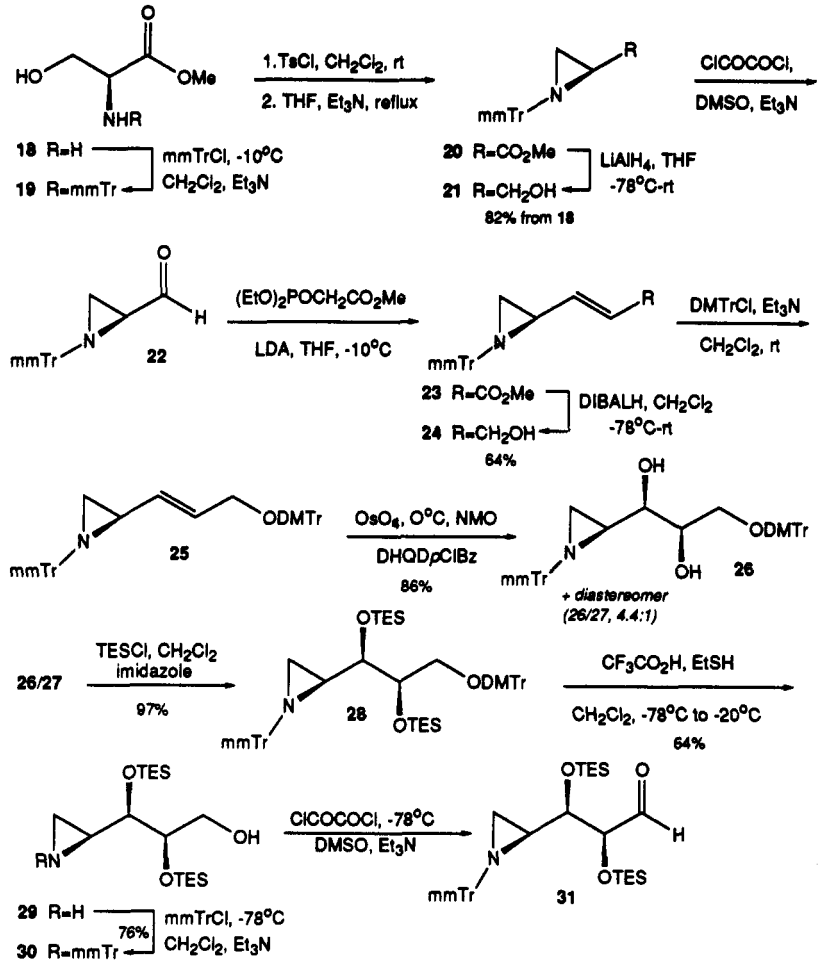
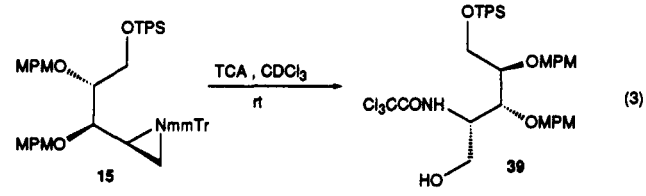
Scheme III



cessfully hydrolyzed to the carboxylic acid, coupled with 1-amino-2-propanol via DCC/HOBt activation, and oxidized to the 2-ketopropanamido derivative **34Z** without purification of intermediates. This was necessary because neither the acid nor the hydroxy amide intermediates withstood exposure to silica gel. Unfortunately, the E-carboxylic acid decomposed without conversion to its corresponding amide under the same conditions successfully used for the *Z* isomer.

Dehydroamino amide **34Z** was brominated using Br_2 in CH_2Cl_2 at −78 °C, followed by DABCO. A single β-bromo dehydroamino amide isomer (**35Z**) was isolated in 71% yield. However, attempts to observe an NOE between either amide proton and the allylic methylene of **35Z** were unsuccessful, leaving the olefin geometry undetermined. TCA deprotection of the mmTr group in $CDCl_3$ led to a set of signals (^{1}H NMR) downfield from the aziridine resonances in **35Z** and consistent with those of the azabicyclo[3.1.0]hex-2-ylidene ring system of the natural product. FAB-MS analysis of the crude mixture, however, indicated that only a very small percentage of product gave rise to a mass corresponding to 586 $[MH]^+$, expected for **36Z**. Instead, two major signals corresponding to masses of 666 (with a monobromo isotope pattern) and 828 (with a monobromo-trichloro isotope pattern) were reported, in accord with structures **37** and **38**. Therefore, the shift of the aziridine resonances in the ^{1}H NMR was not due to the vinylogous urea character of **36Z** but rather was due to protonation of **37** by TCA. Furthermore, TCA was adding to **37** resulting in **38**. Indeed, treatment of **15** with TCA in $CDCl_3$ led to nucleophilic, opening of the aziridine followed by acyl transfer to provide amide **39** (eq 3). To prevent acid hydrolysis, we repeated the experiments with **35Z** but added triethylamine to the NMR tube following TCA deprotection. The aziridine resonances immediately shifted back upfield after triethylamine addition indicating deprotonation by the stronger base.[20] The deprotected aziridine product was chromatographed on silica gel, redissolved in $CDCl_3$, and, after its ^{1}H NMR spectrum was recorded, cyclized to the azabicyclo[3.1.0] compound **36Z** in the presence of triethylamine at 50 °C over an 8-h period.



Full characterization of **36Z** was facilitated by its stability to purification on a silica gel column. An ^{1}H NMR NOE difference experiment conclusively established the *Z* stereochemistry of the product. Not only was an enhancement of the allylic methine H-13[21] observed upon irradiation of NH-16, but irradiation of NH-5 produced an enhancement of the exocyclic aziridine (H-10 exo). Consistent with the data on the natural product azino-

(20) Deyrup, J. A. In *Heterocyclic Compounds*; Hassner, A., Ed.; John Wiley and Sons, Inc.: New York, 1983; Vol. 42, Part 1, p 9.

(21) The bromination of *N*-carbamate-blocked dehydroamino acid derivatives gives different ratios of vinyl bromides: Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1993**, *58*, 4452–4461.

Scheme IV

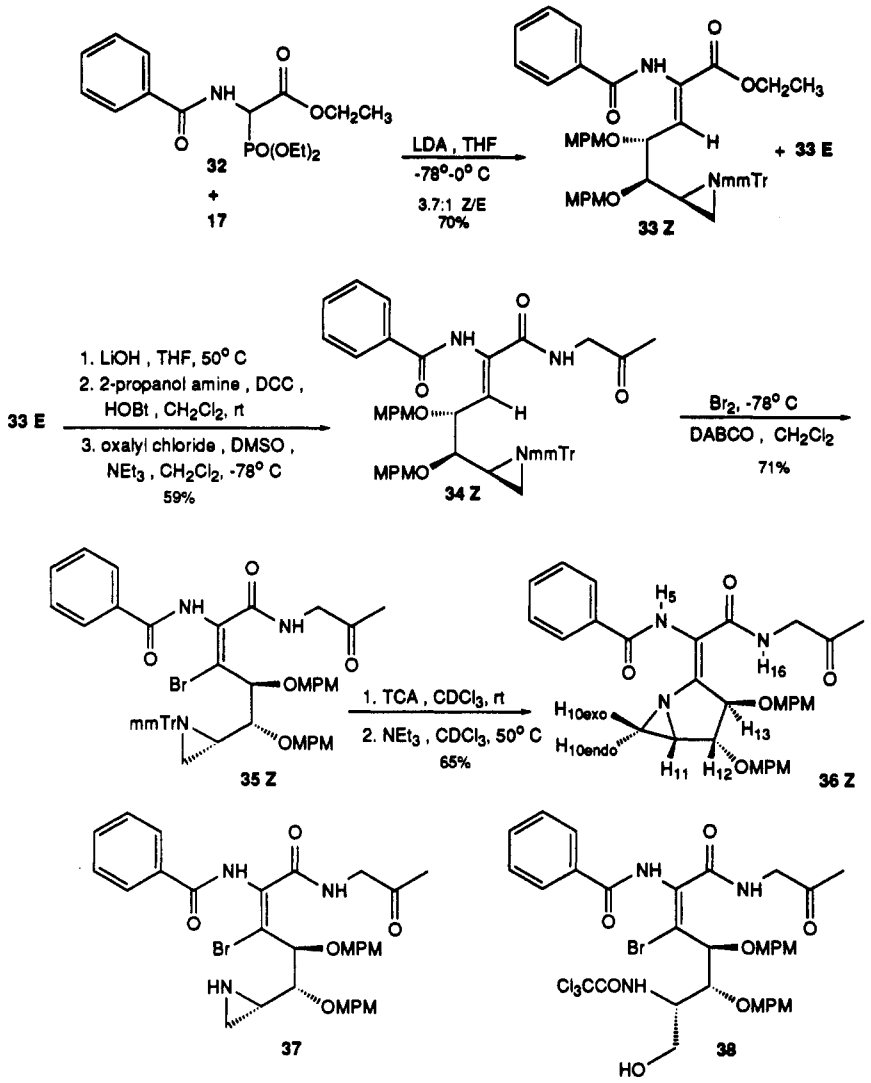


Table I. Comparison of ^{1}H NMR Coupling Constants and Chemical Shifts for Azinomicyn B (2) and Synthetic 1-Azabicyclo[3.1.0]hex-2-ylidenes 36Z, 41Z, and 41E

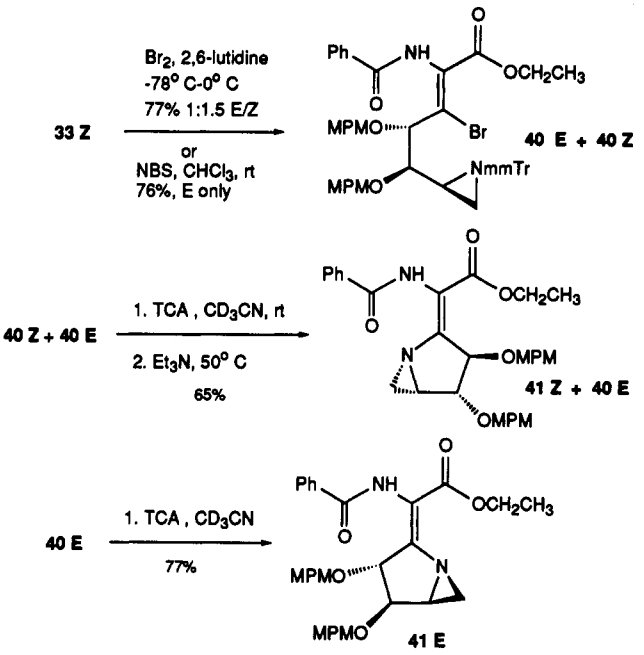
	2[a]		36Z[b]		41Z[b]		41E[b]	
H	δ	J (Hz)	δ	J (Hz)	δ	J (Hz)	δ	J (Hz)
13	5.50	4.0, 0.9[c]	5.12	1, 1[c]	5.05	1.5, 1.8[c]	4.57	4.9, 1[c]
12	4.65	4.0, 5.6	4.42	1, 4.9	4.41	1.5, 4.2	4.53	4.9, 4.9
11	3.39	5.6, 5.4, 4.0	3.03	4.9, 5.3, 3.6	3.00	4.2, 5.5, 3.7	3.00	3.7, 4.9, 4.9
10_{exo}	2.75	5.4, 0.9	2.40	5.3, 1	2.39	5.5, 1.8	2.41	5.0, 1
10_{endo}	2.29	4.0	2.18	3.6	2.14	3.7	2.14	3.7

[a] 400-MHz, $CDCl_3$. [b] 360 MHz, $CDCl_3$. [c] The second value corresponds to long-range coupling between 13-H and 10-H_{exo} as observed for azinomycin B and all three synthetic bicyclic analogs.

mycin B, we also observed an NOE between the H-10_{endo} aziridine hydrogen and the allylic methine H-13. The contrast between the coupling constants in the [3.1.0] ring system in **36Z** and the azinomycins was apparent, however (Table I). Although there is excellent agreement between the data for proton resonances H-10_{exo}, H-10_{endo}, and H-11, those for H-12 and H-13 differ considerably. The substituents on these latter two positions are not the same and obviously could affect the conformation of the five-atom ring.

In an effort to evaluate the substrate specificity of brominations, we reacted dehydroamino ester **33Z** with either NBS or Br_2. Treatment of **33Z** with Br_2 in the presence of 2,6-lutidine in CH_2Cl_2 at −78 °C over 1.5 h followed by DABCO treatment led to an inseparable mixture of vinyl bromides **40Z** and **40E** (1.5:1, respectively). The mixture was then subjected to TCA in $CDCl_3$. Deprotection of one isomer occurred much more rapidly than the other such that, after the addition of triethylamine and warming to 50 °C overnight, a single vinyl bromide **40E** and a single azabicyclo[3.1.0] compound **41Z** were recovered. Assignment of the stereochemistry of **41Z** was based on the close correlation of chemical shifts and coupling constants of the [3.1.0] ring protons with those of **36Z** (Table I). Compelling evidence for the stereochemistry of **40E** was to follow. In contrast to brominations with Br_2, the reaction of **33Z** with *N*-bromosuccinimide in CH_2Cl_2 produced vinyl bromide **40E** exclusively. When **40E** was deprotected by TCA (in CD_3CN) and treated with Et_3N, it cyclized to a single [3.1.0] product **41E**. The coupling constants for the ring protons of **41E** were in contrast with those for **41Z** and **36Z**. However,

Scheme V



they correlate well with those for the natural products **1** and **2**, in particular for H-12 and H-13. The stereochemistry of **41E** was firmly established by an observed NOE relationship between the amide hydrogen H-5 and the allylic methine H-13 in the [3.1.0] ring. Both **41E** and **41Z** show the expected cross ring enhancements between the allylic methine and the endocyclic aziridine methylene confirming their bicyclic structure. In parallel with the natural products, they also exhibit a long-range five-bond coupling (J = 1–2 Hz) between H-13 and H-10_{exo}.

All cyclizations of the vinyl bromides were completely stereospecific. The lack of NOE or chemical shift correlations for vinyl bromides **35Z**, **40E**, and **40Z** leads to a reliance on the stereochemical outcome of their cyclizations for this assignment. The addition/elimination of the aziridine as a multistep process results in a carbanion intermediate upon aziridine addition followed by elimination of the β-halide.[22] If each isomer executes the same mode of facial addition, then E and Z give rise to intermediates which differ only by rotation about the Cα–Cβ bond axis. The intermediate Michael adduct must make either a 60° rotation (retention) or a 120° rotation (inversion) about the α–β bond before expulsion of the β-bromide can occur (Scheme VI). There is a considerable barrier to the 120° rotation in β-halo-substituted ethyl anion systems due to the loss in hyperconjugative stabilization of the α-carbanion by the halide upon rotation. The 60° rotation, in contrast, serves to maximize the stabilization, placing the interacting orbitals parallel for elimination. If the two isomers execute opposite modes of facial addition, then they generate diastereomeric intermediate carbanions, both of which must perform a 120° rotation before eliminating to give complete inversion of stereochemistry. Regardless of the mode of facial addition, the unfavorable 120° α–β bond rotation makes retention of starting olefin geometry highly likely.

