

THE SYNTHESIS OF HETEROCYCLIC C-TERMINAL UNITS WHICH
MIMIC THE TRANSITION STATE IN THE CLEAVAGE OF THE LEU-VAL
BOND OF ANGIOTENSINOGEN BY RENIN

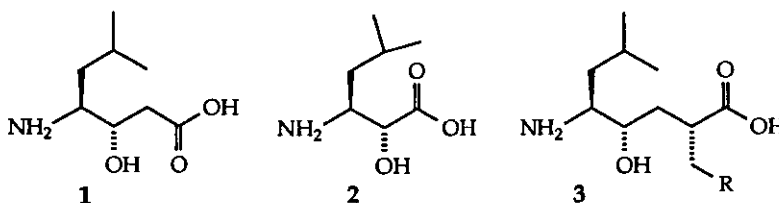
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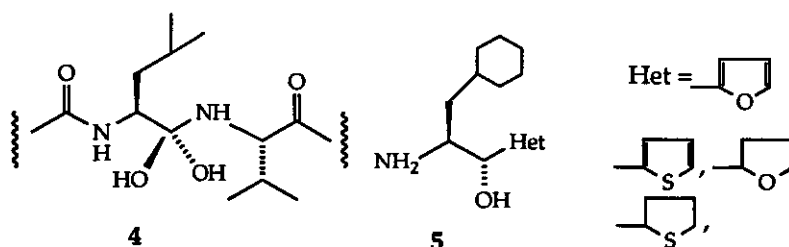
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Abstract - The stereospecific synthesis of (*S*)-2-amino-3-cyclohexyl-(*R*)-1-(2-furanyl)-propan-1-ol (**17**) and (*S*)-2-amino-3-cyclohexyl-(*R*)-1-(2-thienyl)-propan-1-ol (**18**) from *t*-Boc-*L*-phenylalanine is described. Reduction of the furan ring of (4*S*-*trans*)-4-(cyclohexylmethyl)-5-(2-furanyl)-2-oxazolidinone (**15**) gave two tetrahydrofuran diastereomers (**21**) and (**22**). Each tetrahydrofuran oxazolidinone (**21** and **22**) was converted stereospecifically in high yield to the (*S*, *R*, *R*) and the (*S*, *R*, *S*) tetrahydrothienyl oxazolidinones (**29**) and (**27**), respectively.

Discussion

Peptides which contain a non-peptide mimic of the transition state in the cleavage of the Leu-Val bond of angiotensinogen by human renin are potent renin inhibitors. The derivatives statine (**1**), norstatine (**2**) and hydroxyethylene dipeptide isosteres (**3**) serve as transition state mimics when incorporated into analogues of angiotensinogen.¹ In order to develop new derivatives which could serve as mimics of the transition state (**4**), we investigated the synthesis of C-terminal units (**5**) which contain the heterocycles furan, thiophene, tetrahydrofuran, and tetrahydrothiophene.





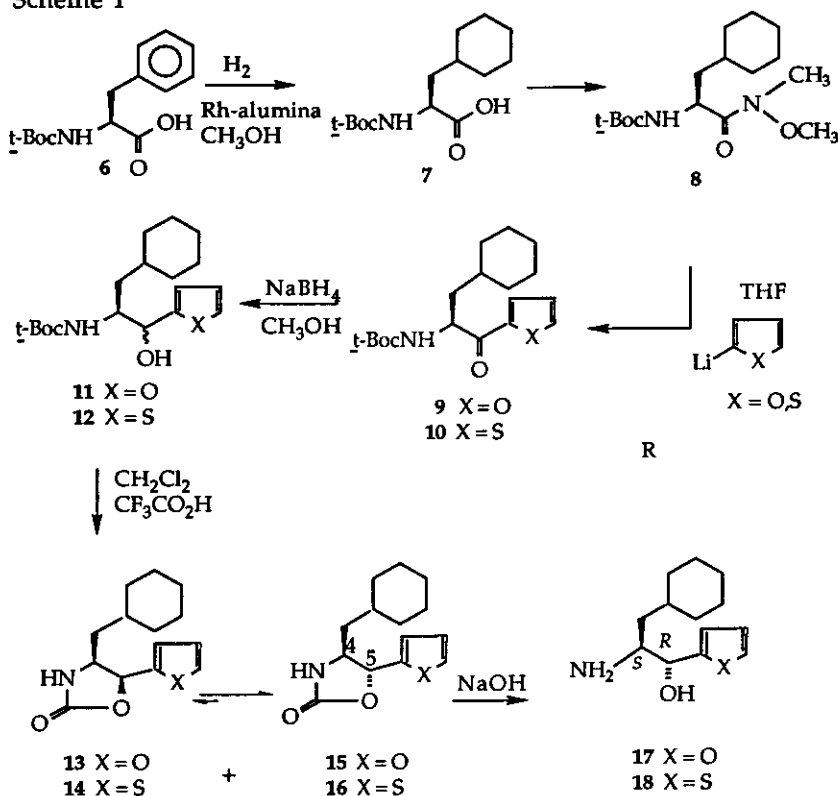
The synthetic efforts were concentrated on derivatives with a cyclohexyl group in place of the isopropyl group in statine (1) and norstatine (2) since analogues containing the cyclohexyl derivatives of statine and norstatine are known to give more potent renin inhibitors.^{2,3}

Reduction (Scheme 1) of *t*-Boc-*L*-phenylalanine (6) with rhodium on alumina gave *t*-Boc-*L*-3-cyclohexylalanine (7) in essentially quantitative yield.² Activation with BOP or phenyl dichlorophosphate-imidazole and reaction with *N*-methoxy-*N*-methylamine gave the amide (8). Reaction of the amide with 2-lithiofuran or 2-lithiothiophene gave the ketones (9) and (10).^{4,5} On large scale runs the crude ketones were reduced with sodium borohydride and the crude mixture of diastereomeric alcohols was treated with trifluoroacetic acid in dichloromethane. This treatment gave initially a mixture of 5-furanyl-2-oxazolidinones (13, 15) or a mixture of 5-thienyl-2-oxazolidinones (14) and (16) respectively. The (4*S*-*cis*)-2-oxazolidinones (13) and (14) are converted *in situ* to give mainly the (4*S*-*trans*)-2-oxazolidinones (15) and (16) (*trans/cis* 98:2) in an equilibrium process. Thus a stereoselective synthesis of the desired furanyl derivative (17) and thienyl derivative (18) was achieved. From reactions on 50 g of *t*-Boc-*L*-phenylalanine, the (*S*) 2-amino-3-cyclohexyl-(*R*)1-(2-furanyl)propan-1-ol B (17) was obtained in 45-50% overall yield (6 steps). In similar runs the (*S*)2-amino-3-cyclohexyl-(*R*)1-(2-thienyl)propan-1-ol (18) was obtained in 30-35% overall yield.

The stereochemistry of the (4*S*-*trans*)- and (4*S*-*cis*)-4-(cyclohexylmethyl)-5-(2-furanyl)-2-oxazolidinones, (13) and (15), respectively was established by their pmr spectra from the coupling constants of the protons at C-4 and C-5, $J = 8.14$ and $J = 7.06$ Hz respectively. Likewise, the stereochemistry of the 2-thienyl-oxazolidinones (14) and (16) were established from their pmr spectra, $J = 7.83$ and $J = 7.01$ Hz respectively.

