cervical dislocation and their uteri were removed, stripped of adhering fat, and weighed.

Stock solutions of estradiol (600 μg/mL) and hexestrol (540 μg/d) were prepared in absoluite ethanol and diluted to the desired concentration with saline. Daily doses of estradiol were 0.08, 0.10, 0.16, or 0.20 μg/0.1 mL or 10.0 μg/0.4 mL. Daily doses of hexestrol were 0.05 or 0.5 μg/0.1 mL. Tamoxifen, aminotamoxifen, and fluorotamoxifen were dissolved in propylene glycol.

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**Registry No.** 1, 345-89-1; (*E*)-2, 97732-60-0; (*Z*)-2, 97732-61-1; 3, 97732-62-2; 4, 97749-43-4; 5, 1151-94-6; 6, 4834-72-4; 7, 97732-63-3; 8, 97732-64-4; 9, 97732-65-5; 10, 97732-66-6; 11, 97732-67-7; 12, 97732-68-8; 13, 97732-69-9; $CH_3CH_2CH(Br)Ph$, 2114-36-5; tamoxifen, 10540-29-1; estradiol, 50-28-2; hexestrol, 84-16-2; diethylstilbestrol, 56-53-1.

**Supplementary Material Available**: Tables of thermal and positional parameters (3 pages). Ordering information is given on any current masthead page.

# Synthesis and Biological Properties of (Carboxyalkyl)amino-Substituted Bicyclic Lactam Inhibitors of Angiotensin Converting Enzyme

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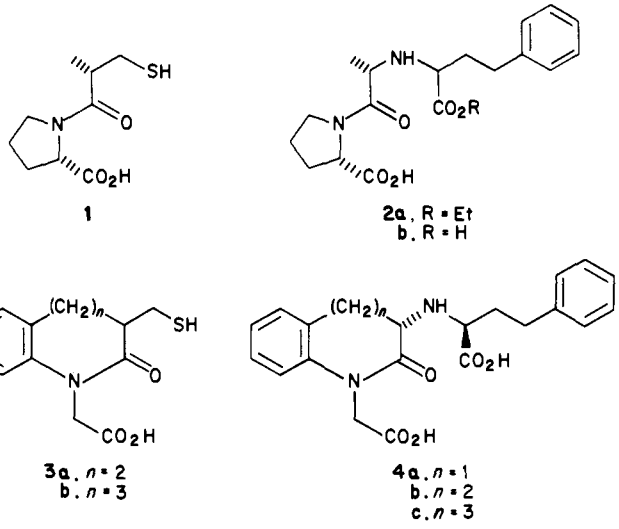
Syntheses of the potent angiotensin converting enzyme inhibitor (3*S*)-1-(carboxymethyl)-3-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one (**4b**; CGS 14831) and the related monoester prodrug (**17a**; CGS 14824A) are described together with preparative details for six- and eight-membered ring analogues. Inhibitory potencies and in vivo biological activity of the compounds are discussed. The data indicate that **17a** has a biological profile comparable to that of enalapril.

Captopril (**1**), the first orally effective angiotensin converting enzyme (ACE) inhibitor, is marketed as an antihypertensive and as an agent for the treatment of congestive heart failure.[1] However, there has been concern about the incidence of side effects associated with captopril therapy,[1] and the suggestion has been made that the mercapto function might be a contributory factor.[1] More recent studies have indicated that captopril is effective at lower doses than originally specified[2] and that, under these circumstances, side effects are effectively restricted to a small subgroup of patients having serious complications prior to initiation of the therapy. Studies reported on the clinical application of the non-thiol inhibitor enalapril (**2a**) are not as extensive as those with captopril, but indications are that the incidence of side effects is low.[3]




In a recent paper,[4] the synthesis of the ACE inhibitors (**3a,b**) was described. We considered it desirable to extend these studies to the synthesis of analogues of **3**, incorporating structural features of the prodrug **2a** and the corresponding enzyme inhibitor **2b**.

**Chemistry**. In order to assess the effect of ring size on the biological activity of the bicyclic lactams, we decided to prepare **4a–c**.

The synthesis of **4a** is outlined in Scheme I. Reductive alkylation of amino lactam **5**[5] with benzylpyruvic acid[6] gave amino acid **6** as a mixture of diastereomers. This mixture was esterified and then alkylated to give diester **8**. Chromatography of **8** gave the individual diastereomers that were separately hydrolyzed to the diacids **4a,d**.

