Toward a General Strategy for the Synthesis of 3,4-Dihydroxyprolines from Pentose Sugars

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A general strategy is proposed, wherein a pentose sugar γ-lactone can be converted, via a series of nine reactions, to a 3,4-dihydroxyproline, suitably protected for use in peptide synthesis. Thus, D-ribonolactone (**6**) has been converted to *N*-fluorenylmethoxycarbonyl-3,4-di-*O*-*tert*-butyldimethylsilyloxy-D-2,3-*cis*-3,4-*cis*-proline (**7**) in 18.9% overall yield. Likewise, L-arabinonolactone (**11**) has been converted to *N*-fluorenylmethoxycarbonyl-3,4-di-*O*-*tert*-butyldimethylsilyloxy-L-2,3-*cis*-3,4-*trans*-proline (**36**) in 13.7% overall yield and L-lyxonolactone (**12**) to *N*-fluorenylmethoxycarbonyl-3,4-di-*O*-*tert*-butyldimethylsilyloxy-L-2,3-*trans*-3,4-*cis*-proline (**37**) in 11.2% overall yield. These building blocks have also been fully deprotected to give the free amino acids. We believe that this series of reactions ought to be applicable to the synthesis of any of the eight stereoisomers of 3,4-dihydroxyproline, by judicious selection of the pentose starting material.

Introduction

3,4-Dihydroxyproline (DHP) contains three stereogenic centers: C2, C3, and C4. There are eight possible stereoisomers. Three members of the L-series have been isolated from natural sources (Figure 1).[1] The L-2,3-*cis*-3,4-*trans* isomer (**1**) was isolated from the cell wall hydrolysates of the diatom *Navicula pelliculosa* almost 30 years ago.[2] In 1980, the L-2,3-*trans*-3,4-*trans* isomer (**2**) was isolated from the acid hydrolysates of the toxic mushroom *Amanita virosa* and identified in the virotoxin cyclic heptapeptides.[3] In 1994, the L-2,3-*trans*-3,4-*cis* isomer **3** was identified as the sixth residue in the repeating decapeptide sequence of Mefp1, an adhesive protein produced by the marine mussel *Mytilus edulis*.[4]

There is a plethora of DHP syntheses in the literature.[5] Indeed, our first synthesis involved an adaptation of Fleet's chemistry[6] to convert D-gulonolactone (**4**) to compound **5** (Scheme 1),[7] a building block that has proven useful in peptide synthesis.[8] However, our ultimate goal was to investigate the role of DHPs in nature. To properly investigate SARs, we sought an alternative synthetic strategy with the potential to afford all eight stereoisomers.

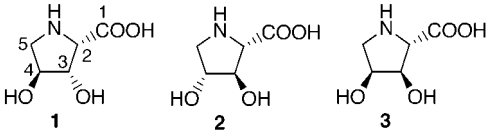
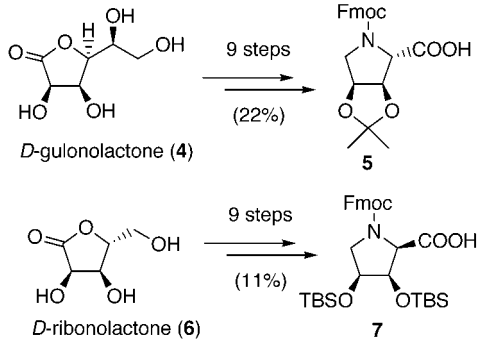


Figure 1. Naturally occurring 3,4-dihydroxyprolines.

Scheme 1



Most existing syntheses were limited, by their reaction chemistry, to the synthesis of only a subset of the eight stereoisomers. For example, *syn*-dihydroxylation of a 3,4-dehydroproline[5c,9] can lead only to DHPs with 3,4-*cis* relative stereochemistry. Conversely, the opening of an epoxide has been a useful tool in the synthesis of DHPs

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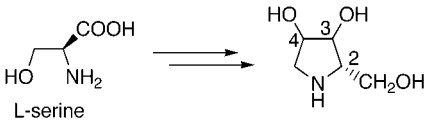
Scheme 2



with 3,4-*trans* relative stereochemistry.[10,11] We had found Fleet's chemistry to be effective and efficient, but valuable reaction steps were expended excising a carbon atom, and a stereogenic center was destroyed in the process. Moreover, the use of the acetonide protecting group is only useful with DHPs that have a 3,4-*cis* relative stereochemistry.

While producing the whole gamut of stereoisomers has not been the objective of previous DHP syntheses, this philosophy has been of interest in a closely related group of compounds. Polyhydroxylated pyrrolidines[5a,12] and piperidines[13] have been recognized as potent glycosidase inhibitors for many years; D-lactams have also been investigated recently.[14] In some syntheses of these molecules, there has been a deliberate attempt to produce a large number of stereoisomers. A good example is the work of Huang et al., who prepared four stereoisomers of 2-hydroxymethyl-3,4-dihydroxypyrroline from L-serine in six steps (Scheme 2).[5a] The other four stereoisomers should be accessible from D-serine. Their approach could be described as "stereodivergent" in that there are two steps in their sequence where stereochemical diversity is introduced. Thus, a mixture of diastereoisomers is produced in some reaction steps, which provides rapid access to variable amounts of each stereoisomer.

Our approach is complementary: while we would potentially like to be able to access any stereoisomer, we would like to be able to produce a single compound in an efficient and predictable manner. Thus, our second-generation synthesis utilizes the pentose sugars as the source of chirality. The three stereogenic centers of the monosaccharide are transmitted, via a predictable series of reactions, to the three stereogenic centers of the amino acid. In a preliminary communication, we described the conversion of D-ribono-γ-lactone (**6**) to compound **7** (Scheme 1).[15] We proposed that this synthesis ought to be generally applicable to the synthesis of 3,4-dihydroxyprolines. We now report the conversion of two additional pentose sugars to 3,4-dihydroxyprolines, to demonstrate the generality of this approach.

Results and Discussion

Our retrosynthetic analysis is outlined in Scheme 3. In the final stages of our synthesis, we need to selectively deprotect the primary alcohol and oxidize it to the carboxylic acid (phase III). The pyrrolidine ring system will be generated using Fleet's double displacement chemistry (phase II). The substrate for this can be envisioned to arise from a pentose γ-lactone (phase I).

Scheme 3

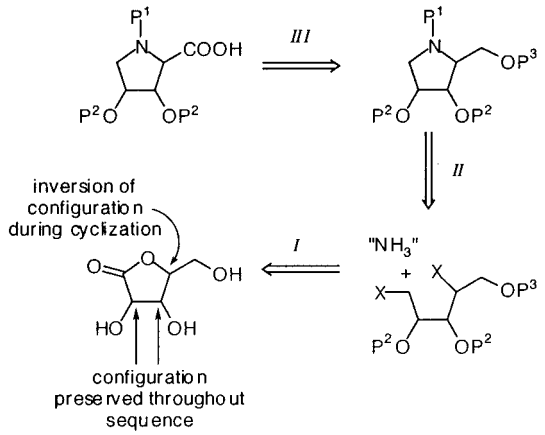


Table 1. Retrosynthetic Analysis of 3,4-Dihydroxyprolines

DHP isomer		pentose precursor
L-2,3-*cis*-3,4-*cis*	2*S*,3*S*,4*R*	L-ribose
L-2,3-*cis*-3,4-*trans*	2*S*,3*S*,4*S*	L-arabinose
L-2,3-*trans*-3,4-*cis*	2*S*,3*R*,4*S*	L-lyxose
L-2,3-*trans*-3,4-*trans*	2*S*,3*R*,4*R*	L-xylose
D-2,3-*cis*-3,4-*cis*	2*R*,3*R*,4*S*	D-ribose
D-2,3-*cis*-3,4-*trans*	2*R*,3*R*,4*R*	D-arabinose
D-2,3-*trans*-3,4-*cis*	2*R*,3*S*,4*R*	D-lyxose
D-2,3-*trans*-3,4-*trans*	2*R*,3*S*,4*S*	D-xylose

In principle, it should be possible to prepare any isomer of DHP, by selection of the appropriate pentose precursor (Table 1). While we appreciated at the outset that each sugar and its derivatives would behave differently, we felt that the transformations ought to be achievable using a common series of reaction conditions. We began our investigations with D-ribonolactone because it is readily available (vide supra). We also sought to prepare two natural products. Compound **1** was an attractive target because the starting sugar (L-arabinose) is inexpensive, and the final product has been isolated from nature and well-characterized.[2] Compound **3** was also pursued because we have prepared this via another route and firmly established the relative and absolute stereochemistry.[7]

Phase I: Development of a Suitably Protected Lactone. Our synthetic strategy required that we be able to selectively deprotect the C5−OH at a late stage in the synthesis. We thought it would be trivial to selectively introduce a protecting group at the primary alcohol. For some time, we focused on silyl protecting groups. Despite good precedents in ribonucleotide chemistry,[16] we invariably obtained mixtures of two monosilylated compounds and one bis-silylated derivative. The only suitable protecting group we were ever able to introduce regioselectively at C5 was the trityl ether, so we have used this throughout our syntheses. We reasoned that a *tert*-butyldimethylsilyl ether would be a good protecting group at C2 and C3; they are reported to be more stable to acid than a trityl ether[17] and ought to survive the hydrogenolysis conditions required later in the synthesis.[18]

