

The Efficient, Enantioselective Synthesis of Aza Sugars from Amino Acids. 1. The Polyhydroxylated Pyrrolidines

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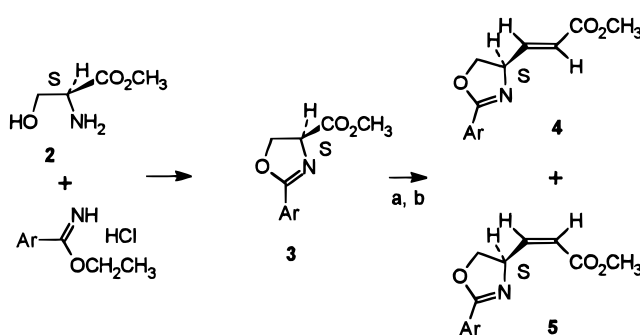
Beginning with (+)-serine or (–)-serine, as appropriate, convenient, high-yield, enantioselective synthesis of all eight stereoisomeric 2-hydroxymethyl-3,4-dihydropyrrolidines (the enantiomeric pairs of iminoribitol, -arabinitol, -xylitol, and -lyxitol) can be effected. The absolute configuration of the starting amino acid defines the set of azasugars produced.

Introduction

It is now clear that carbohydrates mediate the related properties of cell–cell recognition (necessary for cellular aggregation and differentiation)³ and cell–cell fusion (necessary for the subsequent transmission of information).⁴ Glycosidases,⁵ intimately involved in those and related processes, have been shown to be inhibited by some of the members of the group of eight stereoisomeric 2-(hydroxymethyl)-3,4-dihydropyrrolidines, **1**, and related nitrogenous materials. It has even been suggested⁴ that these and other aminosugars could bind directly to viral or host–cell carbohydrate receptors to produce the results of their biological activity. Exploration of their mode(s) of action has only begun.⁶

Both carbohydrate and noncarbohydrate precursors have been employed in syntheses of the members of the pairs of enantiomers of iminoribitol,^{7,8} -arabinitol,^{9,10}

Scheme 1^a



^a DIBAL-H, ROH quench; (b) (C₆H₅)₃P=CHCO₂CH₃.

-xylitol,^{11,12} and -lyxitol.^{13,14} In general, the routes are complex and it is possible that this may have impeded exploration of their full potential.

We report here high-yield, convenient, short, stereoselective syntheses to all of the isomers of **1**, the final stereochemistry of which is defined by the enantiomer of methyl serinate, **2**, with which the synthesis is begun.¹⁵

Results and Discussion

As shown in Scheme 1, when the known,¹⁶ readily available 4-(carbomethoxy)-2-phenyl-Δ²-oxazoline, **3**, de-

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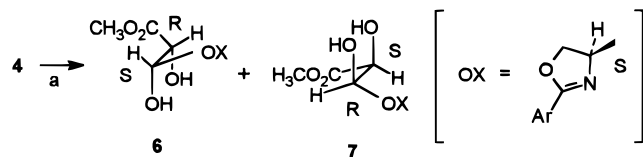
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(15) Within experimental error, both L- and D-serine yield comparable results. The graphics present the synthetic route showing only the L-isomer for purposes of clarity.

Scheme 2^a

^a OsO₄ and NMO or (DHQ)₂PHAL [(DHQD)₂PHAL].

rived from L-serine¹⁵ methyl ester, **2**, is treated with a slight excess of DIBAL-H at low temperature, reduction to the aldehyde occurs. As the aldehyde is labile, an alcohol quench of the reaction mixture is followed, in the same flask, by direct addition of (carbomethoxymethylene)triphenylphosphorane. This results in the formation of a mixture of (S)-(+)-methyl (E)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-2-propenoate, **4**, ([α]_D²⁰ = +60.2°, *c* = 0.018 in CHCl₃), and the corresponding (S)-(–)-methyl (Z)-isomer **5**, ([α]_D²⁰ = –49.5°, *c* = 0.094 in CHCl₃).

Interestingly, the total yield of the mixture of isomers, and their ratio can be varied by altering the conditions of the alcohol quench and the subsequent Wittig reaction. For example, if the reaction mixture is quenched with *tert*-butanol before (carbomethoxymethylene)triphenylphosphorane is added, **4** and **5** are produced in an overall yield of 83% and in a 1.5:1 ratio, respectively. Alternatively, quenching the reaction with methanol but holding everything else the same, provides a 72% yield of the mixture of **4** and **5** but now in a 1:8.5 ratio.

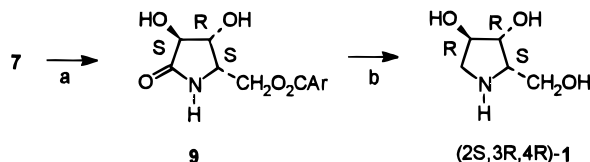
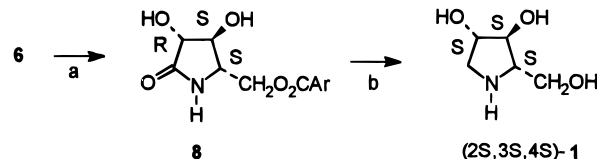
The isomeric alkenes are easily separated by column chromatography.

As shown in Scheme 2, treatment of the (E)-isomer, **4**, in aqueous acetone with a catalytic amount of osmium tetroxide and the *N*-oxide of *N*-methylmorpholine (NMO) at room temperature yields (71%) a mixture of the diol esters **6** (2*R*,3*S*,4*S*; [α]_D²⁰ = –1.2°, *c* = 0.006 in CH₃OH) and **7** (2*S*,3*R*,4*S*; [α]_D²⁰ = +73.9°, *c* = 0.009 in CH₃OH) in a 1.6:1 ratio. The diastereomers are readily separated by column chromatography.

