A Practical and Divergent Way to Trihydroxylated Pyrrolidine Derivatives as Potential Glycosidase Inhibitors *via* Stereoselective Intermolecular *cis*-Amidoalkylations

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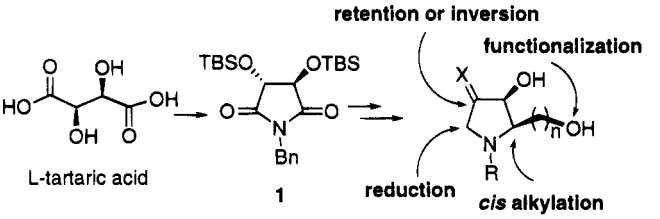
A practical and divergent way from the common tartrimide **1** to trihydroxylated pyrrolidines **2a–h** as potential glycosidase inhibitors has been developed. *cis*-Amidoalkylations on the acyliminium intermediate **5** of the corresponding TBS-protected tartaric imide with the tin reagents afforded the desired structures **6a–c** in good yields and high selectivities. In this reaction the adjacent OTBS group controls the stereoselectivity in the presence of a Lewis acid $MgBr_2$. Transformations to each desired pyrrolidine could be achieved *via* efficient methods including selective protection, functionalization of the unsaturated bonds, and reduction of the amide group.

Inhibitors of glycosidases are known to possess a variety of beneficial therapeutic effects toward tumor metastasis,[1] metabolic disorder,[2] and viral infections.[3] Among many of the reported alkaloid inhibitors which can be viewed as analogues of iminosugars, polyhydroxypyrrolidines have received unabating synthetic and biological interest.[4] Those compounds have been known to potentially inhibit glycosyltransferase as well as glycosidases.[5] Until recently, there has been a considerable amount of work directed toward the synthesis of the polyhydroxylated pyrrolidines. However, most of those synthetic approaches, which are designed for specific targets, are still not frequently used in the general application to potential analogues.[4]

As shown in Scheme 1, we describe herein a new way to trihydroxylated pyrrolidines **2a–h** from the common tartarimide intermediate **1** which is readily obtained in large quantity from L-tartaric acid.[6] This route consists of (i) intermolecular *cis*-amidoalkylation[7] on acyliminium intermediate **5** with tin reagents by exploiting the OTBS group, (ii) retention or inversion of the hydroxy group depending on necessity, (iii) functionalization of the double bond, and (iv) reduction of the amide group. This route would provide the potential glycosidase inhibitors divergently as well as practically.

Scheme 1



2a R= Bn HCl; n=2; X= αOH; βH
2b R= H HCl; n=2; X= αOH; βH
2c R= Bn HCl; n=2; X= βOH; αH
2d R= H HCl; n=2; X= βOH; αH
2e R= Bn HCl; n=1; X= αOH; βH
2f R= H HCl; n=1; X= αOH; βH
2g R= Bn HCl; n=1; X= βOH; αH
2h R= H HCl; n=1; X= βOH; αH

Results and Discussion

In order to examine stereoselective amidoalkylations, the imide **1** was reduced to β-hydroxy lactam **3** with sodium borohydride and $SnCl_2$ in ethanol/CH_2Cl_2 (quantitative yield),[8,9] and the corresponding acetoxy lactam **4** was treated with $MgBr_2$–tin reagents.[10] High syn selectivity margins, 9:1 in allenylation, >20:1 in allylation, exclusive one in propargylation, and excellent yields were observed, yielding compounds **6a**, **6b**, and **6c**, which indicate favorable orbital interaction[11,12] over steric interaction experienced during syn approach of tin nu-

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(9) The reduction afforded virtually a single isomer, which is assumed to be α-OH lactam. For similar precedent: Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987.

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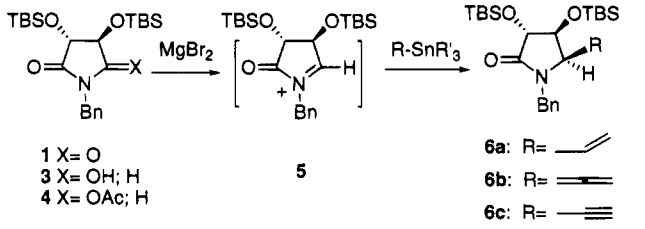
Table 1. $MgBr_2$-Catalyzed Amidoalkylation



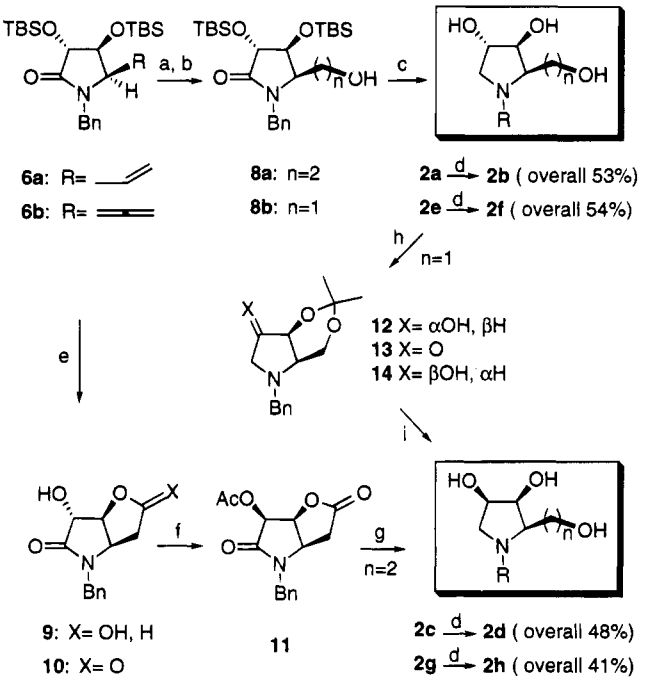
entry[a]	tin	solvent	product	ratio(*cis* : *trans*)[b]	yield[c]
1	$SnBu_3$	CH_2Cl_2	6a	21 : 1	100
2	$SnBu_3$	Toluene	6a	30 : 1	92
3	$SnBu_3$	Toluene	6b	9 : 1	100
4	$SnPh_3$	CH_2Cl_2	6c	cis only	97

[a] All reactions were performed under anhydrous conditions, adding 3 equiv of nucleophile and 2.5 equiv of fresh $MgBr_2$ to a solution of the substrate at 0 °C, slowly warming to rt, and stirring for 15–18 h. [b] As determined by ^1H NMR. [c] Isolated yields (%).

cleophiles to the resident OTBS group of intermediate **5** in the presence of $MgBr_2$ (Table 1). While the explanation of the catalysis and reagent effects on the acyliminium intermediate awaits the theoretical scrutiny, we tried to convert these requisitely functionalized amides to the potential derivatives.

