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Preparation of Aminosaccharides Using Ester-Imine Condensations: Syntheses of Methyl N-Benzoylacosaminide and Methyl N-[Oxo(phenylmethoxy) acetyl]daunosaminide from (S)-Ethyl 3-Hydroxybutyrate

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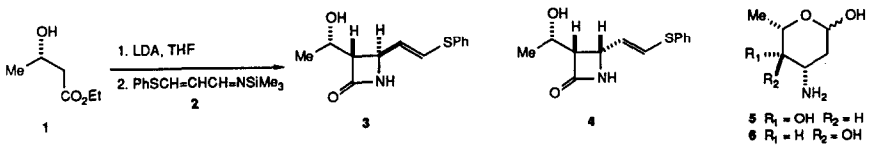
Abstract. The dianion of (S)-ethyl β-hydroxybutyrate (1) was treated with N-trimethylsilyl imine 2 to afford β-lactam 4. The same dianion reacted with N-aryl imine 10 to give β-lactams 11, 12, and 13. A three-step sequence was used to convert 4 into the β-lactam-pyran hybrid 9 while a five-step sequence was developed to transform 11 and 12 into 9. Application of the carboxyinversion reaction to derivatives of 9 afforded protected analogs of the amino-saccharides daunosamine (5) and acosamine (6).

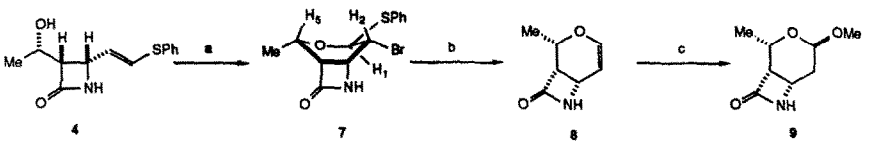
Several years ago we reported that treatment of the dianion of racemic ethyl β-hydroxybutyrate (1) with imine 2 gave a mixture of diastereomeric β-lactams 3 and 4.[3,4] One notable aspect of this transformation was the structural relationship between 3, 4, and the 2,3,6-trideoxy-3-aminohexoses, a large class of aminosaccharides of medicinal importance.[5] For example, β-lactam 4 contains the C(1)-C(6) backbone of daunosamine with the correct stereochemistry at all carbons and the appropriate oxidation state at all carbons save C(4). Insertion of an oxygen into the C(4)-acyl bond with either retention or inversion of configuration would afford intermediates suitable for the preparation of daunosamine (5)[6,7] and acosamine (6)[8,9], respectively. We felt that the development of a



protocol for the transformation of a β-lactam into a vicinal amino alcohol might be of general interest.[10] Thus, we have examined this precedented but little explored process within the context of syntheses of derivatives of aminosaccharides 5 and 6 from β-lactam 4. This paper presents the details of our study.[11,12]

Preparation of β-Lactam-Pyran Hybrids. We began our studies by preparing quantities of β-lactam 4 in optically active form. This was accomplished by treating the dianion of (S)-ethyl β-hydroxybutyrate (1) with 2 as previously described in the racemic series. Although the yield was disappointing, it was possible to prepare gram quantities of 4 in 20% isolated yield without much difficulty.[13] The conversion of 4 into a β-lactam-pyran hybrid suitable for use in the aforementioned oxidation studies was accomplished in three steps (Scheme I). Treatment of 4 with N-bromosuccinimide in dichloromethane gave tetrahydropyran 7 (92%). The stereochemistry of 7 was assigned on the basis of the following NMR evidence. The stereochemical relationship between C(1) and C(2) was suggested by a coupling constant of 8.6 Hz between H_1 and H_2. This was supported by the absence of an NOE between these protons. Furthermore, a large NOE between H_2 and H_5 established their cis relationship and indicates that the pyran ring occupies a boat-like conformation in solution.[14] Treatment of 7 with tri-n-butyltin hydride and AIBN in benzene effected a free radical fragmentation to afford glycal 8 (95%).[15] The structure of 8 was confirmed by X-ray crystallography.[16] Finally, treatment of 8 with methanol in the presence of acidic Dowex-50 ion exchange resin gave 9 (84%).

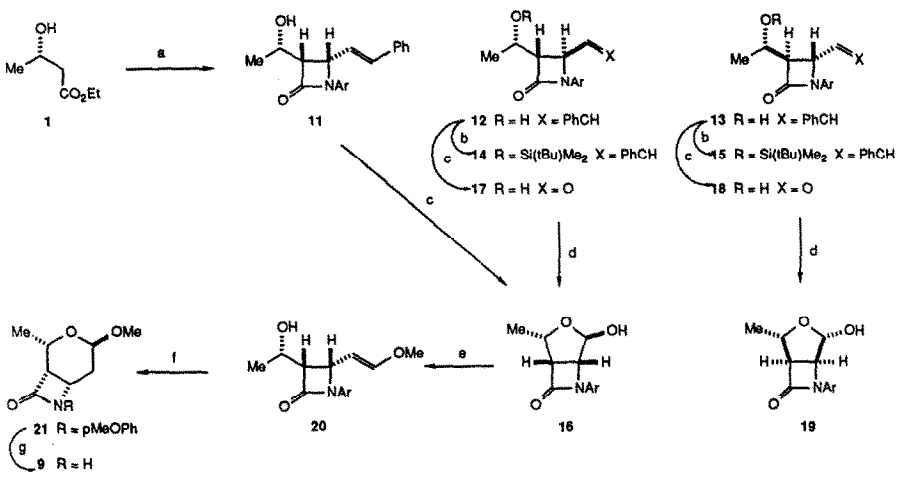
Scheme I



(a) NBS, CH_2Cl_2 (b) nBu_3SnH, AIBN, PhH (c) Dowex-50 (H^+), MeOH

Due to the low yield in the ester-imine condensation (1 + 2 → 4), an alternate route to 9 was developed as outlined in Scheme II. The dianion of 1 reacted with imine 10 to provide a mixture of β-lactams 11-13 in 67% yield as previously reported.[12] Although 11 could be separated from 12 and 13 using column chromatography and the trans β-lactams could be separated after conversion to the corresponding tert-butyldimethysilyl ethers (14 and 15), it was operationally most convenient to continue with the mixture. Sequential treatment of the mixture of 11-13 with ozone and dimethyl sulfide gave hemiacetal 16 and a mixture of trans aldehydes 17 and 18. Isomerization of 17 and 18 to 16 and 19, respectively, was accomplished using 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane. In this manner, the aforementioned mixture of β-lactams 11-13 was converted to 16 and 19 in 68% and 6% yields, respectively. Treatment of 16 with 1.0 equivalent of lithium diisopropylamide followed by 4.0 equivalents of (methoxymethylidene)triphenylphosphorane gave vinyl ether 20 (85%).[17] The olefin geometry was tentatively assigned as trans on the basis of a 12.6 Hz coupling constant between the vinylic protons. Cyclization of 20 using acidic Dowex-50 in methanol gave 21 (98%) and oxidative removal of the p-methoxyphenyl group completed the synthesis of 9 (78%).[18]

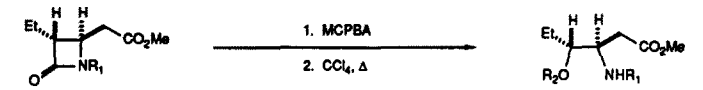
Scheme II



(a) LDA, THF; PhCH=CHCH=NC_6H_4OMe (10) (b) $tBuMe_2SiCl$, DMF, Et_3N (c) O_3; Me_2S (d) DBU, CH_2Cl_2 (e) LDA; Ph_3P=CHOMe (f) MeOH, Dowex-50 (H^+) (g) CAN, CH_3CN, H_2O

Although the sequence to 9 outlined in Scheme II is longer (6 steps from 1) than the route described in Scheme I (4 steps from 1), it proceeds in approximately twice the overall yield (29% compared to 14%).

