identical with those of samples obtained from the cryptand and alkaline iodide. Their purity (95–100%) was also tested by potentiometric titration of iodide ion. [2.2.2,C_{14}] was isolated as the free cryptand after decomplexation in an acidic medium and the addition of LiOH (entry 13).

Registry No. 2 (x = OMes), 80322-79-8; 3 (X = I), 92958-34-4; 3 (free base), 80322-80-1; 4, 294-92-8; 5, 97431-31-7; 6, 97431-32-8; 7, 97431-35-1; 7·Na, 97431-34-0; 8, 6005-35-2; 9, 97431-33-9; 10, 97431-37-3; 11, 80322-78-7; 12, 97431-38-4; 13, 34604-52-9; 15, 24345-74-2; 16, 2752-17-2; 17, 80322-82-3; 18, 80322-83-4; 19, 56741-58-3; 20, 97431-39-5; 21, 60742-62-3; 22, 31249-95-3; 23, 23978-55-4; 24, 31364-42-8; 24 (Li complex), 57064-20-7; 24 (Na complex), 57064-16-1; 24 (K complex), 97467-01-1; 25, 97431-40-8; 25 (Na complex), 97485-93-3; 26, 23978-09-8; 26 (K complex), 97485-94-4; 26 (Na complex), 97485-95-5; 27, 64066-13-3; $CH_3(CH_2)_{13}CH(CO_2H)OCH_2CH_2OH$, 97431-36-2; diglycolic acid dichloride, 21062-20-4; 2-bromopalmitoyl chloride, 69319-95-5; 2-(benzyloxy)ethanol, 622-08-2; methanesulfonyl chloride, 124-63-0; 1,5-dichloro-3-oxapentane, 111-44-4.

Clavalanine (Ro 22-5417), a New Clavam Antibiotic from *Streptomyces clavuligerus*. 4. A Stereorational Synthesis

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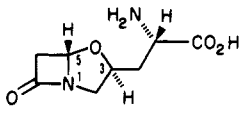
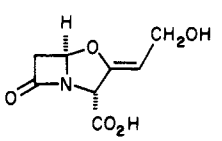
Received February 25, 1985

Clavalanine (Ro 22-5417), a new β-lactam antibiotic, 3-[(3*S*,5*S*)-7-oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-L-alanine (**1**), was synthesized by a route in which D-xylose (**4**) supplied the stereochemical requirements. From **4** was elaborated a (2*S*,4*S*)-2-amino-4,5-dihydroxypentanoic acid derivative (**16**), which was condensed with 4-acetoxy-2-azetidinone (**3**) to afford with good diastereoselectivity, after final removal of protecting groups, the desired clavam **1**.

Streptomyces clavuligerus is known as a prolific producer of β-lactam antibiotics.[1] The latest creation of this organism to have been discovered is the clavam antibiotic clavalanine (Ro 22-5417), the complete structure of which has been determined as 3-[(3*S*,5*S*)-7-oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-L-alanine (**1**).[2-4] Thus, in contrast to



1

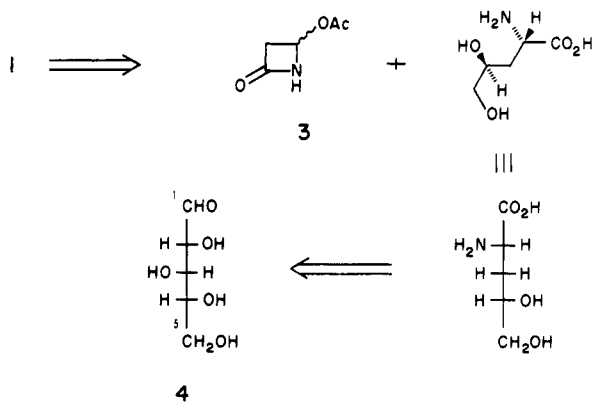


2

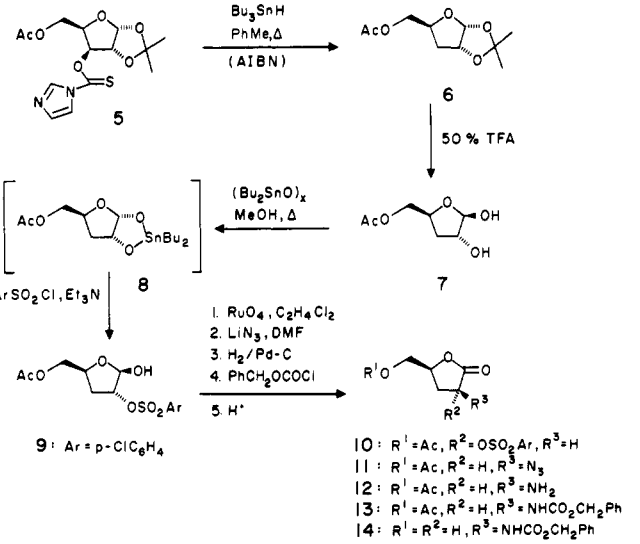
all the previously isolated β-lactams of *S. clavuligerus* such as penicillin N, desacetoxycephalosporin C, cephamycin C, and, most notably in this context, clavulanic acid (**2**), in all of which the carbon atom joining the bicyclic ring system has the *R* configuration, the new congener possesses *S* stereochemistry at the ring juncture.[4] Presumably as a consequence of this profound stereochemical difference, clavalanine (**1**) does not exert its antimicrobial activity, like the other β-lactams, via inhibition of bacterial cell wall synthesis; it is also neither substrate nor inhibitor of β-lactamases. Rather, **1** is an antimetabolite of *O*-succinylhomoserine and as such it intervenes in the biosynthesis of methionine.[2]

We have now completed a synthesis of clavalanine (**1**), which provides unequivocal confirmation of its absolute stereochemistry, previously assigned mainly on the basis of chiroptical and other spectral measurements.[4] Retrosynthetic analysis, following the train outlined in Scheme I, led us to a plan whereby the β-lactam portion of **1** would be obtained from 4-acetoxy-2-azetidinone (**3**) and the remaining five-carbon fragment would come from a carbohydrate. The choice of D-xylose (**4**) for this purpose would ensure the correct chirality at C-3 of **1** and allow the elaboration of that at the α-carbon of the amino acid side chain. While the stereochemistry at C-5, the ring junction,

