A Novel Approach to the Synthesis of Amino-Sugars. Routes To Selectively Protected 3-Amino-3-deoxy-aldopentoses Based on Pyridinium Salt Photochemistry

Haiyan Lu, Zhuoyi Su, Ling Song, and Patrick S. Mariano*

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

mariano@unm.edu

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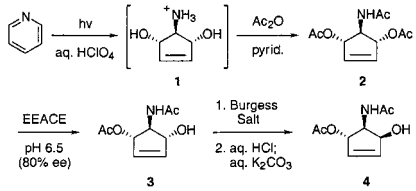
Abstract: A new approach for the synthesis of selectively blocked 3-amino-3-deoxyaldopentoses is presented. The strategy is based on employment of a pyridinium salt photocyclization−aziridine ring-opening sequence to prepare stereochemically defined, enantiomerically enriched aminocyclopentendiol derivatives. Ring-opening reactions transform these substances into terminally differentiated aminopolyols, which serve as precursors to the target aminoaldopentoses. The utility of this strategy is demonstrated by its application to the syntheses of protected derivatives of D- and L-3-amino-3-deoxyxylose, L-3-amino-3-deoxyarabinose, and a late-stage intermediate in a potential route to *N*-acetylneuraminic acid.

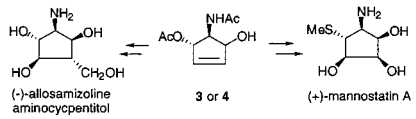
Earlier, we described how pyridinium salt photocyclization−aziridine ring-opening sequences can be used to prepare stereochemically defined, diversely functionalized aminocyclopentenes.[1] An example of this is found in the conversion of pyridine to the aminodiol **1** (isolated as the amido-diacetate **2**) by irradiation in aqueous perchloric acid (Scheme 1). In addition, employing enzymatic desymmetrization[2] and Wipf alcohol inversion[3] procedures allows **2** to be transformed into the cyclopentenols **3** and **4** with modestly high levels of enantiomeric purity.[4] As we have pointed out in previous publications,[4−6] these substances serve as key intermediates in routes for the preparation of a variety of biomedically interesting natural and nonnatural aminocyclopentitols (Scheme 2). The strategies developed for these purposes take advantage of the allylic alcohol functionality in **3** and **4** to promote stereocontrolled dihydroxylation and Wittig rearrangement reactions.

Another, synthetically relevant feature of the doubly allylic enediol functionality present in aminocyclopentenols **3** and **4** relates to ring-opening reactions. Accordingly, oxidative cleavage of olefin moieties in these substances can be used to construct stereochemically defined, terminally differentiated five-carbon aminopolyols. When viewed from this perspective (Scheme 3), the ring-opening process would serve as a strategic element linking pyridinium salt photochemistry to concise routes for the synthesis of selectively protected 3-amino-3-deoxyaldopentoses.[7,8] Below, we summarize the results

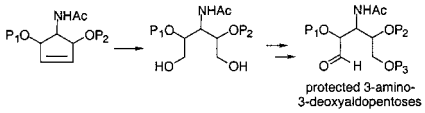
Scheme 1



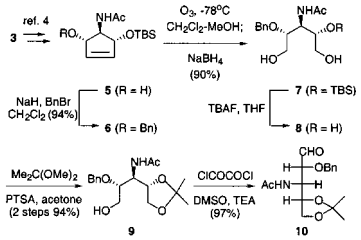
Scheme 2



Scheme 3



Scheme 4



of preliminary studies, which demonstrate the utility of this strategy in the context of the preparation of N- and O-protected derivatives of D- and L-3-amino-3-deoxyxylose and L-3-amino-3-deoxyarabinose.

The route to the D-3-amino-3-deoxyxylose derivative **10** (Scheme 4) begins with the known[4] conversion of amidocyclopentenol **3** to the TBS-analogue **5**. Attempts to carry out ozonolytic cleavage directly on the allylic alcohol moiety in **5** were unsuccessful. In contrast, treatment of the O-benzyl derivative **6** with ozone in a 2:1 CH_2Cl_2−MeOH mixture, followed by addition of $NaBH_4$, efficiently produces the pentanediol **7**. The stage is then set for differentiation of the terminal alcohol groups by use of a silyl ether cleavage−acetonide formation sequence. Swern oxidation of the alcohol **9**, obtained in this way, then yields the selectively protected D-3-amino-3-deoxyxylose **10**.