Studies Regarding the β-Lactam to Vicinal Amino Alcohol Transformation: Preparation of Aminosaccharide Derivatives 5 and 6. Our attempts to insert an oxygen into the C(4)-acyl bond in 9 were based on the reported conversion of 22 to 23 during the course of carbapenem degradation studies.[19] This transformation presumably occurs by opening of the β-lactam by m-chloroperbenzoic acid followed by a carboxyinversion reaction. During the course of model studies, reactions between several derivatives of β-lactam 24a and a variety of oxidizing agents were examined. For example, treatment of imides 24b and 24c with variants of the m-chloroperbenzoic acid system used to convert 22 to 23 gave no formal Baeyer-Villiger oxidation.[20,21] On the other hand, imide 24d did give 25c

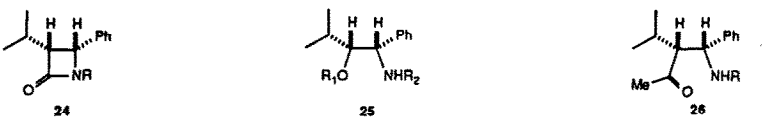


22 23

R_1 = C(O)CO_2PNB PNB = p-nitrobenzyl R_2 = C(O)OC(O)C_6H_4mCl

in 51% overall yield after hydrolysis of intermediate amide **25a** and acetylation of the resulting amino alcohol **25b**.[22]

The conversion of β-lactams of type **24** to methyl ketones followed by Baeyer-Villiger oxidation was also examined. Thus, treatment of **24b** and **24c** with methylmagnesium bromide and methyllithium, respectively, gave **26a** (77%) and **26b** (48%). Baeyer-Villager oxidation of these substrates, however, met with failure. For example, treatment of **26a** with buffered trifluoroperacetic acid in dichloromethane gave only 6% of a Baeyer-Villiger product along with isomerized starting ketone.[21a]



24 **25** **26**

a R = H a R_1 = H R_2 = $COCO_2CH_2Ph$ a R = COPh

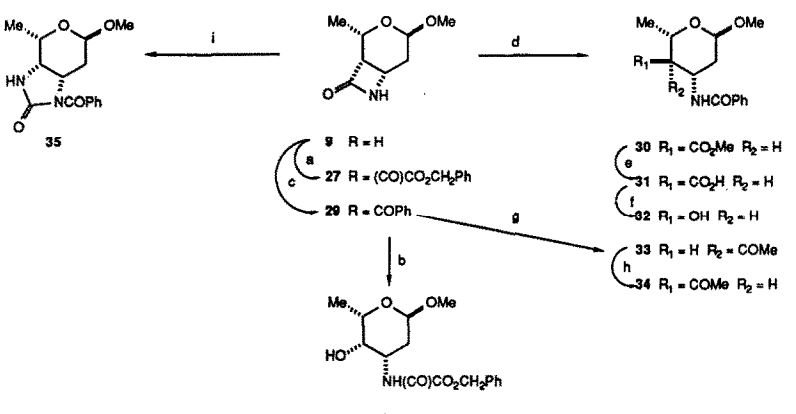
b R = COPh b R_2 = R_2 = H b R = Ts

c R = Ts c R_1 = R_2 = COMe

d R = $C(O)CO_2CH_2Ph$

In the final analysis, it appeared that **9** would best be converted to aminosaccharide derivatives of type **5** and **6** by way of imide **27**. The preparation of **27** was accomplished in 98% yield as shown in Scheme III. Treatment of **27** with buffered *m*-chloroperbenzoic acid did afford daunosamine derivative **28** in 35% yield. Although **28** was not converted to daunosamine, the structure of this material was apparent from spectral data.

Scheme III



35

9 R = H

27 R = $(CO)CO_2CH_2Ph$

29 R = COPh

30 R_1 = CO_2Me R_2 = H

31 R_1 = CO_2H R_2 = H

32 R_1 = OH R_2 = H

33 R_1 = H R_2 = COMe

34 R_1 = COMe R_2 = H

28

(a) $PhCH_2OC(O)COCl$, Et_3N (b) MCPBA, Na_2HPO_4, $(ArS)_2$, CCl_4, Δ (c) PhCOCl, Et_3N (d) MeOH, DBU, Δ (e) LiOH, MeOH (f) MCPBA, DCC; CCl_4, Δ; KOH, MeOH (g) MeLi, THF (h) DBU, PhH, Δ (i) Et_3NH^+ N_3^-, NaN_3, acetone, Δ

The conversion of **9** to a derivative of acosamine (**6**) required that an oxygen be inserted in the C(4)-acyl bond with inversion of configuration. Thus, **9** was treated with benzoyl chloride and the resulting imide **29** (98%) was converted to ester **30** (71%) upon exposure to 1,8-diazabicyclo[5.4.0]-undec-7-ene in methanol under reflux. Ester hydrolysis produced acid **31** (97%) and a carboxyinversion reaction[23] afford methyl *N*-benzoylacosaminide (**32**) in 32% yield.[24]

We also briefly investigated reactions of imide **29** with other nucleophiles. Thus, treatment of **29** with methyllithium in tetrahydrofuran gave methyl ketone **33** (65%) along with recovered **29** (28%) and epimerization of **33** gave the thermodynamically more stable C(4)-isomer **34** (93%). In accord with the aforementioned study with **26a**, attempted Baeyer-Villiger oxidation of these substrates met with failure. Finally, treatment of **29** with sodium azide and triethylammonium azide in acetone gave cyclic urea **35** in 98% yield, illustrating the potential for using β-lactams as precursors to pyrans containing vicinal diamine structures.[25]

In summary, enantioselective syntheses of daunosamine derivative 28 (9.8% yield from 1 in 8 steps) and acosamine precursor 32 (6.6% from 1 in 10 steps) have been accomplished. The syntheses feature an unusual, but unfortunately low yield method for introduction of the C(4) hydroxyl group. The general plan, however, does provide ready access to 2,3,4,6-tetradeoxy-3-aminohexose derivatives with carbon or nitrogen substituents at C(4).

Experimental

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded on Varian Associates EM-390 (90 MHz), Bruker WP-200 (200 MHz), Bruker AM-250 (250 MHz), or Bruker AM-500 (500 MHz) spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants (in hertz), integration, interpretation]. ^{13}C Nuclear magnetic resonance spectra were recorded on Bruker WP-80 (20.11 MHz) or Bruker AM-250 (62.85 MHz) spectrometers and are reported in parts per million from internal tetramethylsilane. ^{13}C Nuclear magnetic resonance data are reported as follows: chemical shift [multiplicity (s=singlet, d=doublet, t=triplet, q=quartet)]. ^{13}C-NMR spectra were recorded as Broad-Band, Off-Resonance-Decoupled or DEPT (Distortionless Enhancement by Polarization Transfer) spectra. Infrared spectra were taken on a Perkin-Elmer 457 instrument. Mass spectra were recorded on Kratos MS-30 instruments at an ionization energy of 70 eV. Samples on which exact masses were measured exhibited no significant peaks at m/e values greater than those of the parent. Optical rotations were measured with a Perkin-Elmer 241 polarimeter and ozonolyses were performed using a Welsbach Model T-408 ozone generator. Combustion analysis were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrahydrofuran, benzene and diethyl ether (distilled from sodium metal); carbon tetrachloride and dichloromethane (passed through activity I alumina); methanol (distilled from magnesium methoxide), acetonitrile, benzene, dimethylformamide, dimethylsulfoxide, toluene and triethylamine (distilled from CaH_2). All reaction temperatures refer to those of reaction mixture unless indicated otherwise. Reactions requiring an inert atmosphere were run under a blanket of argon or nitrogen. Analytical thin-layer chromatography was performed with EM Laboratories 0.25 mm thick precoated silica gel 60 F-254 plates. Column chromatography was performed over EM Laboratories silica gel 60 (70-230 mesh). Medium pressure liquid chromatography (MPLC) was performed over EM Laboratories Lobar prepacked silica gel columns using RPSY lab pump. Rotary disk chromatography (Chromatotron) was performed over EM Laboratories silica gel PF-254 with $CaSO_4$ 1/2H_2O) type 60 plates using an FMI RP G-150 lab pump. Ethyl acetate and n-hexane, used as eluents in column chromatography, were distilled prior to use.

[3S,4R(E)]-3-[1(S)-hydroxyethyl]-4-(2-phenylthio)ethenyl-2-azetidinone (4). To a solution of 28.0 mL (133 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 100 mL of tetrahydrofuran cooled in an dry ice-acetone bath was added 80 mL (128 mmol) of 1.60 M n-butyllithium in hexane over a 10-min period. The solution was stirred for 30 min in the bath and 19.4 g (118 mmol) of 3-phenylthioacrolein[26] in 100 mL of tetrahydrofuran was added at a rate such that the temperature did not exceed -60°C. The mixture was stirred for 1 h at -78°C, and the resulting cold solution of N-trimethylsilyl imine 2 was used directly used in the following reaction.