Scheme I



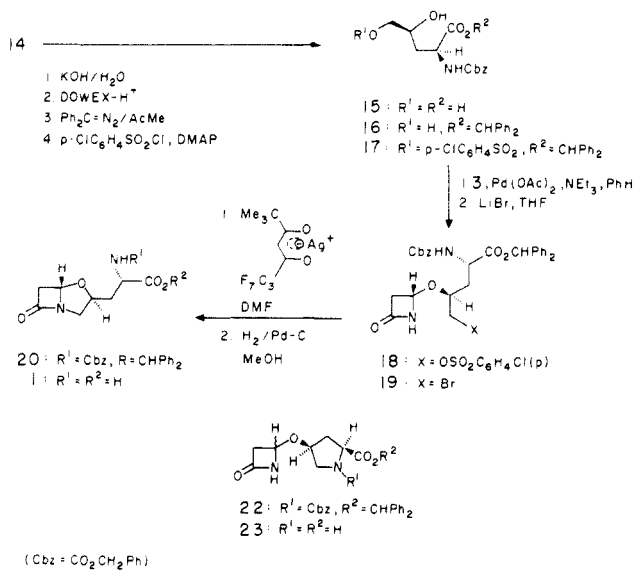
Scheme II



(1) Reading, C; Cole, M. *Antimicrob. Agents Chemother.* **1977**, *11*, 852 and references therein.
(2) Pruess, D. L.; Kellett, M. *J. Antibiot.* **1983**, *36*, 208.
(3) Evans, R. H.; Ax, H.; Jacoby, A.; Williams, T. H.; Jenkins, E.; Scannell, J. *J. Antibiot.* **1983**, *36*, 213.
(4) Muller, J. C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *J. Antibiot.* **1983**, *36*, 217.

0022-3263/85/1950-3457$01.50/0

Scheme III



would remain to be induced, possibly with some selectivity, its chirality would be unequivocally assignable by correlating it to those centers supplied by the D-pentose.

We started with commercial 1,2-*O*-isoproylidene-D-xylofuranose, whose primary 5-hydroxy group was selectively acetylated with acetyl chloride in pyridine/methylene chloride. Further reaction with thiocarbonyldimidazole (TCDI) in refluxing dichloroethane furnished the thionourethane **5** in 85% overall yield (Scheme II). A single-electron-transfer chain reaction[5] of **5** with tributyltin hydride was initiated with azobis(isobutyronitrile) (AIBN) in refluxing toluene and proceeded to afford the 3-deoxy-*erythro*-furanopentose **6** (95%). The isopropylidene protecting group was removed from **6** by hydrolysis with 50% aqueous trifluoroacetic acid (in 78% yield). Reaction of the diol **7** with dibutyltin oxide[6] in methanol at reflux temperature gave quantitatively the dibutylstannylene derivative **8**. The unequal, partially dipolar character of the tin–oxygen bonds in this intermediate directed the subsequent arylsulfonation (with *p*-chlorobenzenesulfonyl chloride and triethylamine in methanol) toward the 2-hydroxy group to yield regiospecifically the derivative **9** (60%), accompanied only by a minor amount of 2,5-disulfonate. The structure of **9** was confirmed by its NMR spectrum, which contained a doublet for the anomeric proton (at 5.14 ppm in Me_2SO-d_6), which collapsed to a singlet upon D_2O exchange of the anomeric hydroxy proton.

Oxidation of **9** with ruthenium tetraoxide in dichloroethane afforded the pentano-γ-lactone **10** (98%), which was converted to the azide **11** (90%) by reaction with lithium azide in dimethylformamide and further to the amine **12**, by subsequent catalytic hydrogenation (in dioxane/water, 1:1, and 1 equiv of hydrogen chloride), followed immediately by reaction with benzyl chloroformate under Schotten–Baumann conditions to afford **13** (70% from **11**). Hydrolysis of the acetate group of **13** was effected with Dowex 50 (H^+) in dioxane/water (at 75 °C) and gave the δ-hydroxy γ-lactone **14** in 93% yield.

It was then required to hydrolyze the lactone ring of **14** and to keep the resulting molecule from recyclizing (Scheme III). This was achieved by titration with KOH, and then reacidifying with Dowex 50 (H^+) and lyophilizing the resulting solution of **15** immediately after filtering off the resin. Reaction of **15** with diphenyldiazomethane in acetone introduced a sufficiently bulky group to furnish the stable ester **16** (78% from **14**). *p*-Chlorobenzenesulfonyl chloride (in dichloroethane/pyridine, 10:1) in the presence of an aliquot of 4-(dimethylamino)pyridine reacted selectively with the terminal hydroxy group of **16** to provide **17** (63%).

With this (2*S*,4*S*)-2-amino-4,5-dihydroxypentanoic acid derivative **17**, a synthon was now on hand which contained two of the three chiral centers of the target molecule and which was suitably functionalized for attachment to the β-lactam portion. Condensation of **17** with racemic 4-acetoxy-2-azetidinone (**3**)[7] was catalyzed with palladium acetate[4,8] and proceeded at room temperature in benzene, containing an equivalent of triethylamine, to give a 2.5:1 mixture (62–65% total) of two diastereomeric products, as evident from the NMR spectrum and from thin-layer chromatography. This mixture proved rather resistant to separation attempts. However, it could readily be ascertained from the circular dichroism spectrum that the major component was indeed the desired diastereomer **18**. The CD spectrum contained a strongly positive Cotton effect at 214 nm, as would be expected according to the octant rule of Rehling and Jensen[9] for the 4*S*-substituted 2-azetidinone **18**. Thus, condensation of the carbohydrate derived synthon **17** with racemic **3** had proceeded with considerable (70%) diastereoselectivity.

Solvolysis of the mixture of **18** and its diastereomer with lithium bromide in tetrahydrofuran gave the corresponding mixture of bromides (95%), in which the desired **19** was again predominant. Upon reaction of this material consisting to ca. 70% of **19**, with silver 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionate (a commercially available, soluble silver complex) in DMF, a product mixture was generated from which the desired **20** was readily separated and obtained in pure form by flash chromatography as a major product (50%, based on the actual amount of **19** present in the starting material). The balance of materials was eluted in subsequent fractions. From these was isolated a small amount (9.7%) of **21**, i.e., the 5*R* isomer of **20**, and a second major product, the L-4-*allo*-hydroxyproline derivative **22** (35%), which for further characterization was hydrogenated to **23** (94%).