The enantiodivergent nature of this strategy for aminosugar synthesis is highlighted by conversion of amidocyclopentenol **3** to the protected L-3-amino-3-deoxyxylose **14**. Accordingly, reversal of the alcohol protection steps transforms **3** into the enantiomeric O-TBS-, O-Bn-blocked amidocyclopentene **13** (Scheme 5). Application of the

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(8) For recent examples of synthetic routes to 3-amino-2,3-dideoxyaldopentoses, see: Hauser, F. M.; Ellenberger, S. R.; Rhee, R. P. *J. Org. Chem.* **1987**, *52*, 5041. Krenitsky, T. A.; Freeman, G. A.; Shaver, S. R.; Beacham, L. M.; Hurlbert, S.; Cohn, N. K.; Elwell, L. P.; Selway, J. W. T. *J. Med. Chem.* **1983**, *26*, 891.

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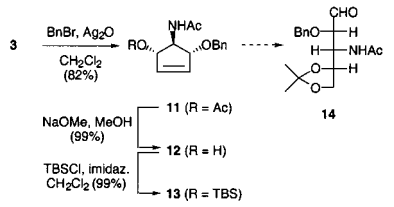
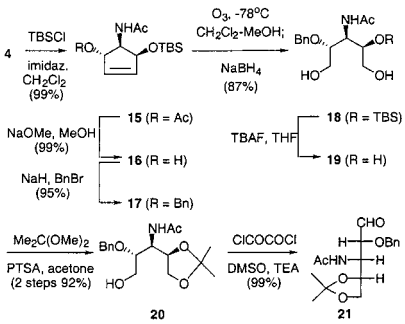
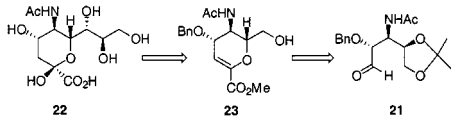
Scheme 5



Scheme 6



Scheme 7



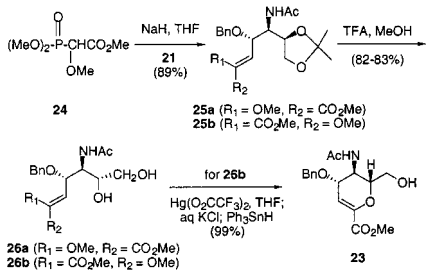
methodology shown in Scheme 4 can be used to convert **13** to the blocked L-aminoxylose derivative **14**.

The ability to perform amide-directed stereochemical inversion at one or both of the allylic hydroxyl centers in the photochemically derived amidocyclopentenes (Scheme 1) opens the way for application of this chemistry to the preparation of other diastereomeric 3-amino-3-deoxyaldopentoses. An example of this is found in the route targeted at the protected L-3-amino-3-deoxyarabinose **21**, starting with amidocyclopentenol **4** (Scheme 6). In a manner similar to that outlined in Scheme 4, **4** is converted to the O-TBS, O-Bn derivative **17**. Ozonolysis followed by reduction provides the diol **18**. Sequential desilylation and acetonide formation then sets the stage for preparation of the L-arabinose analogue **21** by Swern oxidation of the pentanol **20**.

The methods presented above for amino-aldopentose synthesis can be incorporated into sequences targeted at higher homologues in the amino-sugar family. An example of this is found in the strategy for synthesis of the amino-glycero-nonulosonic acid, *N*-acetylneuraminic acid (**22**) shown in Scheme 7. A late intermediate in this proposed route is alcohol **23**, a substance that could be transformed to the target by using sequential alcohol oxidation, Sharpless–Masamune[9] polyol chain introduction, and enol ether to hemiacetal interconversion.[10] In addition, the approach to **23** takes advantage of the aldehyde moiety in the blocked L-amino-arabinose **21** as an ideal site for chain elongation.

Thus, treatment of **21** with the anion of the phosphonate **24** provides the separable unsaturated esters **25** as a 2:1 mixture of (*E*)- and (*Z*)-stereoisomers (**25b** and **25a**, respectively) (Scheme 8). Acetonide removal in each of

Scheme 8



these substances by using TFA/MeOH affords the diols **26a** and **26b**. An oxymercuration–demercuration process[11] is then employed to convert **26b** to the dihydropyran target **23**. Interestingly, the minor diol **26a** does not undergo Hg(II)-induced cyclization to form **23** under these conditions. These results contrast with those obtained earlier by Sinay[11] in his studies of oxymercuration–demercuration reactions on related but more structurally complex substrates.

