Studies of Acyl Nitrene Insertions. A Stereocontrolled Route toward Lankacidin Antibiotics

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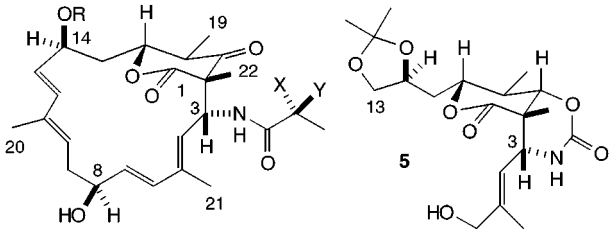
Photochemically generated acyl nitrenes undergo facile addition to 4,5-dihydrofurans **20** and **24b** to yield the novel 2-ethoxyoxazolines **21** and **25**. The regiocontrolled C=C insertion has provided for introduction of the sterically hindered C-3 amido appendage of the lankacidins **1**−**4** with high stereoselectivity. High chemoselectivity for the C=C insertion pathway was demonstrated upon production of the acyl nitrene intermediate from azide **33b**. Intramolecular competition for allylic C_3−H insertion versus C=C addition yielded exclusive formation of seven-membered N-acyl aziridines **34a,b**. The latent aldehydic functionality of oxazolines such as **21** and **25** is exposed upon a brief hydrolysis, permitting further chemical elaboration. Wittig condensation of the lactol from **25** has led to the synthesis of the lactone fragment **5**, containing all of the necessary stereochemistry and functionality for incorporation into the lankacidin antibiotics. The acyl nitrene insertion into 4,5-dihydrofurans affords a route toward unusual *β*-amido acids and amino sugar derivatives as shown via stereocontrolled formation of the amidofuranose derivatives **31** and **32**. The three-step process of acyl nitrene addition, hydrolysis of the resulting 2,5-dialkoxy oxazoline intermediates, and Wittig carbon chain elongation provides the stereocontrolled formation of novel *β*-amido esters.

Introduction

Acyl nitrenes derived from thermal or photochemical decomposition of the corresponding azidoformates undergo characteristic insertions into reactive carbon−hydrogen and olefinic carbon−carbon bonds.[1] This N-alkylation process permits the direct incorporation of amido functionality and allows for the intramolecular delivery of nitrogen in appropriate systems.[2] Our interest in the synthesis of antitumor antibiotics of the lankacidin family,[3] as exemplified by lankacidin C (**1**) and A (**2**), lankacidinol (**3**), and lankacidinol A (**4**), has inspired our investigations of acyl nitrene insertions as a strategy for stereocontrolled introduction of nitrogen.



1 Lankacidin C: X,Y = O, R = H
2 Lankacidin A: X,Y = O, R = Ac
3 Lankacidinol: X = H, Y = OH, R = H
4 Lankacidinol A: X = H, Y = OH, R = Ac

The unusual macrocarbocyclic framework of the lankacidins (**1**−**4**), and particularly the structural features associated with the internally bridging lactone, has stimulated recent synthetic efforts,[4] including a relay synthesis of lankacidin C (**1**) disclosed by Kende and coworkers.[5] Adding to their synthetic appeal, the lankacidins show strong activity against Gram-positive bacteria[3c] and have also proven to be effective in prolonging survival times of mice bearing leukemia, melanoma, and solid lymphosarcoma tumors.[3d]

Our report describes the facile addition of photochemically generated nitrene intermediates to 4,5-dihydrofurans to yield novel oxazolines. These efforts have made possible the construction of the fully functionalized *δ*-lactone core **5** with high stereoselectivity. Lactone **5** contains all but one of the stereocenters required for synthesis of the lankacidin natural products **1**−**4**, including the key neopentyl nitrogen-bearing site at C_3.

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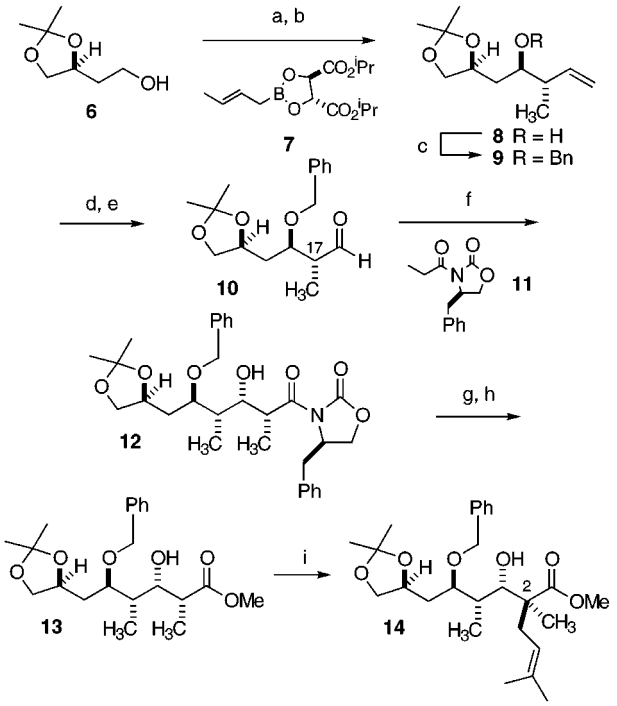
Scheme 1[a]



[a] Key: (a) Swern oxidation; (b) **7**, 4A molecular sieves, $PhCH_3$, −78 °C, 63% from alcohol **6**; (c) BnBr, NaH, Bu_4NI, THF/DMF, 83%; (d) O_3, Sudan Red, CH_2Cl_2, −78 °C; (e) Ph_3P, CH_2Cl_2, 0 °C; (f) **11**, Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 → 0 °C, 74% from olefin **9**; (g) LiOH, H_2O_2, THF/H_2O, 0 °C; (h) CH_2N_2, Et_2O, 76% from imide **12**; (i) $NaN(TMS)_2$, THF, prenyl bromide, −78 → 0 °C, 80%.

Inspired by the efficacy of the nitrene insertion process in the complex lankacidin system, we have examined more general opportunities for 2-aminofuranose synthesis based on analogous chemistry. Electron-rich vinyl ether double bonds react cleanly with photochemically generated acyl nitrenes, yielding amino sugar derivatives in highly stereocontrolled fashion.[6] Overall, we have found that nitrene insertion into carbon−carbon double bonds occurs readily and selectively in both inter- and intramolecular instances and provides an attractive method for nitrogen incorporation at advanced stages of a synthesis route.

Results and Discussion

Our synthesis plan toward the lankacidins has engaged the techniques of acyclic stereocontrol for development of the asymmetry associated with the lactone segment **5** (lankacidin atom numbering is used throughout this text). This key intermediate serves as a platform for extension of the carbon chain, and olefination processes offer attractive opportunities for macrocyclization. The results in Scheme 1 illustrate the assembly of five asymmetric centers of **5**, beginning with the (*S*)-alcohol **6** as derived from (S)-(−)-malic acid.[7] Swern oxidation[8] and addition of the Roush (*E*)-crotyl boronate **7**,[9] derived from (*R*,*R*)-diisopropyl tartrate, provided homoallylic alcohol **8** as a mixture of two diastereoisomers (ratio 87:13). The major product **8** proved readily separable by flash chromatography, permitting the processing of substantial quantities. Hydroxyl protection, followed by ozonolysis in the presence of Sudan Red,[10] led to aldehyde **10**, which was observed to undergo α-epimerization upon brief exposure to silica gel. However, ozonide decomposition with triphenylphosphine permitted precipitation of the byproduct triphenylphosphine oxide from solutions of crude **10** (0 °C; ether/hexanes), providing chromatography-free access to the aldehyde in sufficiently high purity (approximately 95% by NMR) for use in further chemistry. The subsequent direct condensation with the boron enolate of *N*-propionyloxazolidinone **11**[11] yielded a single aldol product **12**. No evidence of base-induced epimerization of intermediate **10** was observed in these reactions.

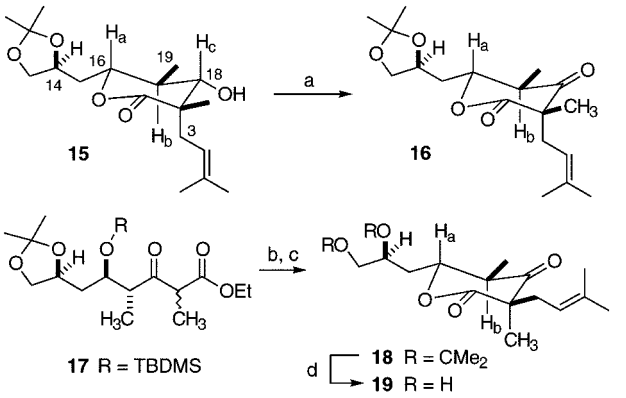


Figure 1. Key: (a) Swern oxidation; (b) NaH, prenyl bromide; (c) TBAF, THF; (d) 1 N HCl, THF/ H_2O.

After imide hydrolysis and esterification, Frater−Seebach alkylation[12] of either the sodium or lithium dianions of **13** afforded the single diastereomer **14**. The assigned stereochemistry of the newly created quaternary asymmetric carbon of **14** is predicted from the published model, assuming the intermediacy of a cyclic, metal-coordinated dianion.

Careful treatment of **14** with the radical anion of 4,4′-di-*tert*-butylbiphenyl[13] (THF at −78 °C; then aqueous NH_4Cl, −78 → 0 °C) induced debenzylation and spontaneous lactonization to yield **15** (86%). This deprotection method proved far superior to other reductive or oxidative protocols.

Evidence for the stereochemical assignments in lactone **15** was provided by the observation in ^1H NMR decoupling experiments that irradiation of the methyl (C_{19}) doublet at 0.98 ppm led to a simplified doublet of doublets signal for H_b (δ 2.32; J_{ab} = 10.7 Hz, J_{bc} = 10.7 Hz) indicative of a contiguous axial disposition of the three-

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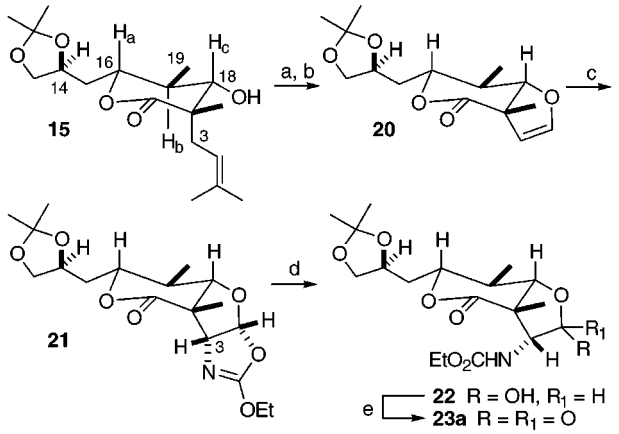
Scheme 2[a]



[a] Key: (a) O_3, CH_2Cl_2, −78 °C then $(CH_3)_2S$ and warm to 23 °C, 75%; (b) MsCl, Et_3N, THF, reflux, 91%; (c) EtO_2CN_3, *hν* (254 nm), −50 → −20 °C; (d) PPTs, THF/H_2O, 80% from **20**; (e) PDC, CH_2Cl_2, 88%.

