Stanton, J. L. In "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983; American Chemical Society: Washington, DC, 1983; Abstr MEDI 93. (c) Watthey, J. W. H., unpublished results. (d) Ksander, G. M., presented in part at the 19th National Medicinal Chemistry Symposium, Tucson, AZ, June 1984.
(10) After we had completed our work, results from other groups appeared; see: Parsons, W. H.; Davidson, J. L.; Taub, D.; Aster, S. D.; Thorsett, E. D.; Patchett, A. A. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 108. Hassall, C. H.; Kröhn, A; Moody, C. J.; Thomas, W. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 155. Harris, E. E.; Patchett, A. A.; Tristram, E. W.; Thorsett, E. D.; Wyvratt, M. J. U.S. Patent 4 415 496, 1983.
(11) (a) Stanton, J. L.; Gruenfeld, N.; Babiarz, J. E.; Ackerman, M. H.; Friedmann, R. C.; Yuan, A. M.; Macchia, W. *J. Med. Chem.* **1983**, *26*, 1267. (b) Hoefle, M. L.; Klutchko, S. U.S. Patent 4 344 949, 1982. (c) Oka, Y.; Nishikawa, K.; Miyake, A. U.S. Patent 4 385 051, 1983. (d) Youssefyeh, R. D.; Jones, H. European Patent Application 66 254, 1982.
(12) (a) A portion of this work has previously been reported: Stanton, J.; Slade, J.; Mazzenga, G.; Ben-David, D. In "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983; American Chemical Society: Washington, DC, 1983; Abstr MEDI 94. (b) Slade, J.; Stanton, J. L. U.S. Patent 4 477 464, 1984.
(13) (a) Iwamoto, R. H.; Acton, E. M.; Ross, L. O.; Skinner, W. A.; Baker, B. R.; Goodman, L. *J. Med. Chem.* **1963**, *6*, 43. (b) Goodman, L.; Ross, L. O.; Baker, B. R. *J. Org. Chem.* **1958**, *23*, 1251.
(14) The analogous reaction between **3** and *N*-(carbobenzyloxy)-cysteine gave lower yields than the procedure outlined here.
(15) Kopple, K. O.; Nitecki, D. E. *J. Am. Chem. Soc.* **1962**, *84*, 4457.
(16) Reuschling, D.; Pietach, H.; Linkies, A. *Tetrahedron Lett.* **1978**, 615.
(17) Ben-Ishai, D. *J. Org. Chem.* **1954**, *19*, 62.
(18) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(19) Purchased from Chemical Dynamics Corp., South Plainfield, NJ.
(20) O'Donnell, M. J. *Tetrahedron Lett.* **1978**, 2641.
(21) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 1793.
(22) This compound is presumed to be a mixture diastereomeric at sulfur.

Table I. 3-Substituted Amino-5-(carboxymethyl)-1,5-benzothiazepin-4-ones



compd	R	R^1	R^2	n	stereochem at A	mp,[a] °C	$[\alpha]_D$, deg	ACE: IC_{50}[b], nm	salt
2a	H	H	$PhCH_2CH_2$	0	R,S[c]	114–117	−165.5 (c 1.0, MeOH)	9.8	
2b	H	H	$PhCH_2CH_2$	0	R	140–144	−201.6 (c 0.5, MeOH)	240	
2c	H	H	$PhCH_2CH_2$	0	S	216–218	−176.3 (c 0.6, 1 N NaOH)	2.9	
14a	H	Et	$PhCH_2CH_2$	0	R,S[d]	108 dec	−120 (c 0.5, MeOH)	860	HCl
14b	H	Et	$PhCH_2CH_2$	0	R	101 dec	−163.7 (c 0.3, EtOH)	8000	HCl
14c	H	Et	$PhCH_2CH_2$	0	S	103 dec	−132.9 (c 0.35, EtOH)	2200	HCl
15b	H	H	$PhCH_2CH_2$	1	S	140–143	−87.2 (c 0.5, MeOH)	5.9	
16b	H	H	$PhCH_2CH_2$	2	R,S[d]	190–194 dec	−113.5 (c 0.2, MeOH)	2900	HCl
1a								1.7[e]	
captopril								15[b]	

[a] All compounds had satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structure. [b] See ref 11a for testing procedure. [c] 2:1 mixture of diastereomers, favoring the S isomer. [d] 1:1 mixture of diastereomers. [e] Reference 9b,c.