Cyclization of (1*R*, 2*S*)-2-benzyloxycarbonylaminoalcohols with trifluoromethanesulfonic anhydride or thionyl chloride to (4*S*-*trans*)-2-oxazolidinones with inversion at the chiral center containing the hydroxyl group has been reported.⁶

Scheme I



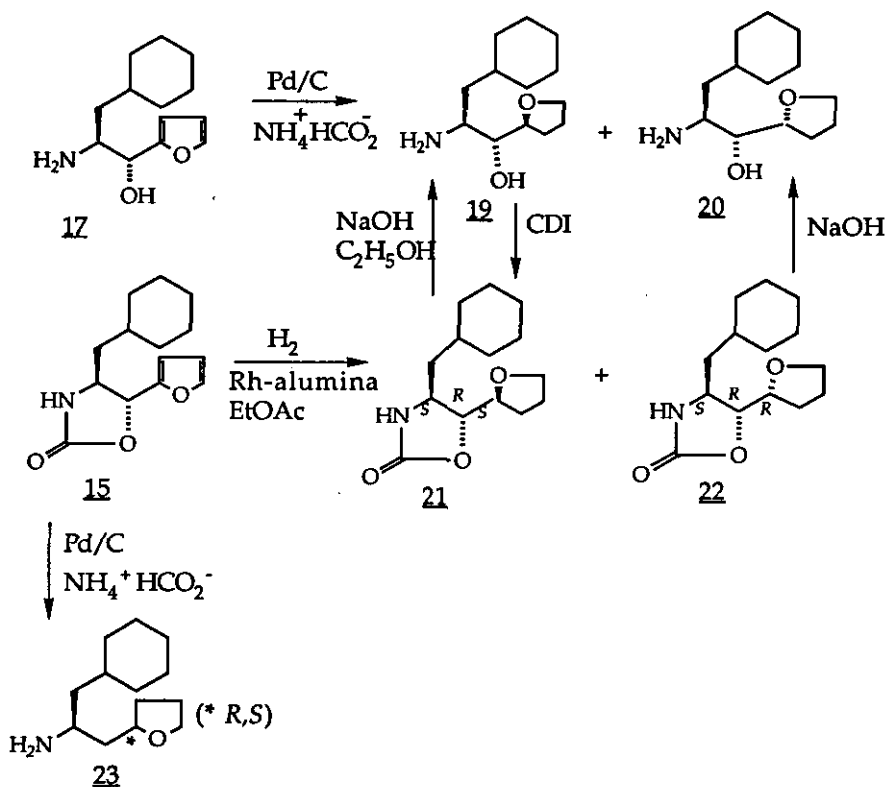
As an alternative route to oxazolidinone (15), N^{α} -*t*-Boc-L-3-cyclohexylalaninal, from reduction (LAH) of *N*-methoxy-*N*-methylamide (8) ^{7,8}, was reacted with 2-lithiofuran and the mixture of diastereomers (*ca* 1:1) (79%) converted to (4*S*-*trans*)-2-oxazolidinone (15). The overall yield of 15 was lower than the yield *via* reduction of 2-furyl ketone (9) and cyclization to 15. *N,N*-Diprotected *D*-alaninals are reported to react with 2-lithiofuran to give 2-amino-1-(2-furanyl)propan-1-ols in 80-90% yields.⁹ Diastereoselective addition of 2-lithiofuran to *N,N*-dibenzyl-*L*-phenylalaninal followed by debenzylation of the major diastereomer is reported to give (*S*) 2-amino-3-phenyl-(*S*)1-(2-furanyl)propan-1-ol and (4*S*-*cis*)-2-oxazolidinone on reaction with phosgene.^{10,11}

In order to prepare the derivative (19) containing the 2-tetrahydrofuranyl moiety, the amino alcohol (17) was reduced under hydrogen transfer conditions ($\text{Pd/C-NH}_4^+\text{HCO}_2^-$)¹²⁻¹⁴ in methanol to give a mixture of diastereomers (19) and (20) (Scheme II). Chromatography (hplc on silica gel) with a Waters-Prep 500 instrument gave poor separations but enough of each pure compound was obtained

for characterization. The mixture of **19** and **20** was converted with *N,N*-carbonyldiimidazole to a mixture of oxazolidinones (**21**) and (**22**) which were readily separated by chromatography on silica gel. X-Ray analysis of oxazolidinone (**21**) established the structural assignments. Hydrolysis (sodium hydroxide) of the oxazolidinone (**21**) then gave the desired 2-amino-4,7-anhydro-1-cyclohexyl-1,2,5,6-tetrahydroxy-*L*-arabino-Heptitol (**19**).

Hydrogenation of 5-(2-furanyl)-2-oxazolidinone (**15**) with rhodium on alumina in ethyl acetate gave the tetrahydrofuranyloxazolidinones (**21**) and (**22**) in good yield (ca 90%). This hydrogenation followed by separation of diastereomers and hydrolysis of the oxazolidine (**21**) was then used to obtain larger quantities of (**19**). Hydrogenation of oxazolidinone (**15**) under hydrogen transfer conditions ($\text{Pd/C-NH}_4^+ \text{HCO}_2^-$) removed the C-5 hydroxyl group¹⁵ along with reduction of the furan ring to give **23**. Reduction with Raney nickel also gave substantial amounts of **23**.

Scheme II



Not unexpectedly, the numerous conditions tried for reduction of the 2-thienyl derivatives (**16**) and (**18**) failed to give the tetrahydrothienyl compounds. These reductions included catalytic (Rh-alumina; Pd/C)¹⁶⁻¹⁸ and ionic (trifluoroacetic acid-triethylsilane) reductions.¹⁹ Catalysts are known to be poisoned by thiophene derivatives. Ionic reduction depends on protonation of the thiophene ring followed by reduction; however, protonation of the carbonyl of the amide function of **16** or the amino group of **18** is expected before protonation of the thiophene ring. Thus, an improbable dication species would be required for successful ionic reductions.

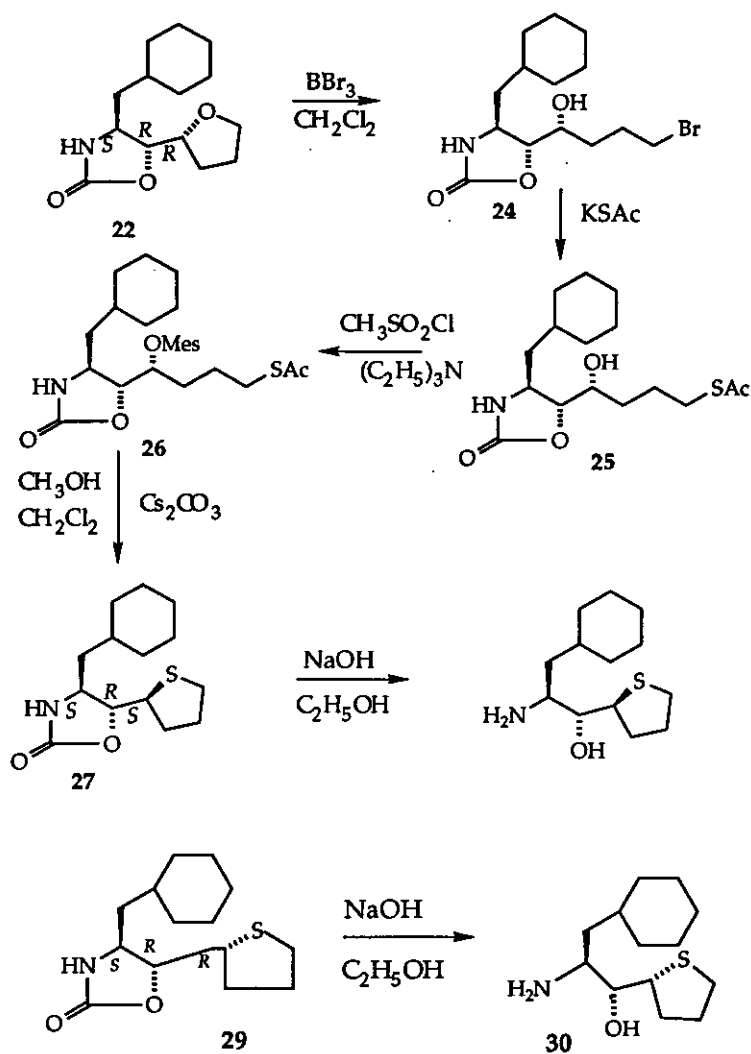
The tetrahydrothiophene derivative (**28**) was synthesized in 5 steps (86% overall yield) through the ring opening of the (*S,R,R*)-tetrahydrofuran-2-yl-oxazolidinone (**22**) with boron tribromide (Scheme III). Conversion of the bromo alcohol (**24**) to the acetylthio alcohol (**25**) and treatment with methanesulfonyl chloride gave the acetylthio *O*-mesylate (**26**). In one step, cesium carbonate in methanol dichloromethane hydrolysed the acetylthio group to the free thiol and initiated displacement of the *O*-mesylate group (ring closure with inversion) to give the (*S,R,S*)-tetrahydrothien-2-yl-oxazolidinone (**27**). Hydrolysis (NaOH-C₂H₅OH) then gave the desired (*S,R,S*)-tetrahydrothiophene derivative (**28**).

