0.45–0.4, benzene:ethyl acetate = 5.1) obtained by flash column chromatography (benzene:ethyl acetate = 10:1) was subjected to further purification by preparative thin layer chromatography (benzene:ethyl acetate = 25:1, 5 developments), resulting in the isolation of 8 mg of pentalenolactone D methyl ester (**20**) (least polar band, UV active). A second band, containing a mixture of pentalenolactone F and pentalenolactone P methyl esters was further purified by HPLC on a μ-Bondapak-CN column (Waters, 3.9 mm × 30 mm) using 30% ethyl acetate in hexane (1 mL/min) to give 3 mg of pentalenolactone F methyl ester (**22**) and 6 mg of pentalenolactone P methyl ester. Pentalenolactone D methyl ester (**20**): ^{13}C NMR ($CDCl_3$) δ 175.4, 164.4, 150.5, 132.6, 68.15, 57.56, 54.71, 51.72, 49.33, 44.87, 41.57, 39.87, 30.98, 28.98, 10.01; IR (neat) 2942, 2865, 2355, 2315, 1750, 1716, 1454, 1430, 1380, 1348 (cm^{-1}); R_f = 0.42 (benzene:ethyl acetate = 5:1); CIMS m/z (NH_3) found 279.1581 (calcd for $C_{16}H_{22}O_4$ [M + H] 279.1596). Pentalenolactone F methyl ester (**22**): IR (neat) 2953, 2919, 1768, 1712, 1398, 1318, 1259, 1187, 1158, 1107, 1097 (cm^{-1}); R_f = 0.4 (benzene:ethyl acetate = 5:1); EIMS m/z found 292.1280 (calcd for $C_{16}O_{20}O_5$ 292.1312).

Pentalenolactone A and Pentalenolactone B Methyl Esters. The fraction (R_f = 0.4–0.30, benzene:ethyl acetate = 5:1) obtained by flash column chromatography was further purified by preparative thin layer chromatography (benzene–ethyl acetate, 30:1, five developments) to give 2 major UV-active bands. The less polar band was pentalenolactone A methyl ester (**23**) (3 mg) while the more polar band corresponded to pentalenolactone B methyl ester (**24**) (2 mg). Pentalenolactone A methyl ester (**23**): ^{13}C NMR ($CDCl_3$) δ 169.5, 164.5, 145.7, 133.2, 130.4, 129.7, 67.7, 65.3, 61.3, 58.2, 53.4, 51.8, 47.6, 46.3, 13.6, 12.8; IR (neat) 2916, 2850, 2358, 2333, 1762, 1712, 1437, 1387, 1350, 1266 (cm^{-1}); R_f = 0.36 (benzene:ethyl acetate = 5:1); EIMS m/z found 290.1140 (calcd for $C_{16}H_{18}O_5$ 290.1154). Pentalenolactone B methyl ester (**24**): ^{13}C NMR ($CDCl_3$) δ 169.5, 166, 151.73, 145.18, 135, 106.61, 67.71, 55.73, 53.41, 51.79, 51.31, 48.94, 48.91, 42.23, 40.39, 13.52; IR (neat) 2990, 2860, 1730, 1650, 1550, 1390, 1300 (cm^{-1}); R_f = 0.34 (benzene:ethyl acetate = 5:1); CIMS m/z (NH_3) found 290.1161 (calcd for $C_{16}H_{18}O_5$ 290.1149).

Isolation and Purification of Phenacyl Esters of Pentalenolactones. A 4-L culture of *S.* UC5319 was extracted as described above and the resulting brown oil (0.85 g) was dissolved in 100 mL of dry diethyl ether, filtered through a cotton plug which was rinsed with additional diethyl ether. Concentration of the solvent provided a brown oil which was dissolved in 50 mL of MeOH and was neutralized to pH 7.5 with a KOH/methanol (1 M) solution. The solvent was removed under vacuum to yield 600 mg of a mixture of potassium salts. A solution containing an excess of the alkylating agent, bromoacetophenone/18-crown-6 ether (20:1) was then added and the total volume of solution brought to 20 mL with acetonitrile. The solution was stirred at room temperature for 1 h and then filtered through 10 g of silica gel to remove crown ether and residual salts. The silica gel column was washed with benzene (40 mL) and the benzene eluent was concentrated in vacuo. The mixture of phenacyl esters was initially purified by flash column chromatography (10:1 = benzene:ethyl acetate) to provide a fraction (R_f = 0.4–0.45, benzene:ethyl acetate = 6:1) containing pentalenolactone and pentalenolactone E phenacyl esters, a fraction (R_f = 0.3, benzene:ethyl acetate = 6:1) containing pentalenolactone D phenacyl ester (**21**), a fraction (R_f = 0.25, benzene:ethyl acetate = 6:1) containing pentalenic acid phenacyl ester, and a fraction (R_f = 0.08, benzene:ethyl acetate = 6:1) containing pentalenolactone O phenacyl ester. The phenacyl esters of the various pentalenolactone metabolites could be further purified by preparative thin layer chromatography (benzene:ethyl acetate = 25:1, 6 developments) to provide pentalenolactone, pentalenolactone E, D, and O, phenacyl esters, and pentalenic acid phenacyl esters. Pentalenolactone D phenacyl ester (**21**) was recrystallized by vapor diffusion from pentane–THF. Pentalenolactone D phenacyl ester (2.5 mg) was transferred to a small tube and dissolved in THF (60 μL). Pentane (6 mL) was added to a larger tube and the small tube was placed in the large tube. The larger tube was then stoppered, left to stand for 2 days at room temperature, and then placed in a refrigerator for 2 days. The colorless crystals of pentalenolactone D phenacyl ester which were obtained were used for X-ray crystallographic structure determination. Pentalenolactone D phenacyl ester (**21**): ^1H NMR ($CDCl_3$) δ 7.91–7.47 (m, Ph, 5 H), 7.03 (t, J = 2.24, 2.24 Hz, H-7, 1 H), 5.31 and 5.50 (AB q, J = 16.4, $-COOCH_2CO-$, 2H), 4.88 (dd, J = 7, 11.4 Hz, H-12α, 1 H), 4.08 (t, J = 11.4, 11.4 Hz, H-12β, 1 H), 3.5 (m, H-5, 1 H), 3.20 (m, H-8, 1 H), 2.78 (q, J = 7, H-9, 1 H), 1.82 (d, J = 13.74 Hz, H-3α, 1 H), 1.69 (dd, J = 10.4, 13.3 Hz, H-1α, 1 H), 1.56 (dd, J = 1.69, 13.3 Hz, H-1β, 1 H), 1.42 (d, J = 13.74 Hz, H-3β, 1 H), 1.19 (d, J = 6.7 Hz, H-10, 3 H), 1.05 (s, H-14, 3 H), 1.03 (s, H-15, 3 H); IR (neat) 2964, 2866, 2360, 2338, 1750, 1734, 1456, 1394, 1266, 1183 (cm^{-1}); mp 158.5–159 °C; R_f = 0.34 (benzene:ethyl acetate = 6:1).

