Articles

Asymmetric Allylboration of 2-*N*,3-*O*-Isopropylidene-*N*-Boc-L-serinal: Diastereoselective Synthesis of the Calicheamicin γ_1^I Amino Sugar

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Syntheses of the calicheamicin amino sugar **6** and its erythro diastereomer **7** have been completed by a sequence involving the asymmetric allylboration of N-Boc-serinal acetonide L-**8** with the tartrate ester modified allylboronates (*R,R*)-**9** and (*S,S*)-**9**, respectively. The reaction of (*R,R*)-**9** and L-**8** in toluene provides **14** with 89:11 selectivity, whereas the reaction of (*S,S*)-**9** with L-**8** in Et_2O provides the diastereomer **15** with 90:10 selectivity. It is shown that the relatively modest diastereoselectivity of these double asymmetric reactions is compromised by the low enantiomeric purity of **8** (86–87% ee), and data are provided indicating that these reactions should be highly diastereoselective (≥95:5 in each case) if performed with enantiomerically pure aldehyde. The two diastereomeric homoallylic alcohols, **14** and **15**, are easily elaborated into the targeted amino sugars **6** and **7** via the acetamide-substituted pyranosides **22** and **26**. Methyl pyranosides **22a** and **22e** were shown to adopt preferentially the unexpected conformations **B** and **D**, with axial acetamide substituents, in nonpolar solvents, while the expected conformations **A** and **C** were strongly favored in d_6-DMSO because of hydrogen bonding interactions with the solvent. The syntheses of **6** and **7** reported herein are expected to facilitate the design and synthesis of analogs of the calicheamicin aryl tetrasaccharide **3**, which should prove useful in further analysis and applications of oligosaccharides as DNA binders.

Calicheamicin γ_1^I (**1**) is an important member of the enediyne class of antitumor antibiotics, which have attracted considerable attention owing to their potent biological activity and novel mechanism of action as double strand DNA cleaving agents.[1] The calicheamicins[2] are of particular interest since they bind with high site selectivity in the DNA minor groove with specificity for oligopyrimidine–oligopurine runs, with the aryl tetrasaccharide unit serving as the major DNA recognition-binding element.[3] On the basis of NMR studies of a calicheamicin–DNA complex, Kahne has suggested that the site selectivity of calicheamicin γ_1^I is dependent on preorganization of the drug into a stiff, extended conformation that induces a conformational change in easily distorted DNA sequences, such as oligopyrimidine runs.[3i] The hydroxylamino glycosidic linkage between the A and B monosaccharide units is believed to play an important role by preorganizing the oligosaccharide into a conformation that complements the shape of the minor groove.[3e,4] Chazin and Nicolaou have shown that the NMR structure of the DNA-bound calicheamicin oligosaccharide **2** is virtually identical to that of the calicheamicin θ_1^I–DNA complex,[3j] although the methyl glycoside binds 2.1 kcal mol^{-1} less strongly than calicheamicin θ_1^I.[3k] The latter work demonstrates conclusively that the iodine substituent on the thiobenzoate C ring plays an important role in DNA binding, as suggested originally by Schreiber.[3c] Further insight into the nature of the interactions of the ABE core trisaccharide with the DNA minor groove is provided by the molecular dynamics simulations of a DNA–esperamicin A_1 complex published by the Bristol-Myers Squibb group.[5]

Calicheamicin γ_1^I (**1**)

[⊗] Abstract published in *Advance ACS Abstracts*, January 1, 1995.

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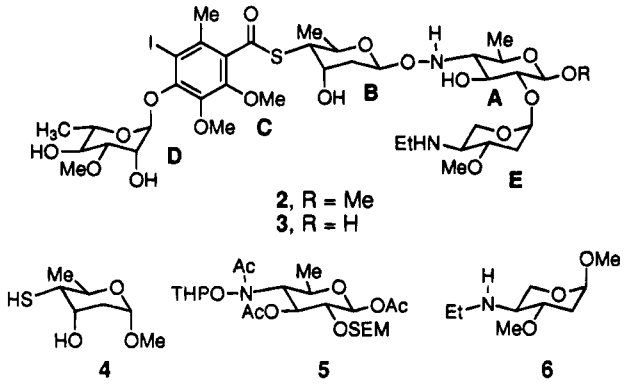
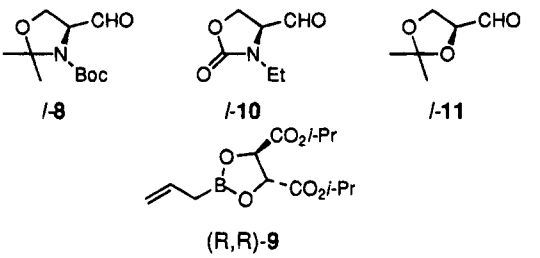
0022-3263/95/1960-0798$09.00/0

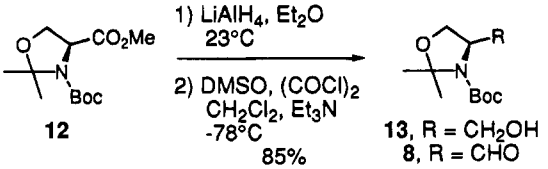
Efforts are ongoing in several laboratories to understand in more detail the nature of the DNA–oligosaccharide interactions and to use the oligosaccharide–DNA recognition properties in the design and synthesis of novel, highly specific DNA binding agents.[1a,3i,j,k,4,6] Three different strategies for the synthesis of the aryl tetrasaccharide, either as the methyl glycoside **2** or the reducing sugar **3**,[7] have been reported, and two elegant total syntheses of calicheamicin γ_1^I have been completed.[8] In anticipation that conjugates of **3** or its stereoisomers can be used to increase the specificity of DNA binding of other therapeutic agents,[5] we have initiated a program focusing on the development of a stereochemically general synthesis of the calicheamicin aryl tetrasaccharide. We have recently reported stereochemically general syntheses of the thiosugar (B residue) **4**[9] and model hydroxylamino sugar **5** (A residue)[10] and describe herein asymmetric syntheses of the amino sugar **6** corresponding to the *E* monosaccharide unit of **1**[11,12] and its *erythro* diastereomer **7**.



Our strategy called for **6** and the *erythro* diastereomer **7** to be synthesized via the asymmetric allylboration of isopropylidene-*N*-Boc-L-serinal **8** with the tartrate ester modified allylboronates (*R,R*)-**9** and (*S,S*)-**9**.[13] Kahne had previously synthesized **6** via the reaction of **8** with Danishefsky's diene,[11a] while Nicolaou synthesized **7** via the asymmetric allylboration of serinal derivative **10** with Brown's chiral $Ipc_2Ballyl$ reagent.[11b] Our synthesis was designed with two purposes in mind: to provide a short, stereoselective and stereochemically versatile route to the calicheamicin γ_1^I amino sugar and to allow us to explore the diastereoselectivity of the reactions of the tartrate allylboronates with a representative α-amino aldehyde, which we have not previously studied. We anticipated at the outset that these reactions would proceed with excellent diastereoselectivity by analogy to the reactions of **10** with glyceraldehyde acetonide **11**.[14]



Protected serine methyl ester **12** was synthesized from L-serine as described by Garner.[13] However, in our hands the DIBAL reduction of **12** on relatively modest scales (up to 2 g) provided **8** contaminated with significant amounts of unreacted methyl ester and primary alcohol **13** that were difficult to separate. These samples were judged to be no more than 50–60% pure based on the yield of homoallylic alcohols **14** and **15** obtained from their reactions with (*R,R*)- or (*S,S*)-**9**. It proved more convenient to prepare **8** by a two stage reduction–oxidation sequence, which provided **8** in 85% yield. The enantiomeric purity of **8**, prepared by either of these routes, was determined to be 86–87% ee by Mosher ester analysis of the corresponding primary alcohol **13** obtained by $NaBH_4$ reduction. This level of enantiomeric purity is considerably lower than that reported by Garner (93–95% ee)[13] and has a significant leveling effect on the diastereoselectivity of the subsequent allylboration reactions.



The results of the allylborations of **8** are summarized below. The reaction of the achiral pinacol allylboronate **16** with **8** showed that the *anti* amino alcohol **15** is the intrinsically favored diastereomer in the reactions with allylboronates. The matched double asymmetric reaction[15] with (*S,S*)-**9** provided **15** with 90:10 selectivity when the reaction was performed in Et_2O, while the mismatched double asymmetric reaction with (*R,R*)-**9** provided the syn diastereomer **14** with maximal 89:11 selectivity when performed in toluene. Because the selectivity of these reactions is considerably lower than that observed in the reactions of (*R,R*)-**9** and (*S,S*)-**9** with glyceraldehyde acetonide **11**,[14] we also examined the reaction of **8** with Brown's *B*-allyl(*l*-diisopinocampheyl)-

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(8) (a) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082. (b) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612. (c) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625. (d) Hitchcock, S. A.; Boyer, S. H.; Chu-Moyer, M. Y.; Olson, S. H.; Danishefsky, S. J. *Angew. Chem., Int Ed. Engl.* **1994**, *33*, 858.