In a similar sequence of reactions (Scheme III), starting with the (*S,R,S*)-oxazolidinone (**21**), the diastomeric (*S,R,R*)-tetrahydrothien-2-yl-oxazolidinone (**29**) was prepared and hydrolyzed to amine (**30**) (60% for five steps).

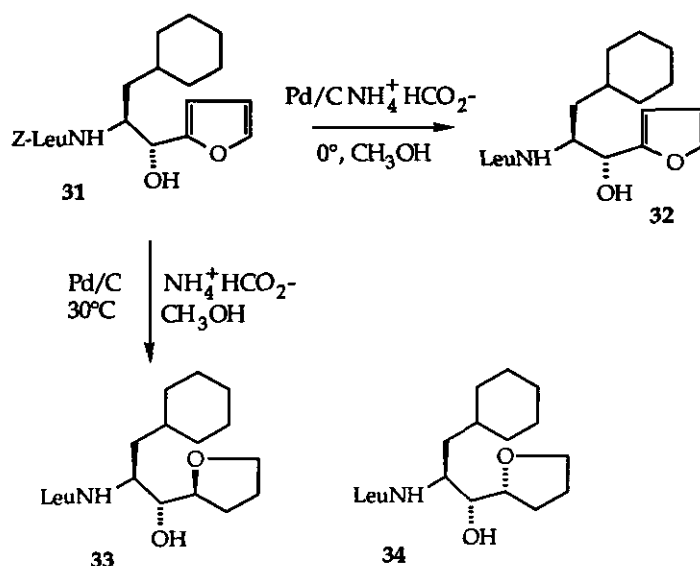
Since the stereochemistry of the (*S,R,S*)-tetrahydrofuran-2-yl-oxazolidinone (**21**) was established by X-ray analysis, the tetrahydrofuran-2-yl-oxazolidinone (**22**) could be assigned unequivocally the (*S,R,R*) stereochemistry and the tetrahydrothien-2-yl-oxazolidinone (**27**) assigned the (*S,R,S*) stereochemistry.

To our knowledge, the reduction of furans to tetrahydrofurans under hydrogen transfer conditions shown in Scheme 2 has not been reported. The reduction of furyl rings with palladium on carbon-ammonium formate in small scale reactions is an attractive alternative to palladium on carbon or Raney nickel hydrogenations under pressure.²²⁻²⁵ Only deblocking (Pd/C-NH₄⁺HCO₂) of *N*-[*N*-(benzyloxy)carbonyl-L-leucyl]-(*S*)-2-amino-3-cyclohexyl-(*R*)-1-(2-furyl)propan-1-ol (**31**) without reduction of the furyl ring occurs at 0°C in methanol while at 25°C to 30°C both removal of the *N*-benzyloxycarbonyl group and ring reduction are observed to give **33** and **34**. The hydrogen transfer reduction of furyl rings is a general one for we have reduced a number of furan derivatives to

Scheme III



tetrahydrofurans. For example 2-furylphenylcarbinol²⁶ was reduced to tetrahydro- α -phenyl-2-furanmethanol²⁷ (62% yield of *erythro* (55%) and *threo* (45%) after separation by hplc on silica gel).



ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus and are not corrected. Samples for analysis were dried *in vacuo* over Drierite at 23°C to 70°C overnight. Pmr spectra were determined with a GE-QE-300 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Solvents were removed under reduced pressure by the use of a rotary evaporator. Magnesol is the trade name for hydrous magnesium silicate.

***N* $^\alpha$ -*t*-Boc-*L*-3-cyclohexylalanine (7).** To a solution of 46.37 g (0.175 mol) of *N* $^\alpha$ -*t*-Boc-*L*-phenylalanine in 87.5 ml of methanol (under argon) was added 4.2 g of 5% rhodium on alumina. The solution was hydrogenated in a Parr shaker (500 ml flask) under 50 pounds psi of hydrogen overnight (16 h). The mixture was filtered through a thin pad of diatomaceous earth (Celite). The pad was washed with methanol and the combined filtrates were concentrated under vacuum to remove the solvent. The solid (51.7 g) was dissolved in 350 ml of 1M NaHCO_3 and the solution was extracted with diethyl ether (3×10 ml). The aqueous layer was made acidic with 350 ml of 2N citric acid (pH 3) and then extracted

with CH_2Cl_2 (3 x 350 ml). The extract was dried (MgSO_4), filtered and the solvent was removed under vacuum to give 44.7 g (94%) of a colorless oil, $[\alpha]_{\text{D}}^{26} -10^\circ \pm 1$ (c. 1.035, CH_3OH), after drying in a vacuum oven at 50°C for 16 h.

N-Methoxy-N-methyl N^α -t-Boc-L-3-cyclohexylalaninamide (8). In a 2 liter three necked Morton flask under argon was added 472 ml of dry CH_2Cl_2 and 56.1 g (0.825 mol) of imidazole. To the solution was added (through a 250 ml dropping funnel) 34.81 g of phenyl dichlorophosphate in 186 ml of CH_2Cl_2 . The mixture was stirred at room temperature for 1 h and then cooled to 0°C (icebath). To this cooled mixture was added a solution of 44.7 g (0.165 mol) of N^α -t-Boc-L-3-(cyclohexyl) alanine in 170 ml of CH_2Cl_2 while keeping the temperature at 0°C . The mixture was stirred at 0°C for 1 h and 16.1 g (0.165 mol) of solid *N,O*-dimethylhydroxylamine hydrochloride amine added. The mixture was stirred overnight (ice bath allowed to melt) and then filtered to remove the imidazole hydrochloride. The filtrate was washed with 2N citric acid (360 ml), 1M sodium bicarbonate (360 ml) and brine (360 ml). The organic layer was dried (MgSO_4), filtered and the solvent removed under vacuum. The product was dried at 50°C in a vacuum oven overnight to give 50.3 g (96%) of a colorless oil.

$[\alpha]_{\text{D}}^{26} -12^\circ \pm 1$ (c. 1.109, CH_3OH).

