

Stereoselective Synthesis of α - and β -L-C-Fucosyl Aldehydes and Their Utility in the Assembly of C-Fucosides of Biological Relevance

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An efficient synthesis of O-benzylated derivatives of the title sugar aldehydes via thiazole addition to tri-O-benzyl-L-fuconolactone followed by highly stereoselective deoxygenation of the resulting thiazolylketose and thiazole to formyl transformation is described. Wittig olefination of these aldehydes with galactopyranose and glucopyranose 6-phosphoranes and reduction of the resulting alkenes afforded α - and β -linked (1 \rightarrow 6)-L-*C*-fucosyl disaccharides, namely, β -L-*C*-Fuc-(1 \rightarrow 6)- α -D-Gal, α -L-*C*-Fuc-(1 \rightarrow 6)- α -D-Gal, and α -L-*C*-Fuc-(1 \rightarrow 6)- α -D-Glc. The α -anomer of the above *C*-fucosyl aldehydes was transformed into a C-fucosylmethyl triphenylphosphonium iodide from which the corresponding *C*-fucosylmethylene phosphorane was generated upon treatment with BuLi. This phosphorane reacted with the Garner aldehyde (N-Boc D-serinal acetonide) and its one-carbon higher homologue to give alkenes whose reduction and unveiling of the glycinyl group from the oxazolidine ring afforded C-fucosyl α -amino acids, namely α -L-linked C-fucosyl serines and C-fucosyl asparagines. As a final test of the synthetic utility of the title aldehydes, the β -anomer was employed as starting material in the stereoselective synthesis of both R- and S-epimer L-C-fucosyl phenylhydroxy acetates. One epimer was obtained by reaction of the sugar aldehyde with phenylmagnesium bromide, oxidation of the resulting alcohol to ketone, addition of 2-lithiothiazole to the latter, and transformation of the thiazole ring into the carboxyl group through an aldehyde intermediate. The other epimer was obtained by the same procedure and inverting the timing of phenyl and thiazolyl group addition. In both routes, the key step establishing the configuration of the quaternary carbon atom of the aliphatic chain was the highly stereoselective addition of the organometal to the ketone intermediate.

Introduction

Anomeric sugar aldehydes, namely formyl *C*-glycosides, have been demonstrated in recent years by extensive research carried out in our laboratory¹ to be readily accessible and versatile reactive building blocks for more complex *C*-glycosides, either isosteres of *O*- and *N*glycoside natural products such as oligosaccharides² and glycosyl amino acids³ or totally artificial (unnatural) compounds such as carbohydrate-heterocycle⁴ and carbohydrate-fullerene conjugates.⁵ Reports by other groups have appeared as well,⁶ thus demonstrating the utility of these compounds as precursors for carbohydrate mimics. Notably, Kishi and co-workers employed properly protected anomeric sugar aldehydes in synthetic routes to *C*-disaccharides and *C*-trisaccharides for conformational studies⁷ and Bednarski's group pioneered the synthesis of *C*-glycopeptides using a *C*-glycosyl amino acid, which in turn was prepared from the corresponding formyl *C*-glycoside.⁸ The replacement of the exocyclic carbon–oxygen or carbon–nitrogen bond of native glycoconjugates with a carbon–carbon bond creates compounds which are impervious to chemical and enzymatic degradation. Therefore the ready access to *C*-glycoside libraries is of great importance in modern carbohydrate chemistry because *C*-glycosides may serve inter alia as (i) biological probes in glycobiology,⁹ (ii) leads for the development of metabolically stable carbohydrate-based therapeutics,¹⁰ and (iii) building blocks for the prepara-

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tion of a variety of biologically important natural products¹¹in meaningful amounts and pure state suitable for biomedical studies. Although several syntheses of *C*-glycosides have been reported based on various types of substitution reactions at the anomeric carbon,¹² most of them were scarcely stereoselective as they afforded mixtures of α - and β -linked products. An alternative approach that allows this stereochemical problem to be avoided is based on establishing first the required configuration at the anomeric center by the introduction of a carbon functionality and then exploiting the chemistry of this functionality for the construction of the target complex carbon chain. This program was fueled by the effectiveness of a formylation methodology of carbohydrates which allowed the preparation of a collection of formyl C-glycosides on a multigram scale and in several cases in both α - and β -anomeric forms.¹³ The methodology is based on the thiazole-aldehyde synthesis¹⁴ and consists of the addition of lithiothiazole or lithiobenzothiazole to readily available sugar lactones, followed by stereoselective deoxygenation of the resulting thiazolylketose and transformation of the thiazole ring into the formyl group.¹⁵ Wishing to extend the scope of this approach to various C-glycosides of special biological relevance, we would like to report here the stereoselective synthesis of the hitherto unknown α - and β -L-fucosyl aldehydes α -1 and β -1 (Figure 1) and demonstrate their synthetic utility in the preparation of three types of C-fucosides, i.e., C-fucosyl disaccharides, C-fucosyl a-amino acids, and

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FIGURE 1. *O*-Benzylated α - and β -L-linked formyl *C*-fucosides α -1 and β -1.

C-fucosyl phenylacetic acids. Fucosylation is very common in nature and it affects significantly the conformation and biological properties of natural glycoproteins and glycolipids. For example, well-known fucose-containing saccharides are sialyl Lewis x (sLe^x) and sialyl Lewis a (sLe^a) of cell-surface glycoproteins and glycolipids. These and other fucosylated oligosaccharide structures play a key role in cell-cell interaction and cell migration phenomena which are involved in vital processes.¹⁶ However, it is well-established that the α -L-linkage of *O*-fucosides is very labile to acids¹⁷ and easily cleaved by glycosidases. Therefore it has been suggested that sLe^x mimics should contain the fucose unit linked through he C-glycosidic bond to achieve sufficient stability in vivo against fucosidases.¹⁸ For similar reasons, such a type of isosteric variation should be highly beneficial for the stability of the fucosylated trisaccharide N-linked to asparagine of CD52 peptides.¹⁹ Another topic of great interest is that regarding the synthesis of C-fucosylated tumor-associated carbohydrate antigens to be used in place of O-fucosylated analogues for the development of potential vaccines against cancer.²⁰ Fortunately, despite structural investigations based on comparative NMR studies having revealed notable conformational differences between unnatural C-glycosides and natural Oglycosides,²¹ recent studies have shown that their binding constants and biological properties are very similar.²²

Results and Discussion

Synthesis of L-*C***-Fucosyl Aldehydes.** *O*-Benzylated L-*C*-fucosyl aldehyde anomers α -**1** and β -**1** were targeted as suitably protected compounds in synthesis because the benzyl protective group is compatible with a variety of reactions of the formyl group and nevertheless can be easily removed from the final products under neutral conditions by catalytic hydrogenation. Hence the synthesis of α -**1** and β -**1** began from known²³ L-fuconolactone **3** (Scheme 1), which in turn was prepared in multigram scale by oxidation of 2,3,4-tri-*O*-benzyl L-fucose **2**.²⁴ Treatment of **3** in Et₂O at -78 °C with a solution of 2-lithiothiazole (2-LTT, **4**), generated in situ from 2-bro-

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⁽¹⁵⁾ Owing to the tolerance of the thiazole ring to a variety of reaction conditions, including oxidative and reductive processes, and the compatibility of the formyl unmasking process with numerous hydroxyl protective groups and free functionalities, the methodology was also employed for the synthesis of complex anomeric aldehydes of O, P, and N-ketosides which are per se important target saccharides. See ref 1a.

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SCHEME 1



SCHEME 2



mothiazole and BuLi, afforded the thiazolylketose 5a as a single isolated anomer (93%). This compound was acetylated under standard conditions (Ac₂O, Et₃N in CH₂Cl₂) to give the *O*-acetate **5b** as a crystalline product in 93% isolated yield by chromatography. The ${}^{1}C_{4}$ structure of this L-ketoside featuring the α -linked acetoxy group was supported by NMR coupling constant values $(J_{2,3} = 10.0 \text{ Hz})$ and nOe experiments showing substantial interactions between the acetyl group and the axial H-3 and H-5 protons. The same structure was assigned to the ketose **5a**.²⁵ Afterward, compound **5b** was obtained in a preparative useful scale by the above reaction sequence starting from 22.7 mmol (9.87 g) of O-benzylated L-fucose 2 and without purification of lactone 3 and ketose **5a**. In a typical procedure, pure compound **5b** was isolated by column chromatography in 92% overall yield.