Table II. ACE Inhibitory Activities in Vitro and in Vivo and Antihypertensive Effects in the SHR

compd	ACE: IC_{50}, nM	AI: % inhibn (mg/kg) iv[a,b]	AI: % inhibn (mg/kg) po[a,c]	SHR:[a,d] max ΔBP, mmHg (mg/kg po)
14c	2200	75 (0.05)	39 (1.0)	−35 (10)
1b[e]	430	77 (0.06)	88 (1.0)	−76 (10)
captopril 15	70 (0.30)	82 (1.0)	−45 (10)	

[a] See ref 11a for details of the procedure. [b] Tabulated results indicate percent inhibition of angiotensin I pressor response 15 min after intravenous administration of test compound to conscious normotensive rats. [c] Results indicate percent inhibition of angiotensin I pressor response 1 h after oral administration of test compound to conscious normotensive rats. [d] Tabulated results indicate maximal change in blood pressure recorded during the 4-day test period. [e] Reference 9b–d.

more potent, thus allowing for the assignment of the stereochemistry at A (see Table I) for all the compounds listed. This assumption is based upon results obtained previously for **1a,b** wherein it was demonstrated that maximal activity was observed for the isomers that possessed the S stereochemistry in the side chain (see A in Table I).[9a–c] Additionally, it can be seen that **2c** has an IC_{50} value comparable to that of **1a**.

A comparison was made between **14c**[23] in relation to **1b** and the reference compound captopril to determine their abilities to inhibit ACE, as judged by the inhibition of the angiotensin I vasopressor responses in normotensive rats upon iv and po administration. The results are presented in Table II. From the data in the table, it can be seen that relative to **1b** and captopril, **14c** showed good activity when administered intravenously; however, at a dose level of 1.0 mg/kg po, **14c** was considerably less active than the aforementioned compounds. Additionally, **14c** had slightly less activity than captopril, but significantly reduced activity relative to **1b** in the oral SHR test.

A comparison of sulfoxide **15c** with **2c** indicates the former to be about half as active in vitro (Table I), possibly due to the fact that **15c** is a 1:1 diastereomeric mixture at sulfur. What is perhaps more interesting is the 300-fold loss in activity on going from the sulfide to the sulfone (cf. **2a** and **16a**). The reasons for this discrepancy have not been fully elucidated as yet, but they may be related to the ability of the active site of the enzyme to accommodate the extra substituents on sulfur while still maintaining the other functional group interactions necessary for maximal binding of the substrate.

In conclusion, although the initial objectives of preparing optically active analogues of **1a,b** from a chiral precursor have been realized, it has been discovered that replacement of the benzylic methylene group in this series with sulfur results in less effective ACE inhibitors, particularly on oral administration.

(23) In vivo activity of other compounds has previously been shown to be improved through esterification resulting in better absorption: see ref 11a.

Experimental Section

Proton NMR spectra were determined on a Varian EM-390 spectrometer using Me_4Si as the internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 457 or Perkin-Elmer Model 137 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Except where indicated, intermediate products were used directly without further purification. High-pressure liquid chromatography (HPLC) was performed on a Waters Prep 500A instrument using radially packed silica gel cartridges. All reactions were run under nitrogen unless stated otherwise. All solvents were removed by evaporation under reduced pressure. Optical rotations were measured at 25 °C.

***S*-(*o*-Nitrophenyl)-*N*-acetyl-L-cysteine (5).** A mixture of 67.8 g (0.42 mol) of **4** and 100.8 g (1.2 mol) of $NaHCO_3$ in 300 mL of H_2O was added to 55.4 mL (0.52 mol) of **3** in 1 L of EtOH. The reaction was heated to reflux for 3 h with mechanical stirring and allowed to cool to room temperature. After the solids were removed by filtration, the solution was concentrated to one-fourth of the original volume and diluted with 1 L of H_2O. The aqueous suspension was washed with 200 mL of ether and acidified to pH 1 with 12 N aqueous HCl. The resulting yellow precipitate was collected by filtration and dried in vacuo at 70 °C over P_2O_5 to afford 99.9 g (85%) of **5**, mp 175–176 °C, used without further purification: NMR (Me_2SO-d_6) δ 1.91 (3 H, s), 3.10–3.67 (2 H, m), 4.59 (1 H, m), 7.45 (1 H, m), 7.79 (2 H, d), 8.30 (2 H, d of d, J = 8 Hz), 13.20 (1 H, br s); IR (KBr) 3375, 3340, 1737, 1717, 1610, 1560, 1510, 1345, 1335, 1302, 1214, 1179 cm^{-1}.