For the preparation of the *xylo*-configurated deoxyimino sugars **2b** and **2f**, compound **6a** was readily transformed to alcohol **8** by ozonolysis followed by reduction (O_3, CH_2Cl_2, MeOH; DMS; $NaBH_4$, MeOH), (Scheme 2). Reduction of **8a** with borane–dimethyl sulfide complex in THF,[13] deprotection of the OTBS groups with 60% aqueous acetic acid under reflux, and purification on Amberite IRA400(OH) resin provided **2a** (75.4%, $[\alpha]^{25}_D = -14.1$ (c = 1.7, MeOH)) upon acidification with HCl. Quantitative conversion of **2a** to **2b** ($[\alpha]^{25}_D = -8.3$ (c = 0.82, H_2O)) was achieved by hydrogenation ($Pd(OH)_2$ on charcoal, 90% aqueous MeOH, 50 psi). The same procedures were applied to compound **6b** to produce **8b** (81%),[14] **2e** (99%, $[\alpha]^{24}_D = -16.1$ (c = 1.16, MeOH)), and **2f** (quantitative yield, $[\alpha]^{24}_D = +8.8$ (c = 0.68, H_2O)) sequentially. The overall yields for the new synthetic products **2b** (1,4-dideoxy-1,4-imino-D-xylitol) and **2f** (1,4,5-trideoxy-1,4-imino-D-*xylo*-hexitol) from L-tartaric acid after 10 steps were 53% and 54%, respectively. Compound **2b** was found to moderately inhibit α-glucosidase (yeast) activity (50% inhibition at 1.9×10^{-5} M), while compound **2d** weakly inhibits α-galactosidase (green coffee beans) activity (50% inhibition at 3.2×10^{-4} M) under standard assay conditions.[15]

Scheme 2[a]



[a] Reaction conditions: (a) (i) O_3; (ii) DMS; (b) $NaBH_4$, MeOH; (c) (i) AcOH, (ii) BH_3–SMe_2; (d) H_2, $Pd(OH)_2$; (e) (i) AcOH, (ii) O_3, (iii) DMS, (iv) Ag_2CO_3; (f) (i) Tf_2O, (ii) KOAc; (g) BH_3-SMe_2 (h) (i) 2,2-dimethoxypropane, (ii) oxalyl chloride, DMSO, TEA, (iii) K-Selectride; (i) AcOH.

Inversion of the C(2)-hydroxyl groups on **2b** and **2f** would afford the known *lyxo*-deoxyimino sugars **2d** and **2h**. For the preparation of **2d** first, deprotection of the OTBS groups on **6a** with 60% AcOH and ozonolysis (O_3, CH_2Cl_2, MeOH; DMS) were performed to obtain a *ca.* 3:1 anomeric mixture of hemiacetals **9** (95%), which was then oxidized by Ag_2CO_3 on Celite[16] to lactone **10** (89%). At this point the enantiomeric purity of compound **10** was determined by ^1H-NMR of its MTPA ester[17] and found to be >96% ee. The desired inversion of stereochemistry was accomplished by a two-step sequence, exposing **10** to triflic anhydride and treating the resulting triflate with potassium acetate and 18-crown-6-ether in DMF.[18] Acetylation of the crude product provided **11** in 84% yield. Treatment of the actate **11** with borane–dimethyl sulfide complex[13] in refluxing THF resulted in complete reduction of the ester and amide groups at once. After removal of excess borane, acidification of the residue with saturated HCl methanol solution afforded a glassy compound **2c** in 96% yield. On catalytic hydrogenation as above, **2c** was converted to the known L-dihydroxyhomoprolinol **2d** in quantitative yield ($[\alpha]^{25}_D = -7.4$ (c = 1.7, MeOH), mp = 135–137 °C; lit.[4b] $[\alpha]^{24}_D = -7.0$ (c = 0.193, MeOH), mp = 137–138 °C).

To prepare the *cis*-L-dihydroxyprolinol **2h**, the selective protection of the two hydroxyl groups on C(3) and C(5) of **2e** with 2,2-dimethoxypropane[19] in *N*,*N*-dimethylformamide containing a catalytic amount of anhydrous

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(12) The observations of syn addition to OTBS group in cyclic systems have been described in a few Lewis acid catalyzed reactions. Danishefsky hypothesized that in the Lewis acid catalyzed processes[12a,b] the stabilization of the emerging σ* orbital by interaction with the adjacent σ bonds becomes critical factors for the syn additions. In this alkylation, however, the possibility of (subsidiary) chelation effect with the Lewis acid cannot be excluded. Further study on the effect is in progress. (a) Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387. (b) Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.

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p-TsOH was performed first, which made the C(2) hydroxyl group of **12** available for inversion to the desired configuration. Swern oxidation[20] of **12** and K-Selectride reduction of **13** by attack exclusively from the convex face at −78 °C in THF furnished the desired product **14** in 78% yield upon single purification on silica gel column chromatography after a three-step sequence. Deprotection of the ketal group of **14** with acetic acid to **2g** and reduction followed by crystalline formation with HCl solution yielded **2h** (near quantitative yield, $[\alpha]^{20}_D$ = +18.8 (*c* = 0.16, H_2O), mp = 154−157 °C; lit.[4c,21] $[\alpha]^{20}_D$ = +19.8 (*c* = 0.45, H_2O), mp = 159−161 °C). Thus, the proline homologues **2d** and **2h** have been also prepared by the highly selective and efficient way employing minimum protecting groups and purification procedures (48% after 11 steps and 41% after 14 steps from L-tartaric acid, respectively).

In summary, we have demonstrated the general and divergent route to the potential glycosidase inhibitors **2a−h** by the selective amidoalkylations using tin reagents with $MgBr_2$ and practical sequences to each compound. This route may be extended to pyrrolizidine and indolizidine analogues *via* cyclization of their pyrrolidine homologues and applied to the therapeutic agent development.

Experimental Section

General. All commercial chemicals were used as obtained without further purification, and all solvents were carefully dried and distilled by standard methods prior to use. Column chromatography was carried out on silica gel 60 (E. Merck, 230−400 mesh) with the flash technique. Thin-layer chromatography was performed on E. Merck 60F-254 precoated silica plates (0.25 mm layer thickness). Melting points were determined on a Thomas-Hoover melting point apparatus and uncorrected. Nuclear magnetic resonance spectra were determined on a Bruker ARX 300 spectrometer. Chemical shifts are reported in δ ppm relative to $(CH_3)_4Si$ for ^1H and ^{13}C NMR. Coupling constants *J* are reported in Hz. Infrared spectra (cm^{-1}) were obtained on a Nicolet 710 FT-IR spectrometer. Mass spectra were determined on a JEOL JMS-DX303 spectrometer. High-resolution mass spectra were obtained from KRICT, Taejon, Korea. Elemental analyses were performed on a Carloerba EA 1108 instrument.