In the course of investigating the condensation of phosphonate **32** with the aldehyde **31**, we inadvertently deprotected the aziridines during preparative thin-layer chromatography (silica gel) purification of a mixture of **42E** and **42Z** (Scheme VII). This resulted in isolation of a *single* diastereomer from each of the elution bands: **42E**, the higher eluting band, produced the saturated 1-azabicyclo[3.1.0] **43**, while **42Z**, the lower eluting band, produced diastereomer **44**. The stereochemical assignments for these bicyclic structures were established by NOE experiments. We had expected the NOE data to indicate that the products shared identical ring stereochemistry and we had assumed that protonation α to the carbonyl had occurred on opposite faces of the enolate intermediate. Surprisingly, the olefin geometry controlled the stereochemistry at the β-carbon. The observation of NOE enhancements between the β-hydrogen and the endo aziridine methylene in both **43** and **44** suggest that they exist in boat-like conformations. The diaxial relationship of the triethylsilyloxy substituents likely destabilizes the chair conformations. This is especially true in the case of **43** which has all substituents in anti relationships in the chair. If the transition states assume boat-like conformations, then the aziridine in **42Z** adds exclusively to the pseudoaxial rotamer, and in **42E** exclusively to the pseudoequatorial rotamer. An intramolecular hydrogen bond is possible between the amide NH and the allylic silyl ether oxygen in **42Z** and not in **42E** for the boat conformations, potentially explaining the opposite rotamer selectivity. In both cases, it appears that the α-anion is protonated stereospecifically. This result is difficult to justify by invoking steric interactions with an external acid source, but could arise from an intramolecular *syn*-protonation by the aziridine following Michael addition. The stereochemistry of the α-amino acid center has yet to be established. These saturated [3.1.0] derivatives of glycine bear a resemblance to the natural product ficellomycin.[23] This method of preparation offers a synthetic approach to the bicyclic ring in this antibiotic.

Conclusion

We have described the first synthesis of the (*E*)- and (*Z*)-1-azabicyclo[3.1.0]hex-2-ylidene derivatives of *N*-benzoyl dehydroamino esters and amides. The oxidation of the β-carbon of dehydroamino esters bearing acid-sensitive functionality was successfully implemented using both bromine and NBS, resulting in moderate to high selectivity in formation of the vinyl bromides. However, this reaction appears to be highly substrate specific. The resulting vinyl bromides undergo conversion to the 1-azabicyclo[3.1.0]-hex-2-ylidene derivatives with retention of stereochemistry with respect to the starting olefin geometry. The dehydroamino ester and amide precursors were synthesized via condensation of glycyl phosphonates with highly functionalized aldehydes of type **5**. These aldehydes were synthesized via two independent routes, proceeding from D-arabinose and L-serine.

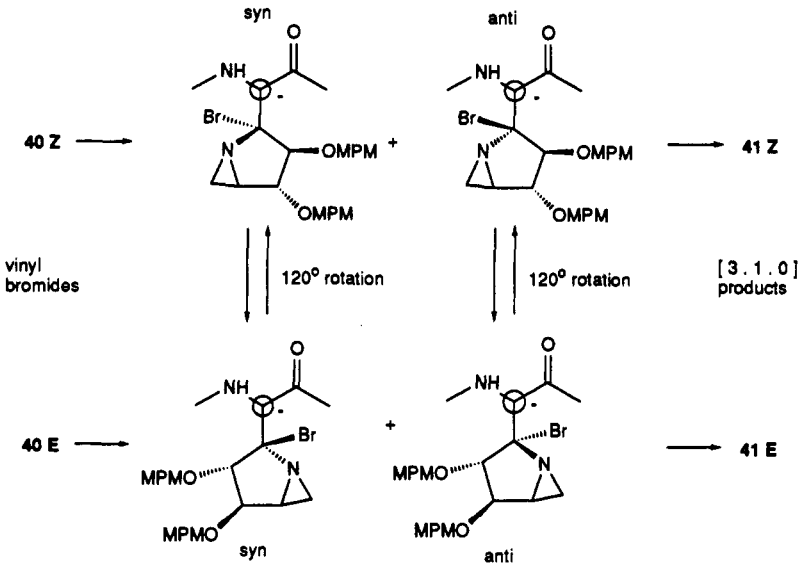
Experimental Section

General Information. ^1H and ^{13}C NMR spectra were recorded at the field strength specified in megahertz. Chemical shifts are reported in ppm with $CHCl_3$, acetone, or DMSO as internal standards. IR absorption frequencies are reported in cm^{-1}. Tetrahydrofuran, diethyl ether, and toluene solvents were distilled from sodium benzophenone ketyl under argon. Meth-

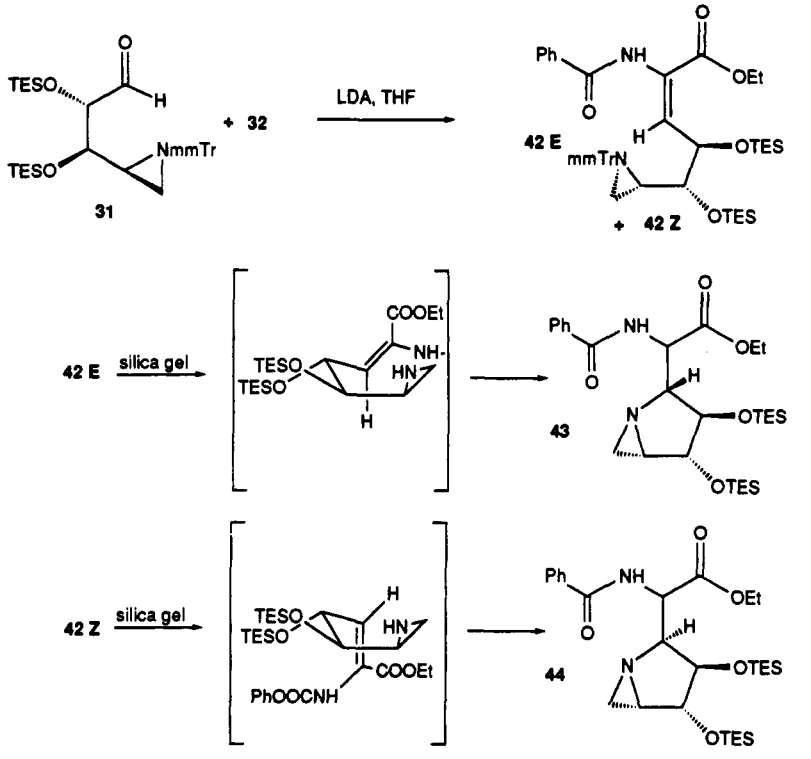
(22) A vinylic substitution occurring as a single-step process would produce Z and E [3.1.0] products from Z and E vinyl bromides, respectively. See, Rappaport, Z. *Acc. Chem. Res.* **1981**, *14*, 7.

(23) Kuo, M. S.; Yurek, D. A.; Mizsak, S. A. *J. Antibiot.* **1989**, *42*, 357.

Scheme VI



Scheme VII



ylene chloride was distilled from P_2O_5. Dimethylformamide and dimethyl sulfoxide were distilled from barium oxide and CaH_2, respectively, under N_2 and stored over 4-Å molecular sieves. Et_3N and 2,6-lutidine were passed through a column of basic alumina immediately prior to use. All other reagents were used as supplied or synthesized according to literature procedures. All reactions were carried out under an inert N_2 atmosphere. Unless otherwise noted, flash chromatography was performed on Merck silica gel 60 (230–400 mesh) using various gradients of hexanes/ethyl acetate as eluants. Acid-sensitive compounds were chromatographed using Et_3N-deactivated silica. Small-scale separations (<60 mg) were done on Fischer Prep-Sep silica columns or E. Merck preparative thin-layer silica chromatography plates (0.25, 0.5, 1.0 and 2.0 mm thicknesses). Elemental analyses were performed by Desert Analytics, Tucson, AZ.

2,3-Bis(*p*-methoxybenzyl)-1,1-bis(ethylthio)-4,5-isopropylidene-D-arabinose (8). To 23 g (77.5 mmol) of 2,3-dihydroxy-1,1-bis(ethylthio)-4,5-isopropylidene-D-arabinose[7] and 23.2 mL (171 mmol) of *p*-methoxybenzyl chloride in 100 mL of DMF at 0 °C was added 5.6 g (233 mmol) of NaH. After 30 min the reaction temperature was raised to 25 °C and stirring continued for 4 h whereupon the contents were poured into a saturated aqueous solution of NH_4Cl and extracted with three portions of CH_2Cl_2. The combined organics were dried over anhydrous Na_2SO_4 and filtered and the solvents removed via evaporation at reduced pressure. Flash silica gel column chromatography (hexanes/EtOAc gradient) yielded 31.7 g (76%) of 8 as a clear oil: $[\alpha]_D = +31°$ ($c = 0.0065$, CH_2Cl_2); IR (neat) 2931, 2834, 1730, 1610, 1512, 1249; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31 (d, $J = 8.9$ Hz, 2 H, MPM*H*), 7.24 (d, $J = 8.9$ Hz, 2 H, MPM*H*), 6.85 (d, $J = 8.9$ Hz, 2 H, MPM*H*), 6.84 (d, $J = 8.9$ Hz, 2 H, MPM*H*), 4.82 (d, $J = 10.2$ Hz, 1 H, MPMCH_2), 4.71 (d, $J = 11.1$ Hz, 1 H, MPMCH_2), 4.66 (d, $J = 10.2$ Hz, 1 H, MPMCH_2), 4.66 (d, $J = 11.1$ Hz, 1 H, MPMCH_2), 4.19 (ddd, $J = 6.2$, 6.2, 7.1 Hz, 1 H, 4-C*H*), 4.12 (d, $J = 6.2$ Hz, 1 H, 1-C*H*), 4.09 (dd, $J = 4.4$, 6.2 Hz, 1 H, 3-C*H*), 4.01 (dd, $J = 6.2$, 8.4 Hz, 1 H, 5-CH_2), 3.84 (dd, $J = 7.1$, 8.4 Hz, 1 H, 5-CH_2), 3.79 (s, 3 H, MPMOCH_3), 3.79 (s, 3 H, MPMOCH_3), 3.76 (dd, $J = 4.4$, 6.2 Hz, 1 H, 2-C*H*), 2.67 (m, 4 H, SCH_2CH$_3$), 1.48 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.25 (t, $J = 7.5$ Hz, 3 H, SCH$_2$CH_3), 1.23 (t, $J = 7.5$ Hz, 3 H, SCH$_2$CH_3); ^{13}C NMR

(90 MHz, $CDCl_3$) δ 159.2, 130.7, 130.5, 129.7, 129.6, 113.7, 113.6, 108.7, 82.8, 79.6, 76.6, 74.8, 74.4, 66.8, 55.2, 53.0, 26.6, 25.8, 25.2, 24.9, 14.4, 14.4; HRMS (FAB) calcd for $C_{28}H_{41}O_6S_2$ 537.2344, found 537.2357.

2,3-*O*-Bis(*p*-methoxybenzyl)-4,5-isopropylidene-D-arabinol (9). NBS (3.4 g, 18.8 mmol) was added in small portions over 5 min to 8 (2.5 g, 4.7 mmol) and 2,6-lutidine (3.3 mL, 28 mmol) stirring at 0 °C in 20 mL of a 90/10 CH_3CN/H_2O solution. An excess of a saturated aqueous sodium sulfite solution was added dropwise, and the reaction was diluted with CH_2Cl_2 and washed twice with NH_4Cl (saturated). The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvents were removed by evaporation at reduced pressure, affording a thick oil. The oil was dissolved in 20 mL of EtOH and the solution cooled to 0 °C. $NaBH_4$ (250 mg, 6.5 mmol) was added and the temperature was raised to 25 °C with continuous stirring. After 2 h, saturated aqueous NH_4Cl was added and the resulting precipitate was filtered, concentrated, and purified by flash silica gel chromatography (hexanes/EtOAc gradient) to yield 1.5 g (74%) of **9** as a clear oil: $[\alpha]_D$ = +11° (*c* = 0.0085, CH_2Cl_2); IR (neat) 3460, 2985, 1612, 1513, 1248; ^1H NMR (360 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 7.24 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.87 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.86 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 4.67 (d, *J* = 11 Hz, 1 H, MPMCH_2), 4.64 (d, *J* = 11 Hz, 1 H, MPMCH_2), 4.55 (s, 2 H, MPMCH_2), 4.20 (ddd, *J* = 4.9, 6.6, 7.5 Hz, 1 H, 4-C*H*), 4.03 (dd, *J* = 6.6, 8.4 Hz, 1 H, 5-CH_2), 3.94 (dd, *J* = 7.5, 8.4 Hz, 1 H, 5-CH_2), 3.80 (s, 6 H, MPMOCH_3), 3.79 (dd, *J* = 4.9 Hz, *J* = 5 Hz, 1 H, 3-C*H*), 3.70 (dd, *J* = 4.9, 12 Hz, 1 H, 1-CH_2), 3.61 (dd, *J* = 4.9, 12 Hz, 1 H, 1-CH_2), 3.55 (ddd, *J* = 4.9, 4.9, 5.0 Hz, 1 H, 2-C*H*), 2.10 (br m, 1 H, 1-CH_2OH), 1.48 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.3, 130.1, 129.9, 129.7, 113.8, 108.5, 79.5, 78.8, 76.5, 74.3, 72.3, 66.2, 61.5, 55.2, 26.5, 25.1; HRMS (FAB) calcd for $C_{24}H_{31}O_7$ 431.2070, found 431.2050.

2,3-*O*-Bis(*p*-methoxybenzyl)-4,5-isopropylidene-1-*O*-(*tert*-butyldiphenylsilyl)-D-arabinol (10). *tert*-Butyldiphenylsilyl chloride (1.2 mL, 4.5 mmol) was added via syringe to **9** (1.5 gm, 3.5 mmol) and imidazole (714 mg, 10.5 mmol) stirring in 10 mL of DMF at rt. After 2 h, the reaction mixture was poured into CH_2Cl_2 and extracted with a saturated aqueous NH_4Cl solution. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated at reduced pressure. The resulting oil was purified by flash silica gel chromatography (hexanes/EtOAc gradient) to yield 2.23 g (95%) of **10** as a clear oil: $[\alpha]_D$ = +12° (*c* = 0.0087, CH_2Cl_2); IR (neat) 2930, 2856, 1513, 1248, 1111, 1073; ^1H NMR (360 MHz, $CDCl_3$) δ 7.63 (m, 4 H, SiAr*H*), 7.45 (m, 2 H, SiAr*H*), 7.38 (m, 4 H, SiAr*H*), 7.19 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 7.12 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.82 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.82 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 4.77 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.62 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 3.98 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 3.86 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.25 (ddd, *J* = 4.9, 6.6, 6.6 Hz, 1 H, 4-C*H*), 3.96 (dd, *J* = 6.6, 14.5 Hz, 1 H, 5-CH_2), 3.94 (dd, *J* = 6.6, 14.5 Hz, 1 H, 5-CH_2), 3.95 (dd, *J* = 3, 4.9 Hz, 1 H, 3-C*H*), 3.75 (s, 3 H, MPMOCH_3), 3.74 (s, 3 H, MPMOCH_3), 3.74 (dd, *J* = 5.8 Hz, *J* = 10.2 Hz, 1 H, 1-CH_2), 3.72 (dd, *J* = 7, 10.2 Hz, 1 H, 1-CH_2), 3.63 (ddd, *J* = 3, 5.8, 7 Hz, 1 H, 2-C*H*), 1.43 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.06 (s, 9 H, SiC(CH_3)$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.1, 135.6, 133.3, 130.6, 130.4, 129.8, 129.7, 127.7, 113.6, 108.1, 79.1, 78.0, 76.7, 74.5, 72.7, 66.1, 62.5, 55.2, 26.8, 26.6, 25.3, 19.1; HRMS (FAB) calcd for $C_{40}H_{49}O_7Si$ 669.3247, found 669.3219.