***S*-(*o*-Nitrophenyl)-L-cysteine (6a).** A solution of 71 g (0.25 mol) of **5** in 300 mL of 18 M H_2SO_4 and 1.2 L of H_2O was heated to reflux for 30 min. The solution was cooled in ice and treated with 700 mL of concentrated NH_4OH. The resulting solid was recrystallized from boiling H_2O to afford 52.8 g (87%) of **6a** after drying in vacuo at 80 °C over P_2O_5, mp 168–171 °C, used without further purification: NMR (TFA-*d*) δ 3.55–4.20 (2 H, m), 4.68 (1 H, m), 7.42–8.00 (3 H, m), 8.26 (1 H, d, J = 8 Hz); IR (Nujol) 3100–2600, 1615, 1468, 1380, 1335, 1310 cm^{-1}.

***S*-(*o*-Nitrophenyl)-*N*-(carbobenzyloxy)-L-cysteine (6b).** To a solution of 48.4 g (0.20 mol) of **6a** in 100 mL of 2 N aqueous

NaOH at 0 °C was added 28.8 mL (0.20 mol) of benzyl chloroformate and 50 mL of 4 N aqueous NaOH simultaneously from two addition funnels. The mixture was mechanically stirred overnight at room temperature and then extracted with 150 mL of ether. The aqueous layer was separated and acidified to pH 1 with 12 N aqueous HCl. The resulting gummy yellow solid was stirred for 3 h in 500 mL of H_2O, collected by filtration, and dried overnight at 70 °C in vacuo to afford 61.1 g (81%) of **6b**, mp 84–88 °C, used without further purification: NMR (Me_2SO-d_6) δ 3.16–3.75 (2 H, m), 4.32 (1 H, m), 5.10 (2 H, s), 7.47 (5 H, s), 7.78 (3 H, m), 8.24 (1 H, d, J = 8 Hz), 11.22 (1 H, br s); IR (Nujol) 3330, 1705, 1675, 1595, 1565, 1510, 1465, 1455, 1380, 1340, 1280, 1060, 1048 cm^{-1}.

***S*-(*o*-Aminophenyl)-*N*-(carbobenzyloxy)-L-cysteine (7).** A 5-L three-neck flask fitted with a mechanical stirrer and condenser was charged with 62.1 g (0.017 mol) of **6b**, 17.6 g (0.33 mol) of NH_4Cl, and 3 L of MeOH. To this mixture was added 150 g (2.3 mol) of zinc dust. The reaction was heated for 4 h at reflux and then stirred overnight at room temperature. The mixture was filtered through Celite, and the solids were further washed with 300 mL of boiling MeOH. The MeOH fractions were combined and concentrated. The residue was dissolved in 1.2 L of 1 N HCl, and this was filtered through Celite. The acidic solution was cooled to 0 °C, and the pH was adjusted to 5 with saturated NaOAc. The resulting white precipitate was collected and dried at 80 °C in vacuo to give 46.9 g (82%) of **7**: mp 161–162 °C; $[\alpha]_D$ −50° (c 1.0, absolute EtOH); NMR (Me_2SO-d_6) δ 2.70–3.25 (2 H, m), 3.90 (1 H, m), 5.02 (2 H, s), 5.52–7.41 (8 H, m), 7.42 (5 H, s); IR (KBr) 3400, 1728, 1690, 1540, 1279, 1220, 1061 cm^{-1}. Anal. ($C_{17}H_{18}N_2O_4S$) C, H, N.

3(*R*)-[(Carbobenzyloxy)amino]-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (8). A 500-mL flask containing 37.6 g (0.11 mol) of **7**, 236 mL of DMF and 20.8 g (0.11 mol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride was stirred for 3 h and then diluted with 940 mL of EtOAc. The solution was washed with 940 mL of 1 N aqueous $NaHCO_3$ and 4 × 940 mL of H_2O. The organic phase was dried over $MgSO_4$ and concentrated to a yellow solid. This was triturated with ether and dried in vacuo to give 29.8 g (84%) of **8**: mp 178–179 °C; $[\alpha]_D$ −96.6° (c 0.99, $CHCl_3$); NMR (Me_2SO-d_6) δ 3.15 (1 H, d of d, J = 12 Hz), 3.57 (1 H, d of d, J = 12 Hz), 4.20 (1 H, m), 4.98 (2 H, s), 7.00–7.97 (5 H, m), 7.40 (5 H, s), 10.22 (1 H, br s); IR (KBr) 3400, 1720, 1670, 1535, 1473, 1268, 1255, 1042 cm^{-1}. Anal. ($C_{17}H_{16}H_2O_3S$) C, H, N.