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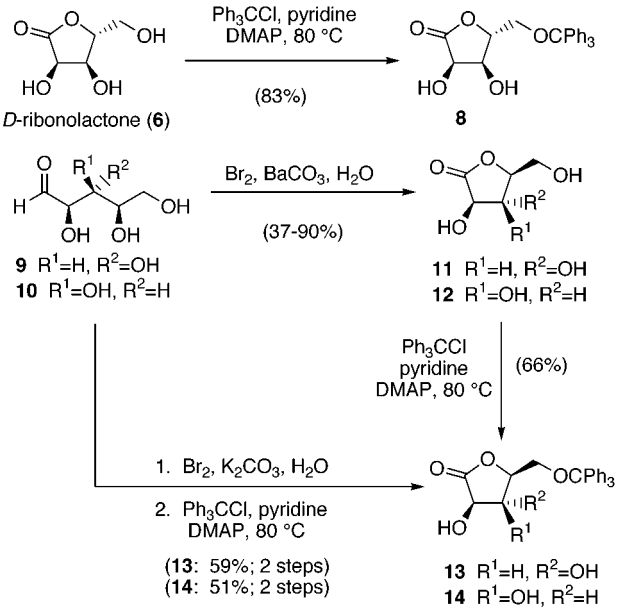
Scheme 4



A prerequisite of our synthetic strategy is access to the pentose γ-lactones. D-Ribonolactone is commercially available at reasonable cost and has been previously converted to its 5-*O*-trityl derivative **8** (Scheme 4).[19] It was necessary for us to prepare the other γ-lactones and there is good precedent for this in the literature. Unfortunately, we experienced inordinate problems in isolating useful quantities of γ-lactones, and we feel compelled to share these trials and tribulations.

The oxidation of aldoses by aqueous bromine is well documented.[20] Specifically, Kiliani isolated L-arabinonic acid as its calcium salt,[21] and Ruff prepared D-arabinonic acid.[22] D-Lyxonic acid was isolated as its lead salt and converted to the lactone by Wohl and List.[23] Following the more modern procedure of Morgenlie,[24] we performed the oxidation in aqueous bromine in the dark; addition of Ag_2CO_3 at the conclusion of the reaction led to the precipitation of AgBr. Filtration and concentration of the filtrate ought to afford the γ-lactone. Unfortunately, using this protocol, we were unable to obtain useful quantities of the lactones in a reproducible manner. In 1997, Bouchez and co-workers reported a different procedure in which barium carbonate was incorporated in the reaction mixture.[25] In our hands, the oxidation of **9** and **10** in this manner was capricious, but **11** and **12**, respectively, were obtained in useful quantities. The limitation of the method seems to be the efficiency with which the lactone can be leached from the barium salts with hot acetone.

It has recently been brought to our attention that D-xylose can be converted to 2,3,5-tri-*O*-acetyl-D-xylono-γ-lactone in an efficient manner.[26,27] The oxidation is performed with bromine in a buffered solution; no heavy metal salts are utilized. The lactone, without any purification, is treated directly with Ac_2O/pyridine. Application of the oxidation procedure to **9** and **10** and subjection of the crude lactone to the tritylation reagents, led to much improved yields of **13** and **14** over two steps (Scheme 4).

The remainder of the reaction chemistry is detailed in Scheme 5. In an attempt to illustrate the "generality" of our sequence we have used a single set of structures that do not specify stereochemistry. Below each structure are the compounds, their absolute stereochemistry, and the yields for each case. The top row refers to the compounds derived from D-ribonolactone, the middle row the L-arabinose series, and the bottom row the L-lyxose series.

II. Conversion of the Lactone to a Pyrrolidine. Silylation of the diols to give **15**−**17** was straightforward. Treatment of D-ribose derivative **15** with $LiBH_4$ gave a good yield of the diol **18** (Scheme 5). L-Lyxose derivative **17** gave a 73% yield of the desired diol **20**; another product was evident by TLC but was not investigated further due to the acceptable yield of **20**. Unfortunately, under these reaction conditions, L-arabinose derivative **16** gave a mixture of two products that were difficult to separate. It transpired that the two products were diols **19** and **39** (Scheme 6); the latter resulting from silyl migration during and/or after the reduction process. The mixture of diols was converted to mesylates **22** and **40**, which were readily separated by flash chromatography, although they could not be distinguished easily by ^{1}H NMR. The major mesylate did not give a cyclic product on treatment with benzylamine, suggesting that it was **40**, since the requisite cyclization would be the disfavored 4-*exo*-*tet* process.

Silyl migration could be minimized by switching to sodium borohydride in methanol and incorporating a stoichiometric amount of cerium(III) chloride.[28,29] While these reaction conditions worked well for the conversion of **16** to **19**, they did not give good results in the attempted reduction of **15** and **17**. This is the one step in our sequence where optimization of reaction conditions led to different reagents for different stereoisomers. Nevertheless, the principle of the transformation (reductive opening of the lactone) remains intact.

Diols **18**−**20** were converted to the corresponding bismesylates under standard conditions. A solution of the diol in pyridine was added dropwise to a premixed suspension of methanesulfonyl chloride and DMAP in pyridine. A side reaction sometimes encountered was the intramolecular reaction of a monomesylate to give a tetrahydrofuran (Scheme 7). In the case of the L-arabinose series, a significant amount of compound **42** was isolated, purified, and characterized. The proton and carbon NMR spectra were reminiscent of lactone **16**, suggesting a conformationally restricted ring system, rather than an open chain. The ^{13}C NMR spectrum of **16** contained a signal at δ 176.1 ppm, reflecting the lactone

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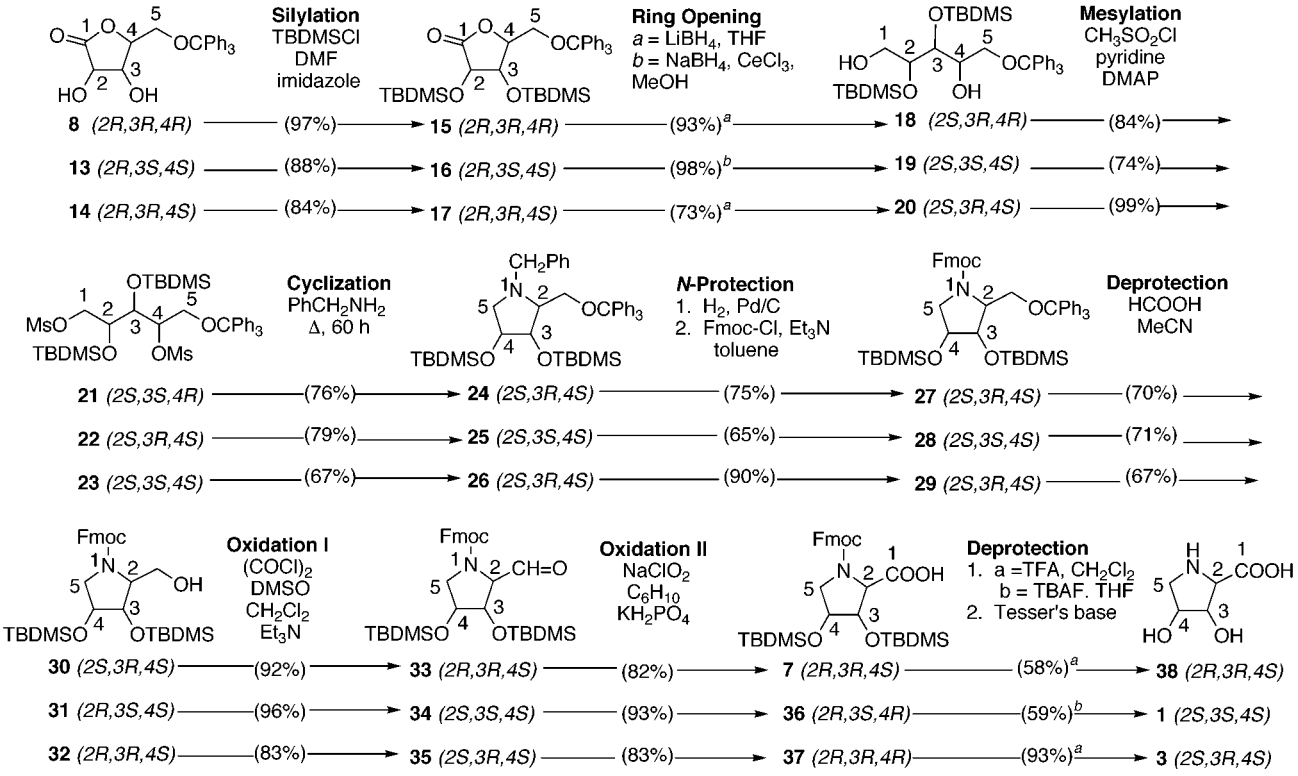
Scheme 5