The chemistry summarized above further highlights the synthetic value of photochemical processes that transform pyridinium salts into functionalized aminocyclopentenes. These processes can be used to prepare gram quantities of enantiomerically enriched substrates, which are ideal starting materials in routes for synthesis of cyclic and acyclic aminopolyol targets.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on $CDCl_3$ solution unless specified otherwise, and chemical shifts are reported in parts per million relative to $CHCl_3$ (δ 7.24 ppm for ^{1}H and δ 77.0 ppm for ^{13}C), which was used as a chemical shift internal standard for samples in $CDCl_3$. ^{13}C NMR resonance assignments were aided by the use of the DEPT-135 technique to determine numbers of attached hydrogens. Optical rotations [α] were measured at 25 °C at 589 nm (sodium D line). Mass spectra were recorded by using electron impact ionization or fast atom bombardment. Infrared absorption bands are recorded in units of cm^{-1}. All compounds were isolated as oils unless otherwise specified, and their purities were determined to be >90% by NMR analysis.

(3*R*,4*R*,5*S*)-4-Acetamido-3-*tert*-butyldimethylsilyloxy-5-benzyloxycyclopentene (6). After a mixture of the known silyl ether **5**[4] (0.7 g, 2.59 mmol) and sodium hydride (0.156 g, 3.9 mmol) in the dry THF (25 mL) was stirred at 25 °C for 1 h, benzyl bromide (0.86 g, 5.18 mmol) and sodium iodide (0.76 g, 5.18 mmol) were introduced. The resulting mixture was stirred at 25 °C for 48 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to afford an oil, which was subjected to column chromatography (silica gel, 2:1 hexane–acetone) to give the cyclopentene **6** (0.86 g, 94%) as a solid. ^{1}H NMR: δ 7.24–7.33 (m, 5H), 6.91 (d, J = 7.5 Hz, 1H, NH), 5.83 (abq, J = 5.5 Hz, 2H), 4.76 (d, J = 5.0 Hz, 1H), 4.58 (abq, J = 8.0 Hz, 2H), 4.50 (d, J = 3.0 Hz, 1H), 3.92 (m, 1H), 1.91 (s, 3H), 0.89 (s, 9H), 0.61 (s, 6H). ^{13}C NMR: δ 170.1 (C=O), 138.4, 135.7, 131.4, 128.3, 128.1, 127.5, 84.2, 78.2, 70.7, 66.7, 25.6, 23.2, −4.8, −5.0. HRMS (FAB) (*m*/*z*): calcd for $C_{20}H_{32}O_3NSi$, 362.2151; found, 362.2154.

(2*R*,3*R*,4*S*)-3-Acetamido-2-*tert*-butyldimethylsilyloxy-4-benzyloxy-1,5-pentanediol (7). Ozone was passed through a −78 °C solution of **6** (0.35 g, 0.97 mmol) in 15 mL of 2:1 CH_2Cl_2–MeOH for 3 h. Solid sodium borohydride (0.37 g, 9.7 mmol) was then added, and the resulting solution was diluted with CH_2Cl_2 and filtered. The filtrate was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to give a residue that was subjected to column chromatography (silica gel, 2:1 hexane–acetone) to afford the diol **7** (0.35 g, 90%) as a crystalline substance. ^{1}H NMR: δ 7.20–

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7.32 (m, 5H), 6.34 (d, J = 8.6 Hz, 1H, NH), 4.53 (abq, J = 11.4 Hz, 2H), 4.20−4.27 (m, 1H), 4.15−4.19 (m, 1H), 3.88−3.93 (m, 1H), 3.64−3.71 (m, 2H), 3.37−3.51 (m, 2H), 1.94 (s, 3H), 0.83 (s, 9H), −0.02 (s, 6H). ^{13}C NMR: δ 172.62, 137.28, 128.41, 127.96, 127.88, 80.37, 71.21, 63.32, 59.34, 48.67, 25.64, 25.38, 22.77, 18.01, −5.71.

(2*S*,3*R*,4*R*)-Benzyloxy-3-acetamido-4,5-*O*-isopropylidene-1-pentanol (9). A solution of diol **7** (0.1 g, 0.25 mmol) and TBAF (0.2 g, 0.35 mmol) in 10 mL of THF was stirred at 25 °C for 2 h. Concentration in vacuo gave a residue that was eluted through Florisil (1:1 hexane−acetone). The eluate was concentrated in vacuo giving a residue, which was dissolved in acetone (6 mL) containing 2,2-dimethoxy-propane (8 mL) and PTSA (0.02 g, 0.1 mmol). The resulting mixture was stirred at 25 °C for 1 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford **9** (0.075 g, 94%). ^{1}H NMR: δ 7.24−7.27 (m, 5H), 6.19 (d, J = 8.9 Hz, 1H, N*H*), 4.50 (abq, J = 11.6 Hz, 2H), 4.20−4.41 (m, 2H), 3.77−3.80 (m, 1H), 3.74−3.76 (m, 1H), 3.63 (s, 1H), 3.46−3.51 (m, 2H), 3.38−3.40 (m, 1H), 1.96 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H). ^{13}C NMR: δ 171.5 (*C*O), 137.7, 1, 128.4, 128.1, 127.9, 109.4, 79.0, 75.0, 72.4, 66.8, 60.3, 49.9, 26.4, 25.3, 22.9. HRMS (FAB) (*m*/*z*): calcd for $C_{17}H_{26}O_5N$ (M + 1), 324.8111; found, 324.1808.