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(11) (a) Kahne, D.; Yang, D.; Lee, M. D. *Tetrahedron Lett.* **1990**, *31*, 21. (b) Nicolaou, K. C.; Groneberg, R. D.; Stylianides, N. A.; Miyazaki, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1275. (c) Mash, E. A.; Nimkar, S. K. *Tetrahedron Lett.* **1993**, *38*, 385.

(12) Synthesis of the amino sugar corresponding to esperimicin A_1: Golik, J.; Wong, H.; Vyas, D. M.; Doyle, T. W. *Tetrahedron Lett.* **1989**, *30*, 2497.

(13) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18.

(14) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.

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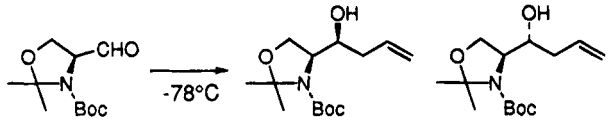
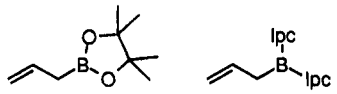
borane (**17**) (prepared from (−)-α-pinene), which is often more enantioselective than **9**.[16] However, this reaction was slightly less selective than the reaction of **8** and (*S,S*)-**9**, providing an 88:12 mixture of **15** and **14**.[17]



8 **14** **15**

Reagent	Solvent	14 : 15[a]	Yield
(R,R)-9	toluene	89 : 11	77%
(R,R)-9	THF	85 : 15	
(R,R)-9	Et_2O	85 : 15	
(S,S)-9	toluene	15 : 85	
(S,S)-9	THF	13 : 87	
(S,S)-9	Et_2O	10 : 90	84%
16	CH_2Cl_2 (23°C)	34 : 66	
17	Et_2O	12 : 88	

(a) Ratio of **14** : **15** was determined by capillary GC analysis (see Experimental Section)

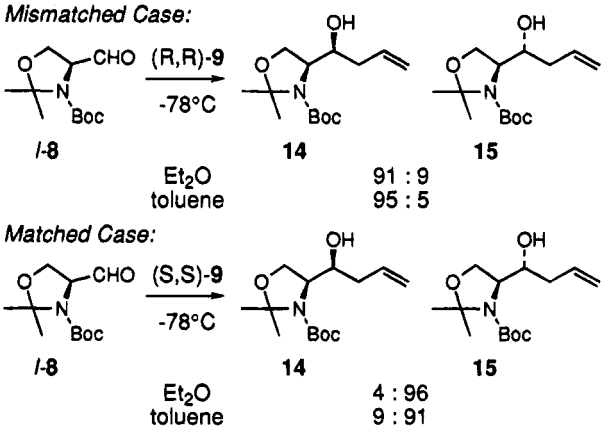


16 **17**

The diastereoselectivities realized in the double asymmetric reactions of **8** are limited by the enantiomeric purity of the chiral aldehyde,[18] which was 86−87% ee in all of the examples reported here. On the basis of the diastereoselectivity data presented above, it can be calculated that the diastereoselectivity of the matched double asymmetric reaction of (*S,S*)-**9** and *enantiomerically pure* L-**8** in Et_2O should be 4:96 (**14**:**15**), while the mismatched double diastereoselectivity of *enantiomerically pure* L-**8** with (*R,R*)-**9** in Et_2O should be 91:9.[19] On the other hand, values of 9:91 (**14**:**15**) for the matched case reaction with (*S,S*)-**9** and 95:5 for the mismatched double asymmetric reaction with (*R,R*)-**9** with *enantiomerically pure* L-**8** in toluene are consistent with the observed diastereoselectivities of the reactions with 86% ee aldehyde. The latter values are very similar to those observed in the double asymmetric reactions of **9** and glyceraldehyde acetonide.[14]

One consequence of the fact that reagent-controlled matched and mismatched double asymmetric pathways are available means that the minor enantiomer of the aldehyde, D-**8**, will be selectively converted to the *enantiomer of the minor diastereomer* in either the matched or mismatched pathways. This in turn requires that the enantiomeric purity of the major product diastereomer will always be greater than that of the enantiomerically impure starting aldehyde and that the enantiomeric purity of the minor product will be less than the starting

Diastereoselectivities Expected for Reactions with Enantiomerically Pure 8



aldehyde; depending on the enantiomeric impurity of the starting aldehyde and the selectivity of the matched and mismatched pathways, it is possible in some cases that the absolute configuration of minor reaction diastereomer will be the same as that of the minor enantiomer of the chiral substrate.[18] Unfortunately, diastereomers **14** and **15** could not be separated by TLC or HPLC, and so enantiomeric purity determinations of the individual diastereomers could not be performed. Nevertheless, one can calculate from the theoretical diastereoselectivity data presented above that the enantiomeric purity of **14** and **15** as the major products of the mismatched and matched double asymmetric reactions will be >98.5% ee in each case.

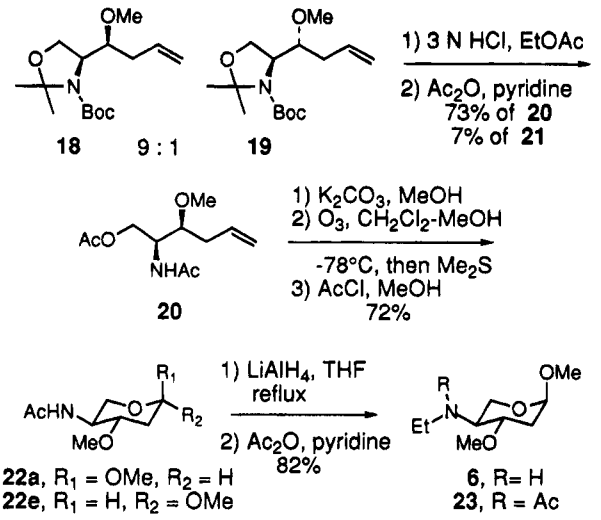
With *syn* amino alcohol **14** in hand, the calicheamicin E saccharide synthesis proceeded as follows. The inseparable 9:1 mixture of diastereomeric homoallylic alcohols **14** and **15** was *O*-methylated (NaH, DMF, MeI, 0−23 °C, 78−83% yield) to give the corresponding mixture of methyl ethers **18** and **19** which also could not be separated. This mixture was deprotected by treatment with 3 N HCl, and the resulting mixture of amine hydrochloride salts was acylated by treatment with excess acetic anhydride in pyridine. Although it was possible to acetylate the amine selectively, it was more difficult to separate the diastereomeric *N*-acetylated alcohol diastereomers than to separate the *N,O*-diacetylated products. Thus, diacetate **20** was separated by flash chromatography from the *anti* diastereomer **21** (deriving from **19**), and then the *O*-acetyl protecting group was removed. Ozonolysis of the vinyl group provided a mixture of pyranose anomers, which was treated with acetyl chloride and methanol to yield methyl pyranosides **22a** and **22e** in approximately a 6:1 ratio (as determined by ^1H NMR analysis of the crude reaction mixture); larger **22a**:**22e** ratios (up to 9:1) could be obtained with longer reaction times, but at the expense of a significant decrease in yield. The pyranoside epimers were separated by flash chromatography, and **22a** was reduced with $LiAlH_4$ to give the targeted calicheamicin amino sugar **6** ($[\alpha]^{23}_D$ −56.7° (*c* 0.90, $CHCl_3$), the optical rotation of which was in excellent agreement with literature values (lit.[11b] $[\alpha]^{23}_D$ −56.7° (*c* 1.0, $CHCl_3$); lit.[11c] $[\alpha]^{26}_D$ −56.8°(*c* 1.4, $CHCl_3$)). Amino sugar **6** was further characterized by N-acetylation, which provided **23** ($[\alpha]^{23}_D$ −99.0° (*c* 0.65, $CHCl_3$); lit.[11a] $[\alpha]^{20}_D$ −96° (*c* 0.9, $CHCl_3$); lit.[11b] $[\alpha]^{25}_D$ −99° (*c* 0.96, $CHCl_3$); lit.[11c] $[\alpha]^{25}_D$ -98° (*c* 0.4, $CHCl_3$)).

(16) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

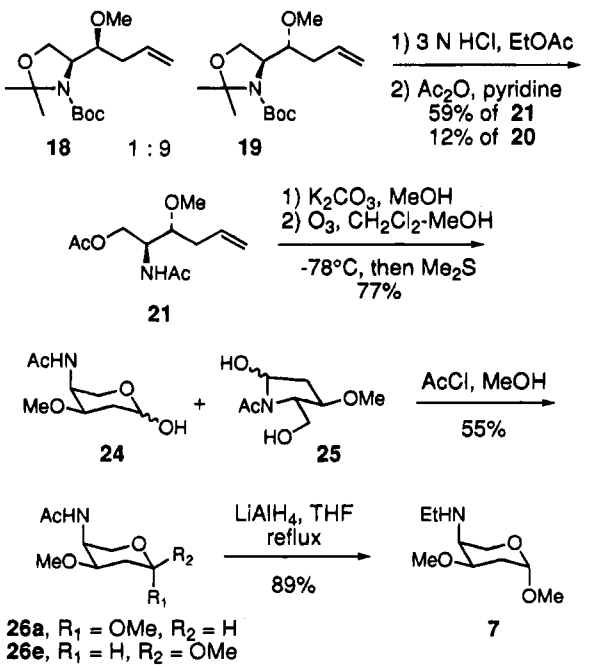
(17) Compounds **14** and **15** have been synthesized with Δ98% de by the enantioselective allylation of **8** with a chiral allyltitanium reagent: Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

(18) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636 and references cited therein.