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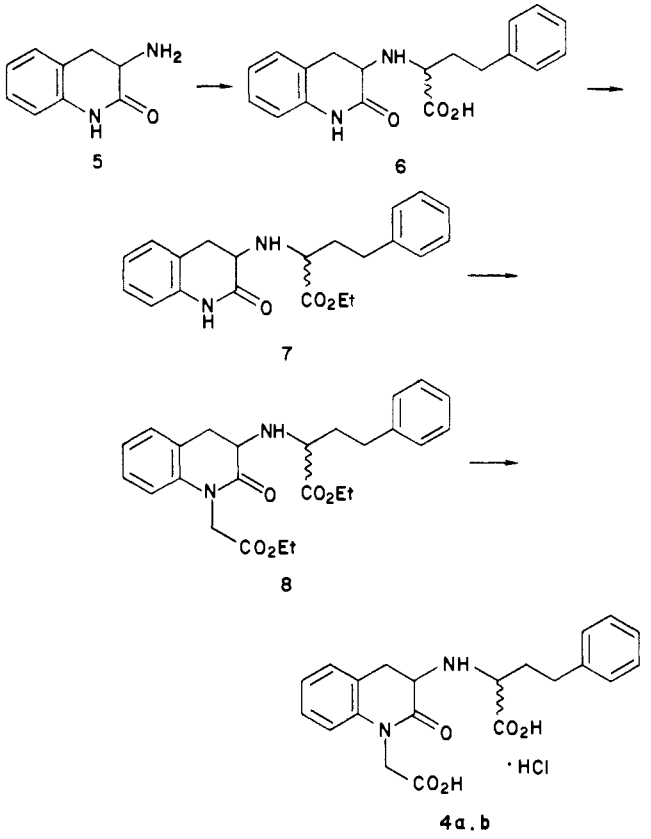
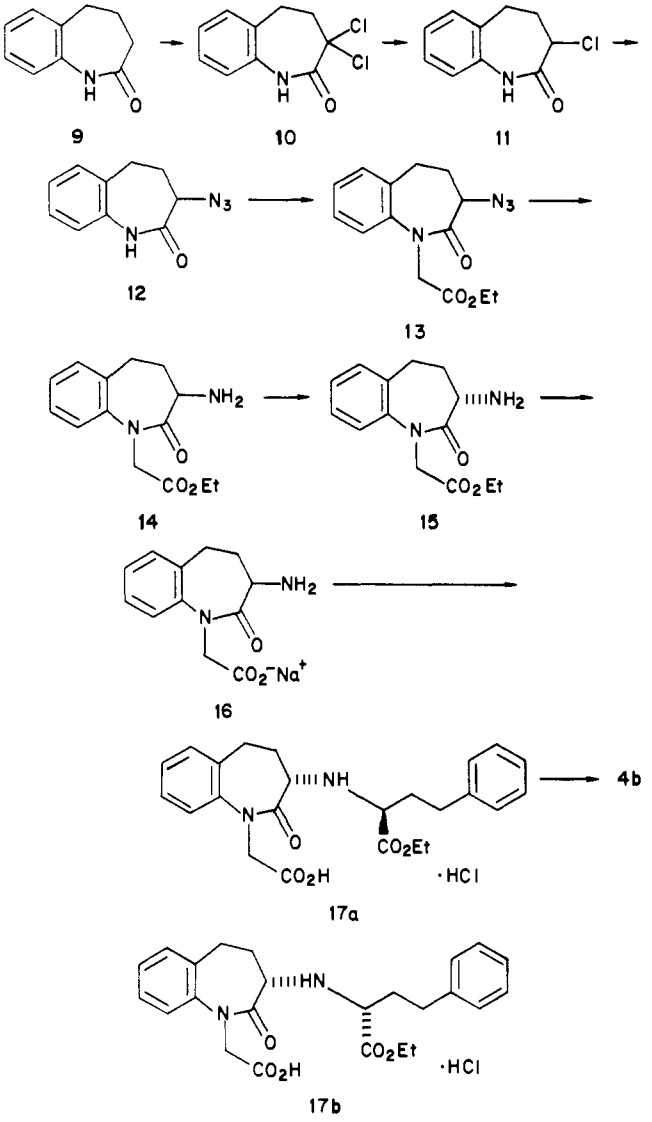
Scheme I



Scheme II



The synthesis of **4b** is outlined in Scheme II. Chlorination of **9**[7] with $PCl_5$ in xylene gave dichloro lactam **10** in excellent yield. This substance was reduced to monochloro lactam **11** by catalytic hydrogenation (Pd/C).

Treatment of **11** with sodium azide in $Me_2SO$ at 80 °C gave azide **12** in excellent yield. Alkylation of **12** with ethyl bromoacetate was effected under phase-transfer conditions with powdered KOH and tetrabutylammonium bromide in THF,[8] and the azide function was reduced by catalytic hydrogenation (Pd/C). Amino ester **14** was resolved via the tartrate salt. The negatively rotating isomer[9] was hydrolyzed to the sodium salt of the carboxylic acid, and this material was condensed with ethyl benzylpyruvate in the presence of sodium cyanoborohydride. Two isomers were obtained in a ratio of 70:30.[10] The major isomer **17a** (CGS 14824A) was obtained pure by recrystallization, while the minor isomer **17b** was purified by preparative HPLC. The major isomer was hydrolyzed to the corresponding diacid **4b** (CGS 14831). The racemic amino ester **14** was also converted to the two racemic diastereomers corresponding to **4b**. These are designated **4e,f**.

Eight-membered ring compounds were obtained by a sequence of reactions similar to that used for the preparation of **4b** and shown in Scheme III. Lactam **18**[11] was brominated with $Br_2/PCl_5$ in the presence of a catalytic quantity of iodine.[12] Azido lactam **20** was prepared with sodium azide in $Me_2SO$ at 60 °C. The azide could not be cleanly alkylated, but when sufficient reaction time was allowed, complete conversion to the N-alkylated α-keto lactam **21** resulted.[13] Reductive alkylation was accomplished by a two-step procedure. Imines were formed from **21a** and **21b** by reaction with ethyl 2-amino-4-phenyl-2-(*S*)-butyrate and dibutyltin dichloride in refluxing chloroform using a water separator.[14] Reduction with sodium

Table I. Inhibitors of Angiotensin Converting Enzyme

| compd | $IC_{50}$, nm |
|---|---|
| **2b** (MK 422) | 4.5 |
| **4a** | 610,[a] 1200[a,b] |
| **4d** | 5100[a] |
| **4b** (CGS 14831) | 1.7, 2.8[a,b] |
| **4e** | 5.2[a] |
| **4f** | 58[a] |
| **4c** | 7.5, 4.0[a,b] |
| **4g** | 62 |

[a] Racemate. [b] Data from ref 13.

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(8) Reuschling, D.; Pietsch, H.; Linkies, A. *Tetrahedron Lett.* **1978**, 615.
(9) The optical rotation of **15** is identical with that of the corresponding intermediate encountered in a synthesis of **4a** from L-tryptophan, manuscript in preparation. On this basis, the substance was assigned the *S* configuration.
(10) The configuration of the newly created center in the two isomers was assigned on the basis of the biological activity of the substances and/or products derived therefrom.
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**Table II.** Effects of 4-Day Repeated Oral Dosing with **17a** (CGS 14824) on Systolic Blood Pressure in Spontaneously Hypertensive Rats ($n = 6$)[a]

| dose, mg/kg | | predose | h post-dose: day 1, 2 | day 1, 24 | day 2, 2 | day 2, 24 | day 3, 2 | day 3, 24 | day 4, 2 | day 4, 24 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.1 | mean | 193.6 | 193.8 | 186.0 | 195.8 | 169.8* | 176.2 | 172.4* | 182.8 | 176.0* |
| | ±SE | 6.1 | 10.3 | 3.9 | 10.5 | 5.3 | 8.1 | 3.4 | 8.9 | 5.6 |
| | diff | | 0.2 | -7.6 | 2.2 | -23.8 | -17.4 | -21.2 | -10.8 | -17.6 |
| 1.0 | mean | 200.0 | 185.7* | 185.8 | 182.8 | 168.7** | 166.5** | 177.3* | 171.3 | 180.2** |
| | ±SE | 8.9 | 8.8 | 10.1 | 9.8 | 8.9 | 8.1 | 10.1 | 10.4 | 10.2 |
| | diff | | -14.3 | -14.2 | -17.2 | -31.3 | -33.5 | -22.7 | -28.7 | -19.8 |
| 10 | mean | 198.0 | 162.2** | 167.5* | 146.0*** | 147.3*** | 131.0*** | 150.2** | 130.8*** | 150.0** |
| | ±SE | 7.3 | 8.2 | 11.2 | 5.0 | 5.4 | 5.4 | 6.6 | 7.4 | 5.2 |
| | diff | | -35.8 | -30.5 | -52.0 | -50.7 | -67.0 | -47.8 | -67.2 | -48.0 |

