= 8.5 Hz, NH), 6.92 (s, 1 H, COOC*H*Ph_2), 7.15 to 7.47 (br m, 15 H, 3 C_6H_5).

3-[(3*S*,5*R*)-7-Oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-*N*-(benzyloxycarbonyl)-L-alanine diphenylmethyl ester (21): 34 mg (9.7%), pale yellow foam; IR ($CHCl_3$) ν_{max} 3420, 1780, 1721, 1508, 1196, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (br m, 2 H, 2 H-8), 2.83, 3.21 (AB of ABX, 2 H, J_{gem} = 16 Hz, J_{vic} = 1 and 2.5 Hz, 2 H-6), 2.96, 3.27 (AB of ABX, 2 H, J_{gem} = 11 Hz, J_{vic} = 7 and 8 Hz, 2 H-2), 4.04 (m, 1 H, H-3), 4.72 (br m, 1 H, H-9), 4.99 (dd, 1 H, J = 1 and 2.5 Hz, H-5), 5.11 (s, 2 H, OCH_2Ph), 5.69 (d, 1 H, J = 8.5 Hz, NH), 6.92 (s, 1 H, COOC*H*Ph_2), 7.20 to 7.44 (m, 15 H, 3 C_6H_5).

An unidentified byproduct, 189 mg, pale yellow gun, probably derived from the opening of the β-lactam ring: IR ($CHCl_3$) ν_{max} 3415, 1748, 1702, 1508, 700 cm^{-1}.

Unreacted starting material (**19**), 154 mg (11.3%).

L-*allo*-1-(Benzyloxycarbonyl)-4-((4-oxoazetidin-2-yl)oxy)proline diphenylmethyl ester (22), 412 mg (35.2%), colorless crystals. After crystallization from AcOEt–Et_2O, 313 mg of **22** was obtained as rotomers (ratio ca. 5:3) of a 1:1 mixture of *S* and *R* diastereomers at 4 °C mp 193–195 °C to a glass; IR ($CHCl_3$) ν_{max} 3410, 1770, 1702, 1421, 1351, 1088, 699 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.08 to 2.37 (m, 2 H, 2 H-3), 2.40 to 2.57 (m, 1 H, one of 2 H-3′), 2.72 to 2.90 (m, 1 H, one of 2 H-3′), 3.30 to 3.50 (m, 1 H, one of 2 H-5), 3.63 to 3.80 (m, 1 H, one of 2 H-5), 4.25 (m, 1 H, H-4), 4.50 to 4.66 (m, 1 H, H-2), 4.83 to 5.19 (7 d, 2 H, 4 different OCH_2Ph), 4.94, 4.95, 5.00, and 5.03 (4dd, 1 H, 4 different H-4′), 6.78, 6.80, and 6.81 (3 s, 1 H, ratio 5:8:3 due to overlap, 3 different COOC*H*Ph_2), 7.17 to 7.50 (m, 15 H, 3 C_6H_5), 8.55 to 8.68 (4 s, 1 H, 4 different NH-1′).

Anal. Calcd for $C_{29}H_{28}N_2O_6$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.26; H, 5.71; N, 5.47.

3-[(3*S*,5*S*)-7-Oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-L-alanine (Clavalanine, 1). A solution of **20** (600 mg, 1.20 mmol) in 60 mL of MeOH was hydrogenated for 3 h at room temperature and normal pressure over 100 mg of 10% Pd/C. After removal of the catalyst and evaporation in vacuo of filtrate and washing (MeOH), the residue was partitioned between 15 mL of H_2O and 20 mL of Et_2O. The aqueous phase was concentrated in vacuo at <30 °C (bath) while absolute EtOH was added in small portions to cause crystallization of the product. After trituration with EtOH the crystals were collected by filtration, washed with Et_2O, and dried in vacuo at room temperature to give 232 mg (96.7%) of pure **1**: mp dec, starting at ca. 235 °C (light yellow) to ca. 270 °C (dark brown); IR (KBr) ν_{max} 3170, 2960, 1760, 1640 cm^{-1}; ^1H NMR (D_2O) δ 2.21 (m, 2 H, 2 H-8), 2.79 (dd, 1 H, J = 11.5 and 7 Hz, one of 2 H-2), 2.98 (d, 1 H, J = 16.5 Hz, one of 2 H-6), 3.41 (dd, 1 H, J = 16.5 and 3 Hz, one of 2 H-6), 3.97 (t, 1 H, J = 5 Hz, H-9), 4.08 (dd, 1 H, J = 11.5 and 6 Hz, one of 2 H-2), 4.45 (m, 1 H, H-3), 5.49 (d, 1 H, J = 3 Hz, H-5); CD (0.005 M, H_2O), $[\theta]_{229}$ −56 000, $[\theta]_{198}$ +34 000.

L-*allo*-4-((4-Oxoazetidin-2-yl)oxy)proline (23). A 4:3 mixture of diastereomers **22** (200 mg, 0.40 mmol) was dissolved with gentle heating in 15 mL of MeOH and 10 mL of H_2O, and the solution was hydrogenated for 1 h at 50 °C and ambient pressure in the presence of 20 mg of 10% Pd/C. After removal of the catalyst, the filtrate was concentrated in vacuo, the water being removed azeotropically with absolute EtOH. Trituration of the residue with EtOH afforded 75 mg (93.8%) **23** as colorless crystals: mp 193–195 °C dec; IR (KBr) ν_{max} 1757, 1621, 1085 cm^{-1}; ^1H NMR (D_2O) δ 2.49 (m, 2 H, 2 H-3), 2.86, 3.20 (AB of ABX, $^3/_7$ of 2 H, J_{gem} = 15.5 Hz, J_{vic} = 0 and 3.5 Hz, 2 H-3′ of minor diastereomer), 2.88, 3.20 (AB of ABX, $^4/_7$ of 2 H, J_{gem} = 15.5 Hz, J_{vic} = 0 and 3.5 Hz, 2 H-3′ of major diastereomer), 3.45, 3.64 (AB of ABX, $^4/_7$ of 2 H, J_{gem} = 13 Hz, J_{vic} = 1 and 4 Hz, 2 H-5 of major diastereomer), 3.47, 3.64 (AB of ABX, $^3/_7$ of 2 H, J_{gem} = 13 Hz, J_{vic} = 1 and 4 Hz, 2 H-5 of minor diastereomer), 4.27 (dd, 1 H, J = 5 and 8 Hz, H-2), 4.52 (br s, 1 H, H-4), 5.25 (d, 1 H, J = 3.5 Hz, H-4′); CD (H_2O, 0.002 M) $[\theta]_{206}$ +8750.

Anal. Calcd for $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 48.06; H, 5.96; N, 13.87.