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-1-benzyl-2,5-pyrrolidinedione (1). A mixture of L-tartaric acid (9 g, 60 mmol) and benzylamine (8.52 mL, 78 mmol) in xylene (150 mL) was heated at reflux and passed through a dropping funnel packed with 4A molecular sieves in order to remove water formed for 15 h. After the mixture cooled to ice-bath temperature the precipitate was filtered and washed with cold CH_2Cl_2 to give a crude hydroxyimide as a white solid (12.5 g). A solution of the resulting solid (6.64 g, 30 mmol), *tert*-butyldimethylsilyl chloride (13.56 g, 90 mmol), and imidazole (10.21 g, 150 mmol) in DMF (100 mL) was stirred at ambient temperature overnight. A large amount of DMF was evaporated under reduced pressure to afforded a glassy mixture, which was separated on silica gel (*n*-hexane:EtOAc = 30:1) to furnish the imide **1** as a colorless oil (10.09 g, 70.4% from L-tartaric acid): $[\alpha]^{22}_D$ = +98.6 (*c* = 4.25, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 0.00, 0.06 (each s, 12H, 2 $SiMe_2$), 0.78 (s, 18H, 2 tBu), 4.17 (s, 2H, benzylic), 4.46 (s, 2H, H-3 and H-4), and 7.06−7.13 (m, 5H, Ph); IR (film) ν 1753, 1727 (imide C=O), 1467, 1346, 1254, 1173, 1135, 1076, 1030, and 905 cm^{-1}; MS (EI) *m/z* 392 (M^+ − tBu, 100), 364 (42); HRMS (Cl, NH_3) exact mass calcd for $C_{19}H_{30}NO_4Si_2$ 392.1714 (M^+ − tBu), found 392.1686.

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-1-benzyl-2-pyrrolidinone (3). To a solution of the imide **1** (7.21 g, 16.03 mmol) and tin(II) chloride (3.04 g, 16.03 mmol) in ethanol/CH_2Cl_2 (7:1,160 mL) was added sodium borohydride (3.03 g, 80.15 mmol) at 0 °C. The mixture was stirred at 0 °C for 40 min and quenched with saturated $NaHCO_3$ solution. The resulting gray mixture was extracted with CH_2Cl_2 (4 × 200 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to give the hydroxy lactam **3** as a white solid (7.23 g, quantitative): mp = 116−118 °C; $[\alpha]^{24}_D$ = −1.7 (*c* = 3.35, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ −0.17, −0.11, 0.00, 0.01 (each s, 12H, 2 $SiMe_2$), 0.64, 0.73 (each s, 18H, 2 tBu), 2.38 (d, *J* = 11.3, 1H, OH), 3.68 (dd, *J* = 2.4, 2.1, 1H, H-4), 3.80 (d, *J* = 2.4, 1H, H-3), 3.97 (d, *J* = 15.2, 1H, PhC*Ha*Hb), 4.38 (ψd, *J* = 11.3, 1H, H-5), and 4.75 (d, *J* = 15.2, 1H, PhCHa*Hb*); ^{13}C-NMR ($CDCl_3$) δ −4.83, −4.62, −4.60, −4.32 (2 $SiMe_2$), 18.10, 18.37, (2 $SiCMe_3$), 25.82, 25.96 (2 CMe_3), 43.30 (benzylic), 76.83, 78.27, 87.40 (C-3, C-4, and C-5), 127.74, 128.24, 128.88, 136.37 (Ph), and 171.99 (C=O); IR (film) ν 3370 (OH), 1690 (C=O st), 1467, 1255, 1126, 839, and 781 cm^{-1}; MS (EI) *m/z* 436 (M^+ − CH_3), 394 (100, M^+-tBu); Anal. Calcd for $C_{23}H_{41}NO_4Si_2$: C, 61.15; H, 9.15; N, 3.10. Found: C, 61.22; H, 9.34; N, 3.10.

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-acetoxy-1-benzyl-2-pyrrolidinone (4). To a solution of the hydroxy imide **3** (4.0 g, 8.85 mmol) in pyridine (30 mL) was added acetic anhydride (4.18 mL, 44.25 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h, and all volatile materials were evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and evaporated to furnish the acetoxy lactam **4** as a colorless oil (4.7 g, quantitative): $[\alpha]^{20}_D$ = +10.5 (*c* = 4.01, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ −0.21, −0.13, −0.05, 0.00 (each s, 12H, 2 $SiMe_2$), 0.62, 0.71 (each s, 18H, 2 tBu), 1.64 (s, 3H, CH_3CO), 3.78 (dd, *J* = 2.7, 1.3, 1H, H-4), 3.85 (d, *J* = 2.7, 1H, H-3), 4.08 (d, *J* = 15.2, 1H, PhC*Ha*CHb), 4.42 (d, *J* = 15.2, 1H, PhCHa*Hb*), 5.57 (d, *J* = 1.3, 1H, H-5), and 7.1 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ −6.04, −6.01, −5.89, −5.42 (2 $SiMe_2$), 16.74, 17.12 (2 $SiCMe_3$), 24.51, 24.66 (2 $SiCMe_3$), 28.68 (acetyl), 43.40 (benzylic), 75.63, 76.06 (C-3 and C-4), 85.96 (C-5), 126.84, 127.26, 127.66, 135.13 (Ph), 169.24, and 171.56 (2 C=O); IR (film) ν 1746, 1729 (C=O st), 1362, 1256, 1226, 1125, 1014, 986, 781 cm^{-1}; MS (FAB) *m/z* 478 (M^+ − Me), 436 (M^+ − tBu, 100).

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-allyl-1-benzyl-2-pyrrolidinone (6a). Method 1. To a mixture of the acetoxy lactam **4** (2.5185 g, 5.1 mmol) and allyltributyltin (2.45 mL, 7.67 mmol) in CH_2Cl_2 (40 mL) was added magnesium bromide (2.35 g, 12.76 mmol) at 0 °C. The reaction temperature was slowly elevated to room temperature with vigorous stirring overnight. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated to a crude oil, which was purified by column chromatography on silica gel with a gradient of *n*-hexane and EtOAc mixture to give a mixture of *cis*- and *trans*-allylated compound (2.43 g, quantitative: *ca.* 21:1, respectively, on the basis of ^1H-NMR).

Method 2. Using toluene instead of CH_2Cl_2 a mixture of *cis*- and *trans*-isomer (*ca.* 30:1, respectively) was obtained in 92% yield.