[a] Values are expressed as systolic pressure (mmHg) ±SE. Values after drug were compared statistically to predose values by student's t-test (two-tailed) for paired data: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. [b] $n = 5$; one animal died immediately after dosing and was not included in calculation.

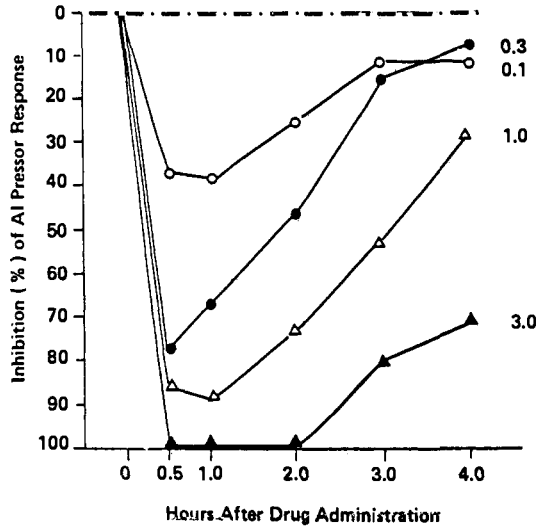


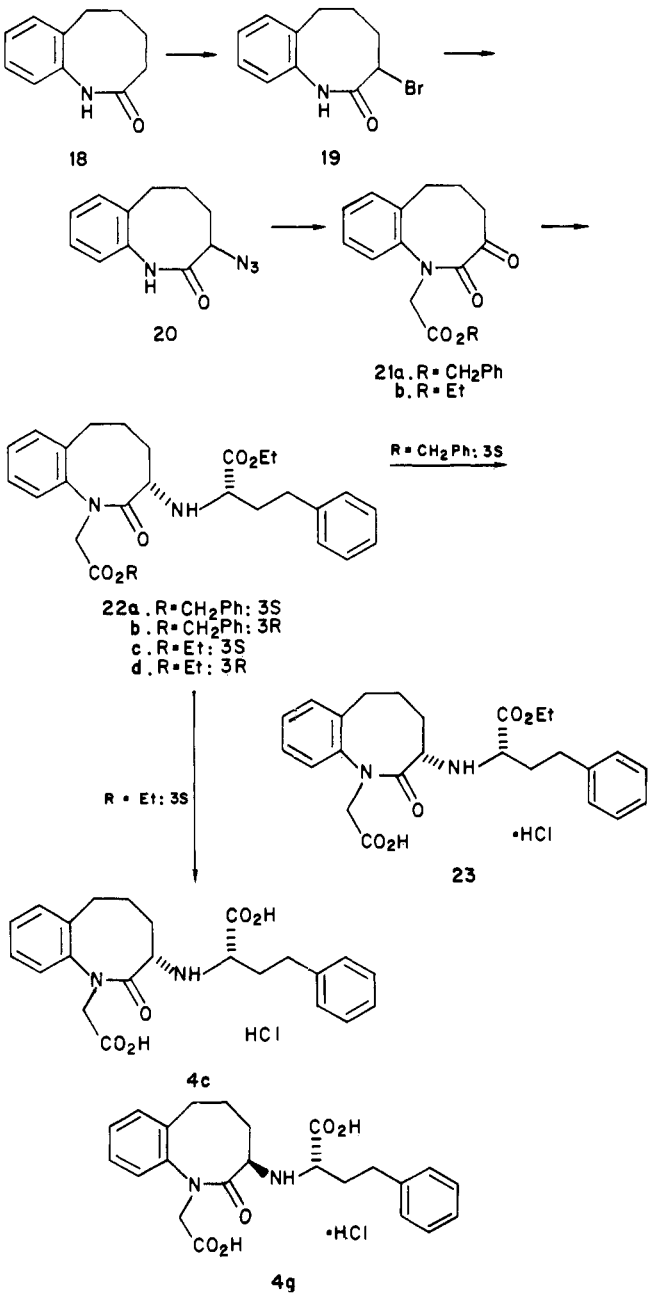

**Figure 1.** Effects of oral administration of **17a** (CGS 14824A; 0.1–3.0 mg/kg) on the pressor responses to angiotensin I (0.66 μg/kg, iv) in conscious normotensive rats ($n = 6$).

cyanoborohydride in methanol/acetic acid gave mixtures of two diastereomeric diesters in each case, which were separated by flash chromatography.[10] The monoethyl ester (**23**) was obtained by hydrogenolysis of the S,S isomer **22a** over 10% Pd/C, while the diethyl esters **22c,d** were separately hydrolyzed to the diacids **4c,g**.

**Biological Activity.** An initial assessment of the biological activity of the various lactams was obtained by determination of the in vitro potency of the diacids as inhibitors of rabbit lung ACE. The results, shown in Table I, indicate that the seven- and eight-membered lactam diacids are potent inhibitors, while the six-membered analogue is much less potent. The data obtained in this study are generally in keeping with those obtained in an investigation of the in vitro properties of the racemic compounds[15] and are in keeping with the results obtained with the sulfhydryl analogues described earlier.[4]

The seven-membered diacid **4b** was found to have only marginal biological activity following oral administration (presumably because of poor absorption), while the corresponding monoester **17a** was much more potent. Also, the eight-membered monoester (**23**) was less potent than **17a**. This is indicated in Figure 1, which shows the effects

**Scheme III**




of oral administration of **17a** (0.1–3.0 mg/kg) on the pressor response to angiotensin I in conscious normotensive rats, and in Figure 2, which shows the effects of **4b** and