3(*R*)-[(Carbobenzyloxy)amino]-5-(carbomethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (9a). To a mixture of 9.84 g (30 mmol) of **8**, 2.16 g (39 mmol) of powdered KOH, 0.97 g (3 mmol) of tetrabutylammonium bromide, and 60 mL of THF at 0 °C was added dropwise 2.8 mL (30 mmol) of methyl bromoacetate. The reaction was allowed to stir for 3 h at room temperature, filtered, and concentrated. The residue was partitioned between 90 mL of ether and 30 mL of H_2O, and the organic phase was separated, washed with 25 mL of H_2O and 25 mL of 0.5 N aqueous HCl, and dried over $MgSO_4$. After solvent removal, the crude material was triturated with 1:1 ether–hexane, which afforded 8.4 g (70%) of **9a** as a gum. This was used without further purification in the following reaction: NMR ($CDCl_3$) δ 7.18 (5 H, s), 4.95 (2 H, s), 3.70 (3 H, s), 2.80 (1 H, d of d); IR (CCl_4) 3420, 1758, 1727, 1680, 1494, 1449, 1439, 1206 cm^{-1}.

3(*R*)-Amino-5-(carbomethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (9b). A mixture of 5.9 g (15 mmol) of **9a** in 24 mL of 31% HBr–HOAc was allowed to stir 1 h at room temperature. Then, 150 mL of ether was added and the resulting white precipitate was filtered and dissolved in 100 mL of saturated aqueous $NaHCO_3$. The solution was extracted with 3 × 60 mL of EtOAc, and the combined organic extracts were dried over K_2CO_3. Solvent removal afforded 2.55 g (65%) of **9b**, mp 114–118 °C, used without further purification in the following reaction: NMR ($CDCl_3$) δ 2.00 (2 H, br s), 2.80 (1 H, d of d, J = 13 Hz), 3.45–3.90 (2 H, m), 3.82 (3 H, s), 4.03 (1 H, d, J = 17 Hz), 4.95 (1 H, d, J = 17 Hz), 7.16–7.80 (4 H, m); IR (Nujol) 3400, 1740, 1665, 1460, 1370 cm^{-1}.

3(*R*)-[*N*-[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-5-(carbomethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4-(5*H*)-one (11a). A toluene solution (80 mL) of 2.05 g (7.7 mmol) of **9b**, 1.59 g (7.7 mmol) of ethyl 4-phenyl-2-ketobutyrate, and 0.1 mL (0.8 mmol) of distilled BF_3·Et_2O was stirred overnight at room temperature and concentrated to give 4.20 g of light orange oil. This oil was dissolved in 8 mL of MeOH followed by the dropwise addition of 0.48 g (7.7 mmol) of sodium cyanoborohydride in 15 mL of MeOH. Glacial HOAc (4.4 mL) was added, and the reaction was stirred overnight at room temperature. The solvent was removed, and the residue was partitioned between 10 mL of cold aqueous saturated Na_2CO_3 and 20 mL of CH_2Cl_2. The aqueous layer was separated and extracted with an additional 20 mL of CH_2Cl_2. The organic portions were combined and dried over K_2CO_3. After concentration, the residue was purified by flash chromatography on silica gel (1:1 ether–hexane as eluent) to afford 1.70 g (48%) of oily **11a** (mixture of diastereomers): $[\alpha]_D$ −175.7° (c 1.15, absolute EtOH); NMR ($CDCl_3$) δ 1.18 (3 H, t), 1.90 (2 H, m), 2.28–4.30 (10 H, m), 3.80 (3 H, s), 4.96 (1 H, d of d, J = 6 Hz), 6.90–7.80 (9 H, m); IR (film) 3320, 1732, 1665, 1472, 1440, 1369, 1205, 1100, 1020 cm^{-1}. Anal. ($C_{24}H_{28}N_2O_5S$) C, H, N.