Bentley and Hunt[10] have found an empirical relationship whereby the relative stereochemistry of 3-substituted 1-aza-4-oxabicyclo[3.2.0]heptan-7-ones can be gleaned from their NMR spectra. Accordingly, when H-3 (at the site of ring substitution) and H-5 (at the ring junction) are syn to each other, the signals observed for the methylene protons in 2-position are separated by less than 0.5 ppm. When H-3 and H-5 are in an anti relationship, the chemical shift difference of the C-2 protons increases to 1–1.4 ppm. In agreement with this finding, the C-2 methylene proton signals in the NMR spectrum of **21** appeared at 3.27 and 2.96 ppm, i.e., with a chemical shift difference of 0.31 ppm. The corresponding methylene protons of **20** gave rise to NMR signals at 3.81 and 2.49 ppm, the shift difference of 1.32 ppm being indicative of an anti disposition of the protons in the 3- and 5-position. Since the absolute configuration of C-3 was preserved throughout the described synthetic sequence as originally present in xylose, that of

(5) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574.
(6) Wagner, D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 24.
(7) Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, 539.
(8) These reaction conditions were worked out by Dr. J. C. Muller; cf. also, ref 4.
(9) Rehling, H.; Jensen, H. *Tetrahedron Lett.* **1972**, 2793.
(10) Bentley, P. H.; Hunt, E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2222.

the ring junction of **20** (and also that of **21**) has now been firmly established by this correlation as well. Catalytic hydrogenation of **20** in methanol over Pd–C removed the amino acid protecting groups and completed the synthesis of clavalanine **1** (97%). All the spectra (IR, NMR, CD) generated with our synthetic material were identical with those obtained with substance isolated from *S. clavuligerus*.

Experimental Section

General Methods. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Infrared (IR) spectra were recorded on a Digilab FTS 15-E spectrometer. ^{1}H NMR spectra were obtained on Varian XL-200 or XL-400 instruments and are reported in parts per million from tetramethylsilane as internal standard. Rotations were measured on a Perkin-Elmer 241 polarimeter and CD spectra on a JASCO automatic recording spectropolarimeter, Model J-20.

Silica gel 60 (0.040–0.063 mm) and plates precoated with silica gel 60 F-254 (both from E. Merck) were used for flash and thin-layer chromatography, respectively. Reaction components were visualized on TLC plates with the chlorine/tolidine spray[11a] or its 4,4′-tetramethyldiaminodiphenylmethane modification[11b] whenever amino or amide functionalities were present or otherwise by spraying the plates first with a 4% phosphomolybdic acid solution in methanol, heating, and then using a $Ce(SO_4)_2$ spray (prepared by dissolving 3.6 g of $Ce(SO_4)_2$ in 10 mL of concentrated H_2SO_4 and diluting with 180 mL of H_2O), followed by gentle heating.

5-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose. A stirred solution of 1,2-*O*-isopropylidene-α-D-xylofuranose (76 g, 0.4 mol) in 500 mL of dry CH_2Cl_2 and 400 mL of dry pyridine was cooled under argon to −10 °C and treated dropwise with a solution of acetyl chloride (30 mL, 0.422 mol) in 200 mL of dry CH_2Cl_2. The mixture was stirred overnight at room temperature, concentrated in vacuo, and the residue was distributed between ice-cold 1 N HCL (1500 mL) and CH_2Cl_2 (2 × 1500 mL). The organic extracts were washed in sequence with cold 3% $NaHCO_3$ (1000 mL) and semisaturated brine (800 mL), dried (Na_2SO_4), and evaporated in vacuo.

Crystallization of the residue from CH_2Cl_2–petroleum ether (30–60 °C) afforded 78.9 g (85.1%) of the monoacetylated product: mp 100–102 °C; $[\alpha]^{25}_D$ +25.8° (*c* 1.0368, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3470, 1722, 1369 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28, 1.47 (2 s, 3 H each, CMe_2), 2.08 (s, 3 H, AcO), 3.02 (d, 1 H, *J* = 4.5 Hz, OH-3), 4.11 (dd, 1 H, *J* = 2.5 and 4.5 Hz, H-3), 4.14, 4.50 (AB of ABX, 2 H, J_{gem} = 11.5 Hz, J_{vic} = 5.5 and 7 Hz, 2 H-5), 4.25 (ddd, 1 H, *J* = 2.5, 5.5, and 7 Hz, H-4), 4.54 (d, 1 H, *J* = 3.5 Hz, H-2), 5.89 (d, 1 H, *J* = 3.5 Hz, H-1).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.64; H, 6.83.

5-*O*-Acetyl-1,2-*O*-isopropylidene-3-*O*-(imidazolylthiocarbonyl)-α-D-xylofuranose (5). A solution of 19.49 g (83.92 mmol) of 5-*O*-acetyl-1,2-*O*-isopropylidene-α-D-xylofuranose and 28.5 g (160 mmol) of 1,1′-thiocarbonyldiimidazole in 440 mL of dry 1,2-dichloroethane was stirred and gently refluxed for 1 h under argon. After cooling, the solvent was evaporated in vacuo and the residue purified by flash chromatography on silica gel, the column (35 × 8 cm) being eluted with AcOEt–cyclohexane, 65:35.

Evaporation in vacuo of the appropriate fractions afforded a quantitative yield of **5** (28.7 g) as a light yellow solid. Crystallization from AcOEt and an excess of cyclohexane gave 27.95 g (97.3%) of analytically pure material as pale yellow crystals, stable when stored below 0 °C: mp 78–80 °C; $[\alpha]^{25}_D$ −0.9° (*c* 0.9961, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1749, 1400, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35, 1.58 (s, 3 H each, CMe_2), 2.05 (s, 3 H, AcO), 4.31, 4.39 (AB of ABX, 2 H, J_{gem} = 12.5 Hz, J_{vic} = 5.5 and 6.5 Hz, 2 H-5), 4.65 (ddd, 1 H, *J* = 3, 5.5, and 6.5 Hz, H-4), 4.76 (d, 1 H, *J* = 4 Hz, H-2), 5.92 (d, 1 H, *J* = 3 Hz, H-3), 6.02 (d, 1 H, *J* = 4 Hz, H-1), 7.06, 7.58, 8.32 (3 H, imidazole, H-4′, H-5′, and H-2′, respectively).

Anal. Calcd for $C_{14}H_{18}N_2O_6S$: C, 49.12; H, 5.30; N, 8.18; S, 9.36. Found: C, 48.89; H, 5.37; N, 8.07; S, 9.21.

5-*O*-Acetyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentose (6). To 1500 mL of dry toluene, gently refluxing under argon, was added in one portion through a syringe 30 mL (32.46 g, 108.2 mmol) of 97% Bu_3SnH (Aldrich), followed by 220 mg of α,α′-azobis(isobutyronitrile). A solution of 22.0 g (64.26 mmol) of **5** in 250 mL of dry toluene was added dropwise over 1 h to the boiling mixture with stirring under argon, and the reaction was refluxed for one additional hour to completion (TLC, AcOEt–cyclohexane, 1:1).