To a solution of 35.0 mL (250 mmol) of diisopropylamine in 100 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 150 mL (240 mmol) of 1.60 M n-butyllithium solution in hexane. The solution was stirred for 30 min in the bath and 15.0 mL (115 mmol) of ethyl (S)-(+)-3-hydroxybutyrate (1)[27,28] in 100 mL of tetrahydrofuran was added at a rate such that the temperature did not exceed -60°C. The solution was stirred for 1 h at -78°C followed by the addition of the silyl imine 2 via cannula over a 5-min period. The mixture was stirred for 1 h at -78°C, the cold bath was removed and the mixture was allowed to warm to room temperature followed by stirring for 20 h. The resulting soluton was diluted with 1 L of dichloromethane and washed with two 500-mL portions of saturated aqueous ammonium chloride. The combined aqueous layers were extracted with three 400-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed twice over 300-g portions of silica gel (ethyl acetate-hexane, 2:1; then ethyl acetate) to give 11.5 g (40%) of 3 + 4 as a mixture of three diastereomeric β-lactams. In experiments conducted with racemic materials, these β-lactams were best characterized as their bis-tert-butyldimethylsilyl ethers.[3] A pure sample of diastereomer 4 was obtained by recrystallization of 8.0 g of the mixture of β-lactams from 150 mL of dichloromethane and ether (1:1, respectively) to afford 3.60 g (20%) of material as a white solid. The spectral data (IR, ^{1}H-NMR) of this material were identical to those reported for racemic material: mp 173-174°C; $[\alpha]_D^{20}$ +6.5 (c 0.78, CH_3OH).

(1S,2S,4S,5R,6R)-5-Bromo-2-methyl-4-phenylthio-3-oxa-7-azabicyclo[4.2.0]octan-8-one (7). A mixture of 2.14 g (8.59 mmol) of lactam 4 and 1.53 g (8.60 mmol) of N-bromosuccinimide in 30 mL of dichloromethane was stirred at room temperature for 24 h. The mixture was concentrated in vacuo and the residue was chromatographed over 80 g of silica gel (ethyl acetate-hexane, 2:3) to give 2.59 g (92%) of 7 as a white solid: mp 145-147°C; IR ($CHCl_3$) 3400, 1770 cm^{-1}; $[\alpha]_D^{20}$ -258.2 (c 1.75, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.42 (d, J = 6.4 Hz, 3H, CH_3), 3.33 (dt, J = 5.5, 2.2 Hz, 1H, CHCO), 4.04 (dd, J = 8.6, 3.4 Hz, 1H, CHBr), 4.17 (dd, J = 5.5, 3.4 Hz, 1H, CHN), 4.26 (dq, J = 6.4, 2.2 Hz, 1H, CHO), 5.60 (d, J = 8.6 Hz, 1H, CHS), 6.1 (br s, 1H, NH), 7.29-7.62 (m, 5H, ArH); ^{13}C-NMR (200 MHz, $CDCl_3$) 17.86 (q), 47.77 (d), 50.97 (d), 55.96 (d), 63.79 (d), 88.49 (d), 128.12 (d), 128.98 (d), 133.56 (d and s), 166.00 (s); exact mass calcd for $C_{13}H_{14}BrNO_2S$ m/e 328.9909, found m/e 328.9904.

Anal. Calcd for $C_{13}H_{14}BrNO_2S$: C, 47.57; H, 4.30. Found: C, 47.29; H, 4.51.

(1S,2S,6S)-2-Methyl-3-oxa-7-azabyclo[4.2.0]oct-4-en-8-one (8). A mixture of 2.47 g (7.53 mmol) of lactam 7, 1.40 mL (7.94 mmol) of tri-n-butyltin hydride[29] and 10 mg of AIBN in 60 mL of benzene was heated at reflux for 3 h. The mixture was concentrated in vacuo and the residue was chromatographed over 50 g of silica gel (ethyl acetate-hexane, 1:1 and 2:1) to give 995 mg (95%) of 8 as a white solid: mp 144-146°C; IR ($CHCl_3$) 3400, 1750 cm^{-1}; $[\alpha]_D^{20}$ -71.3 (c 1.05, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J = 6.6 Hz, 3H, CH_3), 3.54 (dd, J = 5.8, 3.7 Hz, 1H, CHCO), 3.95 (dq, J = 6.6, 3.7 Hz, 1H, CHO), 4.04 (dd, J = 5.8, 4.4, 1H, CHN), 5.18 (dd, J = 6.0, 4.4 Hz, 1H, CH=CHO), 5.85 (br s, 1H, NH), 6.62 (d, J = 6.0 Hz, 1H, CH=CHO); ^{13}C-NMR ($CDCl_3$) 17.93 (q), 42.17 (d), 57.51 (d), 72.41 (d), 103.77 (d), 149.96 (d), 169.43 (s); exact mass calcd for $C_7H_9NO_2$ m/e 139.0633, found m/e 139.0668.

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.67; H, 6.72.

(1S,2S,4R,6S)-4-Methoxy-2-methyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (9). **From 8:** A mixture of 340 mg (2.45 mmol) of lactam 8 and 0.40 g of Dowex 50X8-100 ion-exchange resin in 10 mL of methanol was stirred for 5 h at room temperature. The mixture was filtered and the residual resin was washed with 20 mL of methanol. The filtrate was concentrated in vacuo and the residue was chromatographed twice over 20 g portions of silica gel (ethyl acetate) to give 350 mg (84%) of lactam 9 as a white solid: mp 142-143°C; IR ($CHCl_3$) 3400, 1750 cm^{-1}; $[\alpha]_D^{20}$ -117.0 (c 0.975, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.43 (d, J = 6.5 Hz, 3H, $CHCH_3$), 1.74 (ddd, J = 15.8, 7.4, 3.2 Hz, 1H, CH_2), 2.30 (ddd, J = 15.8, 6.4, 2.4 Hz, 1H, CH_2), 3.17 (dt, J = 5.3, 2.5 Hz, 1H, CHCO), 3.4 (s, 3H, OCH_3) 3.92 (m, 1H, CHN), 4.15 (dq, J = 6.4, 2.5 Hz, 1H, CHO), 4.92 (t, J = 7.0 Hz, 1H, OCHO), 5.95 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) 18.21 (q), 29.74 (t), 44.56 (d), 54.23 (q), 54.73 (d), 63.47 (d), 97.15 (d), 168.72 (s); mass spectrum, m/e (relative intensity) 140 (18, M-OCH_3), 128 (41), 96 (55), 85 (81), 68 (100). 58 (97).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65. Found: C, 55.67; H, 7.58.

From 21: To a solution of 2.29 g (8.23 mmol) of 21 in 120 mL of acetonitrile cooled in a carbon tetrachloride-dry ice bath was added 11.3 g (20.6 mmol) of ceric ammonium nitrate in 40 mL of water over a 10-min period. The mixture was stirred for 10 min in the bath, warmed to 0°C and stirred for 20 min in an ice bath. The mixture was diluted with 300 mL of ethyl acetate and washed with two 300-mL portions of 10% aqueous sodium sulfite, 300 mL of 5% aqueous sodium bicarbonate and 150 mL of brine. The aqueous layers were extracted with two 300-mL portions of ethyl acetate. The aqueous layers were combined, saturated with sodium chloride and extracted with four 300-mL portions of ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed twice over 50-g portions of silica gel (ethyl acetate) to give 1.10 g (78%) of 9 as a white solid: mp 137-141°C; $[\alpha]_D^{20}$ -123.3 (c 1.36, $CHCl_3$).