Registry No. **1**, 74758-63-7; (±)-**3**, 64804-09-7; **5**, 97551-57-0; **6**, 97551-58-1; **7**, 97551-59-2; **8**, 97551-60-5; **9**, 97551-62-7; **9** (5-(4-chlorobenzenesulfonate)), 97551-61-6; **10**, 97551-63-8; **11**, 97551-64-9; **12**·HCl, 97551-65-0; **13**, 97551-66-1; **14**, 97551-67-2; **14** (5-(4-chlorobenzenesulfonate)), 97551-73-0; **15**, 97551-69-4; **15**·K, 97551-68-3; **16**, 97551-70-7; **17**, 97551-72-9; **17** (bis(4-chlorobenzenesulfonate), 97551-71-8; **18**, 97569-84-1; (2′*R*)-**18**, 97569-89-6; **19**, 97569-85-2; (2′*R*)-**19**, 97569-86-3; **20**, 97551-74-1; **21**, 97590-61-9; (2′*S*)-**22**, 97551-75-2; (2′*R*)-**22**, 97590-62-0; (2′*S*)-**23**, 97569-87-4; (2′*R*)-**23**, 97569-88-5; 1,2-*O*-isopropylidene-α-D-xylofuranose, 20031-21-4; 5-*O*-acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose, 80244-96-8; silver 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate, 76121-99-8.

Synthesis of Chiral β-Lactams Using L-Ascorbic Acid[1]

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The discovery of monocyclic β-lactam antibiotics from microbial sources has spawned efforts to generate synthetic analogues with improved antibacterial properties. From such activities, Ro 17-2301 (AMA-1080, **1**) has emerged as an antibacterial with therapeutic potential. The commercial development of **1** required a practical synthesis of the zwitterion (3*S*,4*S*)-3-amino-4-[(carbamoyloxy)methyl]-2-oxoazetidine-1-sulfonic acid (**2**). The preparation of this and of related β-lactams, drawing upon L-ascorbic acid as an inexpensive chiral starting material, is described.

The discovery of sulfazecin[2] and of related monocyclic β-lactams (monobactams)[3] from microbial sources has spawned considerable efforts to generate synthetic analogues with enhanced antibiotic properties. From these activities have emerged two compounds, azetreonam[4] and Ro 17-2301 (**1**),[5] also known as AMA-1080,[6] whose im-

(1) Presented in part at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, NV, October 24–26, 1983; Abstract 324.

(2) Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature (London)* **1981**, *289*, 590.

(3) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. S., *Nature (London)* **1981**, *291*, 489.

(4) *J. Antimicrob. Chemother.* (*Suppl. E*), **1981**, *8*, 1. "Azthreonam, A Synthetic Monobactam"; Sykes, R. B., Phillips, I., Eds; the synthesis related to aztreonam has been described in ref 10.

(5) Christenson, J. G.; Beskid, G.; DeLorenzo, W.; Siegel, J.; Talbot, M. 13th International Congress of Chemotherapy, Vienna, Austria, August 28–September 2, 1983; Abstract PS 4.6/7-19.

(6) Kondo, M.; Kishimoto, S.; Ochiai, M.; Okonogi, K.; Imada, A. 13th International Congress of Chemotherapy, Vienna, Austria, August 28–September 2, 1983; Abstract SE 4.2/15-1.

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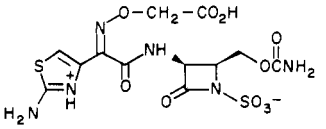
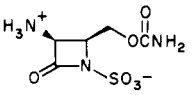
proved antibacterial spectrum and pharmacokinetic characteristics endow them with therapeutic usefulness.



1, Ro17-2301 (AMA-1080)



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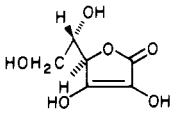

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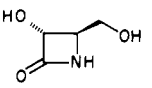


3

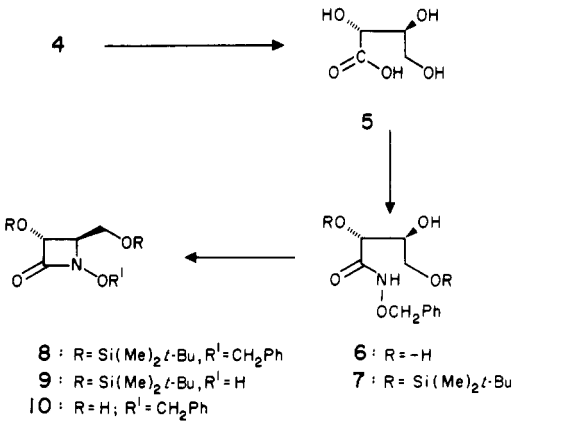
The commercial development of 1 required a practical synthesis of the chiral zwitterion 2. We describe here the preparation of 2 and of related β-lactams such as derivatives of 3 utilizing L-ascorbic acid (4) as a convenient and inexpensive starting material. More precisely, L-threonic acid (5), which can be efficiently obtained from 4 by the degradation method of Isbell and Frush,[7] not only contains a suitably functionalized carbon skeleton for our syntheses, but also the proper chirality.

As summarized in Scheme I, oxidation of 4 with hydrogen peroxide in the presence of calcium carbonate[7] afforded 5 in the form of its easily isolated and purified calcium salt. The (benzyloxy)amide 6 was prepared from 5 and *O*-benzylhydroxylamine in aqueous solution at pH 4.5–5.5 by using 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide as the condensing agent.[8] Selective protection of only two hydroxy groups of the triol 6, leaving the central 3-position available for functionalization, was readily achieved with *tert*-butyldimethylsilyl chloride in pyridine and methylene chloride to give 7. Cyclization of 7, using triphenylphosphine, carbon tetrachloride, and triethylamine in acetonitrile,[8] gave the β-lactam 8. Selective removal of the protecting groups of 8 could be achieved, either by catalytic hydrogenation to afford 9 or under mild acidic conditions (90% trifluoroacetic acid) to give 10.[9]