(2*S*,3*R*,4*R*)-2-Benzyloxy-3-acetamido-4,5-*O*-isopropylidene-pentanal (10). To a solution of oxalyl chloride (42uL, 0.48 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DMSO (90 μL, 1.28 mmol) dropwise. The resulting solution was stirred at −78 °C for 1 h, and then a solution of alcohol **9** (0.1 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1.5 h, followed by the dropwise addition of TEA (178uL, 1.28 mmol) and warming to 25 °C. After stirring at 25 °C for 2 h, the mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed, dried, and concentrated in vacuo to yield aldehyde **10** (0.098 g, 97%). The crude aldehyde was quickly eluted through a Florisil column (1:1 hexane−acetone), and the eluate was concentrated in vacuo to give the pure but unstable **10**. ^{1}H NMR: δ 9.61 (s, 1H), 7.29−7.33 (m, 5H), 5.91 (d, J = 9.0 Hz, 1H, N*H*), 4.64 (abq, J = 11.6 Hz, 2H), 4.47−4.49 (m, 1H), 4.42 (d, J = 4.9 Hz, 1H), 3.92−3.95 (m, 1H), 3.86−3.87 (m, 1H), 3.63−3.66 (m, 1H), 1.99 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H).

(3*S*,4*S*,5*R*)-4-Acetamido-3-acetoxy-5-benzyloxycyclopentene (11). A solution of cyclopentenol **4** (35 mg, 0.18 mmol), Ag_2O (123 mg, 0.53 mmol), and $PhCH_2Br$ (46 mg, 0.26 mmol) in CH_2Cl_2 (1.5 mL) was stirred for 3 days at 25 °C, diluted with CH_2Cl_2, and filtered. The filtrate was concentrated to give a residue that was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford **11** (42 mg, 82%) as a crystalline substance. Mp: 131−132 °C. ^{1}H NMR: δ 7.24−7.34 (m, 5H), 6.00−6.05 (m, 1H), 5.86−5.90 (m, 1H), 5.68−5.72 (d, J = 7.8 Hz, 1H, NH), 5.54−5.57 (m, 1H), 4.58−4.69 (abq, J = 11.9 Hz, 2H), 4.47−4.49 (m, 1H), 4.09−4.17 (m, 1H), 2.05 (s, 3H), 1.95 (s, 3H). ^{13}C NMR: δ 170.9, 170.1, 138.2, 134.9, 131.40, 128.4, 127.9, 127.7, 85.38, 80.7, 71.5. HRMS (FAB) (*m*/*z*): calcd for $C_{16}H_{20}O_4N$ (M + 1), 290.1392; found, 290.1402.

(3*S*,4*S*,5*R*)-4-Acetamido-5-benzyloxycyclopenten-3-ol (12). A solution of **11** (60 mg, 0.21 mmol) and NaOMe (10 mg) in MeOH (5 mL) was stirred for 12 h at 25 °C and concentrated in vacuo to give a residue that was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to afford **12** (51 mg, 99%) as a crystalline solid. Mp: 106−107 °C. ^{1}H NMR: δ 7.29−7.37 (m, 5H), 5.88−5.93 (m, 2H), 5.80 (brs, 1H), 4.71 (s, 1H), 4.47−4.70 (abq, J = 12.0 Hz, 2H), 4.44−4.47 (d, J = 5.0, 1H), 4.32−4.36 (m, 1H), 3.81−3.90 (m, 1H), 1.93 (s, 3H). ^{13}C NMR: δ 172.6, 138.1, 134.8, 130.6, 128.7, 128.1, 128.0, 85.2, 79.8, 71.0, 68.0, 22.9. HRMS (FAB) (*m*/*z*): calcd for $C_{14}H_{18}O_3N$ (M + 1), 248.1287; found, 248.1290.