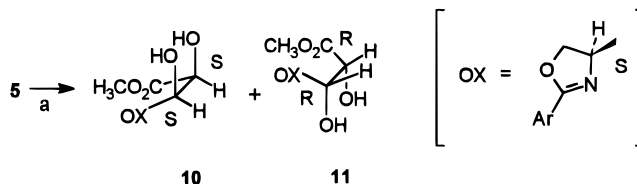
Several attempts to induce preferential formation of one of the diastereomers through stereoselective oxidation of **4** with the quinine-derived, commercially available (DHQ)₂PHAL¹⁷ reagent in the presence of osmium tetroxide produced, in the best case, 65% of **6** and less than 5% of **7**. Interestingly, similar results anticipated with the related (DHQD)₂PHAL reagent were not observed and improvement (both yield and stereochemical outcome) over NMO/OsO₄ was not achieved.

As shown in Scheme 3, when the diol **6** is treated with aqueous acid, hydrolysis of the oxazoline and recyclization to the 3,4-dihydroxy-5-(hydroxymethyl)pyrrolidone benzoate ([α]_D²⁰ = –47.6°, *c* = 0.006 in CH₃OH) (3*R*,4*S*,5*S*)-**8** occurs in 61% yield. The structure of **8** is confirmed by X-ray crystallography.¹⁸ The diastereomer of **6**, the diol **7**, produces the corresponding ester ([α]_D²⁰ = –110°, *c* = 0.006 in CH₃OH) (3*S*,4*R*,5*S*)-**9** under the same conditions in 60% isolated yield.

Then, the lactam-ester **8**, with an excess of borane in tetrahydrofuran, cleanly undergoes reduction of both carbonyl functionalities simultaneously and quantita-

Scheme 3^a

^a Aqueous HCl; (b) B₂H₆/THF.

Scheme 4^a

^a OsO₄ and NMO or (DHQ)₂PHAL [(DHQD)₂PHAL].

tively to yield the known¹⁰ L-iminoarabinitol [(2*S*,3*S*,4*S*)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine], **1**, ([α]_D²⁰ = –11.9°, *c* = 0.044 in CH₃OH; with the corresponding hydrochloride salt, [α]_D²⁰ = –28.8°, *c* = 0.049 in H₂O; for the enantiomer^{9a} [α]_D²⁰ = +7.8°, *c* = 0.46 in H₂O and for the enantiomeric hydrochloride salt,^{9a} [α]_D²⁰ = +37.9°, *c* = 0.53 in H₂O).

A diastereomer of L-iminoarabinitol, the known¹² L-iminoxylitol [(2*S*,3*R*,4*R*)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine], **1**, ([α]_D²⁰ = –4.4°, *c* = 0.010 in CH₃OH; for the corresponding hydrochloride salt, [α]_D²⁰ = –8.6°, *c* = 0.010 in H₂O; lit.^{12b} [α]_D²² = –1.3°, *c* = 0.540 in H₂O) is obtained in 91% yield from **9** in the same way. Then, in direct compliment to the above sequence of reactions, treatment of the (Z)-isomer **5** with osmium tetroxide as shown in Scheme 4 produces a mixture of the diol esters **11** (2*R*,3*R*,4*S*; [α]_D²⁰ = +48.3°, *c* = 0.009 in CH₃OH) and **10** (2*S*,3*S*,4*S*; [α]_D²⁰ = +51.8°, *c* = 0.007 in CH₃OH) in a 3.2:1 ratio (73% overall). As before, these isomers are readily separated by column chromatography.

Here too, several attempts to induce preferential formation of one of the diastereomers through stereoselective dihydroxylation met with limited success. Thus, treatment of **5** with (DHQD)₂PHAL¹⁷ yields 85% of the isomer **11**. However, use of (DHQ)₂PHAL produces only 17% of **10** and 64% of **11**!

As shown in Scheme 5, on treatment of the diol **10** with aqueous acid, hydrolysis and recyclization to the 3,4-dihydroxy-5-(hydroxymethyl)pyrrolidone benzoate (3*S*,4*S*,5*S*)-**12** occurs in 98% yield.¹⁹ The diastereomeric diol **11** produces the corresponding ester ([α]_D²⁰ = –35.9°, *c* = 0.005 in CH₃OH) (3*R*,4*R*,5*S*)-**13** in 97% isolated yield under the same conditions.

Then, reduction of the lactam and removal of the benzoate is accomplished with borane in THF in 86% yield to produce the known⁸ L-iminoribitol [(2*S*,3*S*,4*R*)-

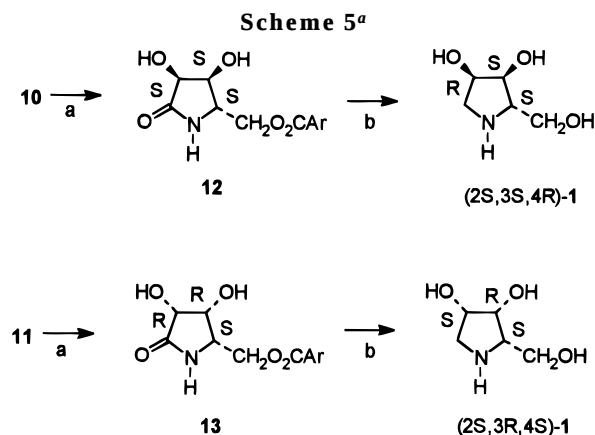
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(18) The X-ray crystal structure of **8** is particularly interesting as there are four molecules in the asymmetric unit. Complete details are provided in the Supporting Information. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(19) This isomer is extraordinarily insoluble in a variety of common and uncommon solvents and its optical rotation was not taken.

(20) ¹H and ¹³C NMR spectra for intermediates and IR spectra for intermediates and azasugars **1** are provided at: http://astro.ocis.temple.edu/~dalton/azasugar_1.html.



^a Aqueous HCl; (b) B₂H₆/THF.