ring hydrogens H_a, H_b, and H_c (Figure 1). Information regarding the asymmetric quaternary center (C_2) was available upon Swern oxidation[8] of **15** to *β*-ketolactone **16** (H_b *δ* 2.66) shown in Figure 1. This compound was identified as the C_2 epimer of **18** (H_b *δ* 2.72), the major product obtained from alkylation and subsequent fluoride-induced lactonization of *β*-ketoester **17**. The relative C_2 stereochemistry in **18** had been previously clarified by an NOE study of the deprotected diol **19**. For example, irradiation of the C_{22} methyl singlet (*δ* 1.40) of compound **19** resulted in a 6% NOE enhancement at H_b (*δ* 2.70).[14]

Initial studies of acyl nitrene insertion are illustrated in Scheme 2. With the stereochemistry of the lactone core established, ozonolysis of the trisubstituted olefin **15** and dehydration of the resulting five-membered lactols provided the *cis*-fused bicyclic dihydrofuran **20** (Scheme 2). The electron-rich vinyl ether **20** was viewed as an excellent substrate for C=C nitrene insertion. Thus, irradiation with ethyl azidoformate at −50 °C (at 254 nm) resulted in the formation of **21** and **22** in high overall conversion. Careful chromatography afforded the oxazoline **21** as a moisture-sensitive crystalline solid, which presumably is formed by the reorganization of an initial acyl aziridine.[6,15] A sharp, intense absorbance at 1665 cm^{-1} (C=N stretch) in the infrared spectrum of **21** was characteristic of the alkoxy oxazoline moiety and would not be expected from an acyl aziridine intermediate. Brief dissolution of **21** in acidic wet tetrahydrofuran quantitatively provided the more polar product of our photolysis, which proved to be a mixture of α- and *β*-lactols **22**. Oxidation of **22** gave a single bis-lactone **23a** in 70% overall yield from dihydrofuran **20**.

We had anticipated that insertion on the convex *β*-face of the [4.3.0]bicyclic vinyl ether of **20** would provide the proper orientation for the new carbon−nitrogen linkage. However, the possible steric influence of the angular C_{22} methyl group coupled with the presence of a single axial hydrogen on the α-face complicated the issue. An X-ray

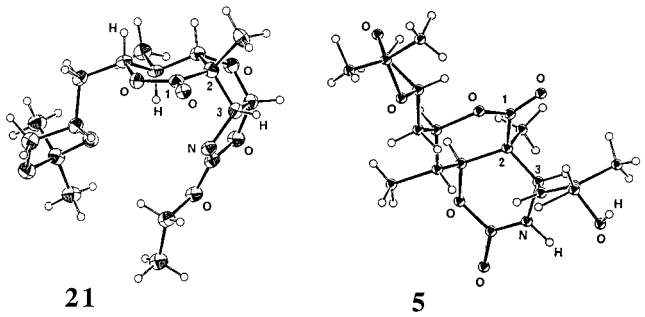


Figure 2. ORTEP diagrams illustrate the structural features and conformations of the caged oxazoline **21** and the bicyclic carbamate **5**.

diffraction study[16] established the stereochemistry of **21**, indicating that nitrene insertion had occurred anti to the bridgehead C_{22} methyl group. The ORTEP diagram (Figure 2) shows ethoxy oxazoline **21** as a highly caged structure with the six-membered lactone in a half-chair conformation. The crystal diffraction data support our conclusions for the conformational analysis of **20** drawn from solution state ^1H NMR studies. Our rationale would suggest that the corresponding twist boat conformer of dihydrofuran **20** does not contribute to the stereocontrolled production of **21**. This unanticipated stereochemical selectivity presented the inappropriate C_3 configuration for our continuing lankacidin efforts.

The high efficiency and stereocontrol featured in the initial study encouraged modification of the vinyl ether component. Hydrolysis of **20**, diazomethane esterification, and hydroxyl protection gave the dihydrofuran **24b**. In this photolysis substrate, it was surmised that the vicinal carbomethoxy and bulky C_{18} side chain would direct addition to the less-hindered *β*-face of the 4,5-dihydrofuran. As summarized in Scheme 3, a solution of **24b** and ethyl azidoformate was irradiated for 4 h at room temperature producing a single oxazoline **25** and lactols **26**. As before, the oxazoline was isolated and fully characterized (IR 1667 cm^{-1}), but was more conveniently converted into the diastereomeric lactols **26** by mild acid hydrolysis.

Chemical correlation verified that the nitrene insertion had occurred on the expected face of vinyl ether **24b**. Thus, desilylation of the lactols **26** ($HF{\cdot}Et_3N$, CH_3CN, 75%) proceeded with concomitant lactonization, and oxidation (PDC, CH_2Cl_2, 80%) gave a single bis-lactone **23b** (Figure 3). Proton NMR data suggested a diastereomeric relationship of **23b** (*δ* 4.82 (H_a), 2.15 (H_b), 5.32 (N−H)) with the previous lactone **23a** (*δ* 4.52 (H_a), 2.40 (H_b), 6.37 (N−H)) shown in Figure 3. This was confirmed upon low-temperature deprotonation of **23a** resulting in epimerization at C_3 and conversion to **23b** upon cold acetic acid quench.

The stereocontrolled installation of the neopentyl C_3 amido linkage allowed for direct elaboration of the lankacidin skeleton. Direct Wittig condensation of lactols **26** using (carbethoxyethylidene)triphenylphosphorane in refluxing toluene gave the α,*β*-unsaturated ester **27** (70% yield) without epimerization at C_3. The fairly vigorous

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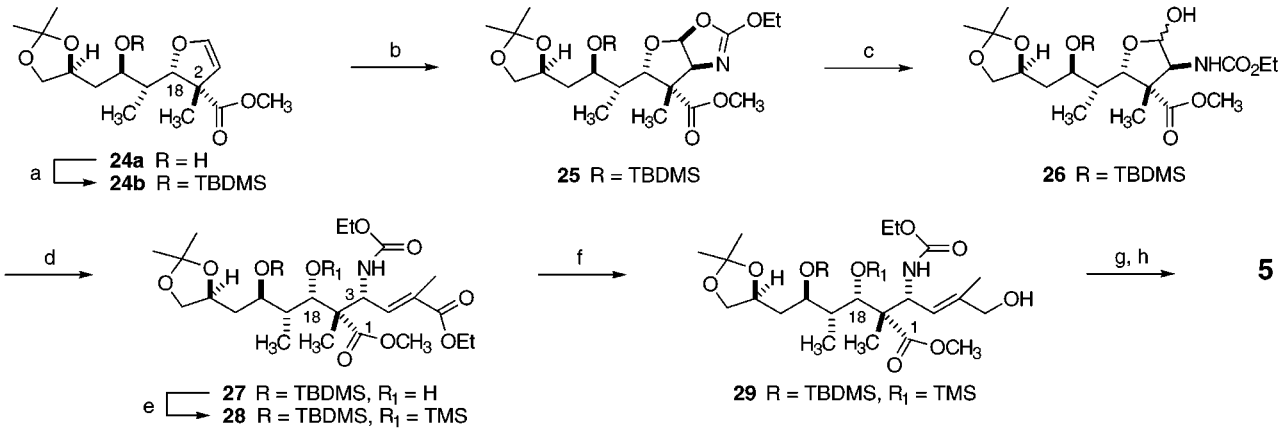
(16) Data resulting from the X-ray diffraction studies for crystals of compounds **5**, **21**, and **34b** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. We acknowledge the collaborative efforts of J. C. Huffman, K. F. Streib, and W. C. Streib of the Indiana University Molecular Structure Center (Reports 93254, 93082, and 91057).

Scheme 3[a]



[a] Key: (a) TBDMSOTf, collidine, CH_2Cl_2, 89% from **20**; (b) EtO_2CN_3, *hν* (400 W Hanovia, Vycor filter), CH_2Cl_2, 23 °C; (c) PPTs, THF/H_2O, 70% from **24b**; (d) $EtO_2CC(Ph_3P)CH_3$, $PhCH_3$, reflux, 15 h, 70%; (e) TMSOTf, Et_3N, CH_2Cl_2, −78 °C, 70%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 85%; (g) Bu_4NF, THF, 0 °C, 90%; (h) *o*-$C_6H_4Cl_2$, DMAP, 170 °C, 35 h, 88%.

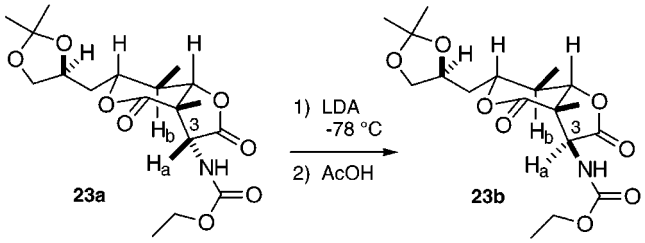


Figure 3.

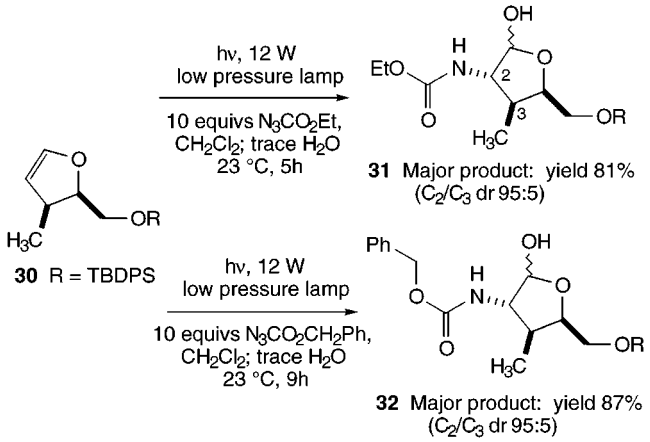
conditions required for this reaction (110 °C, 15 h) led to some cleavage of the C_2-C_{18} bond in a retroaldol process.

Selective hydride reduction of the conjugated ester **27** was not possible in the presence of the secondary (C_{18}) alcohol. Hydride reduction of the hindered methyl ester of **27** to its corresponding aldehyde was competitive with reduction of the α,*β*-unsaturated ethyl (or methyl) ester even under conditions of higher dilution, limited stoichiometry, and low temperature (−95 °C). However, conversion of the C_{18} alcohol to the corresponding trimethylsilyl ether **28** allowed for selective carbonyl reduction to allylic alcohol **29**. Formation of the trimethylsilyl ether **28** may prevent precomplexation of the reducing agent and internal hydride delivery. Desilylation of **29** proceeded with concomitant lactonization, and cyclization to the desired carbamate **5** led to the unambiguous proof of stereochemistry by single-crystal X-ray analysis.[16]

The high level of stereocontrol exhibited in formation of the complex *β*-amido esters **26** and **29** suggested that our initial reactions could prove to be of value in the preparation of unusual *β*-amino acid derivatives or C-2 amido sugars. To probe this possibility, two additional examples were examined using the 4,5-dihydrofuran **30** as shown in Scheme 4.[17] In each case, excellent stereocontrol was observed in the production of furanose derivatives **31** and **32**. This is in contrast to the poor facial selectivity reported by Descotes for intermolecular additions of acyl nitrenes to pyranose glycals.[1g,h]

In our reactions, inclusion of water in the reaction medium and the use of a low-pressure ultraviolet lamp

Scheme 4



were critical for optimizing yields. Under these conditions, intermediate oxazolines undergo in situ hydrolysis for direct isolation of the 2-aminofuranose. Interestingly, benzyl azidoformate serves as an effective acyl nitrene source, without complications from either the aromatic ring or the benzylic C−H positions. Introduction of readily cleaved benzyl carbamates is therefore feasible, as shown by production of amino sugar derivative **32**.