(3*S*,4*S*,5*R*)-4-Acetamido-3-*tert*-butyldimethylsilyloxy-5-benzyloxycyclopentene (13). A solution of **12** (23 mg, 0.09 mmol), imidazole (18 mg, 0.25 mmol), and TBSCl (20 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was stirred for 12 h at 25 °C, diluted with water, and extracted with CH_2Cl_2. The extracts were concentrated in vacuo, and the residue was subjected to column chromatography (silica gel, 2:1 hexane−acetone) affording **13** (33 mg, 99%) as a crystalline solid. Mp: 71−72 °C. ^{1}H NMR: δ 7.32−7.22 (m, 5H), 5.86−5.90 (m, 1H), 5.74−5.82 (m, 2H), 4.80−4.83 (m, 1H), 4.50−4.60 (abq, J = 12.0 Hz, 3H), 3.66−3.74 (m, 1H), 1.93 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 170.1, 138.6, 135.9, 131.6, 128.3, 127.8, 127.6, 84.1, 77.8, 71.2, 67.7, 25.8, 23.6, 18.06, −4.7, −4.8. HRMS (FAB) (*m*/*z*): calcd for $C_{28}H_{32}O_3NSi$, 362.2151; found, 362.2153.

(3*S*,4*R*,5*S*)-5-Acetoxy-4-acetamido-3-*tert*-butyldimethysilyloxy-1-cyclopentene (15). To a solution of cyclopentenol **4** (0.7 g, 3.52 mmol) in dry CH_2Cl_2 (20 mL) was added imidazole (0.67 g, 9.87 mm0l) and *tert*-butyldimethylsilyl chloride (0.74 g, 4.92 mmol). The mixture was stirred at 25 °C for 12 h, diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to provide silyl ether **15** (1.1 g, 100%) as a crystalline substance. Mp: 84−85 °C. [α] = +93.5 (*c* 2.2, $CHCl_3$). ^{1}H NMR: δ 6.10 (d, J = 12.5 Hz, 1H), 5.93 (m, 1H), 5.89 (dd, J = 6.0, 1.5 Hz, 1H), 5.62 (dd, J = 5.2, 1.5 Hz, 1H), 4.69 (ddd, J = 6.0,1.7, 1.7 Hz, 1H), 4.33 (ddd, J = 12.5, 6.0, 5.2 Hz, 1H), 2.01 (s, 3H), 1.93 (s, 3H), 0.84 (S, 9H), 0.03 (S, 3H). ^{13}C NMR: δ 170.9, 169.8, 135.8, 133.7, 81.7, 73.7, 56.4, 25.6, 23.2, 21.0, 18.0, −4.6, −5.1. HRMS (*m*/*z*): calcd for $C_{15}H_{27}O_4NSi$, 313.1709; found, 313.1705.

(1*S*,4*S*,5*R*)-5-Acetamido-4-*tert*-butyldimethylsilyloxy-2-cyclopenten-1-ol (16). A solution of the silyl ether **15** (0.513 g, 1.6 mmol) and NaOMe (0.018 g, 0.329 mmol) in MeOH (25 mL) at 25 °C was stirred for 12 h and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to give alcohol **16** (0.438 g, 100%) as a crystalline substance. Mp: 98−100 °C. [α] = +29.5 (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 6.04 (brs, 1H), 6.00 (dd, J = 6.0, 1.5 Hz, 1H), 5.83 (ddd, J = 6.0, 2.0, 2.0 Hz, 1H), 4.76 (ddd, J = 6.6, 2.0, 2.0 Hz, 1H), 4.68 (m,1H), 3.81 (m, 1H), 3.78 (brs, 1H), 2.01 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR: δ 171.9, 137.5, 132.4, 82.3, 74.6, 61.2, 25.7, 22.9, 18.1, −4.1, −5.0. HRMS (*m*/*z*): calcd for $C_{13}H_{25}O_3NSi$, 271.1604; found, 271.1615.

(3*S*,4*R*,5*S*)-4-Acetamido-3-*tert*-butyldimethylsilyloxy-5-benzyloxy-cyclopentene (17). After a mixture of the silyl ether **16** (0.47 g, 1.73 mmol) and sodium hydride (0.104 g, 2.6 mmol) in THF (25 mL) was stirred at 25 °C for 1 h, benzyl bromide (0.59 g, 3.56 mmol), sodium iodide (0.51 g, 3.46 mmol), and tetrabutylammonium acetate (0.156 g, 0.51 mmol) were sequentially introduced. The resulting mixture was stirred at 25 °C for 48 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to afford a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to give **17** (0.587 g, 95%) as a solid. ^{1}H NMR: δ 7.25−7.36 (m, 5H), 6.10 (d, J = 6.7 Hz, 1H, NH), 5.95 (d, J = 6.1 Hz, 1H), 4.81, 4.63 (abq, J = 11.9 Hz, 2H), 4.45 (brs, 1H), 4.34 (m, 1H), 1.98 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ 169.5 (*C*O), 138.5, 136.0, 134.0, 128.2, 127.8, 127.4, 87.4, 74.6, 71.6, 55.9, 25.7, 23.4, 18.0, −5.0. HRMS (*m*/*z*): calcd for $C_{20}H_{32}NO_3Si$ (M + 1), 362.3152; found, 362.3162.