Procedure I: (4*S*-trans)-4-Cyclohexylmethyl-5-(2-furanyl)-2-oxazolidinone (15). A. **1,1-Dimethyl (S)-[1-(cyclohexylmethyl)-2-(2-furanyl)-2-oxoethylcarbamate. (9)** A solution of 31.0 g (0.0986 mol) of *N*-methoxy-*N*-methyl- N^α -t-butoxy-carbonyl-L-3-(cyclohexyl)alaninamide in 328 ml of dry tetrahydrofuran under argon was cooled to -78°C . To the solution was added dropwise, 112.9 ml (0.0936 mol) of secondary butyllithium (0.83 M in hexane). The mixture was stirred at -78°C for 1.5 h and allowed to warm to 0°C (solution A). To a solution of 14.35 ml (0.197 mol) of furan in 115 ml of dry tetrahydrofuran under argon, cooled to 0°C , was added dropwise 65.73 ml (0.1643 mol) of *n*-butyllithium (2.5 M in hexane). The mixture was stirred for 1.5 h at 0°C and allowed to warm to room temperature for 15 min (yellow solution B).²⁰ The yellow solution B was added dropwise *via* cannula at 0°C to the solution A (at 0°C) and the mixture stirred for 1 h at 0°C . The mixture was quenched with 200 ml of saturated aqueous NH_4Cl solution and then diluted with 40 ml of water. The mixture was concentrated under vacuum to remove the volatile solvents. The aqueous residue was diluted with 600 ml of ethyl acetate and 100 ml of 1N HCl added. The organic layer was separated, washed with 100 ml each of 1N HCl, H_2O , saturated NaHCO_3 solution, brine and dried (Na_2SO_4). The solvent was removed and the residue dried under high vacuum to give 29.6 g (93.5%) of a brown gum. A small scale run (5 mmol) gave 1.63 g of gum which was dissolved in ether-hexane (1:5) and filtered through a thin pad of hydrous magnesium silicate. The pad was washed with ether-hexane (1:5) and the filtrate concentrated to a gum. Trituration with hexane gave 1.23 g (76.9%) of light yellow crystals; $[\alpha] +41^\circ \pm 1$ (c. 1.14, CH_3OH), mp $76-78^\circ\text{C}$. Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_4$: C, 67.3; H, 8.5; N, 4.4. Found: C, 67.4; H, 8.6; N, 4.4. Chromatography of the compound on silica gel with hexane-ethyl acetate (3:1) gave new impurities.

B. 1,1-Dimethylethyl [(S)1-cyclohexylmethyl-(R,S)2-(2-furanyl)-2-hydroxyethyl]carbamate and Cyclization with Trifluoroacetic Acid. (15 from 9). A sample of the crude ketone (59.31 g; 184.8 mmol) (93.7% yield) was dissolved in 730 ml of tetrahydrofuran and 70 ml of methanol under argon and cooled to 0°C. To the solution was added 8.38 g (221.75 mmol) of sodium borohydride in several portions and the mixture stirred at 0°C for 1.5 h. The reaction was quenched with 280 ml of saturated NH₄Cl solution, stirred 10 min and concentrated under vacuum. To the aqueous residue was added 1 liter of ethyl acetate and 300 ml of 1N HCl. The organic layer was separated and washed with 300 ml each of 1N HCl, H₂O, saturated NaHCO₃ and saturated brine. The organic layer was dried (Na₂SO₄) and the solvent was removed to give (after drying under vacuum for 3 h) 57.0 (95%) of a dark brown gum. To a solution of this gum (57.0 g) in 1 liter of dichloromethane (cooled to 0°C) was added slowly 54.2 ml of trifluoroacetic acid. The cooling bath was removed and the solution was stirred at room temperature for 2 h. The solution was cooled to 0°C and 500 ml of 2N NaOH was added slowly, followed by dilution with 700 ml of dichloromethane. The organic layer was separated and the aqueous layer was extracted with 700 ml of CH₂Cl₂. The organic layer and extract were combined, dried (Na₂SO₄) and the solvent was removed to give 48.3 g of crude product. Chromatography (in two equal batches) by hplc on silica gel on a Waters Prep 500 instrument (2 columns) with hexane-ethyl acetate (3:1) as solvent gave a solid. Crystallization from hexane gave 23.5 g (48% over-all yield from 9) of off-white crystals, mp 97-99°C: $[\alpha]_D^{26} -125^\circ \pm 1$ (c, 1.017, CH₃OH); ¹H nmr (CDCl₃) δ 4.15 (m, 1H; C-4H), 5.08 (d, 1H, J = 7.06 Hz; C-5H). Anal. Calcd for C₁₄H₁₉NO₃: C, 67.5; H, 7.7; N, 5.6. Found: C, 67.4; H, 7.5; N, 5.5. Fractions containing a slower moving component from the hplc separation were combined (from a 25.6 g run) to give 150 mg of solid. Recrystallization from hexane gave 72 mg of off-white crystals, of (4S-cis)-4-cyclohexylmethyl-5-(2-furanyl)-2-oxazolidinone, (13), mp 112-114°C; $[\alpha]_D^{26} -6^\circ \pm 2$ (c, 0.473, CH₃OH); ¹H nmr (CDCl₃) δ 4.15 (m, 1H, C-4H), 5.62 (d, 1H, J = 8.14 Hz; C-5H). Anal. Found: C, 67.1; H, 7.7; N, 5.5. Based on hplc-graph peaks and the quantity isolated, the (4S-cis)-oxazolidinone was estimated to be approximately 2% of the mixture of diastereomers.

Procedure II: (4S-trans)-4-Cyclohexylmethyl-5-(2-furanyl)-2-oxazolidinone (15 from 8). To a stirred mixture of 2.73 g (72 mmol) of lithium aluminum hydride in 245 ml of dry ether chilled to -45°C under argon was added dropwise a solution of 18.87 g (60 mmol) of the N-methoxydimethylamide (8) in 45 ml of ether. After the addition (30 min), the mixture was allowed to warm to +5°C, cooled to -35°C and quenched slowly with a solution of 16.0 g of KHSO₄ in 45 ml of water (temp -3°C). The mixture was stirred at room temperature for 1 h, filtered through diatomaceous earth and the filtrate was cooled to 0°C and washed with 100 ml of 1N HCl (3 X), 100 ml of saturated sodium bicarbonate (2X) and 100 ml of brine. The organic layer was dried (MgSO₄) and filtered through a thin pad of hydrous magnesium silicate and the filter pad washed with ether. The filtrate was concentrated under vacuum to give 14.25 g (93%) of N^α-tert-butoxycarbonyl-L-3-cyclohexylalaninal. This aldehyde was dissolved in 100 ml of tetrahydrofuran and the solution cooled to -78°C. (Solution A). To a stirred solution of

12.13 ml (0.167 mol) of furan in 120 ml of tetrahydrofuran cooled to 0°C under argon was added dropwise 66.73 ml of *n*-butyllithium in hexane (2.5 M). After the addition, the mixture was stirred at 0° C for 1.5 h and allowed to warm to room temperature (solution B). The solution B (room temperature) was added dropwise *via* cannula to solution A (-78°C) (internal temperature -65°C to -79°C) and the mixture stirred at -70° for 1 h. The mixture was allowed to warm to room temperature, stirred for 1 h and quenched with 80 ml of saturated NH₄Cl solution. The mixture was concentrated under vacuum and extracted with 300 ml of ethyl acetate. The extract was washed with 100 ml of water (3X) and with 100 ml of brine and dried (Na₂SO₄). The solvent was removed to give 14.17 g (79%) of crude product. To a solution of the crude product (14.17 g; 43.8 mmol) in 250 ml of CH₂Cl₂ cooled to 0°C was added slowly 13.5 ml (0.175 mol) of trifluoroacetic acid. The cooling bath was removed and the solution stirred 1.5 h at room temperature. The solution was cooled (ice bath) and 2N NaOH added until the aqueous layer was pH 14. The organic layer was separated and the aqueous layer extracted with 250 ml of CH₂Cl₂ (2X). The organic layer and extracts were combined, washed with 200 ml of brine (2X), dried (Na₂SO₄) and the solvent was removed to give 12.0 g of solid. Chromatography on silica gel with a Waters-Prep 500 instrument with hexane-ethyl acetate (3:1) as solvent gave a solid. Trituration with hexane gave 4.7 g (43%) of off-white crystals, mp 98-100°C. The overall yield for the three steps was 31%.