After cooling, the solvent was evaporated in vacuo and the residual gum distributed between 1600 mL of MeCN and 1600 mL of hexanes. The MeCN layer was further extracted with 2 × 1000 mL portions of hexanes, all the hexanes extracts being back-washed with 2 × 1000 mL of MeCN.

The combined MeCN layers were evaporated in vacuo and the residue was purified by flash chromatography on silica gel, the column (33 × 8.5 cm) being eluted with AcOEt–cyclohexane, 45:55.

After pooling and evaporation of the appropriate fractions, the residue was dried under high vacuum at room temperature to give 13.18 g (95%) of pure **6** as a colorless liquid, which solidified when stored at 0 °C.

A product of lesser purity, still suitable for further use, could be obtained by Kugelrohr (bulb to bulb) distillation of the residue from the MeCN extracts. Pure **6**: bp 90 °C (0.1 mmHg); $[\alpha]^{25}_D$ −1.6° (*c* 0.9646, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1743, 1378, 1240, 1026 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.24, 1.40 (s, 3 H each, CMe_2), 1.61 (ddd, 1 H, J_{gem} = 13.5 Hz, J_{vic} = 5 and 10.5 Hz, one H of 2 H-3), 1.96 (dd, 1 H, J_{gem} = 13.5 Hz, J_{vic} = 4.5 Hz, one H of 2 H-3), 2.03 (s, 3 H, AcO), 4.01, 4.17 (AB of ABX, 2 H, J_{gem} = 12 Hz, J_{vic} = 3.5 and 6 Hz, 2 H-5), 4.25 (m, 1 H, H-4), 4.75 (dd, 1 H, *J* = 4 and 4.5 Hz, H-2), 5.75 (d, 1 H, *J* = 4 Hz, H-1).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.73; H, 7.61.

5-*O*-Acetyl-3-deoxy-α-D-*erythro*-pentafuranose (7). A solution of **6** (17.8 g, 82.31 mmol) in 350 mL of precooled 45% (v/v) CF_3COOH was stirred at 5 °C for 75 min under argon. Most of the solvents were then evaporated in vacuo, using an oil pump, at 20–25 °C (bath), and the residue was taken up in 250 mL of deionized H_2O. The turbid solution was carefully neutralized to pH 5.7 with saturated $NaHCO_3$ (ca. 110 mL) and evaporated in vacuo as above, and the residue was taken up in 150 mL of MeCN. After removal of solids, the filtrate was concentrated to a small volume (ca. 40 mL) and purified by flash chromatography on silica gel, the column (30 × 6.5 cm) being eluted with 2500 mL of MeCN. After pooling of the appropriate fractions (TLC, $CHCl_3$–2-PrO-H–H_2O, 200:75:100, organic phase) and evaporation, the solid residue was crystallized from hot AcOEt to give 7.013 g of analytically pure **7** as colorless crystals: mp 86–88 °C; $[\alpha]^{25}_D$ 0° → 5.0° in 24 h at room temperature (*c* 1.0604, MeOH); IR ($CHCl_3$) ν_{max} 3610, 3440, 1743, 1374, 1237, 1040 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.78 (m, 2 H, 2 H-3), 2.02 (s, 3 H, AcO), 3.93 (br s, 1 H, H-2), 3.92, 4.09 (AB of ABX, 2 H, J_{gem} = 11 Hz, J_{vic} = 4 and 8 Hz, 2 H-5), 4.28 (m, 1 H, H-4), 4.95 (d, 1 H, *J* = 4 Hz, OH-2, exchangeable), 4.98 (d, 1 H, $J_{(CH-OH)}$ = 4.5 Hz, H-1), 6.11 (d, 1 H, *J* = 4.5 Hz, OH-1).

Anal. Calcd for $C_7H_{12}O_5$: C, 47.73; H, 6.87. Found: C, 47.75; H, 7.01.

One further chromatographic purification of the mother liquors increased the yield of pure **7** to a total of 8.836 g (60.9%), with an additional crop (2.5 g, from AcOEt–Et_2O) of a lesser purity bringing the yield to 77.9%.

5-*O*-Acetyl-2-*O*-[(4-chlorophenyl)sulfonyl]-3-deoxy-β-D-*erythro*-pentafuranose (9). Dibutyltin oxide (7.50 g, 30.12 mmol) was added to a solution of **7** (5.286 g, 30 mmol) in 400 mL of MeOH, and the stirred suspension was heated to reflux under argon for 1.5 h.

The resulting clear solution of 5-*O*-acetyl-3-deoxy-1,2-*O*-dibutylstannylene-α-D-*erythro*-pentafuranose (**8**) was cooled to 4 °C, and to it was added in one portion 33.5 mL (240 mmol) of NEt_3 and then, over 2 min, 50.66 g (240 mmol) of *p*-chlorobenzenesulfonyl chloride dissolved in 110 mL 1,2-dimethoxyethane.

After 1 h at 4 °C the mixture was evaporated to dryness in vacuo, the residue was dissolved in 700 mL of $CHCl_3$, and the

(11) (a) Nitiecki, D. E.; Goodman, T. W. *Biochemistry* **1966**, *5*, 665. (b) von Arx, E.; Faupel, M.; Brugger, M. *J. Chromatogr.* **1976**, *120*, 224.

solution washed with 2 × 250 mL portions of H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel in a column (30 × 8.5 cm) eluted with AcOEt–cyclohexane, 40:60 (1800 mL) and 50:50 (2500 mL), to give a minor amount of 2,5-di-*O*-[(4-chlorophenyl)sulfonyl]-3-deoxy-β-D-*erythro*-pentafuranose (0.527 g, after crystallization from AcOEt–cyclohexane), and 6.366 g (60.5%) of **9** as a colorless gum, which crystallized upon cold storage: mp 20–22 °C; $[\alpha]^{25}_D$ +7.5° (*c* 1.0790, MeOH); IR ($CHCl_3$) ν_{max} 3580, 1733, 1371, 1200–1230 (br), 1183 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.01 (s, 3 H, AcO), 2.03 (m, 2 H, 2 H-3), 3.93, 4.12 (AB of ABX, 2 H, J_{gem} = 11.5 Hz, J_{vic} = 4.0 and 7.5 Hz, 2 H-5), 4.30 (m, 1 H, H-4), 4.75 (t, 1 H, *J* = 2 Hz, H-2), 5.14 (d, 1 H, $J_{(CH-OH)}$ = 4.5 Hz, H-1), 6.81 (d, 1 H, *J* = 4.5 Hz, OH-1), 7.78, 7.98 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, -C_6H_4-*p*-Cl).