3(*R*)-[*N*-(1-Carboxy-3-phenylpropyl)amino]-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2a). A solution of 2.3 g (5.0 mmol) of **11a** in 8 mL of MeOH and 5 mL of 1 N aqueous NaOH was stirred overnight. The reaction mixture was concentrated to dryness, and the resulting solid was dissolved in a minimum amount of H_2O, extracted with an equal volume of ether, and acidified to pH 4 with 2 N aqueous HCl. The acidic solution was then extracted with 2 × 50 mL of EtOAc, and the organic extracts were combined and dried over $MgSO_4$. Removal of solvent afforded 1.98 g (96%) of **2a** (mixture of diastereomers): mp 114–117 °C; $[\alpha]_D$ −165.5° (c 1.0, MeOH); NMR (Me_2SO-d_6) δ 1.77 (2 H, m), 2.30–4.95 (9 H, m), 6.76–7.80 (9 H, m), 8.82 (2 H, br s); IR (KBr) 3420, 1700, 1675, 1472, 1390, 1245, 1210 cm^{-1}. Anal. ($C_{21}H_{22}N_2O_5S$) C, H, N.

3(*R*)-Amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (12). A mixture 29.7 g (90 mmol) of **8** in 105 mL of 31% HBr–HOAc was stirred for 1 h at room temperature, and 200 mL of ether was added. The resulting precipitate was collected by filtration, washed with an additiional 100 mL of ether, and slowly added to 250 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with 3 × 100 mL of EtOAc, and the organic extracts were combined and dried over $MgSO_4$. Solvent removal gave a solid that was triturated with ether and dried at reduced pressure to give 12.0 g (68%) of white crystalline **12**, mp 162–166 °C, used without further purification: NMR (Me_2SO-d_6) δ 2.30 (2 H, br s), 2.66–3.12 (1 H, m), 3.20–3.69 (2 H, m), 6.99–7.89 (4 H, m), 10.10 (1 H, br s); IR (Nujol) 3200, 1680, 1460, 1420, 1335, 1284, 1235 cm^{-1}.

3(*R*)-[*N*-[1(*R*)-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (13b) and 3(*R*)-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (13c). To a solution of 11.9 g (60 mmol) of **12** and 12.6 g (60 mmol) of **10** in 120 mL of $CHCl_3$ was added 0.75 mL (6 mmol) of distilled BF_3·Et_2O. The reaction was stirred 18 h at room temperature, filtered, and concentrated to give 25.4 g of an orange oil. This material was dissolved in 200 mL of EtOH and treated with 4.17 g (66 mmol) of sodium cyanoborohydride and 38 mL of glacial HOAc. After stirring overnight, the solvent was removed and the residue was dissolved in 200 mL of CH_2Cl_2 and washed with 2 × 100 mL of cold aqueous saturated Na_2CO_3. The organic portion was dried over $MgSO_4$ and concentrated to give 22.7 g (98%) of crude **13a** as a viscous oil (mixture of diastereoisomers): NMR ($CDCl_3$) δ 1.28 (3 H, m), 2.05 (2 H, m), 2.25–3.82 (7 H, m), 4.04 (2 H, q), 7.05–8.00 (9 H, m), 8.99 (1 H, br s); IR (film) 3300, 3200, 1727, 1673, 1475, 1180, 1155 cm^{-1}.

The diastereoisomers were separated by preparative HPLC on silica gel using 20% THF in hexane as the eluent. A sample loading of 5.53 g afforded 1.1 g of oily **13b**, used without further purification [NMR ($CDCl_3$) δ 1.20 (3 H, t, J = 6 Hz), 1.92 (2 H, m), 2.50–3.78 (7 H, m), 4.13 (2 H, q, J = 6 Hz), 6.96–7.72 (9 H, m), 9.00 (1 H, br s); IR (film) 3300, 1730, 1675, 1475, 1368, 1180 cm^{-1}] and 2.1 g of **13c** as a waxy solid used without further purification [NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 6 Hz), 1.92 (2 H, m), 2.46–3.85 (7 H, m), 4.05 (2 H, q, J = 6 Hz), 6.90–7.73 (9 H, m), 8.72 (1 H, br s); IR (film) 3375, 1725, 1685, 1473, 1368, 1175, 1025 cm^{-1}].