The next key step toward the stereoselective synthesis of each aldehyde α -**1** or β -**1** consisted of removing the acetoxy group from **5b** to give either α -linked or β -linked thiazolyl *C*-fucoside, i.e., the configurationally stable and ultimate precursors of the target diastereomeric aldehydes. To this aim, the thiazolylketose acetate **5b** was treated with two different deoxygenative systems, namely the trimethylsilyl triflate—triethylsilane mixture (TMSOTf—Et₃SiH) and the samarium iodide—ethylene glycol mixture (SmI₂-(CH₂OH)₂) (Scheme 2). These reagents have been shown in earlier work from our

laboratory²⁶ to give opposite α/β selectivities in their reactions with various thiazolylketose acetates. Gratifyingly, also the reductive deoxygenation of 5b with these reagents showed opposite α/β ratios. Specifically the use of TMSOTf-Et₃SiH afforded exclusively the β -L-linked thiazolyl C-fucoside 6 (95%) whereas SmI₂-(CH₂OH)₂ furnished as main product the α -linked isomer 7 (93%) and only 6% of the stereoisomer 6 (Scheme 2). Both reactions were carried out on preparative scale starting from 1 to 3 g of **5b**. The anomeric configurations of these key intermediates, easily established by ¹H NMR analysis,²⁷ are in agreement with earlier postulated mechanisms of the deoxygenation reactions. In the case of the TMSOTf-promoted reduction, a chairlike transition state^{7a} was formed by an axial attack of the hydride ion (from silane) to the anomeric oxycarbenium ion adopting a halfchair conformation. On the other hand, in the case of the SmI₂-induced reaction, the more thermodynamically stable equatorial organosamarium(III) intermediate,²⁸ formed by a thiazole-assisted two-electron reduction process, underwent a protodesamariation with retention of configuration.

Having constructed both the configurationally stable thiazolyl β - and α -*C*-fucosides **6** and **7**, the final operation for the unveiling of the target aldehydes β -**1** and α -**1** entailed the transformation of the thiazole ring into the formyl group (Th \rightarrow CHO) by the highly reliable standard protocol consisting of *N*-methylation (MeOTf), reduction (NaBH₄), and hydrolysis (H₂O-AgNO₃). Once again this operation turned out to be particularly effective as each crude aldehyde was isolated in high yield (ca. 90%) and sufficiently pure form (ca. 95%) as determined by NMR analysis.²⁹ The whole unmasking operation required about 2 h and was carried out with identical results on 50 mg up to 1–2 g scale.

Synthesis of L-*C***-Fucosyl Disaccharides.** As a first test of the reactivity and synthetic utility of aldehydes α -**1** and β -**1** we considered their Wittig olefination by sugar phosphoranes to pave the way for the synthesis of *C*-fucosyl disaccharides.³⁰ The wide scope of the Wittig-based approach toward the stereoselective assembly of carbohydrate units through a 1,6- or 1,5 ethylene tether² and its superior efficiency with respect to the Henry-based methodology employed in other laboratories³¹ have been demonstrated by the preparation of a collection of

⁽²⁵⁾ No studies were carried out to establish whether **5a** is the product of the kinetic or thermodynamic control resulting from the addition of **4** to the lactone **3**. This would require the quenching of the reaction mixture at low temperature with Ac_2O . However, addressing this issue is unimportant in the context of the present work.

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C-disaccharides as well as various C-oligosaccharides up to a β -D-(1 \rightarrow 6)-pentamer. Thus, the fucosyl aldehyde β -1 was allowed to react with the acetonide-protected galactopyranose³² 6-phosphorane generated in situ by treatment of the known³³ phosphonium iodide **8** with BuLi in THF-HMPA at -30 °C (Scheme 3). The reaction afforded the (Z)-alkene 9 in fair isolated yield (57%) and whose configuration was established by the corresponding proton coupling constant value ($J_{6,7} = 11.5$ Hz). More importantly, it was demonstrated that the configurations at C-8 of the fucosyl moiety and C-5 of the galactosyl moiety of **9** were the same as in the coupling reagents β -1 and 8. Accordingly, the NMR spectrum of 9 showed a $J_{8,9}$ value of 9.5 Hz and a $J_{4,5}$ value of 1.7 Hz.³⁴ Next, compound 9 was subjected to hydrogenolysis over $Pd(OH)_2$ by which the reduction of the carbon–carbon double bond and the concomitant removal of the benzyl groups were accomplished. Then, the crude product was treated with Ac₂O-pyridine and the resulting O-acetyl and *O*-isopropylidene-protected $(1 \rightarrow 6)$ -*C*-fucosyl-galactoside $(\beta$ -L-*C*-Fuc- $(1\rightarrow 6)$ - α -D-Gal) **10** was isolated in a rewarding 84% yield.

Given the large diffusion of the native α -O-fucosidic linkage in oligosaccharides, the synthesis of α -configured carbon-linked analogues appeared to be quite important. Therefore the fucosyl aldehyde α -**1** was reacted with two α -D-glycopyranose 6-phosphoranes, one derived from the aforementioned galactose phosphonium salt **8** and the other from the recently prepared^{2a,b} O-benzylated glucopyranose phosphonium iodide **11** (Scheme 4). In both cases the phosphorane generation and the coupling with the sugar aldehyde α -**1** were carried out as outlined in

(34) For all *C*-disaccharidic olefins and the corresponding alkanes the same IUPAC numbering system outlined for 9 was adopted, i.e., counting starts from the reducing end of the disaccharide.

Scheme 3. These Wittig reactions afforded the alkene 12 (48%) and 14 (37%) as 4:1 and 1:1 Z,E mixtures, respectively. In addition to the desired alkenes 12 and 14, these reactions produced numerous side products as shown by TLC and NMR analyses of the crude reaction mixtures. One of these products was isolated (7-10%)and characterized as the C-formyl glycal 13. Very likely the reactions of α -**1** with the above sugar phosphoranes were sluggish and therefore base-induced β -elimination of the benzyloxy group at C-2 leading to 13 did take place. The alkenes 12 and 14 were elaborated in the usual way, i.e., Pd(OH)₂-catalyzed hydrogenation and acetylation, to give the O-protected (1,6)-linked C-disaccharides α -L-C-Fuc- $(1\rightarrow 6)$ - α -D-Gal **15** (80%) and α -L-*C*-Fuc- $(1\rightarrow 6)$ - α -D-Glc 16 (60%). The NMR spectra of both compounds 15 and 16 showed $J_{8,9}$ values of ca. 5.7 Hz in agreement with the α -L-fucosyl linkage and $J_{4,5}$ values of 1.5 and 10.0 Hz consistent with the D-galacto and D-gluco configuration, respectively.

Synthesis of L-C-Fucosyl Amino Acids. Next, we examined the possibility of preparing C-fucosyl α -amino acids,³⁵ especially methylene isosteres of O-fucosyl serines³⁶ and ethylene isosteres of N-fucosyl asparagines. The synthesis of C-glycosyl α -amino acids can be considered as the gateway to artificial glycopeptides,³⁷ i.e., a class of glycomimetics of great potential for the control of natural glycoprotein biological activity.^{9,38} Also in this endeavor we planned to assemble the fucosyl and amino acid moieties through a carbon-carbon bond generated by a Wittig-type reaction. However, earlier work in our laboratory³⁹ dealing with the synthesis of β -D-C-galactosyl L-serine (Gal β -*CH*_ZSer) demonstrated that the effectiveness of this approach is optimized by coupling an anomeric sugar phosphorane with an aldehyde bearing a masked glycinyl group. Therefore we envisaged the L-fucosylmethyl phosphonium salt **19** as precursor to the desired ylide. This salt was prepared in a few steps and high yield by standard functional group transformations starting from the *C*-fucosyl aldehyde α -**1** (Scheme 5). Succinctly, this aldehyde was reduced (NaBH₄) to the alcohol 17 and this product was transformed (PPh₃, I₂) into the iodomethyl derivative 18. The ¹H NMR spectrum of **18** demonstrated ($J_{2,3} = 3.5$ Hz) that there was no loss of the α -L-configuration at the anomeric carbon of the fucosyl residue. Finally, treatment of **18** with PPh₃ in the absence of solvent at 120 °C afforded the target phosphonium iodide **19** in 85% overall yield from α -**1**.