2,3-*O*-Bis(*p*-methoxybenzyl)-1-*O*-(*tert*-butyldiphenylsilyl)-D-arabinol (11). A solution containing 1.23 g (1.95 mmol) of **10** in 50 mL of MeOH was heated for 56 h at 50 °C in the presence of approximately 100 mg of pyridinium *p*-toluenesulfonate. After cooling to room temperature, 0.2 mL of 3 M NH_4OH was added and the solvent removed. The remaining oil was chromatographed on flash silica gel (hexanes/EtOAc gradient) to yield 370 mg of **10** (30% recovery) and 775 mg (66%) of **11** as a clear oil: $[\alpha]_D$ = +5.2° (*c* = 0.0062, CH_2Cl_2); IR (neat) 33421, 2929, 2856, 1611, 1513, 1249, 1111, 1077; ^1H NMR (360 MHz, $CDCl_3$) δ 7.69 (m, 4 H, SiAr*H*), 7.49 (m, 2 H, SiAr*H*), 7.41 (m, 4 H, SiAr*H*), 7.17 (d, *J* = 8.7 Hz, 2 H, MPM*H*), 7.14 (d, *J* = 8.7 Hz, 2 H, MPM*H*), 6.84 (d, *J* = 8.7 Hz, 2 H, MPM*H*), 6.82 (d, *J* = 8.7 Hz, 2 H, MPM*H*), 4.60 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.48 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.43 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.41 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 3.92 (m, 2 H, 2-C*H* and 3-C*H*), 3.80 (s, 3 H, MPMOCH_3), 3.78 (s, 3 H, MPMOCH_3), 3.75 (m, 2 H, 1-CH_2 and 4-C*H*), 3.62 (m, 1 H, 1-CH_2), 3.60 (m, 2 H, 5-CH_2), 3.24 (d, *J* = 4 Hz, 1 H, 4-CHO*H*), 2.13 (br m, 1 H, 5-CH_2OH), 1.08 (s, 9 H, SiC(CH_3)$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.4, 159.3, 135.6, 133.1, 129.9, 129.8, 129.7, 127.8, 113.8, 113.8, 79.0, 77.0, 73.2, 72.5, 71.4, 63.7, 62.9, 55.2, 26.8, 19.1; HRMS (FAB) calcd for $C_{37}H_{45}O_7Si$ 629.2934, found 629.2920.

5-Azido-5-deoxy-2,3-*O*-bis(*p*-methoxybenzyl)-1-*O*-(*tert*-butyldiphenylsilyl)-D-arabinol (13). A solution of **11** (1.00 g, 1.59 mmol) and pyridine (0.65 mL, 7.95 mmol) in 10 mL CH_2Cl_2 was cooled to −78 °C. Mesyl chloride (123 μL, 1.59 mmol) was added via syringe and the reaction was warmed to 0 °C and allowed to stir overnight. An additional 25 μL of mesyl chloride (0.32 mmol, 0.2 equiv) was added and the reaction was stirred for 5 h. MeOH (2 mL) was added and the mixture was poured into a saturated aqueous NH_4Cl solution. After exhaustive extraction, the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated at reduced pressure. The crude mesylate was dissolved in 3 mL of DMF and heated to 50 °C for 8 h in the presence of NaN_3 (200 mg, 3.1 mmol). The solvent was removed at reduced pressure and the residue dissolved in CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. The resulting oil was chromatographed on flash silica gel column to yield 650 mg (62%) of **13** as a clear oil which was unstable to storage and further purification: $[\alpha]_D$ = +15° (*c* = 0.0056, CH_2Cl_2); IR (neat) 2930, 2856, 2100; ^1H NMR (360 MHz, $CDCl_3$) δ 7.68 (m, 4 H, SiAr*H*), 7.43 (m, 2 H, SiAr*H*), 7.39 (m, 4 H, SiAr*H*), 7.17 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 7.11 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.85 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.81 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 4.60 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.45 (d, *J* = 11 Hz, 1 H, MPMCH_2), 4.40 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.39 (d, *J* = 11 Hz, 1 H, MPMCH_2), 3.91 (dd, *J* = 5.8, 11 Hz, 1 H, 1-CH_2), 3.88 (ddd, *J* = 3.1, 5.8, 8.0 Hz, 1 H, 4-C*H*), 3.80 (s, 3 H, MPMOCH_3), 3.79 (s, 3 H, MPMOCH_3), 3.78 (dd, *J* = 5.8, 11 Hz, 1 H, 1-CH_2), 3.74 (ddd, *J* = 3.5, 5.8, 5.8 Hz, 1 H, 2-C*H*), 3.58 (dd, *J* = 3.5, 8.0 Hz, 1 H, 3-C*H*), 3.36 (dd, *J* = 3.1, 12.8 Hz, 1 H, 5-C*H*), 3.22 (dd, *J* = 5.8, 12.8 Hz, 1 H, 5-C*H*), 3.16 (br, 1 H, 4-CH_2OH), 1.07 (s, 9 H, SiC(CH_3)$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.5, 159.4, 135.6, 133.1, 129.9, 129.8, 129.8, 129.7, 127.8, 113.9, 113.8, 78.3, 76.5, 73.1, 72.4, 71.0, 62.6, 55.3, 53.6, 26.8, 19.1.

(2′*S*)-3-(2′-Aziridinyl)-2(*R*),3(*R*)-bis[(*p*-methoxybenzyl)oxy]-1-*O*-(*tert*-butyldiphenylsilyl)propanol (14). A toluene (3 mL) solution of **13** (280 mg, 0.43 mmol) and triphenylphosphine (170 mg, 0.64 mmol) was warmed to 40 °C for 30 min. The solvent was removed *in vacuo* and the residue chromatographed using flash silica gel to afford 198 mg of **14** as a clear oil (76%): $[\alpha]_D$ = −10° (*c* = 0.0054, CH_2Cl_2); IR (neat) 2929, 2855, 1611, 1513, 1248, 1111, 1078, 1035; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (m, 4 H, SiAr*H*), 7.60–7.30 (m, 6 H, SiAr*H*), 7.20 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 7.19 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.83 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 6.81 (d, *J* = 8.9 Hz, 2 H, MPM*H*), 4.67 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.62 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.58 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 4.44 (d, *J* = 11.5 Hz, 1 H, MPMCH_2), 3.88 (dd, *J* = 5.3, 10.6 Hz, 1 H, 1-CH_2), 3.84 (dd, *J* = 4.0, 10.6 Hz, 1 H, 1-CH_2), 3.80 (s, 3 H, MPMOCH_3), 3.78 (s, 3 H, MPMOCH_3), 3.56 (ddd, *J* = 4.0, 5.3, 5.5 Hz, 1 H, 2-C*H*), 3.20 (dd, *J* = 5.5, 5.5 Hz, 1 H, 3-C*H*), 2.16 (ddd, *J* = 2.7, 5.5, 5.8 Hz, 1 H, 2-C*H*), 1.51 (d, *J* = 5.8 Hz, 1 H, 3-CH_2), 1.29 (d, *J* = 2.7 Hz, 1 H, 3′-CH_2), 1.04 (s, 9 H, SiC(CH_3)$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.1, 159.0, 135.60, 135.56, 133.5, 133.4, 132.1, 132.0, 131.91, 131.90, 131.88, 130.6, 129.67, 129.65, 129.4, 128.5, 128.4, 127.66, 127.65, 113.59, 113.56, 80.5, 72.7, 72.2, 63.1, 55.21, 55.18, 30.9, 26.8, 20.8, 19.1; HRMS (FAB) calcd for $C_{37}H_{46}NO_5Si$ 612.3145, found 612.3156.

(2′*S*)-3-[*N*-(Monomethoxytrityl)-2′-aziridinyl]-2(*R*),3(*R*)-bis[(*p*-methoxybenzyl)oxy]-1-*O*-(*tert*-butyldiphenylsilyl)-propanol (15). A 2-mL solution of monomethoxytrityl chloride (419 mg, 1.36 mmol) was added via syringe to **14** (850 mg, 1.36 mmol) and pyridine (440 μL, 5.44 mmol) being stirred in 5 mL of CH_2Cl_2 at −78 °C. After 15 min, the reaction temperature was raised to 0 °C and the solution poured onto a saturated aqueous NaH_2PO_4 solution, diluted with an equal volume of hexanes, and extracted exhaustively. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated at reduced pres-

sure. The crude oil was chromatographed on a flash silica gel to yield 773 mg (64%) of **15** as a light yellow oil: $[\alpha]_D = -37°$ (c = 0.010, CH_2Cl_2); IR (neat) 3032, 2930, 2856, 1610, 1511, 1249, 1112; ^1H NMR (360 MHz, $CDCl_3$) δ 7.67 (m, 4 H, ArH), 7.58 (m, 2 H, ArH), 7.53 (m, 2 H, ArH), 7.45–7.10 (m, 12 H, ArH), 7.10 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 7.00 (d, J = 8.9 Hz, 2 H, MPMH), 6.98 (d, J = 8.9 Hz, 2 H, MPMH), 6.80 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 6.74 (d, J = 8.9 Hz, 2 H, MPMH), 6.73 (d, J = 8.9 Hz, 2 H, MPMH), 4.58 (d, J = 11 Hz, 1 H, MPMCH_2), 4.53 (d, J = 11.5 Hz, 1 H, MPMCH_2), 4.47 (d, J = 11 Hz, 1 H, MPMCH_2), 4.33 (d, J = 11.5 Hz, 1 H, MPMCH_2), 3.83 (dd, J = 5.3, 10.6 Hz, 1 H, 1-CH_2), 3.75 (dd, J = 5.8, 10.6 Hz, 1 H, 1-CH_2), 3.72 (s, 6 H, MPMOCH_3), 3.69 (s, 3 H, mmTr-OCH_3), 3.63 (dd, J = 4.0, 7.0 Hz, 1 H, 3-CH), 3.56 (ddd, J = 5.3, 5.8, 7.0 Hz, 1 H, 2-CH), 1.68 (d, J = 3.1 Hz, 1 H, 3′-CH_2), 1.58 (ddd, J = 3.1, 4.0, 6.6 Hz, 1 H, 2′-CH), 1.08 (s, 9 H, SiC(CH_3)$_3$), 1.00 (d, J = 6.6 Hz, 1 H, 5-CH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.8, 158.7, 158.0, 147.1, 145.1, 144.8, 135.5, 133.4, 133.3, 131.0, 130.8, 130.5, 129.5, 129.43, 129.37, 129.30, 129.2, 129.1, 127.74, 127.70, 127.6, 127.3, 126.9, 126.3, 113.34, 113.31, 112.5, 80.7, 80.2, 73.8, 72.4, 72.2, 63.3, 54.99, 54.92, 35.1, 26.8, 24.3, 19.0; HRMS (FAB) calcd for $C_{57}H_{62}NO_6Si$ 884.4346, found 884.4323.

(2′*S*)-3-[*N*-(Monomethoxytrityl)-2′-aziridinyl]-2(*R*),3(*R*)-bis[(*p*-methoxybenzyl)oxy]-1-propanol (16). Tetra-*N*-butylammonium fluoride (360 μL of a 1 M soln, 0.36 mmol) was added to **15** (325 mg, 0.36 mmol) being stirred in 5 mL of THF at rt. After 8 h, the solvent was removed *in vacuo* and the residue chromatographed on by flash silica gel (hexanes/EtOAc gradient) yielding 219 mg (92%) of **16** as a clear oil: $[\alpha]_D = -52°$ (c = 0.0042, CH_2Cl_2); IR (neat) 3432, 3054, 2932, 1611, 1513, 1248, 1034; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (m, 2 H, mmTr-ArH), 7.61 (m, 2 H, mmTr-ArH), 7.47 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 7.33 (m, 4 H, mmTr-ArH), 7.27 (m, 2 H, mmTr-ArH), 7.20 (d, J = 8.9 Hz, 2 H, MPMH), 7.13 (d, J = 8.9 Hz, 2 H, MPMH), 6.89 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 6.88 (d, J = 8.9 Hz, 2 H, MPMH), 6.85 (d, J = 8.9 Hz, 2 H, MPMH), 4.70 (d, J = 11 Hz, 1 H, MPMCH_2), 4.61 (d, J = 11 Hz, 1 H, MPMCH_2), 4.61 (d, J = 11.5 Hz, 1 H, MPMCH_2), 4.56 (d, J = 11.5 Hz, 1 H, MPMCH_2), 3.85 (s, 3 H, MPMOCH_3), 3.84 (s, 3 H, MPMOCH_3), 3.74 (s, 3 H, mmTr-OCH_3), 3.70 (m, 2 H, 1-CH_2 and 3-CH), 3.60 (m, 2 H, 1-CH_2 and 2-CH), 2.45 (br, 1 H, 1-CH$_2$OH), 1.90 (d, J = 3.1 Hz, 1 H, 3′-CH_2), 1.59 (ddd, J = 3.1, 6.4, 6.6 Hz, 1 H, 2′-CH), 1.22 (d, J = 6.4 Hz, 1 H, 3′-CH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.2, 159.0, 158.1, 145.0, 144.7, 135.4, 131.1, 130.5, 130.2, 129.5, 129.4, 129.3, 127.4, 126.5, 113.7, 113.6, 112.6, 81.5, 80.0, 73.9, 72.4, 72.4, 61.8, 55.2, 55.1, 34.9, 24.4; MS (FAB) 646 $[MH]^+$, 273, 121; HRMS (FAB) calcd for $C_{41}H_{44}NO_6$ 646.3168, found 646.3138.

(2′*S*)-3-[*N*-(Monomethoxytrityl)-2-aziridinyl]-2(*R*),3(*R*)-bis[(*p*-methoxybenzyl)oxy]-1-propanal (17). DMSO (30 μL, 0.42 mmol) was added via syringe to oxalyl chloride (19 μL, 0.21 mmol) being stirred in 5 mL of CH_2Cl_2 at −78 °C. After 5 min, a solution of **16** (28 mg, 0.042 mmol) in 2 mL of CH_2Cl_2 was added via syringe. Stirring was continued at −78 °C for 10 min, triethylamine (88 μL, 0.63 mmol) was added, and the reaction temperature was allowed to rise to 0 °C over a 20-min period. The solution was diluted with 10 mL of hexanes and washed successively with saturated aqueous NaH_2PO_4 solution and H_2O, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, dissolved in 1 mL of CH_2Cl_2, and passed through a plug of anhydrous $MgSO_4$. Azeotroping this solution with toluene provided 28 mg of **17**, suitable for further condensations. This material was unstable to further purification. The following data was obtained on crude material: IR (neat) 2931, 2834, 1730, 1610; ^1H NMR (360 MHz, $CDCl_3$) δ 9.67 (d, J = 1.8 Hz, 1 H, CHO), 7.54 (m, 2 H, mmTr-ArH), 7.49 (m, 2 H, mmTr-ArH), 7.35 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 7.25 (m, 6 H, mmTr-ArH), 7.09 (d, J = 8.9 Hz, 2 H, MPMH), 7.04 (d, J = 8.5 Hz, 2 H, MPMH), 6.80 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 6.80 (d, J = 8.9 Hz, 2 H, MPMH), 6.80 (d, J = 8.9 Hz, 2 H, MPMH), 4.66 (d, J = 11.5 Hz, 1 H, MPMCH_2), 4.50 (d, J = 11 Hz, 1 H, MPMCH_2), 4.40 (d, J = 11 Hz, 1 H, MPMCH_2), 4.40 (d, J = 11.5 Hz, 1 H, MPMCH_2), 3.87 (dd, J = 3.5, 6.2 Hz, 1 H, 3-CH), 3.82 (dd, J = 1.8, 3.5 Hz, 1 H, 2-CH), 3.80 (s, 6 H, MPMOCH_3), 3.79 (s, 3 H, mmTr-OCH_3), 1.66 (d, J = 3.1 Hz, 1 H, 3′-CH_2), 1.63 (ddd, J = 3.1, 6.2, 6.2 Hz, 1 H, 2′-CH), 1.04 (d, J = 6.2 Hz, 1 H, 3′-CH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.7, 159.1, 158.1, 144.8, 144.6, 135.3, 131.0, 130.0, 129.9, 129.4, 129.3, 128.7, 127.8, 127.4, 126.5, 113.7, 113.5, 112.6, 83.8, 73.9, 72.6, 72.5, 55.1, 55.1, 34.7, 24.5.