(19) These values imply that the matched and mismatched double asymmetric reactions of 86% ee L-**8** should provide 10:90 and 85:15 mixtures of **14** and **15**, respectively.

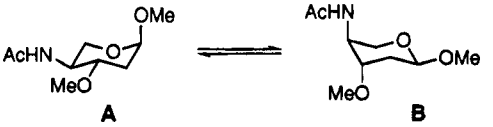


The *erythro* amino sugar diastereomer **7** was synthesized by an analogous procedure starting from an inseparable 9:1 mixture of methyl ethers **19** and **18** (prepared in turn by O-methylation of a 9:1 mixture of **15** and **14**). One difference is that the ozonolysis of **21** provided a mixture of pyranose (**24**) and furanose (**25**) anomers. The reaction of this mixture with acetyl chloride in MeOH was accompanied by substantial color formation and poor yields, especially at long reaction times, which we interpreted as evidence for acid-catalyzed dehydration and elimination of methanol from **25**, leading to an unstable 2-(hydroxymethyl)pyrrole derivative (known to oligomerize in acidic solution).[20] Nevertheless, a 55% yield of a ca. 3:1 mixture of methyl pyranoside anomers **26a,e** was obtained from the **24/25** mixture as long as the reaction was carefully monitored. Elaboration of **26** to **7** proceeded smoothly.



^{1}H NMR analysis of the methyl pyranosides **22** and **26** provided some surprises. We expected to observe large diaxial coupling constants (on the order of 10 Hz) for $J_{2a,3}$, $J_{3,4}$, and $J_{4,5a}$ for **22a**. However, the largest vicinal coupling constant observed in either $CDCl_3$ or C_6D_6 solution at 23 °C was 6.5 Hz. This suggested that amino sugar **22a** exists as a dynamic mixture of two conformers, **A** and **B**, which interconvert rapidly on the NMR time scale, leading to averaged J values for all signals. In d_6-DMSO, however, the expected large diaxial coupling constants are observed, suggesting that conformer **A** is the dominant species under these conditions. Evidently, hydrogen bonds between d_6-DMSO and the equatorial acetamide N−H stabilize conformation **A** relative to **B** which has a more hindered axial acetamide substituent.[21]

Conformational Analysis of 22a



	J values (Hz, 23°C)	
Spin System	C_6D_6	d_6-DMSO
H1-H2e	3.0	3.0
H1-H2a	6.2	3.2
H2e-H2a	13.7	13.2
H2e-H3	4.0	4.3
H2a-H3	6.5	9.7
H3-H4	6.2	9.1
H4-H5e	3.5	4.8
H4-H5a	5.7	9.4
H5e-H5a	11.0	11.3

The observation that **22a** did not preferentially adopt conformation **A** in nonpolar solvents was surprising. Conformer **A** should be stabilized by an anomeric effect (ca. −1.7 kcal/mol)[22] and destabilized by an interaction between the equatorial substituents at C3 and C4 (expected to be between 0.5−1.5 kcal/mol).[23] Conformer **B** should be destabilized by the axial orientation of the substituents at C3 and C4: the *A* value for the acetamido group is 1.6,[24] and the *A* value for the methoxy group is 0.8.[23] Together, these steric and stereoelectronic interactions indicate that conformer **A** should predominate by a significant amount over conformer **B**. However, analysis of the H4−H5 coupling constants indicate that **22a**

(20) Dolphin, D. *The Porphyrins*; Academic Press: New York, 1978; Vol. I, Part A, pp 85−99 and references therein.

(21) The chemical shift of the amide NH in d_6-DMSO is significantly downfield (δ 7.9) compared to the NH chemical shift in C_6D_6 (δ 6.0), suggesting that the amide proton is strongly hydrogen-bonded by d_6-DMSO as compared to C_6D_6; see: Friebolin, G. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH: New York, 1991; p 45.

(22) Juaristi, E.; Cuevas, G *Tetrahedron* **1992**, *48*, 5019.

(23) Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765.

(24) (a) Bernet, B.; Piantini, U.; Vasella, A. *Carbohydr. Res.* **1990**, *204*, 11. (b) The gauche effect also plays an important role in the conformational analysis of δ-lactams: Boudreault, N.; Ball, R. G.; Bayly, C.; Bernstein, M. A.; Leblanc, Y. *Tetrahedron* **1994**, *50*, 7947.

(25) This analysis follows that described by Bernet and Vasella.[23a] Assuming that only chair conformations are involved in the conformational equilibrium, and taking 10.5 Hz and 2.1 Hz as limiting values for J_{aa} and J_{ee}, then the percent of the conformations containing an equatorial acetamide group, x, can be determined as follows:

$$J_{4,5a} = (x)J_{aa} + (1 - x)J_{ee}$$

$$J_{4,5a} = x(10.5) + (1 - x)(2.1)$$

$$x = (J_{4,5a} - 2.1)/8.4 = \%\ \text{conformation with equatorial NHAc}$$

(a) Methyl pyranoside **22a** shows a 5.7 Hz coupling constant between H4 and H5a. This implies that x = 43% and the ratio **A**:**B** is 43:57. (b) Pyranoside **22e** shows a 4.0 Hz coupling constant between H4 and H5a. Thus, x = 23%, and the ratio of **C**:**D** is 23:77. (c) Pyranoside **26a** shows a 3.8 Hz coupling constant between H4 and H5a. Thus, x = 20% and the ratio of **E**:**F** is 20:80.

exists as a ca. 2:3 ratio of the two conformations, with **B** predominating.[25] Clearly, some other factors must be contributing to the surprising stability of conformer **B**.

Bernet and Vasella have analyzed the gauche effect of 3-acetamidotetrahydropyran **27** by ^{1}H NMR spectroscopy.[24a] They found that **27b** was the more stable conformer at room temperature in non-hydrogen-bonding solvents (58% in CD_2Cl_2). The stability of this conformation was attributed to the gauche interaction highlighted by bold bonds in **27b**.[26] The magnitude of this gauche interaction varies with solvent and concentration; for a dilute solution of **27** in CD_2Cl_2 it is −1.7 kcal/mol. An analogous gauche interaction in compound **22a** may be partially responsible for the increased stability of conformer **B** over conformer **A**. In addition, conformer **B** may be further stabilized by an electrostatic effect, since when the methoxy and acetamide groups are axial as in **B**, the dipoles associated with the C3−O and C4−N bonds are anti-parallel. However, these bond dipoles should interact strongly, particularly in nonpolar solvents, when both substituents are equatorial as in conformation **A**.

27a **27b**

Analysis of J data obtained for pyranosides **22e** and **26a** indicates that conformations **D** (for **22e**)[25b] and **F** (for **26a**)[25c] with axial acetamide groups are the most stable for these compounds as well. Large axial−axial coupling constants are not observed for **22e** in C_6D_6, indicating that conformer **D** is at least as stable as conformer **C** in this solvent. In fact, the observed H4−H5a coupling constant corresponds to a **C**:**D** ratio of 23:77.[25b] This is most surprising in the case of **22e**, since a 1,3-diaxial interaction exists between the two axial methoxyl groups in **D**. In d_6-DMSO, however, three large coupling constants are observed, indicating that the relative stability of conformers **C** and **D** invert due to the ability of the less hindered equatorial acetamido substituent in **C** to hydrogen bond to solvent. For compound **26a**, the coupling constants do not change dramatically in C_6D_6 versus d_6-DMSO, indicating that conformer **F** is the more stable conformer in both solvents.[25c]

MMX calculations were performed to estimate the heats of formation, and hence the equilibrium composition, for the mixture of conformers for each of the three diastereomeric methyl pyranosides **22a**, **22e**, and **26a** (Table 1).[27] In every case, the expected equilibrium mixture, calculated from the MMX-derived $\Delta H°$ values, correlate fairly well with the experimentally determined values derived from the J analysis.[25] This lends further support to our conclusion that conformations **B** (for **22a**), **D** (for **22e**), and **F** (for **26a**) with axial acetamide substituents are the most stable in nonpolar, non-hydrogen bonding solvents. However, this conformational problem is unique to the N-acetate derivatives, since the secondary amine **6** appears to exist exclusively in a conformation corresponding to **A**.

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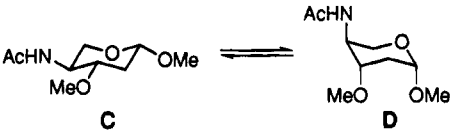
(27) PCModel Molecular Modeling Software from Serena Software, Bloomington, IN, was used for these calculations. For a discussion of the MMX enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McElvey, J. In *Advances in Molecular Modeling*; Liotta, D., Ed.; JAP Press: Greenwich, CT, 1990; Vol. 2.

