A Novel Synthesis of the Monobactam Antibiotic Carumonam

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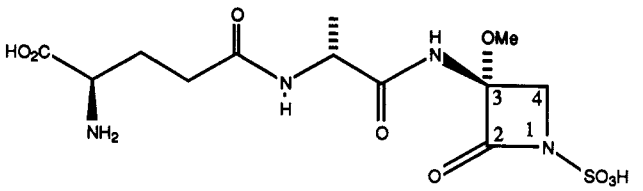
A novel synthesis of the monobactam **4**, a precursor of the antibiotic carumonam (**3**), has been achieved via the epoxide methyl (2*R*,3*S*)-4-acetoxy-2,3-epoxybutyrate (**10**). The latter was prepared from calcium L-threonate in three steps and 85% overall yield. In a related study, ethyl (2*R*,3*S*)-4-hydroxy-2,3-epoxybutyrate (**17**) was prepared from L-(+)-tartaric acid [(2*R*,3*R*)-tartaric acid] in 45% overall yield. Treatment of the sodium salt derived from **10** or **17** with ammonia led to a stereo- and regiospecific opening of the oxirane ring to give **20**, after esterification, amide formation, and protection of the amino group. Conversion of **20** into **4** was accomplished by selective protection of the primary hydroxy group with chloroacetyl chloride, mesylation, sulfonation with 2-picoline–SO_3, and ring closure with potassium bicarbonate.

The monobactams are a new class of β-lactam antibiotics characterized by the presence of a sulfonic acid group on the N(1) position of the β-lactam ring (e.g., sulfazecin, **1**).[1] The original naturally derived monobactams possessed weak to moderate antibacterial activity, including activity against Gram-negative bacteria. In an effort to improve their therapeutic value, considerable structure–activity studies on the monobactams were undertaken, culminating in the introduction of aztreonam (**2**)[2] into clinical practice and the selection of carumonam (**3**, AMA-1080, Ro 17-2301)[3] for clinical trials. Carumonam has shown strong antibacterial activity against a variety of Gram-negative bacteria, including *Pseudomonas aeruginosa*, and has high stability to chromosomal and plasmid-mediated β-lactamases.[3]

Previous syntheses of the β-lactam moiety of carumonam, i.e. **4**, include three[4] that are based on the Staudinger ketene–imine [2 + 2] cycloaddition[5] and two that are based on the cyclization of an appropriately substituted mesylate.[6] The conversion of **4** into carumonam has already been accomplished.[7]

Stereospecific cyclization of an activated amide, with a sulfonate as leaving group, has proved invaluable in the synthesis of monobactams.[8] Using this strategy, Wei et al.[6a] have achieved an expeditious synthesis of **4** from L-threonic acid (**5**) (Scheme I), in which the key cyclization of the mesylate **7** to give **4** was effected with potassium bicarbonate. However, this synthesis was somewhat compromised by the use of sodium azide to introduce the amino group destined to be that at C-3 in the monobactam and by the liberal use of protecting groups. Recently, Sendai et al.[6b] have reported the preparation of **7** in eight steps from the relatively scarce fermentation product (2*R*,3*R*)-2,3-epoxysuccinic acid, using ammonia to introduce the amino group at C-3 (monobactam numbering).

The purpose of the present study was to find a synthesis of **4** that was shorter, more amenable to scale-up, and more economical than those already available. To this end, we have found the epoxides **10** and **17**, which were readily prepared from calcium L-threonate and L-(+)-tartaric acid,



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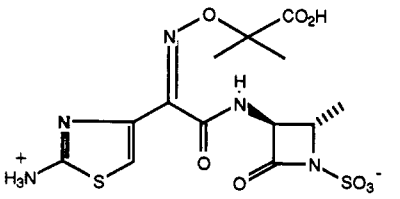

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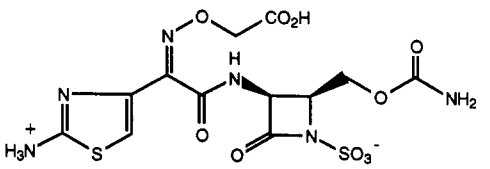

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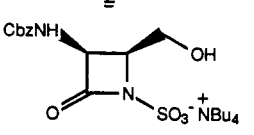

4

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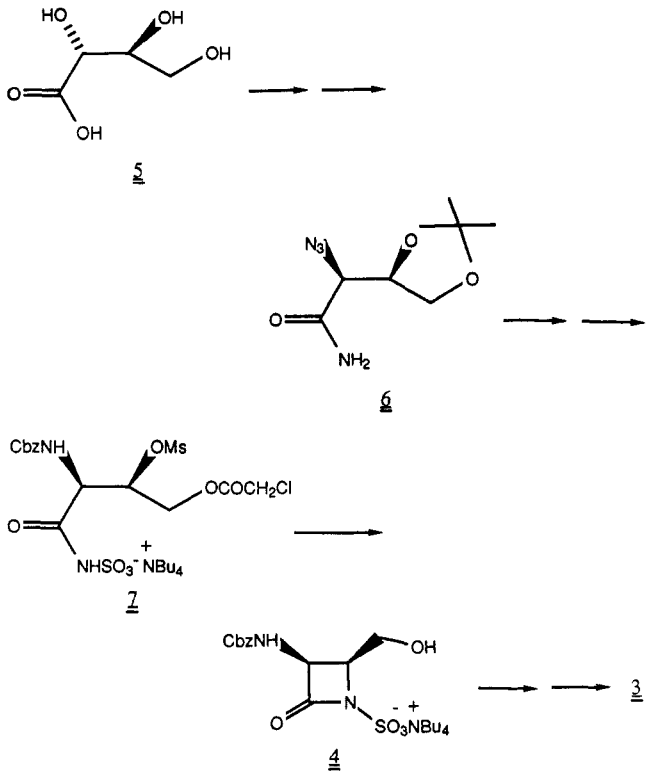
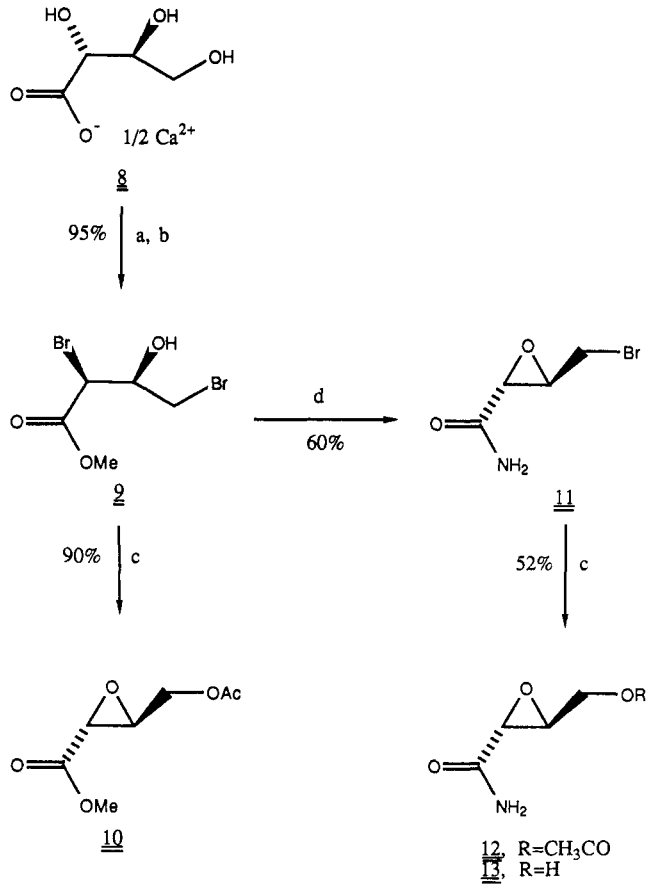
Scheme I