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Table III. Effects of 4-Day Repeated Oral Dosing with Enalapril on Systolic Blood Pressure in Spontaneously Hypertensive Rats ($n$ = 6)[a]

| dose, mg/kg | | predose | h post-dose: day 1, 2 | day 1, 24 | day 2, 2 | day 2, 24 | day 3, 2 | day 3, 24 | day 4, 2 | day 4, 24 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.1 | mean | 197.7 | 197.5 | 175.8 | 172.0 | 173.7** | 175.7** | 173.5 | 168.0* | 204.0 |
| | ±SE | 11.2 | 12.2 | 12.7 | 10.7 | 10.8 | 11.2 | 13.0 | 10.0 | 12.1 |
| | diff | | -0.2 | -21.9 | -25.7 | -24.0 | -22.0 | -24.2 | -29.7 | -6.3 |
| 1.0 | mean | 186.8 | 160.0** | 169.5* | 158.7* | 168.7 | 146.7** | 160.0** | 145.0** | 160.8 |
| | ±SE | 4.3 | 7.4 | 3.7 | 4.2 | 8.7 | 8.8 | 4.2 | 6.2 | 11.3 |
| | diff | | -26.8 | -17.3 | -28.2 | -18.2 | -40.2 | -23.8 | -41.8 | -26.0 |
| 10 | mean | 199.0 | 152.5*** | 168.3** | 138.5** | 163.0** | 124.5*** | 174.0 | 135.5*** | 159.8** |
| | ±SE | 4.8 | 5.6 | 5.3 | 7.1 | 3.5 | 5.7 | 8.2 | 5.1 | 3.2 |
| | diff | | -46.5 | -30.7 | -60.5 | -36.0 | -74.5 | -25.0 | -63.5 | -39.2 |

[a] Values are expressed as systolic pressure (mmHg) ± SE. Values after drug were compared statistically to predose values by student's t-test (two-tailed) for paired data: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

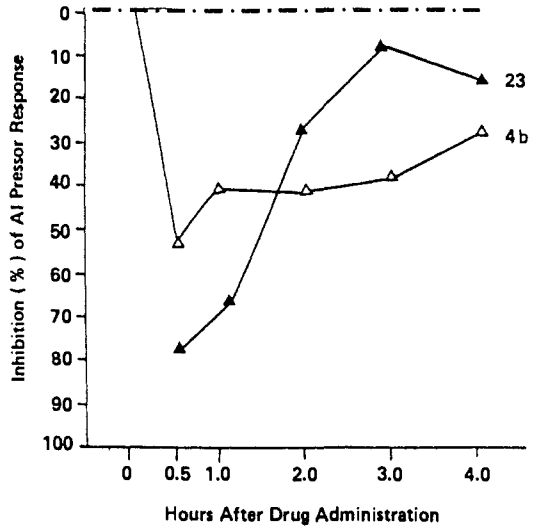


**Figure 2.** Effects of oral administration of **4b** (CGS 14831) and **23** (both at 3.0 mg/kg) on the pressor responses to angiotensin I (0.66 μg/kg, iv) in conscious normotensive rats ($n$ = 6).

**23** at 3.0 mg/kg.[16] Blood pressure effects of **17a** in the spontaneously hypertensive rat[17] at doses of 0.1–10 mg/kg po per day for 4 days are given in Table II with corresponding data for enalapril in Table III. These experiments indicated that **17a** (CGS 14824A) produced dose-dependent antihypertensive effects in this test system that were generally similar to those produced by enalapril.

## Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were obtained on a Varian EM 390 or CFT-20 instrument. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer and mass spectra on a Hewlett-Packard HP 5985 spectrometer. The experimental details for the biological tests have been described previously.[4,18]

**3-[(1-Carbethoxy-3-phenylpropyl)amino]-1,2,3,4-tetrahydroquinolin-2-one (7).** To a solution of **5**[5] (4.1 g, 0.025 mol) and benzylpyruvic acid (9.0 g, 0.05 mol) in MeOH (570 mL) was added sodium cyanoborohydride (2.7 g, 0.043 mol). The solution was stirred at room temperature under $N_2$ for 16 h, and then concentrated HCl (6.8 mL) was added. After the mixture was stirred for 1 h, the solvents were removed under reduced pressure and the residue triturated with $CH_2Cl_2$ (200 mL). The resulting colorless solid was collected by filtration and dried at room temperature to give a mixture of **6** and NaCl (10.4 g). This was added, without further purification, to saturated ethanolic HCl (550 mL), and the solution was refluxed for 16 h. The EtOH was removed under reduced pressure and the residue dissolved in EtOAc (250 ml) and washed with 10% $NH_4OH$ (150 mL). The aqueous phase was extracted with EtOAc (100 mL), and the combined organic solutions were dried ($Na_2SO_4$) and evaporated under reduced pressure to give 6.2 g (70% from **5**) of a diastereomeric mixture of **7** as a yellow oil that was not further purified: NMR ($CDCl_3$) δ 10.10 (br d, 1 H, NH), 7.28 (m, 9, aromatic), 4.25 (d of q, 2 H, $CH_2$), 3.67 (m, 2 H), 2.85 (m, 2 H), 2.05 (m, 2 H), 1.28 (d of t, 3 H, $CH_3$); mass spectrum $m/e$ (relative intensity) 352 ($M^+$, 10), 279 (100), 146 (35), 91 (75).