Table 1. MMX Calculations for Conformers A−F

compd	conformer	MMX ΔH_f	$\Delta H°$ (kcal/mol)	expected ratio[a]	obsd ratio[b]
22a	**A**	−183.94	0.06	47:53 (**A**:**B**)	43:57 (**A**:**B**)
	B	−184.00			
22e	**C**	−182.51	1.06	22:78 (**C**:**D**)	23:77 (**C**:**D**)
	D	−183.57			
26a	**E**	−183.89	1.18	10:90 (**E**:**F**)	20:80 (**E**:**F**)
	F	−185.07			

[a] Calculated from $\Delta H°$ (23 °C). [b] Determined from ^{1}H NMR analysis.[25]

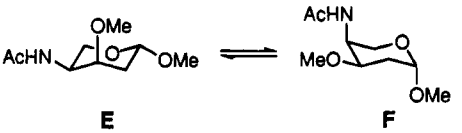
Conformational Analysis of 22e



C **D**

Spin System	J values (Hz, 23°C) C_6D_6	d_6-DMSO
H1-H2e	4.0	2.4
H1-H2a	3.2	8.3
H2e-H3	4.3	4.8
H2a-H3	4.6	9.7
H3-H4	n.d.	n.d.
H4-H5e	2.7	4.6
H4-H5a	4.0	9.1

Conformational Analysis of 26a



E **F**

Spin System	J values (Hz, 23°C) C_6D_6	d_6-DMSO
H1-H2e	3.5	3.0
H1-H2a	3.2	3.0
H2e-H3	4.6	3.5
H2a-H3	9.7	10.7
H3-H4	3.8	4.3
H4-H5e	4.0	2.4
H4-H5a	3.8	3.8

Summary

In conclusion, syntheses of the calicheamicin amino sugar **6** and its erythro diastereomer **7** have been completed by a sequence involving the asymmetric allylboration of N-Boc-serinal acetonide L-**8** and the tartrate ester modified allylboronates (*R*,*R*)-**9** and (*S*,*S*)-**9**, respectively. Although the reactions of (*R*,*R*)-**9** and (*S*,*S*)-**9** with L-**8** were not as diastereoselective as hoped for at the outset because of the low enantiomeric purity of **8** (86−87% ee), data are provided indicating that these reactions should be highly diastereoselective if performed with enantiomerically pure aldehyde. The two diastereomeric homoallylic alcohols, **14** and **15**, are easily elaborated into the targeted amino sugars **6** and **7**. The intermediate methyl pyranosides **22a** and **22e** were shown to adopt preferentially the unexpected conformations **B** and **D** in nonpolar solvents, while the expected conformations **A** and **C** were strongly favored in d_6-DMSO. Finally, the syntheses of **6** and **7** reported herein should facilitate the design and synthesis of analogs of the calicheamicin aryl tetrasaccharide **3** which should prove useful in further analysis and applications of oligosaccharides as DNA binders.

Experimental Section

General. All reactions were conducted in flame-dried glassware under dry argon or nitrogen. All solvents except DMF and pyridine were purified before use: diethyl ether, THF, and toluene were distilled from sodium benzophenone ketyl; dichloromethane and triethylamine were distilled from CaH_2, and methanol was distilled from magnesium turnings. Commercial samples of DMF and pyridine were used as received.

^{1}H NMR spectra were measured at 400 MHz on a Varian VXR-400 instrument. Chemical shifts are reported in δ units; coupling constants are reported in Hz. Residual chloroform (δ 7.26), benzene (δ 7.15), DMSO (δ 2.49), and methanol (δ 3.30) were used as internal references for spectra measured in these solvents. ^{13}C NMR spectra were measured at 100.6 MHz on the Varian VXR-400 instrument, and residual chloroform (δ 77.0), benzene (δ 128.0), DMSO (δ 43.0), and methanol (δ 49.0) were used as internal references for spectra measured in these solvents. High-resolution mass spectra were measured at 70 eV on a Kratos GC/MS 80 RFA mass spectrometer at the Indiana University Mass Spectrometry Laboratory. Optical rotations were measured on a Rudolph Autopol III polarimeter using a quartz cell with 1 mL capacity and a 10 cm path length. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ.

GC analyses were performed with a Shimadzu GC-9A instrument equipped with a 50 m × 0.25 mm Bonded FSOT Carbowax 20M column. Analytical HPLC was performed with a system composed of a Waters 6000A solvent delivery system, a Waters R401 differential refractometer, and a Shimadzu CR601 recorder. Analytical TLC was performed with the use of plates coated with a 0.25 mm thickness of silica gel containing PF254 indicator (Analtech); compounds were visualized with UV light, iodine, *p*-anisaldehyde, ceric ammonium molybdate, or ninhydrin stain. Preparative TLC was performed by using 20 cm × 20 cm plates coated with a 0.50 mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still[28] with Kieselgel 60 (230–400 mesh).

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-serinol (13).** A solution of methyl ester **12**[13] (12.0 g, 46.4 mmol) in 200 mL of Et_2O was added to a suspension of $LiAlH_4$ (3.5 g, 93 mmol) in 200 mL of Et_2O. The mixture was stirred for 1 h, at which point the reaction was complete by TLC analysis (3:2 hexanes–EtOAc, ninhydrin stain). The reaction mixture was cooled to 0 °C and quenched by slow addition of 3.5 mL of H_2O, 3.5 mL of 15% NaOH, and then 10.5 mL of H_2O. This mixture was stirred for 1 h at room temperature and then filtered. The solids were washed generously with Et_2O, and the filtrate was concentrated in vacuo to yield 10.2 g (96%) of the known[13] alcohol **13** as a pale yellow oil. This material was used in the next step without further purification; however, it may be purified by flash chromatography, eluting with 3:2 hexanes–EtOAc: ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 4.58 (t, 5.6 Hz, 1 H), 3.94–3.84 (m, 2 H), 3.80–3.76 (m, 1 H), 3.55 (p, 5.1 Hz, 1 H), 3.24 (dq, 6.2, 10.2 Hz, 1 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 9 H).

1,1-Dimethylethyl 4-Formyl-(*S*)-2,2-dimethyl-3-oxazolidinecarboxylate (8). To a solution of oxalyl chloride (4.7 mL, 54 mmol) in 100 mL of CH_2Cl_2 at −78 °C was added DMSO (6.4 mL, 90 mmol) dropwise via syringe.[29] The resulting solution was stirred for 5 min at −78 °C; then a solution of **13** (10.3 g, 45 mmol) in 100 mL of CH_2Cl_2 was added via cannula. The reaction mixture was stirred for 15 min at −78 °C, and then Et_3N (25 mL, 180 mmol) was added and the solution was allowed to warm to room temperature. The reaction was quenched by addition of 200 mL of saturated $NaHCO_3$ and then diluted with 200 mL of Et_2O. The phases were separated, and the organic phase was washed with 2 × 100 mL of 1 M $NaHSO_4$, 100 mL of saturated $NaHCO_3$, and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 9.07 g (88%) of the known aldehyde **8**:[13] ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 9.52 (d, 2.2 Hz, 1 H), 4.34 (dq, 3.5 Hz, 2.2 Hz, 1 H), 4.05 (m, 2 H), 1.55 (s, 3 H), 1.50 (s, 3 H), 1.40 (s, 9 H).

Determination of Enantiomeric Purity of 8. Aldehyde **8** was reduced with $NaBH_4$ to alcohol **13** as described,[13] and Mosher ester derivatives of **13** were prepared following the standard literature procedure.[30] The ^{1}H NMR spectra of the Mosher esters were measured at 80 °C in d_6-DMSO since at room temperature the spectra showed doubling of resonances because of restricted rotation about the amide bond.

Data for the (*R*)-MTPA: ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 7.45 (s, 5 H), 4.47 (dd, J = 3.2, 10.4 Hz, 1 H), 4.28 (br t, J = 7.2 Hz, 1 H), 4.06 (br s, 1 H), 3.95 (dd, J = 6.0, 10.0 Hz, 1 H), 3.68 (dd, J = 2.4, 9.2 Hz, 1 H), 3.47 (s, 3 H), 1.43 (s, 9 H), 1.42 (s, 6 H).

Data for the (*S*)-MTPA: ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 7.46 (s, 5 H), 4.45 (dd, J = 3.5, 10.7 Hz, 1 H), 4.27 (br t, J = 7.3 Hz, 1 H), 4.08 (br s, 1 H), 3.97 (dd, J = 5.9, 9.1 Hz, 1 H), 3.72 (dd, J = 2.2, 9.4 Hz, 1 H), 3.49 (s, 3 H), 1.42 (s, 9 H), 1.40 (s, 3 H), 1.37 (s, 3 H).