(2*S*,3*R*,4*S*)-3-Acetamido-2-*tert*-butyldimethylsilyloxy-4-benzyloxy-1,5-pentanediol (18). Ozone was passed through a −78 °C solution of the cyclopentene **17** (0.236 g, 0.654 mmol) in 15 mL of 2:1 CH_2Cl_2−MeOH. Solid sodium borohydride (0.248 g, 6.54 mmol) was then added, and the resulting solution was diluted with CH_2Cl_2 and filtered. The filtrate was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to give a residue that was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford diol **18** (0.23 g, 87%) as a solid. ^{1}H NMR: δ 7.25−7.38 (m, 5H), 6.12 (d, J = 6.7 Hz, 1H, NH), 4.62, 4.54 (abq, J = 11.4 Hz, 2H), 4.20 (m, 1H), 4.02 (m, 1H), 3.56−3.74 (m, 4H), 3.32 (dd, J = 11.7, 9.2 Hz, 1H), 1.98 (s, 3H), 0.86 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ 171.8 (*C*O), 137.8, 128.5, 128.1, 128.1, 77.5, 72,8, 71.5, 64.4, 59.9, 50.2, 25.8, 23.0, 18.2, −5.5. HRMS (*m*/*z*): calcd for $C_{20}H_{36}NO_5Si$ (M + 1), 398.2363; found, 398.2386.

(2*S*,3*R*,4*S*)-2-Benzyloxy-3-acetamido-4,5-*O*-isopropylidene-1-pentanol (20). A solution of diol **18** (0.058 g, 0.147 mmol) and TBAF (0.2 g, 0.35 mmol) in THF (10 mL) was stirred at 25 °C for 2 h. Concentration in vacuo gave a residue, which was eluted through Florisil with 1:1 hexane−acetone as the eluant. The eluate was concentrated in vacuo giving a residue, which was dissolved in acetone (4 mL) containing 2,2-dimethoxy-propane (6 mL) and PTSA (0.012 g, 0.06 mmol). The mixture was stirred at 25 °C for 1 h, diluted with water, and extracted

with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo giving a residue, which was subjected to column chromatography (silica gel, 2:1 hexane−acetone) to afford the acetonide **20** (0.043 g, 92%). ^{1}H NMR: δ 7.29−7.34 (m, 5H), 4.13−4.18 (m, 2H), 4.02 (m, 1H), 3.93 (m, 1H), 3.81 (m, 1H), 3.65 (m, 1H), 3.65 (m, 1H), 3.34 (m, 1H), 3.11 (m, 1H), 1.99 (s, 3H), 1.34 (s, 3H), 1.41 (s, 3H). ^{13}C NMR: δ 171.5 (*C*O), 137.9, 128.4, 128.1, 128.0, 109.7, 77.4, 74.2, 73.5, 60.5, 67.6, 52.2, 26.8, 25.4, 23.0. HRMS *m/z:* calcd for $C_{17}H_{25}O_5N$, 323.1733; found, 323.1712.

(2*S*,3*R*,4*S*)-2-Benzyloxy-3-acetamido-4,5-*O*-isopropylidenepentanal (21). To a solution of oxalyl chloride (21 uL, 0.24 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DMSO (45 uL, 0.64 mmol) dropwise. The resulting solution was stirred at −78 °C for 1 h, and then a solution of alcohol **20** (52 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1.5 h; triethylamine (89uL, 0.64 mmol) was added, and the mixture was stirred at 25 °C for 2 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to yield the aldehyde **21** (0.051 g, 100%). The crude aldehyde was quickly eluted through a Florisil column (1:1 hexane−acetone), and the eluate was concentrated in vacuo to give the pure but unstable aldehyde **21**. ^{1}H NMR: δ 9.49 (d, J = 4.3 Hz, 1H, C*H*O), 7.24−7.31 (m, 5H), 6.00 (d, J = 9.6 Hz, 1H, NH), 4.72, 4.46 (abq, J = 11.2 Hz, 2H), 4.43 (m, 2H), 4.28 (d, J = 4.3 Hz, 1H), 4.09 (m, 1H), 3.95 (dd, J = 6.1, 8.5 Hz, 1H, 3.83 (s, 1H), 1.85 (s, 3H), 1.29, 1.31 (s, 6H).