The Wittig coupling of the ylide generated in situ from the fucosylated triphenylmethylphosphonium iodide **19**

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^{(32) 1,2:3,4-}Di-*O*-isopropylidene-D-galactopyranose derivatives do not adopt a chair conformation as proved by the coupling constant values in their ¹H NMR spectra. Moreover, since in the literature there was some confusion concerning the actual conformation of this sugar residue, it is a common practice to draw the structure in a Haworth presentation. However, a very recent study provided evidence that 1,2: 3,4-di-*O*-isopropylidene-D-galactopyranose and 6-*O*-glycosylated derivatives adopt a ⁶S₂ conformation in solid state as well as in solution (Roslund, M. U.; Klika, K. D.; Lehtilä, R. L.; Tähtinen, P.; Sillanpää, R.; Leino, R. *J. Org. Chem.* **2004**, *69*, 18). Therefore the di-*O*isopropylidene-D-galactopyranose moieties presented in this paper are drawn in this conformation.

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⁽³⁵⁾ A few syntheses of *C*-fucosyl amino acids have been reported in the literature. *C*-Fucosyl glycines: (a) Jarvest, R. L.; Berge, J. M.; Brown, P.; Hamprecht, D. W.; McNair, D. J.; Mensah, L.; O'Hanlon, P. J.; Pope, A. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 715. *C*-Fucosyl alanines: (b) Vincent, S. P.; Schleyer, A.; Wong, C.-H. J. Org. Chem. **2000**, *65*, 4440. *C*-Fucosyl serines: (c) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. J. Org. Chem. **1996**, *61*, 8350. *C*-Fucosyl β -hydroxyserines: (d) Huwe, C. M.; Woltering, T. J.; Jiricek, J.; Weitz-Schmidt, G.; Wong, C.-H. *Bioorg. Med. Chem.* **1999**, *7*, 773. (36) (a) Bjoern, S.; Foster, D. C.; Thim, L.; Wiberg, F. C.; Chris-

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(38) Marcaurelle, L. A.; Bertozzi, C. R. *Chem. Eur. J.* 1999, 5, 1384.
(39) Dondoni, A.; Marra, A.; Massi, A. *Tetrahedron* 1998, 54, 2827.

SCHEME 4



SCHEME 5



(BuLi, THF-HMPA, 0 °C) was carried out with the wellknown α -amino aldehyde⁴⁰ **20** (D-serinal) since this reagent contains the masked chiral glycinyl group in the form of the N-Boc oxazolidine ring (Scheme 6). We have demonstrated in earlier syntheses of glycosyl amino acids^{3,39,41} the advantages associated with the use of amino acid equivalents with the desired absolute stereochemistry already in place.⁴² Deceptively, this strategy failed in the present case since under optimized conditions (THF-HMPA, from -20 to 0 °C) the above reaction afforded the alkene **21** (70%) as a 3:1 E_{z} mixture containing *R*- and *S*-configured *N*-Boc oxazolidine rings.⁴³ Evidently, under the above conditions epimerization did take place at the nitrogenated carbon atom of the

(42) This simple yet quite useful strategy has been used by other groups. For illustration of reaction schemes and leading references, see ref 37.

(43) The NMR spectra recorded at room temperature of all compounds containing a N,N-dialkyl-N-Boc amine function showed multiple sets of signals arising from the hindered rotation around the σ -bonds. Consistent spectra were obtained in the range 100–160 °C due to the coalescence of signals (see the Experimental Section).

SCHEME 6



15

OAc

AcÒ

ÒМе

AcC

16

oxazolidine ring of 20. Unfortunately, when milder conditions were adopted such as lowering the temperature to -40 °C, the yields of **21** were in the range of only 15-30% and still substantial epimerization was observed. Pressing forward nonetheless, the mixture of alkenes 21 was duly elaborated by hydrogenation and acetylation to give the mixture of diastereoisomers 22 which in turn was subjected to the one-step oxidative cleavage of the oxazolidine ring by the Jones' reagent $(CrO_3, H_2SO_4 - H_2O)$ and esterification by diazomethane. This reaction sequence furnished a mixture of *C*-fucosyl α -amino ester α -epimers **23** in ca. 3:2 ratio by NMR analysis. The same analysis confirmed the α -configuration at the anomeric carbon of the fucosyl residue since $J_{5.6}$ values of 5.6 Hz were observed for both diastereoisomers. These compounds can be considered as α -L-linked fucosyl serine methylene isosteres (Fucα-CH₂-Ser), i.e., analogues of natural O-fucosyl serines which are widely distributed in human coagulation factors.³⁶ Attempts to isolate each individual diastereoisomer by column flash chromatography failed so far. However, the mixture of these compounds can be profitably employed in the synthesis of C-fucosylated peptides whose stereoisomers

⁽⁴⁰⁾ Garner, P. Tetrahedron Lett. 1984, 25, 5855. For a recent account of the synthetic application of this aldehyde, see: Liang, X.; Andersch, J.; Bols, M. J. Chem. Soc., Perkin Trans. 1 2001, 2136. For an improved synthesis avoiding racemization, see: Dondoni, A.; Perrone, D. Synthesis **1997**, 527. Dondoni, A.; Perrone, D. Org. Synth. 1999, 77, 64.

^{(41) (}a) Dondoni, A.; Marra, A.; Massi, A. Chem. Commun. 1998, 1741. (b) Dondoni, A.; Massi, A.; Marra, A. *Tetrahedron Lett.* **1998**, *39*, 6601. (c) Dondoni, A.; Giovannini, P. P.; Marra, A. J. Chem. Soc., Perkin Trans. 1 2001, 2380. (d) Dondoni, A.; Mariotti, G.; Marra, A.; Massi, A. Synthesis 2001, 2129. (e) Dondoni, A.; Mariotti, G.; Marra, A. J. Org. Chem. 2002, 67, 4475



can hopefully be more easily separable. There are two precedents on the use of mixtures of *C*-glycosyl serine α -epimers, one dealing with the preparation of decapeptides with potential activity on T-cell stimulation,⁴⁴ the other with the synthesis of sialyl Lewis x glycomimetics.^{35c}

More rewarding results were obtained by the Wittig olefination of the configurationally stable homoserine derived aldehyde⁴⁵ 24 (Scheme 7). Treatment of this aldehyde with the fucosylmethylene phosphorane derived from 19 under the above conditions afforded the alkene **25** as a single *Z*-isomer in 75% isolated yield ($J_{4.5} = 11.5$ Hz). The Pd(OH)₂-promoted hydrogenation of **25** in 1:1 MeOH-AcOEt, followed by acetylation with Ac₂Opyridine, furnished the tetra-O-acetate **26** as the major product. Apparently, opening the oxazolidine ring of 25 did take place in the course of the hydrogenation step, very likely because of some content of acetic acid in the solvent. Thus, exclusion of AcOEt appeared to be advisable. Since 25 was scarcely soluble in MeOH, the hydrogenation was carried out with EtOH as the solvent. The acetylation of the resulting product afforded the ester **26** in low yield (15%) and the desired alkyl oxazolidine **27** in fair yield (55%). The oxidative cleavage of the oxazolidine ring of the latter product with Jones' reagent and esterification furnished the O-Ac and N-Boc C-fucosyl α -amino ester **28**, a suitably protected building block for solid-phase *N*-Boc-based peptide synthesis. The α -fucosyl linkage in 28 and in the precursors 25 and 27 was confirmed by a $J_{6.7}$ value of 5.7 Hz in its ¹H NMR spectrum. Thus, the corresponding free amino acid can be regarded as the α -L-linked fucosyl L-asparagine ethylene isostere (Fuc α -*CH*₂*CH*₂-Asn) although the native *N*linked analogue has not been reported to the best of our knowledge.