Data of *cis*-isomer **6a**: $[\alpha]^{23}_D$ = +91.9 (*c* = 2.9, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ −0.16, −0.06, 0.00, 0.06 (each s, 12H, 2 $SiMe_2$), 0.73, 0.79 (each s, 2 tBu), 2.11, 2.28 (each m, 2H, CH_2), 3.25 (ddd, *J* = 7.2, 5.0, 2.0, 1H, H-5), 3.81 (d, *J* = 15.0, 1H, PhC*Ha*Hb), 3.92 (dd, *J* = 7.2, 7.2, 1H, H-4), 4.11 (d, *J* = 7.2, 1H, H-3), 4.85 (m, 2H, terminal olefin), 5.59 (m, 1H, vinyl), and 7.10 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ −6.04, −6.00, −5.74, −5.36 (2 $SiMe_2$), 16.86, 17.35 (2 $SiCMe_3$), 24.60, 24.64 (2 CMe_3), 28.67 (CH_2), 43.62 (benzylic), 56.51, 74.78, 75.02 (C-3, C-4, and C-5), 117.61, 126.34, 127.14, 127.64, 133.25, 135.05 (olefin and Ph), and 170.44 (C=O); IR (film) ν 1714 (C=O st), 1480, 1465, 1400, 1370, 1255, 1121, 840, 780 cm^{-1}; MS (EI) *m/z* 418 (M^+ − tBu, 100), 155 (25), 91 (75); HRMS (Cl, NH_3) exact mass calcd for $C_{22}H_{36}NO_3Si_2$ 418.2234 (M^+ − tBu), found 418.2227.

(3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-allenyl-1-benzyl-2-pyrrolidinone (6b). To a solution of the acetoxy lactam **4** (1.0284 g, 2.08 mmol) and triphenylpropargyltin (1.62

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g, 4.16 mmol) in toluene (7 mL) was added magnesium bromide (0.9570 g, 5.2 mmol) at 0 °C. The mixture was stirred for 22 h which allowed the ice bath temperature to raise to ambient temperature spontaneously, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (*n*-hexane:EtOAc = 30:1) to give a mixture of *cis*- and *trans*-allenylated compound (0.9867 g, quantitative; *ca.* 9:1, respectively, on the basis of ^{1}H-NMR). Data of *cis*-isomer **6b**: ^{1}H-NMR ($CDCl_3$) δ −0.16, −0.10, 0.00, 0.06 (each s, 12H, 2 $SiMe_3$), 0.72, 0.78 (each s, 18H, 2 tBu), 3.72 (m, 2H, PhC*Ha*CHb and H-5), 3.96 (dd, J = 7.0, 6.8, 1H, H-4), 4.06 (d, J = 6.8, 1H, H-3), 4.62 (m, 2H, =CH_2), 4.81 (d, J = 14.9, 1H, PhCHa*Hb*), 4.87 (m, 1H, HC=), and 7.09 (m, 5H, Ph); IR (film) ν 1927 (C=C=C as. st.), 1721 (C=O), 1430, 1256, 1110, 1076, 839, and 782 cm^{-1}; MS (EI) *m/z* 416 (M^+ − tBu, 15), 394 (80), 351 (100), 197 (30), 154 (30), 91 (65); HRMS (Cl, NH_3) exact mass calcd for $C_{22}H_{34}NO_3Si_2$ 416.2078 (M^+ − tBu), found 416.2081.

(3*R*,4*R*,5*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-propargly-1-benzyl-2-pyrrolidinone (6c). To a solution of the acetoxy lactam **4** (0.1580 g, 0.32 mmol) and triphenylallenyltin (0.3735 g, 0.96 mmol) in CH_2Cl_2 (3 mL) was added magnesium bromide (0.1503 g, 0.8 mmol) at 0 °C. The reaction temperature was spontaneously elevated to ambient temperature with constant stirring overnight. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated to give an oil, which was separated on silica gel (*n*-hexane:EtOAc = 30:1) to furnish the *cis*-propagylated compound **6c** as a colorless oil (0.1471 g, 97%): $[\alpha]^{24}_D$ = +93.3 (*c* = 4.65, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ −0.16, −0.06, 0.00, 0.06 (each s, 12H, 2 $SiMe_2$), 0.73, 0.79 (each s, 18H, 2 tBu), 1.83 (dd, J = 2.7, 2.6, 1H, alkynyl), 2.22 (ddd, J = 17.1, 5.0, 2.6, 1H, C*Ha*Hb), 2.36 (ddd, J = 17.1, 5.2, 2.7, 1H, CHa*Hb*), 3.30 (ddd, J = 7.0, 5.2, 5.0, 1H, H-2), 3.96 (dd, J = 7.2, 7.0, 1H, H-3), 3.97 (d, J = 15.1, 1H, PhC*Ha*Hb), 4.33 (d, J = 7.2, 1H, H-4), 4.89 (d, J = 15.1, 1H, PhCHa*Hb*), and 7.08−7.17 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ −4.74, −4.72, −4.60, −4.21 (2 $SiMe_2$), 17.99, 18.39 (2 Si*C*Me_3), 25.75, 25.86 (2 SiC*Me*$_3$), 29.70 (CH_2), 44.74 (benzylic), 56.67, 71.33, 75.20, 75.62, 80.87 (alkynyl, C-3, C-4, and C-5), 127.75, 128.18, 128.70, 135.88 (Ph), and 171.80 (C=O); IR (film) ν 3310 (alkynyl CH st), 2120 (alkynyl st), 1715 (C=O st), 1467, 1255, 1121, 839, 780 cm^{-1}; MS (EI) *m/z* 416 (M^+ − tBu, 100), 388 (5), 268 (5), 91 (75); HRMS (Cl, NH_3) exact mass calcd. for $C_{22}H_{34}NO_3Si_2$ 416.2078 (M^+ − tBu), found 416.2093.