(2′*S*)-[*N*-(Monomethoxytrityl)-2′-aziridinyl]methanol (21). Monomethoxytrityl chloride (100.0 g, 314.1 mmol) in CH_2Cl_2 (500 mL) was added dropwise to a solution of the hydrochloride salt of L-serine ethyl ester (**18**) (57.4 g, 338.7 mmol) and triethylamine (135 mL, 1 mol) in CH_2Cl_2 (1.0 L) at −78 °C. The solution was allowed to warm to −10 °C and stirred for 2 h. After TLC analysis confirmed consumption of **22**, the solution was cooled to −78 °C, tosyl chloride (123.4 g, 647.2 mmol) and triethylamine (100 mL) were added, and the mixture was allowed to warm to rt over a 12-h period. The reaction mixture was concentrated and dissolved in 1 L of ethyl acetate, washed with three portions of 5% aqueous citric acid, once each with $NaHCO_3$ (satd) and H_2O, and dried over Na_2SO_4. The combined organic extracts were evaporated under reduced pressure to obtain a thick yellow oil. The material was azeotroped twice with toluene (100 mL), dissolved in THF (1 L) containing triethylamine (200 mL), and refluxed for 12 h. The reaction was then cooled to rt and concentrated under reduced pressure. The crude mixture was then dissolved in 1 L of EtOAc and washed consecutively with 5% aqueous citric acid, saturated aqueous $NaHCO_3$, and H_2O. The organic extract was dried over Na_2SO_4 and concentrated by evaporation at reduced pressure to afford 184 g of a crude oil corresponding to **20**. $LiAlH_4$ (44.8 g, 1.18 mol) in THF (0.7 L) was added to crude **20** dissolved in THF (1 L) at −78 °C over a period of 30 min. The reaction was allowed to warm to room temperature over a 3-h period and then diluted with 300 mL of 20% aqueous NaOH and stirred an additional 1 h. After filtration of aluminum salts, the filtrate was concentrated and chromatographed on flash silica gel (hexanes/EtOAc gradient) to afford 101 g (90% yield) of alcohol **21**. Analytical samples of **19** and **20** were obtained by preparative TLC using hexanes/EtOAc/triethylamine (87:12:1) as eluant. **19**: $[\alpha]^{20}_D$ +53° (c = 0.057, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 7.51 (br d, 4 H, J = 8.5 Hz, ArH), 7.40 (br d, 2 H, J = 9.0 Hz, ArH), 7.28 (br t, 4 H, J = 7.1 Hz), 7.20 (br t, 2 H, J = 7.2 Hz, ArH), 6.82 (m, 2 H, J = 8.9 Hz, mmTr-MeOArH), 3.81–3.74 (m, 1 H, CHN), 3.76 (s, 3 H, OCH_3), 3.73–3.66 (m, 2 H, CH_2CH$_3$), 3.58–3.50 (m, 2 H, HOCH_2CHN), 1.08 (t, J = 7.2, 3 H, CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.61, 158.01, 145.96, 145.86, 137.66, 129.99, 128.55, 127.82, 126.45, 126.44, 113.08, 70.44, 64.84, 60.96, 57.70, 55.10, 13.78; IR (film) cm^{-1} 1728, 1607; FAB HRMS (FAB) calcd for $C_{25}H_{28}NO_4$ 406.2018, found 406.2008. **20**: $[\alpha]^{20}_D$ −64° (c = 0.015 $CHCl_3$); IR (film) cm^{-1} 1742; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (br d, 4 H, J = 7.2 Hz, ArH), 7.36 (br d, 2 H, J = 8.9 Hz, ArH), 7.16–7.31 (m, 6 H, ArH), 6.82 (br d, 2 H, J = 9.2 Hz, mmTr-MeOArH), 4.23 (q, J = 7.1, 2 H, OCH_2CH$_3$), 3.79 (s, 1 H, OCH_3), 2.24 (dd, 1 H, J = 1.7, 2.7 Hz, aziridine NCH_2), 1.87 (dd, 1 H, J = 2.7, 6.2 Hz, aziridine NCH), 1.40 (dd, 1 H, J = 1.7, 6.2 Hz, aziridine NCH_2), 1.29 (t, 3 H, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.56, 158.36, 144.36, 144.30, 134.97, 130.83, 129.09, 129.08, 127.63, 126.76, 112.82, 73.90, 60.89, 55.18, 31.76, 28.60, 14.26; FAB HRMS (FAB) calcd for $C_{25}H_{25}NO_3$ 387.1834, found 387.1844. **21**: $[\alpha]^{20}_D$ +8.2° (c = 0.033, $CHCl_3$); IR (film) cm^{-1} 3399; ^1H NMR (360 MHz, $CDCl_3$) δ 7.549 (br d, 4 H, J = 8.5 Hz, ArH), 7.19–7.36 (m, 8 H, ArH), 6.83 (br d, 2 H, J = 9.1 Hz, mmTr-MeOArH), 3.89 (br d, 1 H, J = 11.1 Hz, CH_2OH), 3.79 (s, 3 H, OCH_3), 3.71 (ddd, 1 H, J = 3.1, 7.5, 11.1 Hz, CH_2OH), 2.30 (dd, 1 H, J = 3.3, 7.5 Hz, CH$_2$OH), 1.87 (d, 1 H, J = 3.2 Hz, aziridine NCH_2), 1.58 (m, 1 H, aziridine NCH), 1.14 (d, 1 H, J = 6.3 Hz, aziridine NCH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.26, 144.94, 144.82, 135.68, 130.74, 129.07, 129.03, 127.60, 127.57, 126.70, 126.69, 112.76, 73.26, 61.41, 55.16, 33.01, 23.74; HRMS (FAB) calcd for $C_{23}H_{24}NO_2$ 346.1807, found 346.1815.

(*E*)- and (*Z*)-Ethyl-(2′*S*)-3-[*N*-(monomethoxytrityl)-2-aziridinyl]-2-propanoate (23). DMSO (24.2 mL, 342 mmol) was added dropwise to a −78 °C solution of oxalyl chloride (14.9 mL, 171 mmol) in 500 mL of CH_2Cl_2. Alcohol **21** (19.5 g, 56.5 mmol) in 100 mL of CH_2Cl_2 was added via cannula, keeping the temperature of the reaction mix below −60 °C. After 15 min, triethylamine (71 mL, 513 mmol) was added, and the reaction mixture was allowed to warm to room temperature. Hexanes (500 mL) were added, and the mixture was partitioned against 500 mL of potassium phosphate buffer (pH 6.7). The organic phase was collected and rinsed with two 300-mL portions of

phosphate buffer, dried with Na_2SO_4, and passed through a column of $MgSO_4$. Evaporation under reduced pressure gave the crude aldehyde **22** as a brown oil, which was carried directly to the next step. (A sample of aldehyde **22** was purified for analysis by preparative TLC.) LDA (30 mL, 60 mmol, 2.0 M solution in heptane/THF/ethylbenzene) was added to a solution of methyl (diethylphosphono)acetate (12.1 mL, 66 mmol) in 500 mL of THF at −78 °C. Crude **22** dissolved in 75 mL of THF was then added, and the reaction mixture was allowed to warm to −10 °C over 4 h before quenching with 300 mL of saturated aqueous NH_4Cl. The organic layer was collected and the aqueous layer extracted with three 300-mL portions of ether. The combined organic fractions were dried with $MgSO_4$, evaporated under reduced pressure, and chromatographed on a silica gel column to give 13.1 g (58%) of an inseparable mixture of *E*- and *Z*-**23** (6.9:1 *E*/*Z*) as a white foam. Aldehyde **22**: $[\alpha]^{20}_D$ −50° (*c* = 0.040, $CHCl_3$); IR (film) cm^{-1} 1720, 1606; ^1H NMR (360 MHz, $CDCl_3$) δ 9.34 (d, 1 H, *J* = 6.2 Hz, *H*COR), 7.49 (br d, 4 H, *J* = 7.3 Hz, Ar*H*), 7.19–7.34 (m, 8 H, Ar*H*), 6.83 (br d, 2 H, *J* = 8.7 Hz, mmTr-MeOAr*H*), 3.79 (s, 3 H, mmTr-OCH_3), 2.33 (d, 1 H, *J* = 2.5 Hz, aziridine NCH_2), 1.97 (ddd, 1 H, *J* = 2.1, 6.2, 6.4 Hz, aziridine NC*H*), 1.57 (d, 1 H, *J* = 6.4 Hz, aziridine NCH_2); ^{13}C NMR (90 MHz, $CDCl_3$) 200.90, 158.49, 144.06, 144.02, 134.50, 130.71, 128.90, 128.85, 127.77, 127.75, 126.97, 113.00, 73.26, 55.19, 38.97, 27.16; HRMS (FAB) calcd for $C_{23}H_{21}NO_2$ 343.1572, found 343.1568. *E*/*Z*-**23** mix: IR (film) cm^{-1} 3056, 1722, 1655, 1606, 1582; ^1H NMR (360 MHz, $CDCl_3$) E isomer, δ 7.51 (br d, 4 H, *J* = 7.3 Hz, Ar*H*), 7.18–7.38 (m, 8 H, Ar*H*), 6.83 (br d, 2 H, *J* = 8.9 Hz, mmTr-MeOAr*H*), 6.98 (dd, 1 H, *J* = 8.2, 15.7 Hz, MeO_2CCH=C*H*CHN), 6.08 (d, 1 H, *J* = 15.7 Hz, MeO_2CCH=CHCHN)), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 1.94 (dd, 1 H, *J* = 0.7, 2.8 Hz, aziridine NCH_2), 1.86 (ddd, 1 H, *J* = 2.8, 5.6, 8.2 Hz, aziridine NC*H*), 1.51 (dd, 1 H, *J* = 0.7, 6.2 Hz, aziridine NCH_2); HRMS (FAB) calcd for $C_{26}H_{26}NO_3$ 400.1912, found 400.1898.

(*E*)- and (*Z*)-3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-2-propenol (24). DIBAL-H (1.3 mmol, 1.3 mL of 1.0 M solution in hexanes) was added in portions over 1.5 h to a solution of **23** (245 mg, 0.61 mmol, 7.5:1 *E*/*Z*) in 10 mL of CH_2Cl_2 at 0 °C. Potassium phosphate buffer (pH 11.8, 10 mL) was then added and the mixture was stirred at rt for 1 h. The layers were separated, and the aqueous phase was extracted with three 15-mL portions of CH_2Cl_2. The combined organic fractions were evaporated under vacuum and chromatographed (6:1 hexanes/EtOAc eluant) to give 30 mg (62%) of the *Z*-alcohol (higher R_f) as a clear oil and 118 mg (66%) of the *E*-alcohol (lower R_f) as a white foam. **24Z**: ^1H NMR (360 MHz, $CDCl_3$) δ 7.49 (br d, 4 H, *J* = 9.4 Hz, Ar*H*), 7.18–7.36 (m, 8 H, Ar*H*), 6.82 (br d, 2 H, *J* = 8.9 Hz, mmTr-MeOAr*H*), 5.81 (ddd, 1 H, *J* = 6.5, 6.5, 11.2 Hz, $HOCH_2CH$=CHR), 5.52 (dddd, 1 H, *J* = 1.7, 2.3, 9.1, 11.2 Hz, $HOCH_2CH$=*CH*CHN), 4.08 (m, 2 H, HOCH_2R), 3.79 (s, 3 H, mmTr-OCH_3), 1.91 (ddd, 1 H, *J* = 3.0, 6.2, 9.1 Hz, aziridine NC*H*), 1.85 (d, 1 H, *J* = 3.0 Hz, aziridine NCH_2), 1.40 (d, 1 H, *J* = 6.2 Hz, aziridine NCH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.26, 144.90, 135.75, 132.88, 131.40, 130.88, 129.24, 127.49, 126.70, 112.68, 73.94, 58.96, 55.17, 29.87, 29.26. **24E**: $[\alpha]^{20}_D$ −66° (*c* = 0.022, $CHCl_3$); IR (film) cm^{-1} 3346, 3055, 3032; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45 (br d, 4 H, *J* = 7.3 Hz, Ar*H*), 7.18–7.36 (m, 8 H, Ar*H*), 6.81 (br d, 2 H, *J* = 9.1 Hz, mmTr-MeOAr*H*), 5.86 (ddd, 1 H, *J* = 5.6, 5.6, 15.5 Hz, $HOCH_2CH$=CHR), 5.72 (dddd, 1 H, *J* = 1.3, 1.3, 7.5, 15.5 Hz, $HOCH_2CH$=*CH*CHN), 4.16 (app d, 2 H, *J* = 5.6 Hz, HOCH_2R), 3.79 (s, 3 H, mmTr-OCH_3), 1.80 (d, 1 H, *J* = 3.0 Hz, aziridine NCH_2), 1.72 (ddd, 1 H, *J* = 3.0, 6.2, 9.0 Hz, aziridine NC*H*), 1.36 (d, 1 H, *J* = 6.2 Hz, aziridine NCH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.11, 144.91, 144.86, 135.81, 132.55, 131.17, 130.88, 129.29, 129.27, 127.38, 126.53, 126.52, 112.58, 73.84, 63.07, 55.09, 33.79, 28.94; HRMS (FAB) calcd for $C_{25}H_{26}NO_2$ 372.1963, found 372.1844.

(*E*)-3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-1-*O*-(dimethoxytrityl)-2-propenol (25E). Dimethoxytrityl chloride (2.0 g, 5.9 mmol) was added to a solution of **24E** (2.2 g, 5.9 mmol) and triethylamine (2.5 mL, 17.9 mmol) in 120 mL of CH_2Cl_2 at rt. Additional portions of dimethoxytrityl chloride (total 0.5 g, 1.5 mmol) were added until no starting material remained (monitoring by TLC). Methanol (5 mL) was added, followed by hexanes (70 mL) and potassium phosphate buffer (pH 6.7, 150 mL). The organic layer was concentrated, dried over Na_2SO_4, and evaporated to give a brown foam which was carried on to the next step without further purification. Material for analysis was obtained by preparative TLC (hexanes/EtOAc/triethylamine, 87:12:1): $[\alpha]^{20}_D$ −73° (*c* = 0.026, $CHCl_3$); IR (film) cm^{-1} 2907, 1606, 1582, 1514, 1463, 1035; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47–7.57 (m, 6H, Ar*H*), 7.15–7.44 (m, 15H, Ar*H*), 6.85 (br d, 4H, *J* = 8.7 Hz, dmTr-MeOAr*H*), 6.82 (br d, 2H, *J* = 9.0 Hz, mmTr-MeOAr*H*), 5.80 (m, 2H, RC*H*=C*H*R), 3.81 (s, 6H, dmTr-OCH_3), 3.80 (s, 3H, mmTr-OCH_3), 3.63 (br d, 2H, *J* = 3.4 Hz, dmTrOCH_2R), 1.82 (d, 1H, *J* = 2.9 Hz, aziridine NCH_2), 1.74 (m, 1H, aziridine NC*H*), 1.36 (d, 1H, *J* = 6.5 Hz, aziridine NCH_2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.38, 158.16, 145.17, 145.09, 145.06, 136.47, 136.00, 132.42, 131.00, 129.97, 129.41, 129.10, 128.12, 127.78, 127.40, 126.66, 126.52, 113.05, 112.59, 86.18, 73.89, 64.30, 55.19, 55.16, 33.97, 29.02; HRMS (FAB) calcd for $C_{46}H_{44}NO_4$ 674.3270, found 674.3278.