3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine], **1**, ($[\alpha]^{20}_D = -30.5$, $c = 0.039$ in CH₃OH; and for the corresponding hydrochloride salt $[\alpha]^{20}_D = -62.3$, $c = 0.006$ in H₂O, lit.⁸ $= -59.0$, $c = 0.59$ in H₂O). Its diastereomer, the known¹⁴ L-iminolixitol [(2S,3R,4S)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine], **1**, ($[\alpha]^{20}_D = -12.9^\circ$, $c = 0.039$ in CH₃OH; for the hydrochloride salt, $[\alpha]^{20}_D = -13.2$, $c = 0.014$ in H₂O; lit.¹⁴ $[\alpha]^{20}_D = -17.2^\circ$, $c = 0.4$ in H₂O) is obtained in 96% yield from **13** with the same reagents.

Conclusion

The synthesis of all eight (8) isomeric 2-(hydroxymethyl)-3,4-dihydropyrrolidines (the enantiomeric pairs of iminoribitol, -arabinitol, -xylitol, and -lyxitol) from L- or D-serine methyl ester has been effected. Although separation of isomers has proved simple in both of the steps in the syntheses where two compounds form (a single isomer forming in each of the others), it has also been shown that the composition of the mixture can be adjusted by changing the conditions under which the reaction is carried out. In the first of the two isomer-generating steps, the Wittig reaction, simply modifying the solvent substantially changes the (*E*)/(*Z*) ratio. In the second isomer-generating step, suprafacial dihydroxylation of the each of the alkenes (separately) has also been shown to be amenable to adjustment. Again, although it is clear that the ratio can be modified, significant developmental work remains.

Experimental Section

General. Satisfactory elementary analysis (Galbraith Laboratories, Knoxville, TN) and/or high resolution mass spectrometric analysis (The Pennsylvania State University, College Park, PA or Drexel University, Philadelphia, PA) have been obtained for all new compounds. ¹H NMR spectra were obtained at 300 MHz and ¹³C NMR at 75 MHz, and chemical shifts are reported in parts per million (ppm), δ , from TMS = 0.00 ppm. NMR spectra of the imino-sugars **1**, along with the X-ray crystallographic data are provided in the Supporting Information. Infrared (FT-IR) spectra were taken as neat oils (for noncrystalline materials) or as KBr pellets for crystalline samples, and those spectra along with the ¹H and ¹³C NMR spectra of the reported intermediates can be obtained by mail or from the website of the senior author (<http://astro.ocis.temple.edu/~dalton>). Solvents, reactive reagents, and column materials were purchased from Acros Chemical, Fisher Scientific, and/or Aldrich Chemical Companies. Solvents were distilled under argon prior to use. L- and D-serine were obtained from Acros Chemical Co., through Fisher Scientific, Pittsburgh, PA.

D-Serine Methyl Ester Hydrochloride. Acetyl chloride (100 g, 1.27 mol) was slowly added, dropwise, to cold (ice-bath)

methanol (700 mL) with stirring. Ten minutes later, with continued stirring, D-serine (49.0 g, 0.472 mol) was added in one portion and the reaction mixture brought to reflux on the steam bath. Heating was continued for 2.5 h, the solvent removed at reduced pressure, and the resulting methyl ester hydrochloride (73.5 g, 100%) recrystallized from methanol.

Oxazoline Methyl Ester, 3. L-Serine methyl ester hydrochloride (25 g, 161 mmol) was suspended in dry methylene chloride (350 mL) and triethylamine (28 mL, 20.3 g, 200 mmol) added. When the dissolution of the amine hydrochloride was complete, benzimino ethyl ether hydrochloride (29.8 g, 162 mmol) was added as one portion. The reaction mixture was heated at reflux on the steam bath for 4 h and then stirred at room temperature, under argon, overnight. The pink reaction mixture was extracted twice with saturated sodium bicarbonate, and the combined aqueous extracts were back washed twice with half its volume of methylene chloride. The combined methylene chloride extracts were washed with brine, dried over magnesium sulfate, and filtered, and the solvent was removed at reduced pressure. Flash chromatography on silica gel (eluted with 1:1 ether:petroleum ether) provided the known¹⁶ oxazoline methyl ester in 80% yield (26.4 g, 128.8 mmol, $[\alpha]^{20}_D = +117.2^\circ$, $c = 0.053$ in CHCl₃). ¹H NMR (²HCCl₃) δ 7.98–8.01 (m, 2H); 7.48–7.54 (m, 1H); 7.39–7.45 (m, 2H); 4.97 (dd, $J = 7.8, 10.5$, 1H); 4.71 (dd, $J = 8.7, 8.1$, 1H); 4.60 (dd, $J = 10.5, 8.7$, 1H); 3.83 (s, 3H).

(S)(+)-methyl (E)-3-(4,5-Dihydro-2-phenyl-4-oxazolyl)-2-propenoate (4) and (S)(-)-Methyl (Z)-3-(4,5-Dihydro-2-phenyl-4-oxazolyl)-2-propenoate (5). The oxazoline methyl ester **3** (26.5 g, 129 mmol) in dry toluene (800 mL) was cooled to -78°C under an argon atmosphere and DIBAL-H (1.5 M, 137 mL) was added slowly, keeping the temperature of the toluene solution below -70°C throughout. After stirring at -78°C for an additional 3 h, methanol (100 mL) was added, again keeping the temperature below -70°C , to terminate the reaction, and 30 min later, (carbomethoxymethylene)-triphenylphosphorane (48.5 g, 150 mmol) in methanol (300 mL) was added and the reaction solution allowed to warm to room temperature. After stirring overnight, the solution was diluted with diethyl ether (600 mL) and extracted (2 $\times$ 150 mL) with aqueous sodium hydroxide (15%), twice (2 $\times$ 150 mL) with saturated sodium bicarbonate, and twice (2 $\times$ 150 mL) with brine. The solvent mixture was removed at reduced pressure and the residue suspended in light petroleum ether (300 mL). The crystalline triphenylphosphine oxide was removed by filtration and the residue, after removal of the solvent, chromatographed on silica gel, eluting with 80:20 ether:petroleum ether. The mixture (72% of theory) was 64% **5** (19.0 g) and 8.4% **4** (2.5 g). Use of *tert*-butyl alcohol changes the ratio of **4**:**5** to 1.5:1 (83% total yield).