[3S,4S(E)]-3-[1(S)-Hydroxyethyl]-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (11), [3S,4R(E)]-3-[1(S)-Hydroxyethyl]-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (12), and [3R,4S(E)]-3-[1(S)-Hydroxyethyl]-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (13). To a solution of 5.00 mL (35.6 mmol) of diisopropylamine in 15 mL of tetrahydrofuran was added 21.0 mL (33.6 mmol) of 1.60 M n-butyllithium in hexane at -70°C. The solution was stirred for 30 min followed by addition of 2.10 mL (16.2 mmol) of ethyl (3S)-hydroxybutyrate (1) in 10 mL of tetrahydrofuran at a rate such that the temperature did not exceed -60°C. The solution was stirred for 1 h at -78°C followed by addition of 3.80 g (16.0 mmol) of imine 10 in 30 mL of tetrahydrofuran over a 10-min period. The mixture was stirred at -78°C for 1 h, the cold bath was removed and the mixture was allowed to warmed to room temperature followed by stirring for 20 h. The resulting solution was partitioned between 200 mL of dichloromethane and 200 mL of saturated aqueous ammonium chloride. The combined aqueous layers were extracted with two 150-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed over 100 g of silica gel (ethyl acetate-hexane, 1:2) to give 3.40 g of yellow oil. The oil was chromatographed at medium pressure (Lobar size C; ethyl acetate-hexane, 1:4) to give 1.31 g of lactam 11 (25%) and 1.96 g (38%) of a diastereomeric mixture of lactams 12 and 13. Lactam 11: mp 115-117°C; IR ($CHCl_3$) 3500, 1730 cm^{-1}; $[\alpha]_D^{20}$ +187.1 (c 1.40, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.34 (d, J = 6.0 Hz, 3H, CH_3) 1.83 (br s, 1H, OH), 3.45 (t, J = 6.0 Hz, 1H, CHCO), 3.77 (s, 3H, OCH_3), 4.21 (qu, J = 6.0 Hz, 1H, CHOH), 4.76 (dd, J = 8.5, 6.0 Hz, 1H, CHN), 6.44 (dd, J = 16.0, 8.5 Hz, 1H, CH=CHPh), 6.80 (d, J = 16.0 Hz, 1H, CH=CHPh), 6.84 (d, J = 9.1 Hz, 2H, ArH), 7.21-7.48 (m, with d at δ 7.31, 7H, ArH); exact mass calcd for $C_{20}H_{21}NO_3$ m/e 323.1521, found m/e 323.1521.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.05; H, 6.84. Found: C, 73.50; H, 6.46.

Compounds 12 and 13 were best characterized as their tert-butyldimethylsilyl ethers (14 and 15, respectively) as outlined below.

[3S,4R(E)]-3-[1(S)-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (14) and [3R,4S(E)]-3-[1(S)-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone (15). A solution of 1.85 g (5.70 mmol) of a diastereomeric mixture of 12 and 13, 1.00 mL (7.16 mmol) of triethylamine and 1.03 g (6.83 mmol) of tert-butyldimethylsilyl chloride in 15 mL of N,N-dimethylformamide[30] was stirred at room temperature for 24 h, diluted with 100 mL of dichloromethane, and washed with two 50-mL portions of water. The combined aqueous layers were extracted with 50 mL of ether. The combined organic layers were washed with 50 mL of brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed twice at medium pressure (Lobar size C; ethyl acetate-hexane, 1:12) to give 1.77 g (72%) of lactam 14 and 0.59 g (23%) of lactam 15. Lactam 14: mp 97-98°C; IR ($CHCl_3$) 1730 cm^{-1}; $[\alpha]_D^{20}$ -62.9 (c 1.81, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.08 (s, 6H, $SiMe_2$), 0.88 (s, 9H, t-Bu), 1.37 (d, J = 6.3 Hz, 3H, $CHCH_3$), 3.18 (dd, J = 4.0, 2.2 Hz, 1H, CHCO), 3.76 (s, 3H, OCH_3), 4.30 (dq, J = 6.3, 4.0 Hz, 1H, CHOSi), 4.52 (dd, J = 8.1, 2.2 Hz, 1H, CHN), 6.29 (dd, J = 16.0, 8.1 Hz, 1H, CH=CHPh), 6.77 (d, J = 16.0 Hz, 1H, CH=CHPh), 6.82 (d, J = 9.1 Hz, 2H, ArH), 7.25-7.45 (m with d, J = 9.1 Hz, at δ 7.37, 7H ArH); ^{13}C-NMR ($CDCl_3$) 4.19 (q), 4.80 (q), 17.95 (s), 20.95 (q), 25.71 (q), 55.45 (q), 56.00 (d), 64.14 (d), 65.57 (d), 114.33 (d), 118.21 (d), 126.58 (d), 127.62 (d), 128.22 (d), 128.71 (d), 131.88(s), 133.74 (d), 135.98 (s), 155.94 (s), 164.67 (s).

Anal. Calcd for $C_{26}H_{35}NO_3Si$: C, 71.35; H, 8.06. Found: C, 71.60; H, 8.06.

Lactam 15: mp 124-125°C; IR ($CHCl_3$) 1735 cm^{-1}; $[\alpha]_D^{20}$ +114.2 (c 1.44, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.05 (s, 3H, SiMe), 0.08 (s, 3H, SiMe), 0.80 (s, 9H, t-Bu), 1.29 (d, J = 6.1 Hz, 3H, $CHCH_3$), 3.07 (dd, J = 3.9, 2.3 Hz, 1H, CHCO), 3.76 (s, 3H, OCH_3), 4.35 (dq, J = 6.1, 3.9 Hz, 1H, CHOSi), 4.70 (dd, J =

8.1, 2.3 Hz, 1H, CHN), 6.33 (dd, J = 16.0, 8.1 Hz, 1H, CH=CHPh), 6.77 (d, J = 16.0 Hz, 1H, CH=CHPh), 6.82 (d, J = 9.1 Hz, 1H, ArH), 7.37 (m, 7H, ArH); ^{13}C-NMR ($CDCl_3$) 4.25 (q), 4.91 (q), 17.84 (s), 22.54 (q), 25.65 (q), 55.45 (q), 55.67 (d), 64.91 (d), 65.46 (d), 114.33 (d), 118.16 (d), 126.58 (d), 127.89 (d), 128.16 (d), 128.71 (d), 131.99 (s), 133.47 (d), 136.04 (d), 155.94 (s), 164.85 (s); exact mass calcd for $C_{26}H_{35}NO_3Si$ m/e 437.2386, found m/e 437.2380.

Anal. Calcd for $C_{26}H_{35}NO_3Si$: C, 71.35; H, 8.06. Found: C, 71.59; H, 8.09.

(1S,2S,4R,5R)-4-Hydroxy-6-(4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one (16) and (1R,2S,4R,5S)-4-Hydroxy-6-(4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one (19). To a solution of 9.6 g (29.7 mmol) of a diastereomeric mixture of lactams 11, 12 and 13 in 300 mL of dichloromethane cooled in a dry ice-acetone bath was passed ozone (ozone flow rate, 0.76 mmol/min) for 70 min. Dimethylsulfide (50 mL) was added in a single portion. The mixture was warmed to room temperature, stirred for 20 h and concentrated in vacuo. The residue was chromatographed over 200 g of silica gel (ethyl acetate-hexane, 1:1) to give 2.30 g of lactam **16**. Further elution with ethyl acetate gave 4.12 g of a mixture of lactam **16** and two trans aldehydes, **17** and **18**. This mixture was dissolved in 100 mL of dichloromethane and 0.60 mL (4.01 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added. The mixture was heated at reflux for 70 min, diluted with 300 mL of dichloromethane and washed with 300 mL of 0.2 N aqueous hydrochloric acid. The aqueous layer was extracted twice with 200-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed over 200 g of silica gel (ethyl acetate-hexane, 1:2, then 1:1) to give 0.44 g (6%) of lactam **19** and 2.73 g (68%) of lactam **16**. Lactam **16**: mp 174.5-175.5°C; IR ($CHCl_3$) 3300, 1740 cm^{-1}; $[\alpha]_D^{20}$ +100.4 (c 1.17, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.52 (d, J = 6.3 Hz, 3H, CH_3), 3.02 (br s, 1H, OH), 3.73 (dd, J = 5.5, 4.0 Hz, 1H, CHCO), 3.78 (s, 3H, OCH_3), 4.39 (d, J = 4.0 Hz, 1H, CHN), 4.44 (m, 1H, CHMe), 5.56 (s, 1H, OCHO), 6.86 (d, J = 9.1 Hz, 2H, ArH), 7.30 (d, J = 9.1 Hz, 2H, ArH); exact mass calcd for $C_{13}H_{15}NO_4$ m/e 249.1001, found m/e 249.1012. Lactam **19**: mp 171-173°C; IR ($CHCl_3$) 3600, 3300, 1740 cm^{-1}; $[\alpha]_D^{20}$ -19.5 (c 0.95, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.43 (d, J = 6.8 Hz, 3H, $CHCH_3$), 2.82 (br s, 1H, OH), 3.66 (d, J = 4.1 Hz, 1H, CHCO), 3.79 (s, 3H, OCH_3), 4.56 (d, J = 4.1 Hz, 1H, CHN), 4.70 (q, J = 6.8 Hz, 1H, CHMe), 5.59 (s, 1H, OCHO), 6.89 (d, J = 9.2 Hz, 2H, ArH), 7.28 (d, J = 9.2 Hz, 2H, ArH); exact mass calcd for $C_{13}H_{15}NO_4$ m/e 249.1001, found m/e 249.0999.