Trimethyl α-Methoxyphosphonoacetate (24). A general procedure reported by Regitz[12] was used to prepare the diazophosponate intermediate. To a solution of trimethyl phosphonoacetate (10 g, 55 mmol) in THF (50 mL) was slowly added a hexane solution of *n*-BuLi (41 mL, 70 mmol). The mixture was stirred at 25 °C for 1.5 h, followed by addition of tosyl azide (10.83 g, 55 mmol). The resulting mixture was stirred at 25 °C for 4 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to afford a residue, which was subjected to column chromatography (silica gel, 3:1 hexane−acetone) to yield the α-diazophosphonate (2.38 g, 21%). IR: 2960, 2127, 1713, 1438, 1288, 1025. ^{1}H NMR: δ 3.84 (s, 3H, CO_2CH_3), 3.72 (s, 6H, $2OCH_3$).

A general procedure reported by Reimlinger[13] was used to transform the diazophosphonate to **24**. A solution of the diazophosphonate (2.24 g, 10.67 mmol) and rhodium acetate dimer (94 mg, 0.21 mmol) in methanol (50 mL) was stirred at reflux for 6 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with brine and concentrated in vacuo to afford a residue that was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to yield the trimethyl α-methoxyphosphonoacetate (**24**) (1.58 g, 70%). ^{1}H NMR: δ 4.22 (d, J = 18.6 Hz, 1H), 3.83 (d, J = 3.3 Hz, 3H), 3.80 (m, 6H), 3.48 (s, 3H). ^{13}C NMR: δ 167.0 (**C**O_2Me), 78.6, 76.1, 60.1, 59.9, 53.6, 52.3. IR: 3487, 2960, 2853, 1734, 1440, 1260, 1121, 1025.

Methyl (4*S*,5*R*,6*S*)-4-Benzyloxy-5-acetamido-6,7-*O*-isopropylidene-heptenoate (25a and 25b). A solution of the phosphonate **24** (45.5 mg, 0.215 mmol) and sodium hydride (14 mg, 0.36 mmol) in dry THF (10 mL) was stirred at 25 °C for 2 h. To this solution at 0 °C was dropwise added freshly prepared aldehyde **21** (46 mg, 0.14 mmol) in THF (5 mL). The mixture was stirred at 0 °C for 1 h and then at 25 °C for 4 h before being diluted with water. Extraction with CH_2Cl_2 gave CH_2Cl_2 extracts that were concentrated in vacuo to afford a residue, which was subjected to column chromatography (silica gel, 1:2 ethyl acetate−hexane) to provide the **25a** (18 mg, 30%) and **25b** (34 mg, 59%).

25a. ^{1}H NMR: δ 7.24−7.35 (m, 5H), 6.07 (d, J = 9.0 Hz, 1H, vinyl H), 5.86 (d, J = 9.0 Hz, 1H, N*H*), 4.85 (dd, J = 9.0, 1.1 Hz, 1H), 4.52, 4.40 (abq, J = 11.2 Hz, 2H), 4.10 (m, 2H), 3.92 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 1.98 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR: δ 170.0, 163.3, 147.9, 137.8, 128.3, 128.0, 127.8, 109.4, 103.8, 75.2, 71.5, 71.3, 67.2, 60.2, 55.0, 52.1, 26.8, 25.6, 23.3. IR: 3348, 2953, 2858, 1651, 1535, 1469, 1374, 1254, 1112, 835, 778, 735. MS *m/z* (rel intensity): 408 (M + 1, 11), 368 (16), 126 (24), 91 (100). HRMS *m/z*: calcd for $C_{21}H_{30}NO_7$ (M + 1), 408.2022; found, 408.2001.

25b. ^{1}H NMR: δ 7.24−7.35 (m, 5H), 5.86 (d, J = 8.9 Hz, 1H, NH), 5.20−4.99 (abq, J = 9.0 Hz, 2H), 4.53−4.43 (abq, J = 11.5 Hz, 2H), 4.13 (m, 2H), 3.80 (m, 2H), 3.76 (s, 3H), 3.56 (s, 3H), 1.99 (s, 3H), 1.41, 1.33 (s, 6H). ^{13}C NMR: δ 171.7.0, 163.2, 148.0, 138.1, 128.4, 128.0, 127.8, 109.5, 75.5, 72.8, 71.2, 67.2, 55.9, 55.6, 52.3, 26.8, 25.6, 23.4. IR: 3340, 2987, 1731, 1651, 1371, 1233, 1158, 1067, 842. MS *m/z* (rel intensity): 408 (M + 1, 14), 300 (42), 242 (30), 91 (100). HRMS *m/z*: calcd for $C_{21}H_{30}NO_7$, 408.2022; found, 408.2031.