For the *E* isomer, **4**, colorless oil, R_f 0.17, silica gel, 20:80 diethyl ether:petroleum ether, $[\alpha]^{20}_D = +60.2^\circ$, $c = 0.018$ in CHCl₃. ¹H NMR (²HCCl₃) δ 7.96–8.00 (m, 2H); 7.49–7.54 (m, 1H); 7.40–7.46 (m, 2H); 7.00 (dd, $J = 6.3, 15.6$, 1H); 6.11 (dd, $J = 1.5, 15.6$, 1H); 4.95–5.03 (m, 1H); 4.62 (dd, $J = 9.9, 10.2$, 1H); 4.20 (dd, $J = 8.1, 8.4$, 1H); 3.75 (s, 3H). ¹³C NMR (²HCCl₃) δ 166.58, 165.33, 146.67, 131.75, 128.39, 127.12, 122.14, 71.72, 66.74, 51.68. IR (neat film, cm⁻¹) 1722.2, 1650.9, 1603.1, 1580.0, 1495.6, 1450.3, 1359.6, 1280.5, 1192.8, 1082.4, 1025.5, 974.4, 923.7, 864.9, 781.5, 756.0, 696.7. HRMS calcd for C₁₃H₁₃NO₃ 231.0895. Found $[M]^+$ 231.0888.

For the *Z* isomer, **5**, colorless oil, R_f 0.39, silica gel, 20:80 diethyl ether:petroleum ether, $[\alpha]^{20}_D = -49.5^\circ$, $c = 0.094$ in CHCl₃. ¹H NMR (²HCCl₃) δ 7.96–7.99 (m, 2H); 7.48–7.52 (m, 1H); 7.40–7.46 (m, 2H); 6.44 (dd, $J = 7.2, 11.1$, 1H); 5.92 (dd, $J = 11.4, 1.8$, 1H); 5.71–5.80 (m, 1H); 4.87 (dd, $J = 9.9, 10.5$, 1H); 4.10 (dd, $J = 8.4, 8.7$, 1H); 3.76 (s, 3H). ¹³C NMR (²HCCl₃) δ 166.17, 165.29, 151.10, 131.50, 128.31, 127.52, 120.03, 73.38, 65.15, 51.44. IR (neat film, cm⁻¹) 1717.9, 1651.4, 1603.1, 1580.0, 1496.1, 1449.8, 1396.3, 1356.3, 1204.9, 1084.3, 1026.0, 965.2, 896.3, 819.6, 780.5, 696.2. HRMS calcd for C₁₃H₁₃NO₃ 231.0895. Found $[M]^+$ 231.0888.

For (R)(-)-Methyl (E)-3-(4,5-Dihydro-2-phenyl-4-oxazolyl)-2-propenoate (*ent*-4) and (R)(+)-Methyl (Z)-3-(4,5-Dihydro-2-phenyl-4-oxazolyl)-2-propenoate (*ent*-5) from D-Serine. Prepared as with the L-isomer of serine, *ent*-4 has $[\alpha]^{20}_D = -51.5^\circ$, $c = 0.010$ in CHCl₃. HRMS calcd for

$C_{13}H_{13}NO_3$ 231.0895. Found $[M]^+$ 231.0884. For *ent*-**5**, $[\alpha]^{20}_D = +47.7^\circ$, $c = 0.013$ in $CHCl_3$. HRMS calcd for $C_{13}H_{13}NO_3$ 231.0895. Found $[M]^+$ 231.0894.

Preparation of the Diol Esters 6 and 7. The *E*-alkene **4** (2.14 g, 9.3 mmol) in acetone (40 mL) and water (10 mL) was treated with *N*-methylmorpholine *N*-oxide (NMO) monohydrate (1.63 g, 12.0 mmol) and osmium tetroxide (1.0 mL of a 4% aqueous solution). Stirring was continued for 36 h at room temperature, and the reaction was terminated by adding a saturated sodium bisulfite solution (5.0 mL) and stirring the resulting reaction mixture for an additional 30 min. The products were isolated by extracting the aqueous solution with an equal volume of ethyl acetate in three portions, combining the resulting solutions of organic solvents, drying them over sodium sulfate, filtering, and removing the solvent at reduced pressure.

Diol **6**, mp 183 °C, from ethanol, 1.06 g, 4 mmol, 43%, $[\alpha]^{20}_D = -1.2^\circ$, $c = 0.006$ in CH_3OH . 1H NMR ($C^2H_3O^2H$): 7.91–7.95 (m, 2H), 7.50–7.56 (m, 1H), 7.14–7.47 (m, 2H), 4.44–4.63 (m, 4H), 4.00 (dd, $J = 5.7, 2.1$, 1H), 3.76 (s, 3H); ^{13}C NMR ($C^2H_3O^2H$): 173.4, 165.7, 131.5, 128.1, 128.0, 127.1, 73.7, 72.1, 69.5, 67.8, 51.1; IR (KBr pellet, cm^{-1}) 3330.8, 1748.4, 1643.2, 1449.4, 1363.6, 1274.9, 1142.7, 1104.2, 736.8, 694.3. HRMS calcd for $[C_{13}H_{15}NO_5 + H]^+$ 266.1028478. Found $[M + H]^+$ 266.103644. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.96; H, 5.87; N, 5.21.

Diol **7**, mp 106 °C, 668.5 mg, 2.5 mmol, 27%, $[\alpha]^{20}_D = +73.9^\circ$, $c = 0.009$ in CH_3OH . 1H NMR ($C^2H_3O^2H$): 7.91–7.95 (m, 2H), 7.50–7.56 (m, 1H), 7.14–7.47 (m, 2H), 4.48–4.56 (m, 3H), 4.34 (d, $J = 3.0$, 1H), 3.99 (dd, $J = 5.1, 3.0$, 1H), 3.76 (s, 3H); ^{13}C NMR ($C^2H_3O^2H$): 173.1, 165.7, 131.5, 128.1, 128.0, 127.1, 73.1, 71.9, 69.3, 68.6, 51.2; IR (KBr pellet, cm^{-1}) 3356.9, 1732.9, 1656.8, 1449.4, 1359.7, 1244.0, 1139.8, 1093.6, 1045.3, 967.2, 808.1, 770.5, 694.3. HRMS calcd for $[C_{13}H_{15}NO_5 + H]^+$ 266.1028478. Found $[M + H]^+$ 266.103622. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.86; H, 5.78; N, 5.07.