***tert*-Butyl (4*S*,1′*S*)-2,2-Dimethyl-4-(1′-hydroxy-3′-butenyl)oxazolidine-3-carboxylate (14).** A solution of aldehyde **8** (1.01 g, 4.4 mmol) in 10 mL of toluene was stirred over 200 mg of crushed, activated 4 Å sieves for 15 min at room temperature and then cooled to −78 °C. Toluene (20 mL) was dried for 15 min over 400 mg of crushed 4 Å sieves, and then (*R*,*R*)-**9** (2.5 mL, 8.8 mmol, crude reagent[14b]) was added and the solution was stirred for 15 min at room temperature and then cooled to −78 °C. The −78 °C solution of **8** was added dropwise to the −78 °C solution of (*R*,*R*)-**9** via cannula, and the resulting reaction mixture was stirred at −78 °C overnight (approximately 20 h). A trace of starting material still remained by TLC analysis (5:1 hexanes:EtOAc, *p*-anisaldehyde stain). The reaction was quenched by rapid addition of 1 M NaOH (25 mL) via syringe; then the solution was allowed to warm to room temperature and was stirred for 30 min. The reaction mixture was diluted with 20 mL of EtOAc, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to a pale yellow oil. The crude product was purified by flash chromatography, eluting with 5:1 hexanes–EtOAc, to give 916 mg (77%) of a colorless oil consisting of an 89:11 mixture of **14**:**15** according to capillary GC analysis [GC (200 °C/20 min) t_R **14** = 9.43 min, t_R **15** = 9.68 min]. The two isomers did not separate by TLC or analytical HPLC (2:1 hexanes:EtOAc, t_R 10.2 min). Physical and spectral data are for a 9:1 mixture of **14** and the *anti* diastereomer **15**: R_f 0.20 (4:1 hexanes–EtOac); $[\alpha]^{23}_D$ −37.2° (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 5.94–5.80 (m, 1 H), 5.09–4.95 (m, 2 H), 4.55–4.48 (m, 1 H), 4.03–3.92 (m, 1 H), 3.92–3.83 (m, 3 H), 2.21–1.98 (m, 2 H), 1.51–1.37 (5 s, 15 H); ^{13}C NMR (400 MHz, d_6-DMSO, 80 °C) δ 134.6 134.5, 117.5, 94.2, 94.0, 81.2, 73.0, 64.5, 61.6, 38.8, 38.7, 28.3, 27.1, 26.6, 24.4, 24.2; IR (neat) 3500–3400, 2900, 2700, 1700, 1670, 1600, 1590, 1400, 1360, 1260, 1205, 1175, 1110, 1090, 1065, 850; high-resolution mass spectrum calcd for $C_{14}H_{26}NO_4$ *m*/*e* 272.1855, found 272.1866. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29. Found: C, 62.27; H, 9.04.

***tert*-Butyl (4*S*,1′*R*)-2,2-Dimethyl-4-(1′-hydroxy-3′-butenyl)oxazolidine-3-carboxylate (15).** The asymmetric allylboration of **8** (0.99 g, 4.4 mmol) with (*S*,*S*)-**9**[14b] was performed as described for the preparation of **14**, with the exception that the reaction was performed in Et_2O rather than toluene. The crude product was purified by flash chromatography, eluting with 8:1 hexanes–EtOAc, to give 993 mg (84%) of a 90:10 mixture of **15**:**14** (inseparable) according to capillary GC analysis. Physical and spectral data are for the inseparable 9:1 mixture of **15** and the *syn* diastereomer **14**: R_f 0.20 (4:1 Hex–EtOAc); $[\alpha]^{23}_D$ −22.9° (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 5.90–5.85 (m, 1 H), 5.06–4.97 (m, 2 H), 4.51–4.49 (m, 1 H), 4.00–3.96 (m, 1 H), 3.88–3.80 (m, 1.4 H), 3.72–3.67 (m, 1.7 H), 2.40–2.00 (m, 2.2 H), 1.51–1.38 (5s, 15 H); ^{13}C NMR (400 MHz, d_6-DMSO, 80 °C) δ 151.5, 135.7,

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115.5, 92.8, 78.7, 69.6, 69.0, 63.1, 62.7, 60.6, 38.3, 27.7, 26.2, 23.7; IR (neat) 3520–3400, 2980, 2940, 2880, 1700, 1400–1350, 1205, 1170, 1100, 1055, 1050; high-resolution mass spectrum calcd for $C_{14}H_{26}NO_4$ m/e 272.1855, found 272.1862. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 62.06; H, 9.42; N, 5.13.

***tert*-Butyl (4*S*,1′*S*)-2,2-Dimethyl-4-(1′-methoxy-3′-butenyl)oxazolidine-3-carboxylate (18).** To a 0 °C suspension of NaH (240 mg of a 60% dispersion in oil, 6 mmol; prewashed with dry hexanes and dried under vacuum for several min) in 15 mL of DMF was added dropwise via cannula a solution of an inseparable mixture of **14** and **15** (808 mg, 3 mmol of a ca. 9:1 mixture of **14**:**15**) in 5 mL of DMF. The reaction mixture was stirred for 5 min at 0 °C, methyl iodide (0.4 mL, 6 mmol) was added, and the mixture was allowed to warm to room temperature. The reaction mixture was stirred for 4 h and then cooled to 0 °C and quenched by slow addition of 20 mL of H_2O. The reaction mixture was diluted with 25 mL of EtOAc, and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with half-saturated brine solution (20 mL), dried over $MgSO_4$, and concentrated to a yellow liquid. The crude product was purified by flash chromatography, eluting with 12:1 hexanes–EtOAc, to give 709 mg (83%) of a ca. 9:1 mixture of **18** and its *anti* diastereomer **19** as colorless liquid. This mixture was also inseparable by TLC and HPLC. Physical and spectral data are for a ca. 9:1 mixture of **18**:**19**: R_f 0.24 (10:1 hexanes–EtOAc); $[\alpha]^{23}_D$ −25.5° (*c* 0.93, $CHCl_3$); ^1H NMR (400 MHz, d_6-DMSO, 80 °C) δ 5.90–5.80 (m, 1 H), 5.08–4.99 (m, 2 H), 4.08 (dd, J = 4.8, 9.2 Hz, 1 H), 3.93–3.80 (m, 2 H), 3.57–3.53 (br p, 1 H). 3.31–3.30 (2 s, 3 H), 2.27–2.21 (m, 1 H), 2.14–2.05 (m, 1 H), 1.59–1.39 (5s, 15 H); ^{13}C NMR (400 MHz, d_6-DMSO, 80 °C) δ 135.7, 115.7, 93.1, 79.4, 79.0, 62.7, 57.2, 56.7, 32.9, 25.9; IR (neat) 2850, 2650, 1700, 1600, 1590, 1360–1390, 1260, 1170, 1100; high-resolution mass spectrum, calcd for $C_{15}H_{28}NO_4$ m/e 286.2011, found 286.1992. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54. Found: C, 63.40; H, 9.31.

(2*S*,3*S*)-1-Acetoxy-2-acetamido-3-methoxyhex-5-ene (20). A mixture of methyl ether **18** and **19** (1.17 g, 4.1 mmol of a ca. 9:1 mixture of **18**:**19**) in 2 mL of EtOAc and 2 mL of 3 N HCl was stirred vigorously overnight (approximately 20 h) and then concentrated to a thick, colorless oil by rotary evaporation. This material was dried under reduced pressure until it became a solid, and then it was triturated with hexanes to yield 608 mg (81%) of a white solid consisting of a ca. 9:1 mixture of amine hydrochlorides deriving from **18** and **19**, respectively. This solid was recrystallized from EtOAc before the next step (the diastereomers do not separate at this stage). Physical and spectral data are for a ca. 9:1 mixture of the two disatereomeric salts: $[\alpha]^{23}_D$ 48.1° (*c* 0.37, $CHCl_3$); mp 80–82 °C; ^1H NMR (400 MHz, CD_3OD) δ 5.90–5.79 (m, 1 H), 5.23–5.13 (m, 2 H), 3.85 (dd, J = 4.0, 11.6 Hz, 0.3 H), 3.76 (dd, J = 4.0, 12.0 Hz, 1 H) 3.61 (dd, J =6.0, 12.0 Hz, 1.2 H), 3.54–3.39 (m, 4.3 H), 2.82 (ddd, J = 4.0, 6.0, 10.0 Hz, 1 H), 2.36–2.29 (m, 1 H), 2.26–2.18 (m, 0.4 H); ^{13}C NMR (400 MHz, $CDCl_3$ δ 132.0, 119.1, 74.4, 58.8, 57.6, 56.3, 33.4; IR (neat) 3490–2760, 1610, 1590, 1500, 1470, 1100, 1060; high-resolution mass spectrum calcd for $C_7H_{16}NO_2$ ($M^+ - {}^{35}Cl$) m/e 146.1182, found 146.1177. Anal. Calcd for $C_7H_{16}NO_2Cl$: C, 46.27; H, 8.89. Found: C, 46.49; H, 8.79.