3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-2(*R*),3(*R*)-dihydroxy-1-*O*-(dimethoxytrityl)propanol (26) and 3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-2(*S*),3(*S*)-dihydroxy-1-*O*-(dimethoxytrityl)propanol (27). *N*-Methylmorpholine *N*-oxide (1.1 g, 8.0 mmol), dihydroquinidine *p*-chorobenzoate (1.4 g, 3.0 mmol), and OsO_4 (10 mg, 0.04 mmol, added as a 2.5% w/w solution in t-BuOH), were dissolved in acetone (25 mL) and water (3 mL). To this mixture was added a solution of the aziridine **25** (5.9 mmol) in acetone (total solution volume 8 mL) via syringe pump over 25 h at 0 °C. After completion of the addition, the solution was stirred 2 h, $Na_2S_2O_5$ was added, and stirring was continued for 2 h. The solids were removed by filtration and then extracted with eight 15-mL portions of ethyl acetate. The combined organic extracts were dried with Na_2SO_4, evaporated under vacuum, and chromatographed using flash silica gel (hexanes/EtOAc eluant) to give 3.6 g of **26** and **27** as a white foam (4.4:1 mix of diastereomers, 86% from allylic alcohol). Data is given for selected signals in mixture: IR (film) cm^{-1} 3499 (br), 3056, 3033, 2999; HRMS (FAB) calcd for $C_{48}H_{46}NO_6$ 708.3325, found 708.3283. **26**: ^1H NMR (360 MHz, $CDCl_3$) δ 7.37–7.50 (m, 6 H, Ar*H*), 7.16–7.32 (m, 15 H, Ar*H*), 6.81 (br d, 4 H, *J* = 9.0 Hz, dmTr-MeOAr*H*), 6.76 (br d, 2 H, *J* = 7.6 Hz, mmTr-MeOAr*H*), 3.79 (s, 6 H, dmTr-OCH_3), 3.77 (s, 3 H, mmTr-OCH_3), 3.66 (m, 2 H, RC*H*OH), 3.26 (m, 1 H, dmTrOCH_2R), 3.08 (br dd, *J* = 5.6, 9.6 Hz, 1 H, dmTrOCH_2R), 2.79 (br s, 1 H, RCHO*H*), 2.59 (br d, 1 H, *J* = 4.2 Hz, RCHO*H*), 1.80 (d, 1 H, *J* = 3.1 Hz, aziridine NCH_2), 1.50 (m, 1 H, aziridine NC*H*), 1.12 (d, 1 H, *J* = 6.5 Hz, aziridine NCH_2).

3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-2(*R*),3(*R*)-bis[(triethylsilyl)oxy]-1-*O*-(dimethoxytrityl)propanol (28). To a solution of diols **26** and **27** (150 mg, 0.21 mmol, 4.4:1 mix of diastereomers), triethylamine (0.3 mL, 2.1 mmol), and dimethylaminopyridine (15 mg, 0.12 mmol) in 6 mL of CH_2Cl_2 at rt was added chlorotriethylsilane (110 μL, 0.64 mmol). Two additional 40-μL portions of chlorotriethylsilane were added after 9 and 19 h. After 21 h, 5 mL of hexanes was added and the mixture was partitioned against 10 mL of potassium phosphate buffer (pH 6.7). The organic extracts were dried over Na_2SO_4 and evaporated under vacuum. The crude residue was chromatographed on flash silica gel (hexanes/EtOAc) to yield 192 mg (97%, 4.4:1 mixture of diastereomers) of **28** as a colorless oil: IR (film) cm^{-1} 2953; ^1H NMR (360 MHz, $CDCl_3$) major diastereomer, δ 7.55 (m, 4 H, Ar*H*), 7.45 (br d, 2 H, *J* = 7.0 Hz, Ar*H*), 7.14–7.36 (m, 15 H, Ar*H*), 6.83 (br d, 4 H, *J* = 8.8 Hz, dmTr-MeOAr*H*), 6.74 (br d, 2 H, *J* = 9.0 Hz, mmTr-MeOAr*H*), 4.04 (ddd, 1 H, *J* = 3.4, 4.3, 6.4 Hz, dmTrOCH$_2$C*H*OTES), 3.95 (dd, 1 H, *J* = 3.4, 5.0 Hz, TESOCHC*H*(OTES)CHN, 3.82 (s, 3 H, mmTr-OCH_3), 3.76 (s, 6 H, dmTr-OCH_3), 3.21 (dd, *J* = 4.3, 9.2 Hz, 1 H, dmTrOCH_2R), 2.91 (dd, 1 H, *J* = 6.4, 9.2 Hz, dmTrOCH_2R), 1.92 (d, 1 H, *J* = 3.3 Hz, aziridine NCH_2), 1.25 (ddd, 1 H, *J* = 3.3, 5.0, 6.7 Hz, aziridine NC*H*), 1.07 (d, 1 H, *J* = 6.7 Hz, aziridine NCH_2), 0.88–1.08 (m, 18 H, $SiCH_2CH_3$), 0.50–0.68 (m, 12 H, $SiCH_2CH_3$); HRMS (FAB) calcd for $C_{58}H_{73}NO_6Si_2$ 935.4976, found 935.5015.

3-[2′(*S*)-Aziridinyl]-2(*R*),3(*R*)-bis[(triethylsilyl)oxy]propanol (29). Trifluoroacetic acid (43 μL, 0.56 mmol) was added dropwise at −78 °C to a solution of **28** and its diastereomer (238 mg, 0.25 mmol) and ethanethiol (150 μL, 2.1 mmol) in 10 mL of CH_2Cl_2. The reaction mixture was allowed to warm to rt over a period of 30 min, during which time a deep orange color developed and then faded to pale yellow. Triethylamine (250

μL, 1.8 mmol) and potassium phosphate buffer (pH 6.7) were added, and the mixture was exhaustively extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, evaporated in vacuo, and chromatographed on flash silica (hexanes/EtOAc) to afford 58 mg (64%) of product as a colorless oil. This material was immediately carried on to the next step to prevent decomposition: HRMS (FAB) calcd for $C_{17}H_{40}NO_3Si_2$ 362.2547, found 362.2534.

3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-2(*R*),3(*R*)-bis[(triethylsilyl)oxy]-1-propanol (30). Monomethoxytrityl chloride (540 mg, 1.75 mmol, 3.2 M solution in CH_2Cl_2) was added dropwise to a solution of aziridine **29** (58 mg, 0.161 mmol) and triethylamine (110 μL, 0.79 mmol) in 4 mL of CH_2Cl_2 at −78 °C. Methanol (1 mL) was added, and the reaction was allowed to come to rt. After removal of solvents under vacuum, the residue was chromatographed on flash silica (hexanes/triethylamine, 15:1 to 13:1, trace of triethylamine) to give 77 mg (76%, <10% minor diastereomer) of **30** as a clear oil which solidified upon prolonged standing: IR (film) cm^{-1} 2954, 2909; ^1H NMR (360 MHz, $CDCl_3$) major diastereomer, δ 7.54 (br t, 4 H, J = 7.5 Hz, Ar*H*), 7.38 (br d, 2 H, J = 9.0 Hz, mmTr-MeOAr*H*), 7.27 (br t, 4 H, J = 7.7 Hz, Ar*H*), 7.19 (br t, 2 H, J = 7.3 Hz, Ar*H*), 6.81 (br d, 2 H, J = 9.0 Hz, mmTr-MeOAr*H*), 3.88 (app t, 1 H, J = 5.0 Hz, TESOCH-C*H*(OTES)CHN), 3.80 (app q, 1 H, J = 5.0 Hz, dmTrOCH$_2$-C*H*OTES), 3.79 (s, 3 H, mmTr-OC*H*$_3$), 3.61 (ddd, J = 5.0, 5.0, 13.6 Hz, 1 H, HOC*H*$_2$R), 3.43 (ddd, 1 H, J = 5.0, 7.2, 13.6 Hz, HOC*H*$_2$R), 2.49 (dd, 1 H, J = 5.0, 7.2 Hz, *H*OCH$_2$R), 1.99 (d, 1 H, J = 3.3 Hz, aziridine NC*H*$_2$), 1.41 (ddd, 1 H, J = 3.3, 5.0, 6.7 Hz, aziridine NC*H*), 1.15 (d, 1 H, J = 6.7 Hz, aziridine NC*H*$_2$), 0.99 (t, 9 H, J = 7.9 Hz, SiCH$_2$C*H*$_3$), 0.95 (t, 9 H, J = 7.8 Hz, SiCH$_2$C*H*$_3$), 0.63 (q, 6 H, J = 7.9 Hz, SiC*H*$_2$CH$_3$), 0.61 (q, 6 H, J = 7.8 Hz, SiC*H*$_2$CH$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.06, 145.11, 145.09, 135.78, 131.04, 129.38, 129.35, 127.34, 126.40, 126.37, 112.55, 75.69, 74.58, 73.87, 63.74, 55.10, 35.95, 24.30, 6.87, 6.82, 5.16, 4.92; HRMS (FAB) calcd for $C_{37}H_{56}NO_4Si_2$ 634.3748, found 634.3763. Anal. Calcd: C, 70.09; H, 8.74; N, 2.21. Found: C, 69.96; H, 8.68; N, 2.44.

3-[*N*-(Monomethoxytrityl)-2′(*S*)-aziridinyl]-2(*R*),3(*R*)-bis[(triethylsilyl)oxy]-1-*O*-(dimethoxytrityl)propanal (31). DMSO (87 μL, 1.22 mmol) was added dropwise to a 0 °C solution of oxalyl chloride (53 μL, 0.61 mmol) in 3.5 mL of CH_2Cl_2. The reaction mixture was cooled to −78 °C, and alcohol **30** (77 mg, 0.12 mmol, dissolved in 1.5 mL of CH_2Cl_2) was added. The reaction mixture was warmed to ca. −40 °C for 15 min and then cooled to −78 °C. Triethylamine (250 μL, 1.8 mmol) was added, and the reaction mixture was allowed to warm to rt over 45 min. The solution was diluted with hexanes and extracted with potassium phosphate buffer (pH 6.7) and phosphate buffer, dried with Na_2SO_4, and passed through a column of $MgSO_4$. Evaporation under reduced pressure gave 70 mg of aldehyde **31** as a slightly yellow oil, which was approximately 80% (by weight) pure by ^1H NMR (diastereomer ratio ca. 10:1). The instability of this material precluded thorough characterization: ^1H NMR (360 MHz, $CDCl_3$) δ 9.62 (d, 1 H, J = 1.3 Hz, *H*(C=O)R), 7.48 (br t, 4 H, J = 6.1 Hz, Ar*H*), 7.17–7.35 (m, 8 H, Ar*H*), 6.81 (br d, 2 H, J = 7.0 Hz, mmTr-MeOAr*H*), 4.15 (dd, 1 H, J = 4.0, 4.0 Hz, Hα), 4.00 (dd, 1 H, J = 1.3, 4.0 Hz, Hβ), 3.78 (s, 3 H, mmTr-OC*H*$_3$), 1.95 (d, 1 H, J = 3.2 Hz, aziridine NC*H*$_2$), 1.39 (ddd, 1 H, J = 3.2, 4.0, 6.4 Hz, aziridine NC*H*), 1.09 (d, 1 H, J = 6.4 Hz, aziridine NC*H*$_2$), 0.86–1.03 (m, 18 H, SiCH$_2$C*H*$_3$), 0.52–0.68 (m, 12 H, SiC*H*$_2$CH$_3$).

Ethyl *N*-Benzoyl-2-(diethylphosphono)glycinate (32). This compound was prepared according to ref 18. Additional data: ^1H NMR (360 MHz, $CDCl_3$) δ 7.80 (m, 2 H, Ar*H*), 7.48 (m, 1 H, Ar*H*), 7.40 (m, 2 H, Ar*H*), 7.09 (d, J = 8.9 Hz, 1 H, N*H*), 5.36 (dd, J = 8.9 Hz, J = 22.1 Hz, 1 H, C*H*PO(OEt)$_2$), 4.24 (q, J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 4.16 (m, 4 H, PO(OC*H*$_2$CH$_3$)$_2$), 1.27 (t, J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.27 (m, 6 H, PO(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 132.1, 128.7, 127.2, 63.9, 63.8, 63.7, 62.6, 51.8, 50.3, 16.4, 16.3, 16.2, 14.0.