(4*S*-trans)-4-Cyclohexylmethyl-5-(2-thienyl)-2-oxazolidinone (16). A. **1,1-Dimethylethyl (S)-[1-cyclohexylmethyl-2-(2-thienyl)-2-oxoethyl]carbamate (10).** A solution of 31.0 g (0.0986 mmol) of *N*-methoxy-*N*-methyl-*N*^α-*tert*-butoxy-carbonyl-L-3-cyclohexylalaninamide (8) in 295 ml of dry tetrahydrofuran under argon was cooled to -78°C. To the solution was added dropwise 76 ml (0.095 mol) of secondary butyllithium in hexane (1.25 M) over 1 h. The mixture was stirred at -78° C for 1.5 h and allowed to warm to 0°C. (Solution A). To a solution of 11.84 ml (0.147 mol) of thiophene in 98 ml of dry ether under argon cooled to 0°C, was added dropwise 59.16 ml (0.148 mol) of *n*-butyllithium in hexane (2.5 M) over 1 h and the solution was stirred at 0°C for 1.5 h (solution B).²¹ The solution B was added dropwise *via* cannula at 0°C to the solution A at 0°C and the mixture was stirred for 2 h at 0°C. The mixture was quenched with 100 ml of NH₄Cl, diluted with 40 ml of water and was concentrated under vacuum to remove volatile solvents. The aqueous residue was diluted with 600 ml of ethyl acetate and 100 ml of 1N HCl. The organic layer was separated and washed with 100 ml each of 1N HCl, H₂O, saturated NaHCO₃, and saturated NaCl solution and dried (Na₂SO₄). The solution was filtered through a thin pad of hydrous magnesium silicate and the pad washed with ethyl acetate. The filtrate was concentrated under vacuum. The residue was dissolved in 250 ml of dichloromethane and the solution filtered through a 10 cm x 10 cm x bed of silica gel (in a sintered glass funnel). The silica gel was washed with two 500-ml portions of dichloromethane and the combined filtrates concentrated under vacuum to give 18.85 g (56.6%) of a yellow-orange solid, mp 110-114°C; one spot on tlc on silica gel with hexane-ethyl acetate (4:1) as solvent. Chromatography of a small sample on silica gel with

ethyl acetate-hexane (1:20) gave crystals, mp 110°-114°C. From a 15.7 g (50 mmol) run, 14.8 g (88%) of crude product was triturated with hexane (twice) to give 7.8 g (46%) of off-white crystals, mp 114-116°C; $[\alpha]_D^{26} + 24^\circ \pm 1$ (c, 1.10, CH₃OH). Anal. Calcd for C₁₈H₂₇NO₃S: C, 64.1; H, 8.1; N, 4.2; S, 9.5.

Found: C, 64.3; H, 8.1; N, 4.2; S, 9.5.

B. 1,1-Dimethylethyl [(S)1-cyclohexylmethyl-(R,S)2-(2-thienyl)-2-hydroxyethyl]carbamate (12). A solution of 18.8 g (0.0557 mol) (56.6% yield) of 1,1-dimethylethyl (S)-[1-cyclohexylmethyl-2-(2-thienyl)-2-oxoethyl]carbamate (mp 110-114°C) in 195 ml of dry tetrahydrofuran was cooled to -78°C under argon and 111.4 ml (0.1114 mol) of 1.0 M potassium tri-*sec*-butylborohydride in tetrahydrofuran was added dropwise over 1 h. The solution was stirred at -78°C for 2 h and quenched with 122 ml of water. The organic solvent was removed under vacuum and the aqueous residue was diluted with 340 ml of ethyl acetate. To the stirred mixture, cooled to 0°C, was added 56 ml of 30% hydrogen peroxide and the mixture stirred 1 h at room temperature. To the mixture cooled to 0°C was added 122.6 g of sodium sulfite and after stirring 0.5 h at room temperature, the organic layer was separated. The aqueous layer was extracted with 150 ml of ethyl acetate. The organic layer and extract were combined, dried (Na₂SO₄) and the solvent removed. The residue was dried (75°C) under high vacuum to give 18.47 g (97.6%) of yellow-orange gum; $[\alpha]_D^{26} -20^\circ \pm 1$ (c, 1.084, CH₃OH). To a 0.51 g (1.5 mmol) sample of ketone (10) in a mixture of 5 ml of tetrahydrofuran and 0.5 ml of methanol, cooled to 0°C under argon, was added in portions 70 mg (1.8 mmol) of sodium borohydride. The mixture was stirred at 0°C for 1.5 h and quenched with 5 ml of saturated NH₄Cl and concentrated. The residue was diluted with 5 ml of H₂O and extracted with 20 ml of ethyl acetate. The organic layer was washed with saturated solutions of NH₄Cl (5 ml), NaHCO₃ (10 ml), NaCl (10 ml) and dried (Na₂SO₄). The solvent was removed and the solid (0.54 g) chromatographed on silica gel with ethyl acetate-CH₂Cl₂ (1:30) as solvent. Fractions containing the front running component gave 0.36 g of 1,1-dimethylethyl [(S)1-(cyclohexylmethyl)-(R)-2-(2-thienyl)-2-hydroxyethyl]carbamate as a white solid, $[\alpha]_D^{26} -14^\circ \pm 3$ (c, 0.391, CH₃OH). Anal. Calc for C₁₈H₁₉NO₃S: C, 63.7; H, 8.6; N, 4.1; S, 9.4. Found: C, 63.6; H, 8.8; N, 3.9; S, 9.4. Fractions containing the slower moving component gave 0.11 g of 1S, 2S diastereomer as a colorless gum; $[\alpha]_D^{26} -25^\circ \pm 2$ (c, 0.585, CH₃OH). Anal. Found: C, 64.2; H, 8.9; N, 3.9; S, 9.4.