Scheme II[a]



[a] (a) HBr, CH_3CO_2H; (b) MeOH; (c) KOAc, KI, DMF; (d) NH_4OH.

respectively, to be suitable synthons for the elaboration of **4**. Thus, regiospecific opening of the epoxide **18**, derived from **10** or **17** with ammonia, followed by protection of the amino group as the (benzyloxy)carbonyl derivative **20**, selective protection of the primary alcohol, mesylation, sulfonation, and ring closure gave **4** in ca. 20% overall yield from calcium L-threonate.

Results and Discussion

The epoxides **10** and **12** were prepared from calcium L-threonate (**8**) as depicted in Scheme II. Treatment of **8**, which was readily available from the oxidation of ascorbic acid with hydrogen peroxide in the presence of calcium carbonate,[6a,9] with a large excess of anhydrous hydrogen bromide in acetic acid followed by esterification with methanol gave an excellent yield of the dibromo ester **9** in which the original C-2 configuration of L-threonic acid had been inverted.[10] Preparation of the epoxide **10** from **9** was efficiently accomplished in an almost quantitative yield with potassium acetate in the presence of potassium iodide. In a parallel series of experiments, the epoxide **12** was obtained from the reaction of **9** with ammonium hydroxide followed by treatment of the derived crystalline bromide **11** with potassium acetate in the presence of potassium iodide. The absolute stereostructure of **11** was confirmed by an X-ray crystallographic analysis.

In an alternative approach (Scheme III), the epoxide **17** was readily prepared from L-(+)-tartaric acid (**14**), complementing the work of Mori[11] and of Saito et al.[12] Thus, L-(+)-tartaric acid was converted into the bromohydrin **15** with hydrogen bromide in acetic acid followed by esterification with ethanol. Oxirane formation with triethylamine and partial reduction of the product **16** with sodium borohydride at 0 °C gave the alcohol **17** in 45% overall yield from L-(+)-tartaric acid.

Considerable effort was next directed toward ammonolysis of the oxirane ring in **10** (see Scheme IV),[13] but in virtually all cases the amide **13** was the major product. Under vigorous conditions the oxirane ring of **10** could be opened with ammonia and the desired amino alcohol **20** could be prepared. However, the yield of **20** was only 6.75%. In a similar manner, various attempts to open the oxirane ring of amide **12** with ammonia led to a low yield of **20**; the major product in most cases was the alcohol **13**. Eventually it was found that conversion of **10** into its sodium salt **18**, followed by ammonolysis with concentrated ammonia, gave excellent yields of the desired amino acid **19**. The amino acid **19** was not isolated but was converted directly into the crystalline diol **20** after esterification (MeOH, HCl), amide formation (NH_3), and protection of the amino group with benzyl chloroformate. The overall yield of **20** from calcium L-threonate was ca. 30%.

As depicted in Scheme V, the direct preparation of lactone **22** from L-threonic acid was also examined, since the former had already been converted[6a,b] into the diol **20** with ammonia. This was accomplished by first brominating L-(+)-threonic acid with hydrogen bromide in acetic acid, followed by treatment of the resulting dibromo acid **21** with ammonium hydroxide at 60 °C for 48 h. However, after protection of the amino group with benzyl chloro-

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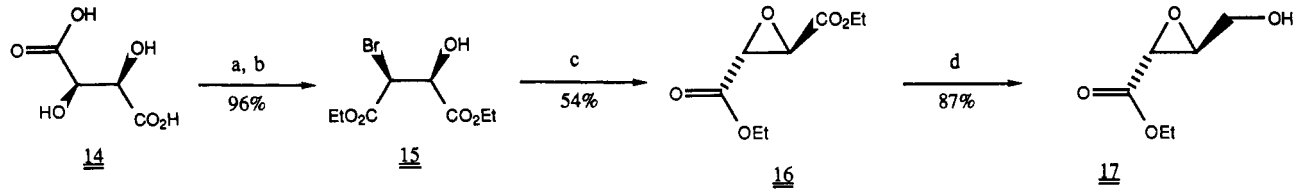
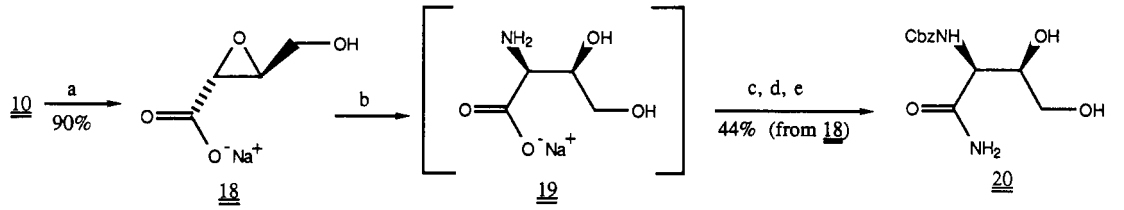
Scheme III[a]



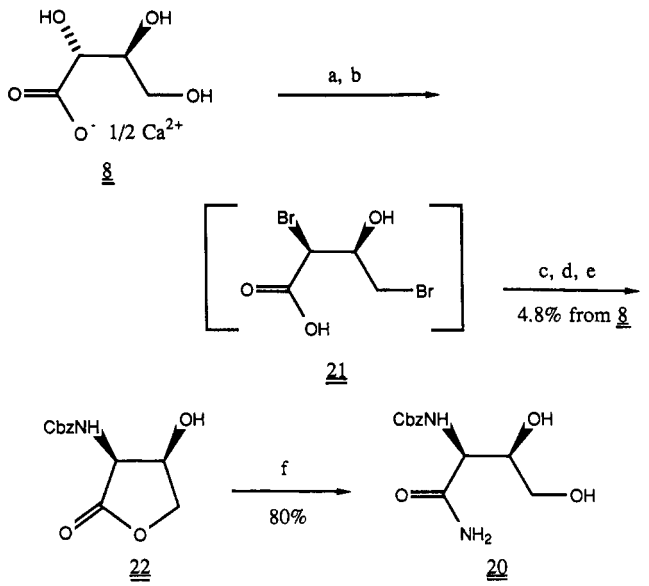
[a] (a) HBr, CH_3CO_2H, Ac_2O; (b) EtOH; (c) Et_3N; (d) $NaBH_4$, EtOH.