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Supplementary Material Available: X-ray crystallographic data for pentalenolactone D (7 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis of Calcium Channel Blockers of the Diltiazem Group

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A lipase-catalyzed kinetic resolution of racemic *trans*-2-phenylcyclohexanol readily provides the (−)-1*R*,2*S* enantiomer. This alcohol is employed as its chloroacetate **10a** in a chiral auxiliary-induced asymmetric Darzens glycidic ester condensation with *p*-anisaldehyde (**9**). Crystallization of the Darzens product affords enantiomerically pure (1*R*,2*S*)-2-phenylcyclohexyl (1*R*,2*S*)-2-(*p*-methoxyphenyl)glycidate (**11**), the structure of which was established by X-ray crystallography. The use of this glycidic ester in syntheses of diltiazem (**1**) and naltiazem (**8**), members of the diltiazem group of calcium channel blockers, provides these drug substances directly in enantiomerically pure form.

Calcium channel blockers inhibit the influx of Ca^{2+} into vascular smooth muscle cells, thereby relaxing arteriolar smooth muscle and decreasing peripheral vascular resistance, with concomitant lowering of blood pressure.[1a] The

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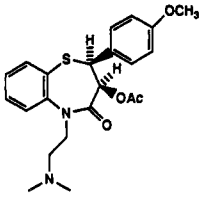
efficacy and side-effect profile of these agents vis-à-vis older classes of antihypertensive agents have led to their wide acceptance in medical practice.

There are three major groups of calcium channel blockers, identified by structural types and represented by diltiazem (1), verapamil (2), and the dihydropyridines (nifedipine (3), etc.). Diltiazem has emerged as one of the most important agents of this group in clinical use.[1] The



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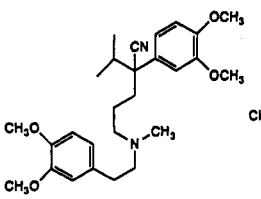

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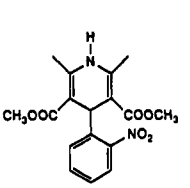
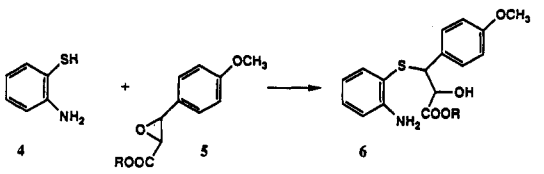


3

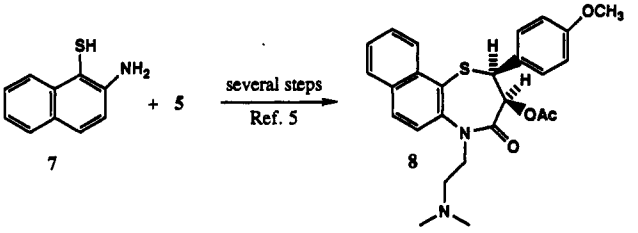
success of diltiazem has stimulated significant activity in related chemical synthesis, directed both to analogues[2] and to enantiomerically pure compound (EPC) synthesis schemes.[3] Since only the 2S,3S diastereomer elicits the desired biological effect, diltiazem was developed and is marketed as a single stereoisomer.

Established processes for the production of this material[13] rely on late-stage resolution as part of a multistage operation involving, in the key event, condensation of o-aminobenzenethiol (4) with the racemic glycidic ester 5. Subsequent transformations of intermediate 6 provide at least two opportunities for effecting classical resolution.



4 5 6

The economic implications of this strategy are of little consequence provided the aminothiol 4 is readily available. However, a major focus of analogue synthesis concerns the effects of additional substituents on this ring.[4] From one such analogue program, conducted in these laboratories,[5a] the naphthalene analogue 8 was identified as a clinical candidate with improved pharmacokinetic properties (the typical duration of a significant decrease in mean systolic blood pressure in spontaneous hypertensive rats after a single po dose of 8 is 2–3 times longer than with 1).[5b]



7 8

Unlike 4, 7 is not commercially available and must be prepared in a process entailing several steps.[6] With this impetus, an exploration of EPC routes to 8 (naltiazem), and hence of 1, was undertaken.

The earliest opportunity to access a single enantiomer series of intermediates appears at the glycidic ester 5 stage, or its synthetic equivalent.[7] Schemes based on Sharpless epoxidation of cinnamyl alcohol precursors,[3a] enzyme-catalyzed kinetic resolution of glycidic esters, and conventional resolution of glycidic acid salts[8] have been reported by other investigators. However, for reasons involving enantiomeric purity and overall efficiency, our efforts were directed to a strategy based on the induction of asymmetry in the Darzens reaction used to prepared glycidic ester 5. While clear-cut precedent[9] to support such a plan was lacking, we nevertheless felt that a systematic survey of chiral auxiliaries incorporated as the alcohol component of chloroacetates might yield the desired asymmetry. Various "chiral pool" and "designer" auxiliaries (e.g., those of Oppolzer,[10] Helmchen,[11] and Whitesell[12]) were surveyed.