Ethyl 2-(*N*-Benzoylamino)-4(*R*),5(*R*)-bis[(*p*-methoxybenzyl)oxy]-5-[*N*-(monomethoxytrityl)-2′(*S*)-aziridinyl]-2-pentenoate (33). LDA (210 μL, 0.42 mmol, 2 M in heptane/THE) was added via syringe to phosphonate **32** (154 mg, 0.45 mmol) being stirred in 4 mL of THE at −78 °C. The reaction temperature was raised to 0 °C for 10 min and then lowered to −78 °C at which time a THE (5 mL) solution of aldehyde **17** (193 mg, 0.30 mmol) was added. The reaction was stirred at −78 °C for 30 min, 1 h at 0 °C, and then stored in a freezer at −20 °C overnight. Saturated aqueous NH_4Cl solution was added and the reaction diluted with 5 mL of CH_2Cl_2. After extraction with CH_2Cl_2, the organic phase was dried over anhydrous Na_2SO_4, concentrated, and chromatographed by flash silica gel (hexanes/EtOAc gradient) to afford 138 mg of **33Z** (55%) and 36 mg of **33E** (15%) in a 3.7:1 *Z*/*E* ratio. **33Z**: $[\alpha]_D$ = 55.8° (c = 0.060, CH_2Cl_2); IR (neat) 3368, 3055, 2933, 2835, 1728, 1675, 1611, 1512, 1249; ^1H NMR (360 MHz, $CDCl_3$) δ 8.51 (br s, 1 H, PhCON*H*), 7.60–7.47 (m, 4 H, Ar*H*), 7.46–7.33 (m, 3 H, Ar*H*), 7.35 (d, J = 8.9 Hz, 2 H, mmTr-MPh*H*), 7.29–7.15 (m, 8 H, Ar*H*), 7.04 (d, J = 8.9 Hz, 2 H, MPM*H*), 7.03 (d, J = 8.9 Hz, 2 H, MPM*H*), 6.80 (d, J = 8.9 Hz, 2 H, mmTr-MPh*H*), 6.73 (d, J = 8.9 Hz, 2 H, MPM*H*), 6.70 (d, J = 8.9 Hz, 2 H, MPM*H*), 6.06 (d, J = 6.6 Hz, 1 H, vinyl C*H*), 4.60 (d, J = 10.6 Hz, 1 H, MPMC*H*$_2$), 4.44 (d, J = 8.4 Hz, 1 H, MPMC*H*$_2$), 4.41 (d, J = 8.4 Hz, 1 H, MPMC*H*$_2$), 4.28 (m, 2 H, OC*H*$_2$CH$_3$), 4.24 (d, J = 10.6 Hz, 1 H, MPMC*H*$_2$), 4.21 (dd, J = 3.5, 6.6 Hz, 1 H, allylic C*H*), 3.76 (s, 3 H, MPMOC*H*$_3$), 3.75 (s, 3 H, mmTr-OC*H*$_3$), 3.74 (s, 3 H, MPMOC*H*$_3$), 3.67 (dd, J = 6.2, 3.5 Hz, 1 H, homoallylic C*H*), 1.82 (d, J = 3.1 Hz, 1 H, aziridine NC*H*$_2$), 1.55 (ddd, J = 3.1, 6.2, 6.6 Hz, 1 H, aziridine NC*H*), 1.32 (t, J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.08 (d, J = 6.6 Hz, 1 H, aziridine NC*H*$_2$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.4, 164.3, 159.24, 159.17, 158.2, 145.0, 144.7, 135.4, 133.0, 131.7, 131.1, 131.0, 130.0, 129.8, 129.7, 129.42, 129.38, 128.7, 127.5, 127.4, 126.54, 126.53, 126.0, 113.7, 113.6, 112.6, 83.1, 76.5, 74.0, 73.2, 71.0, 61.5, 55.21, 55.17, 55.16, 43.9, 24.6, 14.2; HRMS (FAB) calcd for $C_{52}H_{53}N_2O_8$ 833.3802, found 833.3836. **33E**: $[\alpha]_D$ = −58.2° (c = 0.0083, CH_2Cl_2); IR (neat) 3321, 2932, 2834, 1727, 1673, 1610, 1512, 1246; ^1H NMR (360 MHz, $CDCl_3$) δ 8.13 (br s, 1 H, PhCON*H*), 7.83 (m, 2 H, Ar*H*), 7.62–7.45 (m, 7 H, ArH), 7.38 (d, J = 8.9 Hz, 2 H, mmTr-MPh*H*), 7.30 (d, J = 9.3 Hz, 1 H, vinyl C*H*), 7.29–7.15 (m, 6 H, Ar*H*), 7.12 (d, J = 8.4 Hz, 1 H, MPMC*H*$_2$), 7.03 (d, J = 8.9 Hz, 1 H, MPMC*H*$_2$), 6.77 (d, J = 8.9 Hz, 1 H, MPMC*H*$_2$), 6.76 (d, J = 8.8 Hz, 2 H, mmTr-MPh*H*), 6.73 (d, J = 8.4 Hz, 1 H, MPMC*H*$_2$), 4.89 (dd, J = 4.4 Hz, J = 9.3 Hz, 1 H, allylic C*H*), 4.64 (d, J = 11 Hz, 1 H, MPMC*H*$_2$), 4.60 (d, J = 11 Hz, 1 H, MPMC*H*$_2$), 4.58 (d, J = 12 Hz, 1 H, MPMC*H*$_2$), 4.25 (d, J = 12 Hz, 1 H, MPMC*H*$_2$), 4.13 (m, 2 H, OC*H*$_2$CH$_3$), 3.77 (s, 3 H, MPMOC*H*$_3$), 3.75 (s, 3 H, mmTr-OC*H*$_3$), 3.74 (s, 3 H, MPMOC*H*$_3$), 3.54 (dd, J = 7.1, 4.4 Hz, 1 H, homoallylic C*H*), 1.65 (d, J = 2.2 Hz, 1 H, aziridine NC*H*$_2$), 1.62 (ddd, J = 2.2, 7.1, 6.6 Hz, 1 H, aziridine NC*H*), 1.16 (t, J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.03 (d, J = 6.6 Hz, 1 H, aziridine NC*H*$_2$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.4, 163.9, 159.0, 158.8, 158.0, 145.2, 144.8, 135.8, 134.5, 131.9, 131.1, 130.9, 130.3, 129.74, 129.71, 129.6, 129.5, 129.4, 128.8, 127.38, 127.35, 126.9, 126.6, 126.4, 113.40, 113.38, 112.6, 84.5, 75.8, 73.8, 72.6, 70.3, 62.2, 55.19, 55.16, 55.11, 35.7, 25.0, 14.1; HRMS (FAB) calcd for $C_{52}H_{53}N_2O_8$ 833.3802, found 833.3802.

***N*-(2-Oxopropyl)[2-(*N*-benzoylamino)-4(*R*),5(*R*)-bis[(*p*-methoxybenzyl)oxy]-5-[*N*-(monomethoxytrityl)-2′(*S*)-aziridinyl]-2(*Z*)-pentenamide (34Z).** Lithium hydroxide (20 mg, 0.42 mmol) and **33Z** (150 mg, 0.18 mmol) were heated together in 10 mL of THF and approximately 200 μL of H_2O for 8 h at 50 °C. The cooled reaction mixture was poured into a saturated aqueous NaH_2PO_4 solution and washed with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated (crude weight, 130 mg). DCC (9 mg, 0.044 mmol) was added to the crude acid (14 mg, 0.017 mmol), 1-amino-2-propanol (1.1 μL, 0.014 mmol), and 1-hydroxybenzotriazole (2.8 mg, 0.021 mmol) being stirred in 3 mL of CH_2Cl_2 at rt. After 10 min, an additional 1.2 μL of 1-amino-2-propanol (0.015 mmol) was added and stirring was continued for 2 h. The reaction mixture was added to Swern reagent prepared from DMSO (82 μL, 1.16 mmol) and oxalyl chloride (51 μL, 0.58 mmol) in 5 mL of CH_2Cl_2 at −78 °C. Et_3N (242 μL, 1.7 mmol) was added after 10 min, and the reaction vessel was warmed to rt over 20 min. The solution was washed with NH_4Cl, and the organic layer was dried over anhydrous Na_2SO_4. The mixture was purified by preparative TLC (hexanes/EtOAc, 2:1) to afford 8.8 mg (59%) of **40Z** as a clear oil: $[\alpha]_D$ = 0° (c = 0.004, CH_2Cl_2); IR (neat) 3335, 2924, 1731, 1659; ^1H NMR (360 MHz, $CDCl_3$) δ 8.84 (br s, 1 H, PhCON*H*), 7.55–7.45 (m, 4 H, Ar*H*), 7.39 (m, 2 H, Ar*H*), 7.34 (d, J = 8.9 Hz, 2 H, mmTr-MPh*H*), 7.28–7.15 (m, 9 H, Ar*H*), 7.04

(d, J = 8.9 Hz, 2 H, MPMH), 6.97 (d, J = 8.9 Hz, 2 H, MPMH), 6.78 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 6.78 (d, J = 8.9 Hz, 2 H, MPMH), 6.67 (d, J = 8.9 Hz, 2 H, MPMH), 6.65 (br dd, J = 4.7 Hz, J = 4.5 Hz, 1 H, CONHCH$_2$), 5.96 (d, J = 6.1 Hz, 1 H, vinyl CH), 4.58 (d, J = 10.4 Hz, 1 H, MPMCH_2), 4.38 (d, J = 11.6 Hz, 1 H, MPMCH_2), 4.36 (d, J = 11.6 Hz, 1 H, MPMCH_2), 4.28 (dd, J = 4.7 Hz, J = 19 Hz, 1 H, CONHCH_2), 4.22 (dd, J = 4.5 Hz, J = 19 Hz, 1 H, CONHCH_2), 4.20 (d, J = 10.4 Hz, 1 H, MPMCH_2), 4.15 (dd, J = 3.1 Hz, J = 6.1 Hz, 1 H, allylic CH), 3.76 (s, 3 H, MPMOCH_3), 3.74 (s, 3 H, mmTr-OCH_3), 3.73 (s, 3 H, MPMOCH_3), 3.67 (dd, J = 3.1 Hz, J = 5.5 Hz, 1 H, homoallylic CH), 2.23 (s, 3 H, COCH_3), 1.81 (d, J = 3.1 Hz, 1 H, aziridine NCH_2), 1.59 (ddd, J = 3.1, 5.5, 6.7 Hz, 1 H, aziridine NCH), 1.09 (d, J = 6.7 Hz, 1 H, aziridine NCH_2); ^{13}C NMR (90 MHz, CDCl$_3$) δ 202.7, 165.9, 164.4, 159.4, 159.1, 158.2, 144.9, 144.7, 135.2, 134.5, 132.6, 131.8, 131.1, 130.0, 129.8, 129.7, 129.3, 128.3, 127.85, 127.82, 127.47, 127.37, 126.5, 122.6, 113.8, 113.5, 112.7, 83.3, 76.3, 74.0, 73.4, 70.8, 55.2, 55.1, 50.1, 34.9, 27.3, 24.8; HRMS (FAB) calcd for $C_{53}H_{54}N_3O_8$ 860.3911, found 860.3898.

N-(2-Oxopropyl)-2-(N-benzoylamino)-3-bromo-4(S),5(S)-bis[(p-methoxybenzyl)oxy]-5-[N-(monomethoxytrityl)-2′-(S)-aziridinyl]-2(Z)-pentenamide (35Z). A 1% bromine solution in CH_2Cl_2 (126 μL, 0.024 mmol, 1.5 equiv) was added via syringe to **34Z** (14 mg, 0.016 mmol) in 2 mL of CH_2Cl_2 at −78 °C. After 30 s, 25 mg of DABCO was added and the temperature brought to 0 °C. After 3 h, the reaction contents were poured into a saturated aqueous NH_4Cl solution and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhyd Na_2SO_4, concentrated at reduced pressure, and chromatographed by flash silica gel, affording 10.7 mg (71%) of **35** as an amorphous white solid: $[\alpha]_D$ = −21° (c = 0.011, CH_2Cl_2); IR (neat) 2942, 1730, 1670, 1260; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.84 (br s, 1 H, PhCONH), 7.84 (m, 2 H, ArH), 7.60–7.45 (m, 7 H, ArH), 7.35 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 7.25–7.10 (m, 6 H, ArH), 7.14 (d, J = 8.9 Hz, 2 H, MPMH), 6.98 (d, J = 8.9 Hz, 2 H, MPMH), 6.97 (br dd, J = 4.9, 4.9 Hz, 1 H, CONHCH$_2$), 6.77 (d, J = 8.9 Hz, 2 H, mmTr-MPhH), 6.74 (d, J = 8.9 Hz, 2 H, MPMH), 6.73 (d, J = 8.9 Hz, 2 H, MPMH), 4.76 (d, J = 7.5 Hz, 1 H, allylic CH), 4.66 (d, J = 10.6 Hz, 1 H, MPMCH_2), 4.57 (d, J = 10.6 Hz, 1 H, MPMCH_2), 4.50 (d, J = 11.1 Hz, 1 H, MPMCH_2), 4.24 (d, J = 10.4 Hz, 1 H, MPMCH_2), 3.87 (dd, J = 4.9 Hz, J = 19 Hz, 1 H, CONHCH_2), 3.78 (s, 3 H, MPMOCH_3), 3.77 (dd, J = 2.2 Hz, J = 7.7 Hz, 1 H, homoallylic CH), 3.74 (s, 3 H, mmTr-OCH_3), 3.73 (s, 3 H, MPMOCH_3), 3.67 (dd, J = 4.9, 19 Hz, 1 H, CONHCH_2), 2.09 (s, 3 H, COCH_3), 1.85 (d, J = 3.1 Hz, 1 H, aziridine NCH_2), 1.53 (ddd, J = 3.1, 2.2, 6.6 Hz, 1 H, aziridine NCH), 1.15 (d, J = 6.6 Hz, 1 H, aziridine NCH_2); ^{13}C NMR (90 MHz, CDCl$_3$) δ 202.5, 164.6, 162.0, 159.2, 159.0, 158.1, 145.1, 144.8, 135.4, 133.6, 132.6, 131.2, 130.3, 129.8, 129.7, 129.6, 129.44, 129.37, 128.9, 127.44, 127.41, 126.1, 113.53, 113.50, 112.6, 82.5, 79.0, 73.9, 72.8, 71.1, 55.21, 55.19, 55.14, 49.9, 35.5, 27.2, 25.1; HRMS (FAB) calcd for $C_{53}H_{53}BrN_3O_8$ 938.3016, found 938.2996.

N-(2-Oxopropyl)-2-(N-benzoylamino)-2(Z)-[3(R),4(R)-bis[(p-methoxybenzyl)oxy]-5(S)-1-azabicyclo[3.1.0]hex-2-ylidene]acetamide (36Z). A solution of trichloroacetic acid in CDCl$_3$ (1.7 mg in 110 μL, 0.011 mmol) was added to a 5-mm NMR tube containing **35Z** (10 mg, 0.011 mmol) in 1 mL of CDCl$_3$ at rt. The deprotection of the monomethoxytrityl group took approximately 30 min as observed by ^{1}H NMR. The deprotected aziridine was then stabilized by the addition of 5 μL of triethylamine. The sample was chromatographed on silica gel and the 5.6 mg (79%) of product warmed to 50 °C with 5 μL of triethylamine in 750 μL of CDCl$_3$. After 8 h, when formation of the azabicyclic system was complete by TLC and ^{1}H NMR analysis, the solvent was removed and the product chromatographed on prep TLC (hexanes/EtOAc 1:2) affording 3.2 g (65%) of **36Z**: $[\alpha]_D$ = +10.4° (c = 0.0025, CH_2Cl_2); IR (neat) 3347, 2923, 1726, 1662; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.89 (br s, 1 H, PhCONH), 7.88 (m, 2 H, ArH), 7.55 (m, 1 H, ArH), 7.46 (m, 2 H, ArH), 7.25 (d, J = 8.9 Hz, 2 H, MPMH), 7.23 (d, J = 8.9 Hz, 2 H, MPMH), 6.95 (br dd, J = 4.8, 4.8 Hz, 1 H, CONHCH$_2$), 6.88 (d, J = 8.9 Hz, 2 H, MPMH), 6.84 (d, J = 8.9 Hz, 2 H, MPMH), 5.12 (dd, J = 1, 1 Hz, 1 H, allylic CH), 4.51 (br s, 2 H, MPMCH_2), 4.48 (d, J = 11 Hz, 1 H, MPMCH_2), 4.44 (d, J = 11 Hz, 1 H, MPMCH_2), 4.42 (dd, J = 1, 4.9 Hz, 1 H, homoallylic CH), 4.18 (dd, J = 4.8, 19.4 Hz, 1 H, CONHCH_2), 4.13 (dd, J = 4.8, 19.4 Hz, 1 H, CONHCH_2), 3.81 (s, 3 H, MPMOCH_3), 3.79 (s, 3 H, MPMOCH_3), 3.03 (ddd, J = 3.6, 4.9, 5.3 Hz, 1 H, aziridine NCH), 2.40 (dd, J = 1, 5.3 Hz, 1 H, aziridine exo NCH_2), 2.18 (d, J = 3.6 Hz, 1 H, aziridine endo NCH_2), 2.15 (s, 3 H, COCH_3); ^{13}C NMR (90 MHz, CDCl$_3$) δ 202.8, 165.9, 163.5, 159.4, 159.2, 149.5, 133.3, 132.2, 130.0, 129.5, 129.4, 129.3, 128.7, 127.5, 123.3, 113.9, 113.7, 86.1, 81.8, 71.1, 70.8, 55.3, 50.0, 44.1, 38.0, 27.2; HRMS (FAB) calcd for $C_{33}H_{36}N_3O_7$ 586.2553, found 586.2552.