Finally, our studies have also examined the opportunity for an intramolecular acyl nitrene strategy.[2] Such an approach might allow for postponing nitrogen introduction until the very late stages of a lankacidin synthesis, perhaps following the macrocyclization itself. As an initial goal, we noted that, in principle, the C_3 amido functionality of the lankacidins could be directly introduced via C−H insertion into the neighboring allylic position of lactone **33**. To explore this possibility, acylation of **15** (from Scheme 2) with triphosgene[18] smoothly led to the key azidoformate **33b** upon exposure of the intermediate chloroformate **33a** to tetra-*n*-butylammonium azide.[19] Photolysis of **33b** (at 254 nm; CH_2Cl_2 at −40 °C) afforded exclusive C=C insertion with formation and isolation of the novel diastereomeric seven-membered

(17) Optically active dihydrofuran **30** was produced via reduction of (4*S*,5*R*)-4,5-dihydro-5-(*tert*-butyldiphenylsilyloxymethyl)-4-methyl-2(3*H*)-furanone, which was prepared from D-glutamic acid following the literature for the enantiomeric butenolide. Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170.

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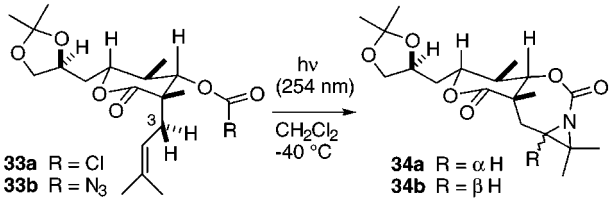

N-acyl aziridines **34a**,**b** (85% yield). Structure **34b** was subsequently confirmed via a single-crystal X-ray diffraction.[16] Aziridine formation was not totally unexpected, given that olefin attack is favored over allylic insertion in the photochemically triggered intermolecular reaction between ethyl azidoformate and cyclohexene.[20] Nevertheless, the exclusive formation of diastereomeric aziridines **34a**,**b** from trisubstituted olefin **33b** highlights the ease of nitrene insertion into electron-rich double bonds, even in the presence of a wide variety of functionality and the obvious proximity effects which might enhance the likelihood of the intramolecular hydrogen abstraction.

In conclusion, it has been shown that acyl nitrenes undergo facile C=C insertions with vinylic ethers. Reactions exhibit high diastereofacial selectivity, based upon steric considerations, affording 2,5-dialkoxyoxazolines. Mild hydrolysis of these heterocycles reveals an aldehydic function for further chemical elaboration. Our efforts have demonstrated the stereocontrolled preparation of complex β-amino acid derivatives. This concept and continuing studies toward the lankacidins will be the subject of future work.

Experimental Section

General. ^{1}H NMR spectra were obtained at either 400 or 500 MHz, and ^{1}H NMR chemical shifts are reported in parts per million, using as a reference the appropriate signal for residual solvent protons. ^{13}C NMR spectra were obtained at either 101 or 125 MHz. The multiplicities of ^{13}C signals were elucidated using DEPT techniques; the designation "o" denotes a carbon (CH or CH_3) giving rise to a positive peak in the 135° pulse DEPT experiment. ^{13}C NMR chemical shifts are reported in parts per million, using the center signal of the solvent signal as a reference. Melting points are uncorrected.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Dimethylformamide (DMF), benzyl bromide, methylene chloride (CH_2Cl_2), *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt), benzene, pyridine, oxalyl chloride, dimethyl sulfoxide (DMSO), triethylamine (Et_3N), methanesulfonyl chloride (MsCl), collidine, toluene, and acetonitrile (CH_3CN) were all distilled from calcium hydride. 4-Bromo-2-methyl-2-butene was freshly distilled from anhydrous potassium carbonate. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) were distilled prior to use. Where appropriate, reactions were carried out in flame or oven-dried glassware under an inert atmosphere.

Solutions of lithium diisopropylamide (LDA) were freshly prepared as follows: To a 0 °C solution of diisopropylamine (1.2 equivs) was added *n*BuLi (1.0 equiv). The resulting thick mixture was cooled to −78 °C and diluted to the desired concentration with THF. The LDA solutions were warmed to 0 °C prior to use.

(*R*)-5-Phenylmethyl-1-propionyl-2-oxazolidinone,[11] tetra-*n*-butylammonium azide,[19] ethyl azidoformate,[20] benzyl azidoformate,[21] pyridinium dichromate,[22] and HF·Et_3N[23] were prepared according to literature procedures. Other reagents were obtained commercially and were used as received. Solutions of *n*-BuLi were titrated regularly to ensure accurate concentrations.

(*S*)-4-[(2*R*,3*S*)-2-(Benzyloxy)-3-methylpent-4-enyl]-2,2-dimethyl(1,3)dioxolane (9). Alcohol **8** (3.90 g, 19.0 mmol) in THF/DMF (25 mL/25 mL) was treated with sodium hydride (1.88 g of a 50% w/w suspension in oil, 39.0 mmol) and tetra-*n*-butylammonium iodide (0.72 g, 1.95 mmol) at 23 °C. After 5 min, benzyl bromide (5.0 g, 29.3 mmol, 3.5 mL) was added and stirring was continued for 3 h. The reaction mixture was partitioned between hexanes (300 mL), and H_2O (300 mL) and the phases were separated. The organic layer was washed with brine (2 × 100 mL), and the combined aqueous phases were back-extracted with hexanes (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a cloudy oil which, on chromatography (5% EtOAc/hexanes, 500 g SiO_2), afforded benzyl ether **9** (4.7 g, 83%) as a clear, nearly colorless oil: R_f = 0.44 (15% EtOAc/hexanes); $[\alpha]_D^{26}$ +35.1° (c = 2.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5H), 5.80 (m, 1H), 5.08 (m, 1H), 5.04 (m, 1H), 4.52 (AB, J_{AB} = 11.6 Hz, $\Delta\nu$ = 45.3 Hz, 2H), 4.20 (m, 1H), 3.88 (m, 1H), 3.46 (m, 1H), 3.36 (dt, J = 7.8, 4.4 Hz, 1H), 2.60 (m, 1H), 2.00−1.58 (m, 2H), 1.40 (m, 3H), 1.34 (m, 3H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.29 (d), 138.46 (s), 128.28 (d), 127.79 (d), 127.56 (d), 115.08 (t), 108.46 (s), 79.44 (d), 73.42 (d), 71.33 (t), 69.39 (t), 40.04 (d), 34.28 (t), 26.94 (q), 25.66 (q), 14.49 (q); HRMS *m*/*e* calcd for $C_{18}H_{27}O_3$ (M^+ + 1) 291.1961, found 291.1957.

(4*R*)-4-(Phenylmethyl)-3-[2,4,6-trideoxy-2,4-dimethyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*glycero*-D-*gluco*-octanoyl]-2-oxazolidinone (12). Olefin **9** (6.93 g, 23.9 mmol) was dissolved in CH_2Cl_2 (100 mL), and a trace of Sudan Red 7B dye was added, producing a burgundy color. The solution was cooled to −78 °C, and a stream of ozone was bubbled through the mixture until the color of the dye was completely discharged (40 min on this scale). The ozone flow was replaced with argon, and this inert gas purge was continued 20 min. Triphenylphosphine (12.5 g, 47.8 mmol) was added, and the reaction mixture was allowed to warm to 23 °C. After 1.5 h stirring at 22 °C, solvent was removed on rotary evaporator, and the residue was taken up in ice-cold hexanes/Et_2O (1/1). The suspension was filtered to remove insoluble material, the filtrate was concentrated, and the precipitation/filtration process was repeated twice. Crude aldehyde **10** (R_f = 0.18, 50% EtOAc/hexanes) thus prepared was used directly, without further purification. A solution of (*R*)-(5-phenylmethyl)-1-propionyl-2-oxazolidinone (**11**) (6.13 g, 26.3 mmol) in CH_2Cl_2 (105 mL) was cooled to 0 °C, followed by addition of dibutyl boron triflate (28.7 mL of a 1.0 M solution in CH_2Cl_2, 28.7 mmol). The reddish color produced was discharged by the subsequent addition of diisopropyl ethylamine (4.0 g, 31 mmol, 5.4 mL). After 30 min of stirring at 0 °C, the mixture was cooled to −78 °C, and a solution of aldehyde **10** (assumed 7.0 g, 24 mmol) in CH_2Cl_2 (105 mL), pre-cooled to −78 °C, was added dropwise, via cannula, over 2 h. Following the addition, the reaction mixture was maintained at −78 °C for 40 min, then was allowed to warm slowly to 0 °C, and was stirred at that temperature for 1 h. An aqueous solution of sodium acetate (120 mL of a 2 M solution, 240 mmol) was added to the 0 °C mixture followed, *carefully*, by 30% H_2O_2 (25 mL). After 2 h of stirring at 0 °C, the reaction mixture was diluted with an equal volume of Et_2O, the layers were separated, and the organic phase was washed with H_2O (1 × 100 mL), saturated $NaHCO_3$ (1 × 100 mL), and brine (1 × 100 mL). The combined aqueous layers were back-extracted with Et_2O (1 × 100 mL), and the combined ethereal extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography (30 → 35% EtOAc/hexanes, 700 g of SiO_2) afforded imide **12** as a light yellow glass (9.30 g, 74% from the olefin): R_f = 0.23 (40%

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(21) Benzyl azidoformate was prepared following adaptation of the published procedure for ethyl azidoformate (ref 20).

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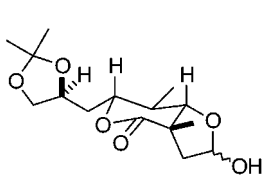
EtOAc/hexanes); $[\alpha]_D^{26}$ −42.8° (c = 0.80, $CHCl_3$); FTIR (neat) 3500, 1780, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.10 (m, 10H), 4.65 (m, 1H), 4.54 (AB, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 53.1 Hz, 2H), 4.24−4.15 (m, 4H), 4.08 (m, 1H), 3.93 (m, 1H), 3.64 (m, 1H), 3.59 (m, 1H), 3.28 (broad s, 1H), 3.22 (dd, J = 13.4, 3.2 Hz, 1H), 2.77 (dd, J = 13.3, 9.5 Hz, 1H), 2.11−1.85 (m, 2H), 1.86 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.96 (s), 152.58 (s), 137.79 (s), 134.89 (s), 129.29 (d), 128.81 (d), 128.33 (d), 127.76 (d), 127.72 (d), 127.28 (d), 108.68 (s), 81.03 (d), 72.89 (d), 72.09 (t), 70.94 (d), 69.57 (t), 65.83 (t), 54.86 (d), 41.02 (d), 37.54 (t), 37.02 (d), 34.81 (t), 27.00 (q), 25.66 (q), 14.51 (q), 11.17 (q); HRMS *m/e* calcd for $C_{30}H_{40}O_7N$ (M^+ + 1) 526.2806, found 526.2803.