Anal. Calcd for $C_{13}H_{15}ClO_7S$: C, 44.51; H, 4.31; Cl, 10.10; S, 9.14. Found: C, 44.69; H, 4.46; Cl, 9.88; S, 8.93.

5-*O*-Acetyl-2-*O*-[(4-chlorophenyl)sulfonyl]-3-deoxy-D-*erythro*-pentonic Acid γ-Lactone (10). To 11.16 g (31.84 mmol) of **9** in 140 mL of 1,2-dichloroethane, stirred under argon and cooled in an ice bath, was added over 10 min a solution of RuO_4 obtained by treating 5.04 g (20.19 mmol) of 53.3% RuO_2 with excess aqueous $NaIO_4$ and extracting with 3 × 100 mL portions of CCl_4. After being stirred for 15 min at 4 °C and 45 min at room temperature, the excess reagent was quenched with 15 mL of 2-PrOH. The solid was removed by filtration through a pad of Celite, and the combined filtrate and washings (1,2-dichloroethane, 400 mL) were evaporated to dryness in vacuo. Upon reevaporation from Et_2O a colorless oil was obtained which crystallized on standing at 0 °C to give 10.87 g (98%) of pure **10**: mp 52–54 °C; $[\alpha]^{25}_D$ +8.2° (*c* 0.9545, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1790, 1740, 1378, 1183 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H, AcO), 2.64 (m, 2 H, 2 H-3), 4.17, 4.33 (AB of ABX, 2 H, J_{gem} = 12.5 Hz, J_{vic} = 2.5 and 4 Hz, 2 H-5), 4.90 (m, 1 H, H-4), 5.24 (t, 1 H, *J* = 8 Hz, H-2), 7.57, 7.93 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, -C_6H_4-*p*-Cl).

Anal. Calcd for $C_{13}H_{13}ClO_7S$: C, 44.77; H, 3.76; Cl, 10.17; S, 9.19. Found: C, 44.54; H, 3.85; Cl, 10.45; S, 9.26.

5-*O*-Acetyl-2-azido-2,3-dideoxy-D-*threo*-pentonic Acid γ-Lactone (11). To a solution of **10** (10.82 g, 31.02 mmol) in 100 mL of dry DMF, cooled to −10 °C under argon, was added with stirring 3.20 g (64.18 mmol) of LiN_3. The mixture was allowed to warm gradually, and the resulting solution was stirred overnight at room temperature. After evaporation of the solvent (40 °C, oil pump), the residue was partitioned between 500 mL of AcOEt and 4 × 100 mL portions of H_2O. The organic phase was dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography on silica gel in a 30 × 6.5 cm column eluted with AcOEt–cyclohexane, 60:40, to give 5.57 g (90.1%) of pure **11** as a very pale yellow oil, which solidified upon cold storage: mp ca. 25–27 °C; $[\alpha]^{25}_D$ −130.5° (*c* 0.9490, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2100, 1785, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (dt, 1 H, J_{gem} = 13 Hz, J_{vic} = 10 Hz, one of 2 H-3), 2.12 (s, 3 H, AcO), 2.65 (ddd, 1 H, J_{gem} = 13 Hz, J_{vic} = 6 and 9 Hz, one of 2 H-3), 4.18, 4.35 (AB of ABX, 2 H, J_{gem} = 12 Hz, J_{vic} = 3 and 6 Hz, 2 H-5), 4.40 (t, 1 H, *J* = 9.5 Hz, H-2), 4.68 (m, 1 H, H-4).

Anal. Calcd for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.31; H, 4.78; N, 21.21.

5-*O*-Acetyl-2-amino-2,3-dideoxy-D-*threo*-pentonic Acid γ-Lactone Hydrochloride (12). A solution of **11** (2.142 g, 10.75 mmol) in 100 mL of absolute EtOH was hydrogenated at normal pressure for 45 min in the presence of 400 mg of Pd/C (10%). Ethanolic HCl (8.40 mL of a 1.28 N solution) was added through a syringe over 5 min at the start of the hydrogenation.

After removal of the catalyst, filtrate and washings (EtOH) were concentrated in vacuo to ca. 40 mL, with concomitant crystallization of the product. The crystals were collected, after dilution of the mixture with an equal volume of Et_2O, to give 1.150 g (51%) of **12**: mp 199–202 °C, with dec from ca. 180 °C; $[\alpha]^{25}_D$ +11.5° (*c* 0.9520, H_2O); IR (KBr) ν_{max} 2975, 2880, 2010, 1787, 1725, 1224 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.08 (s, 3 H, AcO), 2.11 (q, 1 H, *J* = 11.5 Hz, one of 2 H-3), 2.63 (ddd, 1 H, J_{gem} = 11.5 Hz, J_{vic} = 6 and 8.5 Hz, one of 2 H-3), 4.17, 4.33 (AB of ABX, 2 H, J_{gem} = 12 Hz, J_{vic} = 2 and 6 Hz, 2 H-5), 4.44 (dd, 1 H, *J* = 8.5 and 11.5 Hz, H-2), 4.78 (m, 1 H, H-4), 8.95 (br s, 3 H, NH_3^+).

Anal. Calcd for $C_7H_{12}ClNO_4$: C, 40.11; H, 5.77; Cl, 16.91; N, 6.68. Found: C, 40.01; H, 5.86; Cl, 16.84; N, 6.66.

5-*O*-Acetyl-2-[(benzyloxycarbonyl)amino]-2,3-dideoxy-D-*threo*-pentonic Acid γ-Lactone (13). (A) From **11**: A solution of **11** (2.20 g, 11.05 mmol) in 80 mL of 1,2-dimethoxyethane (DME) was diluted with 28.5 mL of H_2O and 11.5 mL of 1 N HCl and 400 mg of 10% Pd/C was added, and the mixture was hydrogenated at ambient pressure to completion (10 h; TLC, $CHCl_3$–2-PrOH–H_2O, 2:1:1, organic phase).

After removal of the catalyst, filtrate and washings (DME–H_2O, 1:1, 100 mL) were concentrated in vacuo to ca. 30 mL at 40 °C.