The diols **6** and **7** were separated and purified by silica gel flash column chromatography (eluting with 98:2 $CH_3Cl:CH_3OH$).

Asymmetric Dihydroxylation of 4 with (DHQD)₂PHAL. The alkene **4** (216 mg, 0.94 mmol), (DHQD)₂PHAL (Aldrich, 7.3 mg, 9.4×10^{-3} mmol), $K_3Fe(CN)_6$ (823 mg, 2.84 mmol), potassium carbonate (387.3 mg, 2.8 mmol), and methansulfonamide (89 mg, 0.94 mmol) were dissolved in *tert*-butanol (5.0 mL) and water (5.0 mL) at room temperature with stirring. With stirring, osmium tetroxide (4% in water, 70 μ L) was added and stirring was continued at room temperature for 48 h before saturated sodium bisulfite solution was added to quench the reaction. After stirring for an additional 20 min, the aqueous solution was extracted with three times its volume of ethyl acetate in three portions. The combined organic extracts were dried over sodium sulfate and filtered and the solvent evaporated. The diols **6** (*vide supra*) (166 mg, 0.63 mmol, 67%) and **7** (11 mg, 0.04 mmol, 4.5%) ratio 15:1 were separated and purified by silica gel flash column chromatography by elution with 98:2 $CHCl_3:CH_3OH$.

Preparation of the Diol Esters 10 and 11. The *Z*-alkene **5** (10.67 g, 46.2 mmol) in acetone (80 mL) and water (10 mL) was treated with *N*-methylmorpholine *N*-oxide (NMO) monohydrate (9.35 g, 69.2 mmol) and osmium tetroxide (6.8 mL of a 4% aqueous solution). Stirring was continued for 16 h at 0 °C, and the reaction was terminated by adding a saturated sodium bisulfite solution (10.0 mL) and stirring the resulting reaction mixture for an additional 30 min. The products were isolated by extracting the aqueous solution with an equal volume of ethyl acetate in four portions, combining the resulting solutions of organic solvents, drying them over sodium sulfate, filtering, and removing the solvent at reduced pressure. Diol **11**, mp 159 °C, 6.79 g, 25.6 mmol, 55.5%, $[\alpha]^{20}_D = +48.3^\circ$, $c = 0.009$ in CH_3OH . 1H NMR ($C^2H_3O^2H$): 7.89–7.93 (m, 2H), 7.50–7.56 (m, 1H), 7.40–7.45 (m, 2H), 4.44–4.60 (m, 3H), 4.28 (d, $J = 4.8$, 1H), 4.05 (dd, $J = 4.2, 4.2$, 1H), 3.75 (s, 3H); ^{13}C NMR ($C^2H_3O^2H$): 172.9, 165.5, 131.4, 128.0, 127.9, 127.2, 73.7, 73.1, 68.6, 67.1, 51.0; IR (KBr pellet, cm^{-1}) 3444.6, 1736.8, 1644.2, 1450.4, 1370.3, 1296.0, 1238.2, 1109.0, 989.4, 949.9, 730.9, 694.3. HRMS calcd for $[C_{13}H_{15}NO_5 + H]^+$

266.1028478. Found $[M + H]^+$ 266.103391. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.33; H, 5.86; N, 5.20.

Diol **10**, mp 157 °C, 2.15 g, 8.1 mmol 17.5%, $[\alpha]^{20}_D = +51.8^\circ$, $c = 0.007$ in CH_3OH . 1H NMR ($C^2H_3O^2H$): 7.93–7.97 (m, 2H), 7.50–7.55 (m, 1H), 7.40–7.45 (m, 2H), 4.50–4.66 (m, 3H), 4.42 (dd, $J = 7.8, 7.8$, 1H), 3.75 (s, 3H); ^{13}C NMR ($C^2H_3O^2H$): 173.8, 165.8, 131.3, 128.1, 128.0, 127.3, 73.0, 72.4, 69.2, 66.9, 51.0; IR (KBr pellet, cm^{-1}) 3393.5, 1710.7, 1640.4, 1449.4, 1373.2, 1238.2, 1063.6, 1034.7, 954.7, 687.5. HRMS calcd for $[C_{13}H_{15}NO_5 + H]^+$ 266.1028478. Found $[M + H]^+$ 266.102911. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.25; H, 5.80; N, 5.22. Diols **10** and **11** were separated and purified by flash chromatography (eluting with 98.5:1.5 $CH_3Cl:CH_3OH$).

Asymmetric Dihydroxylation of 5 with (DHQD)₂PHAL. The alkene **5** (290 mg, 1.25 mmol), (DHQD)₂PHAL (Aldrich, 9.8 mg, 12.5×10^{-3} mmol), $K_3Fe(CN)_6$ (1.24 g, 3.77 mmol), potassium carbonate (520 mg, 3.8 mmol), and methansulfonamide (89 mg, 0.94 mmol) were dissolved in *tert*-butanol (5.0 mL) and water (5.0 mL) at room temperature with stirring. With stirring, osmium tetroxide (4% in water, 74 μ L) was added and stirring was continued at 0 °C for 18 h before saturated sodium bisulfite solution was added to quench the reaction. After stirring for an additional 20 min, the aqueous solution was extracted with three times its volume of ethyl acetate in three portions. The combined organic extracts were dried over sodium sulfate and filtered and the solvent evaporated. The diol **11** (*vide supra*) (281 mg, 1.06 mmol, 84.8%) was purified by silica gel flash column chromatography by elution with 98:2 $CHCl_3:CH_3OH$.