[3S,4S(E)]-3-[1(S)-Hydroxyethyl]-4-(2-methoxyethenyl)-1-(4-methoxyphenyl)-2-azetidinone (20). To a solution of 2.85 mL (20.3 mmol) of diisopropylamine in 50 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 12.5 mL of 1.6 M n-butyllithium in hexane over a 1-min period. The mixture was stirred for 20 min and 5.52 g (16.1 mmol) of anhydrous (methoxymethyl)triphenylphosphonium chloride was added. The mixture was stirred for 10 min in the cold bath, warmed to 0°C and stirred for 10 min in an ice bath. The resulting dark red solution was cooled in a dry ice-acetone bath and 1.00 g (4.01 mmol) of lactam **16** in 40 mL of tetrahydrofuran was added over a 3-min period. The cold bath was removed and the mixture was warmed to room temperature followed by stirring for 10 h. The mixture was diluted with 300 mL of dichloromethane and washed with 300 mL of water. The aqueous layer was extracted with two 150-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residual dark brown oil was flash chromatographed over 50 g of silica gel (ethyl acetate-hexane, 1:1 and 2:1) to give 1.05 g of yellow solid which was crystallized from 50 mL of dichloromethane and ether (1:1) to give 680 mg of **20** as a slightly yellow solid. The mother liquor was concentrated in vacuo and the residue was chromatographed over 25 g of silica gel (ethyl acetate-hexane, 1:1) and crystallized twice from 5 mL portions of dichloromethane and ether (1:1) to give 266 mg (total 946 mg, 85%) of **20** as a slightly yellow solid: mp 189-190°C; IR ($CHCl_3$) 1725, 1650 cm^{-1}; $[\alpha]_D^{20}$ +126.6 (c 1.22, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.34 (d, J = 6.3 Hz, 3H, $CHCH_3$), 2.34 (br s, 1H, OH), 3.32 (dd, J = 6.7, 5.6 Hz, 1H, CHCO), 3.59 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.16 (qu, J = 6 Hz, 1H, $CHCH_3$), 4.54 (dd, J = 9.8, 5.6 Hz, 1H, CHN), 4.95 (dd, J = 12.6, 9.8 Hz, 1H, CH=CHO), 6.73 (d, J = 12.6 Hz, 1H, CH=CHO), 6.85 (d, J = 9.1 Hz, 2H, ArH), 7.38 (d, J = 9.1 Hz, 2H, ArH); exact mass calcd for $C_{15}H_{19}NO_4$ m/e 277.1314, found m/e 277.1324.

(1S,2S,4R,6S)-4-Methoxy-7-(4-methoxyphenyl)-2-methyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (21).
From 20: A mixture of 700 mg (2.53 mmol) of lactam **20** and 2.0 g of Dowex 50X8-100 ion-exchange resin in 50 mL of methanol was stirred for 5 h at room temperature. The mixture was filtered and the residual resin was washed with 50 mL of dichloromethane. The combined filtrate was concentrated in vacuo and the residue was chromatographed over 30 g of silica gel (ethyl acetate-hexane, 1:3) to give 687 mg (98%) of **21** as a white solid: mp 128-129°C; IR ($CHCl_3$) 1735 cm^{-1}; $[\alpha]_D^{20}$ +36.8 (c 1.39, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.49 (d, J = 6.6 Hz, 3H, $CHCH_3$), 1.82 (ddd, J = 15.8, 7.7, 3.4 Hz, 1H, CH_2), 2.60 (ddd, J = 15.8, 6.1, 2.3 Hz, 1H, CH_2), 3.26 (dd, J = 5.8, 2.3 Hz, 1H, CHCO), 3.34 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.17-4.31 (m, 2H, CHN and CHMe), 4.72 (dd, J = 7.7, 6.1 Hz, 1H, OCHO), 6.88 (d, J = 9.1 Hz, 2H, ArH), 7.34 (d, J = 9.1 Hz, 2H, ArH); ^{13}C-NMR ($CDCl_3$) 18.28 (q), 27.41 (t), 47.92 (d), 52.84 (d), 54.75 (q), 55.52 (q), 63.19 (d), 96.85 (d), 114.61 (d), 118.25 (d), 131.03 (s), 156.19 (s), 164.18 (s); exact mass calcd for $C_{15}H_{19}NO_4$ m/e 277.1314, found m/e 277.1322.
From 16 without purification of intermediates: To a solution of 5.20 mL (37.1 mmol) of diisopropylamine in 100 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 23.1 mL of 1.60 M n-butyllithium in hexane over a 1-min period. The mixture was stirred for 20 min at -78°C and 9.50 g (27.7 mmol of anhydrous (methoxymethyl)triphenylphosphonium chloride was added. The mixture was stirred for 10 min in the cold bath, warmed to 0°C and stirred for 10 min in an ice bath. The resulting dark red solution was cooled in a dry ice-acetone bath and 2.30 (9.24 mmol) of lactam **16** in 100 mL of tetrahydrofuran was added over a 5-min period. The cold bath was removed, the mixture was warmed to room temperature and stirred for 10 h. The mixture was cooled in an ice bath and 100 mL of 1.0 N methanolic hydrochloric acid was added over a 5-min period. The mixture was warmed to room temperature, stirred for 5 h, diluted with 400 mL of dichloromethane and washed with 500 mL of 5% aqueous sodium bicarbonate. The aqueous layer was extracted with two 200-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed twice over 100-g portions of silica gel (ethyl acetate-hexane, 3:7) to give 1.82 g (71%) of **21**.

rel-(3S,4S)-1-Benzoyl-3-isopropyl-4-phenyl-2-azetidinone (24b). A solution of 1.62 g (8.56 mmol) of **24a**, 1.2 mL (10.3 mmol) of benzoyl chloride, 1.5 mL (10.8 mmol) of triethylamine, and 5 mg of 4-

(dimethylamino) pyridine in 50 mL of dichloromethane was warmed under reflux for 10 h. The solution was diluted with 150 mL of dichloromethane and washed with two 100-mL portions of saturated aqueous sodium bicarbonate. The combined aqueous washes were extracted with 100 mL of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 80 g of silica gel (ethyl acetate-hexane, 1:8) to give 2.35 g (94%) of imide **24b** as white crystals: mp 119.5-120.5; IR ($CHCl_3$) 1780, 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.5 (d, J = 6 Hz, 3H, CH_3), 1.1 (d, J = 6 Hz, 3H, CH_3), 1.85 (m, 1H, $CHMe_2$), 3.2 (dd, J = 10, 6 Hz, 1H, CHCO), 5.35 (d, J = 6 Hz, 3H, CH_3), 7.4 (m, 8H, ArH), 8.0 (m, 2H, ArH); exact mass calcd for $C_{19}H_{19}NO_2$ m/e 293.1416, found m/e 293.1410.