C. (4S-trans) 4-Cyclohexylmethyl-5-(2-thienyl)-2-oxazolidinone (16). To a solution of 18.4 g (0.0542 mol) of crude 1,1-dimethylethyl [(S) 1-cyclohexylmethyl-(R,S) 2-(2-thienyl)-2-hydroxyethyl]carbamate in 330 ml of dichloromethane, cooled to 0°C, was added 16.75 ml of trifluoroacetic acid. The solution was stirred overnight at room temperature, cooled to 0°C and 300 ml of ice cold 1N NaOH added slowly. The organic layer was separated and the aqueous layer extracted with two 350 ml portions of dichloromethane. The organic layer and extracts were washed with two 250 ml portions of brine and dried (Na₂SO₄). The solvent was removed under vacuum to give 14.5 g (100%) of solid. Trituration with 200 ml of hot hexane and cooling to room temperature gave 7.5 g (52%) of off-white crystals, mp

105-108°C; $[\alpha]_D^{26}$ -117°±1 (c, 1.006, CH₃OH). A 27 g sample (from two runs) (0.102 mol) of unpurified oxazolidinone (gum) was chromatographed (silica gel; 2-columns) by hplc on a Waters-Prep-500 instrument with hexane-ethyl acetate (3:1) as solvent. Fractions containing only pure front moving components were concentrated and the residue was crystallized from hexane to give 6.3 g (33%) of (4*S*-*trans*)-4-cyclohexylmethyl-5-(2-thienyl)-2-oxazolidinone as off-white crystals, mp 108-110°C; $[\alpha]_D^{26}$ -120°± (c, 0.829, CH₃OH); ¹H Nmr (CDCl₃) δ 3.98 (m, 1H, C-4H), 5.31 (d, 1H, J=7.01 Hz, C-5H). Anal. Calc for C₁₄H₁₉NO₂S: C, 63.4; H, 7.2; N, 5.3; S, 12.1. Found: C, 63.6; H, 7.3; N, 5.3; S, 12.2. Fractions containing the slower moving component were concentrated and the solid crystallized from hexane to give 0.190 g of (4*S*-*cis*)-4-cyclohexylmethyl-5-(2-thienyl)-2-oxazolidinone (14) as off-white crystals, mp 155-157°C; $[\alpha]_D^{26}$ -16°±1 (c, 1.003, CH₃OH). ¹H Nmr (CDCl₃) δ 4.17 (m, 1H, C-4H), 5.62 (d, 1H, J = 7.83 Hz, C-5H). Anal. Found: C, 63.3; H, 7.2; N, 5.1; S, 12.2. Based on integration of the hplc-graph peaks, the ratio of (4*S*-*trans*) - to (4*S*-*cis*) oxazolidinone was 97.6% : 2.4%.

(*S*)-2-Amino-3-cyclohexyl-(*R*)-1-(2-furanyl)propan-1-ol (17) CA Name: [*R*-(*R**, *S**)]-α -(1-Amino-2-cyclohexylethyl)-2-furanmethanol. A solution of 11.49 g (46.09 mmol) of (4*S*-*trans*)-4-(cyclohexylmethyl)-5-(2-furanyl)-2-oxazolidinone (15) in 225 ml of ethanol and 225 ml of 1N NaOH was refluxed overnight and concentrated under vacuum. The aqueous residue was extracted with two 230 ml portions of CH₂Cl₂ and the extract dried (Na₂SO₄). The solvent was removed and the solid crystallized from hexane to give 10.0 (97%) of off-white crystals, mp 66-68°C:

$[\alpha]_D^{26}$ -10°±1. (c, 1.014, CH₃OH). Anal. Calcd for C₁₃H₂₁NO₂: C, 69.9; H, 9.5; N, 6.3. Found C, 70.2, H, 9.3; N, 6.0.

(*S*)-2-Amino-3-cyclohexyl-(*R*)-1-(2-thienyl)propan-1-ol (18). A mixture of 7.0 g (0.0264 mol) of (4*S*-*trans*) 4-cyclohexylmethyl-5-(2-thienyl)-2-oxazolidinone in 13 ml of ethanol and 132 ml of 1N NaOH was refluxed for 17 h and the solvent removed under vacuum. The residue was extracted twice with 200 ml of CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and the solvent was removed under vacuum. The residue was triturated with hot hexane to give 4.64 g (73.4%) of off-white crystals, mp 62-64°C; $[\alpha]_D^{26}$ -35°±1 (c, 1.145, CH₃OH). From the mother liquors an additional 0.8 g (12.6%) of crystals mp 60-62°C was obtained. Anal. Calcd for C₁₃H₂₁NOS: C, 65.2; H, 8.8; N, 5.9; S, 13.4. Found: C, 65.5; H, 8.8; N, 5.9; S, 13.6.

4,7-Anhydro-2-carboxyamino-1-cyclohexyl-1,2,4,5-tetradecoxy-*L*-arabino-Heptitol, γ-lactone, (21) and 4,7-Anhydro-2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecoxy-*D*-xylo-Heptitol, γ-lactone (22). To a solution of 12.87 g (51 mmol) of (4*S*-*trans*)-4-cyclohexylmethyl-5-(2-furanyl)-2-oxazolidinone (15) in 108 ml of ethyl acetate was added 5.1 g of 5% rhodium on alumina. The mixture was hydrogenated at 30 psi of hydrogen in a Parr hydrogenator for 4 h. The mixture was filtered through a pad of diatomaceous earth and the pad was washed with warm ethyl acetate. The filtrate was washed with 1 N HCl (2 x 200 ml), 200 ml of 1 M NaHCO₃ and saturated brine. The organic layer was dried (Na₂SO₄)

and removed to give 10.9 g (83%) of solid as a mixture of diastereomers. A 21.9 g sample was chromatographed by hplc on a Waters-Prep 500 instrument (silica gel, 2 columns) with ethyl acetate-dichloromethane (1:5) to give 9.22 g (35%) of *L-arabino*-Heptitol diastereomer (front running component) as white crystals (from hexane), mp 93-96°C (21); $[\alpha]_D^{26} -73^\circ \pm 1$ (c, 0.976, CH₃OH). Anal.

Calcd for C₁₄H₂₃NO₃: C, 66.4; H, 9.2; N, 5.5. Found: C, 66.6; H, 9.2; N, 5.4.

Intermediate fractions gave 4.28 g (16.3%) of the mixture of diastereomers. Later fractions gave 4.18 g (16%) of *D-xyl*-Heptitol diastereomer (22) as white crystals (from hexane), mp 143-145°C; $[\alpha]_D^{26} -110^\circ \pm 1$ (c, 0.958, CH₃OH); Anal. Found: C, 66.1; H, 9.12; N, 5.2.

2-Amino-4,7-anhydro-1-cyclohexyl-1,2,5,6-tetradecoxy-*L-arabino*-Heptitol (19). A solution of 2.63 g (10.38 mmol) of 4,7-anhydro-2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecoxy-*L-arabino*-Heptitol, γ -lactone (21) in 50 ml of ethanol and 50 ml of 1N NaOH was refluxed overnight and concentrated under vacuum. The aqueous residue was extracted with 50 ml of CH₂Cl₂ and the extract was washed with 40 ml each of H₂O and brine and dried (Na₂SO₄). The solvent was removed to give 2.4 g of solid which was sublimed to give 1.86 g (79%) of crystals, mp 72-74°C; $[\alpha]_D^{26} -20^\circ \pm 2$ (c, 0.664, CH₃OH). Anal. Calcd for C₁₃H₂₅NO₂: C, 68.7; H, 11.1; N, 6.2. Found: C, 69.1; H, 11.2; N, 6.1.