Scheme IV[a]



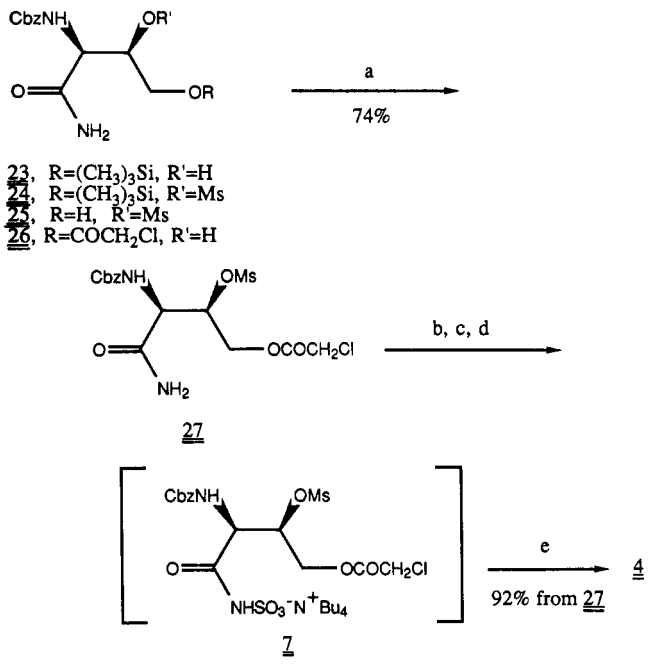
[a] (a) NaOH, MeOH; (b) NH_4OH; (c) HCl(g), MeOH; (d) NH_3(g), MeOH; (e) $NaHCO_3$, $PhCH_2OCOCl$.

Scheme V[a]



[a] (a) Dowex 50 W-X4 resin (H^+); (b) HBr, CH_3CO_2H; (c) NH_4OH; (d) $NaHCO_3$, $PhCH_2OCOCl$; (e) 6 N HCl; (f) NH_4OH.

Scheme VI[a]



[a] (a) CH_3SO_2Cl; (b) SO_3 2-picoline, CH_2Cl_2; (c) $KHSO_4$; (d) $Bu_4N^+HSO_4^-$, (e) $KHCO_3$, $ClCH_2CH_2Cl$, H_2O.

formate, lactonization with hydrochloric acid followed by ammonolysis, only a disappointing 3.6% yield of **20** was realized.

Conversion of the diol **20** into the monobactam **4** (Scheme VI) required selective protection of the primary hydroxyl group. Although such a protection was possible with chlorotrimethylsilane, the silyl group in **23** proved too labile to withstand the subsequent transformations, since on mesylation the silyl derivative **24** obtained was rapidly hydrolyzed to give the crystalline primary alcohol **25**. The use of more stable silyl protecting groups (e.g., *tert*-butyldimethylsilyl) was considered too expensive for our purpose. Selective protection of the primary alcohol group in **20** was subsequently achieved in 91% yield with chloroacetyl chloride.[6a,b] Completion of the synthesis of the monobactam **4** from the chloroacetate **26** was guided by established protocol.[6a,b] Thus, mesylation of **26** with methanesulfonyl chloride to **27**, followed by sulfonation with 2-picoline–SO_3 complex, and treatment with tetrabutylammonium hydrogen sulfate gave **7**. Stereospecific β-lactam formation was finally achieved by potassium bicarbonate treatment of **7**, which also resulted in concomitant hydrolysis of the chloroacetyl group, to afford **4**.

In conclusion, we have found the epoxide **10**, in which each carbon atom of the butanoate moiety is differentiated chemically, useful in the preparation of the β-lactam **4**. Further applications of **10** in synthesis are under investigation.

Experimental Section

General Methods. Melting points were determined in capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and nuclear magnetic resonance spectra (NMR) were determined in $CHCl_3$ and $CDCl_3$, respectively; ^1H and ^{13}C NMR spectra were recorded at 200 and 50.4 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane, and coupling constants (J) are expressed in hertz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass spectra (MS) were determined with a direct inlet system with ionization energy of 70 eV; m/z values are given with relative intensities

in parentheses. Thin-layer chromatograms (TLC, silica gel G) were purchased from Merck (Darmstadt); spots were visible under short-wavelength UV light or made visible by spraying with 10% phosphomolybdic acid in ethanol and heating the plates to 100 °C.

Methyl (2*S*,3*S*)-2,4-Dibromo-3-hydroxybutanoate (9). Anhydrous hydrogen bromide (289.0 g, 3.57 mol) was bubbled into a mixture of 350 mL of acetic acid and 27.5 mL of acetic anhydride. The mixture was cooled to 10 °C and treated with 87.6 g (0.5 mol) of calcium L-threonate (8)[6a,9] with rapid stirring. Stirring was continued at room temperature for 24 h; 1.0 L of methanol was then added at a rate such that the temperature was kept below 30 °C. The mixture was stirred at room temperature overnight (for convenience, ca. 4 h is sufficient) and concentrated in vacuo (water aspirator) at 50 °C to give 258 g of an orange oil. The oil was dissolved in 1.0 L of methanol and 5.0 mL of water, and the mixture was boiled under reflux for 4 h and then evaporated at 50 °C. The residue was extracted with 1.0 L of ethyl acetate, and the extract was washed sequentially with 200 mL of saturated $NaHCO_3$ and 200 mL of saturated brine and dried ($MgSO_4$). Evaporation gave 130.9 g (95%) of **9** as a colorless oil. TLC (40% ethyl acetate in hexane) showed the product at R_f 0.70, with trace impurities at 0.35 and 0.25. An analytical sample was obtained by column chromatography over silica gel 60 (70–230 mesh) with ethyl acetate–hexane (1:1) as eluent; **9** may be distilled: bp 120–121 °C (2.0 Torr); $[\alpha]^{25}_D$ −25.0° (*c* 0.93, $CHCl_3$) [lit.[10] $[\alpha]^{25}_D$ −26.0° (*c* 17, $CHCl_3$)]; ^1H NMR δ 3.0 (1 H, d, *J* = 4, O*H*), 3.80 (2 H, m, *H*-4), 3.87 (3 H, s), 4.26 (1 H, m, *H*-3), and 4.35 (1 H, d, *J* = 4, *H*-2); ^{13}C NMR 36.09 (CH_2-4), 44.5 (*C*H-2), 53.37 (OCH_3), 71.0 (*C*H-3), 167.1 (*C*=O) ppm. Anal. Calcd for $C_5H_8Br_2O_3$: C, 21.77; H, 2.92; Br, 57.92. Found: C, 22.13; H, 2.88; Br, 58.02.