2,4,6-Trideoxy-2,4-dimethyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*glycero*-D-*gluco*-octanoic Acid Methyl Ester (13). A mixture of LiOH (0.64 g, 27 mmol) in water (10 mL) and 30% H_2O_2 (12.1 mL, approximately 105 mmol) was added to a 0 °C solution of imide **12** (4.65 g, 8.86 mmol) in THF (66 mL). After 15 min, Na_2SO_3 (53 mL of a 2 M aqueous solution, 106 mmol) was *carefully* added. The reaction mixture was diluted with an equal volume of Et_2O, and the aqueous layer was adjusted to pH = 1 with 10% HCl. The layers were immediately separated, and the aqueous layer was back-extracted with Et_2O (2 × 50 mL). The combined ethereal extracts were cooled to 0 °C and treated with an excess of diazomethane (from *N*-methyl-*N*-nitrosourea and KOH) so that the bright yellow color of the diazomethane just persisted. Stirring was continued until the yellow color had been absent for several hours (a total of about 5 h on this scale). The reaction mixture was dried ($MgSO_4$), filtered, and concentrated, and the residue was chromatographed (25 → 28% EtOAc/hexanes, 700 g of SiO_2), providing methyl ester **13** (5.09 g, 76%) as a clear, colorless oil: R_f = 0.58 (60% EtOAc/hexanes); $[\alpha]_D^{26}$ −6.9° (c = 1.74, $CHCl_3$); FTIR (neat) 3500, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 4.54 (AB, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 66.8 Hz, 2H), 4.10 (m, 1H), 4.04 (m, 1H), 4.02 (m, 1H), 3.66 (s, 3H), 3.64 (m, 1H), 3.56 (m, 1H), 3.30 (broad s, 1H), 2.62 (m, 1H), 2.08−2.00 (m, 2H), 1.75 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.49 (s), 137.67 (s), 128.28 (d), 127.69 (d), 127.69 (d), 108.66 (s), 81.19 (d), 72.66 (d), 72.08 (t), 71.38 (d), 69.46 (t), 51.37 (q), 43.28 (d), 37.12 (d), 34.83 (t), 26.90 (q), 25.47 (q), 14.34 (q), 10.83 (q); HRMS *m/e* calcd for $C_{21}H_{33}O_6$ (M^+ + 1) 381.2278, found 381.2264. Anal. Calcd for $C_{22}H_{40}O_6Si$: C, 66.29; H, 8.48. Found: C, 66.19; H, 8.39.

(2*S*)-2,4,6-Trideoxy-2,4-dimethyl-2-(3-methyl-2-butenyl)-7,8-*O*-(1-methylethylidene)-D-*altro*-octonic Acid Methyl Ester (14). Methyl ester **13** (2.55 g, 6.70 mmol) in THF (35 mL) was added dropwise via cannula to a −78 °C solution of sodium hexamethyldisilazide (33.5 mL of a 1.0 M solution in hexanes, 33.5 mol). Once addition of the ester was complete, the mixture was warmed to −20 °C (internal thermometer) for 30 min and was then re-cooled to −78 °C. Prenyl bromide (10 g, 70 mmol, 7.8 mL), freshly distilled from anhydrous K_2CO_3, was added, and stirring was continued 3 h at −78 °C. The reaction mixture was gradually warmed to 0 °C over 3 h and was maintained at that temperature for an additional 9 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL), and Et_2O (200 mL) was added. The mixture was extracted with H_2O (1 × 75 mL) and brine (1 × 75 mL). The combined aqueous layers were back-extracted with Et_2O (2 × 50 mL), and the ethereal extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography (23% EtOAc/hexanes, 500 g SiO_2) gave α,α-disubstituted methyl ester **14** (2.41 g, 80%) as a viscous yellow oil: R_f = 0.48 (40% EtOAc/hexanes); $[\alpha]_D^{26}$ −1.6° (c = 9.10, $CHCl_3$); FTIR (neat) 3500, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 5.02 (X of ABX, 1H), 4.52 (apparent s, 2H), 4.18 (m, 1H), 3.98 (m, 1H), 3.86 (dd, J = 7.6, 1.2 Hz, 1H), 3.68 (s, 3H), 3.52 (m, 1H), 3.46 (m, 1H), 3.24 (d, J = 7.5 Hz, 1H), 2.38 (AB of ABX, J_{AB} = 14.1 Hz, J_{AX} = 7.9 Hz, J_{BX} = 7.2 Hz, $\Delta\nu_{AB}$ = 146.2 Hz, 2H), 2.02−1.82 (m, 2H), 1.98 (m, 1H), 1.68 (m, 3H), 1.60 (m, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.10 (s, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.70 (s), 138.28 (s), 135.18 (s), 128.34 (d), 127.84 (d), 127.64 (d), 118.58 (d), 108.43 (s), 80.52 (d), 74.98 (d), 73.16 (d), 72.18 (t), 69.76 (t), 51.83 (q), 50.14 (s), 36.65 (d), 36.10 (t), 34.60 (t), 26.93 (q), 26.01 (q), 25.75 (q), 18.13 (q), 17.92 (q), 9.81 (q); HRMS *m/e* calcd for $C_{25}H_{37}O_5$ (M^+ − OCH_3) 417.2642, found 417.2646.

(2*S*)-2,4,6-Trideoxy-2,4-dimethyl-2-(3-methyl-2-butenyl)-7,8-*O*-(1-methylethylidene)-D-*altro*-octonic Acid δ-Lactone (15). Lithium wire (35 mg, 5.0 mmol) was cleaned to a shiny luster in MeOH, rinsed in THF, and crushed with pliers just prior to being added to a vigorously stirred solution of 4,4′-di-*tert*-butylbiphenyl (1.99 g, 7.5 mmol) in THF (20 mL) at 23 °C. Within 30 min, a deep green color developed, and the solution was cooled to 0 °C. After 6 h of stirring at this temperature, the 0.25 M solution of the radical anion of 4,4′-di-*tert*-butylbiphenyl was added dropwise to a −78 °C solution of benzyl ether **14** (250 mg, 0.56 mmol) in THF (12 mL) until the dark green color of the radical anion persisted. Radical anion solution was added as needed to maintain the green color until starting material had disappeared as judged by TLC (12 mL of a 0.25 M solution of radical anion (3.0 mmol) were required on this scale). The reaction was quenched at −78 °C by addition of just enough saturated NH_4Cl solution to completely discharge the green color. The mixture was allowed to warm to 23 °C before being diluted with Et_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography (40% EtOAc/hexanes, 25 g SiO_2) provided hydroxy lactone **15** (156 mg, 86%) as a thick, slightly yellow oil: R_f = 0.24 (40% EtOAc/hexanes); $[\alpha]_D^{25}$ +4.2° (c = 0.48, $CHCl_3$); FTIR (neat) 3480, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (X of ABX, 1H), 4.38 (m, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.58 (m, 1H), 3.42 (broad dd, J = 10.2, 3.9 Hz, 1H), 2.42 (AB of ABX, J_{AB} = 14.5 Hz, J_{AX} = 8.1 Hz, J_{BX} = 7.5 Hz, $\Delta\nu_{AB}$ = 44.7 Hz, 2H), 2.32 (m, 1H), 2.08−1.94 (m, 2H), 1.96 (m, 1H), 1.72 (m, 3H), 1.64 (m, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 0.98 (d, J = 6.5 Hz, 3H); $^1H-^1H$ decoupling information, upon irradiation at 0.98, the multiplet at 2.32 collapsed to an apparent triplet (J = 10.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.41 (s), 134.97 (s), 119.29 (d), 108.93 (s), 79.92 (d), 77.70 (d), 71.63 (d), 69.28 (t), 48.11 (s), 36.45 (t), 36.01 (d), 32.45 (t), 26.83 (q), 26.00 (q), 25.66 (q), 21.73 (q), 17.87 (q), 14.09 (q); HRMS *m/e* calcd for $C_{18}H_{31}O_5$ (M^+ + 1) 327.2172, found 327.2155. Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 65.92; H, 9.44.

[3a*S*-[3aα,6β(*R),7α,7aα]]-6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-3a,6,7,7a-tetrahydro-3a,7-dimethyl-4*H*-furo-[3,2-c]pyran-4-one (20).** Ozone was bubbled through a −78 °C solution of olefin **15** (86 mg, 0.26 mmol) in CH_2Cl_2 (8 mL) containing a trace of Sudan Red 7B dye until the color of the dye was completely discharged. The cold reaction mixture was purged with argon for 20 min, dimethyl sulfide (49 mg, 0.79 mmol, 58 μL) was added, and the mixture allowed to warm to 23 °C. Stirring was continued 6 h at 23 °C, with two additional portions of dimethyl sulfide being added at regular intervals. After in vacuo removal of solvent and excess dimethyl sulfide, the residue was chromatographed (45% EtOAc/hexanes, 10 g of SiO_2), yielding anomeric hemiacetals **35** (60 mg, 75%) as a thick oil. Data for hemiacetals **35**: R_f = 0.16 (45% EtOAc/



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hexanes); FTIR (CCl_4) 3610, 3440, 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data for the major of two diastereomers) δ 5.52 (broad d, J = 4.8 Hz, 1H), 4.38 (m, 1H), 4.14−4.08 (m, 2H), 3.82 (d, J = 9.1 Hz, 1H), 3.60 (m, 1H), 2.84 (broad s, 1H), 2.57 (dd, J = 14.0, 5.1 Hz, 1H), 2.10−1.92 (m, 2H), 2.06 (m, 1H), 1.74 (m, 1H), 1.61 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.14 (d, J = 6.5 Hz, 3H); HRMS *m/e* calcd for $C_{15}H_{25}O_6$ (M^+ + 1)

301.1651, found 301.1646. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.73; H, 8.13.

The hemiacetals **35** (60 mg, 0.20 mmol) in THF (2.5 mL) at 23 °C were treated with triethylamine (120 mg, 1.20 mmol, 167 μL), followed by methanesulfonyl chloride (46 mg, 0.40 mmol, 31 μL). The mixture was heated at reflux for 90 min, re-cooled, diluted with Et_2O (10 mL), and filtered through a plug of silica gel, washing with a 30% EtOAc/hexanes solution. The filtrate was concentrated and the residue chromatographed (30% EtOAc/hexanes, 5 g of SiO_2), providing vinyl ether **20** (52 mg, 91%) as a white, crystalline solid: $R_f = 0.49$ (45% EtOAc/hexanes); $[\alpha]_D^{26}$ −20.2 (c = 0.42, $CHCl_3$); mp 104−105 °C; FTIR (CCl_4) 1750, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, J = 2.7 Hz, 1H), 5.17 (d, J = 2.7 Hz, 1H), 4.38 (m, 1H), 4.10 (m, 1H), 4.03 (ddd, J = 10.3, 6.1, 4.0 Hz, 1H), 3.98 (d, J = 9.7 Hz, 1H), 3.60 (m, 1H), 2.09−1.93 (m, 2H), 1.92 (m, 1H), 1.47 (s, 3H), 1.41 (m, 3H), 1.34 (m, 3H), 1.15 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.28 (s), 144.82 (d), 108.85 (s), 106.27 (d), 89.19 (d), 76.34 (d), 71.29 (d), 69.20 (t), 51.97 (s), 37.60 (d), 35.12 (t), 27.71 (q), 26.73 (q), 25.57 (q), 14.22 (q); HRMS *m/e* calcd for $C_{15}H_{22}O_5$ (M^+) 282.1468, found 282.1449. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 64.12; H, 7.94.