rel-(3S,4S)-3-Isopropyl-4-phenyl-1-(4-methylphenyl)sulfonyl-2-azetidinone (24c). To a solution of 246 mg (1.3 mmol) of **24a** in 5 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 0.82 mL (1.31 mmol) of 1.6 M n-butyllithium in hexane. The solution was stirred for 10 min and 371 mg (0.42 mmol) of p-toluenesulfonyl chloride in 3 mL of tetrahydrofuran was added. The cold bath was removed and the mixture was allowed to warm to room temperature. The solution was diluted with 50 mL of water and extracted with three 50-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and the residue was chromatographed at medium pressure (LoBar size B; ethylacetate-hexane, 1:6) to afford 238 mg (53%) of imide **24c** as a white solid: mp 120-121°C; IR (CH_2Cl_2) 1785 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.45 (d, J = 6 Hz, 3H, CH_3), 1.05 (d, J = 6 Hz, 3H, CH_3), 2.75 (m, 1H, $CHMe_2$), 2.45 (s, 3H, $ArCH_3$), 3.2 (dd, J = 10, 6 Hz, 1H, CHCO), 5.2 (d, J = 6 Hz, 1H, CHN), 7.35 (m, 7H, ArH) 7.8 (d, J = 8 Hz, 2H, ArH)

Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.44; H, 6.16. Found: C, 66.11; H, 5.93.

rel-(3S,4S)-3-Isopropyl-1-[oxo(phenylmethoxy)acetyl]-4-phenyl-2-azetidinone (24d). To a solution of 885 mg (4.73 mmol) of **24a** and 0.410 mL (5.22 mmol) of triethylamine in 30 mL of dichloromethane cooled in an ice bath was added 0.74 mL (5.31 mmol) of oxo(phenylmethoxy)acetyl chloride.[31] The mixture was stirred for 30 min, diluted with 150 mL of dichloromethane and washed with 100 mL of water. The aqueous layer was extracted with 50 mL of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed over 50 g of silica gel (ethyl acetate-hexane, 1:10) to give 1.56 g (94%) of **24d** as a white solid: mp 100-101°C; IR ($CHCl_3$) 1800, 1750, 1700 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.48 (d, J = 6.3 Hz, 3H, CH_3), 1.07 (d, J = 6.3 Hz, 3H, CH_3), 1.82 (m, 1H, $CHMe_2$), 3.31 (dd, J = 11.0, 7.2 Hz, 1H, CHCO), 5.28 (d, J = 7.2 Hz, 1H, CHN), 5.30 (s, 2H, CH_2Ar), 7.40 (m, 10H, ArH); mass spectrum, m/e (relative intensity) 171 (1), 161 (5), 146 (9), 132 (78), 103 (4), 91 (100), 77 (7).

rel-(1S,2S)-2-Hydroxy-3-methyl-1-phenylbutylamine hydrochloride (25b·HCl). A mixture of 702 mg (2.06 mmol) of **24d**, 1.43 g (8.29 mmol) of m-chloroperbenzoic acid, 1.50 g (10.6 mmol) of disodium hydrogen phosphate and 74 mg (0.206 mmol) of 3-tert-butyl-4-hydroxy-5-methylphenyl disulfide in 25 mL of carbon tetrachloride was heated at reflux for 2.5 h. m-Chloroperbenzoic acid (0.18 g, 1.04 mmol) was added, the mixture was heated at reflux for 30 min and concentrated in vacuo. The residue was dissolved in 20 mL of 3N methanolic hydrochloric acid and heated at 80°C for 12 h in a sealed tube. The mixture was concentrated in vacuo and the residue was flash chromatographed twice over 20-g of portions of silica gel (ethyl acetate-methanol, 10:1 and 5:1) to give 270 mg of yellow solid. This material was recrystallized from methanol-ether to give 233 mg (52%) of **25b** as a white solid: mp 190 (dec); IR (KBr) 3600-3200, 3200-2800 cm^{-1}; ^{1}H-NMR (250 MHz, DMSO-d_6) δ 0.83 (d, = J = 6.7 Hz, 3H, CH_3), 0.86 (d, J = 6.7 Hz, 3H, CH_3), 1.23 (octet, J = 7 Hz, 1H, $CHMe_2$), 3.56 (m, 1H, CHO), 4.24 (d, J = 3.7 Hz, 1H, CHN), 5.40 (br d, 1 H, OH), 7.35-7.55 (m, 5H, ArH), 8.29 (br s, 2H, NH_2); exact mass calcd for $C_{11}H_{18}NO$ m/e 180.1388, found m/e 180.1371.

rel-(1S,2S)-1-Acetamido-2-acetoxy-3-methyl-1-phenylbutane (25c). A mixture of 57 mg (0.264 mmol) of **25b**, 0.20 mL (2.12 mmol) of acetic anhydride and 1.0 mg of 4-(dimethylamino)pyridine in 2 mL of pyridine was stirred for 48 h at room temperature. Toluene (20 mL) was added and the mixture was concentrated in vacuo. The residue was chromatographed twice over 8-g portions of silica gel (ethyl acetate-hexane) to give 69 mg (99%) of **25c** as a white solid: mp 74-77°C; IR ($CHCl_3$) 3440, 1730, 1670 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3H, $CHCH_3$), 1.00 (d, J = 6.5 Hz, 3H, $CHCH_3$), 1.81 (m, 1H, $CHMe_2$), 1.94 (s, 3H, $COCH_3$), 1.96 (s, 3H, $COCH_3$), 4.98 (dd, J = 7.0, 5.5 Hz, 1H, CHO), 5.27 (dd, J = 8.2, 5.5 Hz, 1H, CHN), 6.15 (broad d, J = 8.2 Hz, 1H, NH), 7.27 (m, 5H, ArH); mass spectrum, m/e (relative intensity) 264 (1), 203 (8), 191 (24), 160 (9), 148 (91), 106 (100), 91 (8), 43 (67); exact mass calcd for $C_{15}H_{21}NO_3$+H m/e 264.1599, found m/e 264.1597

rel-(3S,4S)-4-Benzoylamino-3-isopropyl-4-phenyl-2-butanone (26a). To a solution of 718 mg (2.45 mmol) of β-lactam **24b** in 40 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 0.8 mL (2.56 mmol) of a 3.2 M ethereal solution of methylmagnesium bromide over a 1-min period. The resulting solution was stirred for 10 min, the cold bath was removed, and the mixture was allowed to warm to room temperature over a 40 min period. The solution was poured into 100 mL of vigorously stirred saturated aqueous ammonium chloride. The resulting mixture was extracted with three 50 mL-portions of dichloromethane. The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue (760 mg) was chromatographed over 30 g of silica gel (ethyl acetate-hexane, 1:4) to give 581 mg (77%) of methylketone **26a** as a white solid: mp 157-159°C; IR ($CHCl_3$) 1710, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.1 (d, J = 6 Hz, 6H, CH_3), 1.8 (s, 3H, $COCH_3$), 2.2 (m, 1H, $CHMe_2$), 3.2 (dd, J = 10, 6 Hz, 1H, CHCO), 5.6 (t, J = 10 Hz, 1H, CHN), 7.0 (d, J = 10 Hz, 1H, NH), 7.4 (m, 8H, ArH), 7.8 (m, 2H, ArH).

rel-(3S,4R)-4-[(4-Methylphenyl)sulfonyl]amino-3-isopropyl-4-phenyl-2-butanone (26b). To a solution of 172 mg (0.50 mmol) of imide **24c** in 3.0 mL of ether cooled in an ice water bath was added 0.44 mL (0.55 mmol) of 1.24 M ethereal methyllithium. The mixture was stirred for 10 min, poured into 30 mL of stirred saturated aqueous ammonium chloride, and extracted with three 30-mL portions of dichloromethane. The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue (175 mg) was chromatographed over 15 g of silica gel (ethyl acetate-hexane, 1:3) to give 75 mg (48%) of ketone **26b** after recrystallization from dichloromethane-hexane (1:2): mp 149-150°C; IR (CH_2Cl_2) 3360, 3260, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0 (d, J = 6 Hz, 6H, CH_3), 1.7 (s, 3H, $COCH_3$), 2.3 (s, 3H, $ArCH_3$), 2.35 (m, 1H, $CHMe_2$), 3.1 (dd, J = 10, 4 Hz, 1H, CHCO), 4.6 (t, J = 10 Hz, 1H, CHN), 6.0 (d,

J = 10 Hz, 1H, NH), 7.0 (m, 7H, ArH), 7.5 (d, J = 8 Hz, 2H, ArH).
Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82, H, 7.01. Found: C, 66.56; H, 7.15.