3(*R*)-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]amino]-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-

4(5*H*)-one Hydrochloride (14c). Following the procedure outlined for the preparation of **9a** and utilizing bromoacetic acid, 1.1 g (2.9 mmol) of **13c** afforded 0.5 g (36%) of **14c**: mp 103 °C dec; $[\alpha]_D$ −132.9° (*c* 0.35, absolute EtOH); NMR ($CDCl_3$) δ 1.28 (3 H, t, *J* = 7 Hz), 1.55 (2 H, m), 2.15–2.54 (2 H, m), 2.60–3.00 (2 H, m), 3.50 (2 H, q, *J* = 7 Hz), 3.15–4.30 (5 H, m), 7.07–7.80 (9 H, m), 8.30–9.36 (2 H, br s); IR (Nujol) 3320, 1740, 1677, 1465, 1377, 1215 cm^{-1}. Anal. ($C_{23}H_{27}ClN_2O_5S$) C, H, N.

3(*R*)-[*N*-[1(*R*)-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (14b). Following the procedure for the preparation of **14c**, 0.96 g (2.5 mmol) of **13b** afforded 0.47 g (39%) of **14b**: mp 101 °C dec; $[\alpha]_D$ −163.7° (*c* 0.3, absolute EtOH); NMR ($CDCl_3$) δ 1.20 (3 H, t, *J* = 7 Hz), 1.53 (2 H, m), 2.37 (2 H, m), 2.72 (2 H, m), 3.50 (2 H, q, *J* = 7 Hz), 3.70–4.42 (5 H, m), 6.97–7.83 (9 H, m), 8.90 (2 H, br s); IR (Nujol) 3340, 1740, 1680, 1460, 1379, 1218 cm^{-1}. Anal. ($C_{23}H_{27}ClN_2O_5S$) C, H, N.

3(*R*)-[*N*-[(Ethoxycarbonyl)-3-phenylpropyl]amino]-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (14a). Following the procedure for the preparation of **14c**, 1.0 g (2.6 mmol) of **13a** afforded 0.20 g (17%) of **14a**: mp 108 °C dec; $[\alpha]_D$ −120° (*c* 0.5, MeOH); NMR ($CDCl_3$) δ 0.70–1.42 (5 H, m), 2.28 (2 H, m), 2.72 (2 H, m), 3.22–4.40 (7 H, m), 6.69–7.80 (9 H, m), 8.47 (2 H, br s); IR (Nujol) 3340, 1737, 1675, 1460, 1377, 1215 cm^{-1}. Anal. ($C_{23}H_{27}ClN_2O_5S$) C, H, N.

3(*R*)-[*N*-[1(*S*)-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-5-(carbomethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (11c). Following the procedure for the preparation of **14c** and utilizing methyl bromoacetate, 1.05 g (2.7 mmol) of **13c** gave 0.59 g (48%) of **11c** as a viscous oil after flash column chromatography (silica gel; 1:1 ether–hexane eluent). This was used without further purification: NMR ($CDCl_3$) δ 1.09 (3 H, t, *J* = 7 Hz), 1.94 (2 H, m), 2.65 (2 H, m), 3.08–4.20 (6 H, m), 3.76 (3 H, s), 4.04 (2 H, q, *J* = 7 Hz), 4.97 (1 H, d, *J* = 18 Hz), 7.23 (5 H, s), 6.96–7.75 (4 H, m); IR (CCl_4) 3300, 1730, 1671, 1480, 1380, 1195 cm^{-1}.

3(*R*)-[*N*-[1(*R*)-(Ethoxycarbonyl)-3-phenylpropyl]-amino]-5-(carbomethoxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (11b). Following the procedure for the preparation of **11c**, 1.04 g (2.7 mmol) of **13b** produced 0.6 g (48%) of oily **11b**, which was used without further purification: NMR ($CDCl_3$) δ 1.20 (3 H, t, *J* = 7 Hz), 1.82 (2 H, m), 2.40–4.28 (8 H, m), 3.77 (3 H, s), 4.10 (2 H, q, *J* = 7 Hz), 4.87 (1 H, d, *J* = 18 Hz), 6.95–7.80 (9 H, m); IR (CCl_4) 3380, 1760, 1690, 1480, 1450, 1390, 1370, 1210, 1190 cm^{-1}.