[3a*R*-[3aα,4aα,5α,6β(S*),8aα,8bα]]-6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-ethoxy-3a,4a,5,6,8a,8b-hexahydro-5,8a-dimethyl-8*H*-pyrano[3′,4′:4,5]furo[3,2-d]oxazol-8-one (21) and [3*R*-[3β,3aα,6β(R*),7α,7aα]]-6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-3a,7-dimethyl-2-hydroxy-4-oxo-4*H*-furo[3,2-*c*]pyran-3-yl}carbamic Acid Ethyl Ester (22). A −50 °C solution of vinyl ether **20** (34 mg, 0.12 mmol) and ethyl azidoformate (45 mg, 0.39 mmol, 40 μL) in CH_2Cl_2 (4 mL) was photolyzed through quartz with a 75 W, 254 nm peak output UV lamp. During the irradiation process, the temperature was maintained between −50 °C and −30 °C, and an additional amount of ethyl azidoformate (23 mg, 0.20 mmol, 20 μL) was added after 1 h. After a 2-h total irradiation time, the reaction mixture was concentrated, and the residue was chromatographed (50 → 55% EtOAc/hexanes, 5 g of SiO_2). Oxazoline **21** (9.9 mg) was isolated as a white crystalline solid with an R_f slightly higher than that of anomeric carbamates **22** (6.8 mg) which were isolated together as an oil. A number of mixed fractions (9.2 mg aggregate mass) were also recovered. The mixed products (**21** + **22**) were smoothly converted completely to carbamates **22** as follows: The mixed fractions (9.2 mg) were dissolved, with stirring, in a 9/1 THF/H_2O mixture (5 mL) and the solution was cooled to 0 °C. A few crystals of PPTs were added and stirring was continued 10 min at 0 °C. Several drops of saturated aqueous $NaHCO_3$ were added, the mixture was diluted with EtOAc (10 mL), and the layers were separated. The organic phase was washed with H_2O (1 × 3 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (55% EtOAc/hexanes, 5 g of SiO_2), yielding carbamates **22** (8 mg) as a foam. Data for oxazoline **21**: $R_f = 0.25$ (60% EtOAc/hexanes); FTIR-(CCl_4) 1750, 1665 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 5.54 (d, 4.8 Hz, 1H), 4.30 (m, 1H), 4.12 (d, J = 5.1 Hz, 1H), 4.11 (m, 2H), 3.93 (m, 1H), 3.42 (m, 1H), 3.18 (dt, J = 10.6, 4.4 Hz, 1H), 3.15 (d, 11.3 Hz, 1H), 1.83 (m, 1H), 1.80−1.57 (m, 2H), 1.34 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 170.50 (s), 162.30 (s), 108.86 (s), 107.11 (d), 89.38 (d), 79.20 (d), 78.02 (d), 71.78 (d), 69.86 (t), 67.30 (t), 51.92 (s), 37.98 (d), 35.89 (t), 26.98 (q), 26.02 (q), 24.45 (q), 14.24 (q), 13.62 (q). The structure of oxazoline **21** was unambiguously confirmed by a single-crystal X-ray diffraction study conducted at −171 °C. Crystal data for **21**, $C_{18}H_{27}O_7N$, are follows: space group = $P2_1$; cell dimensions at −171 °C, a = 7.392(2), b = 10.329(3), and c = 12.466(3) Å, β = 99.10(1)°; Z/molecules cell $^{-1}$, Z = 2; volume/Å^3, 939.92; calculated density/ g cm^{-3}, 1.305; wavelength, 0.71069; linear absorption coefficient, 0.919. The structure was solved by a combination of direct methods and Fourier techniques and was refined to final residuals = $R(F) = 0.0203$, $R_w(F) = 0.0229$. Complete crystallographic data are available from the Indiana University Chemistry Library (Request Molecular Structure Center Report 93082) or from the Cambridge Crystallographic Data Centre.[16] Data for carbamates **22**: $R_f = 0.18$ (60% EtOAc/hexanes); FTIR (CCl_4) 3615, 3405, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, data for the major of two diastereomers) δ 7.06 (broad d, J = 8.9 Hz, 1H), 5.34 (d, J = 3.8 Hz, 1H), 4.37 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 4.13 (m, 1H), 4.09 (m, 1H), 4.06 (dd, J = 8.7, 4.1 Hz, 1H), 3.1−2.7 (very broad peak, 1H), 3.72 (d, J = 8.3 Hz, 1H), 3.62 (m, 1H), 2.05 (m, 1H), 2.09−1.92 (m, 2H), 1.53 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H); HRMS *m/e* calcd for $C_{16}H_{28}O_7N$ (M^+ −OH) 370.1866, found 370.1840.

Direct Preparation of Carbamates 22. A solution of vinyl ether **20** (33 mg, 0.12 mmol) and ethyl azidoformate (67 mg, 0.20 mmol, 60 μL) in CH_2Cl_2 (4 mL) at −50 °C was photolyzed through quartz with a 75 W, 254 nm peak output lamp. After all starting vinyl ether was consumed (TLC), the reaction mixture was concentrated and the residue was stirred with 9/1 THF/H_2O (4 mL) for 30 min at 23 °C. The mixture was diluted with EtOAc (10 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (55% EtOAc/hexanes, 5 g of SiO_2), providing anomeric carbamates **22** (37 mg, 80%) as a brittle foam. None of oxazoline **21** was detected using this procedure.

[3*R*-[3β,3aα,6β(*R),7α,7aα]]-[6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-3a,7-dimethyl-2,4-dioxo-4*H*-furo[3,2-*c*]pyran-3-yl]carbamic Acid Ethyl Ester (23a).** Lactols **22** (16 mg, 0.041 mmol) in CH_2Cl_2 (2.5 mL) were stirred overnight at 23 °C and then for 4 h at reflux with an excess of pyridinium dichromate. The mixture was cooled, filtered through a pad of Celite, and concentrated. The residue was chromatographed (50% EtOAc/hexanes, 2 g of SiO_2), providing bis-lactone **23a** (14 mg, 88%): $R_f = 0.27$ (60% EtOAc/hexanes) $[\alpha]_D^{25}$ +8.3° (c = 0.240, $CHCl_3$); FTIR (neat) 3460, 1790, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, J = 9.4 Hz, 1H), 4.52 (d, J = 9.7 Hz, 1H), 4.40−4.32 (m, 2H), 4.22−4.12 (m, 2H), 4.18 (d, J = 5.6 Hz, 1H), 4.08 (dd, J = 8.2, 6.0 Hz, 1H), 3.61 (dd, J = 8.2, 7.4 Hz, 1H), 2.40 (m, 1H), 2.02 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.27 (d, J = 6.7 Hz); HRMS *m/e* calcd for $C_{18}H_{28}O_8N$ ($M^+ + 1$) 386.1815, found 386.1793.

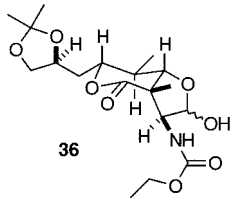
(3*S*)-1,4-Anhydro-2,3,5,7-tetradeoxy-3-(methoxycarbonyl)-3,5-dimethyl-8,9-*O*-(1-methylethylidene)-D-*altro*-non-1-enitol (24a). A THF (150 mL) solution of δ-lactone **20** (5.0 g, 17.7 mmol) was stirred with 2 M LiOH (30 mL) for 2.5 h at 0 °C and 30 min at 23 °C. The reaction mixture was partitioned between EtOAc (500 mL) and 1 M NaH_2PO_4 (250 mL), the layers were separated, and the aqueous phase was acidified to pH = 3 with 1 M phosphoric acid, saturated in NaCl, and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to a volume of ∼200 mL. The solution was cooled to 0 °C and treated with an excess of diazomethane (40 mmol) generated from *N*-methyl-*N*-nitrosourea and 40% KOH in Et_2O at 0 °C. The mixture was stirred at 0 °C until the yellow color of the diazomethane disappeared (1 h) and concentrated to an oil (5.8 g) which was carried on without further purification. An analytical sample of hydroxy ester **24a** (70 mg) was purified by chromatography (5% THF/CH_2Cl_2, 10 g SiO_2) to provide the following data: $R_f = 0.29$ (5% THF/CH_2Cl_2); FTIR (neat) 3511, 1728, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, J = 3.0 Hz, 1H), 5.01 (d, J = 3.0 Hz, 1H), 4.58 (d, J = 2.2 Hz, 1H), 4.25 (m, 1H), 4.08 (m, 1H), 3.68 (m, 1H), 3.66 (s, 3H), 3.54 (m, 1H), 3.43 (d, J = 2.2 Hz, 1H), 2.01 (m, 1H), 1.88−1.50 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 0.75 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.96 (s), 146.04 (d), 109.41 (s), 106.40 (d), 89.50 (d), 76.16 (d), 73.37 (d), 69.72 (t), 55.02 (s), 52.01 (q), 39.83 (d), 37.24 (t), 27.55 (q), 26.81 (q), 25.70 (q), 9.36 (q); HRMS *m/e* calcd for $C_{16}H_{27}O_6$ ($M^+ + 1$) 315.1808, found 315.1809.

(3*S*)-1,4-Anhydro-2,3,5,7-tetradeoxy-3-(methoxycarbonyl)-3,5-dimethyl-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-8,9-*O*-(1-methylethylidene)-D-*altro*-non-1-enitol (24b). Alcohol **24a** (5.8 g, 18 mmol) in CH_2Cl_2 (60 mL) at 0 °C was treated sequentially with collidine (4.0 g, 33 mmol) and *tert*-

butyldimethylsilyl trifluoromethanesulfonate (6.2 g, 23 mmol). After 15 min, saturated aqueous $NaHCO_3$ (15 mL) was added, and the reaction mixture was diluted with Et_2O and washed with saturated aqueous $CuSO_4$ (×1). The aqueous phase was extracted with Et_2O (×2), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (10 → 50% EtOAc/hexanes, 250 g of SiO_2), providing silyl ether **24b** as an oil (6.8 g, 89% from δ-lactone **20**): R_f = 0.61 (5% THF/CH_2Cl_2); $[\alpha]_D^{25}$ −53.6° (*c* = 2.20, $CHCl_3$); FTIR (neat) 1734, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.7 Hz, 1H), 5.00 (d, *J* = 2.7 Hz, 1H), 4.41 (d, *J* = 1.9 Hz, 1H), 4.24 (m, 1H), 4.05 (m, 1H), 3.67 (s, 3H), 3.65 (m, 1H), 3.49 (m, 1H), 2.10 (m, 1H), 2.00−1.60 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.93 (s), 146.26 (d), 108.13 (s), 106.27 (d), 89.56 (d), 72.56 (d), 71.88 (d), 69.97 (t), 55.06 (s), 51.97 (q), 39.31 (d), 36.63 (t), 27.40 (q), 26.89 (q), 25.87 (q), 18.01 (s), 8.57 (q), −4.28 (q), −4.98 (q); HRMS *m/e* calcd for $C_{22}H_{41}O_6Si$ (M^+ + 1) 429.2673, found 429.2671. Anal. Calcd for $C_{22}H_{40}O_6Si$: C, 61.65; H, 9.41. Found: C, 61.50; H, 9.51.