**1-(Carbethoxymethyl)-3-[(1-carbethoxy-3-phenylpropyl)amino]-1,2,3,4-tetrahydroquinolin-2-one (8).** To a suspension of 0.3 g of NaH (60% oil dispersion, 0.008 mol) in DMF (200 mL) was added tetrabutylammonium bromide (2.5 g, 0.008 mol) and a solution of **7** (2.5 g, 0.007 mol) in DMF (25 mL). This mixture was stirred at room temperature for 0.5 h. A solution of ethyl bromoacetate (1.3 g, 0.008 mol) in DMF (25 mL) was added, and the reaction mixture was heated at 50 °C for 22 h under an atmosphere of dry $N_2$. The DMF was removed under reduced pressure and the residue partitioned between $H_2O$ (200 mL) and $CH_2Cl_2$ (250 mL). The layers were separated, and the organic phase was washed with 1 N HCl (100 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure to give a brown oil (6.0 g). This was chromatographed on silica gel (120 g). Elution with 0–15% EtOAc/toluene gave 1.0 g of the faster moving isomer (**8a**) as an oil (32%), $R_f$ 0.40 in 1:1 EtOAc/toluene. Elution with 15–30% EtOAc/toluene gave 1.2 g of the slower moving isomer (**8b**, 38%) as an oil, $R_f$ 0.36 in 1:1 EtOAc/toluene, and elution with 30–50% EtOAc/toluene gave **7** (0.76 g; 30% recovery). **8a**: NMR ($CDCl_3$) δ 7.15 (m, 9 H, aromatic), 4.70 (q, 2 H, $NCH_2$), 4.22 (d of q, 4 H, $CO_2CH_2$), 3.55 (m, 2 H), 2.93 (m, 5 H), 2.00 (m, 2 H), 1.28 (d of t, 6 H, $CH_3$). **8b**: NMR ($CDCl_3$) δ 7.20 (m, 9 H, aromatic), 4.69 (q, 2 H, $NCH_2$), 4.22 (d of q, 4 H, $CO_2CH_2$), 3.60 (m, 2 H), 2.72 (m, 5 H), 2.10 (m, 2 H), 1.28 (d of t, 6 H, $CH_3$). The mass spectra of the two isomers were essentially identical: $m/e$ (relative intensity) 438 ($M^+$, 3), 365 (100), 233 (33), 130 (39), 91 (38).

**1-(Carboxymethyl)-3-[(1-carboxy-3-phenylpropyl)amino]-1,2,3,4-tetrahydroquinolin-2-one (4a and 4d).** A solution of **8a** (1.0 g, 0.002 mol) in 3 N HCl (60 mL) containing EtOH (10 mL) was refluxed for 16 h. The solvents were removed under reduced pressure, and the residue was triturated with acetone/ether (1:5, 100 mL). The resulting colorless solid was dried to give **4a** (0.550 g, 58%): mp 165–170 °C; NMR ($Me_2SO$-$d_6$) δ 7.90 (br s, 4 H, exchangeables), 7.35 (m, 9 H, aromatic), 4.60 (m, 4 H), 2.90 (m, 6 H). Anal. ($C_{21}H_{22}N_2O_5$·HCl) C, H, N.

The second isomer (**4d**) was prepared in 40% yield from **8b** by a procedure similar to that described above: mp 178–180 °C; NMR ($Me_2SO$-$d_6$) δ 11.55 (br s, 4 H, exchangeables), 7.30 (m, 9 H, aromatic), 4.50 (m, 4 H), 2.78 (m, 6 H). The mass spectra of the trimethylsilyl ester derivatives of the two isomers were essentially identical: $m/e$ (relative intensity) 526 ($M^+$, 5), 409 (100), 365 (50), 279 (30). Anal. ($C_{21}H_{22}N_2O_5$·HCl) C, H, N.

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**3,3-Dichloro-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one (10).** To a solution of **9**[7] (48.3 g, 0.3 mol) in xylene (1300 mL) was added $PCl_5$ (188 g, 0.9 mol), and the mixture was gradually heated to 90 °C during 0.5 h. *Caution*! There is a vigorous evolution of HCl gas as the $PCl_5$ dissolves. After 0.5 h at 90 °C the reaction mixture was filtered to remove a small amount of suspended solid, and the filtrate was evaporated under reduced pressure. The residue was added to saturated $Na_2CO_3$ (100 mL), and this mixture was stirred until precipitation of solid material was complete. The solid was collected by filtration, washed with EtOH (2 × 100 mL) and ether (50 mL), and dried to give 69.0 g (90%) of **10**: mp 185–187 °C; NMR ($CDCl_3$/$Me_2SO$-$d_6$) δ 10.35 (br s, 1 H, NH), 7.10 (m, 4 H, aromatic), 3.05 (m, 4 H, $CH_2$); IR 1675 (C=O), 895 $cm^{-1}$ (C—Cl); mass spectrum *m/e* (relative intensity) 229 ($M^+$, 50), 158 (28), 132 (100), 104 (29). Anal. ($C_{10}H_9Cl_2NO$) C, H, N.

**3-Chloro-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one (11).** A mixture of **10** (10.0 g, 0.087 mol), sodium acetate (7.7 g, 0.11 mol), and 5% Pd/C (0.86 g) in acetic acid (460 mL) was hydrogenated at atmospheric pressure and room temperature for 0.5 h with a total $H_2$ uptake of 950 mL. The catalyst was filtered off (Celite) and the filtrate evaporated to dryness under reduced pressure. The residue was partitioned between 10% $NaHCO_3$ (900 mL) and $CH_2Cl_2$ (300 mL). The layers were separated, and the aqueous phase was extracted with additional $CH_2Cl_2$ (3 × 300 mL). The combined organic solutions were dried ($Na_2SO_4$) and evaporated under reduced pressure. The resulting solid was triturated with ether (350 mL) and collected to afford 8.1 g (95%) of **11**: mp 163–167 °C; NMR ($Me_2SO$-$d_6$) δ 10.00 (br s, 1 H, NH), 7.15 (m, 4 H, aromatic), 4.45 (m, 1 H, methine proton), 2.62 (m, 4 H, $CH_2$); IR 1700 (C=O), 890 $cm^{-1}$ (C—Cl); mass spectrum *m/e* (relative intensity) 196 ($M^+$ + 1, 100), 160 (18). Anal. ($C_{10}H_{10}ClNO$) C, H, N.

**3-Azido-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one (12).** A solution of **11** (15.9 g, 0.08 mol) and sodium azide (6.4 g, 0.10 mol) in $Me_2SO$ (320 ml) was maintained at 80 °C for 3 h. The reaction mixture was cooled to room temperature and poured into ice/$H_2O$ (1 L), which precipitated a buff-colored solid. This was collected by filtration and dried at 75 °C under reduced pressure to give 14.7 g (90%) of **12**: mp 142–145 °C; NMR ($Me_2SO$-$d_6$) δ 10.15 (s, 1 H, NH), 7.22 (m, 4 H, aromatic), 3.85 (d of d, 1 H, methine proton), 2.50 (m, 4 H, $CH_2$); IR 1675 (C=O), 2110 $cm^{-1}$ (—N=$N^+$=$N^-$); mass spectrum *m/e* (relative intensity) 202 ($M^+$, 8), 146 (100), 118 (61), 91 (26). Anal. ($C_{10}H_{10}N_4O$) C, H, N.