2-Amino-4,7-anhydro-1-cyclohexyl-1,2,5,6-tetradecoxy-*L-arabino*-Heptitol and 2-Amino-4,7-anhydro-1-cyclohexyl-1,2,5,6-tetradecoxy-*D-xyl*-Heptitol (20). To a solution of 14.12 g (63.23 mmol) of (S)-2-amino-3-cyclohexyl-(R)1-(2-furanyl)propan-1-ol (17) in 330 ml of methanol under argon was added 15.94 g (0.253 mol) of ammonium formate. To the mixture (without stirring) was added, by pipette, a suspension of 7.06 g of 10% Pd/C in 22 ml of H₂O. Stirring was started and the temperature rose from 22°C to 28°C in the reaction mixture. Stirring was continued for 2 h, 5 g of diatomaceous earth was added and the mixture was filtered through a thin pad of diatomaceous earth. The pad was washed with methanol and the total filtrate was concentrated under vacuum. To the residue was added 23 ml of water and 30 ml of 5N NaOH. The mixture was extracted with CH₂Cl₂ (3 x 250 ml), the extract dried (Na₂SO₄) and the solvent removed to give 11.2 g (78%) of white solid crystals, mp 48-54°C. A 2.8 g sample was chromatographed by hplc (silica gel) on a Water-Prep 500 instrument with 2% triethylamine in ethyl acetate as solvent. Fractions containing the first compound eluted gave a solid which was sublimed to give 0.452 g of crystals, mp 74-76°C; $[\alpha]_D^{26} -24^\circ \pm 1$ (c, 1.00, CH₃OH) *D-xyl*-Heptitol diastereomer (20). Anal. Calcd for C₁₃H₂₅NO₂: C, 68.7; H, 11.1; N, 6.2. Found: C, 68.7; H, 11.4; N, 6.0. The later fractions containing only one component gave a solid which was sublimed to give 0.39 g of 19 crystals, mp 72-74°C; $[\alpha]_D^{26} -20^\circ \pm 1$ (c, 1.08, CH₃OH); Anal. Found: C, 68.4; H, 11.0; N, 5.9.

2-Amino-1-cyclohexyl-1,2,4,5,6,7-hexadeoxy-4,7-epithio-*L-arabino*-Heptitol (28) and 2-Amino-1-cyclohexyl-1,2,4,5,6,7-hexadeoxy-4,7-epithio-*D-xyl*-Heptitol (30). A. To a solution of 7.73 g (30.6 mmol) of 4,7-anhydro-2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecoxy-*D-xyl*-Heptitol, oxazolidine (22) in 77 ml of CH₂Cl₂, cooled in an ice-methanol bath (0° to -5°C) under argon, was added slowly 77

ml of 1M BBr₃ in CH₂Cl₂. The cooling bath was removed and the mixture stirred at room temperature for 2 h. The mixture was poured into 50 ml of cold water and the CH₂Cl₂ was removed. The residue containing crystals was triturated with 100 ml of ice water, filtered and the crystals were washed thoroughly with H₂O. The solid was dried under vacuum to give 10.03 g (98%) of [4S-[4 α , 5 β (S*)]]-5-(4-bromo-1-hydroxybutyl)-4-cyclohexylmethyl-2-oxazolidinone as crystals, mp 120-122°C. A small sample from a previous run was recrystallized from CH₂Cl₂-diisopropyl ether to give crystals, mp 124-125°C; $[\alpha]_D^{26}$ -64° ± 1 (c, 1.018, CH₃OH). Anal. Calcd for C₁₄H₂₄NO₃Br: C, 50.3; H, 7.2; N, 4.2; Br, 23.9.

Found: C, 50.1; H, 7.2; N, 4.0; Br, 24.4. Similarly from 3.0 g (11 mmol) of 4,7-anhydro-2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecyloxy-L-arabino-Hexitol, oxazolidinone (21) was obtained 4 g (100%) of diastomeric [4S-[4 α , 5 β (R*)]]-5-(4-bromo-1-hydroxybutyl)-4-cyclohexylmethyl-2-oxazolidinone, mp 100-112°C. A sample recrystallized from CH₂Cl₂-diisopropyl ether had mp 103-106°C; $[\alpha]_D^{26}$ -62° ± 1 (c, 1.12, CH₃OH). Anal. Found: C, 47.3; H, 7.2; N, 3.7; Br 20.7.

B. To a solution of 10.03 g (30 mmol) of unpurified [4S-[4 α , 5 β (S*)]]-5-(4-bromo-1-hydroxybutyl)-4-cyclohexylmethyl-2-oxazolidinone (24) in 100 ml of acetonitrile under argon was added 3.8 g (33 mmol) of potassium thioacetate. After stirring 1 h, the mixture (containing solid) was refluxed 5 min (solid dissolved) and poured into 450 ml of ice-cold water. Chilling and filtering gave 9.8 g (99%) of 2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecyloxy-7-thio-D-xylo-Heptitol-7-acetate, intramol-2,3-ester (25) as crystals, mp 110-112°C. A small sample from a previous run was recrystallized from CH₂Cl₂-diisopropyl ether to give crystals, mp 110-111°C; $[\alpha]_D^{26}$ -60° ± 1 (c, 1.005, CH₃OH).

Anal. Calcd for C₁₆H₂₇NO₄S; C, 58.3; H, 8.3; N, 4.3; S, 9.7. Found: C, 57.0; H, 8.0; N, 3.9; S, 10.0.

Similarly, from the 3.57 g (10.68 mmol) of the diastomeric bromo alcohol was obtained 3.4 g (96%) of 2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecyloxy-7-thio-L-arabino-Heptitol-7-acetate, intramol-2,3-ester, mp 113-114°C. A sample recrystallized from CH₂Cl₂-diisopropyl ether gave needles of the hemihydrate, mp 117-118°C, $[\alpha]_D^{26}$ -73° ± 1, (c, 1.05, CH₃OH). Anal. Calcd for C, 56.8; H, 8.3; N, 4.1; S, 9.5. Found: C, 56.5; H, 7.9; N, 4.1; S, 9.3.

C. To a solution of 9.8 g (30 mmol) of unpurified 2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecyloxy-7-thio-D-xylo-Heptitol-7-acetate, intramol-2,3-ester (25) in 55 ml of CH₂Cl₂ cooled in an ice-methanol bath under argon was added 6.2 ml (45 mmol) of triethylamine and 3.5 ml (45 mmol) of methane-sulfonyl chloride was added dropwise over 10 min. After 1 h, 55 ml of H₂O and 100 ml of CH₂Cl₂ were added and the mixture warmed to 37°C. The organic layer was separated, dried (MgSO₄ + activated carbon) and the solvent removed to give 12.2 g (100%) of crystals, mp 163-164°C. A small sample from a previous run was recrystallized from diisopropyl ether to give crystals, mp 162-163°C; $[\alpha]_D^{26}$ -45° ± 1 (c, 1.064, CHCl₃). Anal. Calcd for C₁₇H₂₉NO₆S₂: C, 50.1; H, 7.2; N, 3.4; S, 15.7. Found: C, 49.6; H, 7.1; N, 3.0; S, 15.1. Similarly, from 3.23 g (10 mmol) of 2-carboxyamino-1-cyclohexyl-1,2,5,6-tetradecyloxy-7-thio-L-arabino-Heptitol-7-acetate, intramol-2,3-ester yielded 3.73 g (93%) of the mesylate mp 151-154°C. A

sample recrystallized from ethyl acetate had mp 165-166°C, $[\alpha]_D^{26} - 9^\circ \pm 1^\circ$ (c, 1, CH₃OH). Anal. Found: C, 49.8; H, 7.2; N, 3.3; S, 15.9.

D. To a suspension of 12.2 g (30 mmol) of unpurified *O*-mesylate (26) in 150 ml of CH₂Cl₂ was added 120 ml of dry CH₃OH and 14.5 g (45 mmol) of Cs₂CO₃. The mixture was stirred (solids dissolved) and after 2 h, 210 ml of water was added. The aqueous layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 ml). The combined organic layer and extract were dried (MgSO₄) and filtered through a thin pad (1.0 g) of hydrous magnesium silicate. The pad was washed with CH₂Cl₂ and the filtrate was concentrated under vacuum to give 8.9 g of crystals. This solid was dissolved in a mixture of 140 ml of diisopropyl ether and 30 ml of CH₂Cl₂, concentrated to 100 ml and filtered to remove traces of solid. The filtrate was concentrated and chilled to give 7.5 g (95%) (in two crops) of 2-carboxyamino-1-cyclohexyl-1,2,4,5,6,7-hexadeoxy-4,7-epithio-*L*-arabino-Heptitol, intramol-2,3-ester (27) as crystals, mp 128-129°C. A small sample from a previous run was recrystallized from CH₂Cl₂-diisopropyl ether to give crystals, mp 132-133°C; $[\alpha]_D^{26} - 22^\circ \pm 1^\circ$ (c, 1.055, CH₃OH). Anal. Calcd for C₁₄H₂₃NOS; C, 62.4; H, 8.6; N, 5.2; S, 11.9. Found: C, 62.5; H, 8.6; N, 5.5; S, 11.6.