[3a*S*-[3aα,5α[1R*,2S*,3(R*)],6α,6aα]]-5-[3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-1-methylpropyl]-2-ethoxy-3a,5,6,6a-tetrahydro-6-methyl-furo[3,2-d]oxazole-6-carboxylic Acid Methyl Ester (25) and (2*S*,3*S*)-1,4-Anhydro-2,3,5,7-tetradeoxy-6-O-[(1,1-dimethylethyl)dimethylsilyl]-2-[(ethoxycarbonyl)amino]-1-hydroxy-3-(methoxycarbonyl)-3,5-dimethyl-8,9-*O*-(1-methylethylidene)-D-*altro*-nonitol (26). A solution of vinyl ether **24b** (3.4 g, 7.9 mmol) in CH_2Cl_2 (160 mL) was degassed with an argon stream for 15 min, ethyl azidoformate (3.4 g, 30 mmol) was added, and the solution was photolyzed for 3 h with a 400 W Hanovia Hg-vapor lamp through a Vycor filter. An aliquot (8 mL) of the yellow reaction mixture was concentrated and the residue was chromatographed (2.5 → 3.5% THF/CH_2Cl_2), providing oxazoline **25** (165 mg) as a colorless oil. To the bulk of the reaction mixture was added additional ethyl azidoformate (1.1 g, 9.6 mmol), and photolysis was continued 1 h. The solution was concentrated, and the residue was stirred with 9/1 THF/H_2O (50 mL) for 30 min. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ (×1). The aqueous phase was extracted with Et_2O (×2), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (30 → 50% EtOAc/hexanes, 200 g of SiO_2), providing anomeric carbamates **26** as an oil (2.7 g, 65%, 70% after accounting for isolated oxazoline). Data for oxazoline **25**: R_f = 0.38 (5% THF/CH_2Cl_2); FTIR (neat) 1730, 1667 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.15 (d, *J* = 4.8 Hz, 1H), 4.61 (d, *J* = 5.1 Hz, 1H), 4.36 (m, 1H), 4.15 (d, *J* = 1.6 Hz, 1H), 4.11 (m, 2H), 3.95 (apparent dd, *J* = 8.1, 5.9 Hz, 1H), 3.73 (dt, *J* = 7.8, 4.2 Hz, 1H), 3.45 (t, *J* = 8.1 Hz, 1H), 3.26 (s, 3H), 2.26 (m, 1H), 1.98−1.58 (m, 2H), 1.46 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.95 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.13 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 174.05 (s), 162.97 (s), 108.65 (s), 108.39 (o), 84.19 (o), 74.53 (o), 72.90 (o), 72.71 (o), 70.28 (t), 66.56 (t), 54.59 (s), 51.70 (o), 37.34 (t), 37.14 (o), 27.19 (o), 26.13 (o), 18.16 (s), 16.24 (o), 14.22 (o), 9.46 (o), −4.15 (o), −4.74 (o); HRMS *m/e* calcd for $C_{25}H_{46}NO_8Si$ (M^+ + 1) 516.2994, found 516.2986. Data for carbamates **26**: R_f = 0.13 (5% THF/CH_2Cl_2); FTIR (neat) 3439, 3403, 1730 cm^{-1}; ^1H NMR data for major anomer (400 MHz, $CDCl_3$) δ 5.54 (broad, 1H), 5.27 (broad, 1H), 4.94 (broad, 1H), 4.25 (m, 1H), 4.18−4.00 (m, 4H), 3.73 (s, 3H), 3.58 (m, 1H), 3.54−3.33 (broad, 1H), 3.50 (t, *J* = 7.8 Hz, 1H), 2.07−1.55 (m, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.26−1.16 (m, 6H), 0.88 (m, 9H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); HRMS *m/e* calcd for $C_{25}H_{46}O_8NSi$ (M^+ − OH) 516.2988, found 516.2981.

[3*S*-[3α,3aα,6β(*R),7α,7aα]]-[6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-3a,7-dimethyl-2-hydroxy-4-oxo-4*H*-furo[3,2-*c*]pyran-3-yl]carbamic Acid Ethyl Ester (36).** A solution of silyl ether **26** (10 mg, 0.019 mmol) and HF·Et_3N (17 mg, 0.19 mmol) in CH_3CN (1.5 mL) was heated overnight at 75 °C. The reaction mixture was concentrated,



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and the residue purified by column chromatography (80% EtOAc/hexanes, 2 g of SiO_2), providing lactols **36** (5 mg, 75%): R_f = 0.25 (80% EtOAc/hexanes); FTIR (neat) 3364, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) indicated ca. 2:1 mixture of anomers. Data for major anomer: δ 5.40 (br s, 1H), 5.22 (br d, *J* = 9.1 Hz, 1H), 4.55 (dd, *J* = 9.3, 4.7 Hz, 1H), 4.39 (m, 1H), 4.20−4.00 (m, 4H), 3.82 (d, *J* = 9.7 Hz, 1H), 3.59 (t, *J* = 7.8 Hz, 1H), 3.27 (broad, 1H), 2.08−1.92 (m, 2H), 1.82 (m, 1H), 1.41 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.27 (t, *J* = 7.4 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H); HRMS *m/e* calcd for $C_{18}H_{30}NO_8$ (M^+ + 1) 388.1972, found 388.1978.

[3*S*-[3α,3aα,6β(*R),7α,7aα]]-[6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-3a,7-dimethyl-2,4-dioxo-4*H*-furo[3,2-c]pyran-3-yl]carbamic acid Ethyl Ester (23b). From hemiacetals 36**: A solution of hemiacetals **36** (5 mg, 0.013 mmol) and pyridinium dichromate (19 mg, 0.051 mmol) in CH_2Cl_2 (2.5 mL) was heated at reflux 90 min, recooled to ambient temperature, filtered through Celite, and concentrated. The residue was purified by column chromatography (50% EtOAc/hexanes, 2 g of SiO_2), providing bis-lactone **23b** (4 mg, 80%). **From epimerization of bis-lactone 23a**: Bis-lactone **23a** (14 mg, 0.036 mmol) in THF (1 mL) was added to a −78 °C solution of LDA (0.55 mL of a freshly prepared 0.33 M solution in THF, 0.18 mmol), giving a yellow color. After 10 min, acetic acid (22 mg, 0.36 mmol) was added, followed by saturated aqueous NH_4Cl. The mixture was warmed to ambient temperature, diluted with Et_2O, and washed with H_2O. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (60% EtOAc/hexanes, 2 g of SiO_2), providing the epimeric bis-lactone **23b** (7 mg, 50%): R_f = 0.40 (60% EtOAc/hexanes); FTIR (neat) 3528, 3324, 1788, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (broad, 1H), 4.82 (d, *J* = 8.3 Hz, 1H), 4.41 (pentet, *J* = 6.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.18−4.08 (m, 3H), 3.61 (t, *J* = 7.8 Hz, 1H), 2.17 (m, 1H), 2.05 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H); HRMS *m/e* calcd for $C_{18}H_{28}NO_8$ (M^+ + 1) 386.1815, found 386.1822.

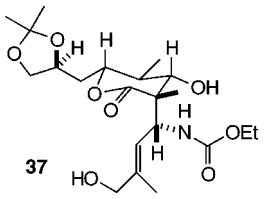
(5*S*)-2,3,4,5,7,9-Hexadeoxy-8-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-4-[(ethoxycarbonyl)amino]-5-(methoxycarbonyl)-2,5,7-trimethyl-10,11-*O*-(1-methylethylidene)-D-*glycero*-D-*manno*-undec-2-enonic acid ethyl ester (27). Anomeric hemiacetals **26** (2.6 g, 4.9 mmol) and (carbethoxyethylidene)triphenylphosphorane (8.9 g, 24.6 mmol) were heated in refluxing toluene (225 mL) for 15 h. The reaction mixture was cooled to ambient temperature, and the solvent was removed on the rotovap. The residue was chromatographed (30 → 35% EtOAc/hexanes), yielding the α,β-unsaturated ethyl ester **27** as an oil (70%): R_f = 0.25 (35% EtOAc/hexanes); $[\alpha]_D^{25}$ +6.0° (c = 0.51, $CHCl_3$); FTIR (neat) 3520, 3351, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (apparent dd, *J* = 10.5, 1.3 Hz, 1H), 5.75 (br d, *J* = 9.7 Hz, 1H), 4.72 (t, *J* = 10.2 Hz, 1H), 4.22−3.92 (m, 5H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.84 (m, 1H), 3.75 (s, 3H), 3.46 (m, 1H), 3.24 (broad d, *J* = 3.0 Hz, 1H), 2.01 (s, 3H), 2.00−1.70 (m, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.12 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.21, 167.64, 155.81, 135.46, 132.00, 108.82, 75.88, 72.36, 71.96, 69.79, 61.09, 60.84, 53.21, 52.92, 52.41, 38.77, 35.70, 26.93, 25.86, 25.70, 17.85, 15.37, 14.45, 14.17, 13.20, 12.26, −4.37, −4.85; HRMS *m/e* calcd for $C_{30}H_{56}NO_{10}Si$ (M^+ + 1) 618.3670, found 618.3704.

(5*S*)-2,3,4,5,7,9-Hexadeoxy-8-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-4-[(ethoxycarbonyl)amino]-5-(methoxycarbonyl)-6-*O*-(trimethylsilyl)-2,5,7-trimethyl-10,11-*O*-(1-

methylethylidene)-D-*glycero*-D-*manno*-undec-2-enonic Acid Ethyl Ester (28). Alcohol **27** (1.2 g, 1.9 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and triethylamine (0.78 g, 7.7 mmol) was added, followed by trimethylsilyl trifluoromethanesulfonate (0.86 g, 3.9 mmol). After 20 min the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The mixture was allowed to warm to ambient temperature, diluted with Et_2O and washed with brine (×1). The aqueous phase was extracted with Et_2O (×2), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (10 → 20% EtOAc/hexanes), providing bis-silyl ether **28** as an oil (0.95 g, 70%): R_f = 0.50 (30% EtOAc/hexanes); FTIR (neat) 3405, 1721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (m, 2H), 4.44 (t, J = 9.9 Hz, 1H), 4.28−4.20 (m, 6H), 4.00 (dd, J = 7.9, 5.8 Hz, 1H), 3.74 (s, 3H), 3.53 (dd, J = 7.8, 7.0 Hz, 1H), 3.39 (dd, J = 9.8, 4.7 Hz, 1H), 2.04−1.84 (m, 2H), 1.96 (s, 3H), 1.50−1.40 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.3 Hz, 3H), 1.05 (s, 3H), 0.88 (s, 9H), 0.86 (obscured d, 3H), 0.16 (s, 3H), 0.10 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.85 (s), 167.63 (s), 155.59 (s), 136.12 (o), 131.21 (s), 108.57 (s), 74.03 (o), 73.97 (o), 71.99 (o), 68.81 (t), 61.00 (t), 60.80 (t), 55.99 (s), 52.38 (o), 52.10 (o), 40.25 (o), 36.29 (t), 27.03 (o), 25.79 (o), 25.55 (o), 17.97 (s), 14.62 (o), 14.16 (o), 13.01 (o), 8.30 (o), 0.79 (o), −3.84 (o), −5.38 (o); HRMS *m/e* calcd for $C_{29}H_{54}NO_{10}Si_2$ ($M^+ - C_4H_9$) 632.3287, found 632.3267.