Success arrived in unexpected form. None of the auxiliaries screened induced asymmetry leading to acceptable levels of enantiomeric excess. However, (−)-(1R,2S)-2-phenylcyclohexanol ((−)-10) afforded a diastereomeric pair of glycidic esters, 11 and 12, possessing marked differences in solubility. Direct crystallization of the crude product mixture provided ready access to 11, the required (and major) isomer, in 54% yield as a stereochemically pure entity. Moreover, recycling of the chiral auxiliary contained in the mother liquor as 12 is easily accomplished by a simple base hydrolysis, a trivial operation. NMR analysis of the crude reaction mixture indicated a level of asymmetric induction corresponding to a 62:38 ratio of 11:12. Single-crystal X-ray crystallographic analysis was used to determine the relative and absolute stereochemistry of 11, based on the known chirality of (−)-10.[12b] The corresponding *cis*-epoxides are formed in negligible amounts, if at all.

The preparation of 11 in either gram or kilogram quantities proved to be equally efficacious, and its incorporation into the established synthetic routes provided[13] ready access to multikilogram quantities of enantiomeri-

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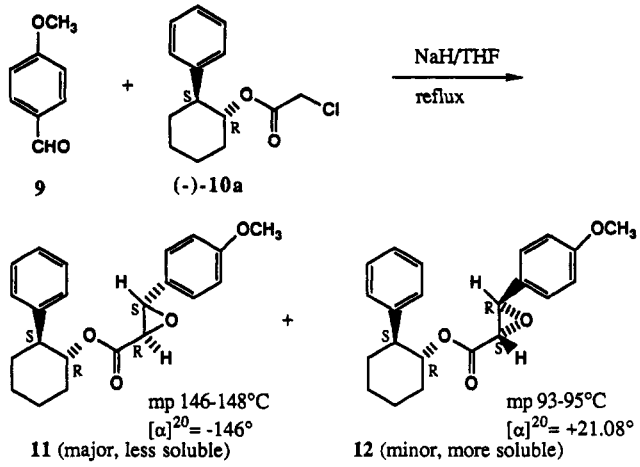
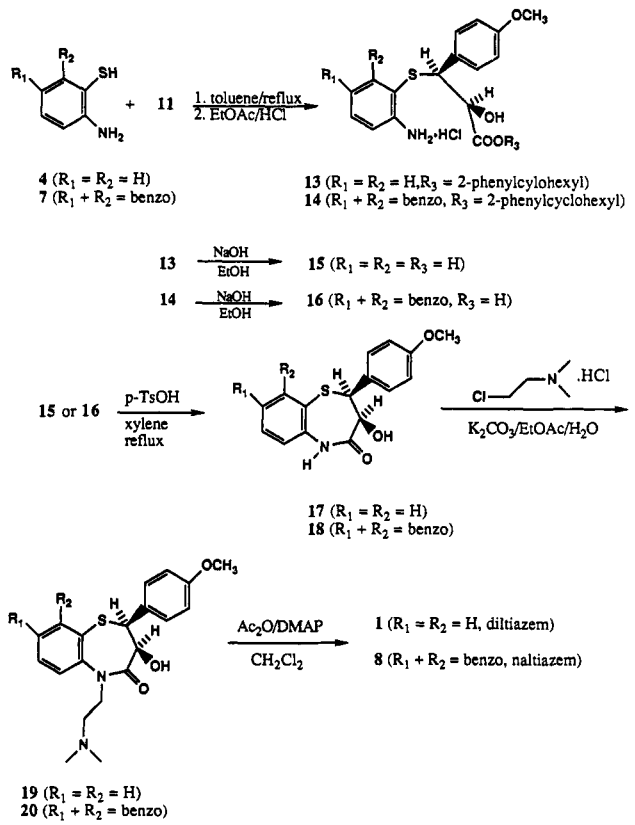


cally pure naltiazem (8) and diltiazem (1). The stereochemical integrity of the system secured at the compound 11 stage was verified by determination of the relative and absolute stereochemistry of naltiazem (8) and its precursor 20, achieved by X-ray crystallographic analysis of their protonated salts.



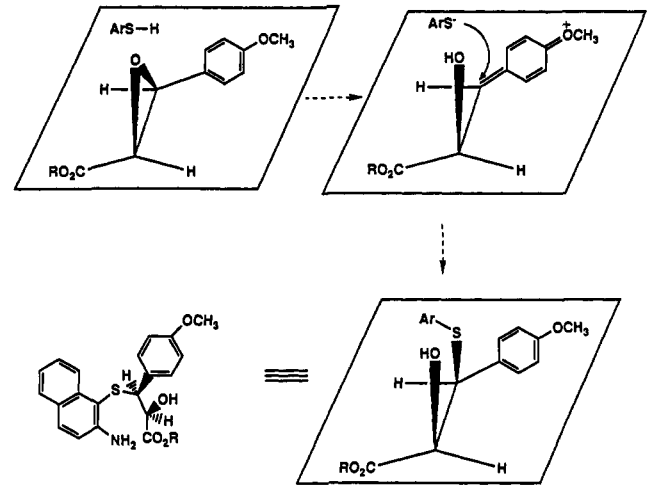
One feature of this synthesis route entails an intriguing stereochemical outcome. In order to obtain the correct relative configuration, the condensation of arylamino thiols 4 and 7 with glycidic ester 11 must proceed with *retention* of configuration at the reacting center. Both acid- and base-catalyzed reactions fail to give this outcome, with the acid leading to loss of stereochemical integrity at the reacting center and base leading to inversion.

Under purely thermal conditions, the process can be understood as one in which the thiol first acts as a weak acid, protonating the epoxide from the proximal side of a plane defined by the four atoms attached to it. Opening of the protonated epoxide would be facilitated by the *p*-anisyl group, leading to the resonance-stabilized *p*-quinone methide cation depicted below. If collapse of the

Table I. Crystal Data for 11

crystal system	monoclinic
space group	$P2_1$
a	19.627 (1) Å
b	5.664 (1) Å
c	8.465 (1) Å
β	99.30 (1)°
Z	2
d_{calcd}	1.260 g cm^{-3}
μ(Cu Kα)	6.5 cm^{-1}

resulting ion pair proceeds faster than migration of the thiol anion, the observed retention of configuration becomes comprehensible. Alternative mechanisms have previously been proposed by Inoue and co-workers,[13] who studied the effects of solvent, temperature, and catalyst variation in the opening of the racemic version of the glycidic ester (R = CH_3) by nitrothiophenols and nitroanilines.