Methyl (2*R*,3*S*)-4-Acetoxy-2,3-epoxybutanoate (10). To a stirred solution of 130.9 g (474 mmol) of **9** in 500 mL of dimethylformamide was added 102.3 g (1.044 mol) of potassium acetate and 3.94 g (23.77 mmol) of potassium iodide. The mixture was stirred under argon at 50–55 °C for 4 h, and at room temperature overnight (for convenience), diluted with 1.0 L of ethyl acetate, and filtered. The filter cake was washed with 250 mL of ethyl acetate, and the combined filtrate and washings were washed with 500 mL of saturated $NaHCO_3$ and 2 × 500 mL of saturated brine, dried ($MgSO_4$), and evaporated to give 82.0 g of **10** as a dark-colored oil, virtually pure by TLC (40% ethyl acetate in hexane; **10** had R_f 0.60, **9** had R_f 0.70). In some experiments crude **10** was contaminated with some dimethylformamide. An analytical sample of **10** was obtained by passing the crude material through a short plug of silica gel (70–230 mesh) with 1:1 ethyl acetate–hexane as eluent to give an oil (90% recovery), which crystallized on standing: mp 25–26 °C; $[\alpha]^{25}_D$ −65.8° (*c* 1.00, CH_3OH); ^1H NMR ($CDCl_3$) δ 2.12 (3 H, s), 3.45 (2 H, m, *H*-2 and *H*-3), 3.80 (3 H, s), 4.05 (1 H, dd, *J* = 12, 4 Hz, H_A-4), 4.42 (1 H, dd, *J* = 12, 2 Hz, H_B-4); ^{13}C NMR 20.62 (CH_3), 50.76 (*C*H), 52.65 (OCH_3), 54.95 (*C*H), 62.62 (CH_2O), 168.57 (*C*=O), and 170.40 (*C*=O) ppm; IR 1745 cm^{-1}; MS, *m*/*z* 132 ($M^+ - CH_2CO$). Anal. Calcd for $C_7H_{10}O_5$: C, 48.28; H, 5.79. Found: C, 48.01; H, 6.05.

(2*R*,3*R*)-3-(Bromomethyl)oxiranecarboxamide (11). A mixture of 10 g (31.4 mmol) of **9** and 100 mL of concentrated NH_4OH was stirred at room temperature for 2 h, diluted with saturated brine, and extracted with ethyl acetate (2 × 200 mL). The extract was dried ($MgSO_4$) and evaporated to give 3.4 g (60%) of **11** as a white solid, homogeneous by TLC (60% ethyl acetate in hexane, 0.05% bromocresol green spray). Crystallization from 50 mL of hot ethyl acetate gave an analytical sample of **11** as colorless crystals: mp 123–124 °C; $[\alpha]^{25}_D$ −6.65° (*c* 0.932, CH_3OH); IR 3375–3230 and 1682 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.40 (2 H, m), 3.51 (1 H, m), 3.84 (1 H, dd, *J* = 8, 4 Hz), 7.42 (N*H*), and 7.56 (N*H*); MS, *m*/*z* 180 (M^+, 0.5), 163 (1), 137 (5), 100 (70), 86 (70), 57 (60), 44 (100). Anal. Calcd for $C_4H_6BrNO_2$: C, 26.67; H, 3.36; N, 7.78; Br, 44.39. Found: C, 26.71; H, 3.30; N, 7.57; Br, 44.52.

X-ray Crystallographic Analysis of 11 (with L. J. Todaro and A.-M. Chiu). Crystals of **11**, $C_4H_6BrNO_2$, are monoclinic, space group $P2_1$, with *a* = 7.659 (1) Å, *b* = 5.153 (1) Å, *c* = 7.914 (1) Å, β = 97.74 (1)°, *Z* = 2, d_{calcd} = 1.931 g cm^{-3}, and μ(Cu Kα) = 84.47 cm^{-1}. The intensity data were collected on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω − 2θ scans) with use of a crystal of ca. 0.12 × 0.16 × 0.32 mm. The data were corrected for absorption. Of 711 independent reflections for θ < 75°, 701 were considered to be observed [$I > 3.0\sigma(I)$]. The structure was solved by a multiple-solution procedure[14] and was refined by full-matrix least squares. Thirteen reflections, which were strongly affected by extinctions, were excluded from the final refinement. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.037 and R_w = 0.051 for the remaining 688 observed reflections. The major peaks of the final difference map, none of which are greater than 0.7 e $Å^{-3}$, are near the bromine atom. The absolute configuration is based on the anomalous scattering of the bromine atom and was established by refining both enantiomers. The final weighted R values were 0.0509 for the configuration shown above and 0.0524 for its antipode. Thus, by Hamilton's test,[15] the configuration shown corresponds to the absolute configuration.

(2*R*,3*S*)-3-[(Acetyloxy)methyl]oxiranecarboxamide (12). A solution of 1.80 g (10 mmol) of bromide **11** in 20 mL of DMF was treated with 1.96 g (20 mmol) of potassium acetate and 80 mg (0.48 mmol) of potassium iodide. The mixture was stirred at 50–55 °C under argon for 6 h and concentrated in vacuo at 45 °C, and the residue was diluted with 25 mL of water and then extracted with ethyl acetate (2 × 100 mL). The extract was dried ($MgSO_4$) and evaporated to give 1.1 g of **12** as a white solid, homogeneous by TLC (ethyl acetate); **12** had R_f 0.62 and **11** had R_f 0.47. Crystallization from 20 mL of hot ethyl acetate gave 840 mg (52%) of **12** as colorless crystals: mp 135–136 °C; $[\alpha]^{25}_D$ −53.49° (*c* 0.93, CH_3OH); IR (KBr) 3415, 3280, 3225, 1748, 1718, and 1667 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.06 (3 H, s), 3.34 (2 H, br s, *H*-2 and *H*-3), 3.95 (1 H, dd, *J* = 8, 4 Hz, H_A-4), 4.42 (1 H, dd, *J* = 8, 2 Hz, H_B-4), 7.37 (N*H*), and 7.50 (N*H*); ^{13}C NMR (Me_2SO-d_6) 20.39 (CH_3), 51.65 (*C*H), 54.25 (*C*H), 62.90 (CH_2), 168.91 (*C*=O), and 169.93 (*C*=O) ppm; MS, *m*/*z* 160 (M^+ + H, 0.5), 115 (M − $CONH_2$, 20), 86 (15), 43 (100). Anal. Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.25; H, 5.75; N, 8.75.