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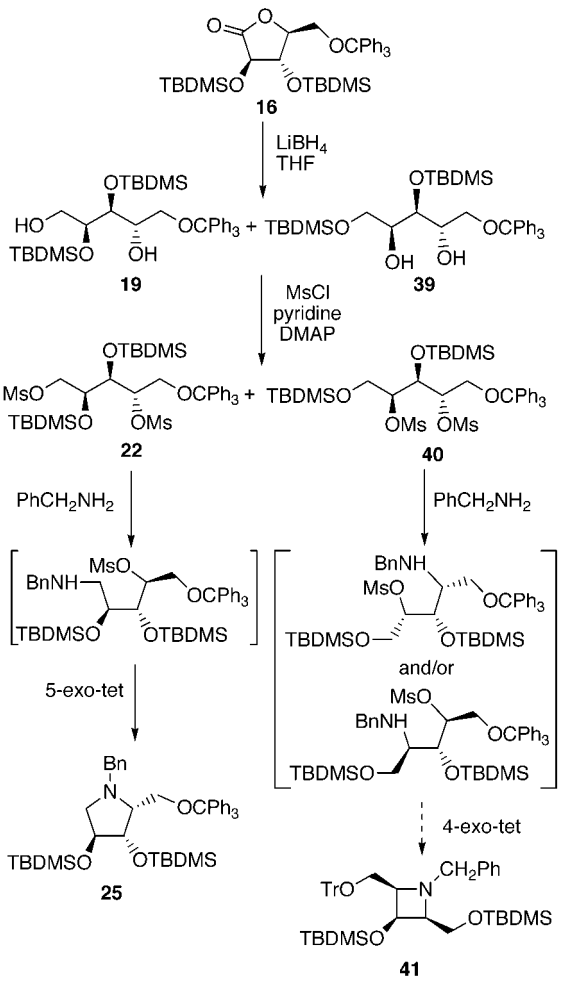

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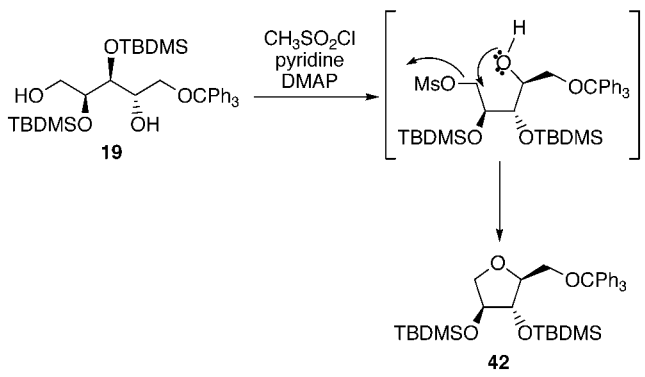

functionality. There was no such signal in the ^{13}C NMR spectrum of **42**; instead, there was a signal at δ 74.5 ppm, which was inverted in the 135° DEPT spectrum. We took this as evidence for the tetrahydrofuran structure.

Heating the bis-mesylates **21**−**23** in neat benzylamine led to the formation of pyrrolidines **24**−**26**, respectively, in good yield. The benzyl group was removed by hydrogenolysis at atmospheric pressure with Pd/C catalyst, and the resulting secondary amine was readily protected by reaction with fluorenylmethyl chloroformate (Fmoc-Cl) to give the Fmoc-derivatives **27**−**29**. Attempts to protect the amine in situ by incorporating Fmoc-OSucc in the hydrogenolysis reaction, as described by Dzubeck and Schneider,[30] were unsuccessful.

III. Elaboration to Carboxylic Acid. Selective cleavage of the trityl ether from **27** was not straightforward. Following literature precedent,[31] we attempted to simul-

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taneously cleave the benzylic ether bond during the hydrogenolysis step (vide infra). However, the trityl ether remained intact, even at elevated pressures (3 atm H_2). Under acidic conditions, one of the TBDMS groups turned out to be quite labile.[15] However, a carefully controlled concentration of formic acid in acetonitrile led to reasonable yields of primary alcohols **30**−**32**. While **30** was oxidized to **7** using ruthenium tetroxide, the yield was mediocre.[15] It turned out to be more efficient to perform the oxidation in two steps: a Swern oxidation followed by sodium chlorite oxidation gave acids **7**, **36**, and **37** in good overall yields. We believe that these compounds will be useful building blocks in peptide synthesis.

Correlation with the Natural Products. While we had produced useful building blocks for peptide synthesis, it remained for us to establish the relative and absolute stereochemistry of our DHPs. We were unsuccessful in our attempts to secure crystallographic data for any of our pyrrolidine derivatives. Proof of the relative and absolute stereochemistries therefore relied on the conversion of **35** and **36** to the corresponding natural products **1** and **3**. Removal of the protecting groups was accomplished in two steps and the free DHPs were purified by ion-exchange chromatography. The proton NMR data for compounds **1** and **3** agreed well with that reported for the natural products and all three DHPs gave ^{1}H and ^{13}C NMR data, which was in good agreement with previous data where available.

Conclusion

We have now synthesized two naturally occurring L-DHPs (**1** and **3**), in addition to D-2,3-*cis*-3,4-*cis*-DHP (**38**). We have synthesized DHPs with a 2,3-*cis* relationship (**1** and **38**) and a 2,3-*trans* relationship (**3**). We have also synthesized DHPs with a 3,4-*cis* relationship (**3** and **38**) and a 3,4-*trans* relationship (**1**). We believe that these three examples demonstrate the potential generality of this series of reactions. Moreover, building blocks **7**, **36**, and **37** will be useful compounds in the synthesis of peptides, which will enable us to continue our studies into the role of hydroxylated prolines in nature.

Experimental Section

General Methods. Reactions were carried out under an atm of nitrogen. THF was freshly distilled from sodium/benzophenone. Toluene was freshly distilled from sodium. Acetonitrile and dichloromethane were freshly distilled from calcium hydride. Pyridine, benzylamine, and triethylamine were each dried and distilled from calcium hydride and stored over KOH pellets. Cyclohexene was dried and distilled from calcium hydride and stored over 4 Å molecular sieves. *tert*-Butyl alcohol was dried over $MgSO_4$, distilled from calcium hydride, and stored over 4 Å molecular sieves. Methanesulfonyl chloride was dried and distilled from phosphorus pentoxide under vacuum and stored over 4 Å molecular sieves. Methanol was dried and distilled from magnesium turnings and stored over 4 Å molecular sieves. DMF was dried and distilled from BaO and stored over 4 Å molecular sieves. All other reagents were from commercial suppliers and were used without further purification. Tesser's base was prepared by mixing together 1,4-dioxane, methanol, and 4 N NaOH in a 30:9:1 ratio by volume.

General Procedure for Formation of γ-Lactone and Protection of C5-OH as Its Triphenylmethyl Ether. The aldopentose (1 equiv) was dissolved in Milli-Q water (3 mL/mmol), and K_2CO_3 (1.15 equiv) was added. The solution was cooled to 0 °C, and bromine (1.1 equiv) was added in four equal portions, at 20 min intervals. The resulting orange solution was stirred at 0 °C for 1 h and then at rt for 18 h. The reaction mixture was quenched by the addition of formic acid (0.5 mL/mmol) and the solution concentrated. The residue was dispersed in glacial acetic acid (5 mL/mmol), the solution concentrated, and the residue dried in vacuo overnight.

The residue was dissolved in pyridine (3 mL/mmol) and triphenylmethyl chloride (1.2 equiv) and DMAP (0.2 equiv) added. The solution was stirred under an atmosphere of nitrogen at 70 °C for 16 h. The cooled mixture was concentrated, diluted with dichloromethane (30 mL/mmol), and washed with 10% aq HCl (2 × 25 mL/mmol) and satd aq $NaHCO_3$ (25 mL/mmol). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 1:1 hexanes−EtOAc.

5-*O*-Triphenylmethyl-L-arabinono-γ-lactone (13): on a scale of 3.33 mmol (59%); TLC R_f 0.36 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D = -20.2$ (*c* 1.18, $CHCl_3$) (lit.[32] $[\alpha]^{20}_D = +17$ (*c* 1.18, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (dd, J = 11.1, 4.8 Hz, 1H), 3.36 (dd, J = 11.1, 2.7 Hz, 1H), 3.84 (br. s, 1H), 4.11−4.16 (m, 1H), 4.17 (dd, J = 16.6, 8.3 Hz, 1H), 4.38 (d, J = 8.3 Hz, 1H), 4.73 (br. s, 1H), 7.10−7.36 (m 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 62.3, 74.5, 75.0, 80.3, 87.4, 127.7, 128.4, 129.0, 143.7, 175.3; HRMS (EI) calcd for M^+ $C_{24}H_{22}O_5$ 390.1467, obsd 390.1467.

5-*O*-Triphenylmethyl-L-lyxono-γ-lactone (14): on a scale of 3.33 mmol (51%); TLC R_f 0.22 (1:1 hexanes−EtOAc); $[\alpha]^{20}_D = +8.4$ (*c* 0.35, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.41 (dd, J = 10.6, 4.6 Hz, 1H), 3.59 (dd J = 10.6, 6.6 Hz, 1H), 4.30 (dd, J = 4.5, 2.9 Hz, 1H), 4.35−4.39 (m, 1H), 4.41 (d, J = 4.6 Hz, 1H), 7.10−7.49 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 61.5, 69.5, 70.8, 79.4, 87.2, 127.2, 127.9, 128.5, 143.3, 175.9; HRMS (EI) calcd for M^+ $C_{24}H_{22}O_5$ 390.1467, obsd 390.1454.

5-*O*-Triphenylmethyl-D-ribono-γ-lactone (8). Prepared according to Ireland et al. from D-ribonolactone:[19] TLC R_f 0.22 (1:1 hexanes−EtOAc); $[\alpha]^{20}_D = +52.2$ (*c* 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.99 (dd, J = 11.0, 2.6 Hz, 2H), 4.25 (d, J = 5.5 Hz, 1H), 4.51 (app. t, J = 2.6 Hz, 1H), 4.87 (d, J = 5.5 Hz, 1H), 7.20−7.69 (m, 15H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 64.1, 69.8, 70.9, 84.3, 88.2, 127.8, 128.2, 128.4, 128.5, 128.9, 129.4, 129.6, 144.4, 145.3, 176.3; HRMS (EI) calcd for M^+ $C_{24}H_{22}O_5$ 390.1467, obsd 390.1459.