To a solution of the amine hydrochloride prepared in the preceeding step (584 mg, 3.2 mmol of a ca. 9:1 mixture of diastereomers) in 5 mL of dry pyridine was added acetic anhydride (1.8 mL, 19.2 mmol). The reaction mixture was stirred overnight, then diluted with EtOAc and washed with 1 M $KHSO_4$ and saturated $NaHCO_3$. The aqueous washes were extracted with EtOAc (2 × 30 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was diluted with heptane and concentrated to remove pyridine. The resulting yellow oil was purified by flash chromatography, eluting with 1:1 hexanes–EtOAc, to yield 531 mg of the major (*syn*) diastereomer **20** (73%) and 51 mg (7%) of the minor (*anti*) diastereomer **21**, both as colorless, sticky oils (80% overall yield). Data for **20**: R_f 0.36 (1:1 hexanes–EtOAc); $[\alpha]^{23}_D$ 7.5° (*c* 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.83–5.70 (m, 2 H), 5.15–5.09 (m, 2 H), 4.29 (ddt, J = 7.3, 1.4, 9.1 Hz, 1 H), 4.10 (dq, J = 7.3, 11.0 Hz, 2 H), 3.39 (s, 3 H) 3.29 (ddd, J = 1.4, 7.8, 5.6 Hz, 1 H), 2.41–2.34 (m, 1 H), 2.19–2.12 (m, 1 H), 2.06 (s, 3 H) 2.00 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.9, 169.9, 133.4, 118.4, 79.0, 63.7, 58.2, 49.8, 34.9, 23.3, 20.9; IR (neat) 3600–3100, 2960–2860, 1730, 1715, 1670–1610, 1540–1500, 1355, 1220, 1080; high-resolution mass spectrum calcd for $C_{11}H_{20}NO_4$ m/e 230.1387, found 230.1387. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35. Found: C, 57.36; H, 8.21.

Methyl 2,4-Dideoxy-4-acetamido-3-*O*-methyl-L-*threo*-pentopyranoside (22). A solution of **20** (767 mg, 3.36 mmol) and ca. 50 mg of K_2CO_3 in 5 mL of MeOH was stirred at room temperature for 3 h until the reaction was judged complete by TLC analysis (10:1 CH_2Cl_2–MeOH, ceric ammonium molybdate stain). The solids were removed by filtration, and the filtrate was stirred over Dowex H^+ resin for 5 min. The resin was filtered off and washed liberally with MeOH, and the filtrate was concentrated to yield (2*S*,3*S*)-1-hydroxy-2-acetamido-3-methoxyhex-5-ene as a yellow oil that was used in the next step without further purification. This intermediate can be purified by flash chromatography, eluting with EtOAc: R_f 0.18 (10:1 CH_2Cl_2–MeOH); $[\alpha]^{23}_D$ 27.4° (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (br d, 1 H), 5.83–5.73 (m, 1 H), 5.14–5.08 (m, 2 H), 4.09–4.03 (m, 1 H), 3.74 (dd, J = 5.4, 11.0 Hz, 1 H) 3.65 (dd, J = 5.6, 11.0 Hz, 1 H) 3.51–3.48 (m, 1 H), 3.41 (s, 3 H). 2.79 (br s, 0.8 H), 2.43–2.36 (m, 1 H), 2.24–2.16 (m, 1 H), 2.03 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.9, 133.4, 118.3, 80.4, 64.6, 57.9, 52.7, 34.9, 23.3; IR (neat) 3520–3160, 2910, 1650, 1555–1520, 1450, 1370, 1090; high-resolution mass spectrum calcd for $C_9H_{18}NO_3$ m/e 188.1282, found 188.1284.

A solution of the alcohol prepared in the preceding step in 9 mL of 2:1 CH_2Cl_2–MeOH was cooled to −78 °C. A stream of O_3 in O_2 was bubbled through this solution until it turned blue, and then the solution was flushed with N_2 for 5 min. Dimethyl sulfide (0.62 mL, 8.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred overnight and then concentrated in vacuo to a yellow oil. The crude product was purified by flash chromatography, eluting with a gradient of CH_2Cl_2 to 9:1 CH_2Cl_2–MeOH, to yield 539 mg (85% for two steps) of 2,4-dideoxy-4-acetamido-3-*O*-methyl-L-*threo*-pentopyranose as a white solid: R_f 0.30 (9:1 CH_2Cl_2–MeOH); mp 123–24 °C; $[\alpha]^{23}_D$ −0.6° (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (br d, 1 H), 5.12–5.04 (m, 1 H), 4.85 (br d, 0.5 H), 4.40 (m, 0.6 H), 4.10–3.99 (m, 1.1 H), 3.96–3.90 (m, 0.5 H), 3.70–3.57 (m, 1.6 H), 3.50 (s, 1.4 H), 3.46–3.38 (m, 2 H), 2.02 (s, 3 H), 1.98–1.84 (m, 1.1 H), 1.81–1.73 (m, 0.5 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.9, 92.6, 75.4, 63.5, 56.6, 46.7, 33.5; IR (neat) 3500–3220, 2940, 1660, 1560, 1450, 1380, 1320, 1160, 1130, 1100, 1025, 950; high-resolution mass spectrum, calcd for $C_8H_{16}NO_4$: m/e 190.1075, found 190.1076. Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99. Found: C, 51.00; H, 7.82.

To a 0 °C solution of acetyl chloride (215 μL, 3.0 mmol) in 0.5 mL of dry methanol was added a solution of the above pyranose (124 mg, 0.66 mmol) in 0.5 mL of dry methanol. The mixture was stirred for 30 min at 0 °C and for 1 h at room temperature and then diluted with 5 mL of EtOAc and extracted with 2 mL of saturated $NaHCO_3$ solution. The aqueous phase was extracted with additional EtOAc (3 × 5 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to a red oil. This oil was purified by flash chromatography, eluting with 95:5 EtOAc–MeOH, to yield 83 mg (62%) of **22a** and 13 mg of **22e**, both as white solids (72% overall yield).

Data for **22a**: R_f 0.29 (95:5 EtOAc–MeOH); mp 100–103 °C; $[\alpha]^{23}_D$ −73.8° (*c* 0.42, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 5.90, (br s, 1 H), 4.52 (dd, J = 3.0, 6.2 Hz, 1 H), 4.18–4.05 (m, 1 H), 3.92 (dd, J = 3.5, 10.7 Hz, 1 H), 3.42 (ddd, J = 6.2, 6.2, 4.0 Hz, 1 H), 3.15 (dd, J = 11.0, 5.4 Hz, 1 H), 3.20 (s, 3 H) 3.05 (s, 3 H), 1.78 (ddd, J = 13.7, 4.0, 3.0 Hz, 1 H), 1.64 (ddd J = 13.7, 6.5, 6.2 Hz, 1 H), 1.42 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.8, 99.3, 75.4, 62.8, 55.8, 53.8, 47.8, 33.0, 23.4; IR (neat) 3060, 3000, 1680, 1515, 1430, 1280, 1135, 1055, 750, 720; high-resolution mass spectrum calcd for $C_9H_{18}NO_4$ m/e

204.1231, found 204.1218. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43. Found: C, 53.16; H, 8.41.

Data for **22e**: R_f 0.25 (95:5 EtOAc–MeOH); mp 155–157 °C; $[\alpha]^{23}_D$ +99.1° (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 5.90 (br s, 1 H) 4.55 (dd, J = 3.2, 4.0 Hz, 1 H), 4.28 (dd, J = 2.7, 11.8 Hz, 1 H), 3.94 (m, 1 H), 3.43–3.39 (m, 7 H), 3.28 (dd, J = 11.8, 4.0 Hz, 1 H), 2.05–1.99 (m, 4 H) 1.80 (dt, J = 4.0, 14.5 Hz, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.8, 98.5, 75.3, 59.3, 56.8, 55.9, 47.0, 31.1, 23.4; IR (neat) 3280, 3090, 2960, 2940, 2840, 1650, 1560, 1410, 1375, 1150, 1100, 1055, 950; high-resolution mass spectrum calcd for $C_9H_{18}NO_4$ *m/e* 204.1231, found 204.1246. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 52.98; H, 8.47; N, 6.66.

Methyl 2,4-Dideoxy-4-(ethylamino)-3-*O*-methyl-L-*threo*-pentopyranoside (6). To a suspension of $LiAlH_4$ (34 mg, 0.88 mmol) in 1 mL of THF was added a solution of methyl pyranoside **22a** (90 mg, 0.44 mmol) in 1 mL of THF. The mixture was heated to reflux and stirred for 12 h at this temperature, at which point another 25 mg of $LiAlH_4$ was added. The mixture was stirred for one more hour at reflux and then cooled to room temperature and quenched by addition of 60 μL of H_2O, 60 μL of 15% NaOH solution, and 180 μL of H_2O. The mixture was stirred for 45 min and then filtered. The solid white residue was washed liberally with cold Et_2O and then hot $CHCl_3$. The filtrate was dried over $MgSO_4$, filtered, and concentrated to a colorless oil (83 mg, 99%) which was used in the next step without further purification. This oil was purified by flash chromatography, eluting with 9:1 CH_2Cl_2–MeOH, to yield 67 mg (75%) of the known[11b,c] pyranoside **6** as a colorless oil: R_f 0.29 (9:1 CH_2Cl_2–MeOH); $[\alpha]^{23}_D$ −56.7° (*c* 0.90, $CHCl_3$) (lit.[11b] $[\alpha]^{23}_D$ −56.7° (*c* 1.0, $CHCl_3$), lit.[11c] $[\alpha]_D^{26}$ −56.8° (*c* 1.4, $CHCl_3$)); ^{1}H NMR (400 MHz, C_6D_6) δ 4.66 (dd, J = 2.2, 3.5, 1 H), 3.80 (dd, J = 4.6, 11.0, 1 H), 3.58 (dd, J = 9.9, 11.0, 1 H), 3.54 (ddd, J = 8.9, 4.6, 10.5, 1 H), 3.15 (s, 3 H), 3.03 (s, 3 H) 2.75 (ddd, J = 4.6, 8.9, 9.7, 1 H), 2.52–2.37 (m, 2 H), 2.12 (ddd J = 4.6, 2.2, 12.6, 1 H), 1.48 (ddd J = 3.5, 10.5, 12.6, 1 H), 1.36 (br s, 1 H), 0.92 (t, J = 7, 3 H); ^{13}C NMR (400 MHz, C_6D_6) δ 99.4, 77.5, 62.6, 59.8, 55.6, 54.4, 42.4, 34.2, 15.9; IR (neat) 2980, 2940, 2900, 2830, 1470, 1445, 1375, 1355, 1220, 1200, 1130, 1100, 1050, 990, 960, 900. Anal. Calcd for $C_9H_{19}NO_3$: C, 57.11; H, 10.12; N, 7.40. Found: C, 56.89; H, 10.32; N, 7.09.