(2*R*,3*S*)-3-(Hydroxymethyl)oxiranecarboxamide (13). A solution of 570 mg (3.6 mmol) of acetate **12** in 10 mL of methanol saturated with ammonia was kept in a Fischer-Porter bomb at 60–65 °C for 4 h, cooled to room temperature, and evaporated. The residue was dissolved in ethyl acetate and purified by chromatography on 15 g of silica gel 60 (70–230 mesh) with 30% methanol in ethyl acetate as eluent to give 400 mg (95%) of **13** as an oil, which solidified at 0 °C: mp 43–48 °C; $[\alpha]_D$ −18.29° (*c* 1.02, CH_3OH); IR (KBr) 3350, 1680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.14 (1 H, br s, *H*-3), 3.25 (1 H, d, *J* = 2 Hz, *H*-2), 3.44 (1 H, dd, *J* = 8, 4 Hz, H_A-4), 3.67 (1 H, ddd, *J* = 8, 4, 2 Hz, H_B-4), 4.99 (1 H, t, *J* = 4 Hz, O*H*), 7.31 (N*H*), 7.43 (N*H*); ^{13}C NMR (Me_2SO-d_6) 51.50 (*C*H), 57.8 (*C*H), 59.9 (CH_2), 169.9 (*C*=O) ppm; MS, *m*/*z* 117 (0.5), 99 (5, $M^+ - H_2O$), 86 (97, $M^+ - CH_2OH$), and 44 (100).

Diethyl (2*S*,3*S*)-2-Bromo-3-hydroxysuccinate (15). A stirred suspension of 50 g (333 mmol) of (2*R*,3*R*)-(+)-tartaric acid (**14**) in 250 mL of acetic acid was treated with 58 g (717 mmol) of gaseous hydrogen bromide during 30 min. After the addition of 15.7 mL (116 mmol) of acetic anhydride, the mixture was stirred at room temperature for 3 days and then treated with 320 mL of ethanol. After 2 h, the mixture was evaporated and the residue was dissolved in 700 mL of ethanol and 5 mL of water. The solution was then boiled under reflux for 16 h and evaporated to give 86.4 g (96.4%) of **15**, pure enough for use in the next step. An analytical sample was obtained (60% yield) by flash column chromatography on silica gel with ether–hexane (1:1) as eluent, $[\alpha]^{20}_D$ −20.4° (*c* 0.465, ether) [lit.[11] $[\alpha]^{20}_D$ −28.9° (neat)].

Diethyl (2*R*,3*R*)-2,3-Epoxysuccinate (16). A solution of 86.4 g (0.333 mol) of crude **15** (from the preceding experiment) in 50 mL of ether was added slowly, with stirring, to 170 mL of triethylamine at 15–20 °C. The mixture was stirred at room temperature overnight and filtered, and the filtrate was diluted with

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ether. The ether was washed with saturated brine, dried ($MgSO_4$), and evaporated to give 42 g of a yellow oil, which was distilled, bp 70–75 °C (0.15 Torr), to give 32.7 g (52.2% from **14**) of **16**, $[\alpha]^{20}_D$ −107.4° (*c* 1.03, ether) [lit.[11] $[\alpha]^{21}_D$ −88.47° (*c* 1.03, ether)]. The 2*S*,3*S* enantiomer was reported[11] to have $[\alpha]^{23}_D$ +105.49° (*c* 1.413, ether).

Ethyl (2*R*,3*S*)-4-Hydroxy-2,3-epoxybutyrate (17). A solution of 16.08 g (425 mmol) of sodium borohydride in 500 mL of ethanol was added to a stirred solution of 100 g (531 mmol) of **16** in 1.2 L of ethanol at 0 °C. The mixture was stirred at this temperature for 2.5 h and then at 15 °C for 1 h. After the mixture was cooled to 0 °C, 50 mL of acetone was slowly added followed by 25.5 mL of acetic acid, and the mixture was evaporated. The residue was extracted with CH_2Cl_2 (2 × 700 mL), washed with saturated brine, dried ($MgSO_4$), and evaporated to give 67.4 g (86.8%) of **17**, mp 43–45 °C, with a purity of 98.3% as indicated by gas chromatography. An analytical sample was obtained by column chromatography (silica gel, 20% acetone in methylene chloride): mp 45–46 °C; $[\alpha]^{20}_D$ −33.8° (*c* 1, ethanol); IR 3381, 1743, and 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, *J* = 7 Hz), 2.02 (br s, O*H*), 3.38 (1 H, m, *H*-3), 3.53 (1 H, d, *J* = 2 Hz, *H*-2), 3.76 (1 H, br d, *J* = 4 Hz, H_A-4), 4.0 (1 H, dd, *J* = 4, 2 Hz, H_B-4), 4.25 (2 H, q, *J* = 7 Hz); MS, *m/z* (147, $M^+ + H$), 128 ($M^+ - H_2O$), 118 ($M^+ - C_2H_4$), 115 ($M^+ - CH_2OH$). Anal. Calcd for $C_6H_{10}O_4$: C, 49.37; H, 6.90. Found: C, 49.31; H, 6.74. Examination of the ^1H NMR spectrum in the presence of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated that **17** was enantiomerically homogeneous.

In addition, the enantiomeric and diastereomeric purity of **17** was evaluated on the corresponding camphanic ester. Thus, a solution of 1.9 g (13 mmol) of **17** in 20 mL of pyridine was treated during 25 min at −10 °C with 3.38 g (15.6 mmol) of camphanic acid chloride (Fluka) in 10 mL of CH_2Cl_2. The mixture was stirred at room temperature for 2 h and worked up in the usual manner to give 4.26 g of the crude ester. Chromatography on 100 g of silica gel with methylene chloride as eluent gave 4.21 g (99.2%) of pure material: mp 55–56 °C; GC analysis (SE-30, 180 °C/2 min) showed only one peak (t_R 10.80 min); IR ($CHCl_3$) 1791, 1750 cm^{-1}; MS, *m/z* 327 ($M^+ + 1$). Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 59.03; H, 7.04.