General Procedure for Protection of C3-OH and C4-OH as *tert*-Butyldimethylsilyl Ethers. A solution of the 5-*O*-trityl-protected lactone (1.0 equiv) in DMF (1 mL/mmol) was added dropwise to a solution of *tert*-butyldimethylsilyl chloride (3.4 equiv) and imidazole (5.4 equiv) in DMF (1 mL/mmol), and the resulting solution was stirred under N_2 at rt for 48 h. The reaction mixture was diluted with chloroform (50 mL/mmol) and washed with water (2 × 50 mL/mmol). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 5:1 hexanes−EtOAc.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-5-*O*-triphenylmethyl-D-ribono-γ-lactone (15): on a scale of 2.09 mmol (97%); TLC R_f 0.46 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D = +22.7$ (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 3H), 0.09 (s, 3H), 0.19 (s, 3H), 0.26 (s, 3H), 0.87 (s, 9H), 1.00 (s, 9H), 3.28 (dd, J = 11.0, 3.0 Hz, 1H), 3.69 (dd, J = 11.0, 3.0 Hz, 1H), 4.02 (d, J = 5.4 Hz, 1H), 4.35 (app. t, J = 3.0 Hz, 1H), 4.76 (d, J = 5.4 Hz, 1H), 7.25−7.67 (m, 15H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.3, −4.9, −4.8, −4.7, 17.9, 18.3, 25.5, 25.8, 62.2, 70.2, 71.9, 84.5, 87.5, 127.3, 127.9, 128.4, 142.9, 174.9; HRMS (FAB) calcd for MH^+ $C_{36}H_{51}O_5Si_2$ 619.3275, obsd 619.3261. Anal. Calcd for $C_{36}H_{50}O_5Si_2$: C, 69.86; H, 8.14. Found: C, 69.94; H, 8.24.

(31) Mirrington, R. N.; Schmalzl, K. J. *J. Org. Chem.* **1972**, *37*, 2877−2881.

(32) (a) Tatsuta, K.; Takahashi, M.; Tanaka, N. *J. Antibiot.* **2000**, *53*, 88−91. (b) Concerned by the vast discrepancy in these values, we measured the rotation of both D-arabinono-γ-lactone and L-arabinono-γ-lactone prepared in our laboratory from D-arabinose and L-arabinose, respectively. For D-arabinono-γ-lactone: $[\alpha]^{20}_D = +43.4$ (*c* 1.38, H_2O); for L-arabinono-γ-lactone: $[\alpha]^{20}_D = -40.2$ (*c* 0.99, H_2O), lit.[24a] $[\alpha]^{20}_D = -33$ (*c* 1.0, H_2O), lit.[24b] $[\alpha]^{20}_D = -74$ (*c* 0.54, H_2O). When we protect the 5-OH of this L-arabinono-γ-lactone as its trityl ether we most definitely observe a negative rotation.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-5-*O*-triphenylmethyl-L-arabino-γ-lactone (16): on a scale of 1.07 mmol (88%); TLC R_f 0.63 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D = -9.0$ (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.29 (s, 3H), −0.01 (s, 3H), 0.13 (s, 3H), 0.20 (s, 3H), 0.73 (s, 9H), 0.91 (s, 9H), 3.16 (dd, J = 10.7, 5.4 Hz, 1H), 3.40 (dd, J = 10.7, 2.2 Hz, 1H), 4.20 (q, J = 6.9 Hz, 1H), 4.21−4.26 (m, 1H), 4.32 (d, J = 6.9 Hz, 1H), 7.16−7.29 (m, 9H), 7.41−7.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −2.0, −1.9, −1.4, −1.3, 20.6, 21.0, 28.5, 28.6, 65.4, 78.3, 79.1, 84.0, 89.7, 128.7, 130.1, 131.0, 146.2, 176.1; HRMS (EI) calcd for $[M - C_6H_5]^+$ $C_{30}H_{45}O_5Si_2$ 541.2806, obsd 541.2809. Anal. Calcd for $C_{36}H_{50}O_5Si_2$: C, 69.86; H, 8.14. Found: C, 70.03; H, 8.07.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-5-*O*-triphenylmethyl-L-lyxono-γ-lactone (17): on a scale of 0.19 mmol (84%); TLC R_f 0.39 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D = +24.2$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.17 (s, 3H), 0.00 (s, 3H), 0.15 (s, 3H), 0.19 (s, 3H), 0.65 (s, 9H), 0.92 (s, 9H), 3.17 (dd, J = 10.8, 2.8 Hz, 1H), 3.60 (dd, J = 10.8, 7.9 Hz, 1H), 4.26 (dd, J = 4.0, 2.8 Hz, 1H), 4.32 (d, J = 4.0 Hz, 1H), 4.48 (dt, J = 7.9, 2.8 Hz, 1H), 7.20−7.35 (m, 9H), 7.42−7.54 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.5, −4.1, −3.8, 18.5, 19.0, 26.0, 26.4, 64.0, 72.7, 73.3, 80.3, 87.5, 127.5, 128.3, 129.1, 144.0, 174.6; HRMS (DCI) calcd for MH^+ $C_{36}H_{51}O_5Si_2$ 619.3275, obsd 619.3265. Anal. Calcd for $C_{36}H_{50}O_5Si_2$: C, 69.86; H, 8.14. Found: C, 69.74; H, 8.20.

General Procedure for Reductive Ring Opening of Lactone. A solution of lithium borohydride (2 mol/L in THF, 4.0 equiv) was added dropwise over 30 min to a stirred solution of the 5-*O*-triphenylmethyl-2,3-di-*O*-*tert*-butyldimethylsilyl-γ-lactone (1.0 equiv) in dry THF (2.5 mL/mmol). The resulting colorless solution was stirred under N_2 at rt for 18 h. The excess borohydride was quenched by the addition of satd aq NH_4Cl solution (2 mL/mmol). The reaction mixture was partitioned between brine (50 mL/mmol) and ethyl acetate (75 mL/mmol) and the organic layer separated, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 5:1 hexanes−EtOAc.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-5-*O*-triphenylmethyl-D-ribitol (18): on a scale of 2.06 mmol (93%); TLC R_f 0.42 (3:1 hexanes−EtOAc); $[\alpha]^{20}_D = +5.2$ (*c* 1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.15 (s, 3H), 0.29 (s, 3H), 0.32 (s, 3H), 0.33 (s, 3H), 1.10 (s, 9H), 1.20 (s, 9H), 2.74 (br. s, 1H), 3.11 (br. s, 1H), 3.44 (t, J = 9.0 Hz, 1H), 3.61 (dd, J = 9.5, 3.3 Hz, 1H), 3.84−3.93 (br. m, 2H), 4.00−4.07 (m, 2H), 4.23−4.27 (m, 1H), 7.47−7.61 (m, 9H), 7.69−7.79 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −4.9, −4.6, −4.5, −4.3, 17.9, 18.1, 25.8, 25.9, 63.2, 65.1, 71.9, 73.9, 76.1, 86.8, 127.0, 127.8, 128.6, 143.7; HRMS (DCI) calcd for $[M - C_4H_9]^+$ $C_{32}H_{45}O_5Si_2$ 565.2805, obsd 565.2809.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-5-*O*-triphenylmethyl-L-lyxitol (20): on a scale of 0.04 mmol (73%); TLC R_f 0.43 (3:1 hexanes−EtOAc); $[\alpha]^{20}_D = -4.1$ (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.34 (s, 3H), −0.04 (s, 3H), −0.01 (s, 3H), 0.04 (s, 3H), 0.59 (s, 9H), 0.81 (s, 9H), 2.76 (t, J = 9.0 Hz, 1H), 2.77 (br. s, 1H), 3.17 (dd, J = 9.0, 5.9 Hz, 1H), 3.34 (dd, J = 11.2, 3.2 Hz, 1H), 3.55−3.68 (m, 3H), 3.80 (t, J = 7.0 Hz, 1H), 3.94 (d, J = 3.2 Hz, 1H), 7.07−7.21 (m, 9H), 7.27−7.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.9, −4.3, −4.2, −3.6, 18.4, 18.5, 26.2, 26.3, 62.4, 65.0, 70.7, 73.6, 76.1, 87.1, 127.4, 128.3, 129.1, 144.1; HRMS (FAB) calcd for $[M + Na]^+$ $C_{36}H_{54}O_5Si_2Na$ 645.3408, obsd 645.3383.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-5-*O*-triphenylmethyl-L-arabinitol (19). A mixture of lactone (502 mg, 0.81 mmol, 1.0 equiv) and anhydrous cerium(III) chloride (801 mg, 3.25 mmol, 4.0 equiv) in dry methanol (10 mL) was stirred under N_2 at −10 °C for 10 min. Sodium borohydride (123 mg, 3.25 mmol, 4.0 equiv) was added and the mixture stirred at −10 °C for 30 min. Excess $NaBH_4$ was quenched by the addition of NH_4Cl (500 mg) and the mixture concentrated. The residue was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 5:1 hexanes−EtOAc to give the titled compound as a colorless oil (492 mg, 98%): TLC R_f 0.45 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D = -7.1$ (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.38 (s, 3H), −0.15 (s, 3H), 0.01 (s, 3H), 0.02 (s, 3H), 0.58 (s, 9H), 0.80 (s, 9H), 3.02 (dd, J = 9.7, 6.9 Hz, 1H), 3.22 (dd, J = 9.7, 2.4 Hz, 1H), 3.57−3.70 (m, 3H), 3.71−3.77 (m, 1H), 3.87 (dt, J = 6.9, 2.4 Hz, 1H), 7.06−7.18 (m, 9H), 7.34−7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.4, −4.3, −4.0, 18.1, 18.4, 26.0, 26.2, 63.1, 66.2, 72.6, 73.4, 75.8, 87.0, 127.3, 128.2, 129.3, 144.5; HRMS (FAB) calcd for $[M + Na]^+$ $C_{36}H_{54}O_5Si_2Na$ 645.3408, obsd 645.3422.