To the solution, cooled in ice–water and made alkaline by addition of 2.90 g (3.12 equiv) of solid $NaHCO_3$, was added 2.40 mL (1.26 equiv) of benzyl chloroformate in 20 mL of Et_2O. Vigorous mechanical stirring was maintained in order to keep the phases thoroughly mixed throughout the reaction.

A second addition of chloroformate (1.2 mL, 0.63 equiv) in 10 mL of Et_2O was made after 10 min. The mixture was stirred for 2 h at 4 °C and then 30 min at room temperature. The reaction mixture was extracted with 3 × 50 mL portions of AcOEt, the extracts were dried (Na_2SO_4), and the residue from the evaporation was flash-chromatographed on a 30 × 6.5 cm silica gel column with AcOEt–cyclohexane, 65:35, as eluant, giving 2.385 g (70.3%) of pure **13**, after crystallization from AcOEt–Et_2O: mp 84–84.5 °C; $[\alpha]^{25}_D$ +47.1° (*c* 0.9965, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3430, 1787, 1730, 1300, 1220 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.94 (q, 1 H, *J* = 11.5 Hz, one of 2 H-3), 2.06 (s, 3 H, AcO), 2.46 (m, 1 H, one of 2 H-3), 4.10, 4.27 (AB of ABX, 2 H, J_{gem} = 12 Hz, J_{vic} = 2 and 6.5 Hz, 2 H-5), 4.58 (m, 1 H, H-2), 4.67 (m, 1 H, H-4), 5.05 (s, 2 H, OCH_2Ph), 7.36 (s, 5 H, C_6H_5), 7.84 (d, 1 H, *J* = 8.5 Hz, NH).

Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.61; H, 5.79; N, 4.51.

(B) From **12**: Treatment of 1.108 g (5.28 mmol) of the amine hydrochloride **12** with $NaHCO_3$/$PhCH_2OCOCl$ in a two-phase system as above afforded 1.470 g (90.5%) of crystalline **13**, mp 84–84.5 °C.

2-[(Benzyloxycarbonyl)amino]-2,3-dideoxy-D-*threo*-pentonic Acid γ-Lactone (14). A solution of **13** (5.180 g, 16.86 mmol) in 270 mL of 1,4-dioxane and water (1:1) was stirred for 24 h at 73–75 °C with 13 g of Dowex AG 50W-X4 (H^+), 100–200 mesh, a second 8-g portion of the resin being added after 5 h. After cooling, the resin was removed by filtration. Filtrate and washings (1:1 dioxane–H_2O, 100 mL) were concentrated in vacuo to ca. 120 mL, and the turbid solution was extracted with 3 × 300 mL of AcOEt. The combined extracts were dried (Na_2SO_4) and evaporated, the AcOH was removed from the residue azeotropically with toluene, and the colorless solid was recrystallized from hot AcOEt. After dilution with Et_2O, 3.521 g of pure **14** was collected.

Flash chromatography of the mother liquors on a silica gel column (28 × 4.5 cm) with AcOEt–MeCN, 9:1, increased the yield of crystalline **14** to 4.177 g (93.4%): mp 112–115 °C; $[\alpha]^{25}_D$ +3.3° (*c* 1.1479, MeOH); IR (KBr) ν_{max} 3375, 3290, 1790, 1693 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.96 (q, 1 H, *J* = 11.5 Hz, one of 2 H-3), 2.37 (ddd, 1 H, J_{gem} = 11.5 Hz, J_{vic} = 6 and 9 Hz, one of 2 H-3), 3.48 (dt, 1 H, J_{gem} = 12 Hz, J_{vic} = 6 Hz, one of 2 H-5), 3.61 (ddd, 1 H, J_{gem} = 12 Hz, J_{vic} = 3 and 6 Hz, one of 2 H-5), 4.47 (m, 1 H, H-4), 4.58 (dt, 1 H, *J* = 8.5, 8.5 and 12 Hz, H-2), 5.05 (s, 2 H, OCH_2Ph), 5.08 (t, 1 H, OH), 7.37 (s, 5 H, C_6H_5), 7.81 (d, 1 H, *J* = 8.5 Hz, NH).

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.62; H, 5.78; N, 5.25.

***N*-(Benzyloxycarbonyl)-4,5-dihydroxy-D-*threo*-L-norvaline (15).** A stirred, warm (50–60 °C) solution of **14** (2.12 g, 8 mmol) was neutralized with 79.5 mL of 0.1 N KOH (99.4% of theory) over 90 min, never allowing the pH to rise above 9.0. The clear solution of the salt was cooled to 20 °C over 1 h, with a concomitant drop of the pH to 7.4, at which point it was treated under vigorous magnetic stirring with 13 g of meticulously washed Dowex AG 50W-X4 (H^+), 100–200 mesh, for less than 1 min. The resin was immediately removed by filtration and washed with small portions of deionized H_2O, and the combined filtrates were freeze-dried to a colorless gum, consisting of pure **15**: ^1H NMR (Me_2SO-d_6) δ 1.67 (br m, 2 H, 2 H-3), 3.27 (d, 2 H, *J* = 10 Hz, 2 H-5), 3.50 (br m, 1 H, H-4), 4.15 (br m, 1 H, H-2), 4.60–6.00 (br, 3 H, COOH, OH-4, OH-5), 5.03 (s, 2 H, OCH_2Ph), 7.21 (br, 1 H, NH), 7.35 (s, 5 H, C_6H_5).

***N*-(Benzyloxycarbonyl)-4,5-dihydroxy-D-*threo*-L-norvaline Diphenylmethyl Ester (16).** Freshly lyophilized **15** (from 2.12

g, 8 mmol of **13**) was dissolved in 80 mL of Me_2CO and the resulting clear solution was treated with an excess (2.20 g) of diphenyldiazomethane in 40 mL of Me_2CO, added over 10 min. The reaction was kept at room temperature for 4 h. After evaporation of the solvent in vacuo at 35 °C, the residue was flash chromatographed on a silica gel column (30 × 6.5 cm).

Elution with AcOEt (2000 mL) and then AcOEt–MeCN, 9:1 (800 mL), afforded 2.82 g (78.3%) of pure **16**, which crystallized to a colorless solid after evaporation: mp 101–102 °C; $[\alpha]^{25}_D$ −3.3° (*c* 0.9075, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3585, 3420, 1738, 1700, 1512, 1060, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.73 (br m, 2 H, 2 H-3), 3.28 (br m, 2 H, 2 H-5), 3.52 (br m, 1 H, H-4), 4.42 (br m, 1 H, H-2), 4.56 (t, 1 H, *J* = 5 Hz, primary OH), 4.75 (d, 1 H, *J* = 5.5 Hz, secondary OH), 5.02, 5.07 (AB, 2 H, J_{gem} = 13 Hz, OCH_2Ph), 6.79 (s, 1 H, $COOCHPh_2$), 7.14 to 7.56 (br m, 15 H, 3 C_6H_5), 7.76 (d, 1 H, *J* = 8 Hz, NH).

Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.26; H, 6.02; N, 3.05.

From the more polar eluate was recovered 0.370 g (17.4%) of crystalline **14**.

***N*-(Benzyloxycarbonyl)-5-[[(4-chlorophenyl)sulfonyl]oxy]-4-hydroxy-D-*threo*-L-norvaline Diphenylmethyl Ester (17).** To a solution of **16** (3.82 g, 8.50 mmol) in 50 mL of dry 1,2-dichloroethane and 11 mL of dry pyridine, cooled to −10 °C under argon, was added 1.04 g (8.51 mmol) of 4-(dimethylamino)pyridine. To this was added dropwise with stirring a solution of 2.70 g (12.78 mmol) of 4-chlorobenzenesulfonyl chloride in 30 mL of dry 1,2-dichloroethane, and the solution was stirred for 5 h at −10 °C and then 15 h at room temperature.

After evaporation of the solvents in vaco, the residue was taken up in 500 mL of AcOEt. The solution was washed in sequence with 200 mL of ice-cold 0.25 N HCl, 200 mL of cold 3% $NaHCO_3$, and 100 mL of H_2O, dried (Na_2SO_4), and evaporated in vacuo.

Purification of the residual oil by flash chromatography on silica gel in a column (30 × 6.5 cm) eluted with AcOEt–cyclohexane, 30:70 afforded first 0.650 g (9.6%) of the byproduct *N*-(benzyloxycarbonyl)-4,5-bis[[(4-chlorophenyl)sulfonyl]oxy]-D-*threo*-L-norvaline diphenylmethyl ester as a white solid: $[\alpha]^{25}_D$ −14.4° (*c* 1.0445, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3440, 1728, 1377, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10, 2.34 (br m, 2 H, 2 H-3), 4.04, 4.17 (AB of ABX, 2 H, J_{gem} = 11 Hz, J_{vic} = 2 and 4.5 Hz, 2 H-5), 4.32 (m, 1 H, H-2), 4.88 (m, 1 H, H-4), 5.05 (s, 2 H, OCH_2Ph), 5.42 (d, 1 H, *J* = 8 Hz, NH), 6.86 (s, 1 H, $COOCHPh_2$), 7.32 (br s, 15 H, 3 C_6H_5), 7.42, 7.74 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, C_6H_4-*p*-Cl), 7.48, 7.73 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, C_6H_4-*p*-Cl).

Anal. Calcd for $C_{38}H_{33}ClNO_{10}S_2$: C, 57.14; H, 4.16; Cl, 8.88; N, 1.75; S, 8.03. Found: C, 57.45; H, 4.15; Cl, 8.88; N, 1.76; S, 7.76.

Further elution provided 3.32 g (62.6%) of the more polar **17** as a white foam, stable when stored at 0 °C: $[\alpha]^{25}_D$ −0.2° (*c* 1.0830, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600, 3420, 1740, 1702, 1512, 1189, 701 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.72 (m, 2 H, 2 H-3), 3.75 (m, 1 H, H-4), 3.92, 3.99 (AB of ABX, 2 H, J_{gem} = 10 Hz, J_{vic} = 4 and 6.5 Hz, 2 H-5), 4.36 (m, 1 H, H-2), 5.00 and 5.07 (AB, 2 H, J_{gem} = 12.5 Hz, OCH_2Ph), 5.36 (d, 1 H, *J* = 6 Hz, OH), 6.78 (s, 1 H, $COOCHPh_2$), 7.10 to 7.50 (br m, 15 H, 3 C_6H_5), 7.74, 7.92 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, C_6H_4-*p*-Cl), 7.75 (d, 1 H, *J* = 8 Hz, NH).

Anal. Calcd for $C_{32}H_{30}ClNO_8S$: C, 61.58; H, 4.85; Cl, 5.68; N, 2.24; S, 5.14. Found: C, 61.23; H, 5.08; Cl, 5.42; N, 2.38; S, 5.30.

***N*-(Benzyloxycarbonyl)-5-[[(4-chlorophenyl)sulfonyl]oxy]-4-(4-oxo-2-azetidinyloxy)-D-*threo*-L-norvaline Diphenylmethyl Ester (18).** A solution of 4.215 g (6.75 mmol) of **17** and 0.268 g (1.19 mmol) of $Pd(OAc)_2$ in 50 mL of dry benzene was treated under argon with a solution of 0.978 g (7.57 mmol) of 4-acetoxy-2-azetidinone (**3**) and 1.05 mL (7.53 mmol) of NEt_3 in 40 mL of dry benzene. After 16 h at room temperature, a second portion of 0.611 g (4.73 mmol) **3** and 0.61 mL (4.40 mmol) of NEt_3 in 25 mL of benzene was added, and the mixture was stirred under argon for 22 h. Suspended solids were removed by filtration through Celite and washed with 500 mL of AcOEt. The combined filtrates were extracted with 200 mL of H_2O, dried (Na_2SO_4), and evaporated in vacuo, and the residual oil was purified by flash chromatography on silica gel. Elution of the column (30 × 6.5 cm) with AcOEt–cyclohexane, 50:50 (1800 mL) and 60:40 (1500 mL), initially afforded 0.352 g (11.8%) of a byproduct, 2-[(benzyloxycarbonyl)amino]-5-*O*-[(4-chlorophenyl)sulfonyl]-2,3-dideoxy-D-*threo*-pentafuranonic acid γ-lactone, as a colorless solid after crystallization from AcOEt–Et_2O: mp 81–83 °C, with previous softening; $[\alpha]^{25}_D$ +62.8° (*c* 1.0742, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3415, 1780, 1709, 1494, 1369, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (q, 1 H, *J* = 11.5 Hz, one of 2 H-3), 2.78 (m, 1 H, one of 2 H-3), 4.21, 4.32 (AB of ABX, 2 H, J_{gem} = 11.5 Hz, J_{vic} = 2 and 4.5 Hz, 2 H-5), 4.50 (m, 1 H, H-2), 4.64 (m, 1 H, H-4), 5.12 (s, 2 H, OCH_2Ph), 5.43 (d, 1 H, *J* = 5.5 Hz, NH), 7.36 (s, 5 H, C_6H_5), 7.56, 7.86 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, C_6H_4-*p*-Cl).