(3*R*,4*R*,5*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-(2-hydroxyethyl)-1-benzyl-2-pyrrolinone (8a). A solution of **6a** (350 mg, 0.7356 mmol) in methanol (15 mL) was treated with O_3/O_2 stream at −78 °C until the blue color persisted (*ca.* 1 h). After N_2 purging methyl sulfide (0.5 mL) was added to the reaction mixture, which was stirred overnight. To the resulting mixture was added sodium borohydride (0.2241 g, 5.92 mmol) at 0 °C. After the mixture was stirred for 2 h at 0 °C, saturated $NaHCO_3$ solution was added to the solution, which was extracted with CH_2Cl_2 several times. The combined organic extracts were dried over $MgSO_4$ and evaporated to give an oil, which was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 10:1) to afford a glassy compound **8a** (0.3530 g, quantitative): $[\alpha]^{22}_D$ = +54.7 (*c* = 3.96, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ −0.13, −0.04, 0.00, 0.07 (each s, 12H, 2 $SiMe_2$), 0.73, 0.78 (each s, 18H, 2 tBu), 1.59, 1.79 (each m, 2H, CH_2), 2.24 (bs, 1H, OH), 3.38 (m, 3H, CH_2OH and H-5), 3.86 (d, J = 15.0, 1H, PhC*Ha*Hb), 3.97 (dd, J = 7.2, 7.2, 1H, H-4), 4.15 (d, J = 7.2, 1H, H-3), 4.73 (d, J = 15.0, 1H, PhCHa*Hb*), and 7.10 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ −4.47, −4.43, −4.29, −3.95 (2 $SiMe_2$), 18.13, 18.59 (2 Si*C*Me_3), 26.00, 26.09, (2 C*Me*$_3$), 30.50 (CH_2), 45.01 (benzylic), 55.99, 58.69, 75.86, 75.99 (C-3, C-4, C-5, and CH_2OH), 127.88, 128.46, 128.84, 136.34 (Ph), and 171.76 (C=O); IR (film) ν 3438 (OH), 1710, 1689 (C=O free and H-bonded), 1464, 1394, 1360, 1255, 1186, 1123, 840 cm^{-1}; MS (FAB) *m/z* 464 (M^+ − Me), 422 (M^+ − tBu).

(2*R*,3*R*,4*R*)-2-(2-Hydroxyethyl)-3,4-dihydroxy-1-benzylpyrrolidine Hydrochloride (2a). To a solution of **8a** (0.1369 g, 0.2855 mmol) in THF (5 mL) was added borane−methyl sulfide complex (2 M solution in THF, 0.7 mL, 1.4 mmol) at 0 °C. The solution was stirred for 24 h, quenched with saturated Na_2SO_4 solution, and evaporated *in vacuo*. The resulting aqueous residue was extracted with CH_2Cl_2 several times. The combined organic extracts were dried over $MgSO_4$ and evaporated to give a colorless oil, which was mixed with 60% aqueous AcOH (20 mL) and heated at reflux overnight. After the solution cooled to ambient temperature, it was evaporated under reduced pressure to give an oily residue, which was dissolved in water and filtered. The filtrate was eluted through a column packed with Amberlite IRA400(OH) ion exchange resin. The effluent was acidified by 1 N HCl and lyophilized to give **2a** as a thick oil (58.9 mg, 75.4%): $[\alpha]^{25}_D$ = −14.1 (*c* = 1.7, MeOH); ^{1}H-NMR (CD_3OD) δ 1.82, 2.08 (each m, 2H, CH_2), 3.22 (m, 2H, CH_2OH), 3.54 (m, 1H), 3.58 (m, 1H), 3.68 (m, 1H), 3.88 (m, 1H), 4.19 (bs, 1H), 4.24 (d, J = 12.8, 1H, PhC*Ha*Hb), 4.59 (d, J = 12.8, 1H, PhCHa*Hb*), 7.45 (m, 5H, Ph); ^{13}C-NMR (CD_3OD) δ 27.80 (CH_2), 57.99, 58.56, 58.89, 66.95, 74.43, 75.25 (C-2, C-3, C-4, C-5, CH_2OH and benzylic), 129.13, 129.39, 130.93, and 131.80 (Ph); MS (FAB) *m/z* 238 (M^+ − Cl).

(2*R*,3*R*,4*R*)-2-(2-Hydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (2b). A mixture of **2a** (68.6 mg, 0.251 mmol) and $Pd(OH)_2$ on charcoal (200 mg) in 90% aqueous MeOH (10 mL) was hydrogenated at 50 psi overnight. The mixture was filtered, and the filtrate was acidified with 1 N HCl. After the organic solvent was evaporated the aqueous solution was lyophilized to afford a glassy compound **2b** (46.0 mg, quantitative): $[\alpha]^{25}_D$ = −8.3 (*c* = 0.82, H_2O); ^{1}H-NMR (D_2O) δ 1.98 (m, 2H, CH_2), 3.16 (d, J = 13.1, 1H), 3.56 (dd, J = 13.1, 4.5, 1H), 3.67 (m, 2H), 3.79 (m, 1H), and 4.15 (d, J = 2.5, 1H), 4.29 (d, J = 4.5, 1H); ^{13}C-NMR (D_2O) δ 28.17, 50.88, 58.87, 60.36, 74.18, and 75.41; MS (FAB) *m/z* 148 (M^+ − Cl, 100).

(1*R*,4*R*,5*R*)-2-Benzyl-4,7-dihydroxy-6-oxa-2-azabicyclo-[3.3.0]octan-3-one (9). A mixture of **6a** (0.2041 g, 0.4289 mmol) in 60% aqueous AcOH (75 mL) was heated at 100 °C overnight. The mixture was cooled to ambient temperature and evaporated *in vacuo* to give a diol (0.1061 g, quantitative). A solution of the diol (0.6372 g, 2.577 mmol) in MeOH (35 mL) was treated with O_3/O_2 stream at −78 °C for 2 h. After N_2 purging, methyl sulfide (2.5 mL) was added to the colorless solution, which was stirred overnight and evaporated to give an oil. Crystallization of the resulting oil in CH_2Cl_2 afforded a crystalline hemiacetal **9** (0.6102 g, 95.0%; *ca.* 3:1 mixture of anomers on the basis of ^{1}H-NMR): ^{1}H-NMR of major anomer (DMSO-d_6) δ 1.89, 1.94 (each m, 2H, CH_2), 3.97 (dd, J = 5.6, 1.5, 1H, H-4), 4.10 (d, J = 15.0, 1H, PhC*Ha*Hb), 4.11 (m, 1H, H-1), 4.30 (dd, J = 4.3, 1.5, 1H, H-5), 4.66 (d, J = 15.0, 1H, PhCHa*Hb*), 5.38 (m, 1H, H-7), 6.01 (d, J = 5.6, 1H, OH), 6.32 (d, J = 4.9, 1H, hemiacetal OH), and 7.30 (m, 5H, Ph).