General Procedure for Formation of Bis-Methanesulfonates. A solution of the diol (1.0 equiv) in dry pyridine (2.0 mL/mmol) was added dropwise to a cooled (0 °C), premixed suspension of methanesulfonyl chloride (4.0 equiv) and DMAP (0.2 equiv) in dry pyridine (1.0 mL/mmol). The resulting orange solution was stirred under N_2 at rt for 14 h. The reaction mixture was diluted with chloroform (60 mL/mmol) and washed with 10% aq HCl (2 × 25 mL/mmol), satd aq $NaHCO_3$ (25 mL/mmol), and water (25 mL/mmol). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 5:1 hexanes−EtOAc.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-1,4-bis-*O*-methanesulfonyl-5-*O*-triphenylmethyl-D-ribitol (21): on a scale of 1.91 mmol (84%); TLC R_f 0.35 (3:1 hexanes−EtOAc); $[\alpha]^{20}_D = +9.0$ (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.16 (s, 3H), 0. 17 (s, 3H), 0.82 (s, 9H), 1.00 (s, 9H), 3.11 (s, 3H), 3.19 (s, 3H), 3.43 (dd, J = 11.1, 8.6 Hz, 1H), 3.57 (dd, J = 11.1, 2.7 Hz, 1H), 3.88−3.93 (m, 1H), 4.04 (dd, J = 5.2, 3.6 Hz, 1H), 4.19 (dd, J = 10.3, 5.8 Hz, 1H), 4.41 (dd, J = 10.3, 3.6 Hz, 1H), 5.25 (dt, J = 8.6, 2.7 Hz, 1H), 7.31−7.53 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.9, −4.8, −4.5, 17.9, 25.8, 37.4, 38.8, 62.5, 70.2, 72.2, 74.9, 82.5, 87.6, 127.3, 127.9, 128.6, 143.1; HRMS (FAB) calcd for MH^+ $C_{38}H_{59}O_9S_2Si_2$ 779.3139, obsd 779.3150.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-1,4-bis-*O*-methanesulfonyl-5-*O*-triphenylmethyl-L-arabinitol (22): on a scale of 0.69 mmol (74%); TLC R_f 0.30 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D = -22.3$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.03 (s, 3H), −0.01 (s, 3H), −0.01 (s, 3H), 0.05 (s, 3H), 0.76 (s, 9H), 0.81 (s, 9H), 2.84 (s, 3H), 3.02 (s, 3H), 3.26 (dd, J = 11.7, 2.0 Hz, 1H), 3.49 (dd, J = 11.7, 8.9 Hz, 1H), 3.82−3.87 (m, 3H), 4.23 (d, J = 8.6 Hz, 1H), 5.03 (d, J = 8.6 Hz, 1H), 7.18−7.32 (m, 9H), 7.40−7.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.7, −4.5, −4.4, −4.3, 18.3, 18.4, 26.0, 26.1, 37.4, 39.4, 63.4, 71.1, 73.9, 74.7, 84.0, 88.1, 127.6, 128.3, 129.0, 143.7; HRMS (CI) calcd for $[M - C_6H_5]^+$ $C_{32}H_{53}O_9S_2Si_2$ 701.2670, obsd 701.2694.

2,3-Bis-*O*-*tert*-butyldimethylsilyl-1,4-bis-*O*-methanesulfonyl-5-*O*-triphenylmethyl-L-lyxitol (23): on a scale of 0.59 mmol (99%); TLC R_f 0.33 (3:1 hexanes−EtOAc); $[\alpha]^{20}_D = -25.6$ (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.05 (s, 3H), −0.04 (s, 3H), −0.01 (s, 3H), 0.05 (s, 3H), 0.75 (s, 18H), 2.84 (s, 3H), 3.00 (s, 3H), 3.39 (dd, J = 10.9, 7.7 Hz, 1H), 3.49 (dd, J = 10.9, 2.6 Hz, 1H), 3.51 (s, 1H), 3.88−3.98 (m, 2H), 4.15 (d, J = 8.4 Hz, 1H), 4.70−4.78 (m, 1H), 7.14−7.30 (m, 9H), 7.32−7.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.5, −4.1, −4.0, 18.4, 18.5, 26.1, 26.2, 37.6, 39.0, 63.0, 70.7, 73.6, 75.0, 83.2, 88.0, 127.8, 128.5, 129.0, 143.8; HRMS (FAB) calcd for $[M + Na]^+$ $C_{38}H_{58}O_9S_2Si_2Na$ 801.2959, obsd 801.2975.

General Procedure for *N*-Benzylpyrrolidine Formation. The bis-mesylate (1.0 equiv) was dissolved in benzylamine (1 mL/mmol) and the solution heated at 85 °C under N_2 for 60 h. The excess benzylamine was removed under reduced pressure and the residue partitioned between chloroform (200 mL/mmol) and brine (100 mL/mmol). The organic layer was washed with water (100 mL/mmol), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 15:1 hexanes−EtOAc.

(2*S*,3*R*,4*S*)-1-Benzyl-3,4-bis(*tert*-butyldimethylsilyloxy)-2-triphenylmethoxymethylpyrrolidine (24): on a scale of 0.36 mmol (76%); TLC R_f 0.40 (10:1 hexanes−EtOAc); $[\alpha]^{20}_D = +24.9$ (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.02 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.86 (s, 9H), 0.89 (s, 9H), 2.67 (dd, J = 10.3, 4.7 Hz, 1H), 2.98 (dd, J = 10.3, 3.7 Hz, 1H), 3.30−3.41 (m, 2H), 3.66−3.76 (m, 1H), 3.92 (d, J =

13.7 Hz, 1H), 4.06−4.11 (m, 1H), 4.20−4.28 (m, 1H), 4.54 (d, J = 13.7 Hz, 1H) 7.33−7.67 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 1.9, 2.0, 2.2, 2.3, 18.1, 25.8, 25.9, 57.1, 60.9, 65.3, 66.3, 73.2, 74.3, 86.7, 126.6, 127.6, 128.1, 128.9, 140.1, 144.6; HRMS (FAB) calcd for MH^+ $C_{43}H_{60}NO_3Si_2$ 694.4111, obsd 694.4092.

(2*R*,3*S*,4*S*)-1-Benzyl-3,4-bis(*tert*-butyldimethylsilyloxy)-2-triphenylmethoxymethylpyrrolidine (25): on a scale of 0.26 mmol (79%); TLC R_f 0.45 (10:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = −21.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.14 (s, 3H), 0.01 (s, 3H), 0.02 (s, 3H), 0.05 (s, 3H), 0.75 (s, 9H), 0.90 (s, 9H), 2.34 (dd, J = 10.4, 3.7 Hz, 1H), 3.14 (dd, J = 10.6, 4.9 Hz, 1H), 3.17−3.22 (m, 1H), 3.28 (dd, J = 9.7, 3.7 Hz, 1H), 3.39 (dd, J = 9.7, 7.2 Hz, 1H), 3.67 (d, J = 13.6 Hz, 1H), 4.00 (app. q, J = 3.7 Hz, 1H), 4.06 (dd, J = 5.7, 3.7 Hz, 1H), 4.30 (d, J = 13.6 Hz, 1H), 7.19−7.37 (m, 14H), 7.47−7.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.2, −4.1, −4.1, 18.3, 26.2, 26.3, 59.0, 61.4, 65.7, 66.3, 78.2, 79.7, 87.6, 126.9, 127.2, 128.1, 128.5, 129.0, 129.3, 140.9, 144.5; HRMS (DEI) calcd for M^+ $C_{43}H_{59}NO_3Si_2$ 693.4034, obsd 693.4024.

(2*R*,3*R*,4*S*)-1-Benzyl-3,4-bis(*tert*-butyldimethylsilyloxy)-2-triphenylmethoxymethylpyrrolidine (26): on a scale of 0.02 mmol (67%); TLC R_f 0.56 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = −5.3 (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.03 (s, 3H), −0.01 (s, 6H), 0.03 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 2.59 (t, J = 8.4 Hz, 1H), 2.87−2.98 (m, 4H), 3.67 (d, J = 13.1 Hz, 1H), 3.84 (d, J = 3.8 Hz, 1H), 3.92−3.99 (m, 2H), 7.17−7.34 (m, 14H), 7.40−7.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.3, −4.2, −4.1, −3.8, 18.6, 18.7, 26.4, 26.5, 57.4, 61.9, 65.8, 71.0, 72.8, 75.8, 87.0, 127.3, 128.0, 128.2, 128.7, 129.2, 129.3, 140.1, 144.6; HRMS (DEI) calcd for M^+ $C_{43}H_{59}NO_3Si_2$ 693.4034, obsd 693.4033.