Methyl 2,4-Dideoxy-4-(*N*-ethylacetamido)-3-*O*-methyl-L-*threo*-pentopyranoside (23). A solution of amino pyranoside **6** (15 mg, 0.08 mmol) in 0.5 mL of pyridine was treated with acetic anhydride (75 mL, 0.8 mmol) for 18 h at room temperature. The reaction mixture was diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to a yellow oil. The crude product was purified by preparative TLC, eluting with 95:5 EtOAc–MeOH, to yield 15 mg (83%) of the known[11] *N*-acetate derivative **23** as a colorless oil: *Rf* 0.52 (9:1 CH_2Cl_2); $[\alpha]^{23}_D$ −99.0° (*c* 0.65, $CHCl_3$) (lit.[11a] $[\alpha]^{20}_D$ −96° (*c* 0.9, CH_3Cl), lit.[11b] $[\alpha]^{25}_D$ −99° (*c* 0.96, CH_3Cl), lit.[11c] $[\alpha]^{25}_D$ −98° (*c* 0.4, CH_3Cl)). Compound **23** showed two sets of proton and carbon resonances because of restricted rotation about the amide bond: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80–4.77 (m, 1 H) 4.10–4.00, (br s, 0.5 H), 3.90–3.82 (br t, 0.5 H), 3.74–3.26 (m, 10 H), 3.18–3.08 (m, 1 H), 2.40–2.28 (m, 1 H), 2.15 (s, 1.7 H) 2.11 (s, 1.1 H) 1.60–1.48 (m, 1 H), 1.22–1.18 (t, 1.2 H), 1.14–1.10 (t, 1.7 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.4, 170.2, 99.0, 98.9, 72.7, 71.8, 59.9, 59.7, 59.2, 56.5, 55.5, 55.0, 54.8, 36.9, 35.3, 35.2, 22.4, 22.3, 15.4, 14.7; IR (neat) 2920, 1730, 1650–1620, 1420, 1365, 1120, 1100, 995; high-resolution mass spectrum calcd for $C_{11}H_{22}NO_4$ *m/e* 232.1543, found 232.1543. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 56.99; H, 9.36; N, 5.88.

***tert*-Butyl (4*S*,1′*R*)-2,2-Dimethyl-4-(1′-methoxy-3′-butenyl)oxazolidine-3-carboxylate (19).** Methylation of an inseparable 9:1 mixture of **15** and **14** (2.2 g, 8.2 mmol) using NaH (645 mg of a 60% dispersion in oil, 16 mmol; prewashed with hexanes (2×) and dried under vacuum for several min) and MeI (1.0 mL, 16 mmol) in DMF (40 mL total) was performed by using the procedure described for the synthesis of **14**. The crude product was purified by flash chromatography, eluting with 9:1 hexanes–EtOAc, to give 1.81 g (78%) of a colorless liquid consisting of an inseparable 9:1 mixture of **19** and **18** (data obtained on the mixture): R_f 0.24 (10:1 Hex-EtOAc); $[\alpha]^{23}_D$ −39.8° (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, d_6-DMSO, 80 °C) δ 5.92–5.78 (m, 1 H), 5.12–4.98 (m, 2 H), 4.10–4.06 (m, 0.2 H), 3.94–3.79 (m, 3 H), 3.64–3.52 (m, 1 H), 3.30 (s, 3 H), 2.28–2.19 (m, 1 H), 2.16–2.08 (m, 1 H), 1.52–1.38 (5s, 16 H); ^{13}C NMR (400 MHz, d_6-DMSO, 80 °C) δ 134.7, 116.2, 93.0, 78.8, 62.6, 59.1, 57.8, 35.4, 27.7, 27.6, 25.6; IR (neat) 2980, 2930, 1705, 1480, 1460, 1395, 1380, 1370, 1260, 1180, 1100, 920, 860, 770; high-resolution mass spectrum, calcd for $C_{15}H_{28}NO_4$ *m/e* 286.2011, found 286.2008. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.29; H, 9.42; N, 4.71.

(2*S*, 3*R*)-1-Acetoxy-2-acetamido-3-methoxyhex-5-ene (21). A 9:1 mixture of **19** and **18** (1.4 g, 4.9 mmol) in 3 mL of EtOAc and 3 mL of 3 N HCl was stirred vigorously overnight (approxmately 20 h) and then concentrated to a light red oil by rotary evaporation. This oil was dried under reduced pressure for 48 h to yield 815 mg (91%) of a light red syrup, consisting of a ca. 9:1 mixture (inseparable) of (2*S*,3*R*)-1-hydroxy-2-amino-3-methoxyhex-5-ene hydrochloride and its *syn* diastereomer, which was used without further purification. Physical and spectral data are for a ca. 9:1 mixture of the two diastereomeric hydrochlorides: $[\alpha]^{23}_D$ −13.7° (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 5.89–5.79 (m, 1 H), 5.23–5.12 (m, 2 H), 3.84 (dd, J = 4.4, 11.6 Hz, 0.8 H), 3.76 (dd, J = 4.0, 11.6 Hz, 0.2 H) 3.68–3.59 (m, 1.2 H), 3.53 (dt, J = 7.2, 4.0 Hz, 0.8 H), 3.49–3.44 (m, 0.2 H), 3.43–3.39 (2 s, 2.5 H), 3.14 (ddd, J = 3.6, 6.0, 10.0 Hz, 0.3 H), 2.62–2.55 (m, 0.2 H), 2.53–2.45 (m, 0.9 H), 2.36–2.29 (m, 0.3 H); 2.25–2.19 (m, 1 H); ^{13}C NMR (400 MHz, CD_3OD) δ 134.6, 118.9, 80.1, 58.9, 58.4, 56.2, 35.1; IR (neat) 3500–3200, 3100–2800, 1745, 1640, 1600, 1500, 1385, 1360, 1230, 1190, 1100, 1055, 1025, 920, 840; high-resolution mass spectrum calcd for $C_7H_{17}NO_2Cl$ *m/e* 182.0942, found 182.1255.

To a solution of the preceeding amine hydrochloride (453 mg, 2.5 mmol of a ca. 9:1 mixture of diastereomers) in 5 mL of dry pyridine was added acetic anhydride (1.2 mL, 12.5 mmol). The reaction mixture was stirred overnight and then diluted with EtOAc and washed with 1 M $KHSO_4$ and saturated $NaHCO_3$. The aqueous washes were extracted with EtOAc (2 × 30 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was diluted with heptane and concentrated to dryness. The resulting yellow oil was purified by flash chromatography, eluting with 2:1 hexanes–EtOAc, to yield 334 mg (59%) of the major (*anti*) diastereomer **21** and 70 mg (12%) of the minor (*syn*) diastereomer **20**, both as colorless, sticky oils (71% overall yield). Data for **21**: R_f 0.30 (1:1 Hex–EtOAc); $[\alpha]^{23}_D$ −9.8° (*c* 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83–5.72 (m, 1 H), 5.51 (br d, J = 8.9, 1 H), 5.09–4.99 (m, 2 H), 4.54–4.48 (m, 1 H), 4.23 (d, J = 6.2 Hz, 2 H), 3.14 (dt, J = 6.2, 4.8, 1 H), 3.02 (s, 3 H), 2.42–2.17 (m, 1 H), 2.12–2.104 (m, 1 H), 1.69 (s, 3 H) 1.58 (s, 3 H); ^{13}C NMR (400 MHz, C_6D_6) δ 170.5, 168.8, 134.3, 117.7, 81.2, 62.9, 57.5, 50.7, 35.1, 22.9, 20.4; IR (neat) 3600–3200, 3070, 2980, 2930, 2835, 1740, 1660, 1560, 1530, 1435, 1370, 1250–1230, 1140, 1095, 830; high-resolution mass spectrum calcd for $C_{11}H_{20}NO_4$ *m/e* 230.1387, found 230.1391.