Ready access to large quantities of enantiomerically pure (−)-*trans*-2-phenylcyclohexanol ((−)-10) was another requirement for the success of this work. At the outset, this material was available in rather limited amounts using a kinetic resolution catalyzed by pig liver esterase,[12] or by other methods cited in ref 12. Prior success with large-scale resolutions using the cheap bacterial lipase Amano P-30[14] prompted an examination of its applicability to this problem. With the racemic *trans*-2-phenylcyclohexanol chloroacetate ((±)-10a) as the substrate, this enzyme showed a very high degree of antipodal discrimination. The overall practicality of the entire process is greatly enhanced by the high level of chiral auxiliary recovery (>90%).

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Digilab FTS-15-E spectrophotometer. NMR spectra were obtained on a Varian XL-400 spectrometer. Mass spectra were obtained by using a Varian-MAT CH5 spectrometer at 70 eV. All of the solvents and reagents were of ACS-certified grade purchased from either Fisher Scientific or Aldrich and used without purification.

(−)-*trans*-2-Phenylcyclohexyl Chloroacetate ((−)-10a). A

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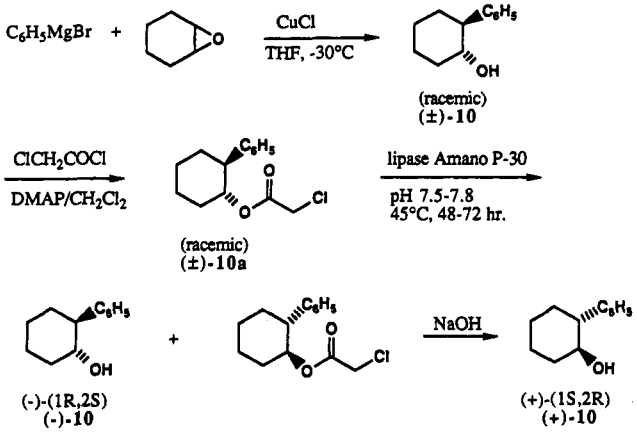

mixture of 790 g (4.48 mol) of (−)-*trans*-2-phenylcyclohexanol ((−)-**10**),[15] 1.5 L of CH_2Cl_2, 450 mL (5.63 mol) of chloroacetyl chloride, and 2.2 g (0.018 mol) of DMAP was heated at reflux for 8 h. On cooling, the reaction mixture was stirred with 2 × 1.5 L of saturated $NaHCO_3$ for 30 min. The organic layer was dried (Na_2SO_4) and evaporated to dryness to afford 1.136 kg of (−)-**10a** (100%) as an oil, which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20–2.16 (m, 8 H, cyclohexyl CH), 2.78 (1 H, m, CHPh), 3.68–3.82 (2 H, q, J = 4.0 Hz, $COCH_2Cl$), 5.03 (1 H, m, COO cyclohexyl C*H*), 7.14–7.30 (5 H, m, PhH). Anal. Calcd for $C_{14}H_{17}ClO_2$: C, 66.53; H, 6.78; Cl, 14.03. Found: C, 66.69; H, 6.79; Cl, 14.27.

(2*R*,3*S*)-3-(4-Methoxyphenyl)oxirane-2-carboxylic Acid (1*R*,2*S*)-2-Phenylcyclohexyl Ester (11). A 5-L three-necked flask equipped with a stirrer, a gas bubbler, a thermometer, an addition funnel, and a condenser was charged with 100 g (3.33 mol) of NaH (80% in mineral oil) and triturated with three 500-mL portions of hexanes. Under an argon atmosphere, 1.5 L of THF was added followed by the addition of a solution of 568 g (2.247 mol) of (−)-*trans*-2-phenylcyclohexyl chloroacetate ((−)-**10a**) and 352 g (2.589 mol) of anisaldehyde in 250 mL of THF over 0.5 h via an addition funnel. A vigorous evolution of H_2 gas ensued along with an exotherm to ~55 °C. After the initial reaction subsided, the mixture was then stirred under argon at ambient temperature overnight. The mixture was heated at 55–60 °C for 1 h and poured into 8.0 L of ice water. The pH was adjusted to 7 (pH meter) with 390 mL of 3 N H_2SO_4, and the resulting mixture was extracted first with 4 L followed by 2 × 2 L of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to an oily, partially solid residue, which on crystallization from 0.5 L of (9:1) hexanes–EtOAc afforded colorless needles. These crystals were collected by filtration, washed with 2 × 200 mL of 9:1 hexanes–EtOAc followed by 2 × 500 mL of cold hexanes, and finally dried in vacuo to give 415 g (52%) of 11: mp 146–148 °C; $[\alpha]^{20}_D$ −146° (*c* 1, $CHCl_3$). On another reaction run at 0.4 M scale, 54% yield was obtained: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34–2.15 (8 H, m, cyclohexyl CH), 2.66 (1 H, m, cyclohexyl C*H*Ph), 3.24 (1 H, d, J = 1.4 Hz, CHAr), 3.40 (1 H, d, J = 1.4 Hz, CHCO), 3.79 (3 H, s, OCH_3), 5.14 (1 H, m, CHOCO), 6.83–7.05 (4 H, dd, J = 9 Hz, *p*-OCH_3Ar*H*), 7.17–7.22 (5 H, m, Ph*H*); IR (KBr) 1732 cm^{-1}; mass spectrum m/e 352 (EI, M^+). Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 74.80; H, 6.88. X-ray-quality crystals were obtained by placing a dilute solution of 11 in Et_2O in a covered crystallizing dish. Slow evaporation of the Et_2O overnight produced a variety of crystals that were suitable for single-crystal X-ray diffraction analysis. The crystal data are summarized in Table I. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω-2θ scans). The crystal size used for data collection was approximately 0.43 × 0.47 × 0.65 mm; the data were not corrected for absorption. Of the 2110 independent reflections for θ < 75°, 1848 were considered observed ($I > 3.0\sigma(I)$). The structure was solved by a multiple-solution procedure[18] and was refined by full-matrix least squares. Seven reflections, which were strongly affected by extinction, were excluded from the final refinement and difference map. In the final refinement, the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.050 and R_w = 0.072 for the remaining 1841 observed reflections. The final difference map has no peaks greater than ±0.2 e $Å^{-3}$.