(2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-3,4-dihydroxybutanamide (20). A. From Epoxy Ester 10. A solution of 81.8 g (465 mmol) of epoxide **10** in 450 mL of methanol was cooled to 5 °C and treated with 37.4 g (0.935 mol) of NaOH at a rate such that the temperature was kept below 15 °C. The mixture was stirred at 5 °C for 3 h, diluted with 1.35 L of CH_2Cl_2, and stirred at room temperature for 30 min. The solid was collected by filtration, washed with 200 mL of CH_2Cl_2, and dried in vacuo at room temperature overnight to give 58.8 g (90%) of the corresponding salt **18**, $[\alpha]^{25}_D$ −16.19° (*c* 1.01, H_2O); IR (KBr) 3050, 1615 cm^{-1}; ^1H NMR (D_2O) δ 3.15 (1 H, m, *H*-3), 3.38 (1 H, d, *J* = 2 Hz, *H*-2), 3.64 (1 H, dd, *J* = 4, 2 Hz, H_A-4), 3.97 (1 H, d, *J* = 4 Hz, H_B-4); ^{13}C NMR (D_2O) 54.4, 59.8, 62.2, and 177.1 ppm; MS (FAB), *m/z* 139 ($M^+ - H^+$). Anal. Calcd for $C_4H_5O_4Na$: C, 34.30; H, 3.60; Na, 16.42. Found: C, 34.11; H, 3.88; Na, 16.18.

The preceding salt **18** (58 g) was treated with 600 mL of NH_4OH (29.9%), stirred at 50–55 °C for 45 h, and evaporated in vacuo at 50 °C. Residual water was removed by azeotroping with 400 mL of toluene to give 73.4 g of **19** as a dark viscous oil, which was dissolved in 400 mL of methanol, cooled to 5 °C (ice bath), and treated during 20 min with 50 g of anhydrous hydrogen chloride gas in 40 mL of methanol. The mixture was stirred at room temperature overnight and evaporated in vacuo to give 106 g of a brown oil, which was dissolved in 100 mL of methanol. The stirred solution was cooled to 5 °C and was treated with a solution of 50 g of ammonia in 400 mL of methanol. Stirring was continued at room temperature overnight, and the mixture was evaporated in vacuo; 200 mL of methanol was added, and the mixture was evaporated again. The residue was dissolved in 1.0 L of 50% aqueous methanol. To the stirred solution was added 53.4 g (0.636 mol) of $NaHCO_3$, followed, after cooling to 5 °C, by 98.3 g (0.576 mol) of benzyl chloroformate at a rate such that the temperature was kept below 10 °C. The mixture was stirred at room temperature for an additional 4 h, evaporated to remove ca. 450 mL of methanol, cooled to 5 °C, and diluted with 250 mL of ether. After 30 min of stirring, the product was collected by filtration and washed with 200 mL of water, followed by 300 mL of cold (5 °C) ether, to give 49.86 g (40% from **10**) of **20**: mp 170–172 °C; homogeneous by TLC ($CHCl_3$–CH_3OH, 9:1); $[\alpha]^{25}_D$ +12.5° (*c* 1.005, Me_2SO) [lit.[6a] +11.47° (*c* 0.8722, Me_2SO)]; IR (KBr) 3500–3200, 1699 (infl), 1664, and 1543 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.40 (2 H, dd, *J* = 5 and 6 Hz, *H*-4), 3.69 (1 H, m, *H*-3), 4.05 (1 H, m, *H*-2), 4.60 (1 H, t, *J* = 4.5 Hz, O*H*), 4.90 (1 H, d, *J* = 5 Hz, O*H*), 5.02 (2 H, s, OCH_2Ph), 7.05 (1 H, s, CON*H*), 7.14 (1 H, d, *J* = 4, N*H*), 7.22 (1 H, s, CON*H*), and 7.38 (5 H, s, aromatic); ^{13}C NMR (Me_2SO-d_6) 56.5 (*C*H), 62.0 (CH_2), 64.8 (CH_2), 70.7 (*C*HOH), 126.9–127.5 (5 *C*H, aromatic), 136.1 (s, aromatic), 155.0 (O*C*ON), 173.1 ($OCONH_2$) ppm; MS, *m/z* 268 (M^+, 1), 237 ($M - CH_2OH$, 2), 224 ($M - CONH_2$, 5), 208 ($M - C_2H_4O_2$, 14), 147 (14), 91 (100). Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.67; H, 5.83; N, 10.26.

B. From Epoxy Amide 12. Amide **12** (4.77 g, 27 mmol) was allowed to react with 50 mL of concentrated NH_4OH in a Fischer–Porter bomb (internal pressure of 20 psi) at 60 °C for 2 days. The reactor was cooled to room temperature, and the mixture was evaporated at 60 °C to give a gum, which was dissolved in 50 mL of water and treated with 9.0 g of $NaHCO_3$ followed by 9 mL of benzyl chloroformate with cooling (ice bath). The mixture was stirred at room temperature for 4 h and extracted with CH_2Cl_2 (2 × 50 mL), and the extract was dried ($MgSO_4$) and evaporated. The residue was triturated with ether to give 600 mg of **20**.