Cyclization of 3.6 g (8.9 mmol) of the diastomeric mesylate, mp 151-154°C gave, after chromatography on silica gel with a Waters-Prep 500 instrument in 3:1 hexane-ethyl acetate, 1.8 g (75%) of 2-carboxyamino-1-cyclohexyl-1,2,4,5,6,7-hexadeoxy-4,7-epithio-*D*-xylo-Heptitol, 2,3-intramol-ester, mp 157-158°C, $[\alpha]_D^{26} - 171^\circ \pm 1^\circ$ (c, 1.04, CH₃OH). Anal. Found: C, 61.9; H, 8.7; N, 5.0; S, 11.8.

E. To a solution of 7.5 g (28 mmol) of compound (27) (not purified) in 135 ml of ethanol was added 135 ml of 1N NaOH and the solution was refluxed overnight. The solution was concentrated to 80 ml, chilled and filtered to give 6.8 g (100%) of crystals, mp 56-60°C. This solid was sublimed to give 6.41 g (94%) of crystals, mp 60-61°C; $[\alpha]_D^{26} + 50^\circ \pm 1^\circ$ (c, 1.005, CH₃OH) (86.2% overall yield for 5 steps). Anal.

Calcd for C₁₃H₂₅NOS; C, 64.2; H, 10.4; N, 5.8; S, 13.2. Found: C, 64.0; H, 10.1; N, 5.7; S, 13.1.

Similarly, hydrolysis of 0.269 g (12 mmol) of the diastomeric oxazolidinone (29) gave a solid which was sublimed to give 0.222 g (91%) of crystals, mp 112-113°C; $[\alpha]_D^{26} - 77^\circ \pm 1^\circ$ (c, 1.10, CH₃OH). Anal.

Found: C, 64.3; H, 10.1; N, 5.7; S, 12.9.

N-*L*-Leucyl-(*S*)-2-amino-3-cyclohexyl-(*R*)-1-(2-furanyl)propan-1-ol (32). A. *N*-[*N*-(Benzyloxy)carbonyl-*L*-leucyl]-(*S*)-2-amino-3-cyclohexyl-(*R*)-1-(2-furanyl)propan-1-ol (31). To a solution 4.99 g (18.8 mmol) of *N*-(benzyloxy)carbonyl-*L*-leucine in 40 ml of dry tetrahydrofuran was added 3.05 g (18.8 mmol) of *N,N*-carbonyldiimidazole. The solution was stirred at room temperature for 2.0 h and then 4.0 g (17.9 mmol) of (*S*)-2-amino-3-cyclohexyl-(*R*)-1-(2-furanyl)propan-1-ol (17) was added. After stirring 5 h under argon, the solvent was removed and the residue was dissolved in 80 ml of dichloromethane. The solution was washed twice with 40 ml of 2N citric acid, and with 40 ml each of water, 1 M sodium bicarbonate and brine to give an oil. Crystallization from diisopropyl ether gave 7.0 g (83%) of white

crystals, mp 95-97°C: $[\alpha]_D^{26} -39^\circ \pm 1$ (c, 1.029, CH₃OH). Anal Calcd for C₂₇H₃₈N₂O₅: C, 68.9; H, 8.1; N, 5.9. Found: C, 68.9, H, 8.1, N, 5.9.

B. The preceding compound (1.85 g; 3.93 mmol) and 1.0 g (15.86 mmol) of ammonium formate in 24 ml of methanol under nitrogen was warmed on a steam bath and then the solution chilled to 0°C under nitrogen. To this mixture (without stirring) was added (by pipette) 0.96 g of 10% Pd/C suspended in 5 ml of ethanol. The mixture was chilled at 0°C and stirred for 1 h. Diatomaceous earth was added and the mixture was filtered on a pad of diatomaceous earth and was washed with methanol. The filtrate was evaporated to dryness and the residue partitioned between concentrated ammonium hydroxide and CH₂Cl₂. The organic layer was separated, dried (MgSO₄) and the solvent removed to give 1.24 g of gum. Crystallization from 5 ml of diisopropyl ether gave 0.74 g (54%) of colorless needles 32 mp 83-84°C. $[\alpha]_D^{26} -17^\circ \pm 1$ (c, 1.031, CH₃OH). Anal. Calcd for C₁₉H₃₂N₂O₃: C, 67.8; H, 9.6; N, 8.3. Found C, 67.6; H, 9.2, N, 7.9.

(S)-2-[(2-Amino-4-methyl-1-oxopentyl)amino]-4,7-anhydro-1-cyclohexyl-1,2,5,6-tetradecoxy-L-arabino-Heptitol (33) and (S)-2-[(2-Amino-4-methyl-1-oxopentyl)amino]-4,7-anhydro-1-cyclohexyl-1,2,5,6-tetradecoxy-D-xylo-Heptitol (34). N-(N-Benzoyloxycarbonyl-L-leucyl)-(S)-2-amino-3-cyclohexyl-(R)-1-(2-furanyl)propan-1-ol (31) (7 g; 14.87 mmol) was dissolved in 80 ml of methanol under argon and 6.12 g (97 mmol) of ammonium formate added. To this mixture under argon was added a suspension of 10% Pd/C (3.17 g) in 10 ml of water. The suspension was added from a pipette and an additional 2 ml of water used as a rinse of the pipette. After the addition, the solution was stirred and the temperature rose from 22°C to 30°C. After stirring for 1 h, 5 ml of water and 3 g of diatomaceous earth was added and the mixture filtered through a pad of diatomaceous earth. The filter pad was washed with methanol and the filtrate was concentrated under vacuum until solid began to separate. The mixture was acidified with 20 ml of 2N citric acid and extracted with three 40 ml portions of ether. The aqueous layer was made basic with concentrated ammonium hydroxide and extracted with three 80 ml portions of diethyl ether. The extract was dried (Na₂SO₄) and the solvent was removed to give 3.7 g of an oil. The preceding oil was chromatographed with a Waters-Prep 500 hplc instrument (silica gel, two columns) with 1% triethylamine in ethyl acetate as solvent. Cuts containing the less polar component were combined, the solvent was removed and the residue was crystallized from diisopropyl ether to give 0.916 g (18%) of white crystals, mp 77-78°C: $[\alpha]_D^{26} -25^\circ \pm 2$ (c, 0.421, CH₃OH) assigned D-xylo- diastereomer (34). Anal. Calcd for C₁₉H₃₆N₂O₃: C, 67.0; H, 10.7; N, 8.2. Found: C, 67.0; H, 10.7; N, 8.0. Fractions containing the more polar component were combined, the solvent was removed and the residue was crystallized from diisopropyl ether to give 1.23 g (24%) of white crystals, mp 90-92°C: $[\alpha]_D^{26} -26^\circ \pm 1$ (c, 1.067, CH₃OH) assigned L-arabino- diastereomer (33). Anal. Found: C, 67.0; H, 10.6; N, 8.0.

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