(1*R*,5*R*,8*R*)-6-Benzyl-8-hydroxy-2-oxa-6-azabicyclo[3.3.0]-octane-3,7-dione (10). A mixture of the hemiacetal **9** (0.6680 g, 2.6798 mmol) and Ag_2CO_3/Celite (15.4 g) in toluene (120 mL) was heated at reflux overnight. The mixture was cooled to room temperature and filtered and the filtrate evaporated to give the lactone **10** was a thick oil (0.5921 g, 89.4%): $[\alpha]^{25}_D$ = +66.0 (c = 1.085, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.54 (dd, J = 18.5, 3.1, 1H, Ha-4), 2.64 (dd, J = 18.5, 7.0, 1H, Hb-4), 4.13 (d, J = 15.0, 1H, PhC*Ha*Hb), 4.33 (ddd, J = 7.0, 6.0, 3.1, 1H, H-5), 4.52 (bs, 1H, H-8), 4.86 (d, J = 15.0, 1H, PhCHa*Hb*), 4.90 (dd, J = 6.0, 1.4, 1H, H-1), and 7.25 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ 32.85, 45.63, 55.97, 73.69, 81.31 (C-1, C-4, C-5, C-8, and benzylic), 128.39, 128.66, 129.46, 134.49 (Ph), 173.02, and 173.79 (2 C=O); IR (film) ν 3323 (OH), 1788, 1689 (2 C=O st), 1447, 1359, 1236, 1164, 1054 cm^{-1}; MS (EI) *m/z* 247 (M^+, 30), 184 (10), 163 (15), 106 (90), 91 (100); HRMS (Cl, NH_3) exact mass calcd for $C_{13}H_{13}NO_4$ 247.0845, found 247.0837.

(1*R*,5*R*,8*S*)-6-Benzyl-8-acetoxy-2-oxa-6-azabicyclo[3.3.0]-octane-3,7-dione (11). To a solution of the lactone **10** (0.5921 g, 2.3947 mmol) in CH_2Cl_2 (5 mL) were added pyridine (1 mL, 12.4 mmol) and trifluoromethanesulfonic anhydride (0.8 mL, 4.7077 mmol) at 0 °C. The solution was stirred for 1 h, and all volatile materials were evaporated *in vacuo*. The residue was dissolved in DMF (10 mL), and anhydrous potassium acetate (2.35 g, 23.94 mmol) and 18-crown-6-ether (6.33 g, 23.95 mmol) were added at 0 °C. The solution was stirred for 26 h at ambient temperature and evaporated to give an oil,

which was dissolved in CH_2Cl_2, washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine in sequence, dried over $MgSO_4$, and evaporated to afford an amber-brown oil. This material was treated with acetic anhydride (2.4 mL, 25.18 mmol) and pyridine (5 mL) in CH_2Cl_2 (5 mL) overnight. After concentration *in vacuo* the residue was chromatographed on silica gel (*n*-hexane:EtOAc = 5:1) to give the acetate **11** as a colorless oil (0.5834 g, 84.2%): $[\alpha]^{19}_D = +68.6$ (c = 2.72, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.16 (s, 3H, acetyl), 2.57 (dd, J = 18.4, 6.1, 1H, Ha-4), 2.66 (J = 18.4, 1.8, 1H, Hb-4), 4.06 (d, J = 15.0, 1H, PhC*Ha*Hb), 4.14 (ddd, J = 6.1, 5.5, 1.8, 1H, H-5), 4.89 (d, J = 15.0, 1H, PhCHa*Hb*), 5.11 (dd, J = 5.9, 5.5, 1H, H-1), 5.26 (d, J = 5.9, 1H, H-8), and 7.15–7.28 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ 20.40 (CH_2), 32.22, 44.91, 51.84, 70.65, 74.03 (C-3, C-4, C-5, benzylic, and acetyl), 128.14, 128.45, 129.23, 134.67 (Ph), 167.48, 170.20, and 173.01 (3 C=O); IR (film) ν 1790, 1749, 1715 (3 C=O st), 1444, 1358, 1228, 1114 cm^{-1}; MS (EI) m/z 229 (M^+-CH_3CO_2H, 65), 184 (60), 156 (15), 91 (100); HRMS (Cl, NH_3) exact mass calcd for $C_{13}H_{11}NO_3$ 229.0739, found 229.0738.

(2*R*,3*R*,4*S*)-2-(2-Hydroxyethyl)-3,4-dihydroxy-1-benzylpyrrolidine Hydrochloride (2c). To a solution of the acetate **11** (0.3471 g, 1.2 mmol) in THF (2 mL) was added BH_3–SMe_2 (2 M solution in THF, 9 mL, 18 mmol) at 0 °C. The solution was heated at reflux overnight and cooled to room temperature. Methanol (10 mL) was added dropwise to the mixture, which was stirred overnight and evaporated to dryness. The residue was acidified with saturated HCl solution in methanol. Evaporation gave a glassy compound **2c** (0.3150 g, 96%): $[\alpha]^{25}_D = -20.4$ (c = 1.93, MeOH); ^{1}H-NMR (D_2O) δ 1.82, 2.04 (each m, 2H, CH_2), 3.42 (dd, J = 12.4, 7.3, 1H, Ha-5), 3.52 (dd, J = 12.4, 7.3, 1H, Hb-5), 3.53 (m, 1H), 3.60 (m, 2H, CH_2OH), 4.15 (d, J = 13.0, PhC*Ha*Hb), 4.25 (dd, J = 3.9, 3.1, 1H), and 4.33–4.45 (m, 2H); ^{13}C-NMR (D_2O) δ 28.07 (CH_2), 54.92, 58.14, 61.74, 67.38, 68.82, 70.31 (C-2, C-3, C-4, C-5, CH_2OH, and benzylic), 129.44, 129.57, 130.45, and 131.18 (Ph).

(2*R*,3*R*,4*S*)-2-(Hydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (2d). A solution of **2c** (0.1461 g, 0.5337 mmol) in 90% aqueous MeOH (10 mL) was hydrogenated at 50 psi over $Pd(OH)_2$ on charcoal (200 mg) for 12 h. The mixture was filtered, and the filtrate was acidified with 2 N HCl solution. After organic solvent was evaporated the aqueous residue was lyophilized to furnish **2d** as an off-white solid (98 mg, quantitative): mp = 135–137 °C (lit.[4b] mp 137–138 °C); $[\alpha]^{25}_D = -7.4$ (c = 1.7, MeOH) (lit.[4b] $[\alpha]^{25}_D = -7.0$ (c = 0.193, MeOH)); ^{1}H-NMR (D_2O) δ 1.95 (m, 2H), 3.02 (dd, J = 12.0, 8.1, 1H), 3.44 (dd, J = 12.0, 8.2, 1H), 3.55–3.66 (m, 3H), 4.14 (dd, J = 3.6, 3.5, 1H), and 4.41 (ddd, J = 12.0, 4.0, 3.9, 1H); ^{13}C-NMR (D_2O) δ 28.88, 47.08, 58.56, 60.25, 70.18, and 70.80.