Methyl 2,4-Dideoxy-4-(acetamido)-3-*O*-methyl-L-*erythro*-pentopyranoside (26). To a solution of **21** (900 mg, 4.09 mmol) in 5 mL of MeOH was added ca. 100 mg of K_2CO_3. This mixture was stirred at room temperature for about 30 min until the reaction was complete by TLC analysis (10:1 CH_2Cl_2–MeOH, ceric ammonium molybdate stain). The solids were removed by filtration, and the filtrate was stirred over Dowex H^+ resin for 5 min. The resin was filtered off and washed liberally with MeOH, and the filtrate was concentrated to yield 725 mg (91%) of a yellow oil that was used without further purification. This oil can be purified by flash chromatography, eluting with EtOAc, to yield the intermediate primary alcohol as a colorless oil: R_f 0.15 (10:1 CH_2Cl_2–MeOH); $[\alpha]^{23}_D$ −10.0° (*c* 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.37 (br d, J = 5.9, 1 H), 5.81–5.68 (m, 1 H), 5.17–5.08 (m, 2 H), 4.00–3.94 (m, 2 H), 3.60 (dd, J = 4.6, 12.9 Hz, 1 H) 3.53 (dt, J = 6.7, 3.2 Hz, 1 H), 3.39 (s, 3 H), 2.94 (br s, 1

H), 2.52–2.44 (m, 1 H), 2.30–2.20 (m, 1 H), 2.01 (s, 3 H); ^{13}C NMR (400 MHz, C_6D_6) δ 170.1, 133.5, 118.1, 82.9, 61.8, 58.4, 52.0, 35.2, 23.4; IR (neat) 3500–3200, 3070, 2980, 2930, 2830, 1650, 1550, 1435, 1375, 1295, 1100, 1060, 1000, 915; high-resolution mass spectrum calcd for $C_9H_{18}NO_3$ m/e 188.1282, found 188.1285.

A solution of the above alcohol (650 mg, 3.5 mmol) in 4 mL of CH_2Cl_2–MeOH (2:1) was cooled to −78 °C. A stream of O_3 in O_2 was bubbled through this solution until it turned blue, and then the solution was flushed with N_2 for 5 min. Dimethyl sulfide (0.25 mL, 3.5 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The mixture was stirred overnight and then concentrated to a yellow oil. The crude product was purified by flash chromatography, with 9:1 EtOAc–MeOH, to yield 600 mg of a sticky yellow oil (89%) that was determined by ^{1}H NMR spectroscopy to be approximately a 1:2:2.5:5 mixture of the two furanose isomers and the two pyranose isomers, **24**α, **24**β, **25**α, 25β, respectively. Physical and spectral data for this inseparable mixture follow: R_f 0.32 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR (400 MHz, C_6D_6) δ 6.12–6.06 (br d, J = 8.8 Hz, 1 H), 6.02–5.94 (br d, J = 8.4, Hz 1.9 H), 5.77–5.74 (br t, J = 6.0 Hz, 0.4 H), 5.45 (br s, 0.8 H), 5.28–5.25 (m, 1 H), 5.41 (br s, 2 H), 5.02 (br d, J = 7.6 Hz, 1.3 H), 4.92 (br s, 1.3 H), 4.80 (br d, J = 9.6, 0.9 H), 4.70 (br s, 0.5 H), 4.47 (br s, 1.8 H), 4.33 (br t, J = 5.6 Hz, 1.3 H), 4.22 (m, 4.3 H), 3.96–3.81 (m, 7.8 H), 3.68–3.51 (m, 11.6 H), 3.42 (s, 3.7 H), 3.37–3.36 (2s, 9 H), 3.27 (s, 5 H), 2.35–2.29 (m, 0.6 H), 2.25–1.82 (m, 25.7 H), 1.71 (ddd, J = 4.0, 6.0, 14.0 Hz, 2.3 H); ^{13}C NMR (400 MHz, C_6D_6) δ 171.8, 171.5, 170.4, 170.2, 92.5, 91.8, 83.5, 82.4, 82.0, 81.5, 81.1, 76.0, 73.7, 65.7, 64.2, 63.6, 63.2, 62.7, 62.1, 62.0, 60.3, 57.1, 56.8, 56.6, 55.3, 56.2, 46.6, 45.8, 41.5, 39.7, 37.1, 33.3, 32.6, 23.3, 23.2, 22.4, 22.1, 21.6; IR (neat) 3350–3120, 2940, 2840, 1670–1630, 1560–1540, 1450, 1380, 1320, 1295, 1220, 1195, 1090, 1060, 980, 905; high-resolution mass spectrum calcd for $C_8H_{16}NO_4$ m/e 190.1075, found 190.1071.

To a 0 °C solution of acetyl chloride (212 μL, 3.0 mmol) in 6 mL of dry methanol was added a solution of the mixture of **24**α,β–**25**α,β (225 mg, 1.2 mmol) in 0.5 mL of dry methanol. The mixture was stirred for 30 min at 0°C and for 1 h at room temperature and then diluted with 20 mL of EtOAc and quenched with 5 mL of saturated $NaHCO_3$ solution. The aqueous phase was extracted 4 × 10 mL of EtOAc, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to a red oil. This oil was purified by flash chromatography, eluting with 95:5 EtOAc–MeOH, to yield 123 mg (55%) of a ca. 3:1 mixture of **26a** and **26e** and 10 mg (3%) of a mixture of α and β furanosides (58% overall yield). Attempts to separate the mixture of **26a** and **26e** by flash chromatography or by HPLC were unsuccessful. Data for a ca. 3:1 mixture of pyranoside **26a** and **26e**: R_f 0.52 (9:1 EtOAc–MeOH); ^{1}H NMR (400 MHz, C_6D_6) δ 5.80–5.60 (m, 1.3 H) 4.52 (dd, J = 3.5, 3.2 Hz, 1 H), 4.37 (ddd, J = 8.3, 4.0, 3.0 Hz, 1 H), 4.31 (m, 0.3 H), 4.03 (dd, J = 3.3, 6.2 Hz, 0.3 H), 3.83 (dd, J = 5.6, 11.6, 0.3 H), 3.63 (m, 2.2 H) 3.43 (dt, J = 4.6, 9.7 Hz, 1 H), 3.21 (s, 9 H), 3.17–3.15 (m, 1.3 H), 3.11 (s, 3 H), 3.09 (s, 3 H), 2.98–2.90 (m, 0.4 H), 1.82–1.65 (m, 3 H), 1.58 (s, 3 H), 1.50 (s, 0.9 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.0, 99.8, 98.9, 74.9, 73.2, 62.5, 61.9, 55.7, 55.6, 54.9, 46.2, 45.8, 32.8, 22.9, 22.7; IR (neat) 3380–3250, 2930, 2820, 1660–1640, 1550–1530, 1440, 1370, 1205, 1130, 1110, 1100, 1085, 1065, 1040, 875; high-resolution mass spectrum calcd for $C_9H_{18}NO_4$ m/e 204.1231, found 204.1244.

Methyl 2,4-Dideoxy-4-(ethylamino)-3-*O*-methyl-L-*erythro*-pentopyranoside (7). To a solution of methyl pyranosides **31** (30 mg, 0.15 mmol) in 1 mL of THF was added 0.9 mL of a 1.0 M solution of $LiAlH_4$ in THF. The mixture was brought to reflux and stirred for 12 h at this temperature, at which point TLC analysis (95:5 CH_2Cl_2–MeOH, ceric ammonium molybdate stain) showed some starting material still remained. Another 0.9 mL of $LiAlH_4$ solution was added, and the mixture was stirred for 24 h at reflux and then cooled to room temperature and quenched by addition of 70 μL of H_2O, 70 μL of 15% NaOH solution, and then 200 μL of H_2O. The mixture was stirred for 45 min at room temperature and then filtered. The white solid was washed liberally with cold Et_2O and then hot $CHCl_3$, and the filtrate was dried over $MgSO_4$, filtered, and concentrated to a colorless oil (25 mg, 89%). The α and β isomers were separated by flash chromatography, eluting with 9:1 $CHCl_3$–*i*-PrOH, to yield 16 mg (57%) of the major isomer **7**: R_f 0.11 (95:5 CH_2Cl_2–MeOH); $[\alpha]^{27}_D$ −33.8° (c 0.08, C_6H_6); ^{1}H NMR (400 MHz, C_6D_6) δ 4.67 (dd, J = 2.7, 3.2 Hz, 1 H), 3.76 (d, J = 3.8 Hz, 2 H), 3.57 (dt, J = 3.8, 9.4 Hz, 2 H), 3.20 (s, 3 H), 3.00 (s, 3 H) 2.67 (dd, J = 3.8, 7.5 Hz, 1 H), 2.60 (dq, 7.0, 11.0 Hz, 1 H), 2.45 (dq, 7.0, 11.0 Hz, 1 H), 2.22 (ddd J = 3.2, 9.4, 12.6 Hz, 1 H), 1.75 (dt J = 4.0, 12.8 Hz, 1 H), 1.00 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (400 MHz, C_6D_6) δ 98.9, 73.2, 60.1, 56.0, 55.4, 54.6, 41.8, 31.4, 29.7; IR (CCl_4) 2970, 2930, 1465, 1370, 1205, 1150, 1120, 1060, 1000, 880 cm^{-1}; high-resolution mass spectrum calcd for $C_9H_{20}NO_3$ m/e 190.1438, found 190.1440.

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Supplementary Material Available: ^{1}H NMR spectra for **21**, **26a/26e**, and **7** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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