Synthesis of L-*C*-Fucosyl Phenylhydroxy Acetates. The above *C*-fucosyl disaccharides and amino acids belong to families of *C*-glycosides whose convenient synthesis from anomeric sugar aldehydes was previously established. A demonstration of the utility of formyl *C*-glycosides in the synthesis of a new class of *C*-glycosides was undertaken following a recent publication by Pasetto and Franck.⁴⁶ These researchers were faced with the nontrivial task of developing a stereoselective synthesis of both epimers of α -D-linked *C*-altrosyl phenylhydroxy acetate **29** (Figure 2). One of these epimers



FIGURE 2. Hydroxy- and phenyl-substituted *C*-altrosyl and *C*-fucosyl acetates **29** and **30**.

represents the glycosidic part of the natural antitumor antibiotic Altromycin B. Starting from either D-glucose or D-altrose, Pasetto and Franck succeeded in preparing both (R)-29 and (S)-29 by a rather laborious synthetic sequence. The reaction scheme involved first the synthesis of S-glycosides and the Ramberg-Bäcklund rearrangement of their sulfones to set up the C-glycosidic linkage. Then, a multistep elaboration of the resulting exo-glycals was carried out to build up the chiral phenylhydroxy acetate moieties with opposite configurations. Thus, we were spurred to develop an alternative and expeditious synthesis of C-glycosyl phenylhydroxy acetates starting from formyl *C*-glycosides. In particular we focused on the use of the fucosyl aldehyde β -1 as a starting material since this would lead to the C-7 epimer of **29**, i.e., the *C*-fucosyl phenylhydroxy acetate **30** (Figure 2). If successful, this new synthesis would constitute a model route for an alternative approach to 29. In addition to that, we realized that the synthesis of chiral tertiary alcohols, particularly those bearing complex substituents, was a topic of current interest.⁴⁷

We envisaged the construction of the chiral side chain of **30** by transformation of the aldehyde β -**1** into a tertiary alcohol bearing fucosyl, phenyl, and thiazolyl substituents. The heterocycle substituent would serve as a masked formyl group readily transformable into the desired carboxylate. To this aim, β -**1** was first reacted with phenylmagnesium bromide in THF at low temperature (-60 to -35 °C) and the resulting mixture of diastereomeric alcohols was oxidized by pyridinium chlorochromate (PCC) to furnish the ketone **31** in 67% isolated yield (Scheme 8). Then, addition of 2-LTT **4** to this ketone in Et₂O-THF at low temperature afforded

⁽⁴⁴⁾ Tedebark, U.; Meldal, M.; Panza, L.; Bock, K. Tetrahedron Lett. **1998**, *39*, 1815.

⁽⁴⁵⁾ The synthesis of this aldehyde was previously reported but the compound was not characterized by suitable physical and spectroscopic data (Ksander, G. M.; de Jesus, R.; Yuan, A.; Ghai, R. D.; Trapani, A.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 495). An improved synthesis and full characterization of this compound are described in the Experimental Section.

⁽⁴⁶⁾ Pasetto, P.; Franck, R. W. J. Org. Chem. 2003, 68, 8042.

⁽⁴⁷⁾ Ramón, D. J.; Yus, M. Angew. Chem., Int. Ed. 2004, 43, 284.

JOC Article





^a Reagents: (a) BnBr, NaH; (b) MeOTf, then NaBH₄, then AgNO₃, H₂O; (c) Jones' reagent; (d) CH₂N₂.

the tertiary alcohol 32 in 75% isolated yield. The absolute configuration at the newly formed quaternary carbon in this compound was assigned as detailed below. After this stereoselective transformation was carried out, we reasoned that inverting the timing of phenyl and thiazolyl group addition in the above reaction sequence might lead to the epimer of **32**, providing that the diastereofacial selectivity of the organometal addition to the carbonyl was the same. Accordingly, β -1 was treated with 2-trimethylsilylthiazole⁴⁸ (2-TST, 35) (1.2 equiv) in CH₂Cl₂ at room temperature. Under these conditions a sluggish reaction took place. The almost complete consumption of β -1 was reached after 50 h and treatment with two additional portions (1.2 equiv each) of 2-TST 35. The resulting mixture of diastereomeric silvlated alcohols⁴⁹ was oxidized by the Moffat reagent (Ac₂O-DMSO) to the ketone 36, which was isolated in 72% yield from the aldehyde β -1. The addition of phenylmagnesium bromide to **36** in THF at -50 °C occurred with high selectivity too as the tertiary alcohol 37 was isolated as the sole product in almost quantitative yield.

The *R*- and *S*-configurations of the quaternary carbon atom of the alcohols 32 and 37, both displaying the pyranose moiety in a ${}^{2}C_{5}$ conformation, were tentatively assigned by nOe difference experiments (400 MHz, CDCl₃). In the case of compound **32**, irradiation of the OH-1 proton led to a strong enhancement of the H-3 signal and a weak nOe with the Hortho of the phenyl ring at C-1. Upon irradiation of these protons, a weak nOe with OH-1 and a strong enhancement of the H-2 signal were observed. We concluded that the tertiary alcohol 32 adopted a preferential conformation where the OH group was anti to H-2 and the compound was R-configured (Figure 3). Assuming the S-configuration for this compound one would expect the absence of nOe between OH-1 and the H_{ortho} of the phenyl ring. Similar NMR experiments carried out on compound 37 showed strong nOes between OH-1 and both H-2 and H-3. Moreover, irradiation of the Hortho of the phenyl ring showed significant enhancements of the same H-2 and H-3

⁽⁴⁸⁾ Although 2-TST is commercially available, the high price leads to recommend its preparation on a multigram scale from inexpensive 2-bromothiazole. See: Dondoni, A.; Merino, P. *Org. Synth.* **1995**, *72*, 21.





FIGURE 3. Nuclear Overhauser effects observed for the tertiary alcohol **32**.

signals. These effects indicated a free rotation around the *C*-glycosidic bond, thus excluding the possibility of any stereochemical assignment by this NMR technique. Hence, the *S*-configuration at C-1 in compound **37** was forcedly indirectly assigned as that of the epimer of the alcohol **32**.

Completion of the synthetic plan required only the transformation of the thiazole ring of compounds 32 and 37 into the carboxyl group. Guided by our extensive experience in this chemistry we were well aware of the need to proceed stepwise through aldehyde intermediates because no mild conditions were known to transform the thiazole ring directly into a carboxylate functionality.⁵⁰ Hence the thiazole-substituted alcohols 32 and 37 were first protected as O-benzyl ethers which in turn were subjected to the standard thiazole-to-formyl unmasking protocol.⁵¹ The resulting aldehydes 33 and 38 were isolated in good to fair yields, i.e., 50% and 70%, respectively. Finally these aldehydes were considered for oxidation to carboxylic acids. This transformation was conveniently carried out with compound 33 by using the Jones' reagent. Esterification of the carboxylic group with

⁽⁵⁰⁾ The cleavage of the thiazole ring to amide via reaction with singlet oxygen has been reported in two instances (Matsuura, T.; Saito, I. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2973. Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445). This method appears to be rather impractical and requires workup operations which are hardly compatible with the integrity of stereocenters and acid sensitive protective groups in the substrate.

⁽⁵¹⁾ It is worth noting that in this case the reduction of the *N*-methyl thiazolium salt with NaBH₄ required heating in ethanol at 60 $^{\circ}$ C instead of the usual conditions (MeOH, 0 $^{\circ}$ C to room temperature).