General Procedure for Debenzylation and Fmoc Protection. *N*-Benzyl-protected pyrrolidine (1.0 equiv) was dissolved in absolute ethanol (15 mL/mmol), and 10% palladium on carbon was added (300 mg/mmol). The reaction vessel was evacuated, and the reaction mixture was stirred under an atmosphere of H_2 at rt for 8 h. The catalyst was removed by filtration through a pad of Celite and washed thoroughly with ethanol (15 mL/mmol). The filtrate and washings were concentrated, and the crude amine residue was dissolved in toluene (5 mL/mmol). The amine solution was added dropwise to a solution of fluorenylmethyl chloroformate (1.1 equiv) in toluene (10 mL/mmol). Triethylamine (1.1 equiv) was added and the solution stirred at rt under N_2 for 16 h. The solid was removed by filtration and rinsed thoroughly with toluene (6 mL/mmol). The filtrate and washings were concentrated and purified by flash column chromatography, eluting with 10:1 hexanes−EtOAc.

(2*S*,3*R*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-triphenylmethoxymethylpyrrolidine (27): on a scale of 0.35 mmol (75%); TLC R_f 0.35 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = +18.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) (mixture of rotamers) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.13 (s, 3H), 0.80 (s, 6H), 0.84 (s, 6H), 0.86 (s, 6H), 3.20−3.47 (m, 2H), 3.69−3.95 (m, 2H), 4.12−4.23 (m, 2H), 4.47−4.78 (m, 4H), 7.22−7.37 (m, 12H), 7.41−7.59 (m, 8H), 7.73−7.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −5.1, −4.9, 17.8, 18.0, 25.6, 25.8, 47.2 and 47.4, 53.2 and 53.7, 59.3 and 59.6, 63.3 and 63.8, 67.2 and 67.6, 70.9 and 72.1, 72.9 and 73.5, 86.5, 119.9, 125.2 and 125.7, 126.5 and 126.7, 127.0, 127.3, 128.8, 141.3, 143.7 and 144.0, 144.3 and 144.5, 155.2 and 156.1; HRMS (FAB) calcd for MH^+ $C_{51}H_{64}NO_5Si_2$ 826.4323, obsd 826.4324. Anal. Calcd for $C_{51}H_{63}NO_5Si_2$: C, 74.14; H, 7.69; N, 1.70. Found: C, 74.14; H, 7.96; N, 1.78.

(2*R*,3*S*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-triphenylmethoxymethylpyrrolidine (28): on a scale of 0.21 mmol (65%); TLC R_f 0.27 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = +18.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) (mixture of rotamers) δ −0.01 (s, 3H), 0.10 (s, 1.5H), 0.11 (s, 1.5H), 0.13 (s, 1.5H), 0.15 (s, 1.5H), 0.17 (s, 1.5H), 0.18 (s, 1.5H), 0.83 (s, 4.5H), 0.85 (s, 4.5H), 0.93 (s, 4.5H), 0.98 (s, 4.5H), 3.11 (dd, J = 9.6, 3.6 Hz, 0.5H), 3.15−3.27 (m, 1.5H), 3.39 (d, J = 10.4 Hz, 0.5H),3.46 (dd, J = 9.6, 3.6 Hz, 0.5H), 3.61 (br. d, J = 8.0 Hz, 0.5H), 3.83 (ddd, J = 11.0, 8.0, 3.0 Hz, 0.5H), 3.90−3.95 (m, 0.5H), 4.00 (t, J = 6.3 Hz, 0.5H), 4.07−4.16 (m, 1H), 4.15 (t, J = 6.3 Hz, 0.5H), 4.26−4.44 (m, 2.5H), 4.71−4.84 (m, 1H), 7.13−7.49 (m, 20H), 7.64 (t, J = 7.3 Hz, 1H), 7.71 (t, J = 7.3 Hz, 1H), 7.79 (d, J = 7.3, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −4.9, −4.6, −4.5, −4.4, 17.9, 18.0, 25.9, 47.0 and 47.3, 51.1 and 51.4, 58.8, 59.9, 66.7 and 67.1, 74.8 and 75.4, 77.4 and 77.1, 87.4, 119.7 and 119.8, 119.9, 124.7 and 124.8, 125.0 and 125.1, 126.9 and 127.0, 127.4 and 127.6, 127.7 and 128.8, 141.2 and 141.3, 143.8 and 143.9, 144.1 and 144.2, 154.3 and 154.4; HRMS (FAB) calcd for MH^+ $C_{51}H_{64}NO_5Si_2$ 826.4323, obsd 826.4274. Anal. Calcd for $C_{51}H_{63}NO_5Si_2$: C, 74.14; H, 7.69; N, 1.70. Found: C, 73.58; H, 7.93; N, 1.70.

(2*R*,3*R*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-triphenylmethoxymethylpyrrolidine (29): on a scale of 0.34 mmol (90%); TLC R_f 0.33 (5:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = −14.3 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ −0.03 (s, 1.5H), −0.02 (s, 6H), −0.01 (s, 1.5H), 0.00 (s, 3H), 0.79 (s, 13.5H), 0.83 (s, 4.5H), 3.01 (dd, J = 9.7, 6.0 Hz, 0.5H), 3.06 (dd, J = 9.7, 2.5 Hz, 0.5H), 3.15−3.37 (m, 2H), 3.43−3.52 (m, 1H), 3.58−3.64 (m, 0.5H), 3.78−3.84 (m, 0.5H), 3.92−3.97 (m, 1H), 4.00−4.11 (m, 1H), 4.14−4.27 (m, 2H), 4.30−4.41 (m, 1H), 7.06−7.44 (m, 20H), 7.52 (t, J = 6.3 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.65 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −4.3, −4.1, −3.9, 18.6, 18.7, 26.4, 26.5, 47.7 and 47.8, 50.5 and 50.8, 62.4 and 62.7, 65.6 and 66.1, 67.5, 71.3 and 71.7, 75.1 and 75.7, 87.4, 120.2, 120.4, 120.5, 125.3, 125.4, 125.6, 126.3, 127.5, 127.6, 128.3, 129.1, 141.8, 143.9, 144.3, 144.5, 144.7, 155.6; HRMS (FAB) calcd for $[M + Na]^+$ $C_{51}H_{63}NO_5Si_2Na$ 848.4143, obsd 848.4117. Anal. Calcd for $C_{51}H_{63}NO_5Si_2$: C, 74.14; H, 7.69; N, 1.70. Found: C, 74.43; H, 7.65; N, 1.55.

General Method for Cleavage of Trityl Ether. The pyrrolidine derivative (1.0 equiv) was dissolved in dry acetonitrile (20 mL/mmol), formic acid (100 equiv) was added, and the progress of the reaction was monitored by TLC. When the reaction had proceeded to a satisfactory point, the solution was diluted with EtOAc (100 mL/mmol) and washed with water (100 mL/mmol), satd aq $NaHCO_3$ (2 × 100 mL/mmol), and brine (100 mL/mmol). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 5:1 hexanes−EtOAc.

(2*S*,3*R*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-hydroxymethylpyrrolidine (30): on a scale of 0.12 mmol, with a reaction time of 10 min (70% plus 25% recovered starting material): TLC R_f 0.28 (3:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = +12.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) (mixture of rotamers) δ 0.09 (s, 6H), 0.11 (s, 6H), 0.89 (s, 3H), 0.93 (s, 15H) 3.33−3.41 (m, 1H), 3.46−3.57 (m, 2H), 3.79−3.85 (m, 0.5H), 3.89−3.99 (m, 1.5H), 4.06−4.15 (m, 2H), 4.18−4.29 (m, 2H), 4.41 (dd, J = 13.5, 6.7 Hz, 1H), 4.48−4.52 (m, 1H), 7.29−7.43 (m, 4H), 7.49−7.56 (m, 2H), 7.74−7.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) (mixture of rotamers) δ −4.9, −4.8, 18.1, 18.2, 25.6, 25.8, 47.2 and 47.3, 52.4 and 53.1, 58.7 and 61.5, 60.1 and 62.0, 67.1 and 67.4, 70.9 and 71.9, 73.2 and 73.3, 119.9, 124.9 and 125.1, 127.0 and 127.2, 127.6 and 127.7, 141.3 and 141.4, 143.8 and 143.9, 155.0 and 156.1; HRMS (CI) calcd for MH^+ $C_{32}H_{50}NO_5Si_2$ 584.3228, obsd 584.3229.

(2*R*,3*S*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-hydroxymethylpyrrolidine (31): on a scale of 0.12 mmol, with a reaction time of 4 h (71%); TLC R_f 0.23 (7:2 hexanes−EtOAc); $[\alpha]^{20}_D$ = −8.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) (mixture of rotamers) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 6H), 0.88 (s, 9H), 0.89 (s, 9H), 3.35 (dd, J = 11.2, 1.5 Hz, 1H), 3.61 (dd, J = 11.2, 4.1 Hz, 1H), 3.67−3.89 (m, 2H), 3.90−4.13 (m, 3H), 4.26 (t, J = 6.7 Hz, 1H), 4.41 (s, 1H), 4.43−4.57 (m, 2H), 7.27−7.47 (m, 4H), 7.59 (dd, J = 7.1, 3.4 Hz, 2H), 7.76 (d, J = 7.1, Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) (mixture of rotamers) δ −5.1, −4.8, −4.6, −4.5, 17.9, 25.6, 25.7, 47.2, 53.1, 63.3, 63.4, 67.5, 74.8, 77.0 and 78.3, 120.0, 124.9 and 125.0, 127.0, 127.7, 141.3, 143.9, 157.0; HRMS (CI) calcd for MH^+ $C_{32}H_{50}NO_5Si_2$ 584.3228, obsd 584.3218.