C. From L-Threonic Acid. A suspension of 6.20 g (27 mmol) of calcium L-threonate (**8**) in 120 mL of water was heated until a solution was obtained. To the solution was added 50 mL of Dowex 50W-X4 ion exchange resin (H^+ form, 100–200 mesh), and the suspension was stirred for 30 min. The resin was removed by filtration and washed with 50 mL of water. The combined filtrate and washing were evaporated in vacuo, followed by azeotroping with toluene (2 × 300 mL), to give 4.2 g of a red oil, which was dissolved in 80 mL of warm acetic acid, cooled to 15 °C, and saturated with anhydrous hydrogen bromide (23 g). The mixture was stirred at room temperature for 4 h, cooled to 5 °C (ice bath), diluted with 100 mL of water, left at room temperature overnight, and then evaporated in vacuo at 35 °C to give 10.0 g of a red oil. The oil was dissolved in 100 mL of concentrated NH_4OH (30%), transferred to a Fischer–Porter bomb, and stirred at 60 °C for 48 h. After being cooled to room temperature, the mixture was evaporated in vacuo and the residue was treated with 15 g of $NaHCO_3$ in 160 mL of water. The solution was cooled to 5 °C, and 15 mL (100 mmol) of benzyl chloroformate was added, with stirring. Stirring was continued for 45 min at 5 °C and then at room temperature for 4 h. After washing with ethyl acetate, the aqueous phase was acidified to pH 2.5 with 6 N HCl, and the solution was evaporated in vacuo to dryness. Acetonitrile (160 mL) and 20 mL of 2 N HCl were added, and the mixture was stirred at room temperature for 3 h and then evaporated in vacuo. The residue was extracted with warm ethyl acetate (2 × 100 mL), and the extract was washed with 50 mL of saturated $NaHCO_3$ and 100 mL of saturated brine, dried ($MgSO_4$), and evaporated to give 2 g of an oil, which solidified on standing. Purification by high-pressure liquid chromatography (Waters Prep. 500) with ethyl acetate–hexane (1:1) as eluent gave 300 mg (4.5%) of (2*S*,3*R*)-2-[(benzyloxycarbonyl)amino]-3-hydroxy-4-butanolide (**22**), which was crystallized from hot ethyl acetate: mp 123–126 °C; $[\alpha]^{25}_D$ +38.5° (*c* 1.000, ethyl acetate) [lit.[6b] mp 128–131 °C; $[\alpha]^{25}_D$ +36.9° (*c* 0.5, ethyl acetate)]; IR (KBr) 3425 (NH and OH), 1789 (lactone), 1722, and 1718 (infl) cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 4.35 (2 H, s, CH_2O), 4.55 (1 H, br s, C*H*), 4.65 (1 H, br s, C*H*), 4.95 (1 H, d, *J* = 2 Hz, O*H*), 5.15 (2 H, s, CH_2Ph), 6.00 (1 H, d, *J* = 4, N*H*), and 7.38 (5 H, s, aromatic); MS, *m/z* 251 (M^+, 40). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.22; H, 5.22; N, 5.32. Treatment of the lactone with ammonium hydroxide as described by Sendai et al.[6b] gave **20** in 80% yield, mp 170–172 °C.

(2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-3-hydroxy-4-(trimethylsiloxy)butanamide (23). A solution of 0.75 mL (5.5 mmol) of chlorotrimethylsilane in 2.0 mL of anhydrous tetrahydrofuran was added to a stirred slurry of 1.34 g (5.0 mmol) of **20** in 20.0 mL of anhydrous tetrahydrofuran and 0.830 g of triethylamine. The mixture was stirred at room temperature for 5 h, poured into 100 mL of saturated brine, and extracted with

100 mL of ethyl acetate. The extract was dried ($MgSO_4$) and evaporated, and the residue was triturated with ca. 5 mL of ether. The mixture was filtered, and the filtrate was collected and subjected to chromatography on 15 g of silica gel 60 (70–230 mesh) with 15% ethyl acetate in hexane as eluent. Removal of the solvents gave 1.4 g of **23** as a foam: $[\alpha]^{25}_D$ +0.46° (*c* 1.00, ethyl acetate); IR 3490, 3410, 1715, 1690, and 1503 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.11 (9 H, s), 3.70 (3 H, m, O*H* + CH_2), 3.90 (1 H, m), 4.35 (1 H, s), 5.09 (2 H, s, CH_2Ph), 6.02 (1 H, s, CON*H*), 6.10 (1 H, d, *J* = 4, N*H*), 6.67 (1 H, s, CON*H*), 7.35 (5 H, s, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) 0.50 ($SiMe_3$), 56.0 (*C*H), 63.8 (CH_2), 67.4 (CH_2), 72.0 (*C*H), 128.2 (2 *C*H), 128.4 (*C*H), 128.7 (2 *C*H), 137.0 (s, aromatic), 158.8 (OCON<), 173.1 ($CONH_2$) ppm; MS (FAB), *m/z* 341 (M^+ + H, 100). Anal. Calcd for $C_{15}H_{24}N_2O_5Si$: C, 52.92; H, 7.11; N, 8.23. Found: C, 52.40; H, 7.00; N, 8.14.

(2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-4-hydroxy-3-(mesyloxy)butanamide (25). A stirred solution of 5.37 g (20 mmol) of **20** in 80 mL of anhydrous tetrahydrofuran and 8.88 g (64 mmol) of triethylamine was treated dropwise, under argon, with 3.72 mL (29 mmol) of chlorotrimethylsilane. The mixture was stirred at room temperature for 3 h, cooled to −10 °C, and treated with 1.86 mL of methanesulfonyl chloride in 3.0 mL of anhydrous tetrahydrofuran. Stirring was continued at 0 °C for 2 h, 300 mL of ether was added, and the mixture was filtered. The filtrate was evaporated to give 9.52 g of a solid, to which 100 mL of 2-propanol was added, and the mixture stirred at room temperature for 30 min. The product was collected by filtration to give 5.7 g of **25**, an analytical sample of which was obtained by crystallization from hot methanol (80% return): mp 155–157 °C; $[\alpha]^{25}_D$ +9.00° (*c* 1.000, Me_2SO); IR 3568, 3405, 3345, 3320, 1696, 1661, 1548, and 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.20 (3 H, s), 3.65 (2 H, s, *H*-4), 4.50 (1 H, m), 4.84 (1 H, m), 5.08 (2 H, s, ArCH_2), 7.45 (5 H, s, aromatic), 7.36 (1 H, s, CON*H*), 7.50 (1 H, d, *J* = 4 Hz, N*H*), 7.64 (1 H, s, CON*H*); ^{13}C NMR ($CDCl_3$) 38.0 (CH_3), 55.2 (*C*H), 59.9 (CH_2), 65.8 (CH_2), 82.0 (*C*H), 127.8 (3 *C*H, aromatic), 128.3 (2 *C*H, aromatic), 136.8 (s, aromatic), 155.90 (*C*=O), 170.20 (*C*=O) ppm. Anal. Calcd for $C_{13}H_{18}N_2O_7S$: C, 45.08; H, 5.24; N, 8.09; S, 9.26. Found: C, 45.32; H, 5.35; N, 7.80; S, 9.30.