**Ethyl 3-Azido-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one-1-acetate (13).** To a mixture of **12** (3.0 g, 0.015 mol), tetrabutylammonium bromide (0.5 g, 0.0015 mol), and powdered KOH (1.1 g, 0.016 mol) in THF (30 mL) was added ethyl bromoacetate (1.9 mL, 0.016 mol; mild exotherm). The reaction mixture was stirred vigorously at room temperature for 1.5 h under an atmosphere of dry $N_2$ and was then partitioned between $H_2O$ (50 mL) and $CH_2Cl_2$ (100 mL). The organic phase was washed with additional $H_2O$ (2 × 50 mL). The combined organic solutions were dried ($Na_2SO_4$) and evaporated under reduced pressure to give **13** (4.1 g, 96%) as an amber oil used without further purification: NMR ($CDCl_3$) δ 7.30 (m, 4 H, aromatic), 4.50 (q, 2 H, $NCH_2$), 4.15 (q, 2 H, $CO_2CH_3$), 3.45 (m, 2 H), 2.45 (m, 3 H), 1.20 (t, 3 H, $CH_3$); IR 1675 (C=O, lactam), 1750 (C=O, ester), 2110 $cm^{-1}$ (—N=$N^+$=$N^-$); mass spectrum *m/e* (relative intensity) 288 ($M^+$, 2), 232 (68), 186 (36), 132 (100), 91 (66).

**Ethyl 3-Amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one-1-acetate (14).** A mixture of **13** (20.0 g, 0.070 mol) and 10% Pd/C (1.0 g) in EtOH (100 mL) was hydrogenated at 3 atm at room temperature for 1.5 h, with periodic venting to remove the nitrogen formed. The catalyst was filtered off (Celite) and the filtrate evaporated under reduced pressure to give a yellow oil. Trituration with ether (100 mL) gave a colorless solid that was collected by filtration to afford **14** (17.0 g, 93%): mp 101–102 °C; NMR ($CDCl_3$) δ 7.24 (m, 4 H, aromatic), 4.55 (q, 2 H, $NCH_2$), 4.23 (q, 2 H, $CO_2CH_2$), 3.31 (m, 2 H), 2.15 (m, 3 H), 1.60 (br s, exchangeable, 2 H, $NH_2$), 1.28 (t, 3 H, $CH_3$); mass spectrum *m/e* (relative intensity) 262 ($M^+$, 15), 244 (30), 217 (25), 161 (28), 132 (100), 91 (70). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

**Ethyl (3*S*)-3-Amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one-1-acetate (15).** A solution of **14** (25.1 g, 0.096 mol) and L-tartaric acid (14.4 g, 0.096 mol) in hot EtOH (200 mL) was allowed to cool and stand at room temperature overnight. The resulting solid was filtered off and dried under reduced pressure to give 30.7 g of white powder. This material was recrystallized an additional two times from EtOH (200 mL) to afford 13.6 g (34%) of ethyl (3*S*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one-1-acetate tartrate salt, mp 168–169 °C. The free base was obtained with 10% $NH_4OH$ to give **15** (8.0 g) as a colorless solid: mp 104–106 °C; $[\alpha]_D$ −285.5° (*c* 0.99, EtOH).

**(3*S*)-3-Amino-1-(carboxymethyl)-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one Sodium Salt (16).** To a solution of **15** (4.0 g, 0.056 mol) in MeOH (150 mL) was added a solution of NaOH (2.1 g, 0.053 mol) in $H_2O$ (5 mL), and the resulting solution was stirred at room temperature for 2 h. The solvents were evaporated under reduced pressure, and the residue was dried and triturated with ether (100 mL) to give **16** (12.9 g, 89%). This material was used without further purification.

**(3*S*)-1-(Carboxymethyl)-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one Hydrochloride (17a; CGS 14824A)[10] and the *SR* Isomer (17b).**[10] A solution of **16** (12.9 g, 0.050 mol) and ethyl 2-keto-4-phenylbutanoate (31.0 g, 0.15 mol) in acetic acid (100 ml) and MeOH (75 mL) was stirred at room temperature for 1 h under an atmosphere of dry $N_2$. A solution of sodium cyanoborohydride (3.8 g, 0.062 mol) in MeOH (30 mL) was then added dropwise during 4 h. The resulting solution was stirred overnight at room temperature after which concentrated HCl (10 mL) was added. After the mixture was stirred for 1 h at room temperature, the solvents were evaporated under reduced pressure and the residue was partitioned between $H_2O$ (400 mL) and ether (100 mL). The pH was adjusted to 9.3 with concentrated $NH_4OH$, the layers were separated, and the pH of the aqueous phase was adjusted to 4.3 with concentrated HCl. The aqueous solution was extracted with EtOAc (3 × 100 mL). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (150 mL), and dry HCl gas was bubbled through the solution for 5 min. The solvent was evaporated under reduced pressure, and the resulting foam was dissolved in hot methyl ethyl ketone (100 mL). The solid that precipitated on cooling was collected by filtration to give the product as a 95:5 diasteriomeric mixture as determined by HPLC (Whatman ODS-3 reversed-phase column, eluent 25% $H_2O$/MeOH containing 0.025% HOAc, 1.0 mL/min flow rate). The product was recrystallized from 10:1 3-pentanone/MeOH (110 mL) to give **17a** (5.8 g, 25%): mp 188–190 °C; $[\alpha]_D$ −141.0° (*c* 0.9, EtOH); mass spectrum *m/e* (relative intensity) 424 ($M^+$, 2), 351 (100), 190 (22), 91 (65). Anal. ($C_{24}H_{28}N_2O_5$·HCl) C, H, N.

The mother liquor from the original methyl ethyl ketone recrystallization was evaporated under reduced pressure and the residue stirred with EtOAc (50 mL). The remaining solid was subjected to preparative HPLC using a Waters Prep 500A machine with $C_{18}$ reversed-phase columns and 30% $H_2O$/MeOH containing 0.05% HOAc as the solvent system. The appropriate fractions were combined, evaporated, and dissolved in $CH_2Cl_2$ (75 mL). HCl gas was bubbled into the solution for a few minutes and the solvent was evaporated under reduced pressure. The residue was recrystallized from methyl ethyl ketone to give **17b** (2.8 g, 12%): mp 181–183 °C; $[\alpha]_D$ −188° (*c* 0.8, EtOH). Anal. ($C_{24}H_{28}N_2O_5$·HCl) C, H, N.