(2*R*,3*R*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-hydroxymethylpyrrolidine (32): on a scale of 0.25 mmol, with a reaction time of 1 h (67%); TLC R_f 0.24 (7:2 hexanes−EtOAc); $[\alpha]^{20}_D$ = +7.7 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.11 (s, 3H), 0.12 (s, 3H), 0.88 (s, 4.5H), 0.92 (s, 13.5H), 3.22−3.30 (m, 0.5H), 3.37−3.45 (m, 2H), 3.58−3.66 (m, 1H), 3.80−3.85 (m, 1H), 3.87 (q, *J* = 4.0 Hz, 1H), 4.00−4.06 (m, 0.5H), 4.08−4.15 (m, 1H), 4.27 (t, *J* = 6.8 Hz, 1H), 4.39−4.50 (m, 1.5H), 4.51−4.67 (m, 0.5H), 7.33 (dt, *J* = 7.5, 1.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 0.5H), 7.60 (d, *J* = 7.5 Hz, 1.5H), 7.78 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −5.0 and −4.9, −4.5, −4.5, −4.3 and −4.2, 18.2, 25.9, 47.3, 51.0 and 51.4, 61.2, 65.8 and 66.0, 66.6, 70.8 and 71.1, 74.4, 119.9 and 120.1, 125.0 and 125.1, 127.1 and 127.2, 127.9 and 128.0, 141.4 and 141.5, 143.8 and 144.0, 155.6 and 156.9; HRMS (FAB) calcd for MH^+ $C_{32}H_{50}NO_5Si_2$ 584.3228, obsd 584.3256.

General Procedure for Oxidation to Aldehyde. Dimethyl sulfoxide (4.0 equiv) was added dropwise to a solution of oxalyl chloride (2.0 equiv) in CH_2Cl_2 (20 mL/mmol) at −78 °C. The solution was stirred under N_2 at −78 °C for 20 min. A solution of the primary alcohol (1.0 equiv) in CH_2Cl_2 (20 mL/mmol) was added dropwise and the solution stirred under N_2 at −78 °C for a further 30 min. The reaction mixture was diluted with CH_2Cl_2 (500 mL/mmol) and washed with 1 M HCl solution until just acidic. The organic layer was washed with satd aq $NaHCO_3$ (300 mL/mmol) then brine (300 mL/mmol), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 7:2 hexanes−EtOAc.

(2*R*,3*R*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-formylpyrrolidine (33): on a scale of 0.29 mmol (92%); TLC R_f 0.56 (7:2 hexanes−EtOAc); $[\alpha]^{20}_D$ = −0.7 (*c* 2.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.09−0.16 (m, 12H), 0.90−0.94 (m, 18H), 3.51 (app. t, *J* = 3.2 Hz, 1H), 3.97 (dd, *J* = 7.8, 3.2 Hz, 0.5H), 4.07 (dd, *J* = 7.8, 3.2 Hz, 0.5H), 4.13−4.22 (m, 1.5H), 4.26−4.42 (m, 2.5H), 4.49 (dd, *J* = 10.5, 6.5 Hz, 0.5H), 4.54 (dd, *J* = 10.5, 6.5 Hz, 0.5H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.38−7.44 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 0.5H), 7.55 (d, *J* = 7.5 Hz, 0.5H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 2H), 9.47 (d, *J* = 3.2 Hz, 0.5H), 9.53 (d, *J* = 2.9 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −4.5, −4.3, −4.2, 18.5, 18.7, 26.1, 26.2, 47.5 and 47.6, 52.4 and 52.9, 66.2, 67.9 and 68.2, 72.1 and 72.8, 76.3 and 77.1, 120.4, 125.3 and 125.5, 127.4, 128.1, 141.6 and 141.7, 143.9, 144.2 and 144.3, 155.4 and 155.7, 199.7 and 199.9; HRMS (FAB) calcd for MH^+ $C_{32}H_{48}NO_5Si_2$ 582.3026, obsd 582.3060.

(2*S*,3*S*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-formylpyrrolidine (34): on a scale of 0.04 mmol (96%): TLC R_f 0.33 (7:2 hexanes−EtOAc); $[\alpha]^{20}_D$ = −38.7 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.03−0.08 (m, 12H), 0.84 (s, 4.5H), 0.86 (s, 4.5H), 0.86 (s, 4.5H), 0.87 (s, 4.5H), 3.48 (d, *J* = 11.1 Hz, 0.5H), 3.61 (d, *J* = 11.1 Hz, 0.5H), 3.78 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.97 (br. s, 0.5H), 4.02 (br. s, 0.5H), 4.05−4.09 (m, 0.5H), 4.18 (t, *J* = 6.2 Hz, 0.5H), 4.22−4.32 (m, 2H), 4.38−4.53 (m, 2H), 7.25−7.33 (m, 2H), 7.34−7.43 (m, 2H), 7.48 (d, *J* = 7.5 Hz, 0.5H), 7.51 (d, *J* = 7.5 Hz, 0.5H), 7.60 (t, *J* = 8.6 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 9.28 (d, *J* = 2.9 Hz, 0.5H), 9.50 (d, *J* = 2.9 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −5.3, −4.8, −4.7, 17.8, 25.5, 25.6, 47.1 and 47.2, 53.2 and 53.7, 67.5 and 67.8, 75.0 and 75.9, 79.1 and 80.4, 120.0, 124.7 and 124.8, 124.9 and 125.0, 127.0 and 127.7, 141.3, 143.8, 155.1 and 156.0, 201.1 and 201.2; HRMS (DEI) calcd for M^+ $C_{32}H_{47}NO_5Si_2$ 581.2993, obsd 581.2978.

(2*S*,3*R*,4*S*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-fluorenylmethoxycarbonyl-2-formylpyrrolidine (35): on a scale of 0.10 mmol (83%); TLC R_f 0.30 (7:2 hexanes−EtOAc); $[\alpha]^{20}_D$ = +11.8 (*c* 0.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.08−0.17 (m, 12H), 0.90 (s, 4.5H), 0.92 (s, 4.5H), 0.94 (s, 9H), 3.41 (dd, *J* = 9.9, 6.8 Hz, 0.5H), 3.47 (dd, *J* = 9.9, 6.6 Hz, 0.5H), 3.60 (q, *J* = 5.6 Hz, 1H), 3.93 (dd, *J* = 3.5, 2.1 Hz, 0.5H), 3.96−4.05 (m, 1H), 4.14 (t, *J* = 7.1 Hz, 0.5H), 4.20−4.27 (m, 1.5H), 4.25 (t, *J* = 6.7 Hz, 0.5H), 4.43−4.58 (m, 2H), 7.30−7.39 (m, 2H), 7.42 (q, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.62 (dd, *J* = 7.3, 3.8 Hz, 1H), 7.78 (app t, *J* = 8.5 Hz, 2H), 9.26 (d, *J* = 1.8 Hz, 0.5H), 9.59 (d, *J* = 1.8 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −4.1, −4.0, −3.8, −3.7, −3.6, −3.5, 19.1, 26.8, 48.0 and 48.1, 51.3 and 51.4, 68.4 and 68.5, 72.0 and 72.1, 72.3 and 72.9, 74.8 and 75.6, 120.9, 121.0, 125.6, 125.7, 125.9, 126.0, 127.9, 128.0, 128.7, 128.9, 142.3, 144.6, 144.7, 155.6 and 156.4; HRMS (FAB) calcd for MH^+ $C_{32}H_{48}NO_5Si_2$ 582.3071, obsd 582.3052.

General Method for Oxidation to Carboxylic Acid. A solution of the aldehyde (1.0 equiv) in a mixture of *tert*-butanol (40 mL/mmol) and cyclohexene (4 mL/mmol) was added over 10 min to a solution of sodium chlorite (10.0 equiv) and potassium dihydrogen phosphate (10.0 equiv) dissolved in Milli-Q water (20 mL/mmol). The resulting solution was stirred at rt under N_2 for 4 h. The reaction mixture was diluted with EtOAc (1 L/mmol) and washed with brine (1 L/mmol), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography, eluting with 100% EtOAc.

D-2,3-*cis*-3,4-*cis*-*N*-Fluorenylmethoxycarbonyl-3,4-dihydroxy-3,4-di-*O*-*tert*-butyldimethylsilylproline (7): on a scale of 0.17 mmol (82%); TLC R_f 0.54 (1:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = +13.1 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.16 (s, 6H), 0.18 (s, 6H), 0.88 (s, 18H), 3.42−3.54 (m, 1.5H), 3.62−3.70 (m, 0.5H), 4.21−4.17 (m, 1H), 4.25 (t, *J* = 6.8 Hz, 2H), 4.37−4.42 (m, 3H), 7.31 (t, *J* = 7.1 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.51−7.60 (m, 1H), 7.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −5.0, −4.8, 18.2, 25.6, 25.8, 46.9, 51.9 and 52.6, 62.9, 67.6 and 68.7, 72.9 and 73.2, 73.7, 119.9, 125.2 and 125.6, 127.1, 127.7, 141.3, 155.2 and 155.3, 168.6; HRMS (CI) calcd for MH^+ $C_{32}H_{48}NO_6Si_2$ 598.3020, obsd 598.3022.