Preparation of the Lactam 8. With stirring, the diol **6** (2.646 g, 99.4 mmol) in THF (100 mL) was treated with aqueous hydrochloric acid solution (1.5 M, 20 mL). After 24 h at room temperature, the reaction mixture was neutralized by addition of solid sodium bicarbonate, the solvent removed at reduced pressure, and the product isolated and purified from the residue by flash column chromatography over silica gel. The elution was begun with 10:90 $CH_3OH:CHCl_3$ mixture and this was followed by a mixture of 60:20:10:10 $CH_2Cl_2:CH_3CH_2OH:CH_3OH:NH_4OH$. Lactam **9**, a white solid (1.5148 g, 60.4%, mp 138 °C was recrystallized in acetone/chloroform. $R_f = 0.17$ in 10:90 $CH_3OH:CHCl_3$, $[\alpha]^{20}_D = -47.6^\circ$ ($c = 0.006$, methanol). 1H NMR ($C^2H_3O^2H$): 8.04–8.08 (m, 2H), 7.58–7.63 (m, 1H), 7.44–7.49 (m, 2H), 4.60 (dd, $J = 11.7, 3.0$, 1H), 4.32 (dd, $J = 12.0, 5.4$, 1H), 4.17 (d, $J = 7.5$, 1H), 4.05 (dd, $J = 7.2, 7.5$, 1H), 3.63 (ddd, $J = 7.2, 5.4, 3.0$, 1H); ^{13}C NMR ($C^2H_3O^2H$): 175.0, 166.3, 133.0, 129.5, 129.1, 128.2, 75.8, 75.5, 63.4, 56.3; IR (KBr pellet, cm^{-1}) 3369.4, 3289.4, 1672.1, 1600.8, 1453.8, 1384.8, 1323.1, 1280.6, 1129.2, 1102.2, 891.0, 707.8, 630.6. HRMS calcd for $[C_{12}H_{13}NO_5 + H]^+$ 252.0871978. Found $[M + H]^+$ 252.087132. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.19; H, 5.43; N, 5.50.

Preparation of Lactam 9. The diol **7** (95.2 mg, 0.36 mmol) was dissolved in methanol (3 mL) at room temperature and aqueous 1 N HCl (1.0 mL) added. The resulting solution was permitted to stir at room temperature for 20 h and then neutralized by addition of solid sodium bicarbonate. The solvent was evaporated, and the product was isolated and purified by flash column chromatography over silica gel, initially eluted with 10:90 $CH_3OH:CHCl_3$ and then a 60:20:10:10 mixture of $CH_2Cl_2:CH_3CH_2OH:CH_3OH:NH_4OH$. Lactam **9**, a white solid (59.8 mg, 66.1%, mp 192 °C, was recrystallized in ethanol, $R_f = 0.15$ ($CH_3OH(10)/CHCl_3(90)$, $[\alpha]^{20}_D = -110^\circ$ ($c = 0.006$, methanol). 1H NMR ($C^2H_3O^2H$): 8.00–8.04 (m, 2H), 7.58–7.63 (m, 1H), 7.46–7.50 (m, 2H), 4.54 (dd, $J = 11.7, 3.3$, 1H), 4.33 (dd, $J = 11.7, 4.8$, 1H), 4.38 (dd, $J = 7.5, 8.1$, 1H), 4.29 (d, $J = 8.1$, 1H), 3.93 (ddd, $J = 7.5, 4.8, 3.3$, 1H); ^{13}C NMR ($C^2H_3O^2H$): 175.0, 166.2, 133.0, 129.3, 129.0, 128.2, 74.5, 74.2, 63.0, 54.4; IR (KBr pellet, cm^{-1}) 3408.9, 3209.4, 1722.3, 1665.4, 1600.6, 1434.0, 1377.1, 1317.3, 1264.2, 1124.4, 1089.7, 1019.3, 920.0, 787.6, 707.8. HRMS calcd for $[C_{12}H_{13}NO_5 + H]^+$ 252.0871978. Found $[M + H]^+$ 252.087232. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.32; H, 5.30; N, 5.40.

Preparation of Lactam 12. Lactam **12** (3.16 g, 126 mmol, 98% of theory) was obtained from diol **10** (3.40 g, 128 mmol)

by the same procedure used in the preparation of lactam **9** from diol **7** above. The product was recrystallized from methanol/diethyl ether with difficulty because of its limited solubility. Optical rotation was not taken because of its limited solubility.

For **12**, mp 212 °C, ^1H NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 8.00–8.05 (m, 2H), 7.58–7.65 (m, 1H), 7.40–7.52 (m, 2H), 4.47 (dd, $J = 11.4$, 4.5, 1H), 4.35 (dd, $J = 11.4$, 5.1, 1H), 4.33 (d, $J = 5.7$, 1H), 4.27 (dd, $J = 5.7$, 1.5, 1H), 3.80 (ddd, $J = 5.1$, 4.5, 1.5, 1H); ^{13}C NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 176.5, 166.0, 133.0, 129.4, 129.1, 128.3, 70.0, 69.9, 64.2, 59.0; IR (KBr pellet, cm^{-1}) 3242.1, 1719.4, 1690.5, 1438.6, 1264.2, 1146.6, 1102.2, 767.6, 706.8. HRMS calcd for $[\text{C}_{12}\text{H}_{13}\text{NO}_5 + \text{H}]^+$ 252.0871978. Found $[\text{M} + \text{H}]^+$ 252.087255. Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.07; H, 5.38; N, 5.59.