3(*R*)-[*N*-[1(*S*)-Carboxy-3-phenylpropyl]amino]-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2c). Following the procedure for the preparation of **2a**, 0.51 g (1.1 mmol) of **11c** gave 0.46 g (100%) of **2c**: mp 216–218 °C; $[\alpha]_D$ = −176.3° (*c* 0.6, 1 N aqueous NaOH); NMR (Me_2SO-d_6) δ 1.77 (2 H, m), 2.36–3.68 (7 H, m), 4.08 (1 H, d, *J* = 18 Hz), 4.68 (1 H, d, *J* = 18 Hz), 7.12 (5 H, s), 6.92–7.79 (4 H, m), 8.72 (2 H, br s); IR (film) 3420, 1695, 1676, 1510, 1495, 1475, 1390, 1365, 1245, 1210 cm^{-1}. Anal. ($C_{21}H_{22}N_2O_5S$) C, H, N.

3(*R*)-[*N*-[1(*R*)-Carboxy-3-phenylpropyl]amino]-5-(carboxymethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (2b). Following the procedure for the preparation of **2a**, 0.58 g (1.3 mmol) of **11b** gave 0.52 g (96%) of **2b**: mp 140–144 °C; $[\alpha]_D$ −201.6° (*c* 0.5, MeOH); NMR (Me_2SO-d_6) δ 1.64 (2 H, m), 2.22–3.59 (7 H, m), 4.02 (1 H, d, *J* = 18 Hz), 5.58 (1 H, d, *J* = 18 Hz), 6.77–7.69 (9 H, m), 8.50–9.50 (2 H, br s). Anal. ($C_{21}H_{22}N_2O_5S$) C, H, N.

3(*R*)-[*N*-(1-Carboxy-3-phenylpropyl)amino]-5-(carboxymethyl)-2,3-dihydro-1,1-dioxo-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (16a). To a solution of 4 g (10 mmol) of **9a** in 40 mL of CH_2Cl_2 was added 1.68 g (20 mmol) of $NaHCO_3$ followed by 4.52 g (21 mmol) of 80% *m*-chloroperoxybenzoic acid. The reaction mixture was stirred overnight at room temperature, filtered, and concentrated. The resulting semisolid was triturated with ether to give 3.56 g (82%) of sulfone, used without further purification in the following reaction: NMR ($CDCl_3$) δ 3.25–4.92 (3 H, m), 3.84 (1 H, d, *J* = 17 Hz), 4.82 (3 H, s), 5.05 (2 H, s), 4.99 (1 H, d, *J* = 17 Hz), 6.10 (1 H, d), 7.28 (5 H, s), 7.11–8.22 (4 H, m); IR (CCl_4) 3420, 1756, 1725, 1693, 1492, 1479, 1455, 1440, 1418, 1340, 1208, 1160 cm^{-1}. CBZ removal was effected on 1.7 g (3.9 mmol) of the above sulfone by the procedure previously outlined for the preparation of **9b**. The resulting gum **9b** (0.68 g, 59%) was used without further purification: NMR (Me_2SO-d_6) δ 2.39 (2 H, br s), 3.77 (3 H, s), 3.40–4.21 (3 H, m), 4.21 (1 H, d, *J* = 18 Hz), 4.64 (1 H, d, *J* = 18 Hz), 7.50–8.10 (4 H, m); IR (Nujol) 3350, 1740, 1680, 1450, 1370, 1300, 1260, 1210, 1155, 1120, 1050 cm^{-1}.

Following the procedure for the preparation of **11a**, 0.52 g (1.8 mmol) of the above amino ester gave 0.3 g (35%) of the corresponding sulfone diester as a 2:1 mixture of diastereomers by NMR. The material was used without further purification in the following reaction: TLC (40% acetone–hexane, silica gel) R_f 0.4, one homogeneous spot; NMR ($CDCl_3$) δ 1.11 (3 H, overlapping t), 1.91 (2 H, m), 2.62 (2 H, m), 3.83–4.33 (7 H, m), 4.82 (3 H, s), 7.25 (5 H, s), 6.82–7.95 (4 H, m), 8.05 (2 H, d, *J* = 6 Hz).