(1S,2S,4R,6S)-4-Methoxy-2-methyl-7-[oxo(phenylmethoxy)acetyl]-3-oxa-7-azabicyclo[4.2.0]octan-8-one (27). To a solution of 430 mg (2.51 mmol) of lactam **9** and 0.44 mL (3.6 mmol) of triethylamine in 20 mL of dichloromethane cooled in an ice bath was added 0.58 mL (3.15 mmol) of benzyloxyoxalyl chloride. The mixture was stirred for 30 min at 0°C, warmed to room temperature and stirred for 10 min. The mixture was diluted with 100 mL of dichloromethane and washed with 100 mL of water. The aqueous layer was extracted with 50 mL of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed over 25 g of silica gel (ethyl acetate-hexane, 1:2) to give 821 mg (98%) of **27** as a colorless oil: IR ($CHCl_3$) 1805, 1750, 1700 cm^{-1}; $[\alpha]_D^{20}$ -20.0 (c 1.07, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.41 (d, J = 6.5 Hz, 3H, $CHCH_3$), 1.79 (ddd, J = 16.0, 7.6, 3.7 Hz, 1H, CH_2), 2.80 (ddd, J = 16.0, 6.3 2.5 Hz, 1H, CH_2), 3.33 (dd, J = 6.8, 2.5 Hz, 1H, CHCO), 3.36 (s, 3H, OCH_3), 4.19 (dq, J = 6.5, 2.5 Hz, 1H, CHMe), 4.38 (m, 1H, CHN), 4.84 (t, J = 7.0 Hz, 1H, OCHO), 5.34 (ABq, J = 18.2 Hz, 2H, CH_2Ar), 7.37 (m, 5H, ArH); mass spectrum, m/e (relative intensity) 258 (1), 155 (3), 128 (1), 111 (8), 96 (22), 91 (97), 49 (100).

Methyl 2,3,6-Trideoxy-3-[[oxo(phenylmethoxy)acetyl]amino]-α-L-lyxo-hexopyranoside (28). A mixture of 490 mg (1.47 mmol) of lactam **27**, 1.05 g (7.39 mmol) of disodium hydrogen phosphate, 1.02 g (5.91 mmol) of m-chloroperbenzoic acid and 264 mg (0.736 mmol) of 3-tert-butyl-4-hydroxy-5-methylphenyl disulfide in 20 mL of carbon tetrachloride was heated at reflux for 30 min. m-Chloroperbenzoic acid (250 mg, 1.45 mmol) was added and the mixture was heated at reflux for 90 min. The resulting yellow solution was diluted with 100 mL of dichloromethane, and washed sequentially with 100 mL of saturated aqueous sodium bisulfite and 100 mL of saturated aqueous sodium bicarbonate. Each aqueous layer was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed over 25 g of silica gel (ethyl acetate-hexane, 1:2 and 1:1) to give 166 mg (35%) of **28** as a colorless oil: IR ($CHCl_3$) 3400, 1700 cm^{-1}; $[\alpha]_D^{20}$ -104.0 (c 0.82, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.22 (d, J = 7 Hz, 1H, CH_3), 1.80 (td, J = 12, 3 Hz, 1H, H_{2a}), 1.88 (dd, J = 12, 5 Hz, 1H, H_{2e}), 1.94 (br s, 1H, OH), 3.33 (s, 3H, OCH_3), 3.56 (broad s, 1H, CHOH), 4.00 (q, J = 6.5 Hz, 1H, CHMe), 4.35 (dddd, J = 12, 9, 5, 2.5 Hz, 1H, CHN), 4.75 (broad d, J = 3 Hz, 1H, CHOMe), 5.28 (s, 2H, CH_2Ar), 7.37 (m, 6H, NH and ArH); ^{13}C-NMR ($CDCl_3$) 16.68 (q), 29.71 (t), 46.32 (d), 54.82 (q), 65.55 (d), 68.61 (t), 69.25 (d), 97.87 (d), 128.79 (three d's), 134.54 (s), 155.75 (s), 160.54 (s); mass spectrum m/e (relative intensity) 292 (1, M-OCH_3) 291 (1), 273 (1), 221 (2), 111 (8), 91 (100), 44 (3), 43 (20).

(1S,2S,4R,6S)-7-Benzoyl-4-methoxy-2-methyl-3-oxa-7-azabicyclo[4.2.0]octan-8-one (29). A mixture of 528 mg (3.09 mmol) of lactam **9**, 0.64 mL (4.59 mmol) of triethylamine, 0.53 mL (4.57 mmol) of benzoyl chloride and 20 mg (0.16 mmol) of 4-(dimethylamino)pyridine[33] in 25 mL of dichloromethane was heated at reflux for 15 h. The mixture was diluted with 100 mL of dichloromethane and washed with 100 mL of water. The aqueous layer was extracted with 100 mL of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed over 50 g of silica gel (ethyl acetate-hexane, 1:5) to give 834 mg (98%) of lactam **29** as a white solid: mp 87.5-88.5 °C; IR ($CHCl_3$) 1785, 1670 cm^{-1}; $[\alpha]_D^{20}$ +164.2 (c 1.37, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.47 (d, J = 6.5 Hz, 3H, CH_3), 1.82 (ddd, J = 15.8, 8.2, 3.5 Hz, 1H, CH_2), 2.86 (ddd, J = 15.8, 6.4, 2.5 Hz, 1H, CH_2), 3.24 (dd, J = 6.7, 2.5 Hz, 1H, CHCO), 3.40 (s, 3H, OCH_3), 4.28 (dq, J = 6.5, 2.5 Hz, 1H, CHO), 4.50 (m, 1H, CHN), 4.89 (t, J = 7.0 Hz, 1H, OCHO), 7.42-7.98 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) 18.15 (q), 27.39 (t), 47.13 (d), 52.27 (d), 55.00 (q), 62.98 (d), 97.54 (d), 128.21 (d), 129.85 (d), 132.14 (s), 133.29 (d), 164.24 (s), 166.48 (s); exact mass calcd for $C_{15}H_{17}NO_4$ m/e 275.1157, found m/e 275.1163.
Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22. Found: C, 65.28; H, 5.97.

(2S,3R,4S,6R)-Methyl 4-(Benzoylamino)-tetrahydro-6-methoxy-2-methyl-2H-pyran-3-carboxylate (30). To a solution of 391 mg (1.42 mmol) of lactam **29** in 7 mL of methanol was added 0.410 mL (2.74 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene. The mixture was stirred for 10 min at room temperature and heated at reflux for 32 h. The mixture was diluted with 100 mL of dichloromethane and washed with 100 mL of water. The aqueous layer was extracted with two 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), conentrated in vacuo and the residue was chromatographed over 30 g of silica gel (ethyl acetate-hexane, 1:2 and 1:1) to give 310 mg (71%) of **30** as a white solid: mp 153-155°C; IR ($CHCl_3$) 3430, 1725, 1660 cm^{-1}; $[\alpha]_D^{20}$ -68.4 (c 1.70, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.22 (d, J = 6.2 Hz, 3H, CH_3), 1.67 (dt, J = 12.9, 3.5 Hz, 1H, CH_2), 2.23 (ddd, J = 12.9, 4.5, 1.3 Hz, 1H, CH_2), 2.38 (t, J = 10.7 Hz, 1H, $CHCO_2$), 3.38 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 4.14 (dq, J = 12, 6 Hz, 1H, CHMe), 4.72 (m, 1H, CHN), 4.81 (d, J = 3.0 Hz, 1H, OCHO), 6.03 (d, J = 8.7 Hz, NH), 7.34-7.74 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) 19.55 (q), 35.59 (t), 45.30 (d), 52.01 (q), 54.63 (d), 55.78 (d), 65.04 (q), 98.00 (d), 126.94 (d), 128.53 (d), 131.41 (d), 134.67 (s), 166.99 (s), 172.04 (s); exact mass calcd for $C_{16}H_{21}NO_5$ m/e 307.1420, found m/e 307.1445.