(2*S*,3*R*)-3-(4-Methoxyphenyl)oxirane-2-carboxylic Acid (1*R*,2*S*)-2-Phenylcyclohexyl Ester Hydrochloride (12). The mother liquors obtained from the crystallization of 11 were evaporated to an oil and allowed to stand. After 1 week, the oil had crystallized. The crystals were filtered and washed with 100 mL of 20:1 hexanes–EtOAc followed by 2 × 200 mL of cold hexanes to give 210 g (26.5%) of 12: mp 93–95 °C; $[\alpha]^{20}_D$ +21.08° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34–2.19 (8 H, m, cyclohexyl CH), 2.75 (1 H, m, cyclohexyl C*H*Ph), 3.22 (1 H, d, J = 1.7 Hz, CHAr), 3.25 (1 H, d, J = 1.4 Hz, CHCO), 3.78 (3 H, s, OCH_3), 5.07 (1 H, m, CHOCO), 6.81–7.00 (4 H, dd, J = 8.8 Hz, *p*-OCH_3Ar*H*), 7.22–7.35 (5 H, m, Ph*H*); IR (KBr) 1738, 700 cm^{-1}; mass spectrum m/e 352 (EI, M^+). Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 74.83; H, 6.48.

(2*R*,3*S*)-3-[(2-Amino-1-naphthalenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propanoic Acid (1*R*,2*S*)-2-Phenylcyclohexyl Ester Hydrochloride (14). A mixture of 409.5 g (1.162 mol) of 11, 221 g (1.26 mol) of 2-aminonaphthalene-1-thiol (7), and 2.2 L of toluene was stirred and heated at reflux under argon for 20 h, cooled to ~50 °C, and then treated with 240 mL (1.16 mol) of HCl(g) in ethyl acetate (4.83 M). Solids began to form, and the mixture was diluted with 500 mL of acetonitrile and stirred for 1 h. The precipitated solids were collected by filtration, washed first with 3 × 500 mL of acetonitrile, then with 500 mL of ether, and dried at 70 °C in vacuo overnight to afford 645 g (98%) of 14 as a light yellow solid: mp 184–186 °C; $[\alpha]^{20}_D$ +52° (*c* 0.1, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34–2.00 (8 H, m, cyclohexyl CH), 2.65 (1 H, t, CHAr), 3.64 (3 H, s, OCH_3), 3.74 (1 H, d, J = 4.7 Hz, OH), 4.44 (1 H, d, J = 4.6 Hz, C*H*OH), 4.85 (1 H, br s, CHOCO), 6.41–6.77 (4 H, dd, *p*-OCH_3Ar*H*), 7.13–7.94 (11 H, m, ArH); IR (KBr) 3450, 1740 cm^{-1}; mass spectrum m/e 527 (EI, M^+). Anal. Calcd for $C_{22}H_{33}NO_4S$·HCl: C, 68.13; H, 6.07; N, 2.48. Found: C, 68.85; H, 6.09; N, 2.63.

(+)-3-[(2-Amino-1-naphthalenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propanoic Acid (16). To a 1-L three-necked flask equipped with magnetic stir bar, condenser, and nitrogen bubbler were added 66.6 g (0.11 mol) of 14 and 350 mL of ethanol, creating a slurry of solids. Then, after 124 mL (0.25 mol) of 2 N NaOH was added, the mixture was refluxed for 4 h and then stirred at rt overnight. The reaction mixture was extracted with 3 × 500 mL of ether to recover the chiral auxiliary (−)-**10**, suitable for reuse after simple recrystallization from hexanes. The aqueous layer was acidified to pH 3 with 3 N H_2SO_4, then 100 mL of acetonitrile was added, and the mixture was stirred overnight. In the morning the pH (5–6) was adjusted to 3 with 3 N H_2SO_4, and the mixture was stirred for another 24 h, whereupon the heterogeneous mixture was filtered and dried overnight under vacuum to yield 41.2 g (94.5%) of 16: mp 174–177 °C dec; $[\alpha]^{20}_D$ +288.0° (*c* 0.50, MeOH) (lit.[17] mp 143–145 °C; $[\alpha]^{25}_D$ +269.51° (*c* 0.52, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.63 (3 H, s, OCH_3), 4.22 (1 H, d, J = 5.9 Hz, C*H*OH), 4.30 (1 H, d, J = 5.9 Hz, ArSC*H*), 6.05 (2 H, br s, NH_2), 6.64–8.0 (10 H, m, ArH); IR (KBr) 3370, 1722, 1608 cm^{-1}; mass spectrum m/e 369 (EI, M^+). Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; S, 8.68. Found: C, 64.88; H, 5.16; N, 3.64; S, 8.96.

The preparation of enantiomerically pure 16 via classical resolution was reported previously.[17]

(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-naphtho[1,2-*b*][1,4]thiazepin-4(5*H*)one (18) via Cyclization of Acid 16. To a 2-L round-bottomed flask equipped with a magnetic stir bar, a Dean–Stark trap, a condenser, and a nitrogen bubbler was added 41.0 g (0.11 mol) of 16 which was suspended in 1.34 L of xylenes. After addition of 4.0 g (0.02 mol) of PTSA, the mixture was refluxed for 19 h. Upon cooling to room temperature, the precipitated solids were filtered out and washed first with 100 mL of EtOAc and then with 500 mL of ether. After air drying, the yield of fluffy, white crystalline 18 was 33.0 g (85%): mp 243–245 °C; $[\alpha]^{20}_D$ +24.2° (*c* 0.5, acetone) (lit.[17] mp 240–241 °C; $[\alpha]^{25}_D$ +24.65° (*c* 0.495, acetone)); ^{1}H NMR (DMSO-d_6, 400

(18) Main, P.; Fiske, S.; Hull, S.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. Multan 11/82, University of York, England, and University of Louvain, Belgium, 1982.

Table II. Crystal Data for 20

crystal system	monoclinic
space group	$P2_1$
a	17.496 (1) Å
b	7.187 (1) Å
c	8.944 (1) Å
β	91.76 (1)°
Z	2
d_{calcd}	1.356 g cm^{-3}
μ(Cu Kα)	25.98 cm^{-1}

MHz) δ 3.73 (3 H, s, OCH_3), 4.35 (1 H, d, J = 6.8 Hz, C*H*OH), 5.19 (1 H, d, J = 6.8 Hz, ArSC*H*), 6.92–8.63 (11 H, m, ArH), 10.53 (1 H, s, N*H*CO); IR (KBr) 3380, 3310, 1685 cm^{-1}; mass spectrum m/e 351 (EI, M$^+$). Anal. Calcd for $C_{20}H_{17}NO_3S$: C, 68.36; H, 4.88; N, 3.99; S, 9.12. Found: C, 68.51; H, 4.85; N, 3.97; S, 8.96.