(5*S*)-2,3,4,5,7,9-Hexadeoxy-8-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-4-[(ethoxycarbonyl)amino]-5-(methoxycarbonyl)-6-*O*-(trimethylsilyl)-2,5,7-trimethyl-10,11-*O*-(1-methylethylidene)-D-*glycero*-D-*manno*-undec-2-ene-1-ol (29). A 1.0-M solution of diisobutyl aluminum hydride in CH_2Cl_2 (9.6 mL) was added over 30 min to diester **28** (2.6 g, 3.8 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The reaction was quenched by addition of MeOH (10 mL), and the mixture was warmed to ambient temperature, diluted with EtOAc, and stirred vigorously for 2 h with saturated aqueous Na/K tartrate. The layers were separated, and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography (30 → 35% EtOAc/hexanes, 150 g of SiO_2), providing allylic alcohol **29** as an oil (2.1 g, 85%): R_f = 0.35, 50% EtOAc/hexanes); $[\alpha]_D^{25}$ +56.5° (c = 1.05, $CHCl_3$); FTIR (neat) 3407, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (d, J = 9.4 Hz, 1H), 4.88 (d, J = 9.9 Hz, 1H), 4.35 (t, J = 9.7 Hz, 1H), 4.20 (m, 1H), 4.12−3.97 (m, 4H), 3.96 (s, 2H), 3.72 (s, 3H), 3.53 (t, J = 7.3 Hz, 1H), 3.38 (dd, J = 10.5, 4.6 Hz, 1H), 2.04−1.78 (m, 3H), 1.75 (s, 3H), 1.44 (m, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.04 (s, 3H), 0.88 (s, 9H), 0.85 (d, J = 7.3 Hz, 3H), 0.17 (s, 3H), 0.09 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.11 (s), 155.67 (s), 139.54 (s), 120.95 (o), 108.53 (s), 74.07 (o), 73.94 (o), 71.93 (o), 68.79 (t), 67.53 (t), 60.77 (t), 56.57 (s), 52.14 (o), 51.97 (o), 40.04 (o), 36.32 (t), 27.01 (o), 25.78 (o), 25.52 (o), 17.96 (s), 14.64 (o), 14.24 (o), 13.80 (o), 8.27 (o), 0.79 (o), −3.85 (o), −5.44 (o); HRMS *m/e* calcd for $C_{31}H_{62}NO_9Si_2$ (M^+ + 1) 648.3965, found 648.3961. Anal. Calcd for $C_{31}H_{61}NO_9Si_2$: C, 57.46; H, 9.49. Found: C, 57.68; H, 9.81.

[4*R*-[4α(*E*),4aβ,7α(*S),8β,8aβ]]-7-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-4-(3-hydroxy-2-methyl-1-propenyl)-4a,8-dimethyl-2*H*,5*H*-pyrano[3,4-*e*]-1,3-oxazine-2,5-dione (5).** Bis-silyl ether **29** (2.1 g, 3.3 mmol) in THF (60 mL) at 0 °C was treated with tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 9.8 mL). After 2 h, saturated aqueous NH_4Cl was added, and the mixture was extracted with $CHCl_3$ (×4). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (80 → 100% EtOAc/hexanes, 100 g of SiO_2), providing diol **37** as an amorphous white solid (1.3 g, 90%). Data for diol **37**: R_f = 0.28 (100% EtOAc); $[\alpha]_D^{25}$ +26.3° (c = 1.00, MeOH); mp 193−195 °C; FTIR (KBr) 3509, 3241, 1717, 1686 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 5.65 (d, J = 10.5 Hz, 1H), 4.98 (d, J = 10.5 Hz, 1H), 4.25 (pentet, J = 6.9 Hz, 1H), 4.12−3.98 (m, 4H), 3.92 (s, 2H), 3.56 (t, J = 7.8 Hz, 1H), 3.45 (d, J = 11.3 Hz, 1H),



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2.23 (m, 1H), 2.02 (dt, J = 14.2, 5.6 Hz, 1H), 1.92 (ddd, J = 14.6, 7.5, 3.4 Hz, 1H), 1.65 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 174.85 (s), 157.47 (s), 139.04 (s), 121.86 (o), 109.25 (s), 80.50 (o), 79.65 (o), 72.20 (o), 69.75 (t), 67.37 (t), 61.82 (t), 52.93 (o), 51.86 (s), 37.54 (o), 36.99 (t), 26.96 (o), 25.79 (o), 23.78 (o), 14.78 (o), 14.24 (o), 13.99 (o); HRMS *m/e* calcd for $C_{21}H_{36}NO_8$ (M^+ + 1) 430.2442, found 430.2443. Anal. Calcd for $C_{21}H_{35}NO_8$: C, 58.73; H, 8.21. Found: C, 58.42; H, 8.40.

Diol **37** (0.73 g, 1.7 mmol) and (dimethylamino)pyridine (0.10 g, 0.85 mmol) were heated at 170 °C in 1,2-dichlorobenzene for 35 h. The mixture was cooled to ambient temperature and applied directly to a column of silica gel (90 g of SiO_2) loaded with 100% hexanes. Subsequent elution was with 100% EtOAc → 5% MeOH/EtOAc, providing cyclic carbamate **5** (0.43 g, 77%, 88% based on recovered starting material) as an oil and recovered diol **37** (80 mg). The product **5** could be crystallized from chloroform: R_f = 0.18 (5% MeOH/EtOAc), $[\alpha]_D^{26}$ +74.2° (c = 0.81, MeOH); mp 135−138 °C; FTIR (neat) 3410, 1713 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 5.65 (apparent dd, J = 10.5, 1.3 Hz, 1H), 4.33 (pentet, J = 6.4 Hz, 1H), 4.22 (m, 3H), 4.07 (dd, J = 8.2, 6.0 Hz, 1H), 3.93 (s, 2H), 3.60 (dd, J = 8.1, 7.5 Hz, 1H), 2.48 (m, 1H), 2.06 (dt, J = 14.8, 6.1 Hz, 1H), 1.97 (ddd, J = 14.8, 6.1, 3.8 Hz, 1H), 1.65 (d, J = 0.8 Hz, 3H), 1.58 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.46 (s), 154.51 (s), 142.91 (s), 121.94 (o), 110.19 (s), 85.31 (o), 80.30 (o), 73.11 (o), 70.32 (t), 67.47 (t), 56.78 (o), 45.94 (s), 38.39 (o), 37.04 (t), 27.16 (o), 26.06 (o), 24.31 (o), 14.11 (o), 13.92 (o); HRMS *m/e* calcd for $C_{19}H_{30}NO_7$ (M^+ + 1) 384.2023, found 384.2008. Anal. Calcd for $C_{19}H_{29}NO_7$: C, 59.52; H, 7.62. Found: C, 59.16; H, 7.76. The structure of cyclic carbamate **5** was confirmed by a single-crystal X-ray diffraction study conducted at −62 °C. Crystal data for **5**, $C_{19}H_{29}NO_7$, were as follows: space group, $P2_12_12_1$; cell dimensions at −62 °C, a = 11.568(3), b = 11.880(3), and c = 17.802-(5) Å; Z/molecules cell^{-1}, 4; volume/Å^3, 2446.36; calculated density/g cm^{-3}, 1.365; wavelength, 0.71069; linear absorption coefficient, 4.120. The structure was solved by a combination of direct methods and Fourier techniques and was refined to final residuals: $R(F)$ = 0.829, $R_w(F)$ = 0.797. Complete crystallographic data are available from the Indiana University Chemistry Library (request Molecular Structure Center Report 93254) or from the Cambridge Crystallographic Data Centre.[16]

(4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-4-methyl-4,5-dihydrofuran (30). To a −78 °C solution of (4*S*,5*R*)-4,5-dihydro-5-(*tert*-butyldiphenylsilyloxymethyl)-4-methyl-2(3*H*)-furanone[17] (7.4 g, 20.0 mmol) in CH_2Cl_2 (50 mL) was added DIBAL (24 mL of 1.0 M solution in hexanes, 24 mmol). After 30 min, 10 mL of MeOH was added, and the mixture allowed to warm to ambient temperature. EtOAc (100 mL) and saturated aqueous Na/K tartrate (150 mL) were added, and the mixture was stirred vigorously for 2 h. The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by column chromatography (20% EtOAc/hexanes, SiO_2), providing (4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxymethyl)-4-methyltetrahydrofuran-2-ol (7.0 g, 94%) as a mixture of two lactol diastereomers: R_f = 0.21 (20% EtOAc/hexanes); FTIR ($CHCl_3$) 3637, 2934, 2865, 1467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.67 (m, 4H), 7.49−7.36 (m, 6H), 5.60−5.59 and 5.46−5.41 (bs, 1H), 4.26−4.22 and 4.02−3.98 (m, 1H), 3.86−3.70 (m, 2H), 3.69−3.63 (m, 2H), 2.70−2.37 (m, 2H), 2.02−1.87 (m, 2H),

1.09−1.08 (d, J = 4.8 Hz, 3H), 1.05 (s, 9H); HRMS *m/e* calcd for $C_{22}H_{29}O_2Si$ (M^+-OH) 353.1937, found 353.1946.

To a room-temperature solution of the lactols (7 g, 18.9 mmol) in THF (200 mL) and Et_3N (15.2 mL, 113.4 mmol, 6.0 equiv) was added MsCl (2.93 mL, 37.8 mmol, 2.0 equiv). The solution was brought to reflux for 1 h and then cooled, diluted with EtOAc, and filtered through a plug of Celite. The filtrate was concentrated, and the residue was chromatographed (3% EtOAc/hexanes, SiO_2) providing **30** (5.4 g, 81%): R_f = 0.30 (3% EtOAc/hexanes); $[\alpha]_D^{26}$ +17.6° (c = 1.56, $CHCl_3$); FTIR ($CHCl_3$) 3076, 2937, 1778, 1608, 1453 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.82−7.79 (m, 4H), 7.22−7.15 (m, 6H), 6.19−6.17 (broad s, 1H), 4.70−4.68 (broad s, 1H), 4.59−4.53 (m, 1H), 4.01 (A of ABX, J_{AB} = 10.8 Hz, J_{AX} = 6.4 Hz, 1H), 3.91 (B of ABX, J_{BA} = 10.8 Hz, J_{BX} = 5.6 Hz, 1H), 2.77−2.73 (m, 1H), 1.18 (s, 9H), 0.79 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 144.4 (d), 135.6 (d, 4C), 133.5 (s, 2C), 129.6 (d, 4C), 107.1 (d), 83.6 (d), 62.5 (t), 37.6 (d), 26.8 (q, 3C), 19.2 (s), 14.9 (q); HRMS *m/e* calcd for $C_{22}H_{29}O_2Si$ (M^+ + 1) 353.1936, found 353.1930.