Preparation of Lactam 13. Lactam **13**, a white solid (20.0 mg, 0.08 mmol), was obtained from diol **11** (21.8 mg, 0.08 mmol, 98%) by the same procedure which was used in the preparation of lactam **9**. It was recrystallized in acetone/hexanes. $R_f = 0.20$ in 10:90 $\text{CH}_3\text{OH}:\text{CHCl}_3$. For **13**, mp 145 °C, $[\alpha]_D^{20} = -35.9^\circ$ ($c = 0.005$, methanol), ^1H NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 8.06–8.09 (m, 2H), 7.58–7.63 (m, 1H), 7.45–7.51 (m, 2H), 4.60 (dd, $J = 11.4$, 5.1, 1H), 4.43 (dd, $J = 5.4$, 3.6, 1H), 4.40 (dd, $J = 11.1$, 7.8, 1H), 4.27 (d, $J = 5.1$, 1H), 3.95 (ddd, $J = 7.8$, 5.1, 3.6, 1H); ^{13}C NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 176.7, 166.4, 132.9, 129.7, 129.3, 128.1, 71.3, 69.1, 63.8, 54.4; IR (KBr pellet film, cm^{-1}) 3365.5, 1706.9, 1448.4, 1281.6, 1162.4, 1120.5, 712.5. HRMS calcd for $[\text{C}_{12}\text{H}_{13}\text{NO}_5 + \text{H}]^+$ 252.0871978. Found $[\text{M} + \text{H}]^+$ 252.087147; Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 56.31; H, 5.31; N, 5.38.

L-Iminoarabinitol [(2S,3S,4S)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine, 1]. Lactam **8** (252 mg, 1.0 mmol) in THF (5.0 mL) at 0 °C was treated with borane in THF (1.0 M, 15 mL, 15 mmol) and the reaction, under an atmosphere of argon, brought to reflux and heated, with stirring, overnight. The solvent was removed at reduced pressure and methanol added to destroy unreacted borane. The methanol solution was treated with aqueous hydrogen chloride (6 N, 1 mL), slowly added dropwise, and, at room temperature, the solution was stirred for an additional 30 min. Then, solid sodium hydroxide was added until the solution was basic and the product directly isolated (133 mg, 96% of theory) by aqueous solution ion-exchange chromatography on DOWEX 50WX8-100 and a final flash-chromatographic purification over a short silica gel column where it eluted with a 50:20:20:10 mixture of $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{CH}_2\text{OH}:\text{CH}_3\text{OH}:\text{NH}_4\text{OH}$ to yield material with $[\alpha]_D^{20} = -11.9^\circ$, $c = 0.044$ in CH_3OH ; for the enantiomer^{7a} $[\alpha]_D^{20} = +7.8^\circ$, $c = 0.46$ in H_2O . ^1H NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 4.06 (ddd, $J = 5.7$, 3.9, 3.9, 1H), 3.77 (dd, $J = 3.9$, 3.9, 1H), 3.67 (dd, $J = 11.4$, 4.8, 1H), 3.58 (dd, $J = 11.7$, 6.6, 1H), 3.25 (s, NH), 3.08 (dd, $J = 12.3$, 5.7, 1H), 2.97 (ddd, $J = 6.6$, 4.8, 3.9, 1H), 2.80 (dd, $J = 12.3$, 3.9, 1H); ^{13}C NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 78.5, 77.0, 65.3, 61.5, 50.4; IR (neat film, cm^{-1}) 3423, 1645.2, 1530.4, 1422.4, 1206.4, 1115.7. HRMS calcd for $[\text{C}_5\text{H}_{11}\text{NO}_3 + \text{H}]^+$ 134.0817184. Found $[\text{M} + \text{H}]^+$ 134.081568. Found $[\text{M} + \text{H}]^+$ 134.081568. The hydrochloride, obtained on treatment of the free base with 6 N HCl and recrystallized from methanol/acetone had $[\alpha]_D^{20} = -28.8^\circ$, $c = 0.049$ in H_2O (lit.^{7a} for the enantiomeric hydrochloride salt, $[\alpha]_D^{20} = +37.9^\circ$, $c = 0.53$ in H_2O); ^1H NMR ($\text{C}_2\text{H}_2\text{O}$): 4.26 (ddd, $J = 4.5$, 3.3, 2.4, 1H), 4.02 (dd, $J = 3.6$, 3.3, 1H), 3.88 (dd, $J = 12.0$, 5.7, 1H), 3.76 (dd, $J = 12.3$, 8.1, 1H), 3.55 (ddd, $J = 8.1$, 5.7, 3.9, 1H), 3.51 (dd, $J = 12.6$, 4.5, 1H), 3.29 (dd, $J = 12.6$, 2.4, 1H); ^{13}C NMR ($\text{C}_2\text{H}_2\text{O}$): 75.7, 74.3, 66.5, 58.9, 50.0; IR (KBr pellet, cm^{-1}) 3352, 1625.9, 1112.8, 1059.4, 1019.3.

L-Iminoxytilitol [(2S,3R,4R)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine, 1]. Lactam **9** (58.4 mg, 0.23 mmol) in THF (6.0 mL) at 0 °C was treated with borane in THF (1.0 M, 3.5 mL, 3.5 mmol, 15 equiv) and the reaction, under an atmosphere of argon, brought to reflux and heated, with stirring, for 5 h. The solvent was removed at reduced pressure and methanol added to destroy unreacted borane. The methanol solution was treated with aqueous hydrogen chloride (6 N, 1 mL), slowly added dropwise, and, at room temperature, the solution was stirred for an additional 30 min. Then, solid sodium hydroxide was added until the solution was basic and the product directly isolated (21.8 mg, 91% of theory) by ion-