(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-naphtho[1,2-*b*][1,4]thiazepin-4(5*H*)-one (18) via Cyclization of Ester 14. A 40-L extractor was charged with 12.0 L of 3 N Na_2CO_3, 575 g (1.02 mol) of 14, and 8.0 L of CH_2Cl_2. The aqueous layer was successively extracted with an additional 2 × 3 L of CH_2Cl_2. The combined organic layers were dried by filtration through a pad of anhydrous K_2CO_3 and evaporated in vacuo to afford the free base, which was taken up in 11.5 L of xylene. Then 16 g of PTSA was added, and the mixture was stirred at reflux under argon for 16 h. After cooling, the product was collected by filtration, washed with 500 mL of EtOAc, followed by 3 × 500 mL of ether, and air dried overnight to afford 318 g (89%) of 18 as colorless needles: mp 235–238 °C dec; $[\alpha]^{20}_D$ +24.87° (c 0.4; acetone). The lactam obtained from this route was indistinguishable spectrally from the product obtained by cyclization of acid 16.

(+)-*cis*-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-5-[2-(dimethylamino)ethyl]naphtho[1,2-*b*][1,4]thiazepin-4-(5*H*)-one (20). A 1-L three-necked flask equipped with a mechanical stirrer and a reflux condenser open to the atmosphere was charged with 25.0 g (0.071 mol) of 18, 20.5 g (0.141 mol) of 2-(dimethylamino)ethyl chloride hydrochloride, 40 g (0.29 mol) of finely pulverized K_2CO_3, 3 mL of water, and 500 mL of EtOAc, and the heterogeneous mixture was refluxed on a steam bath for 16 h. TLC analysis (8:1 CH_2Cl_2–MeOH) showed the reaction to be complete, and the mixture was filtered while warm and washed with 2 × 50 mL of EtOAc. The combined organic filtrate was concentrated to near dryness, and the resultant crystals were collected by vacuum filtration and washed with 3 × 50 mL of ether. The solids were air dried to give 25.6 g (85%) of a white solid, **20**: mp 153–154 °C; $[\alpha]^{20}_D$ +44° (c 0.5, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (6 H, s, NCH_3), 2.48–2.52 (2 H, m, NCH_2), 2.76–2.82 (2 H, m, NCH_2), 2.86 (1 H, d, J = 9.7 Hz, OH), 3.77–3.81 (1 H, m, $CONCH_2$), 3.83 (3 H, s, OCH_3), 4.32 (1 H, t, J = 7.7 Hz, C*H*OH), 4.60–4.65 (1 H, m, NCH_2), 4.94 (1 H, d, J = 7.7 Hz, ArSC*H*), 6.93–8.79 (10 H, m, Ar*H*); IR (KBr) 3495, 2775, 1668 cm^{-1}; mass spectrum m/e 422 (EI, M$^+$). Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63; S, 7.59. Found: C, 68.30; H, 6.10; N, 6.59; S, 7.29. A second crop of tan crystalline **20**, 1.1 g (3.6%), was obtained by concentration of the mother liquors and trituration with EtOAc: mp 149–153 °C; $[\alpha]^{20}_D$ +41.2° (c 0.5, MeOH). X-ray quality crystals of the hydrochloride salt of **20** were obtained by addition of methanolic HCl to **20** and a slow addition of Et_2O to near clouding in a covered crystallizing dish. Overnight, crystals were produced that were suitable for single-crystal X-ray diffraction analysis. The crystal data are summarized in Table II. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω-2θ scans). The crystal size used for data collection was approximately 0.04 × 0.20 × 0.35 mm; the data were corrected for absorption. Of the 1813 independent reflections for θ < 60°, 1661 were considered observed ($I > 3.0\sigma(I)$). The structure was solved by a multiple-solution procedure[18] and was refined by full-matrix least squares. In the final refinement, the non-hydrogen atoms were refined anisotropically; the other non-hydrogen atoms were refined isotropically. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.0260 and R_w = 0.035 for the remaining 1661 observed reflections. The final difference map has no peaks greater than ±0.1 e Å^{-3}.

Table III. Crystal Data for 8

crystal system	orthorhombic
space group	$P22_12_1$
a	8.029 (9) Å
b	8.336 (3) Å
c	43.733 (16) Å
Z	4
d_{calcd}	1.359 g cm^{-3}
μ(Cu Kα)	14.3 cm^{-1}