L-2,3-*cis*-3,4-*trans*-*N*-Fluorenylmethoxycarbonyl-3,4-dihydroxy-3,4-di-*O*-*tert*-butyldimethylsilylproline (36): on a scale of 0.05 mmol (93%); TLC R_f 0.14 (3:1 hexanes−EtOAc); $[\alpha]^{20}_D$ = −31.5 (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.07 (s, 3H), 0.09 (s, 6H), 0.10 (s, 3H), 0.86 (s, 13.5H), 0.86 (s, 4.5H), 3.40 (d, *J* = 10.6 Hz, 0.5H), 3.46 (d, *J* = 10.6 Hz, 0.5H), 3.72−3.81 (m, 1H), 4.05−4.19 (m, 1.5H), 4.22−4.32 (m, 1.5H), 4.33−4.47 (m, 2.5H), 4.55 (d, *J* = 5.8 Hz, 0.5H), 7.26−7.33 (m, 2H), 7.34−7.43 (m, 2H), 7.49−7.64 (m, 2H), 7.70 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −5.1, −4.8, 17.8, 25.6, 25.7, 47.1 and 47.2, 52.2, 62.9 and 63.1, 67.6 and 67.8, 74.6 and 75.2, 77.4 and 78.3, 119.9, 124.9, 125.0 and 125.1, 127.0 and 127.7, 141.3, 144.0, 155.3, 173.4 and 173.9; HRMS (FAB) calcd for MH^+ $C_{32}H_{48}NO_6Si_2$ 598.3020, obsd 598.3017.

L-2,3-*trans*-3,4-*cis*-*N*-Fluorenylmethoxycarbonyl-3,4-dihydroxy-3,4-di-*O*-*tert*-butyldimethylsilylproline (37): on a scale of 0.082 mmol (83%); TLC R_f 0.36 (10:1 CH_2Cl_2−MeOH); $[\alpha]^{20}_D$ = −2.1 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) (mixture of rotamers) δ 0.07 (s, 1.5H), 0.09 (s, 6H), 0.11 (s, 4.5H), 0.88 (s, 9H), 0.91 (s, 9H), 3.34−3.47 (m, 1H), 3.60 (dd, *J* = 9.6, 6.4 Hz, 0.5H), 3.66 (dd, *J* = 10.2, 6.4 Hz, 0.5H), 4.12−4.24 (m, 2.5H), 4.23 (d, *J* = 2.0 Hz, 1H), 4.29 (t, *J* = 7.0 Hz, 0.5H), 4.36 (dd, *J* = 3.5, 2.0 Hz, 0.5H), 4.40 (t, *J* = 7.0 Hz, 0.5H), 4.44 (d, *J* = 2.2 Hz, 0.5H), 4.46 (d, *J* = 2.9 Hz, 0.5H), 7.27−7.45 (m, 4H), 7.51−7.62 (m, 2H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers) δ −4.8, −4.7, −4.4, −4.3, −4.2, −4.1, 18.5, 26.1, 26.2, 47.5, 50.3 and 50.5, 66.1 and 66.4, 68.1 and 68.3, 71.4 and 71.9, 75.9, 120.3 and 120.4, 125.4 and 125.5, 127.4 and 127.5, 128.0 and 128.2, 141.6 and 141.7, 144.1 and 144.4, 155.0 and 156.2, 174.9 and 175.9; HRMS (FAB) calcd for MH^+ $C_{32}H_{48}NO_6Si_2$ 598.3020, obsd 598.3049.

General Procedure* for the Removal of Protecting Groups To Afford Dihydroxyprolines. Trifluoroacetic acid (1 mL) was added to a solution of the protected dihydroxyproline (20−50 μmol) in dichloromethane (1 mL) and the solution stirred under an atmosphere of nitrogen at rt overnight. The reaction mixture was concentrated, dissolved in Tesser's base (2 mL), and stirred at rt for 1 h. The reaction mixture was diluted with water (20 mL) and washed with ethyl acetate (2 × 10 mL). The aqueous phase was concentrated and the

residue purified by ion-exchange chromatography (Dowex H^+) eluting with 0.5 M NH_4OH.

D-2,3-*cis*-3,4-*cis*-Dihydroxyproline (38). [This isomer has been synthesized previously.[33] The enantiomer has been synthesized several times.[5b,34−37] For a racemic synthesis see ref 9.] On a scale of 52.0 μmol to give **38** as a colorless solid (4.4 mg, 58%): TLC R_f 0.37 (6:4:1 $CHCl_3$−CH_3OH−H_2O); $[\alpha]^{20}_D$ = +26.7 (*c* 0.18, H_2O) (lit.[33] $[\alpha]^{20}_D$ = +55.9 (*c* 0.6, H_2O) [for the enantiomer: lit.[34] $[\alpha]^{20}_D$ = −56.8 (*c* 0.16, H_2O)]); ^1H NMR (D_2O, 400 MHz) δ 3.10 (dd, *J* = 11.4, 8.7 Hz, 1H), 3.41 (dd, *J* = 11.4, 7.6 Hz, 1H), 4.01 (d, *J* = 3.9 Hz, 1H), 4.23−4.37 (m, 2H); ^{13}C NMR (D_2O, 68 MHz) δ 47.1, 64.9, 70.7, 71.0, 170.8; HRMS (FAB+) calcd for MH^+ $C_5H_{10}NO_4$ 148.0609, obsd 148.0618.

L-2,3-*trans*-3,4-*cis*-Dihydroxyproline (3). [This isomer has been synthesized several times.[5b,6a,7,33,38,39] The enantiomer has also been synthesized.[38,40] For racemic syntheses see ref 9 and 41.] On a scale of 22.0 μmol to give **3** as a colorless solid (3.0 mg, 93%): TLC R_f 0.34 (6:4:1 $CHCl_3$−CH_3OH−H_2O); $[\alpha]^{20}_D$ = +1.9 (*c* 0.27, H_2O) (lit.[6a] $[\alpha]^{20}_D$ = +7.5 (*c* 0.16, H_2O), lit.[7] $[\alpha]^{20}_D$ = +5.9 (*c* 0.35, H_2O), lit.[33] $[\alpha^{20}]_D$ = +7.2 (*c* 0.5, H_2O), lit.[38] $[\alpha]^{20}_D$ = +7.5 (*c* 0.5, H_2O), [enantiomer: lit.[38] $[\alpha]^{20}_D$ = −7.4 (*c* 0.5, H_2O), lit.[40] $[\alpha]^{20}_D$ = −6.8 (*c* 0.43, H_2O)]); ^1H NMR (D_2O, 400 MHz) δ 3.16 (dd, *J* = 12.4, 4.4 Hz, 1H), 3.40 (dd, *J* = 12.4, 4.9 Hz, 1H), 3.83 (d, *J* = 4.8 Hz, 1H), 4.14−4.25 (m, 2H); ^{13}C NMR (D_2O, 100 MHz) δ 48.7, 64.7, 70.3, 74.5, 172.6; HRMS (FAB) calcd for MH^+ $C_5H_{10}NO_4$ 148.0609, obsd 148.0634.

*The removal of the TBDMS groups from **36** was sluggish under acidic conditions and it was adventitious to use TBAF in this case: **L-2,3-*cis*-3,4-*trans*-Dihydroxyproline (1).** [This isomer has been synthesized previously.[10b,42−44] The enantiomer has also been synthesized.[45,46]] A 1 M solution of tetrabutylammonium fluoride in THF (163 μL, 163 μmol, 3.0 equiv) was added to a solution of compound **36** (32.3 mg, 54.2 μmol) in THF (2 mL) and the solution stirred under an atm of N_2 at rt for 4 h. The reaction mixture was concentrated and then dissolved in Tesser's base (2 mL) and stirred at rt for 1 h. The reaction mixture was diluted with water (20 mL) and washed with EtOAc (2 × 10 mL). The aqueous phase was concentrated and the residue purified by ion-exchange chromatography (Dowex H^+) eluting with 0.5 M NH_4OH to afford the titled compound as a white solid (4.7 mg, 59%): TLC R_f 0.30 (6:4:1 $CHCl_3$−CH_3OH−H_2O); $[\alpha]^{20}_D$ = −37.5 (*c* 0.24, H_2O) (lit.[2a] $[\alpha]^{20}_D$ = −61.2 (*c* 0.5%, H_2O), lit.[10b] $[\alpha]^{24}_D$ = −56 (*c* 0.62, H_2O); lit.[43] $[\alpha]^{27}_D$ = −63.2 (*c* 0.5, H_2O), lit.[44] $[\alpha]^{22}_D$ = −63.0 (*c* 0.8, H_2O) [enantiomer: lit.[45] $[\alpha]^{20}_D$ = +46.2 (*c* 1.0, H_2O), lit.[46] $[\alpha]^{20}_D$ = +63.4 (*c* 0.35, H_2O)]); ^1H NMR (D_2O, 400 MHz) δ 3.14 (d, *J* = 12.8 Hz, 1H), 3.53 (dd, *J* = 12.8, 3.8 Hz, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 4.26 (br d, *J* = 7.7 Hz, 1H), 4.30 (br d, *J* = 7.7 Hz, 1H); ^{13}C NMR (D_2O, 68 MHz) δ 51.3, 65.6, 75.4, 75.9, 171.5. HRMS (FAB+) calcd for MH^+ $C_5H_{10}NO_4$ 148.0609, obsd 148.0612.

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Supporting Information Available: ^{13}C NMR spectra for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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