(2S,3R,4S,6R)-4-(benzoylamino)-tetrahydro-6-methoxy-2-methyl-2-pyran-3-carboxylic acid (31). A mixture of 300 mg (0.977 mmol) of **30** and 2.0 mL of 2 N aqueous lithium hydroxide in 6 mL of methanol was heated at reflux for 3 h and passed through Dowex 50X8-400 ion-exchange resin column (80 mm X 18 mm) eluted with methanol to give 290 mg of the crude acid. This material was chromatographed over 15 g of silica gel (ethyl acetate-hexane, 2:1; ethyl acetate; ethyl acetate-methanol, 10:1 and 5:1) to give 278 mg (97%) of **31** as a white solid: mp 140°C (dec.); IR ($CHCl_3$) 3600-3100, 1710, 1645 cm^{-1}; $[\alpha]_D^{20}$ -71.5 (c 1.31, CH_3OH); ^{1}H-NMR (200 MHz, CD_3OD) δ 1.24 (d, J = 6.2 Hz, 3H, CH_3), 1.74 (dt, J = 12.8, 3.3 Hz, 1H, CH_2), 2.06 (dd, J = 12.8, 4.4 Hz, 1H, CH_2), 2.35 (t, J = 11.3 Hz, 1H, $CHCO_2$), 3.34 (s, 3H, CH_3), 4.08 (dq, J = 11, 6 Hz, 1H, CHMe), 4.75-4.86 (m, 2H, CHN and OCHO), 7.34-7.83 (m, 5H, ArH); exact mass calcd for $C_{15}H_{19}NO_5$ m/e 293.1263, found m/e 293.1263.

Methyl 3-Benzamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside (32). To a solution of 150 mg (0.152 mmol) of **31** and 353 mg (2.05 mmol) of m-chloroperbenzoic acid in 10 mL of dichloromethane was added 160 mg (0.775 mmol) of dicyclohexylcarbodiimide. The mixture was stirred for 5 h at room temperature, concentrated in vacuo, and the residue was dissolved in 15 mL of carbon tetrachloride. Disodium hydrogen phosphate (300 mg, 2.11 mmol) and 3-tert-butyl-4-hydroxy-5-methylphenyl

disulfide[32] were added, and the mixture was heated at reflux for 2 h and concentrated in vacuo. The residue was dissolved in 10 mL of methanol, 3 mL of 1 N aqueous potassium hydroxide was added followed by stirring for 10 h at room temperature. The mixture was diluted with 60 mL of dichloromethane and washed with 50 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted twice with 50-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$) and conentrated in vacuo. The residue was chromatographed twice over 10-g portions of silica gel (dichloromethane; ethyl acetate-hexane, 1:2 and 1:1) to give 46 mg (34%) of **32** as a white solid: mp 185-189°C; IR ($CHCl_3$) 3420, 3290, 1630, 1540, 1060 cm^{-1}; $[\alpha]_D^{20}$ - 87.7 (c 0.69, CH_3OH) [lit.[24] -92.0]; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.33 (d, J = 6.3 Hz, 3H, CH_3), 1.78 (td, J = 12.6, 3.5 Hz, 1H, H_{2a}), 2.17 (ddd, J = 12.6, 4.7, 1.1 Hz, H_{2e}), 3.17 (t, J = 9.4 Hz, 1H, CHOH), 3.37 (s, 1H, OCH_3), 3.73 (dq, J = 9.4, 6.3 Hz, 1H, CHMe), 4.20 (br s, 1H, OH), 4.37 (dddd, J = 12, 9, 6, 4.5, 1H, CHN), 4.78 (broad d, J = 2.5 Hz, 1H, C_1H), 6.15 (br d, J = 6 Hz, 1H, NH), 7.38-7.79 (m, 5H, ArH); mass spectrum m/e (relative intensity) 233 (1, M-CH_3OH), 215 (4), 186 (7), 176 (4), 121 (13), 105 (100), 97 (7), 77 (38). This material was recrystallized twice from 5-mL portions of dichloromethane and hexane (3:2, respectively) to give 18 mg of 32 with enriched enantiomeric purity: mp 205-207°C (lit.[24] 204-206°C), $[\alpha]_D^{20}$ -97.9 (c 0.73, CH_3OH).

(2S,3S,4S,6R)-3-acetyl-4-benzoylamino-6-methoxy-2-(methyl)tetrahydro-2H-pyran (33). To a solution of 301 mg (1.09 mmol) of lactam **29** in 10 mL of tetrahydrofuran cooled in a dry ice-acetone bath was added 1.00 mL (1.40 mmol) of 1.40 N methyllithium in ether over a 3-min period. The mixture was stirred for 30 min at -78°C, poured into 30 mL of vigorously stirred aqueous ammonium chloride and extracted with four 30-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was chromatographed over 20 g of silica gel (ethyl acetate-hexane, 1:3 and 1:2) to give 206 mg (65%) of **33** as a white solid. Further elution of the column gave 52 mg (28%) of **29**. Ketone **33**: mp 189-191°C; IR ($CDCl_3$) 3440, 1705, 1655 cm^{-1}; $[\alpha]_D^{20}$ -149.0 (c 1.04, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.32 (d, J = 6.8 Hz, 3H, CH_3), 1.83 (dd, J = 12.7, 4.0 Hz, 1H, H_{2e}), 2.17 (s, 3H, CH_3CO), 2.47 (td, J = 12.7, 4.0 Hz, 1H, H_{2a}), 3.34 (s, 3H, OCH_3), 3.44 (t, J = 3.2 Hz, 1H, CHCO), 4.24 (dq, J = 6.7, 3.2 Hz, 1H, $CHCH_3$), 4.66 (m, 1H, CHN), 4.90 (d, J = 3.7 Hz, 1H, OCHO), 6.04 (br d, J = 5 Hz, 1H, NH), 7.40-7.66 (m, 5H, ArH); exact mass calcd for $C_{16}H_{21}NO_4$ m/e 291.1470, found m/e 291.1470.

(2S,3R,4S,6R)-3-acetyl-4-benzoylamino-6-methoxy-2-(methyl)tetrahydro-2H-pyran (34). A mixture of 41 mg (0.141 mmol) of **33** and 0.040 mL (0.267 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 3 mL of benzene was heated at reflux for 5 h. The mixture was chromatographed over 15 g of silica gel (ethyl acetate-hexane, 1:1) to give 38 mg (93%) of **34** as a white solid: mp 177-178°C; IR ($CHCl_3$) 3430, 1700, 1660 cm^{-1}; $[\alpha]_D^{20}$ -61.5 (c 0.93, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.18 (d, J = 6.3 Hz, 3H, CH_3), 1.78 (dt, J = 12.9, 3.5 Hz, 1H, H_{2a}), 2.17 (ddd, J = 12.9, 4.4, 1.2 Hz, 1H, H_{2e}), 2.20 (s, 3H, CH_3CO), 2.58 (t, J = 10.8 Hz, 1H, CHCO), 3.37 (s, 3H, OCH_3), 4.13 (dq, J = 10.5, 6.3 Hz, 1H, CHMe), 4.75 (m, 1H, CHN), 4.83 (broad d, J = 2.6 Hz, 1H, OCHO), 5.98 (d, J = 7.1 Hz, 1H, NH), 7.38-7.70 (m, 5H, ArH); exact mass calcd for $C_{16}H_{21}NO_4$ m/e 291.1470, found m/e 291.1470.

(3aR,4S,6R,7aS)-1-Benzoyl-hexahydro-6-methoxy-4-methylpyrano[3,4-d]imidazol-2(3H)-one (35). A mixture of 89 mg (0.324 mmol) of lactam **29**, 56 mg (0.39 mmol) of triethylammonium azide and 26 mg (0.40 mmol) of sodium azide in 3 mL of acetone was heated at reflux for 12 h. The mixture was concentrated in vacuo and the residue was chromatographed over 10 g of silica gel (ethyl acetate-hexane, 1:1 and 2:1) to give 92 mg (98%) of **35** as a white solid: mp 203-205°C; IR ($CHCl_3$) 1740, 1660 cm^{-1}; $[\alpha]_D^{20}$ +3.64 (c 0.66, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.15 (d, J = 6.3 Hz, 3H, CH_3), 1.95 (ddd, J = 15.2, 6.9, 4.3 Hz, 1H, CH_2), 2.52 (dt, J = 15.2, 5.1 Hz, 1H, CH_2), 3.64 (dm, 1H, H_{7a}), 4.00 (qd, J = 6.3, 3.3 Hz, 1H, CHMe), 4.73-4.89 (m, 2H, OCHO and H_{3a}), 6.06 (br s, 1H, NH), 7.31-7.67 (m, 5H, ArH); exact mass calcd for $C_{15}H_{18}N_2O_4$ m/e 290.1260, found m/e 290.1315.

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