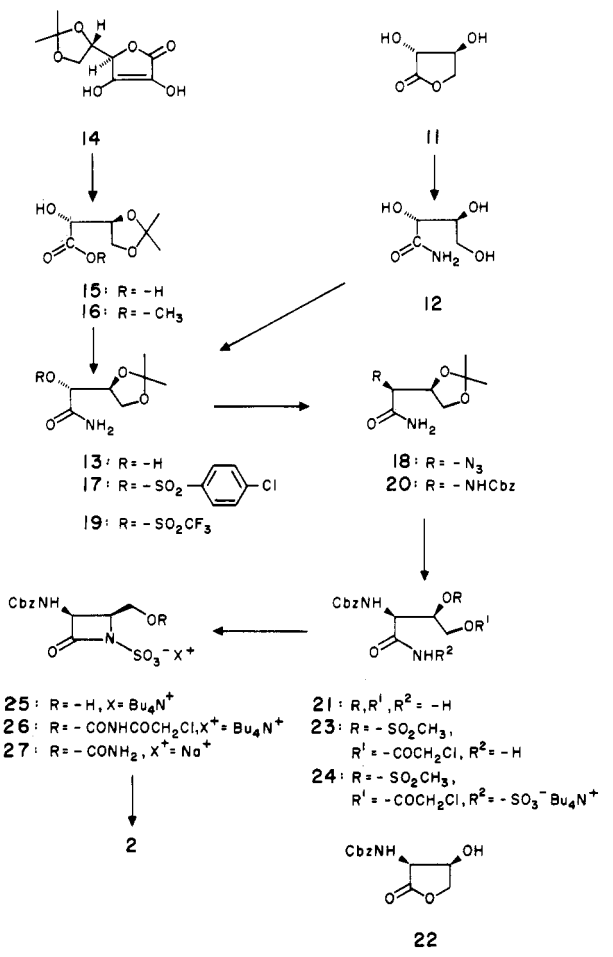
The synthesis of 2 required selective protection of the C-3 and C-4 hydroxy groups of L-threonic acid (5). This was accomplished by heating 5 in acetonitrile with a catalytic amount of *p*-toluenesulfonic acid and with azeotropic removal of water to give L-threonolactone (11) (Scheme II). Solvolysis with methanolic ammonia yielded the L-threonamide 12. Treatment with 2,2-dimethoxypropane in dimethylformamide gave selectively the 3,4-*O*-isopropylidene derivative 13, accompanied by only a trace amount of the diisopropylidene compound. This key intermediate 13 was, however, more conveniently obtained by an alternative route starting with 5,6-*O*-isopropylidene-L-ascorbic acid 14, obtained quantitatively from 4 upon treatment with 2,2-dimethoxypropane and anhydrous hydrogen chloride. Oxidation of 14 with hydrogen peroxide yielded the threonic acid derivative 15, which was transformed to the methyl ester 16 with dimethylsulfate and sodium bicarbonate in water and subsequently to the amide 13 with ammonia in tetrahydrofuran. Conversion of 13 with *p*-chlorobenzenesulfonyl chloride and triethylamine in 1,2-dichloroethane to 17, followed by reaction with sodium azide in dimethylformamide, gave the (*S*)-azide 18. A better yield of 18 was realized via the triflate 19 obtained from 13 with trifluoromethanesulfonic anhydride and pyridine in methylene chloride. Catalytic reduction of 18 followed by treatment with (benzyloxy)carbonyl chloride afforded quantitatively compound 20 which was then deprotected with mild acid (0.015 N HCl in acetonitrile) to give the 4-hydroxy-L-*allo*-threonamide 21. The conditions for the hydrolysis step were critical since at higher acid concentration the formation of lactone 22 was favored.

Our initial plans to introduce at this stage the urethane group required in 2 were abandoned, since this function proved too labile to survive the conditions of the ensuing reactions. Thus, the primary hydroxy group of 21 was first protected by reaction with chloroacetyl chloride and 2,6-lutidine in dimethylformamide and dichloromethane.

Scheme I



Scheme II



(7) Isbell, H. S.; Frush, H. L., *Carbohydr. Res.* **1979**, *72*, 301.
(8) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
(9) Further utilization of 10 will be described elsewhere.

Subsequent mesylation with methanesulfonyl chloride and triethylamine in dimethoxyethane gave **23** which was further converted to **24** by sulfonation with 2-picoline·SO_3 complex and treatment with tetrabutylammonium hydrogen sulfate. Stereospecific β-lactam formation proceeded at reflux in a two-phase system consisting of 1,2-dichloroethane and aqueous potassium bicarbonate[10] with concomitant hydrolysis of the chloroacetyl protecting group giving rise to **25**. Introduction of the urethane function in **26** was then achieved by reaction with chloroacetyl isocyanate. The chloroacetyl group could be removed with sodium *N*-methyldithiocarbamate converting the intermediate **26** to **27**. The synthesis of the zwitterion **2** was completed by catalytic hydrogenation to remove the carbobenzoxy group from **27**.

All reactions have been scaled-up and the sequence described in Scheme II has been used to prepare kilogram quantities of (3*S*,4*S*)-3-amino-2-[(carbamoyloxy)-methyl]-2-oxoazetidine-1-sulfonic acid (**2**), a key intermediate in the synthesis of therapeutically useful monocyclic β-lactam antibiotics.

Experimental Section

Melting points (uncorrected) were taken on a Thomas-Hoover capillary apparatus. Infrared spectra were recorded on Digilab FTS 14 spectrometer. Proton NMR spectra were obtained on a Varian XL-100 instrument. Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Calcium L-Threonate (5). L-Ascorbic acid (528 g, 3.0 mol) was dissolved in distilled water (7.5 L). To the solution was added calcium carbonate (600 g, 6.0 mol), and the stirred slurry was cooled to 15 °C. Hydrogen peroxide (30% w/w, 1.2 L) was added at 12–15 °C over a period of 60 min, and the mixture was then stirred at room temperature for 16 h. The stirred reaction mixture was treated with 120 g of charcoal (Norite SG) and heated to 75 °C until no more oxygen was evolved (as indicated by bubbling in a water trap). The suspension was filtered at 70–75 °C, and the filter cake was washed with distilled water (2 × 100 mL). The combined filtrates were concentrated to about 2 L at 50 °C under reduced pressure. Methanol (1.5 L) was added until the solution became cloudy, and the mixture was then stirred at room temperature for 16 h. The solids were isolated by filtration, washed with methanol (2 × 100 mL), dried at 60 °C under reduced pressure to constant weight, and dissolved in distilled water (6.6 L, 92 °C), and the solution was filtered. The filtrate was concentrated to about 2 L, and about 2 L of methanol was added until the solution became cloudy. The solution was stirred at room temperature for 16 h and filtered, and the precipitate was washed with methanol (2 × 100 mL). The solids were dried to a constant weight at 60 °C under vacuum to give 409.8 g (78.8%) of calcium L-threonate monohydrate: mp >300 °C; $[\alpha]^{25}_D$ +14.6° (*c* 1.0, H_2O); IR (KBr) ν_{max} 1600 cm^{-1}; ^1H NMR (D_2O) δ 3.57–3.74 (m, 2 H, $-CH_2O-$), 4.0 (t, *J* = 3 Hz, 1 H, >CHOH), 4.12 (s, 1 H, >CHOH).

L-Threonic Acid (Benzyloxy)amide (6). To a stirred solution of calcium L-threonate monohydrate (25.95 g, 0.15 mol) in 600 mL of H_2O was added 26.34 g (0.165 mol) of *O*-benzylhydroxylamine hydrochloride while the pH was maintained at 4.5 with saturated $NaHCO_3$. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (37.38 g, 0.195 mol) was added in four equal portions over 20 min, and the pH was maintained between 4.5 and 5.25 with 1 N HCl during the addition and the subsequent 4 h. The reaction mixture was then saturated with NaCl and extracted with 4 × 1000 mL portions of $CHCl_3$–EtOH, 3:2. The combined extracts were filtered through Whatman IPS siliconized paper and concentrated in vacuo, and the residue was dissolved in hot EtOH. The urea byproduct that crystallized upon concentration was removed by filtration and the residue from mother liquors and washings was purified by column chromatography on a 2 kg of silica gel 60 (Merck, 0.063–0.200 mm) with AcOEt–Me_2CO–MeOH–H_2O (6:1:1:1) as the eluent. After concentration of the appropriate fractions, crystallization of the residue from MeOH/Et_2O afforded 26.20 g (72.4%) of **6** as colorless crystals: mp 125–126 °C; $[\alpha]^{25}_D$ +50.8° (*c* 1.0138, MeOH); IR (KBr) ν_{max} 3410, 3352, 3250, 1660, 1643, 1517, 1040, 740, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.38 (m, 2 H, $-CH_2O-$), 3.74 (br m, 1 H, >CHOH), 3.97 (br m, 1 H, >CHOH), 4.59 (t, 1 H, *J* = 6 Hz, OH), 4.61 (d, 1 H, *J* = 6 Hz, OH), 4.80 (s, 2 H, OCH_2Ph), 5.08 (d, 1 H, *J* = 6,5 Hz, OH), 7.39 (m, 5 H, C_6H_5), 10.95 (s, 1 H, NH).