SCHEME 9



diazomethane furnished the ester 34 in 72% yield. On the other hand, the aldehyde 38 turned out to be impervious to the treatment by usual oxidizing systems such as the Jones' reagent, TEMPO-BAIB, and I₂-KOH-MeOH. This may be ascribed to the heterogeneous conditions of these reactions since 38 was sparingly soluble in the relevant polar solvents. Moreover it is likely that this aldehyde is more encumbered than the isomer **33** and therefore less reactive. Deceptively, despite intense experimentation we were unable to find suitable conditions for the transformation of **38** to the ester **39**. This problem was overcome by using the hydroxy-free aldehyde 40 (Scheme 9) which, fortunately enough, displayed sufficient solubility in methanol. Noteworthy, this aldehyde was obtained in good yield from compound 37 by thiazole-to-formyl conversion despite the presence of the free hydroxy group, which in other systems was incompatible with this transformation.52 Then, to our great delight, 40 was effectively oxidized to the methyl ester 41 simply by treatment with I₂ and KOH in 5:1 MeOH-CCl₄. This final transformation concluded successfully the synthetic plan.53 Validation of this methodology by extension to the synthesis of other C-glycosyl phenylhydroxy acetates including the altrosyl derivatives (R)-**29** and (S)-**29** now appears of interest.

Conclusions

The ease of preparation of L-*C*-fucosyl aldehyde epimers α -**1** and β -**1** and their convenient use in synthetic approaches to three families of *C*-fucosides demonstrate once again the synthetic utility of anomeric sugar aldehydes as building blocks for complex *C*-glycosides without facing the task of controlling the anomeric configuration. Noteworthy is the new as well as highly stereoselective approach to *C*-glycosyl phenylhydroxy acetates as shown by the synthesis of the *C*-fucosyl derivatives (*R*)-**30** and (*S*)-**30**. However, the effectiveness and generality of this approach need to be demonstrated by the use of a significant number of *C*-glycosyl aldehydes. This issue is addressed by research underway in our laboratory. In addition to that, we foresee another possible route to the above sugar acetates via the Beau and Skrydstrup

 $\rm SmI_{2}$ -mediated coupling⁵⁴ of glycosylated pyridyl sulfones with phenyl thiazolyl ketone. However, crucial to the success of this approach is the full control of its stereochemical outcome to establish the required configuration at both the anomeric carbon of the sugar moiety and the newly formed quaternary carbon of the side chain.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere in oven-dried glassware. Anhydrous solvents were dried over standard drying agents⁵⁵ and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μ m average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F₂₅₄ with detection by charring with sulfuric acid and/or ninhydrin. Flash column chromatography56 was performed on silica gel 60 (230-400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20 \pm 2 °C in the stated solvent; [α]_D values are given in deg·mL·g⁻¹·dm⁻¹. ¹H NMR spectra (300 and 400 MHz) were recorded for CDCl₃ solutions at room temperature unless otherwise specified; chemical shifts are in ppm (δ) from SiMe₄ (TMS) as internal standard; peak assignments were performed by 1H-1H COSY experiments. MALDI-TOF mass spectra were acquired with use of α -cyano-4-hydroxycinnamic acid as the matrix. Fuconolactone 323 was prepared by oxidation of the corresponding hemiacetal $2^{2\hat{4}}$ with pyridinium chlorochromate.⁵⁷ The aldehyde **24** was synthesized by oxidation of the corresponding primary alcohol, $^{\rm 58}$ prepared as described.⁵⁹ 2-Trimethylsilylthiazole (2-TST, 31), phenylmagnesium bromide, and 2-bromothiazole were commercially available. Alternatively, 2-TST 31 can be prepared as described.48

2,3,4-Tri-O-benzyl-1-C-(2-thiazolyl)-L-fucopyranose (5a). To a cooled (-78 °C), stirred solution of *n*BuLi (12.0 mL, 19.1 mmol, of a 1.6 M solution in hexane) in anhydrous Et_2O (25 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (1.50 mL, 16.40 mmol) in anhydrous Et₂O (6.5 mL) over a 30-min period. The yellow solution was stirred at -75 °C for 30 min, then a solution of fuconolactone **3** (5.90 g, 13.64 mmol) in anhydrous Et₂O (25 mL) was added slowly (30 min). After an additional 30 min at -75 °C the mixture was allowed to warm to -65 °C in 30 min and then poured into 150 mL of a 1 M phosphate buffer at pH 7. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 \times 150 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 5:1 to 2:1) to give 5a (6.56 g, 93%) as a syrup. $[\alpha]_D$ -6.5 (c 1.3, CHCl₃). ¹H NMR (300 MHz) δ 7.82 (d, 1 H, J = 3.2 Hz, Th), 7.48–7.19 and 7.08– 7.04 (2 m, 16 H, 3 Ph, Th), 5.07 and 4.78 (2 d, 2 H, J = 12.0Hz, PhCH₂), 4.80 (s, 2 H, PhCH₂), 4.70 and 4.31 (2 d, 2 H, J= 10.6 Hz, PhCH₂), 4.54 (s, 1 H, OH), 4.51 (d, 1 H, J_{2,3} = 9.7 Hz, H-2), 4.26 (dq, 1 H, $J_{4,5} = 1.3$ Hz, $J_{5,6} = 6.4$ Hz, H-5), 4.04 (dd, 1 H, $J_{3,4} = 2.8$ Hz, H-3), 3.77 (dd, 1 H, H-4), 1.26 (d, 3 H, 3 H-6). Anal. Calcd for C₃₀H₃₁NO₅S: C, 69.61; H, 6.04; N, 2.71. Found: C, 69.55; H, 5.82; N, 2.98.

1-O-Acetyl-2,3,4-tri-O-benzyl-1-C-(2-thiazolyl)-L-fucopyranose (5b). To a solution of 5a (6.56 g, 12.68 mmol) in anhydrous CH_2Cl_2 (68 mL) were added at rt triethylamine (19 mL) and acetic anhydride (14 mL). The solution was kept at

⁽⁵²⁾ Dondoni, A.; Marra, A.; Perrone, D. J. Org. Chem. 1993, 58, 275.

⁽⁵³⁾ As requested by two reviewers, we have checked that compounds **34** and **41** are quantitatively hydrogenated under standard conditions (H₂, 1 bar, Pd(OH)₂, MeOH, rt, 1 h) to give *R*-**30** and *S*-**30**, respectively. Compound *R*-**30**: $[\alpha]_D$ –28.4 (*c* 0.2, MeOH). ¹H NMR (400 MHz, D₂O) δ 7.54–7.50 (m, 2 H, Ar), 7.28–7.18 (m, 3 H, Ar), 4.13 (d, 1 H, *J*_{3,4} = 9.5 Hz, H-3), 3.67 (dd, 1 H, *J*_{4,5} = 9.5 Hz, H-4), 3.66 (dq, 1 H, *J*_{6,7} = 0.6 Hz, *J*_{7,8} = 6.5 Hz, H-7), 3.61 (dd, 1 H, *J*_{5,6} = 3.4 Hz, H-6), 3.58 (s, 3 H, OMe), 3.47 (dd, 1 H, H-5), 1.03 (d, 3 H, 3 H-8). Compound *S*-**30**: $[\alpha]_D$ –28.4 (*c* 0.6, MeOH). ¹H NMR (400 MHz, D₂O) δ 7.50–7.46 (m, 2 H, Ar), 7.31–7.26 (m, 2 H, Ar), 7.24–7.20 (m, 1 H, Ar), 4.22 (d, 1 H, *J*_{3,4} = 9.6 Hz, H-3), 3.80 (dd, 1 H, *J*_{4,5} = 9.2 Hz, H-4), 3.64 (dq, 1 H, *J*_{6,7} = 0.8 Hz, *J*_{7,8} = 6.4 Hz, H-7), 3.61 (dd, 1 H, *J*_{5,6} = 3.6 Hz, H-6), 3.59 (dd, 1 H, H-5), 3.46 (s, 3 H, OMe), 0.86 (d, 3 H, 3 H-8).