(3*R*,4*R*,5*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-(hydroxymethyl)-1-benzyl-2-pyrrolidinone (8b). A solution of the allene **6b** (a 9:1 mixture of *cis*- and *trans*-isomer; 0.8800 g, 1.86 mmol) in MeOH (45 mL) and CH_2Cl_2 (5 mL) was treated with O_3/O_2 stream for 8 h. After N_2 purging, methyl sulfide (1.5 mL) was added to the colorless solution, which was stirred overnight. To a resulting solution was added sodium borohydride (0.700 g, 18.6 mmol) at 0 °C. The mixture was stirred for 2 h at rt. Saturated $NaHCO_3$ solution was added to the mixture, which was extracted with CH_2Cl_2 (50 mL × 5). The combined organic extracts were dried over $MgSO_4$ and evaporated to give an oily mixture (0.8148 g, *ca.* 9:1 mixture of *cis*- and *trans*-isomer). A separation of the mixture of *cis*- and *trans*-isomer by column chromatography on silica gel (*n*-hexane:EtOAc = 10:1) afforded a pure *cis*-isomer **8b** as a white solid (0.6504 g, 81.0%): mp = 84–85 °C; $[\alpha]^{22}_D = +84.9$ (c = 0.325, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ −0.12, −0.04, 0.00, 0.07 (each s, 12H, 2 $SiMe_2$), 0.70, 0.78 (each s, 18H, 2 tBu), 1.89 (bs, 1H, OH, exchangeable), 3.18 (ddd, J = 7.4, 2.6, 2.4, 1H, H-5), 3.49 (dd, J = 12.5, 2.6, 1H, C*Ha*Hb), 3.57 (dd, J = 12.5, 2.4, 1H, CHa*Hb*), 3.98 (d, J = 15.1, 1H, PhC*Ha*Hb), 4.08 (dd, J = 7.4, 6.7, 1H, H-4), 4.26 (d, J = 6.7, 1H, H-3), 4.73 (d, J = 15.1, 1H, PhCHa*Hb*), and 7.13 (m, 5H, Ph); IR (film) ν 3454 (OH), 1696 (C=O), 1467, 1255, 1121, 838, 779 cm^{-1}; MS (EI) m/z 450 (M − CH_3), 408 (100, M − tBu). Anal. Calcd for $C_{24}H_{43}NO_4Si_2$: C, 61.89; H, 9.31; N, 3.01. Found: C, 62.20; H, 9.60; N, 2.96.

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)-3,4-dihydroxy-1-benzylpyrrolidine Hydrochloride (2e). To a solution of **8b** (0.5721 g, 1.2283 mmol) in THF (16 mL) was added BH_3–SMe_2 (2 M solution in THF, 6.14 mL, 12.3 mmol) at 0 °C. The mixture was stirred overnight at ambient temperature, quenched by an addition of saturated Na_2SO_4 solution, and evaporated. The aqueous residue was extracted with CH_2Cl_2 several times. The combined organic extracts were dried over $MgSO_4$ and evaporated to give a colorless oil, which was treated with refluxing 60% aqueous AcOH (40 mL) overnight. After evaporation of all volatile materials the oily residue was dissolved in water. The aqueous solution was passed through a column of Amberlite IRA400(OH) ion exchange resin. The effluent was acidified with 2 N HCl solution and lyophilized to furnish a glassy product **2e** (0.3157 g, 99%): $[\alpha]^{24}_D = -16.1$ (c = 1.16, MeOH); ^{1}H-NMR (CD_3OD) δ 3.26 (m, 1H), 3.55 (dd, J = 12.7, 3.8, 1H), 3.82–3.94 (m, 3H), 4.17 (m, 1H), 4.21–4.30 (m, 2H), 4.71 (d, J = 12.7, 1H), and 7.31–7.54 (m, 5H, Ph); ^{13}C-NMR (CD_3OD) δ 59.28, 59.28, 63.97, 73.80, 76.22, 77.09 (C-2, C-3, C-4, C-5, CH_2OH, and benzylic), 130.65, 131.36, 132.27, and 132.49 (Ph); MS (FAB) m/z 224 (M^+ − Cl, 100).

(2*R*,3*R*,4*R*)-2-(Hydroxymethyl)-3,4-dihydroxypyrrolidine Hydrochloride (2f). A solution of **2e** (0.1640 g, 0.6314 mmol) in 90% aqueous MeOH (10 mL) was hydrogenated (50 psi) over $Pd(OH)_2$ on charcoal (200 mg) overnight. The mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in water and passed through a column of Amberlite IRA400(OH) ion exchange resin. The aqueous effluent was acidified with 2 N HCl solution and lyophilized to give the pyrrolidine hydrochloride **2f** as a thick oil (0.1070 g, quantitative): $[\alpha]^{24}_D = +8.8$ (c = 0.68, H_2O); ^{1}H-NMR (D_2O) δ 3.15 (d, J = 13.0, 1H), 3.50 (dd, J = 13.0, 4.1, 1H), 3.75 (m, 2H), 3.86 (d, J = 13.0, 8.7, 1H), 4.17 (bs, 1H), and 4.22 (d, J = 3.3, 1H); ^{13}C-NMR (D_2O) δ 50.81, 57.52, 63.28, 74.60, and 74.60; MS (FAB) m/z 134 (M^+ − Cl, 53), 116 (20), 102 (100).

(1*R*,4*R*,5*R*)-2-Benzyl-4-hydroxy-7-dimethyl-6,8-dioxa-2-azabicyclo[3.4.0]nonane (12). A solution of **2e** (91.68 mg, 0.353 mmol), *p*-toluenesulfonic acid anhydrous (61.4 mg, 0.353 mmol), and 2,2-dimethoxypropane (0.221 mL, 1.765 mmol) in DMF (2 mL) was stirred overnight at ambient temperature. The solution was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to give **12** as a colorless oil (90.5 mg, 97.4%): ^{1}H-NMR ($CDCl_3$) δ 1.41, 1.42 (each s, 6H, CMe_2), 2.32 (dd, J = 9.8, 6.5, 1H), 2.90 (m, 2H), 3.28 (dd, J = 9.8, 6.2, 1H), 3.55 (m, 2H), 3.66 (ABq, J = 13.0, 2H, benzylic), 4.07 (dd, J = 6.2, 2.5, 1H), 4.22 (ddd, J = 6.5, 6.2, 2.5, 1H) and 7.25 (m, 5H, Ph); IR (film) ν 3407 (OH), 1456, 1379, 1282, 1173, 1124, 1090 cm^{-1}.