Methyl (4*S*,5*R*,6*S*)-4-Benzyloxy-5-acetamido-6,7-dihydroxyheptenoates (26a and 26b). A solution of **25a** (148 mg, 0.36 mmol) in 15 mL of 1:4 TFA−MeOH was stirred at 25 °C for 3 h, washed with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to yield a residue that was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to afford diol **26a** (93 mg, 82%). ^{1}H NMR: δ 7.24−7.36 (m, 5H), 6.18 (d, J = 8.7 Hz, 1H, N*H*), 6.12 (d, J = 9.1 Hz, 1H, vinyl H), 5.02 (dd, J = 9.1, 1.0 Hz, 1H), 4.55, 4.42 (abq, J = 11.2 Hz, 2H), 3.80, 3.69 (s, 6H), 3.56 (m, 4H), 2.04 (s, 3H). ^{13}C NMR: δ 172.0, 163.2, 148.3, 137.4, 128.4, 128.1, 128.0, 123.3, 71.7, 70.4, 70.3, 62.2, 60.2, 55.0, 52.2, 23.1. IR: 3369, 2952, 1728, 1651, 1436, 1309, 1245, 1072, 784, 740, 700. MS *m/z* (rel intensity): 368 (M + 1, 55), 260 (74), 91 (100). HRMS *m/z*: calcd for $C_{18}H_{26}NO_7$, 368.1709; found, 368.1735.

A solution of **25b** (93 mg, 0.23 mmol) in 15 mL of 1:4 TFA−MeOH was stirred at 25 °C for 3 h, washed with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were concentrated in vacuo to yield a residue that was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to afford diol **26b** (60 mg, 83%). ^{1}H NMR: δ 7.24−7.34 (m, 5H), 6.26 (d, J = 8.8 Hz, 1H, NH), 5.35 (d, J = 8.6 Hz, 1H), 5.06 (d, J = 8.6 Hz, 1H), 4.55, 4.46 (abq, J = 11.3 Hz, 2H), 3.77, 3.59 (s, 3H), 3.52−3.61 (m, 4H), 2.02 (s, 3H). ^{13}C NMR: δ 171.7, 163.2, 147.9, 137.6, 128.4, 128.1, 128.0, 110.3, 72.3, 71.6, 71.1, 62.7, 55.6, 55.6, 52.4, 23.0. IR: 3369, 2952, 1728, 1651, 1436, 1309, 1245, 1072, 784, 740, 700. MS *m/z* (rel intensity): 368 (M + 1, 55), 260 (74), 91 (100). HRMS *m/z*: calcd for $C_{18}H_{26}NO_7$ (M + 1), 368.1709; found, 368.1735.

Methyl (2*S*,3*R*,4*S*)-2-Hydroxymethyl-3-acetamido-4-benzyloxy-1,2-dihydropyranosyl-6-carboxylate (23). A solution of diol **26b** (0.134 g, 0.367 mmol) and $Hg(O_2CCF_3)_2$ (0.313 g, 0.734 mmol) in THF (20 mL) was stirred at 0 °C for 2 h. Saturated aqueous KCl (2 mL) was added. After stirring at 0−25 °C for 12 h, the mixture was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to yield a residue. To a solution of the residue in toluene (15 mL) was added Ph_3SnH (0.322 g, 0.917 mmol) and NaOAc (10 mg). The resulting mixture was stirred at 25 °C for 12 h, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated in vacuo to yield an oil, which was subjected to column chromatography (silica gel, 1:1 hexane−acetone) to furnish dihydropyran **23** (0.121 g, 99%) as a crystalline material. Mp: 100−102 °C. ^{1}H NMR: δ 7.23−7.32 (m, 5H), 6.1 (d, J = 3.33 Hz, 1H), 5.64 (d, J = 7.4 Hz, 1H, N*H*), 4.58 (abq, J = 11.8 Hz, 2H), 4.26 (m, 1H), 4.09 (d, J = 3.6 Hz, 2H), 3.78 (s, 3H), 3.77 (m, 2H), 3.36 (s, 1H, O*H*), 1.95 (s, 3H). ^{13}C NMR: δ 171.0, 162.4, 144.4, 137.4, 128.5, 128.1, 127.9, 108.0, 78.7, 71.0, 70.3, 60.5, 52.5, 47.2, 23.1. HRMS *m/z*: calcd for $C_{17}H_{21}NO_6$ (M + 1), 336.1447; found, 336.1459.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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