Hydrolysis to the diacid was carried out on 0.31 g (0.64 mmol) of the above diester following the procedure outlined for the preparation of **2a**, affording 0.050 g (18%) of **16a**: mp 190–194 °C dec; $[\alpha]_D$ −113.5° (*c* 0.2, MeOH); NMR (Me_2SO-d_6) δ 1.72 (2 H, m), 2.40–4.08 (8 H, m), 4.65 (1 H, d, *J* = 18 Hz), 6.90–8.12 (12 H, m); IR (KBr) 3420, 1700, 1690, 1605, 1590, 1480, 1455, 1429, 1410, 1388, 1332, 1285, 1157 cm^{-1}. Anal. ($C_{21}H_{23}ClN_2O_7S$) C, H, N.

3(*R*)-[*N*-[1(*S*)-Carboxy-3-phenylpropyl]amino]-5-(carboxymethyl)-2,3-dihydro-1-oxo-1,5-benzothiazepin-4(5*H*)-one (15c). To a 0 °C solution of **11c** (0.27 g, 0.60 mmol) in 5 mL of MeOH was added 0.122 g (0.60 mmol) of sodium periodate in 1 mL of H_2O. The reaction was stirred 72 h at room temperature and filtered. The solvent was removed and the residue dissolved in 10 mL of CH_2Cl_2 and dried over K_2CO_3. Evaporation of solvent afforded the sulfoxide as a mixture of diastereoisomers at sulfur, which was used without further purification: NMR ($CDCl_3$) δ 1.02 (3 H, overlapping t), 1.97 (2 H, m), 2.60 (3 H, m), 2.98–4.62 (7 H, m), 3.72 (3 H, s), 4.95 (1 H, d of d, *J* = 18 Hz), 7.18 (5 H, s), 6.76–8.10 (4 H, m); IR (CCl_4) 3330, 1745, 1675, 1475, 1448, 1439, 1370, 1205, 1180, 1060 cm^{-1}.

Following the procedure for the preparation of **2c**, 0.20 g (0.40 mmol) of the above sulfoxide mixture was hydrolyzed to give 0.080 g (44%) of **15c**: mp 140–143 °C; $[\alpha]_D$ −87.2° (*c* 0.5, MeOH); NMR (Me_2SO-d_6) δ 1.79 (2 H, m), 2.55 (2 H, m), 2.82–4.95 (7 H, m), 7.28 (5 H, s), 5.60–8.55 (6 H, m); IR (KBr) 3430, 1720, 1675, 1475, 1455, 1385, 1220, 1010 cm^{-1}. Anal. ($C_{21}H_{22}N_2O_6S$) C, H, N.

Acknowledgment. The authors thank Dr. Ed Ku, Dr. Barbara Petrack, Carol Signor, and Hilda Hankin for the biochemical data, Dr. D. Chen and R. Dotson for the in vivo biological data, L. Raabis for the proton NMR spectra, G. Robertson and his staff for performing the elemental analyses, and Leo Sylvester for the preparation of intermediates. Helpful discussions with Dr. J. Watthey and J. Babiarz are also gratefully acknowledged.

Registry No. **2b**, 94590-57-5; **2c**, 97277-71-9; **3**, 1493-27-2; **4**, 616-91-1; **5**, 91088-54-9; **6a**, 60115-45-9; **6b**, 94590-53-1; **7**, 94590-54-2; **8**, 94590-55-3; **9a**, 94590-56-4; **9a** (sulfone), 94590-67-7; **9b**, 94604-92-9; **9b** (imide), 97293-67-9; **9b** (sulfone), 94590-65-5; **10**, 64920-29-2; **11b**, 97277-69-5; **11b** (sulfone), 97277-76-4; **11c**, 97277-70-8; **11c** (sulfone), 97277-77-5; **11c** (sulfoxide isomer 1), 97370-89-3; **11c** (sulfoxide isomer 2), 97335-11-0; **12**, 94590-63-3; **12** (imide), 97277-73-1; **13b**, 94590-61-1; **13c**, 97277-72-0; **14b**, 95779-68-3; **14b**·HCl, 94590-62-2; **14c**, 97277-78-6; **14c**·HCl, 97293-61-3; **15c** (isomer 1), 97335-12-1; **15c** (isomer 2), 97335-13-2; **16a** (isomer 1), 97277-79-7; **16a** (isomer 1)·HCl, 97277-74-2; **16a** (isomer 2), 97277-80-0; **16a** (isomer 2)·HCl, 97277-75-3; $ClC(O)OCH_2Ph$, 501-53-1; $BrCH_2CO_2Me$, 96-32-2; $BrCH_2CO_2H$, 79-08-3; angiotensin converting enzyme, 9015-82-1.