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(57) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(58) Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M.; Taylor,

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⁽⁵⁹⁾ Hou, D.-R.; Reibenspies, J. H.; Burgess, K. J. Org. Chem. 2001, 66, 206.

rt for 42 h and then concentrated. Crystallization of the crude product from hot cyclohexane gave pure **5b** (3.00 g, 42%) as white crystals. The mother liquor was concentrated and the residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 3:1 to 1:1) to give **5b** (3.59 g, 51%) as a white solid. Mp 125–126 °C (cyclohexane); $[\alpha]_D$ –41.5 (*c* 0.8, CHCl₃); ¹H NMR (400 MHz) δ 7.80 (d, 1 H, *J* = 3.2 Hz, Th), 7.40–7.25 (m, 16 H, 3 Ph, Th), 5.05 and 4.75 (2 d, 2 H, *J* = 11.8 Hz, PhC*H*₂), 4.66 and 4.78 (2 d, 2 H, *J* = 11.8 Hz, PhC*H*₂), 4.51 and 4.25 (2 d, 2 H, *J* = 10.7 Hz, PhC*H*₂), 4.13 (dd, 1 H, *J*_{4.5} = 1.3 Hz, *J*_{5.6} = 6.5 Hz, H-5), 3.89 (dd, 1 H, H-4), 2.19 (s, 3 H, Ac), 1.32 (d, 3 H, 3 H-6). Anal. Calcd for C₃₂H₃₃NO₆S: C, 68.67; H, 5.94; N, 2.50. Found: C, 68.77; H, 5.70; N, 2.65.

When the crude thiazolylketose 5a derived from lactone 3 (9.80 g) was directly acetylated as described above, the compound 5b was isolated by column chromatography in 92% overall yield from 1.

2-(2,3,4-Tri-*O***-benzyl**- β -L-fucopyranosyl)thiazole (6). To a stirred mixture of 5b (1.60 g, 2.86 mmol), activated 4-Å powdered molecular sieves (2.8 g), and triethylsilane (4.61 mL, 28.60 mmol) in anhydrous CH₂Cl₂ (47 mL) was added TMSOTf (776 μ L, 4.29 mmol). The mixture was stirred at rt for 1 h, then diluted with triethylamine (2.5 mL) and CH₂Cl₂ (50 mL), filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 3:1 to 1:1) to give 6 (1.37 g, 95%) as a white solid. Mp 113–114 °C (cyclohexane); $[\alpha]_{D}$ +6.3 (*c* 1.0, CHCl₃). ¹H NMR $(300 \text{ MHz}) \delta$ 7.84 (d, 1 H, J = 3.3 Hz, Th), 7.48–7.20 and 7.12– 7.06 (2 m, 16 H, 3 Ph, Th), 5.08 and 4.77 (2 d, 2 H, J = 11.7 Hz, PhCH₂), 4.81 (s, 2 H, PhCH₂), 4.69 and 4.31 (2 d, 2 H, J= 10.7 Hz, PhC H_2), 4.68 (d, 1 H, $J_{1,2} = 9.5$ Hz, H-1), 4.24 (dd, 1 H, $J_{2,3} = 9.0$ Hz, H-2), 3.76 (dd, 1 H, $J_{3,4} = 2.7$ Hz, H-3), 3.75-3.68 (m, 2 H, H-4, H-5), 1.27 (d, 3 H, $J_{5,6} = 6.3$ Hz, 3 H-6). Anal. Calcd for C₃₀H₃₁NO₄S: C, 71.83; H, 6.23; N, 2.79. Found: C, 72.02; H, 6.10; N, 2.95.

Preparation of the SmI₂ **Solution.** To a stirred mixture of commercially available samarium (1.65 g, 11.0 mmol, <40 mesh powder) and I₂ (2.55 g, 10.0 mmol) in a septum-equipped vial was added anhydrous THF (100 mL) under a nitrogen atmosphere. An exothermic reaction took place and the solution turned brownish while large amounts of SmI₃ were formed as a yellow solid after ca. 15 min. The septum was replaced by a gastight screw-cap and the mixture was stirred at 75 °C for an additional 3 h. Upon stirring at high temperature the yellow precipitate dissolved and the suspension turned deep blue due to the formation of SmI₂. The ca. 0.1 M samarium-(II) iodide solution was stored at rt and used within 1 day.

2-(2,3,4-Tri-O-benzyl-α-L-fucopyranosyl)thiazole (7). A vigorously stirred solution of 5b (1.08 g, 1.93 mmol) and anhydrous ethylene glycol (1.20 g, 19.30 mmol) in anhydrous THF (10 mL) was degassed under vacuum and saturated with argon three times, then a ca. 0.1 M solution of SmI₂ in THF was added dropwise by means of a gastight syringe until the reaction mixture turned a persistent blue (usually after 10-20 min). The mixture was stirred for an additional 10 min, then diluted with saturated aqueous NaHCO₃ (100 mL) and concentrated to remove the THF. The residue was extracted with Et_2O (2 × 100 mL), and the combined organic phases were dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 4:1 to 1:1) to give first 7 (0.90 g, 93%) as a syrup. $[\alpha]_D$ -40.5 (*c* 1.3, CHCl₃); ¹H NMR (400 MHz) δ 7.78 (d, 1 H, J = 3.3 Hz, Th), 7.36-7.23 and 7.11-7.06 (2 m, 16 H, 3 Ph, Th), 5.40 (d, 1 H, $J_{1,2} = 3.3$ Hz, H-1), 4.69 (s, 2 H, PhC H_2), 4.67 and 4.58 (2 d, 2 H, J = 12.0 Hz, PhCH₂), 4.39 and 4.36 (2 d, 2 H, J = 11.5 Hz, PhC H_2), 4.34 (dq, 1 H, $J_{4,5} = 4.6$ Hz, $J_{5,6} = 6.5$ Hz, H-5), 4.19 (dd, 1 H, $J_{2,3} = 5.7$ Hz, H-2), 3.99 (dd, 1 H, $J_{3,4} = 3.1$ Hz, H-3), 3.95 (dd, 1 H, H-4), 1.42 (d, 3 H, 3 H-6). Anal. Calcd for C₃₀H₃₁NO₄S: C, 71.83; H, 6.23; N, 2.79. Found: C, 71.45; H, 6.01; N, 2.82. Eluted second was 6 (64 mg, 6%).

2,6-Anhydro-3,4,5-tri-O-benzyl-7-deoxy-aldehydo-L-glycero-D-gluco-heptose (a-1). A mixture of 7 (960 mg, 1.91 mmol), activated 4-Å powdered molecular sieves (2.0 g), and anhydrous CH₃CN (19 mL) was stirred at rt for 10 min, then methyl triflate (280 μ L, 2.48 mmol) was added. The suspension was stirred at rt for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of the crude N-methylthiazolium salt in CH₃OH (19 mL) was added NaBH₄ (146 mg, 3.82 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. To a vigorously stirred solution of the thiazolidines in CH₃CN (20 mL) was added dropwise H₂O (2 mL) and then AgNO₃ in one portion (486 mg, 2.86 mmol). The mixture was stirred at rt for 10 min, then diluted with 1 M phosphate buffer at pH 7 (40 mL) and partially concentrated to remove CH₃CN (bath temperature not exceeding 40 °C). The suspension was extracted with CH_2Cl_2 (100 + 50 mL), and the combined organic phases were dried (Na₂SO₄) and concentrated to give a yellow syrup. A solution of the residue in Et_2O (ca. 150 mL) was filtered through a pad of Celite (1 \times 4 cm, h \times d), and concentrated to afford α -1 (770 mg, 90%) as a colorless syrup ca. 95% pure by ¹H NMR analysis. ¹H NMR (400 MHz) δ 9.79 (s, 1 H, H-1), 7.39-7.23 (m, 15 H, 3 Ph), 4.73 and 4.65 (2 d, 2 H, *J* = 11.8 Hz, PhC*H*₂), 4.72 and 4.59 (2 d, 2 H, *J* = 12.0 Hz, PhCH₂), 4.67 and 4.59 (2 d, 2 H, J = 11.8 Hz, PhCH₂), 4.42 (d, 1 H, $J_{2,3} = 4.6$ Hz, H-2), 4.21 (dd, 1 H, $J_{3,4} = 7.0$ Hz, H-3), 4.18 (dq, 1 H, $J_{5,6} = 3.7$ Hz, $J_{6,7} = 6.5$ Hz, H-6), 3.80 (dd, 1 H, $J_{4,5}$ = 2.8 Hz, H-5), 3.67 (dd, 1 H, H-4), 1.32 (d, 3 H, 3 H-7)

2,6-Anhydro-3,4,5-tri-*O***-benzyl-***7***-deoxy***-aldehydo***-***L-glycero*-**D***-manno***-heptose** (β -1). The thiazolyl *C*-glycoside **6** (260 mg, 0.51 mmol) was treated as described for the preparation of α -1 to give β -1 (213 mg, 92%) as a colorless syrup ca. 95% pure by ¹H NMR analysis. ¹H NMR (400 MHz) δ 9.65 (d, 1 H, $J_{1,2} = 1.5$ Hz, H-1), 7.40–7.28 (m, 15 H, 3 Ph), 4.99 and 4.70 (2 d, 2 H, J = 11.6 Hz, PhC H_2), 4.88 and 4.68 (2 d, 2 H, J = 10.7 Hz, PhC H_2), 4.78 and 4.75 (2 d, 2 H, J = 11.5 Hz, PhC H_2), 4.06 (dd, 1 H, $J_{2,3} = 10.1$ Hz, $J_{3,4} = 8.4$ Hz, H-3), 3.73 (dd, 1 H, H-2), 3.69–3.65 (m, 2 H, H-4, H-5), 3.56 (dq, 1 H, $J_{5,6} = 0.8$ Hz, $J_{6,7} = 6.4$ Hz, H-6), 1.22 (d, 3 H, 3 H-7).