Ethyl 2-(N-Benzoylamino)-3-bromo-4(S),5(R)-bis[(p-methoxybenzyl)oxy]-5-(N-monomethoxytrityl)-2′(S)-aziridinyl]-2-pentenoate (40E and 40Z). Bromination with Br$_2$. A 2.5% bromine solution in CH_2Cl_2 (92 μL, 0.045 mmol) was added via syringe to **33Z** (25 mg, 0.03 mmol) being stirred with 2,6-lutidine (35 μL, 0.3 mmol) in 1.5 mL of CH_2Cl_2 at −78 °C. The temperature was raised to −10 °C and the reaction stirred for 1.5 h. The reaction course could be followed by removing small aliquots and mixing with DABCO at 25 °C prior to TLC analysis. The reaction was completed with the addition of DABCO (160 mg, 1.5 mmol) followed by warming to 25 °C for 10 min. The reaction contents were poured into a saturated aqueous NH_4Cl solution and exhaustively extracted. The combined organic extracts were dried over amorphous Na_2SO_4, filtered, and concentrated at reduced pressure. The resulting clear oil was chromatographed by flash silica gel (hexanes/EtOAc, 1:1) to afford 21 mg (77%) of an inseparable mixture (1.5:1) **40Z/40E** as a clear oil: IR (neat) 3357, 2933, 1733, 1675; ^{1}H NMR (360 MHz, CDCl$_3$) signals assignable (by comparison to pure **40E**) to **40Z**, δ 7.91 (br s, 1 H, PhCONH), 7.83 (m, 2 H, ArH), 7.65–7.40 (m, 6 H, ArH), 7.38 (d, J = 9 Hz, 2 H, mmTr-MPhH), 7.30–7.10 (m, 9 H, ArH), 6.95 (d, J = 8 Hz, 2 H, MPMH), 6.78 (d, J = 9 Hz, 2 H, mmTr-MPhH), 6.72 (d, J = 8 Hz, 2 H, mmTr-MPhH), 6.72 (d, J = 8 Hz, 2 H, MPMH), 4.73 (d, J = 10 Hz, 1 H, MPMCH_2), 4.64 (d, J = 10 Hz, 1 H, MPMCH_2), 4.53 (d, J = 11 Hz, 1 H, MPMCH_2), 4.51 (d, J = 9 Hz, 1 H, allylic CH), 4.50 (m, 2 H, OCH_2CH$_3$), 4.22 (d, J = 11 Hz, 1 H, MPMCH_2), 3.78 (s, 3 H, MPMOCH_3), 3.78 (s, 3 H, MPMOCH_3), 3.74 (s, 3 H, mmTr-OCH_3), 3.66 (dd, J = 9, 6 Hz, 1 H, homoallylic CH), 1.76 (d, J = 3.4 Hz, 1 H, aziridine NCH_2), 1.43 (ddd, J = 3.4, 6, 6.4 Hz, 1 H, aziridine NCH), 1.15 (d, J = 6.4 Hz, 1 H, aziridine NCH_2), 1.08 (t, J = 7 Hz, 3 H, OCH$_2$CH$_3$). **Bromination with NBS.** NBS (10 mg, 0.056 mmol) was added at rt to **33Z** (10 mg, 0.021 mmol) in 1 mL of CDCl$_3$. After 2 h, the reaction contents were applied directly to a silica gel prep TLC plate (eluted with hexanes/EtOAc, 2:1). Two products were obtained, corresponding to **40E** and the C-bromo iminium intermediate. The latter material converted quantitatively upon sitting over a 12-h period to **40E**. The combined material totaled 8.4 mg of a clear oil (76%): $[\alpha]_D$ = +7.03° (c = 0.0148, CH_2Cl_2); IR (neat) 3357, 2933, 1733, 1675; ^{1}H NMR (360 MHz, CDCl$_3$) δ 9.71 (br s, 1 H, PhCONH), 7.48 (m, 4 H, ArH), 7.40–7.20 (m, 11 H, ArH), 7.15 (m, 2 H, ArH), 7.04 (d, J = 8.7 Hz, 2 H, MPMH), 6.98 (d, J = 8.6 Hz, 2 H, MPMH), 6.81 (d, J = 9.1 Hz, 2 H, mmTr-MPhH), 6.65 (d, J = 8.6 Hz, 2 H, MPMH), 6.59 (d, J = 8.7 Hz, 2 H, MPMH), 4.59 (d, J = 10 Hz, 1 H, MPMCH_2), 4.52 (d, J = 11 Hz, 1 H, MPMCH_2), 4.58 (m, 2 H, OCH_2CH$_3$), 4.45 (d, J = 11 Hz, 1 H, MPMCH_2), 4.35 (d, J = 1.5 Hz, 1 H, allylic CH), 4.30 (d, J = 10 Hz, 1 H, MPMCH_2), 4.03 (d, J = 1.5, 4.9 Hz, 1 H, homoallylic CH), 3.78 (s, 3 H, MPMOCH_3), 3.71 (s, 3 H, MPMOCH_3), 3.61 (s, 3 H, mmTr-OCH_3), 1.73 (d, J = 3.4 Hz, 1 H, aziridine NCH_2), 1.59 (ddd, J = 3.4, 4.9, 6.4 Hz, 1 H, aziridine NCH), 1.46 (t, J = 7 Hz, 3 H, OCH$_2$CH_3), 1.02 (d, J = 6.4 Hz, 1 H, aziridine NCH_2); ^{13}C NMR (90 MHz, CDCl$_3$) δ 164.0, 163.4, 159.4, 159.3, 158.2, 144.7, 144.6, 135.4, 132.7, 132.0, 131.6, 131.0, 130.6, 130.4, 129.4, 129.3, 129.1, 128.1, 127.9, 127.5, 127.3, 126.6, 113.6, 112.7, 108.9, 83.5, 80.1, 74.3, 73.9, 70.8, 61.9, 55.2, 55.1, 55.0, 33.9, 25.2, 14.0; HRMS (FAB) calcd for $C_{52}H_{52}BrN_2O_8$ 911.2907, found 911.2929.

Ethyl 2-(N-Benzoylamino)-2(Z)-[3(R),4(R)-bis[(p-methoxybenzyl)oxy]-5(S)-1-azabicyclo[3.1.0]hex-2-ylidene]acetate (41Z). A solution of trichloroacetic acid (1.1 mg in 20 μL) in CD_3CN was added to a 5-mm NMR tube containing the isomeric mix 1.5:1 **40Z/40E** (4 mg, 0.0055 mmol) in 1 mL of CD_3CN at rt and deprotection was monitored by ^{1}H NMR analysis. After 30 min, 6 μL of triethylamine (0.044 mmol) in 30 μL of CD_3CN was added, and the mixture was heated to 50 °C. After 16 h, formation of the azabicyclo system was complete by TLC and ^{1}H NMR analysis. The solvent was removed and the resulting

oil was purified by prep TLC (hexanes/EtOAc, 2:1) to yield 1.3 mg of recovered **40E** (32%) and 1.6 mg (65%) of an amorphous solid **41Z**: $[\alpha]_D$ = +0.6° (c = 0.0051, $CHCl_3$); IR (neat) 3306, 2929, 1723; ^1H NMR (360 MHz, $CDCl_3$) δ 7.88 (br s, 1 H, PhCONH), 7.87 (m, 2 H, ArH), 7.54 (m, 1 H, ArH), 7.46 (m, 2 H, ArH), 7.25 (d, J = 9.8 Hz, 2 H, MPMH), 7.23 (d, J = 9.8 Hz, 2 H, MPMH), 6.89 (d, J = 9.1 Hz, 2 H, MPMH), 6.88 (d, J = 8.5 Hz, 2 H, MPMH), 5.05 (br dd, J = 1.8, 1.5 Hz, 1 H, allylic CH), 4.50 (d, J = 11 Hz, 1 H, MPMCH_2), 4.49 (d, J = 11.5 Hz, 1 H, MPMCH_2), 4.45 (d, J = 11 Hz, 1 H, MPMCH_2), 4.42 (d, J = 11.5 Hz, 1 H, MPMCH_2), 4.41 (br dd, J = 1.5, 4.2 Hz, 1 H, homoallylic CH), 4.25 (dt, 1 H, J = 11, 6.7 Hz, OCH_2CH$_3$), 4.16 (dt, 1 H, J = 11, 6.7 Hz, OCH_2CH$_3$), 3.81 (s, 3 H, MOMPCH_3), 3.79 (s, 3 H, MPMOCH_3), 3.00 (ddd, J = 4.2, 3.7, 5.5 Hz, 1 H, aziridine NCH), 2.39 (dd, J = 1.8, 5.5 Hz, 1 H, aziridine exo NCH_2), 2.19 (d, J = 3.7 Hz, 1 H, aziridine endo NCH_2), 1.23 (t, 3 H, J = 6.7 Hz, OCH$_2$CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.3, 163.7, 159.5, 159.3, 151.2, 133.6, 132.0, 130.0, 129.5, 129.40, 129.37, 128.6, 127.5, 121.0, 113.9, 113.7, 85.9, 82.6, 71.3, 71.2, 61.3, 55.30, 55.27, 44.0, 37.6, 14.1; HRMS (FAB) calcd for $C_{32}H_{35}N_2O_7$ 559.2444, found 559.2416.

Ethyl 2-(*N*-Benzoylamino)-2(*E*)-[3(*R*),4(*R*)-bis[(*p*-methoxybenzyl)oxy]-5(*S*)-1-azabicyclo[3.1.0]hex-2-ylidene]acetate (41E). A solution of trichloroacetic acid in CD_3CN (1.2 mg in 57 μL, 0.0071 mmol, 1.3 equiv) was added to a 5-mm NMR tube containing **40E** (5 mg, 0.0055 mmol, 1 equiv) in 1 mL of CD_3CN at room temperature. The deprotection of the monomethoxytrityl group took approximately 45 min as observed by ^1H NMR. The deprotected aziridine was stabilized by the addition of a solution of 3.1 μL of triethylamine in 78 L of CD_3CN and warmed to 50 °C. After 16 h, when the formation of the azabicyclic system was complete by TLC and ^1H NMR analysis, the solvent was removed and the product chromatographed on a silica gel column to yield 2.8 mg (91%) of an amorphous solid **41E**: $[\alpha]_D$ = +33.04° (c = 0.0046, $CHCl_3$); IR (neat) 3362, 2923, 2853, 1725, 1670, 1611, 1513, 1468, 1249, 1177, 1032, 821, 709 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.37 (br s, 1H, PhCONH), 7.53 (m, 2H, ArH), 7.49 (m, 1H, ArH), 7.31 (m, 2H, ArH), 7.29 (d, J = 8.5 Hz, 2H, MPMH), 7.11 (d, J = 8.5 Hz, 2H, MPMH), 6.90 (d, J = 8.5 Hz, 2H, MPMH), 6.73 (d, J = 8.5 Hz, 2H, MPMH), 4.64 (d, J = 11 Hz, 1H, MPMCH_2), 4.59 (d, J = 11 Hz, 1H, MPMCH_2), 4.57 (br dd, J = 1, 4.9 Hz, 1H, allylic CH), 4.53 (br dd, J = 4.9, 4.9 Hz, 1H, homoallylic CH), 4.51 (d, J = 11 Hz, 1H, MPMCH_2), 4.31 (m, 2H, OCH_2CH$_3$), 4.31 (d, J = 11 Hz, 1H, MPMCH_2), 3.81 (s, 3H, MPMOCH_3), 3.78 (s, 3H, MPMOCH_3), 3.00 (ddd, J = 3.7, 4.9, 5.0 Hz, 1H, aziridine NCH), 2.41 (dd, J = 1, 5.0 Hz, 1H, aziridine exo NCH_2), 2.14 (d, J = 3.7 Hz, 1H, aziridine endo NCH_2), 1.29 (t, 3H, J = 7.3 Hz, OCH$_2$CH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.0, 163.3, 159.7, 159.6, 147.7, 133.2, 131.8, 130.1, 129.6, 129.3, 128.5, 127.3, 122.1, 114.0, 85.4, 81.9, 71.5, 70.9, 61.3, 55.30, 55.26, 43.9, 36.3, 14.1. HRMS (FAB) calcd for $C_{32}H_{35}N_2O_7$ 559.2444, found 559.2424.

2(*R*)-[1-(*N*-Benzoylamino)-2-oxo-2-ethoxyethyl]-3(*R*),4-(*R*)-bis[(triethylsilyl)oxy]-5(*S*)-1-azabicyclo[3.1.0]hexane (43) and 2(*S*)-[1-(*N*-Benzoylamino)-2-oxo-2-ethoxyethyl]-3-(*R*),4(*R*)-bis[(triethylsilyl)oxy]-5(*S*)-1-azabicyclo[3.1.0]hexane (44). A 2 M lithium diisopropylamide solution (21 μL, 0.042 mmol, in heptane/THF solvent) was added via syringe to the phosphonate **32** (21 mg, 0.062 mmol) being stirred in 1.2 mL of THF at 78 °C under a dry nitrogen atmosphere. The reaction temperature was raised to 0 °C for 10 min and then lowered to −78 °C again before a 1.2-mL THF solution of the aldehyde **31** (13 mg, 0.021 mmol) was added via syringe. The reaction was stirred at −78 °C for 30 min, 1 h at 0 °C, and then at rt overnight. The excess anion was quenched with a saturated aqueous NH_4Cl solution and diluted with 5 mL of CH_2Cl_2. This solution was dried over anhyd Na_2SO_4, filtered, and concentrated. Elution on a silica gel prep plate (4:1 hexanes/EtOAc) separated a higher running trityl-protected isomer (R_f = 0.4, **42E**) from a lower running one (R_f = 0.3, **42Z**). *After development, the plate was left untouched for 4–6 h before the compounds were desorbed from the support.* The lower band yielded 8.9 mg (52%) and the upper band 9.1 mg (53%) of product which appeared by ^1H NMR analysis to contain no trityl group (free aziridine). Subjecting this material to silica gel yielded 4.5 mg of **43** derived from the purified **42E** (39%) and 4.4 mg of **44** from the purified **42Z** (38%) as clear oils: **43** (higher eluting isomer, 1:1 hexanes/EtOAc): $[\alpha]_D$ = −5.0° (c = 0.0016, CH_2Cl_2); IR (neat) 3400, 2954, 2916, 2876, 1742, 1666, 1530, 1463, 1237, 1157, 1124 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48 (m, 2H, *o*-ArH), 7.54 (m, 1H, *p*-ArH), 7.47 (m, 2H, *m*-ArH), 6.90 (d, J = 8.4 Hz, 1H, NH), 4.99 (dd, J = 4.0, 8.4 Hz, 1H, α-CH), 4.39 (dd, J = 5.8, 5.8 Hz, 1H, γ-CH), 4.27 (m, 2H, OCH_2CH$_3$), 3.78 (dd, J = 5.8, 8.8 Hz, 1H, δ-CH), 3.57 (dd, J = 4.0, 8.8 Hz, 1H, β-CH), 2.39 (ddd, J = 3.1, 3.5, 5.8 Hz, 1H, aziridine NCH), 1.90 (d, J = 3.1 Hz, 1H, aziridine exo NCH_2), 1.63 (d, J = 3.5 Hz, 1H, aziridine endo NCH_2), 1.31 (t, J = 7.5 Hz, 3H, OCH$_2$CH_3), 0.96 (m, 18H, 2[Si(CH$_2$CH_3)$_3$]), 0.66 (m, 12H, 2[Si(CH_2CH$_3$)$_3$]); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.2, 167.4, 133.9, 131.7, 128.6, 127.0, 79.4, 75.4, 66.9, 61.8, 53.0, 38.0, 25.6, 14.0, 6.7, 5.1, 4.9; HRMS (FAB) [MH]$^+$ calcd for $C_{28}H_{49}N_2O_5Si_2$ 549.3180, found 549.3204. **44** (lower eluting isomer, 1:1 hexanes/EtOAc): $[\alpha]_D$ = −62.4° (c = 0.0033, CH_2Cl_2); IR (neat) 3437, 2954, 2918, 2876, 1741, 1670, 1513, 1482 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.85 (m, 2H, *o*-ArH), 7.51 (m, 1H, *p*-ArH), 7.44 (m, 2H, *m*-ArH), 7.15 (d, 1H, J = 9.5 Hz, NH), 5.37 (dd, J = 2.4, J = 9.5 Hz, 1H, α-CH), 4.45 (dd, J = 5.3, 5.3 Hz, 1H, γ-CH), 4.16 (m, 1H, δ-CH), 4.13 (m, 2H, OCH_2CH$_3$), 3.93 (dd, J = 2.4, 7.5 Hz, 1H, β-CH), 2.40 (ddd, J = 5.3, 5.3, 3.5 Hz, 1H, aziridine NCH), 1.79 (d, J = 5.3 Hz, 1H, aziridine exo NCH_2), 1.63 (d, J = 3.5 Hz, 1H, aziridine endo NCH_2), 1.27 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 0.94 (m, 18H, 2[Si(CH$_2$CH_3)$_3$]), 0.61 (m, 12H, 2[Si(CH_2CH$_3$)$_3$]); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.5, 167.0, 134.2, 131.6, 127.0, 80.1, 79.8, 67.2, 61.4, 54.8, 41.2, 29.6, 14.0, 6.7, 5.0, 4.6; HRMS (FAB) [MH]$^+$ calcd for $C_{28}H_{49}N_2O_5Si_2$ 549.3180, found 549.3167.