2,4-Bis(*O*-*tert*-butyldimethylsilyl)-L-threonic Acid (Benzyloxy)amide (7). (A) To a stirred solution of **6** (9.650 g, 40 mmol) in 60 mL of dry pyridine and 120 mL of dry 1,2-dichloroethane, cooled under argon to −10 °C, was added dropwise 16.27 g (108 mmol) of *tert*-butyldimethylsilyl chloride dissolved in 90 mL of 1,2-dichloroethane over a period of 45 min. After being stirred at −10 °C for 4 h and then at room temperature overnight, the mixture was concentrated in vacuo and the residue partitioned between 200 mL of H_2O and 600 mL of chloroethane. The organic extract was washed in sequence with ice-cold 1 N HCl (400 mL), diluted $NaHCO_3$ (300 mL), and H_2O (200 mL). After drying (Na_2SO_4) and evaporation of the solvent in vacuo, the residue was purified by flash chromatography on silica gel 60 (Merck, 0.040–0.063 mm). Elution of the column (30 × 6.5 cm) with AcOEt/cyclohexane, 30:70 (1500 ml) and 70:30 (1400 mL), afforded 2.30 g (9.8%) of 2,4-*O*,*N*-tris(*tert*-butyldimethylsilyl)-L-threonic acid (benzyloxy)amide,[11] as an unstable oil, followed by 13.82 g (73.5%) of **7** as a colorless oil which upon prolonged storage gave a colorless solid: mp 55–57 °C after softening; $[\alpha]^{25}_D$ +44.9° (*c* 0.9570, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3565, 3415, 1693, 1472, 1255, 837 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.04, 0.05, 0.06, 0.07 (4 s, 3 H each, 4 CH_3Si), 0.89, 0.91 (2 s, 9 H each, 2 $C(CH_3)_3$), 3.46 to 3.74 (m, 3 H, $-CH_2O-$ and >CHO−), 4.12 (d, 1 H, *J* = 2 Hz, >CHO−), 4.85 (br s, 1 H, OH), 4.86 (s, 2 H, OCH_2Ph), 7.43 (m, 5 H, C_6H_5), 10.66 (s, 1 H, NH). Anal. Calcd for $C_{23}H_{43}NO_5Si_2$: C, 58.81; H, 9.23; N, 2.98. Found: C, 58.61; H, 9.14; N, 3.10. A more polar component (2.30 g, 16.2%), 4-*O*-(*tert*-Butyldimethylsilyl)-L-threonic acid (benzyloxy)amide was isolated as a second product. Recrystallization from Et_2O/petroleum ether (30–60 °C) gave 1.95 g of colorless crystals: mp 70–72 °C; $[\alpha]^{25}_D$ +12.5° (*c* 1.0134, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3570, 3410, 1693, 1474, 1255, 837, 697 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.04 (s, 6 H, 2 CH_3Si), 0.87 (s, 9 H, $C(CH_3)_3$), 3.49, 3.61 (AB of ABX, 2 H, J_{gem} = 10 Hz, J_{vic} = 6 and 7 Hz, $-CH_2O-$), 3.79 (br m, 1 H, >CHO−), 3.97 (dd, 1 H, *J* = 2.5 and 7 Hz, >CHO−), 4.75 (d, 1 H, *J* = 6 Hz, OH), 4.82 (s, 2 H, OCH_2Ph), 5.13 (d, 1 H, *J* = 7 Hz, OH), 7.40 (m, 5 H, C_6H_5), 10.98 (s, 1 H, NH). Anal. Calcd for $C_{17}H_{29}NO_5Si$: C, 57.44; H, 8.22; N, 3.94. Found: C, 57.65; H, 8.32; N, 3.96.

(B) To a stirred solution of **6** (1.93 g, 8 mmol) in 30 mL of dry 1,2-dichloroethane and 15 mL of dry pyridine, cooled to 0 °C under argon, was added dropwise 4.80 g (32 mmol) of *tert*-butyldimethylsilyl chloride in 15 mL of 1,2-dichloroethane. After being stirred overnight at room temperature, the reaction mixture was evaporated, and the residue was subjected to the same washing procedure described above (A) to yield 4.6 g of 2,4-*O*,*N*-tri-(*tert*-butyldimethylsilyl)-L-threonic acid (benzyloxy)amide as a colorless oil,[11] which was dissolved in 80 mL of 1,4-dioxoane. The solution was diluted with 25 mL of H_2O and stirred for 1 h with 10 g of Dowex AG 50W-X4 (H^+, 100–200 mesh). After removal of the resin and concentration of the filtrate in vacuo, the residual water was removed by azeotropic evaporation with MeCN to give a residue of **7** suitable for further use. Pure **7**, 3.48 g (92.6%), was obtained by flash chromatography on silica gel, using AcOEt/cyclohexane, 30:70, as the eluant.

(3*R*,4*S*)-1-(Benzyloxy)-3-[(*tert*-butyldimethylsilyl)-oxy]-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-azetidinone (8). To a solution of **7** (12.68 g, 27 mmol) and triphenylphosphine (7.87 g, 29.7 mmol) in 180 mL of dry MeCN, stirred 15 min at room temperature, was added dropwise 5.65 mL (40.51 mmol) dry NEt_3, followed by 2.92 mL (30 mmol) of CCl_4 dissolved in 6 mL of MeCN. After being stirred overnight at room temperature under argon, the reaction mixture was concentrated in vacuo. Most of the triphenylphosphine oxide and triethylammonium chloride were removed by filtration after slurrying the residue

(10) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

(11) The presence of the third silyl substituent could be identified by the disappearence of the NH signal at δ 10.66 in the ^1H NMR spectrum.

with 80 mL of Et_2O and diluting the mixture with 200 mL of cyclohexane, added in small portions. The residue from the filtrate was purified by flash chromatography in a column (30 × 6.5 cm) eluted with AcOEt/cyclohexane, 1:9, to yield 9.45 g (77.5%) of **8** as a colorless oil: $[\alpha]^{25}_D$ +63.2° (*c* 0.9528, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1774, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, 2 MeSi), 0.09 (s, 3 H, MeSi), 0.12 (s, 3 H, MeSi), 0.87 (s, 9 H, $C(CH_3)_3$), 0.89 (s, 9 H, $C(CH_3)_3$), 3.36 (dt, 1 H, *J* = 1.5, 3.5, and 3.5 Hz, H-4), 3.69 (d, 2 H, *J* = 3.5 Hz, CH_2OSi), 4.59 (d, 1 H, *J* = 1.5 Hz, H-3), 4.96, 5.00 (AB, 2 H, J_{gem} = 11 Hz, OCH_2Ph), 7.40 (m, 5 H, C_6H_5). Anal. Calcd for $C_{23}H_{41}NO_4Si_2$: C, 61.15; H, 9.15; N, 3.10. Found: C, 61.02; H, 9.02; N, 3.30.