**(3*S*)-1-(Carboxymethyl)-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one (4b; CGS 14831).** A solution of sodium hydroxide (0.27 g, 0.007 mol) in $H_2O$ (2 mL) was added to a solution of **17a** (1 g, 0.002 mol) in MeOH (10 mL). The reaction mixture was stirred for 18 h at room temperature, and the solvents were removed under reduced pressure. The residue was dissolved in water (25 mL) and the pH adjusted to 3 by the addition of 4 N HCl. The resulting solid was filtered off, washed with $H_2O$, and dried to give **4b** (0.7 g, 69%): mp 270–272 °C; $[\alpha]_D$ −200.5° (*c* 1, 3% aqueous $NH_4OH$). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

**3-Bromo-3,4,5,6-tetrahydro-1-benzazocin-2(1*H*)-one (19).** To a solution of **18**[11] (12.0 g, 0.068 mol) in $CHCl_3$ (150 mL) at 0 °C was added phosphorus pentachloride (15.0 g, 0.072 mol) followed by iodine (0.15 g). The reaction mixture was stirred for 30 min, and then bromine (12.0 g) was added during 5 min. The reaction mixture was refluxed for 4 h, cooled to room temperature, and poured into ice/$H_2O$ (200 g). The $CHCl_3$ layer was washed

with $H_2O$ (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give **19** (8.7 g, 50%), mp 192–194 °C, homogeneous by silica gel thin-layer chromatography ($R_f$ 0.6 in 1:1 EtOAc/toluene): NMR ($CDCl_3$) δ 8.56 (br, 1 H), 6.69–7.94 (m, 4 H), 4.34 (t, 1 H), t), 1.02–3.33 (m, 6 H); mass spectrum *m/e* (relative intensity) 253. Anal. ($C_{11}H_{12}BrNO$) C, H, N.

**3-Azido-3,4,5,6-tetrahydro-1-benzazocin-2(1*H*)-one (20).** A solution of **19** (1.0 g, 0.0039 mol) and sodium azide (0.30 g, 0.0046 mol) in $Me_2SO$ (20 mL) was stirred for 5 h at 60 °C. The reaction mixture was poured into cold $H_2O$ (125 mL) to give a solid that was collected by filtration and dried in vacuo at 60 °C to give **20** (0.7 g, 83%): mp 143–145 °C dec; IR (Nujol) 2110, 1650 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 10.2 (br, 1 H), 7.02–7.61 (m, 4 H), 3.36 (m, 1 H), 1.18–2.95 (m, 6 H); mass spectrum *m/e* (relative intensity) 188 (M - 28), 187, 132. Anal. ($C_{11}H_{12}N_4O$) C, H, N.

**1-[(Carbobenzyloxy)methyl]-3,4,5,6-tetrahydro-1-benzazocine-2,3(1*H*)-dione (21a).** To a solution of **20** (4.0 g, 0.018 mol) in THF (250 mL) was added potassium *tert*-butoxide (2.3 g, 0.020 mol). The reaction mixture was stirred for 1 h at room temperature, and benzyl bromoacetate (4.7 g; 0.021 mol) in THF (10 mL) was added. The reaction mixture was stirred for 36 h at room temperature, and the solvents were evaporated under reduced pressure. The residue was dissolved in $H_2O$ (50 mL), and the solution was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure to give **21a** (3.4 g, 57%) as an oil, used without further purification: IR (neat) 1660, 1720, 1750 $cm^{-1}$.

**(3*S*)-1-[(Carbobenzyloxy)methyl]-3-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-3,4,5,6-tetrahydro-[1]benzazocin-2(1*H*)-one (22a) and the *RS* Isomer (22b).**[10] A solution of **21a** (5.9 g, 0.017 mol) and ethyl (2*S*)-2-amino-4-phenylbutyrate (3.8 g, 0.018 mol) in $CHCl_3$ (200 mL) containing di-*n*-butyltin dichloride (0.15 g, 0.0005 mol) was refluxed for 24 h with use of a water separator. The solvent was evaporated under reduced pressure to give the imine (9.2 g), which was used directly. To a solution of the imine (9.0 g, 0.017 mol) in MeOH (80 mL) and HOAc (15 mL) was added sodium cyanoborohydride (1.4 g, 0.022 mol). The reaction mixture was stirred at room temperature for 18 h, when 12 N HCl (3.0 mL) was added. The solvents were removed under reduced pressure, and the residue was dissolved in 10% sodium carbonate (75 mL). The solution was extracted with $CH_2Cl_2$ (3 × 75 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil (8.0 g). The diastereomeric amines were separated by flash column chromatography (silica gel, 3:1 toluene/EtOAc) to give **22b** as an oil (2.8 g) [$R_f$ 0.53 in 1:1 EtOAc/toluene; NMR ($CDCl_3$) 7.31 (s, 5 H), 7.18 (m, 9 H), 5.07 (s, 2 H), 4.36 (s, 2 H), 4.02 (q, 2 H, $J$ = 7 Hz), 1.11 (t, 3 H, $J$ = 7 Hz)] and **22a** (1.0 g) as an oil, used without further purification [$R_f$ 0.50 in 1:1 EtOAc/toluene; NMR ($CDCl_3$) δ 7.35 (s, 5 H), 7.21 (m, 9 H), 5.18 (s, 2 H), 4.47 (s, 2 H), 4.02 (q, 2 H $J$ = 7 Hz), 1.3–4.3 (13 H), 1.01 (t, 3 H, $J$ = 7 Hz).