exchange chromatography on DOWEX 50WX8-100 and a final flash-chromatographic purification over a short silica gel column where it was eluted with a 50:20:20:10 mixture of $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{CH}_2\text{OH}:\text{CH}_3\text{OH}:\text{NH}_4\text{OH}$ to yield material with $[\alpha]_D^{20} = -4.4^\circ$, $c = 0.010$ in CH_3OH . ^1H NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 4.13 (m, 1H), 4.07 (m, 1H), 3.75 (dd, $J = 11.4$, 6.3, 1H), 3.63 (dd, $J = 11.4$, 67.2, 1H), 3.35 (m, 1H), 3.28 (dd, $J = 12.9$, 5.1, 1H), 2.78 (dd, $J = 12.9$, 1.8, 1H); ^{13}C NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 75.9, 75.6, 61.7, 58.8, 50.6; IR (neat film, cm^{-1}) 3380, 1654.8, 1420.5, 1048.2. HRMS calcd for $[\text{C}_5\text{H}_{11}\text{NO}_3 + \text{H}]^+$ 134.0817184. Found $[\text{M} + \text{H}]^+$ 134.081675. The hydrochloride, obtained on treatment of the free base with 6 N HCl and recrystallized from methanol/acetone had $[\alpha]_D^{20} = -8.6^\circ$, $c = 0.010$ in H_2O ; ^1H NMR ($\text{C}_2\text{H}_2\text{O}$): 4.32 (d, br, $J = 3.3$, 1H), 4.25 (s, br, 1H), 3.95 (dd, $J = 15.3$, 8.7, 1H), 3.83 (m, 2H), 3.60 (dd, $J = 12.9$, 4.2, 1H), 3.23 (d, br, $J = 12.9$, 1H); ^{13}C NMR ($\text{C}_2\text{H}_2\text{O}$): 74.3, 74.2, 63.0, 57.2, 50.5. IR (KBr pellet, cm^{-1}) 3383, 1625.9, 1412.8, 1308.6, 1101.3, 1047.3, 978.8, 913.2.

L-Iminoribitol [(2S,3S,4R)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine, 1]. As described above for L-iminoarabinatol and L-iminoxylitol, L-iminoribitol (152 mg, 1.13 mmol, 86%) $[\alpha]_D^{20} = -30.5^\circ$, $c = 0.039$ in CH_3OH . ^1H NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 4.06 (ddd, $J = 5.1$, 5.1, 3.9, 1H), 3.79 (dd, $J = 6.9$, 5.1, 1H), 3.66 (dd, $J = 11.7$, 4.2, 1H), 3.54 (dd, $J = 11.7$, 6.0, 1H), 3.26 (s, NH), 3.09 (dd, $J = 12.3$, 5.1, 1H), 3.00 (ddd, $J = 6.9$, 6.0, 4.2, 1H), 2.75 (dd, $J = 12.3$, 3.9, 1H); ^{13}C NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 73.0, 71.1, 62.3, 61.8, 49.9; IR (neat film, cm^{-1}) 3380, 1651.9, 1532.3, 1426.2, 1346.2, 1103.2. HRMS calcd for $[\text{C}_5\text{H}_{11}\text{NO}_3 + \text{H}]^+$ 134.0817184. Found $[\text{M} + \text{H}]^+$ 134.081789. The hydrochloride salt, obtained with 6 N HCl in ethanol had $[\alpha]_D^{20} = -62.3^\circ$, $c = 0.006$ in H_2O . ^1H NMR ($\text{C}_2\text{H}_2\text{O}$): 4.31 (ddd, $J = 3.9$, 3.9, 1.8, 1H), 4.13 (dd, $J = 8.7$, 3.9, 1H), 3.90 (dd, $J = 12.3$, 3.3, 1H), 3.75 (dd, $J = 12.3$, 6.0, 1H), 3.56 (ddd, $J = 8.7$, 6.0, 3.3, 1H), 3.43 (dd, $J = 12.9$, 3.9, 1H), 3.30 (dd, $J = 12.9$, 1.8, 1H); ^{13}C NMR ($\text{C}_2\text{H}_2\text{O}$): 71.1, 69.4, 61.7, 57.9, 49.5. IR (KBr pellet, cm^{-1}) 3395, 163.5, 1418.5, 1339.4, 1141.8, 106.1, 1043.4.

L-Iminolxitol [(2S,3R,4S)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine, 1]. As described above for L-iminoarabinatol, L-iminoxylitol, and L-iminoribitol (24.9 mg, 0.18 mmol, 96%), $[\alpha]_D^{20} = -12.9^\circ$, $c = 0.014$ in CH_3OH . ^1H NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 4.42 (ddd, $J = 7.5$, 7.2, 3.9, 1H), 4.27 (dd, $J = 4.2$, 3.9, 1H), 3.91 (dd, $J = 12.0$, 5.1, 1H), 3.81 (dd, $J = 12.0$, 8.4, 1H), 3.66 (ddd, $J = 8.4$, 5.1, 3.9, 1H), 3.45 (dd, $J = 12.0$, 7.5, 1H), 3.12 (dd, $J = 12.0$, 7.2, 1H); ^{13}C NMR ($\text{C}_2\text{H}_3\text{O}_2\text{H}$): 70.0, 69.8, 62.4, 57.7, 47.0; IR (neat film, cm^{-1}) 3318.3, 1770.5, 1634.5, 1418.5, 1133.1. HRMS calcd for $[\text{C}_5\text{H}_{11}\text{NO}_3 + \text{H}]^+$ 134.0817184. Found $[\text{M} + \text{H}]^+$ 134.081579) was obtained from the lactam **13** (48.9 mg, 0.194 mmol).

The hydrochloride obtained with 6 N HCl in ethanol had $[\alpha]_D^{20} = -13.2^\circ$, $c = 0.014$ in H_2O . ^1H NMR ($\text{C}_2\text{H}_2\text{O}$): 4.44 (ddd, $J = 8.2$, 4.8, 3.9, 1H), 4.29 (dd, $J = 4.2$, 3.9, 1H), 3.93 (dd, $J = 12.0$, 4.8, 1H), 3.84 (dd, $J = 12.0$, 8.2, 1H), 3.69 (ddd, $J = 8.2$, 4.8, 4.2, 1H), 3.48 (dd, $J = 12.0$, 7.5, 1H), 3.27 (s, NH), 3.15 (dd, $J = 12.0$, 7.5, 1H); ^{13}C NMR ($\text{C}_2\text{H}_2\text{O}$): 70.0, 69.8, 62.5, 57.6, 47.0; IR (KBr pellet, cm^{-1}) 3423.4, 1612.4, 1406.9, 1341.4, 1137.9, 1101.2, 1041.5.

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Supporting Information Available: The X-ray crystal structure data for the lactam **8** and ^1H and ^{13}C NMR spectra for the isomers **1** (free bases and hydrochloride salts) (see ref 20) (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.