(3*S*,4*S*,5*R*)-[5-(*tert*-Butyldiphenylsilyloxymethyl)-2-hydroxy-4-methyltetrahydrofuran-3-yl]carbamic Acid Ethyl Ester (31). To a room-temperature solution of **30** (705 mg, 2.0 mmol) in CH_2Cl_2 (150 mL) was added ethyl azidoformate (2.3 g, 20 mmol, 10 equiv) followed by a few drops of H_2O. The solution was then photolyzed through a Vycor filter with a 12 W, 254 nm low-pressure lamp. After all vinyl ether was consumed (5 h), the reaction was concentrated and chromatographed (40% EtOAc/hexanes, SiO_2) providing **31** (740 mg, 81%) (no oxazoline was detected). Data for the major diastereomer: R_f = 0.26 (40% EtOAc/hexanes); FTIR ($CHCl_3$) 3416, 2952, 1715, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.68 (m, 4H), 7.45−7.37 (m, 6H), 5.41 (d, J = 3.9 Hz, 1H), 5.09 (d, J = 8.6 Hz, 1H), 4.26−4.19 (m, 2H), 4.14 (q, J = 7.0 Hz, 2H), 3.73 (A of ABX, J_{AB} = 11.2 Hz, J_{AX} = 3.8 Hz, 1H), 3.62 (B of ABX, J_{BA} = 11.2 Hz, J_{BX} = 2.8 Hz, 1H), 2.36−2.32 (m, 1H), 1.27−1.20 (m, 6H), 1.07 (s, 9H); HRMS *m/e* calcd for $C_{21}H_{26}O_5Si$ N ($M^+ - C_4H_9$) 400.1580, found 400.1576.

(3*S*,4*S*,5*R*)-[5-(*tert*-Butyldiphenylsilyloxymethyl)-2-hydroxy-4-methyltetrahydrofuran-3-yl]carbamic Acid Benzyl Ester (32). To a room-temperature solution of **30** (353 mg, 1.0 mmol) in CH_2Cl_2 (150 mL) was added benzyl azidoformate (1.77 g, 10 mmol, 10 equiv) followed by a few drops of H_2O. The solution was then photolyzed through a Vycor filter with a 12 W, 254 nm low-pressure lamp. After all vinyl ether was consumed (9 h), the reaction was concentrated and chromatographed (40% EtOAc/hexanes, SiO_2) providing **32** (452 mg, 87%) (no oxazoline was detected): R_f = 0.24 (40% EtOAc/hexanes); FTIR ($CHCl_3$) 3617, 3447, 3061, 2952, 1716, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 7.45−7.28 (m, 11H), 5.41 (d, J = 4.4 Hz, 1H), 5.17−5.10 (m, 2H), 4.26 (td, J = 10.0, 5.2 Hz, 1H), 4.25−4.20 (m, 1H), 3.74 (A of ABX, J_{AB} = 11.2 Hz, J_{AX} = 3.8 Hz, 1H), 3.62 (B of ABX, J_{BA} = 11.2 Hz, J_{BX} = 2.8 Hz, 1H), 2.84 (bs, 1H), 2.40−2.31 (m, 1H), 1.22 (d, J = 6.9 Hz, 3H), 1.08 (s, 9H); HRMS *m/e* calcd for $C_{26}H_{28}O_5Si$ N ($M^+ - C_4H_9$) 462.1736, found 462.1729.

(2*S*)-2,4,6-Trideoxy-2,4-dimethyl-2-(3-methyl-2-butenyl)-3-*O*-(chlorocarbonyl)-7,8-*O*-(1-methylethylidene)-D-*altro*-octonic Acid δ-Lactone (33a). A 23 °C solution of alcohol **15** (15 mg, 0.047 mmol) in benzene (1 mL) was treated with pyridine (11 mg, 0.14 mmol, 11 μL), followed by triphosgene (14 mg, 0.047 mmol). A white precipitate formed immediately, and after 15 min the reaction mixture was diluted with Et_2O (5 mL), washed with H_2O (1 × 1 mL) and brine (1 × 1 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography (23% EtOAc/hexanes) provided chloroformate **33a** (13.8 mg, 75%) as an oil: R_f = 0.49 (40% EtOAc/hexanes); FTIR (neat) 1790, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (X of ABX, 1H), 4.88 (d, J = 10.5 Hz, 1H), 4.36 (m, 1H), 4.10 (m, 1H), 4.40 (dt, J = 10.7, 4.4 Hz, 1H), 3.58 (m, 1H), 2.66 (m, 1H), 2.45 (AB of ABX, J_{AB} = 14.3 Hz, J_{AX} = 7.9 Hz, J_{BX} = 7.4 Hz, $\Delta\nu_{AB}$ = 9.7 Hz, 2H), 2.20 (m, 2H), 1.73 (s, 3H), 1.65 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.05 (d, J = 6.4 Hz, 3H).

(2*S*)-2,4,6-Trideoxy-2,4-dimethyl-2-(3-methyl-2-butenyl)-3-*O*-(azidocarbonyl)-7,8-*O*-(1-methylethylidene)-D-*altro*-octonic Acid δ-Lactone (33b). Addition of pyridine (76 mg, 0.96 mmol, 77 μL) followed by triphosgene (95 mg, 0.32 mmol) to a 23 °C solution of alcohol **15** (104 mg, 0.32 mmol) in benzene (4 mL) gave a cloudy white suspension. After 10 min the mixture was diluted with Et_2O (10 mL), washed with H_2O (1 × 4 mL) and brine (1 × 4 mL), dried ($MgSO_4$), filtered, and concentrated. The crude chloroformate **33a** was dissolved, with stirring, in benzene (4 mL) at 22 °C, and tetra-*n*-butylammonium azide (1.9 mL of a 0.5 M solution in benzene, 0.96 mmol) was added. Conversion to the acyl azide could be monitored by TLC, using 3% THF/CH_2Cl_2 as a solvent and eluting twice. After 30 min, solvent was removed on a rotary evaporator, and the orange residue was chromatographed (25% EtOAc/hexanes, 10 g of SiO_2), giving azidoformate **33b** (91 mg, 71%) as a yellow oil: R_f = 0.49 (40% EtOAc/hexanes); $[\alpha]_D^{25}$ −12.0° (c = 0.250, $CHCl_3$); FTIR (neat) 2200, 2140, 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (X of ABX, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.36 (m, 1H), 4.08 (m, 1H), 4.04 (dt, J = 10.8, 4.6 Hz, 1H), 3.58 (m, 1H), 2.58 (m, 1H), 2.41 (AB of ABX, J_{AB} = 14.0 Hz, J_{AX} = 8.0 Hz, J_{BX} = 6.5 Hz, $\Delta\nu_{AB}$ = 16.4 Hz, 2H), 2.00 (m, 2H), 1.72 (m, 3H), 1.61 (m, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.05 (d, J = 6.4 Hz, 3H); HRMS *m/e* calcd for $C_{19}H_{30}O_6N_3$ (M^+ + 1) 396.2136, found 396.2129.

[4a*S*-[4aα,5α,6β(*R),8aα,9aβ]]-6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-1,1,5,8a-tetramethyl-1*H*,3*H*,8*H*-azirinio[1,2-*c*]pyrano[3,4-*f*][1,3]oxazepine-3,8-dione (34a) and [4a*S*-[4aα,5α,6β(*R**),8aα,9aα]]-6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]hexahydro-1,1,5,8a-tetramethyl-1*H*,3*H*,8*H*-azirinio[1,2-*c*]pyrano[3,4-*f*][1,3]oxazepine-3,8-dione (34b). Thermolysis procedure:** A solution of azidoformate **33b** (30 mg, 0.076 mmol) in CH_2Cl_2 (4 mL) was heated at 140 °C for 90 min in a sealed tube. The reaction mixture was concentrated and chromatographed (50 → 55 → 60% EtOAc/hexanes, 5 g of SiO_2), providing two diastereomeric products. The upper R_f adduct (**34a**, 3.0 mg, 11%) was isolated as an oil, while the lower R_f material (**34b**, 9.6 mg, 34%) was a white crystalline solid. **Photolysis procedure:** In a quartz vessel, azidoformate **33b** (21 mg, 0.053 mmol) was dissolved in CH_2Cl_2 (9 mL) and photolyzed with a 75 W, 254 nm peak output UV lamp at a temperature maintained between −20 and −50 °C. Once starting material had disappeared as judged by TLC (2.5 h irradiation time on this scale), the solvent was removed under reduced pressure and the residue chromatographed (55 → 60% EtOAc/hexanes, 5 g of SiO_2), providing two products. The upper R_f adduct **34a** (9.0 mg, 47%) was isolated as an oil while the lower R_f material **34b** (7.2 mg, 38%) was a white, crystalline solid. R_f and ^1H NMR (400 MHz, $CDCl_3$) data for the products were identical with that for **34a** and **34b** from the thermal reaction. Data for aziridine **34a**: R_f = 0.27 (60% EtOAc/hexanes); $[\alpha]_D^{25}$ +49.0° (c = 0.245, $CHCl_3$); FTIR (CCl_4) 3055, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (m, 1H), 4.10 (m, 1H), 4.05 (dt, J = 10.5, 4.9 Hz, 1H), 3.92 (d, J = 12.4 Hz, 1H), 3.58 (m, 1H), 2.96 (m, 1H), 2.82 (dd, J = 14.3 Hz, 2.3 Hz, 1H), 2.15 (dd, J = 12.1, 2.4 Hz, 1H), 2.05 (m, 2H), 1.49 (s, 3H), 1.42 (dd, J = 14.2, 12.1 Hz, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.16 (d, J = 6.5 Hz, 3H); HRMS *m/e* calcd for $C_{18}H_{26}O_6N$ ($M^+ - CH_3$) 352.1761, found 352.1761. Data for aziridine **34b**: R_f = 0.15 (60% EtOAc/hexanes); $[\alpha]_D^{26}$ −37.5° (c = 0.275, $CHCl_3$); mp 166−169 °C; FTIR (CCl_4) 3060, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (d, J = 3.8 Hz, 1H), 4.38 (m, 1H), 4.34 (m, 1H), 4.09 (m, 1H), 3.63 (m, 1H), 2.41−2.28 (m, 2H), 2.33 (m, 1H), 2.10−1.95 (m, 2H), 1.78 (m, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.26 (d, J = 7.3 Hz, 3H); HRMS *m/e* calcd for $C_{19}H_{30}O_6N$ (M^+ + 1) 368.2074, found 368.2079. The assigned aziridine structure of **34b** was unambiguously confirmed by a single-crystal X-ray diffraction study conducted at −171 °C. Crystal data for **34b**, $C_{19}H_{29}O_6N$, were as follows: space group,: $P2_12_12_1$; cell dimensions/Å at −171 °C, a = 10.573 (8), b = 24.911 (19), and c = 6.977(5); Z/molecules $cell^{-1}$, 4; volume/$Å^3$, 1837.51; calculated density/g cm^{-3}, 1.328; wavelength, 0.71069; linear absorption

coefficient, 0.919. The structure was solved using a combination of direct methods and Fourier techniques and was refined to final residuals: $R(F) = 0.0918$, $R_w(F) = 0.0839$. Complete crystallographic data are available from the Indiana University Chemistry Library (request Molecular Structure Center Report 91057) or from the Cambridge Crystallographic Data Centre.[16]

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Supporting Information Available: Proton NMR spectra are available for compounds **5**, **9**, **12**−**15**, **20**, **21**, **23a**,**b**, **24a**,**b**, **25**−**29**, and **34a**,**b**, as well as ^{1}H NMR spectrum for aldehyde **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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