(+)-*cis*-3-(Acetyloxy)-2,3-dihydro-2-(4-methoxyphenyl)-5-[2-(dimethylamino)ethyl]naphtho[1,2-*b*][1,4]thiazepin-4-(5*H*)-one Hydrochloride (8). In a 500-mL flask equipped with a magnetic stir bar and a nitrogen bubbler were placed 25.0 g (0.059 mol) of **20**, 250 mL of CH_2Cl_2, 0.25 g (0.002 mol) of DMAP, and 4.8 g (0.145 mol) of Ac_2O, and the homogeneous mixture was stirred overnight. TLC analysis (1:1 EtOAc–MeOH, shortwave ultraviolet light source (SWUV)) showed the reaction to be complete, and therefore 200 g of ice–water was added to the mixture, producing a milky, opaque mixture. The layers were separated, the CH_2Cl_2 layer was washed with 150 mL of 5% NH_4OH, and the layers were allowed to separate in a separatory funnel. The organic layer was placed on a rotary evaporator and concentrated to a foam, 29.5 g. Because of polar impurities, the oil was dissolved into 150 mL of ether and applied to a 50-g plug of silica, eluting first with 500 mL of Et_2O and then with 2 × 150 mL of EtOAc. The fractions were free of polar impurities and were combined and concentrated to an oil, 29.0 g. After the oil was dissolved into 100 mL of EtOAc, 20 mL of 4.8 M HCl in EtOAc was added dropwise over 15 min, whereupon 25 mL of ether was added, causing a solid mass to precipitate. The mixture was heated on a steam bath until solution occurred, and then solids began to precipitate slowly on cooling. The mixture was filtered to give 19.1 g of off-white solid 8: mp 229–230 °C; $[\alpha]^{20}$ +218° (c 0.65, MeOH; *316-nm Hg lamp*); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87 (3 H, s, $COCH_3$), 2.84–3.01 (6 H, br d, NCH_3), 3.23–3.29 (1 H, m, NCH_2), 3.58–3.65 (1 H, m, NCH_2), 375 (3 H, s, OCH_3), 4.48–4.73 (2 H, m, NCH_2), 5.06–5.16 (2 H, dd, J = 8.0 Hz, SC*H*C*H*CO), 6.94–7.48 (4 H, dd, J = 8.7 Hz, p-OCH_3Ar*H*), 7.28–8.69 (6 H, m, ArH); IR (KBr) 1741, 1672 cm^{-1}; mass spectrum m/e 465 (EI, M$^+$, free base). Anal. Calcd for $C_{26}H_{28}N_2O_4S$·HCl: C, 62.33; H, 5.83; N, 5.59; S, 6.40; Cl, 7.08. Found: C, 62.43; H, 5.64; N, 5.37; S, 6.16; Cl, 7.15. The mother liquors were concentrated to give 8.1 g, mp 229–230 °C, of a pure white solid, $[\alpha]^{20}_D$ +214.6° (c 0.5; MeOH; *316-nm Hg lamp*). A third crop of 1.0 g of tan solid was obtained (mp 225–230 °C). The total yield of 8 was 95%. The monohydrated fumaric acid salt of 8 was prepared from compound 8 (free base) and fumaric acid in ethanol–ether solution, and crystals were produced from slow crystallization. The crystal data are summarized in Table III. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω-2θ scans). The crystal used for data collection, approximately 0.04 × 0.15 × 0.40 mm, was cooled with a nitrogen gas stream of 110 K. The data were corrected for absorption. Of the 2539 independent reflections for θ < 60°, 1726 were considered observed ($I > 3.0\sigma(I)$). The structure was solved by a multiple-solution procedure[18] and was refined by full-matrix least squares. Due to poor quality of the crystal, only the sulfur atom was refined anisotropically in the final refinement; the other non-hydrogen atoms were refined isotropically. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.125 and R_w = 0.145 for the remaining 1726 observed reflections. The final difference map has no peaks greater than ±1.2 e Å^{-3}.

***cis*-(+)-3-(Acetyloxy)-2,3-dihydro-5-[2-(dimethylamino)-ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (Diltiazem Hydrochloride, 1). (α*S*,-β*S*,1*R*,2*S*)-β-[(2-Aminophenyl)thio]-α-hydroxy-β-(4-methoxyphenyl)propanoic Acid 2-Phenylcyclohexyl Ester Hydrochloride (13).** A mixture of 352.4 g (1.0 mol) of 11, 1.41 L of toluene, and 123 mL (1.14 mol) of 2-aminobenzenethiol (4) was stirred at reflux under argon for 16 h. TLC (7:3 hexanes–EtOAc, SWUV) indicated that the reaction was complete, and the reaction mixture was cooled to ~50 °C, treated with 240 mL (1.16 mol)

of HCl(g) in ethyl acetate (4.83 M), and then evaporated in vacuo to dryness. The oily residue, on crystallization from ethanol–ether, afforded, on cooling, 297 g (62.2%) of **13** as colorless needles, mp 131–133 °C. An additional 9.5 g of **13**, mp 129–131 °C, was obtained, for a total of 65%. On a 25-g scale, an 81% yield of **13** was obtained: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–2.02 (8 H, m, cyclohexyl CH), 2.75 (1 H, m, cyclohexyl C*H*Ph), 3.72 (1 H, s, OH), 3.74 (3 H, s, OCH_3), 4.31 (2 H, s, NH_2), 4.36–4.63 (2 H, q, SC*H*C*H*OH), 4.94–5.02 (1 H, m, cyclohexyl C*H*OH), 6.41–7.06 (7 H, m, ArH), 7.25–7.37 (5 H, m, phenyl H); IR (KBr) 3465, 3385, 1708 cm^{-1}; mass spectrum *m/e* 477 (EI, M$^+$). Anal. Calcd for $C_{28}H_{31}NO_4S$: C, 70.41; H, 6.54; N, 2.93. Found: C, 70.34; H, 6.56; N, 3.02.

(α*S*,β*S*,1*R*,2*S*)-β-[(2-Aminophenyl)thio]-α-hydroxy-β-(4-methoxyphenyl)propanoic Acid (15). A mixture of 24 g (0.05 mol) of **13**, 100 mL (0.20 mol) of 2 N NaOH, and 200 mL of EtOH was stirred at reflux under argon for 2 h (TLC indicated complete reaction). The mixture was evaporated in vacuo to a volume of ~100 mL, diluted with 50 mL of water, and extracted with 2 × 250 mL of ether. The ether layer contained the chiral auxiliary (−)-**10**, suitable for reuse after simple recrystallization from hexanes. The aqueous layer was acidified with 3 N H_2SO_4 to pH 4, extracted into 2 × 150 mL of CH_2Cl_2, dried (Na_2SO_4), and evaporated in vacuo. The residue, on trituration with acetonitrile, afforded, in two crops, 13.0 g (81%) of **15** as a light yellow solid: mp 138–140 °C; $[\alpha]^{20}_D$ +357.1° (*c* 0.3, EtOH) (lit.[8b] $[\alpha]^{20}_D$ +346.0° (*c* 3.5, EtOH)); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (3 H, s, OCH_3), 4.21 (1 H, d, *J* = 5.0 Hz, C*H*CO_2H), 4.36 (1 H, d, *J* = 5.2 Hz, C*H*Ar), 6.29–7.20 (8 H, m, ArH); IR (KBr) 3365, 3355, 1715 cm^{-1}; mass spectrum *m/e* 319 (EI, M$^+$). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.38. Found: C, 59.96; H, 5.21; N, 4.54.