Acknowledgment. Support from NSF (CHE 88-58059), Bristol Myers-Squibb (Dr. T. Doyle), and BASF (fellowship to J.E.T.) is gratefully acknowledged.

Supplementary Material Available: Copies of the ^{13}C NMR spectra for all new compounds (31 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.

First Synthesis of Aldopentono-1,4-thiolactones

Oscar Varela* and Patricia A. Zunszain

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Pabellón II, 1428, Buenos Aires, Argentina

Received May 25, 1993•

A convenient synthesis of enantiomerically pure aldopentono-1,4-thiolactones is described. Thus, 4-thio-D-ribono-1,4-lactone (12) has been prepared from D-gulono-1,4-lactone (1), *via* its 2,3-*O*-isopropylidene derivative 3. The 5,6-glycol system of 3 was oxidized with $NaIO_4$. Chemoselective reduction of the resulting aldehyde function with $NaBH_3CN$ led to 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (7). Tosylation of 7 and subsequent treatment of the tosylate 8 with sodium methoxide afforded methyl 4,5-epoxy-2,3-*O*-isopropylidene-L-lyxonate (9) as a key intermediate. Treatment of 9 with thiourea gave the 4,5-thiirane derivative having the D-*ribo* configuration (10). Regioselective opening of the thiirane ring and simultaneous thiolactonization took place by heating 10 with KOAc–HOAc–DMF. The resulting 5-*O*-acetyl-2,3-*O*-isopropylidene-4-thio-D-ribono-1,4-lactone (11) was readily converted, by acid removal (2% HCl) of the protecting groups, into the crystalline thiolactone 12. A similar approach was employed for the synthesis of 4-thio-L-lyxono-1,4-lactone (19), starting from D-ribono-1,4-lactone (13).

Introduction

D-Ribono-1,4-lactone has been considered[1] a "chiral cornerstone" because of its use as a chiral template in the synthesis of natural products and molecules of biological interest.[2-4] In spite of the numerous derivatives described for D-ribonolactone, its 4-thio analogue, the 4-thio-D-ribono-1,4-lactone, had not been previously synthesized. In fact, only a few attempts to prepare sugar thiolactones from aldonic acids have been reported.[5] Thus, 2,3-*O*-isopropylidene-4-thio-D-erythrono-1,4-lactone was obtained by nucleophilic attack of potassium thioacetate on C-4 of the 2,3-acetal derivative of D-erythronolactone. However, this procedure proved to be unsuccessful for higher-carbon sugar lactones having C-4 substitution. Recently, per-*O*-alkylated derivatives of 5-thio-D-glucono-1,5-lactone were obtained by HO-1 oxidation of the corresponding 2,3,4,6-tetra-*O*-alkyl-5-thio-D-glucopyanoses.[6] As far as we know, the above-mentioned are the only examples of the preparation of sugar thiolactones. In the search for a general synthetic procedure for the preparation of 4-thioaldopentono-1,4-lactones, and in connection with our project on the synthesis and properties of 4-thiosugars,[7-11] we report here the first syntheses of 4-thio-D-ribono-1,4-lactone (12) and 4-thio-L-lyxono-1,4-lactone (19). Compounds 12 and 19, enantiomerically pure and with the opposite configuration at C-4, may be employed as convenient chiral precursors for the synthesis of naturally occurring thiolactones.[12,13]

Results and Discussion

The retrosynthetic analysis for the construction of the thiolactone ring is depicted in Scheme I. Disconnection of the C-1–S bond produces a synthon i (D-*ribo* configuration), which would derive from an open-chain precursor ii, with opposite configuration at C-4 (L-*lyxo*) since the thiol group is commonly introduced by nucleophilic displacement of conveniently substituted HO-4.[7-9] Since the synthetic equivalent of ii, the L-lyxono-1,4-lactone, is not commercially available, we employed D-gulono-1,4-lactone (1) as a suitable starting material.

Isopropylidenation of 1 with acetone–H_2SO_4 afforded the 2,3:5,6-di-*O*-isopropylidene derivative 2, which was selectively hydrolyzed to 2,3-*O*-isopropylidene-D-gulono-1,4-lactone[14] (3) in 82% overall yield (Scheme II). The 5,6-diol functionality of 3 was oxidized with 1 mol equiv of sodium periodate in water to give the L-arabinuronic acid 2,5-lactone derivative 4 in almost quantitative yield. The ^{13}C NMR spectrum of 4 showed that the aldehyde carbonyl group was partially hydrated, since besides the aldehyde carbon signal (195.0 ppm), a characteristic resonance[15] for the hydrated carbonyl (88.7 ppm) was observed.

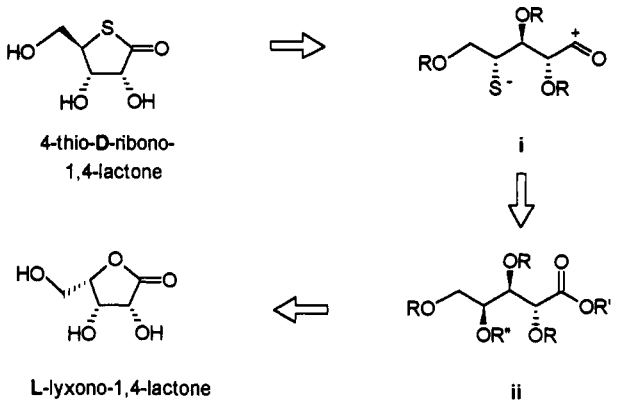
Attempted selective reduction of the aldehyde function of 4 with 1 mol of $NaBH_4$ in ethanol resulted also in the reduction of the lactone carbonyl group, affording 2,3-*O*-isopropylidene-α-L-lyxofuranose (5) in 62% yield. This procedure itself constitutes a short and convenient synthesis of an L-lyxose derivative. Conventional acetylation of 5 with acetic anhydride–pyridine gave the diacetate 6. Compound 6 gave the same mp and optical rotation value (but opposite in sign) as its enantiomer, obtained on acetonation of D-lyxose under kinetic control, followed by

• Abstract published in *Advance ACS Abstracts,* November 15, 1993.

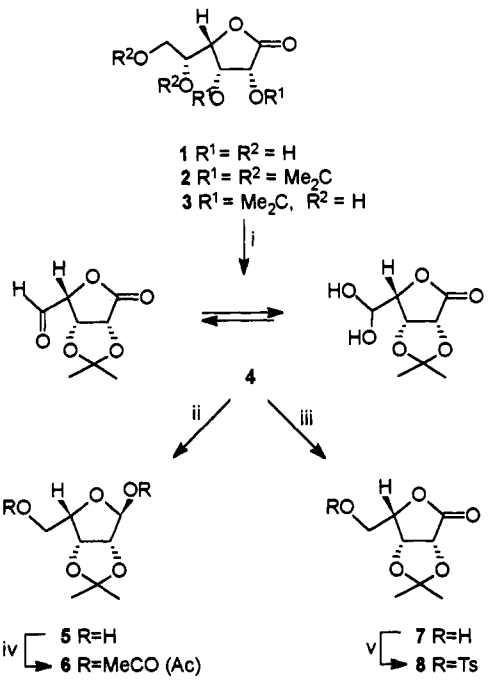
(1) *Aldrichim. Acta* **1989**, *22*, 49.
(2) Lederkremer, R. M.; Varela, O. *Adv. Carbohydr. Chem. Biochem.*, in press.
(3) Bhat, K. L.; Chen, S. Y.; Joullié, M. M. *Heterocycles* **1985**, *23*, 691.
(4) Drew, M. G. B.; Mann, J.; Thomas, A. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2279.
(5) Dominguez, J. N.; Owen, L. N. *Carbohydr. Res.* **1979**, *75*, 101.
(6) Yuasa, H.; Tamura, J.; Hashimoto, H. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2763.
(7) Varela, O.; Cicero, D.; Lederkremer, R. M. *J. Org. Chem.* **1989**, *54*, 1884.
(8) Cicero, D.; Varela, O.; Lederkremer, R. M. *Tetrahedron* **1990**, *46*, 1131.
(9) Cicero, D.; Varela, O.; Lederkremer, R. M. *Carbohydr. Res.* **1991**, *211*, 295.
(10) Cicero, D.; Varela, O. *Tetrahedron* **1990**, *46*, 8019.
(11) Zunszain, P. A.; Varela, O. *Carbohydr. Res.* **1991**, *222*, 131.
(12) Chambers, M. S.; Thomas, E. J. *J. Chem. Soc. Chem. Commun.* **1989**, 23.
(13) Dolak, L. A.; Castle, T. M.; Truesdell, S. E.; Sebek, O. K. *J. Antibiot.* **1986**, *39*, 26.
(14) Hulyalkar, R. K.; Jones, J. K. N. *Can. J. Chem.* **1963**, *41*, 1898.
(15) Wu, J.; Serianni, A. S. *Carbohydr. Res.* **1991**, *210*, 51.

0022-3263/93/1958-7860$04.00/0

Scheme I



Scheme II[a]



[a] (i) $NaIO_4$; (ii) $NaBH_4$, EtOH; (iii) $NaBH_3CN$, pH 4; (iv) Ac_2O, pyridine; (v) TsCl, pyridine, $CHCl_3$.

acetylation.[16] The ^1H and ^{13}C NMR spectra for **5** and **6** are shown in Tables I and II. On the other hand, when **4** was treated with 0.25 mol of $NaBH_4$ in order to avoid the reduction of the lactone group, a mixture of at least three products and some unreacted **4** were detected by TLC. The mixture was not further analyzed.

Chemoselective reduction of the aldehyde function of **4** was achieved by using $NaBH_3CN$ in acid medium (pH 4). Under these conditions the 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**7**) was obtained with a yield (74% from **3**) much higher than those reported[17,18] for the preparation of the enantiomer of **7**. Furthermore, the synthesis of **7** by these published procedures would require the very expensive L-lyxose[17] or L-galactose[18] as the starting sugar.

Sulfonylation of the free hydroxyl group of **7** with *p*-toluenesulfonyl chloride (tosyl chloride) in pyridine gave the tosylate **8** in 60% yield. A better yield (78%) was obtained by conducting the reaction in chloroform and with pyridine–tosyl chloride in a 1.3:1 molar ratio.[19] Treatment of compound **8** with sodium methoxide caused opening of the lactone ring by methanolysis, followed by nucleophilic attack of the resulting C-4 alkoxide on C-5 and displacement of the tosylate, to give the 4,5-epoxide **9** (Scheme III). The formation of the oxirane ring was readily determined by the ^1H and ^{13}C NMR spectra of **9**. Thus, H-4, 5, and 5′ showed the same chemical shift pattern (δ 3.01, 2.80, and 2.69, respectively) and coupling constant values ($J_{4,5}$ 4.0, $J_{4,5'}$ 2.6, and $J_{5,5'}$ 5.1 Hz) as those described for similar epoxide derivatives of sugars.[20] As C-4 and C-5 are now incorporated within the three-membered oxirane ring, their resonances are shifted considerably upfield (25 and 23 ppm, respectively) relative to the same signals of **8**. Reaction of epoxide **9** with thiourea gave the thiirane derivative **10**, with inversion of the C-4 configuration. The replacement of the ring oxygen atom of the epoxide by sulfur produces a further upfield displacement for the C-4 and C-5 signals (20 ppm) in the ^{13}C NMR spectrum of **10**.

Attempts to open the thiirane ring under acid or alkaline conditions proved unsuccessful, as decomposition took place. However, regioselective ring opening and simultaneous thiolactonization could be accomplished on treatment of **10** with KOAc in HOAc–DMF, at reflux temperature. The formation of the thiolactone ring was evident from the ^{13}C NMR spectrum of **11**, which showed a downfield shift of the thiolactone carbon resonance (δ 203.6) and a strong upfield shift of the C-4 signal (δ 47.5) relative to the same signals of D-ribono-1,4-lactone[21,22] (180.0 and 88.3 ppm, respectively). Removal of the 5-*O*-acetyl and the 2,3-*O*-isopropylidene groups of **11** by hydrolysis with HCl in H_2O–THF afforded the free 4-thio-D-ribono-1,4-lactone (**12**) in crystalline form. The ^{13}C NMR spectrum in ^2H_2O of **12** showed a signal characteristic of a thiolactone carbonyl at 210.1 ppm. The mass spectrum of the 2,3,5-tris-*O*-trimethylsilyl (TMS) derivative of **12** showed a fragmentation pattern similar to that of the TMS derivative of D-ribonolactone.[23]

A similar sequence of reactions was employed for the synthesis of 4-thio-L-lyxono-1,4-lactone (**19**) from D-ribono-1,4-lactone (**13**) (Scheme IV). Isopropylidenation of the *cis*-diol system of **13**, followed by tosylation of HO-5 led to 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribono-1,4-lactone (**15**) in 80% overall yield from **13**. Treatment of **15** with sodium methoxide afforded the 4,5-epoxide derivative **16**, whose ^1H NMR spectrum was like that of **9**. The $J_{3,4}$ values (5.8 Hz for **9** and 6.4 Hz for **16**) would indicate some degree of conformational unstability around the C-3–C-4 bond, the rotamer having H-3–H-4 in an antiperiplanar relationship being preferential. The epoxide function of **16** reacted with thiourea in methanol to give the thiirane derivative **17**. Its ^1H and ^{13}C NMR spectra were also similar to those of **10**. The large value for $J_{3,4}$ for **10** (8.7 Hz) and for **17** (8.5 Hz) would indicate that the most populated conformation is the one having an antiperplanar disposition of H-3 and H-4. These rotamers are free of unstabilizing effects such as 1,3-parallel interactions and

(16) Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1991**, *219*, 115.
(17) Schaffer, R. *J. Res. Natl. Bur. Stand. Sect. D* **1961**, *65A*, 507.
(18) Morgenlie, S. *Acta Chem. Scand.* **1975**, *B29*, 367.
(19) Kabalka, G. W.; Varma, M.; Varma, R. S.; Srivastava, P. C.; Knapp, F. F., Jr. *J. Org. Chem.* **1986**, *51*, 2386.
(20) Hashimoto, H.; Fujimori, T.; Yuasa, H. *J. Carbohydr. Chem.* **1990**, *9*, 683.
(21) Angelotti, T.; Krisko, M.; O'Connor, T.; Serianni, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 4464.
(22) Horton, D.; Walaszek, Z. *Carbohydr. Res.* **1982**, *105*, 111.
(23) Petersson, G.; Samuelson, O.; Anjou, K.; von Sydow, E. *Acta Chem. Scand.* **1967**, *21*, 1251.