(3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-hydroxy-2-azetidinone (9). A solution of **8** (4.52 g, 10 mmol) in 100 mL of MeOH was treated with hydrogen for 45 min at room temperature and ambient pressure in the presence of 400 mg of 10% Pd/C. After removal of the catalyst, the filtrate was concentrated in vacuo. The resulting oil crystallized spontaneously to give 3.61 g (100%) **9** as a colorless solid: mp 75–78 °C with softening; $[\alpha]^{25}_D$ +28.8° (*c* 0.9585, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3110, 1762, 1258, 1124, 838 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.00 (s, 6 H, 2 MeSi), 0.05 (s, 6 H, 2 MeSi), 0.82 (br s, 18 H, 2 $C(CH_3)_3$), 3.49 (dt, 1 H, *J* = 1, 3.5 and 3.5 Hz, H-4), 3.73, 3.78 (AB of ABX, 2 H, J_{gem} = 11.5 Hz, J_{vic} = 3.5 Hz, CH_2OSi), 4.51 (d, 1 H, *J* = 1 Hz, H-3), 10.09 (s, 1 H, –NOH). Anal. Calcd for $C_{16}H_{35}NO_4Si_2$: C, 53.14; H, 9.76; N, 3.87. Found: C, 52.87; H, 9.46; N, 3.87.

(3*R*,4*S*)-1-(Benzyloxy)-3-hydroxy-4-(hydroxymethyl)-2-azetidinone (10). A solution of **8** (1 g, 2.21 mmol) in 20 mL of 90% trifluoroacetic acid was stirred 2 h at room temperature. The solvents were evaporated by using an oil pump and the residue was purified by flash chromatography on silica gel (Merck, 0.040–0.063 mm). Elution of the column (30 × 3.5 cm) with AcOEt and evaporation of the appropriate fractions afforded 318 mg (64.4%) **10** as a colorless oil: IR ($CHCl_3$) ν_{max} 3590, 3390, 1767, 701 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60 (m, 3 H, H-4 and CH_2OH), 4.40 (m, 1 H, H-3), 4.94 (s, OCH_2Ph), 5.01 (t, 1 H, *J* = 5 Hz, primary OH), 6.13 (d, 1 H, *J* = 7 Hz, secondary OH), 7.41 (m, 5 H, C_6H_5).

L-Threonolactone (11). Calcium L-threonate monohydrate (46.73 g, 0.27 mol) in water (1 L) was heated on a steam bath until complete dissolution was achieved. The Bio-Rad resin AG 50W-X4 (H^+ form, 300 mL) was added, and the hot mixture was vigorously stirred for 30 min. The resin was removed by filtration, and the filtrate was evaporated to dryness under high vacuum. The residue was azeotropically evaporated twice with acetonitrile. The residue was suspended in acetonitrile (500 mL) and *p*-toluenesulfonic acid (1 g) was added. The mixture was heated at reflux temperature for 1 h, cooled, and filtered. The filtrate was concentrated and the residue was crystallized from acetonitrile/ether. White crystals (25.07 g) were collected after refrigeration overnight. The mother liquor was concentrated to give a second crop of white crystals (0.57 g); total yield 76%: mp 66 °C; $[\alpha]^{25}_D$ +48.37° *c* 0.9840, CH_3CN); IR (KBr) ν_{max} 1780 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.85 (dd, *J* = 3.0 Hz, 4.0 Hz, 1 H, $-CH_2O-$), 4.04–4.22 (m, 1 H, >CHO), 4.10 (dd, *J* = 3.0 Hz, 4.0 Hz, 1 H, $-CH_2O-$), 4.35 (dd, *J* = 3.0 Hz, 3.50 Hz, 1 H, >CHOH), 5.78 (d, *J* = 2 Hz, 1 H, OH), 6.13 (d, *J* = 3.0 Hz, 1 H, OH). Anal. Calcd for $C_4H_6O_4$: C, 40.68; H, 5.12. Found: C, 40.44; H, 4.85.

L-Threonamide (12). A solution of L-threonolactone (5.50 g, 46.6 mol) in MeOH (100 mL), previously saturated with anhydrous NH_3 at 0 °C, was kept at room temperature for 48 h in a pressure bottle. The solvent was evaporated in vacuo, and the residual oil was dissolved in absolute EtOH and evaporated to dryness. The residue was crystallized from boiling EtOH. The crystals were collected after cooling at 0 °C, washed with ethanol/ether (1:1) and then with ether, and dried at 40 °C (0.005 mmHg) to give 6.02 g (95.7%) of analytically pure products: mp 105–107 °C; $[\alpha]^{25}_D$ +77.46° (*c* 1.0096, MeOH); ^1H NMR (Me_2SO-d_6) δ 3.24–3.48 (m, 2 H, $-CH_2O-$), 3.74 (d, *J* = 3.0 Hz, 1 H, >CHOH), 3.84 (d, *J* = 3.0 Hz, 1 H, >CHOH), 4.49 (d, *J* = 3.0 Hz, 1 H, OH), 4.52 (d, *J* = 3.0 Hz, 1 H, OH), 5.00 (d, *J* = 3.0 Hz, 1 H, OH), 7.12 and 7.18 (s, 2 H, $CONH_2$). Anal. Calcd for $C_4H_9NO_4$: C, 35.56; H, 6.71; N, 10.37. Found: C, 35.54; H, 6.47; N, 10.25.

3,4-*O*-Isopropylidene-L-threonamide (13). Method A. To a solution of L-threonamide **12** (5.0 g, 37 mmol) dissolved in dry dimethylformamide (50 mL) was added 2,2-dimethoxypropane (16.4 mL, 132.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.12 g). The solution was stirred at room temperature under argon for 4.5 h. The reaction mixture was then stirred with ca. 2.5 g of Dowex AG 1-X4 (OH^- form, 100–200 mesh) for 2 min, the resin was removed by filtration, and the combined filtrated and washings were evaporated in vacuo (oil pump) at 55 °C to give a colorless syrup. Crystallization from ethyl acetate/ether/hexane afforded 3.6 g (55.5%) of pure 3,4-*O*-isopropylidene-L-threonamide as colorless crystals. Flash chromatography of the residue from the mother liquors on silica gel 60 (Merck) gave 0.56 g (6.5%) of a diisopropylidene derivative (ethyl acetate/acetonitrile, 100:15, as eluant) and an additional 0.61 g (after crystallization) of the desired product (ethyl acetate/acetonitrile, 100:30, as eluant). The total yield of **13** was 4.2 g (65%): mp 77–79 °C; $[\alpha]^{25}_D$ +29.41° (*c* 0.9386, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.43 (d, *J* = 5.0 Hz, 1 H, OH), 4.0–4.16 (m, 2 H, $-CH_2O-$), 4.07 (t, *J* = 5.0 Hz, 1 H, >CHOH), 4.28–4.36 (m, 1 H, >CHO–), 6.06 and 6.68 (br s, 2 H, $CONH_2$). Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.90; H, 7.46;, N, 7.98.