(Z)-8,12-Anhydro-9,10,11-tri-O-benzyl-6,7,13-trideoxy-1,2:3,4-di-O-isopropylidene-a-L-glycero-D-manno-D-galactotridec-6-eno-1,5-pyranose (9). A mixture of phosphonium salt 8 (280 mg, 0.44 mmol), activated 4-Å powdered molecular sieves (0.40 g), anhydrous THF (2.3 mL), and anhydrous HMPA (1.1 mL) was stirred at room temperature for 10 min, then cooled to -30 °C. To the stirred mixture was added dropwise *n*-butyllithium (275 μ L, 0.44 mmol of a 1.6 M solution in hexanes) and, after 5 min, a solution of β -1 (182 mg, 0.40 mmol) in anhydrous THF (1 mL) over a 10-min period. The mixture was stirred at -30 °C for an additional 30 min, then allowed to reach -10 °C in 1.5 h, diluted with Et₂O (100 mL), and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3 \times 10 mL), dried (Na₂SO₄), and concentrated. Column chromatography (5:1 cyclohexane-AcOEt containing 0.2% of Et₃N) of the residue afforded **9** (157 mg, 57%) as a syrup. [α]_D –49.8 (*c* 1.4, CHCl₃); ¹H NMR (400 MHz) δ 7.39-7.24 (m, 15 H, 3 Ph), 5.75 (ddd, 1 H, $J_{5,6} = 6.9$ Hz, $J_{6,7} = 11.5$ Hz, $J_{6,8} = 1.0$ Hz, H-6), 5.69 (dd, 1 H, $J_{7,8} = 5.1$ Hz, H-7), 5.54 (d, 1 H, $J_{1,2} = 5.0$ Hz, H-1), 4.99 and 4.69 (2 d, 2 H, J = 11.7 Hz, PhCH₂), 4.86 and 4.75 (2 d, 2 H, J = 11.3 Hz, PhCH₂), 4.80 (dd, 1 H, $J_{4,5} = 1.7$ Hz, H-5), 4.74 and 4.71 (2 d, 2 H, J = 11.9 Hz, PhCH₂), 4.51 (dd, 1 H, J_{2,3} = 2.3 Hz, J_{3,4} = 7.8 Hz, H-3), 4.36 (dd, 1 H, H-4), 4.27 (dd, 1 H, H-2), 3.92 (ddd, 1 H, J_{8,9} = 9.5 Hz, H-8), 3.81 (dd, 1 H, $J_{9,10} = 9.2$ Hz, H-9), 3.64 (dd, 1 H, $J_{10,11} = 2.7$ Hz, $J_{11,12} = 0.9$ Hz, H-11), 3.56 (dd, 1 H, H-10), 3.48 (dq, 1 H, J_{12,13} = 6.4 Hz, H-12), 1.50, 1.46, 1.32, and 1.25 (4 s, 12 H, 4 Me), 1.17 (d, 3 H, 3 H-13). Anal. Calcd for C₄₀H₄₈O₉: C, 71.41; H, 7.19. Found: C, 71.13; H, 7.01.

9,10,11-Tri-O-acetyl-8,12-anhydro-6,7,13-trideoxy-1,2: 3,4-di-O-isopropylidene-α-L-*glycero*-D-*manno*-D-*galacto*-

trideco-1,5-pyranose (10). A vigorously stirred mixture of 9 (90 mg, 0.13 mmol), 20% palladium hydroxide on carbon (31 mg), and 1:1 CH₃OH-AcOEt (4 mL) was degassed under vacuum and saturated with hydrogen (by a H₂-filled balloon) three times. The suspension was stirred at rt for 3 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated. A solution of the crude triol in pyridine (2 mL) and acetic anhydride (2 mL) was kept at rt for 20 h, then concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 3:1 to 1:1) to give **10** (60 mg, 84%) as a syrup. $[\alpha]_D$ -41.1 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz) δ 5.53 (d, 1 H, $J_{1,2} = 5.1$ Hz, H-1), 5.27 (dd, 1 H, $J_{10,11} = 3.3$ Hz, $J_{11,12} = 1.2$ Hz, H-11), 5.09 (dd, 1 H, $J_{8,9} = 9.4$ Hz, $J_{9,10} = 10.0$ Hz, H-9), 5.00 (dd, 1 H, H-10), 4.60 (dd, 1 H, $J_{2,3} = 2.3$ Hz, $J_{3,4} = 8.0$ Hz, H-3), 4.30 (dd, 1 H, H-2), 4.15 (dd, 1 H, $J_{4,5} = 1.8$ Hz, H-4), 3.77–3.69 (m, 1 H, H-5), 3.73 (dq, 1 H, $J_{12,13} = 6.5$ Hz, H-12), 3.44–3.37 (m, 1 H, H-8), 2.19, 2.06, and 1.99 (3 s, 9 H, 3 Ac), 1.68-1.62 (m, 4 H, 2 H-6, 2 H-7), 1.53, 1.47, 1.36, and 1.34 (4 s, 12 H, 4 Me), 1.17 (d, 3 H, 3 H-13). Anal. Calcd for C₂₅H₃₈O₁₂: C, 56.59; H, 7.22. Found: C, 56.32; H, 7.11.

(Z,E)-8,12-Anhydro-9,10,11-tri-O-benzyl-6,7,13-trideoxy-1,2:3,4-di-O-isopropylidene-a-L-glycero-D-gluco-D-galactotridec-6-eno-1,5-pyranose (12). The aldehyde α-1 (270 mg, 0.60 mmol) was allowed to react with the phosphonium salt 8 (419 mg, 0.67 mmol) in the presence of BuLi (425 $\mu L,$ 0.68 mmol of a 1.6 M solution in hexanes) as described for the preparation of 9. The crude product was eluted from a column of silica gel with 4:1 cyclohexane-AcOEt (containing 0.3% of Et₃N) to give first syrupy **12** (194 mg, 48%) as a ca. 4:1 $Z_{,E}$ mixture. (Z)-12: ¹H NMR (400 MHz) (selected data) δ 5.94 (dd, 1 H, $J_{6,7} = 11.5$ Hz, $J_{7,8} = 6.5$ Hz, H-7), 5.84 (ddd, 1 H, $J_{5,6} = 7.9$ Hz, $J_{6,8} = 0.8$ Hz, H-6), 5.53 (d, 1 H, $J_{1,2} = 5.3$ Hz, H-1). (E)-12: 1H NMR (400 MHz) & 7.40-7.25 (m, 15 H, 3 Ph), 6.04 (dd, 1 H, $J_{6,7} = 16.1$ Hz, $J_{7,8} = 4.0$ Hz, H-7), 5.97 (ddd, 1 H, $J_{5,6} = 5.8$ Hz, $J_{6,8} = 1.4$ Hz, H-6), 5.61 (d, 1 H, $J_{1,2} = 5.0$ Hz, H-1), 4.85 and 4.65 (2 d, 2 H, J = 11.8 Hz, PhCH₂), 4.74 (s, 2 H, PhCH₂), 4.67 (ddd, 1 H, J_{8,9} = 4.8 Hz, H-8), 4.65 (s, 2 H, PhCH₂), 4.62 (dd, 1 H, $J_{2,3} = 2.4$ Hz, $J_{3,4} = 7.8$ Hz, H-3), 4.36 (dd, 1 H, $J_{4,5} = 2.0$ Hz, H-5), 4.35 (dd, 1 H, H-2), 4.22 (dd, 1 H, H-4), 4.04 (dd, 1 H, $J_{9,10} = 8.1$ Hz, H-9), 4.02 (dq, 1 H, $J_{11,12} = 2.6$ Hz, $J_{12,13} = 6.5$ Hz, H-12), 3.76 (dd, 1 H, $\hat{J}_{10,11} =$ 2.8 Hz, H-11), 3.72 (dd, 1 H, H-10), 1.55, 1.44, 1.36, and 1.33 (4 s, 12 H, 4 Me), 1.24 (s, 3 H, 3 H-13). Anal. Calcd for C₄₀H₄₈O₉: C, 71.41; H, 7.19. Found: C, 71.28; H, 7.13.