**(3*S*)-1-(Carboxymethyl)-3-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-3,4,5,6-tetrahydro-[1]benzazocin-2-(1*H*)-one (23).** A solution of **22a** (1.0 g, 0.0019 mol) in EtOH (150 mL) was exhaustively hydrogenated at room temperature and atmospheric pressure with 10% Pd/C (1.0 g) as catalyst. The catalyst was filtered off and the filtrate evaporated under reduced pressure. The residue was dissolved in ether (40 mL), and HCl gas was bubbled through the solution for 5 min. The solvent was removed under reduced pressure and the residue triturated with ether (3 mL). The resulting solid was filtered off and dried to give **23** (0.6 g), mp 96–98 °C. Anal. ($C_{25}H_{30}N_2O_5 \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

**1-(Carbethoxymethyl)-3,4,5,6-tetrahydro[1]benzazocine-2,3(1*H*)-dione (21b).** To a solution of **20** (5.0 g, 0.023 mol) in THF (250 ml) at room temperature was added potassium *tert*-butoxide (2.9 g, 0.026 mol). The reaction mixture was stirred for 1 h and ethyl bromoacetate (4.3 g, 0.026 mol) in THF (10 mL) was added. The reaction mixture was stirred at room temperature for 36 h, and the solvents were removed under reduced pressure. The residue was dissolved in water (50 mL) and the solution extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give **21b** (40 g, 63%) as an oil, used without further purification; IR ($CHCl_3$) 1640, 1720, 1750 $cm^{-1}$; mass spectrum *m/e* 274, 247, 202, 174.

**(3*S*)-1-(Carbethoxymethyl)-3-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-3,4,5,6-tetrahydro-[1]benzazocin-2(1*H*)-one (22c) and the *RS* Isomer (22d).**[10] A solution of **21b** (2.75 g, 0.01 mol) and ethyl (2*S*)-2-amino-4-phenylbutyrate (2.1 g, 0.01 mol) in $CHCl_3$ (200 mL) containing di-*n*-butyltin dichloride (0.15 g, 0.0005 mol) was refluxed for 24 h with use of a water separator. The reaction mixture was evaporated under reduced pressure to give the crude imine, which was used directly. To a solution of the imine (4.6 g, 0.01 mol) in MeOH (75 mL) and HOAc (15 mL) was added sodium cyanoborohydride (0.85 g, 0.014 mol). The reaction mixture was stirred at room temperature for 20 h when 12 N HCl (2.5 mL) was added. The reaction mixture was evaporated and the residue dissolved in 10% sodium carbonate (50 mL). The solution was extracted with $CH_2Cl_2$ (3 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give an oil. The diastereomeric amines were separated by flash column chromatography (silica gel, 3:1 toluene/EtOAc) to give **22d** as an oil (1.5 g, 34%) [$R_f$ 0.5 in 1:1 EtOAc/toluene; NMR ($CDCl_3$) δ 6.93–7.42 (m, 9 H), 4.41 (s, 2 H), 4.13 (q, 4 H, $J$ = 7 Hz), 1.22 (t, 3 H, $J$ = 7 Hz)] and **22c** (1.7 g, 38%) as an oil, used without further purification [$R_f$ 0.48 in 1:1 EtOAc/toluene; NMR ($CDCl_3$) δ 7.24 (m, 9 H), 4.44 (s, 2 H), 4.19 (q, 4 H, $J$ = 7 Hz), 1.26 (t, 3 H, $J$ = 7 Hz), 1.02 (t, 3 H, $J$ = 7 Hz).

**(3*S*)-1-(Carboxymethyl)-3-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]-3,4,5,6-tetrahydro-[1]benzazocin-2(1*H*)-one Hydrochloride (4c).** To a solution of **22c** (0.56 g, 0.001 mol) in MeOH (40 mL) at room temperature was added a solution of sodium hydroxide (0.11 g, 0.002 mol) in $H_2O$ (5 mL). The reaction mixture was stirred at room temperature for 2 h and then evaporated under reduced pressure. The residue was dissolved in $H_2O$ (5 mL) and washed with ether (2 × 50 mL). The aqueous layer was brought to pH 2 with 6 N HCl, which produced a precipitate. The solid was collected by filtration and dried in vacuo at 50 °C to give **4c** (0.3 g, 60%): mp 148–150 °C; $[\alpha]_D$ 24° (*c* 1.0, MeOH). Anal. ($C_{23}H_{26}N_2O_5 \cdot HCl$) C, H, N.

**(3*R*)-1-(Carboxymethyl)-3-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]-3,4,5,6-tetrahydro-[1]benzazocin-2(1*H*)-one Hydrochloride (4g).** Starting with (3*R*)-1-[(ethoxycarbonyl)-methyl]-3-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-3,4,5,6-tetrahydro[1]benzazocin-2(1*H*)-one (1.0 g, 0.002 mol) in MeOH (50 mL) and sodium hydroxide (0.2 g, 0.005 mol) in $H_2O$ (5 mL), a procedure similar to that described above was followed to give **4g** (0.7 g, 70%): mp 169–171 °C; $[\alpha]_D$ +104° (*c* 1.0, MeOH). Anal. ($C_{23}H_{26}N_2O_5 \cdot HCl$) C, H, N.

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**Registry No.** (±)-**4a**, 97278-81-4; (±)-**4a**·HCl, 97278-66-5; **4b**, 86541-78-8; **4c**, 97278-82-5; **4c**·HCl, 97278-79-0; (±)-**4d**, 97293-69-1; (±)-**4d**·HCl, 97293-68-0; **4g**, 97278-83-6; **4g**·HCl, 97278-80-3; (±)-**5**, 85115-10-2; (±)-(*R**,*R**)-**7**, 97278-62-1; (±)-(*R**,*S**)-**7**, 97278-63-2; (±)-(*R**,*R**)-**8**, 97278-65-4; (±)-(*R**,*S**)-**8**, 97278-64-3; **9**, 4424-80-0; **10**, 86499-22-1; (±)-**11**, 97278-67-6; (±)-**12**, 97278-68-7; (±)-**13**, 97278-69-8; (±)-**14**, 88391-85-9; **15**, 86499-52-7; **15** tartrate, 97278-70-1; **16**, 86499-53-8; **17a**, 86541-75-5; **17a**·HCl, 86541-74-4; **17b**, 86541-76-6; **17b**·HCl, 86541-77-7; **18**, 22246-75-9; (±)-**19**, 97278-71-2; (±)-**20**, 97278-72-3; **21a**, 97278-73-4; **21b**, 93749-43-0; **22a**, 97278-74-5; **22b**, 97278-75-6; **22c**, 97278-77-8; **22d**, 97278-78-9; **23**·HCl, 97278-76-7; $Ph(CH_2)_2COCO_2H$, 710-11-2; $PhCH_2COCO_2Et$, 64920-29-2; $BrCH_2CO_2Et$, 105-36-2; $BrCH_2CO_2CH_2Ph$, 5437-45-6; (*S*)-$Ph(CH_2)_2CH(NH_2)CO_2H$, 46460-23-5.