Method B. Into a 1.0-L, round-bottomed flask was placed methyl 3,4-*O*-isopropylidene-L-threonate **16** (21.6 g, 113 mmol), tetrahydrofuran (280 mL), and 29% aqueous ammonium hydroxide (95 mL). The reaction mixture was cooled in an ice bath and ammonia gas bubbled in for 5 min. The reaction vessel was then stoppered and stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and azeotroped with absolute ethanol. The residue was recrystallized from ethyl acetate/hexane to give 17.7 g (89%) of **13** as colorless crystals, mp 77–79 °C.

5,6-*O*-Isopropylidene-L-ascorbic Acid (14). A mixture of L-ascorbic acid (1600 g, 9 mol), acetone (8 L), and 2,2-dimethoxypropane (1.88 L) was stirred for 15 min and hydrogen chloride was then added slowly through a bubbler over 2–4 min. The solution turned from colorless to dark yellow. The reaction mixture was stirred for 1 h during which it became very viscous. The product was isolated by filtration and washed with cold acetone, and the solid was air-dried to give 1.521 g (77%) of **14**. The mother liquor was concentrated to afford an additional 387 g (19.7%) of **14**, mp 218–219 °C.

Calcium 3,4-*O*-Isopropylidene-L-threonate (15). A suspension of **14** (86.4 g, 0.4 mol) in water (1.0 L) was treated with calcium carbonate (80.0 g, 0.8 mol). The resulting mixture was cooled in an ice bath, and 30% aqueous hydrogen peroxide (160 mL, 1.6 mol) was added dropwise. After the addition, the mixture was allowed to slowly warm to about 20 °C (exothermic!) and kept below 30 °C with cooling. When the reaction had subsided, the mixture was heated at 30–40 °C for 30 min. To the reaction mixture was added 16.0 g of charcoal (DARCO G-60, Fisher) and 1.0 g of 10% Pd/C. It was heated on a steam bath until a negative test to starch iodide paper was obtained (30 min). The suspended material was removed by filtration and the filtrate was concentrated in vacuo. Crystallization of the residue from water/acetone afforded 62.0 g (78%) of **15** as white crystals: mp >250 °C; $[\alpha]^{25}_D$ +23.60° (*c* 0.974, H_2O); IR (KBr) ν_{max} 1610 cm^{-1}; ^1H NMR (D_2O) δ 1.35 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3), 4.35–4.70 (m, 2 H, $-CH_2O-$), 4.47 (d, *J* = 4.0 Hz, 1 H, >CHOH), 4.8–5.0 (m, 1 H, >CHO–). Anal. Calcd for $C_{14}H_{22}CaO_{10}\cdot{}^1/_2H_2O$: C, 42.09; H, 5.79; H_2O, 2.25. Found: C, 41.77; H, 5.77; H_2O, 2.34.

Methyl 3,4-*O*-Isopropylidene-L-threonate (16). Method A. A suspension of calcium L-threonate **15** (23.4 g, 0.12 mol) in dimethylacetamide (150 mL) under argon, protected from light, was treated with sodium bicarbonate (73.2 g, 0.87 mol) and methyl iodide (67.2 mL, 1.08 mol). The mixture was stirred at room temperature for 2 days. The resulting mixture was poured into 1.2 L of ethyl acetate, and the precipitate was removed by filtration. The filtrate was evaporated in vacuo to remove the ethyl acetate and the dimethylacetamide was then removed under high vacuum. The residue was dissolved in ethyl acetate (500 mL), and the resulting solution was washed with brine (2 × 250 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 21.7 g of light yellow oil (95% as is). The material was used for the preparation of **13** without further purification.

Method B. To a suspension of calcium L-threonate **15** (24.0 g, 0.12 mol) in water (300 mL) was added slowly sodium bi-

carbonate (45 g) followed by dimethylsulfate (50 mL). The mixture was heated at 40 °C for 6 h. After the reaction mixture was filtered, the filtrate was extracted with methylene chloride (5 × 250 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 16.9 g (72.3%) of the ester **16**. An analytical sample was obtained by distillation at 70–75 °C (0.001 mmHg): $[\alpha]^{25}_D$ +18.39° (*c* 1.0442, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 2.93 (d, *J* = 4.0 Hz, 1 H, OH), 3.84 (s, 3 H, OCH_3), 3.96–4.16 (m, 3 H, $-CH_2O-$, >CHOH), 4.4 (dt, *J* = 1.7 Hz, 3 Hz, 1 H, >CHO–). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.21; H, 7.48.

2-*O*-[(4-Chlorophenyl)sulfonyl]-3,4-*O*-isopropylidene-L-threonamide (17). To a solution of amide **13** (10.5 g, 60 mmol) and triethylamine (24 mL) in 1,2-dichloroethane (100 mL) at room temperature was added *p*-chlorobenzenesulfonyl chloride (19.0 g, 90 mmol), and the reaction mixture was stirred at room temperature for 30 h. Ethyl acetate (150 mL) was added, and the mixture was washed successively with 1 N HCl, 5% $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, the solvent was removed, and the residue was crystallized from ethyl acetate/hexane to give 15.8 g (74%) of the product: mp 136–138 °C; $[\alpha]^{25}_D$ +57.67° (*c* 1.0040, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 6 H, 2 CH_3), 3.78–4.70 (m, 3 H, $-CH_2O-$, >CHO–), 4.92 (d, *J* = 4.7 Hz, 1 H, $>CHOSO_2-$), 6.5 (br d, 2 H, $CONH_2$), 7.7 (d, *J* = 9 Hz, 2 H, aromatic), 8.09 (d, *J* = 9 Hz, 2 H, aromatic). Anal. Calcd from $C_{13}H_{16}NO_6SCl$: C, 44.64; H, 4.61; N, 4.00. Found: C, 44.79; H, 4.66; N, 4.27.

2-Azido-2-deoxy-3,4-*O*-isopropylidene-L-erythronamide (18). Method A. To a mixture of threonamide **13** (1.6 g, 9.1 mmol), dry 1,2-dichloroethane (15 mL), and pyridine (2 mL) was slowly added trifluoromethanesulfonic anhydride (1.7 mL, 10 mmol) at −10 °C. The reaction mixture was stirred at −10 °C for 30 min and then at 0 °C for an additional 30 min. To the reaction mixture was added ether (50 mL), and the mixture was washed with brine (twice), dried (Na_2SO_4), concentrated to give the crude triflate **19**, which was treated with lithium azide (1.2 g, 24 mmol) in dimethylformamide (15 mL), and stirred at room temperature for 15 h. Ethyl acetate (100 mL) was added to the reaction mixture and the mixture was washed with brine (twice), dried (Na_2SO_4), and evaporated to dryness. The crude azido product was purified by flash chromatography [silica gel 60; ethyl acetate/hexane, 1:1] to give 1.3 g (72%) of crystalline **18**. Recrystallization from ether/hexane (1:1) afforded 1.24 g of **18**: mp 98–99 °C; $[\alpha]^{25}_D$ +73.12° (*c* 0.9820, $CHCl_3$); IR (KBr) ν_{max} 2125, 1665, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 3.89–4.06 (m, 2 H, $-CH_2O-$), 4.32 (d, *J* = 4 Hz, 1 H, CHN_3), 4.68 (m, 1 H, >CHO–), 6.00 and 6.46 (br s, 2 H, $CONH_2$). Anal. Calcd for $C_7H_{12}N_4O_3$: C, 41.99; H, 6.04; N, 27.99. Found: C, 41.85; H, 6.00; N, 27.89.