***cis*-(+)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (17). A. From 13.** A mixture of 351 g (0.735 mol) of **13**, 10.5 g of PTSA, and 6.0 L of xylenes was stirred at reflux under argon using a Dean–Stark apparatus for 16 h. TLC (1:1 hexanes–EtOAc, SWUV) indicated a complete reaction, and the mixture was then cooled to 5 °C using an ice bath. The precipitated solids were collected by filtration and washed with 2 × 250 mL of hexanes to afford 162 g (73.2%) of **17** as a light yellow solid: mp 203–205 °C; $[\alpha]^{20}_D$ + 107.9° (*c* 0.3, EtOH); ^{1}H NMR (DMSO, 400 MHz) δ 3.22 (1 H, d, *J* = 9.0 Hz, OH), 3.79 (3 H, s, OCH_3), 4.42 (1 H, t, *J* = 6.8 Hz, CHAr), 5.07 (1 H, d, *J* = 6.8 Hz, C*H*OH), 6.83–7.65 (8 H, m, ArH), 9.86 (1 H, s, NH); IR (KBr) 3375, 1715 cm^{-1}; mass spectrum *m/e* 301 (EI, M$^+$). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.65; H, 4.97; N, 4.53; S, 10.37.

B. From 15. A mixture of 13 g (0.041 mol) of **15**, 0.4 g of PTSA, and 125 mL of xylenes was stirred at reflux under argon using a Dean–Stark apparatus for 16 h (overnight). TLC (1:1 hexanes–EtOAc, SWUV) indicated that the reaction was complete. On cooling, the precipitated solids were collected by filtration and washed with hexanes to afford 10.8 g (88%) of **17** as a colorless solid: mp 201–203 °C; $[\alpha]^{20}_D$ +124.1° (*c* 0.3, EtOH). The NMR spectrum was identical to that of the material obtained above.

***cis*-(+)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (19).** Into a 5-L three-necked flask equipped with a heating mantle, a mechanical stirrer, and a condenser were placed 162 g (0.54 mol) of **17** and then 1 L of EtOAc. After stirring to dissolve the solution, 100 g (0.694 mol) of 2-(dimethylamino)ethyl chloride hydrochloride was added in one portion followed by 300 g (2.16 mol) of finely ground K_2CO_3 and 5 mL of H_2O. After the heterogeneous mixture was rapidly stirred at reflux for 5 h, the reaction was shown to be complete by TLC (8:1 CH_2Cl_2–MeOH, SWUV) and was cooled to room temperature. Insoluble K_2CO_3 was removed from the reaction mixture by filtration through a sintered-glass funnel. The solvent was evaporated, and on standing, the residual oil crystallized. Recrystallization from ether gave 140 g (70%) of colorless crystalline **19**: mp 79–81 °C; $[\alpha]^{20}_D$ +156.4° (*c* 1, $CHCl_3$) (lit.[16] $[\alpha]^{20}_D$ +134.4° (*c* 1, $CHCl_3$), $[\alpha]^{20}_D$ +169.5° (*c* 1.0, MeOH)); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (6 H, s, NCH_3), 2.43–2.75 (2 H, m, NCH_2), 2.88 (1 H, br d, OH), 3.71 (1 H, m, NCH_2), 3.82 (3 H, s, OCH_3), 4.30 (1 H, br t, C*H*OH), 4.48 (1 H, m, NCH_2), 4.89 (1 H, d, *J* = 7.2 Hz, SC*H*Ar), 6.89–7.72 (8 H, m, ArH); IR (KBr) 3450, 1668 cm^{-1}; mass spectrum *m/e* 372 (EI, M$^+$). Anal. Calcd for $C_{20}H_{24}N_2O_3S$: C, 64.50; H, 6.50; N, 7.52; S, 8.59. Found: C, 64.83; H, 6.63; N, 7.28; S, 8.40. The residual mother liquor contained more **19** by TLC which would not crystallize. This material was acylated separately to diltiazem hydrochloride; by isolation of this final product it can be determined that at least 36.5 g (18.2%) of additional **19** was contained in these mother liquors for a total yield of 88.2%.

***cis*-(+)-3-(Acetyloxy)-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (Diltiazem Hydrochloride, 1).** A mixture of 118 g (0.317 mol) of **19**, 375 mL of CH_2Cl_2, 1.85 g of DMAP, and 50 mL of Ac_2O was heated at reflux under argon for 3 h. TLC (1:1 EtOAc–MeOH, SWUV) indicated complete reaction. The mixture was poured into 500 mL of ice–water, and 100 mL of brine was added. The organic layer was separated, and the aqueous layer was extracted with an additional 250 mL of CH_2Cl_2. The combined organic layers were washed with 800 mL of 5% NH_4OH, and the aqueous layer was extracted with 200 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to dryness. The residue was dissolved in 250 mL of MeOH and treated with anhydrous HCl(g) to pH 2. To the resulting solution was added 350 mL of ether. The precipitated solids were collected by filtration and washed with 10% MeOH–ether to afford 131.5 g (92%) of **1** as a colorless solid: mp 208–210 °C; $[\alpha]^{20}_D$ +102.0° (*c* 1, MeOH) (lit.[3a] $[\alpha]^{20}_D$ +98.3° (*c* 1, MeOH)); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (3 H, s, $COCH_3$), 2.85–2.94 (6 H, dd, *J* = 4.9 Hz, NCH_3), 3.20–3.58 (2 H, m, NCH_2), 3.83 (3 H, s, OCH_3), 4.37–4.62 (2 H, m, NCH_2), 5.02 (1 H, d, *J* = 7.8 Hz, C*H*OCOCH_3), 5.13 (1 H, d, *J* = 7.8 Hz, SC*H*Ar), 6.90–7.73 (8 H, m, ArH); IR (KBr) 3425, 1742, 1680 cm^{-1}; mass spectrum *m/e* 414 (EI, M$^+$). Anal. Calcd for $C_{22}H_{26}N_2O_4S$·HCl: C, 58.59; H, 5.80; N, 6.21; S, 7.10. Found: C, 58.22; H, 6.05; N, 6.13; S, 6.93. Also ~5% of **19** was obtained, probably through solvolysis of the 3-acetate by MeOH.

Supplementary Material Available: ORTEP drawings, tables of positional and thermal parameters, bond lengths, and bond angles for **8**, **11**, and **20** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.