(1*R*,4*R*,5*R*)-2-Benzyl-7-dimethyl-6,8-dioxa-2-azabicyclo-[3.4.0]nonan-4-one (13). To a solution of oxalyl chloride (0.226 mL, 2.6 mmol) in CH_2Cl_2 (2 mL) at −60 °C was added a solution of methyl sulfoxide (0.403 mL, 5.68 mmol) in CH_2Cl_2 (0.2 mL). A solution of **12** (0.3423 g, 1.3 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the reaction mixture at −70 °C. The solution was stirred at −15 °C for 40 min. At −30 °C a solution of triethylamine (18 mL) in CH_2Cl_2 (0.6 mL) was added to the solution, which was stirred at −15 °C for 10 min. After addition of water the mixture was extracted with CH_2Cl_2. The organic layer was washed with cold 1 N HCl, saturated $NaHCO_3$ solution, and brine in sequence, dried over $MgSO_4$, and evaporated to give the ketone **13** (0.3363 g, 99%): ^{1}H-NMR ($CDCl_3$) δ 1.41, 1.42 (each s, 6H, CMe_2), 2.89 (d, J = 17.6, 1H, Ha-3), 3.10 (dd, J = 10.7, 5.1, 1H), 3.47 (d, J = 17.6, 1H, Hb-3), 3.62 (d, J = 13.2, 1H, PhC*Ha*Hb), 3.87 (m, 2H), 3.93 (d, J = 13.2, 1H, PhCHa*Hb*), 4.15 (d, J = 6.1, 1H), and 7.25 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$) δ 22.30, 26.61 (CMe_2), 29.92, 41.15, 45.81, 58.29, 70.78 (C-1, C-3, C-5, C-9, and benzylic), 99.99 (CMe_2), 127.88, 128.78, 129.11, 137.14 (Ph), and 209.18 (C=O); IR (film) ν 1655 (C=O st), 1452, 1380, 1270, 1236, 1200, 1118 cm^{-1}; MS (EI) m/z 261 (M^+, 3), 149 (100), 133 (28), 91 (85); HRMS (Cl, NH_3) exact mass calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1339.

(1*R*,4*S*,5*R*)-2-Benzyl-4-hydroxy-7-dimethyl-6,8-dioxa-2-azabicyclo[3.4.0]nonane (14). To a solution of K-Selectride in THF (1M solution, 2 mL, 2 mmol) was added dropwise a solution of the ketone **13** (0.120 g, 0.4592 mmol) in THF (1 mL) at −78 °C. The solution was stirred for 30 min at −78 °C and quenched with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 several times. The combined extracts were dried over $MgSO_4$ and evaporated to give a yellow oil, which was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2.1) to give a pure compound **14** (95.7 mg, 79%): ^{1}H-NMR ($CDCl_3$) δ 1.40, 1.42 (each s, 6H, CMe_2), 2.04 (bs, 1H), 2.51 (dd, J = 10.7, 5.2, 1H), 2.70 (dd, J = 12.2, 6.1, 1H), 3.07 (dd, J = 10.7, 2.2, 1H), 3.56 (m, 2H), 3.65 (ABq, J = 13.2, 2H, benzylic), 4.26 (m, 2H), and 7.29 (m, 5H, Ph); IR (film) ν 3430 (OH), 1456, 1377, 1232 cm^{-1}; MS (EI) *m/z* 263 (M^+, 13), 191 (46), 149 (81), 91 (100); HRMS (Cl, NH_3) exact mass calcd for $C_{15}H_{19}NO_3$ 263.1521, found 263.1513.

(2*R*,3*R*,4*S*)-2-(Hydroxymethyl)-3,4-dihydroxy-1-benzylpyrrolidine Hydrochloride (2g). A mixture of **14** (90.7 mg, 0.3444 mmol) in 80% aqueous AcOH (20 mL) was heated at 100 °C for 30 min. All volatile materials were evaporated *in vacuo*, and the residue was dissolved in water. The aqueous solution was eluted through a column of Amberlite IRA400-(OH) ion exchange resin. The effluent was acidified with 2 N HCl solution and lyophilized to afford **2g** as a colorless thick oil (89.3 mg, 99.8%): $[\alpha]^{25}_D$ = −8.5 (*c* = 0.27, MeOH); ^{1}H-NMR (CD_3OD) δ 3.31 (m, 1 H), 3.44 (dd, J = 11.9, 5.6, 1H), 3.78−3.90 (m, 2H), 4.02 (dd, J = 11.9, 8.0, 1H), 4.37 (d, J = 12.9, 1H, PhC*Ha*Hb), 4.39 (m, 1H, 2H), 4.70 (d, J = 12.9, 1H, PhCHa*Hb*), and 7.40−7.64 (m, 5H, Ph); ^{13}C-NMR (CD_3OD) δ 57.30, 59.69, 61.32, 70.68, 71.68, 72.42 (C-2, C-3, C-4, C-5, CH_2-OH, and benzylic), 130.58, 131.43, 131.61, and 132.66 (Ph); MS (FAB) *m/z* 224 (M^+ − Cl, 100).

(2*R*,3*R*,4*S*)-2-(Hydroxymethyl)-3,4-dihydroxypyrrolidine Hydrochloride (2h). A solution of **2g** (46.2 mg, 0.1779 mmol) in 90% aqueous MeOH (5 mL) was hydrogenated at 50 psi over $Pd(OH)_2$ on charcoal (50 mg) for 18 h. The mixture was filtered, and the filtrate was acidified with 2 N HCl solution. Lyophilization of the solution gave the pyrrolidine hydrochloride **2h** as an off-white solid (30.1 mg, 99.8%): mp = 154−157 °C (lit.[21] mp = 159−161 °C); $[\alpha]^{20}_D$ = +18.8 (*c* = 0.16, H_2O) (lit.[21] $[\alpha]^{20}_D$ = +19.8 (*c* = 0.45, H_2O)); ^{1}H-NMR (D_2O) δ 3.12 (dd, J = 12.1, 7.3, 1H, C*Ha*HbOH), 3.45 (dd, J = 12.1, 7.3, 1H, CHa*Hb*OH), 3.66 (ddd, J = 8.3, 4.9, 4.1, 1H, H-4), 3.80 (dd, J = 12.1, 8.3, 1H, Ha-5), 3.90 (dd, J = 12.1, 4.9, 1H, Hb-5), 4.26 (dd, J = 4.1, 4.1, 1H, H-3), 4.41 (ddd, J = 7.3, 7.3, 4.1, 1H, H-2); ^{13}C-NMR (D_2O) δ 47.31, 57.86, 62.71, 70.03, and 70.19.

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Supplementary Material Available: Copies of both ^{1}H and ^{13}C NMR spectra of **1**, **2a**, **2b**, **2c**, **2e**, **2f**, **2g**, **4**, **6a**, **6c**, **8a**, **10**, **11**, and **13** and ^{1}H NMR spectra of **6b**, **9**, **12**, and **14** (32 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.

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