Method B. A mixture of the *p*-chlorobenzenesulfonate **17** (10.5 g, 30 mmol) and NaN_3 (2 g, 36 mmol) in dimethylformamide (30 mL) was heated at 60 °C for 48 h. After the reaction was complete, the mixture was added to ethyl acetate (150 mL) and filtered, and the filtrate was washed with 5% aqueous $NaHCO_3$ and brine. The organic layer, dried over Na_2SO_4, was stripped to dryness and purified by HPLC (methylene chloride/acetonitrile, 8:2) to give the azide **18** as colorless crystals (4.2 g, 70%): mp 98–99 °C; $[\alpha]^{25}_D$ +73.66° (*c* 1.0223, $CHCl_3$).

2-[(Benzyloxycarbonyl)amino]-2-deoxy-3,4-*O*-isopropylidene-L-erythronamide (20). A solution of the azide **18** (12.3 g, 61 mmol) in ethanol (500 mL) was hydrogenated in the presence of 1.3 g of 10% Pd/C at 25 °C and atmospheric pressure for 2 h (the system was evacuated and refilled with hydrogen 3 times). The mixture was filtered through Celite, and the catalyst was washed with ethanol (75 mL). The combined filtrates were evaporated to dryness under vacuum to give a white solid. This was dissolved in a mixture of methylene chloride (250 mL) and water (200 mL) containing potassium carbonate (8.48 g, 61 mmol). Benzyl chloroformate (11.3 mL, 76 mmol) was added slowly to this stirred mixture at 0 °C, and the resultant mixture was allowed to stir for 2 h at 0 °C. The white precipitate was separated by filtration, and the filtrate was concentrated in vacuo to remove the organic solvent, giving a second precipitate. The combined precipitates were recrystallized from hot ethyl acetate (700 mL), affording 15.7 g (83.5%) of **20**, as white crystals. The mother liquor gave a second crop of 1.4 g, bringing the total yield to 90.9%: mp 181–182 °C; $[\alpha]^{25}_D$ +6.11° (*c* 0.9665, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 1.24 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 3.70–4.0 (m, 2 H, $-CH_2O-$), 4.10–4.25 (m, 2 H, >CHO– and >CHN), 5.05 (s, 2 H, OCH_2Ph), 7.36 (s, 5 H, aromatic), 7.10 and 7.30 (br s, 2 H, $CONH_2$), 7.42 (br s, 1 H, –NHCO–). Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.59; H, 6.55; N, 9.09.

***N*-(Benzyloxycarbonyl)-4-hydroxy-L-*allo*-threonamide (21).** A suspension of compound **20** (6.44 g, 20.9 mmol) and 413 mL of a solution obtained by mixing 6.6 mL of 2 N HCl with 13.3 mL of water and diluting to 900 mL with acetonitrile was stirred vigorously at room temperature for 2 h, then cooled to 0 °C for 20 min, and filtered to give 4.65 g (83%) of the desired diol **21** (TLC: methylene chloride/methanol, 8:2). The filtrate was concentrated to about 100 mL and placed in a refrigerator overnight. The resulting precipitate was filtered to give an additional 0.45 g, to bring the total yield of **21** to 91%: mp 175–176 °C; $[\alpha]^{25}_D$ +11.47° (*c* 0.8722, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 3.42 (dd, *J* = 5 Hz, 6 Hz, 2 H, $-CH_2O-$), 3.69 (m, 1 H, >CHO), 4.06 (dd, *J* = 6 Hz, 7 Hz, 1 H, NCH–), 4.62 (t, *J* = 4.5 Hz, 1 H, OH), 4.93 (d, *J* = 5 Hz, 1 H, OH), 5.03 (s, 2 H, OCH_2Ph), 7.08 and 7.2 (br d, 3 H, $-CONH_2$ and –CONH–), 7.35 (s, 5 H, aromatic). Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.77; H, 5.91; N, 10.46.

***N*-(Benzyloxycarbonyl)-4-(chloroacetoxy)-3-*O*-(methylsulfonyl)-L-*allo*-threonamide (23).** A solution of diol **21** (4.08 g, 15 mmol) in dry dimethylformamide (40 mL) and 2,6-lutidine (2 mL) was cooled to −10 °C, and 18 mL of a 1 M solution of chloroacetyl chloride in methylene chloride was added slowly. The reaction mixture was stirred at −10 °C for 1 h and 0 °C for 0.5 h and then concentrated under high vacuum at room temperature to about 15 mL. The mixture was partitioned between brine (60 mL) and ethyl acetate (60 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo to dryness. Crystallization of the residue from 95% ethanol (120 mL) gave 4.18 g (76%) of the 4-chloroacetyl ester of diol **21**, mp 119–122 °C.

The monochloroacetate (4.0 g, 10.8 mmol) which contains 0.5 mol of ethanol as estimated by NMR in 30 mL of dry 1,2-dimethoxyethane and triethylamine (3.15 mL, 22 mmol) was cooled to −20 °C, and to this solution was added methanesulfonyl chloride (1.58 mL, 20 mmol) slowly. The reaction was stirred at −15 to −20 °C for 1 h. The reaction mixture, diluted with ethyl acetate (50 mL), was washed with brine (2 × 15 mL), dried over Na_2SO_4, and evaporated to dryness. Crystallization from ethanol gave 3.9 g (86%) of white crystalline **23**: mp 140–141 °C; $[\alpha]^{25}_D$ +5.16° (*c* 0.5042, MeOH); ^1H NMR (Me_2SO-d_6) δ 3.18 (s, 3 H, $-SO_2CH_3$), 4.37 (s, 2 H, $-COCH_2Cl$), 4.25–4.65 (m, 3 H, $-CH_2O-$ and –CONCH–), 5.04 (m, 1 H, –CHO–), 5.56 (s, 2 H, $-OCH_2Ph$), 7.36 s, 5 H, aromatic), 7.42 and 7.73 (br s, 2 H, $-CONH_2$), 7.71 (br s, 1 H, –CONH–). Anal. Calcd for $C_{15}H_{19}ClN_2O_8S$: C, 42.61, H, 4.53; N, 6.62; S, 7.58; Cl, 8.38. Found: C, 42.62; H, 4.61; N, 6.43; S, 7.75; Cl, 8.41.