Anal. Calcd for $C_{19}H_{18}ClNO_7S$: C, 51.88; H, 4.12; Cl, 8.06; N, 3.18; S, 7.29. Found: C, 52.14; H, 4.07; Cl, 7.90; N, 3.18; S, 7.35.

The major reaction product **18** was isolated from the more polar fractions as a white foam (2.387 g, 51.5%), consisting of a 2.5:1 mixture of diastereomers: IR ($CHCl_3$) ν_{max} 3415, 1777, 1720, 1513, 1373, 1347, 1190, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 and 1.70 (m, 1 H, one of 2 H-3), 1.97 and 1.98 (ddd, 1 H, J_{gem} = 14 Hz, J_{vic} = 3 and 11 Hz, one of 2 H-3), 2.76 and 2.79 (d, 1 H, J_{gem} = 15.5 Hz, one of 2 H-3′), 3.03 and 3.11 (dt, 1 H, J_{gem} = 15.5 Hz, J_{vic} = 4 Hz, one of 2 H-3′), 3.70 (m, 1 H, H-4), 3.86 to 4.00 (m, 2 H, 2 H-5), 4.60 to 4.76 (m, 1 H, H-2), 4.85 and 5.19 (dd, 1 H, *J* = 2 and 4 Hz, H-4′), 5.07 and 5.09 (s, 2 H, OCH_2Ph), 5.39 and 5.47 (d, 1 H, *J* = 9.5 Hz, NH-2), 6.38 and 7.06 (br s, 1 H, NH-1′), 6.87 and 6.88 (s, 1 H, $COOCHPh_2$), 7.20 to 7.47 (br m, 15 H, 3 C_6H_5), 7.54 and 7.55, 7.80 (AA′BB′, 4 H, J_{ortho} = 8.5 Hz, C_6H_4-*p*-Cl); CD (0.0078 M, MeOH) $[\theta]_{238}$ −1090, $[\theta]_{215}$ +7690.

***N*-(Benzyloxycarbonyl)-5-bromo-4-(4-oxo-2-azetidinyloxy)-D-*threo*-L-norvaline Diphenylmethyl Ester (19).** To a solution of **18** (1.870 g, 2.70 mmol) in 70 mL of dry THF was added 510 mg (4.86 mmol) of LiBr, and the reaction mixture was refluxed with magnetic stirring under argon for 6.5 h. After evaporation of the solvent in vacuo, the residue was distributed between 500 mL of AcOEt and 200 mL of H_2O, the organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography on silica gel. Elution of the column (30 × 5 cm) with AcOEt–cyclohexane, 60:40, and evaporation of the appropriate fractions afforded 1.490 g (94.9%) **19** (a 70:30 mixture of *S* and *R* diastereomers) as a white foam. A small amount of the less polar *S* diastereomer could be isolated in a fairly pure form from the first fractions: IR ($CHCl_3$) ν_{max} 3415, 1775, 1740, 1718, 1512, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (dd, 1 H, J_{gem} = 15 Hz, J_{vic} = 10.5 Hz, one of 2 H-3), 2.04 (ddd, 1 H, J_{gem} = 15 Hz, J_{vic} = 2.5 and 10.5 Hz, one of 2 H-3), 2.87 (d, 1 H, J_{gem} = 15.5 Hz, one of 2 H-3′), 3.08 (dt, 1 H, J_{gem} = 15.5 Hz, J_{vic} = 4 Hz, one of 2 H-3′), 3.24 (m, 2 H, 2 H-5), 3.57 (m, 1 H, H-4), 4.61 (t, 1 H, *J* = 9.5 Hz, H-2), 4.87 (d, 1 H, *J* = 4 Hz, H-4′), 5.08 (s, 2 H, OCH_2Ph), 5.54 (d, 1 H, *J* = 9.5 Hz, NH-2), 6.88 (s, 1 H, $COOCHPh_2$), 7.04 (s, 1 H, NH-1′), 7.34 (s, 15 H, 3 C_6H_5).

3-[(3*S*,5*S*)-7-Oxo-1-aza-4-oxabicyclo[3.2.0]hept-3-yl]-*N*-(benzyloxycarbonyl)-L-alanine Diphenylmethyl Ester (20) and Its 5*R* Diastereomer (21). To a solution of 1.360 g of **19** (2.339 mmol) in 40 mL of dry DMF was added 2.0 g (5.39 mmol) of silver 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate, and the reaction mixture was stirred under argon at 70 °C for 6 h. A second portion (1 g, 2.70 mmol) of the soluble silver reagent was added, and the stirring was continued for another 4 h. The mixture was evaporated in vacuo (40 °C, oil pump), the residue was taken up in 100 mL of AcOEt, and the insoluble silver salts were removed by filtration through a pad of Celite. Filtrate and washings (AcOEt, 150 mL) were washed in a separatory funnel with 140 mL of a semisaturated NaCl solution. After removal of the precipitated AgCl by filtration through Celite, filtrate and washings (AcOEt) were dried (Na_2SO_4) and evaporated in vacuo.

The residue was purified by flash chromatography on silica gel. The column (30 × 5 cm) was eluted with an increasingly polar mixture of solvents, starting with AcOEt–cyclohexane, 30:70 (800 mL), 40:60 (700 mL), and 60:40 (700 mL), and then MeCN–AcOEt, 10:90 (600 mL), and 20:80 (1200 mL). After initial elution of some 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione, the following products were progressively isolated.

20: 350 mg (50%), pale yellow foam; IR ($CHCl_3$) ν_{max} 3425, 1785, 1722, 1512, 1190, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (dd, 2 H, *J* = 5.5 and 6 Hz, 2 H-8), 2.49, 3.81 (AB of ABX, 2 H, J_{gem} = 11.5 Hz, J_{vic} = 6 and 7 Hz, 2 H-2), 2.69, 3.20 (AB of ABX, 2 H, J_{gem} = 16 Hz, J_{vic} = 1 and 2.5 Hz, 2 H-6), 4.00 (p, 1 H, J_{avg} = 6 Hz, H-3), 4.70 (dt, 1 H, *J* = 5.5, 5.5, and 8.5 Hz, H-9), 5.12 (s, 2 H, OCH_2Ph), 5.24 (dd, 1 H, *J* = 1 and 2.5 Hz, H-5), 5.78 (d, 1 H, *J*

= 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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Received February 25, 1985

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.

0022-3263/85/1950-3462$01.50/0