(2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-4-(chloroacetoxy)-3-hydroxybutanamide (26). A suspension of 100 g (373 mmol) of **20** in 480 mL of *N*,*N*-dimethylacetamide was stirred at room temperature until a solution was obtained (ca. 10 min), cooled to −20 °C, and treated dropwise during 25 min with 41.7 mL (523 mmol) of chloroacetyl chloride. Stirring was continued at −20 °C, and the mixture was poured into 1.4 L of water and 1.6 L of ethyl acetate. The organic layer was separated and washed with 330 mL of saturated brine. The combined aqueous extracts were treated with 22.4 g of solid $NaHCO_3$ and 100 g NaCl and extracted with ethyl acetate (2 × 550 mL). The combined organic was dried ($MgSO_4$) and evaporated, and the residue was crystallized from ethanol to give 117.1 g (91%) of **26**, mp 113–115 °C; $[\alpha]^{25}_D$ +10.92° (*c* 1.0076, Me_2SO); IR (KBr) 3445–3205, 1742, 1700, 1660, 1548 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.90 (1 H, m), 4.10 (3 H, m, *H*-2 and *H*-4), 4.40 (2 H, s, CH_2Cl), 5.04 (2 H, s, CH_2Ph), 5.41 (1 H, d, *J* = 4 Hz, O*H*), 7.16 (1 H, s, CON*H*), 7.40 (7 H, m, CON*H*, N*H*, aromatic); ^{13}C NMR (Me_2SO-d_6) 40.5 (CH_2Cl), 56.0 (*C*HNH), 65.0 (CH_2Ar), 66.1 (CH_2O), 67.7 (*C*HOH), 126.8–127.5 (5 *C*H, aromatic), 136.1 (s, aromatic), 155.1 (O*C*ON), 166.5 (O*C*O), 170.9 ($CONH_2$) ppm; MS, *m/z* 344 (M^+, 0.1), 300 ($M^+ - NH_2CO$, 7), 251 ($M^+ - CO_2CH_2Cl$, 3), 233 ($M^+ - CO_2CH_2Cl - H_2O$, 25). Anal. Calcd for $C_{14}H_{17}ClN_2O_6$: C, 48.78; H, 4.97; Cl, 10.28; N, 8.13. Found: C, 48.60; H, 5.71; Cl, 9.00; N, 8.37. NMR spectroscopy indicated that **26** contained ca. 0.4 mol of ethanol.

(2*S*,3*R*)-2-[(Benzyloxycarbonyl)amino]-4-(chloroacetoxy)-3-(mesyloxy)butanamide (27). A stirred solution of 117 g of **26** in 1.5 L of 1,2-dimethoxyethane under argon was cooled to −20 °C and treated with 144.2 mL of triethylamine followed by the dropwise addition of 63.7 mL (0.823 mol) of methanesulfonyl chloride. The mixture was stirred at −20 °C for 1 h, diluted (slowly) with 1 L of saturated brine, and extracted with 1 L of ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated at 30 °C to give 199 g of crude **27**. Crystallization from 380 mL of ethanol gave 105.55 g (73.6%) of **27** after washing with 75 mL of cold (−10 °C) ethanol and drying in vacuo overnight: mp 141–142 °C; $[\alpha]^{25}_D$ +5.01° (*c* 1.08, MeOH) [lit.[6a] mp 140–141 °C; $[\alpha]^{25}_D$ +5.16° (*c* 0.504, MeOH); IR (KBr) 3435, 3345, 3215, 1742, 1695, 1678, 1530, 1180, and 1168 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.21 (3 H, s, SO_2CH_3), 4.39 (s, 2 H, $COCH_2Cl$), 4.41 (2 H, s, CH_2O), 4.57 (1 H, dd, *J* = 6, 3 Hz, *H*-2), 5.06 (3 H, m, PhCH_2 and *H*-3), 7.40 (5 H, s, aromatic), 7.48 (1 H, s, N*H*), 7.73 (2 H, br s, 2 N*H*); ^{13}C NMR (Me_2SO-d_6) 37.2 (CH_3SO_2), 40.3 (CH_2Cl), 54.0 (*C*H), 62.6 (CH_2), 65.2 (CH_2), 77.1 (*C*H), 127.0–127.5 (5 *C*H, aromatic), 135.7 (s, aromatic), 155.1 (*C*O), 166.0 (O*C*O), 168.7 (*C*ON) ppm; MS (FAB), *m/z* 423 (M^+ + H). Anal. Calcd for $C_{15}H_{19}ClN_2O_8S$: C, 42.61; H, 4.53; Cl, 8.38; N, 6.63; S, 7.58. Found: C, 42.77; H, 4.58; Cl, 8.51; N, 6.59; S, 7.53.

Tetrabutylammonium (3*S*,4*S*)-3-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)-2-oxoazetidine-1-sulfonate (4). Sulfur trioxide–2-picoline complex was prepared as follows: Chlorotrimethylsilane (212.9 g) was added dropwise under argon with stirring to 156.9 g of sulfur trioxide at 5 °C. The mixture was stirred at room temperature overnight and distilled to give 91.5 g of a colorless oil, bp 80–82 °C (25 Torr). This was added under argon to a stirred solution of 45.17 g of 2-picoline in 970 mL of carbon tetrachloride at 0–5 °C. Stirring was continued at 5 °C for 15 min, and the mixture was evaporated. The residue was kept at 2.5 Torr overnight to give 83.9 g of the complex. A mixture of 105.4 g (0.249 mol) of **27** in 470 mL of CH_2Cl_2 was treated with 75.0 g of sulfur trioxide–2-picoline, and the mixture was stirred under argon for 2 h, and then diluted with 460 mL of 0.6 mol of $KHSO_4$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL). The combined CH_2Cl_2 extracts were extracted with 2% $NaHCO_3$ (2 × 925 mL), the CH_2Cl_2 was discarded, and to the combined aqueous extracts was added (cautiously) 110 g (0.324 mol) of tetrabutylammonium hydrogen sulfate. The mixture was stirred at room temperature for 10 min, and the organic layer was collected. The aqueous layer was reextracted with CH_2Cl_2 (2 × 660 mL), and the combined extracts were evaporated to give crude **7**. This was dissolved in 3.5 L of 1,2-dichloroethane and added slowly to a stirred solution of 74.9 g of $KHCO_3$ in 2.2 L of water at 60–65 °C. The mixture was stirred at 70 °C for 70 min and at room temperature overnight, and the organic phase was collected. The aqueous phase was reextracted with CH_2Cl_2 (2 × 1.5 L), and the combined extracts were dried ($MgSO_4$) and evaporated to give 131.7 g of **4** as an amber oil: IR ($CHCl_3$) 3665 (OH), 3410 (NH), 1768 (β-lactam), 1720 (urethane), 1230, and 1040 (SO_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (12 H, t), 1.45 (8 H, q), 1.65 (8 H, m), 3.26 (8 H, m, $(CH_2)_4N$), 3.70 (1 H, t, *J* = 6 Hz, O*H*), 3.90 (1 H, m), 4.14 (1 H, m), 4.48 (1 H, d, *J* = 8 Hz), 5.11 (2 H, s, CH_2Ph), 5.17 (1 H, dd, *J* = 8 and 4 Hz, *H*-3), 6.03 (1 H, d, *J* = 4 Hz, N*H*), and 7.36 (5 H, s, C_6H_5).

Conversion of **4** into carumonam (**3**) has been disclosed.[7]

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Supplementary Material Available: Listings of X-ray crystallographic data, final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, torsion angles, and an ORTEP drawing for **11** (6 pages); listings of structure factors for **11** (4 pages). Ordering information is given on any current masthead page.