Tetrabutylammonium (3*S*,4*S*)-3-(Benzyloxycarboxamide)-4-(hydroxymethyl)-2-oxoazetidine-1-sulfonate (25). A solution of 2-picoline (3.7 mL, 37 mmol) in 1,2-dichloroethane (35 mL) was cooled to −10 °C under argon, and to it was slowly added chlorosulfonic acid (1.25 mL, 19 mmol). Stirring was continued at −10 °C for 5 min and then **23** (2.0 g, 4.8 mmol) was added to the solution. The reaction mixture was heated at 75 °C for 1 h and then quickly cooled. The mixture was washed with 35 mL of 0.6 M aqueous potassium bisulfate and then extracted with 2% aqueous sodium bicarbonate (2 × 25 mL). The combined bicarbonate extracts were treated with tetrabutylammonium hydrogen sulfate (1.61 g, 4.8 mmol) and extracted with 1,2-dichloroethane (2 × 20 mL). The combined organic extracts containing **24** and potassium bicarbonate (1.85 g, 18.5 mmol) in water (25 mL) were stirred vigorously and heated to reflux for 15 min (oil bath 80–85 °C). Upon cooling, the organic layer was separated, and the aqueous layer was extracted with 1,2-dichloroethane. The combined organic extracts were dried (Na_2SO_4) and evaporated at reduced pressure to give 2.34 g (87%) of **25** as an amber oil which was used for the preparation of **27** without further purification. A portion of the tetrabutylammonium salt **25** was converted to the sodium salt by stirring with AG 50W-X4 (Na^+ form). Purification on a Diaion column gave the pure sodium salt: $[\alpha]^{25}_D$ −7.63° (*c* 0.6288, H_2O); ^1H NMR (Me_2SO-d_6) δ 3.53–4.0 (m, 3 H, $-CHCH_2O-$), 4.52 (t, *J* = 5.0 Hz, 1 H, OH), 4.88 (dd, *J*

= 5.5 Hz, 8.0 Hz, 1 H, –CONCH–), 5.05 (s, 2 H, OCH_2Ph), 7.36 (s, 5 H, aromatic), 7.7 (d, J = 8.0, 1 H, –CONH). Anal. Calcd for $C_{12}H_{13}N_2O_7SNa·H_2O$: C, 38.92; H, 4.08; N, 7.56; H_2O, 4.86. Found: C, 38.98; H, 4.14; N, 7.69; H_2O, 5.14.

Sodium (3*S*,4*S*)-3-(Benzyloxycarboxamido)-4-[(carbamoyloxy)methyl]-2-oxoazetidine-1-sulfonate (27). A solution of azetidinone **25** (2.42 g, 4.2 mmol) in dry methylene chloride (40 mL) was cooled to 0 °C, and chloroacetylisocyanate (0.42 mL, 8.4 mmol) was added slowly under argon. The reaction mixture was stirred at 0 °C for 1 h, and sodium *N*-methyldithiocarbamate (1.2 g, 8.16 mmol) in water (15 mL) was added. The mixture was stirred vigorously at room temperature for 1 h. The organic layer was separated, and the aqueous phase was extracted once with methylene chloride. The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in 40 mL of ethanol/water (1:2) and stirred with about 30 mL of AG 50W-X4 resin (100–200 mesh, Na^+ form) for 15 min. The resin was removed by filtration and washed with water (30 mL). The filtrate was concentrated under high vacuum to about half of the original volume and washed with ethyl acetate (2 × 10 mL). The aqueous solution was evaporated to dryness under high vacuume. The solid residue was slurried with methanol and filtered. The crystals were washed with cold methanol and ether and dried to give 580 mg (36%) of azetidinone **27**. The mother liquor was concentrated and applied to a column of Diaion (60 mL), which was eluted with water, followed by 5% ethanol/water. The desired fractions were combined, concentrated, and slurried with acetone to give an additional 220 mg (14%) of product: mp 206–207 °C dec; $[\alpha]^{25}_D$ +31.23° (*c* 0.5796, H_2O); IR (KBr) ν_{max} 1797, 1715, 1694, 1273, 1254 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.90–4.35 (m, 3 H, –$CHCH_2O$–), 4.91 (dd, J = 5.5 Hz, 8.0 Hz, 1 H, –CONCH–), 5.06 (s, 2 H, OCH_2Ph), 6.4 (br s, 2 H, $CONH_2$), 7.38 (s, 5 H, aromatic) 7.98 (d, J = 8.0 Hz, 1 H, –CONH–). Anal. Calcd for $C_{13}H_{14}N_3O_8SNa$: C, 39.50; H, 3.57; N, 10.63; S, 8.11. Found: C, 39.53; H, 3.77; N, 10.55; S, 8.30.

(3*S*,4*S*)-3-Amino-4-[(carbamoyloxy)methyl]-2-oxoazetidine-1-sulfonic Acid (2). The mixture of azetidinone **27** (1.97 g, 5 mmol) and 0.4 g of 10% Pd/C in 70 mL of methanol/H_2O (1:1) was treated with hydrogen at atmospheric pressure for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated to about 10 mL. The solution, chilled in an ice bath, was adjusted to pH 2 with 1 N HCl, and ethanol (10 mL) was added. Crystals were collected to give 1.14 g (95% yield) of **2**: mp 208–209 °C dec; $[\alpha]^{25}_D$ –6.09° (*c* 0.5, Me_2SO); IR (KBr) ν_{max} 3470, 3355, 3100–2635, 1785, 1742, 1708, 1532, 1248, 1208, 1050 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.08–4.24 (m, 1 H, >CH), 4.24–4.44 (m, 2 H, –CH_2O–), 4.68 (d, J = 6.3 Hz, 1 H, >(N)CH), 6.52 (s, 2 H, $CONH_2$), 8.5 (br s, 3 H, –$^+NH_3$). Anal. Calcd for $C_5H_9N_3O_6S$: C, 25.11; H, 3.79; N, 17.57; S, 13.40. Found: C, 25.27; H, 3.84; N, 17.44; S, 13.66.

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Regioselective Synthesis of Dihydrofurans from 2,2-Dibromo 1,3-Diones and Olefins Using Copper

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2,2-Dibromo 1,3-diones reacted with copper powder and olefin to give 2,3-dihydrofuran derivatives in a highly regioselective fashion. Acetylenes and 1,3-dienes also reacted with 2,2-dibromo 1,3-diones and copper to afford furan derivatives and 2-vinyl-2,3-dihydrofuran derivatives, respectively. In benzene copper was converted into copper(I) bromide during the course of reaction, whereas in Me_2SO copper was converted into copper(II) bromide. The reactions with (*E*)- and (*Z*)-β-methylstyrene proceeded in a nonstereospecific way and only the *E* isomer of the dihydrofuran derivative was obtained. Hammett study with substituted styrenes gave a ρ value of –0.90. A mechanism involving a radical intermediate rationalizes the results.

1,3-Dipolar addition reactions are an important tool to construct various heterocyclic compounds as well as to functionalize carbon–carbon unsaturated bonds.[1,2] It is well-known that α-keto carbenes and α-keto carbenoids serve as 1,3-dipoles,[3] and several methods for their preparation have been developed. For example, thermolysis of diazo ketones in the presence of trapping agents such as olefins, acetylenes, and nitrile is reported to produce the corresponding cycloadducts.[4] Copper catalysts promote decomposition of diazo ketones.[5] It is also reported that α-elimination of dibromo ketones affords α-keto carbenes[6] which are effectively trapped by olefins.[6a] Al-

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