Eluted second was **13** (20 mg, 8%) slightly contaminated by uncharacterized by products. ¹H NMR (300 MHz) δ 9.20 (s, 1 H, H-1), 7.42–7.26 (m, 10 H, 2 Ph), 5.85 (dd, 1 H, $J_{3,4} = 2.4$ Hz, $J_{3,5} = 1.8$ Hz, H-3), 5.00 and 4.76 (2 d, 2 H, J = 11.8 Hz, PhC H_2), 4.77 and 4.73 (2 d, 2 H, J = 12.0 Hz, PhC H_2), 4.47 (ddd, 1 H, $J_{4,5} = 4.1$ Hz, $J_{4,6} = 1.3$ Hz, H-4), 4.17 (ddq, 1 H, $J_{5,6} = 1.5$ Hz, $J_{6,7} = 6.7$ Hz, H-6), 3.78 (ddd, 1 H, H-5), 1.40 (d, 3 H, 3 H-7).

Methyl 8,12-Anhydro-2,3,4,9,10,11-hexa-*O*-benzyl-6,7,-13-trideoxy-α-L-*glycero*-D-*gluco*-D-*gluco*-tridec-6-(*Z*, *E*)eno-1,5-pyranoside (14). The aldehyde α-1 (200 mg, 0.44 mmol) was allowed to react with the phosphonium salt 11 (370 mg, 0.44 mmol) in the presence of BuLi (275 μL, 0.44 mmol of a 1.6 M solution in hexanes) as described for the preparation of 9. The crude product was eluted from a column of silica gel with cyclohexane–AcOEt (from 7:1 to 4:1) to give 14 (144 mg, 37%) as a 1:1 mixture of *E*,*Z*-isomers. ¹H NMR (300 MHz) (selected data) δ 6.15 (dd, 1 H, $J_{6,7} = 16.0$ Hz, $J_{7,8} = 4.4$ Hz, H-7*E*), 6.05 (dd, 1 H, $J_{6,7} = 11.2$ Hz, $J_{7,8} = 6.8$ Hz, H-7*Z*), 5.91 (dd, 1 H, $J_{5,6} = 6.7$ Hz, $J_{6,8} = 1.8$ Hz, H-6*E*), 5.69 (ddd, 1 H, $J_{5,6} = 9.0$ Hz, $J_{6,8} = 1.2$ Hz, H-6*Z*), 3.41 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 1.24 (d, 3 H, $J_{12,13} = 6.5$ Hz, 3 H-13), 1.10 (d, 3 H, $J_{12,13} = 6.5$ Hz, 3 H-13). Anal. Calcd for C₅₆H₆₀O₉: C, 76.69; H, 6.90. Found: C, 76.38; H, 6.77.

9,10,11-Tri-O-acetyl-8,12-anhydro-6,7,13-trideoxy-1,2: 3,4-di-O-isopropylidene- α -L-glycero-D-gluco-D-galactotrideco-1,5-pyranose (15). The alkene 12 (197 mg, 0.29 mmol) was hydrogenated and acetylated as described for the preparation of **10** to give, after column chromatography on silica gel (2:1 cyclohexane–AcOEt), **15** (121 mg, 80%) as a syrup. $[\alpha]_D -97.7$ (c 0.9, CHCl₃); ¹H NMR (300 MHz) δ 5.55 (d, 1 H, $J_{1,2} = 5.1$ Hz, H-1), 5.35 (dd, 1 H, $J_{8,9} = 5.8$ Hz, $J_{9,10} = 10.2$ Hz, H-9), 5.29 (dd, 1 H, $J_{10,11} = 3.3$ Hz, $J_{11,12} = 1.7$ Hz, H-11), 5.22 (dd, 1 H, H-10), 4.62 (dd, 1 H, $J_{2,3} = 2.3$ Hz, $J_{3,4} = 8.0$ Hz, H-3), 4.33 (dd, 1 H, H-2), 4.22–4.16 (m, 1 H, H-8), 4.16 (dd, 1 H, $J_{4,5} = 1.7$ Hz, H-4), 3.96 (dq, 1 H, $J_{12,13} = 6.4$ Hz, H-12), 3.76–3.71 (m, 1 H, H-5), 2.18, 2.08, and 2.02 (3 s, 9 H, 3 Ac), 1.76–1.65 (m, 4 H, 2 H-6, 2 H-7), 1.56, 1.48, 1.37, and 1.36 (4 s, 12 H, 4 Me), 1.16 (d, 3 H, 3 H-13). Anal. Calcd for C₂₅H₃₈O₁₂: C, 56.59; H, 7.22. Found: C, 56.37; H, 7.00.

Methyl 2,3,4,9,10,11-Hexa-O-acetyl-8,12-anhydro-6,7,-13-trideoxy-a-L-glycero-D-gluco-D-gluco-trideco-1,5-pyranoside (16). The alkene 14 (144 mg, 0.16 mmol) was hydrogenated and acetylated as described for the preparation of 10 to give, after column chromatography on silica gel (1:1 cyclohexane–AcOEt), 16 (58 mg, 60%) as a syrup. $[\alpha]_D$ +31.3 (c 0.5, CHCl₃); ¹H NMR (400 MHz, C₆D₆) δ 5.84 (dd, 1 H, $J_{2,3}$ = 10.3 Hz, $J_{3,4} = 9.4$ Hz, H-3), 5.68 (dd, 1 H, $J_{8,9} = 5.7$ Hz, $J_{9,10}$ = 10.3 Hz, H-9), 5.43 (dd, 1 H, J_{10,11} = 3.5 Hz, H-10), 5.36 (dd, 1 H, $J_{11,12} = 1.7$ Hz, H-11), 5.08 (dd, 1 H, $J_{4,5} = 10.0$ Hz, H-4), 5.00 (dd, 1 H, $J_{1,2} = 3.7$ Hz, H-2), 4.86 (d, 1 H, H-1), 4.26 (ddd, 1 H, $J_{7a,8} = 4.0$ Hz, $J_{7b,8} = 10.4$ Hz, H-8), 3.71 (ddd, 1 H, $J_{5,6a}$ = 2.8 Hz, $J_{5,6b}$ = 7.4 Hz, H-5), 3.38 (dq, 1 H, $J_{12,13}$ = 6.5 Hz, H-12), 2.96 (s, 3 H, OMe), 1.72, 1.71, 1.70, 1.64, 1.62, and 1.60 (6 s, 18 H, 6 Ac), 1.72-1.65 and 1.35-1.30 (2 m, 4 H, 2 H-6, 2 H-7), 0.95 (d, 3 H, 3 H-13). Anal. Calcd for C₂₆H₃₈O₁₅: C, 52.88; H, 6.49. Found: C, 52.50; H, 6.39.

2,6-Anhydro-3,4,5-tri-O-benzyl-7-deoxy-L-glycero-D-gluco-heptitol (17). (a) To a cooled (0 °C), stirred solution of aldehyde $\alpha\text{-}1$ (730 mg, 1.63 mmol) in Et_2O (9 mL) and CH₃OH (9 mL) was added NaBH₄ (120 mg, 3.26 mmol). The mixture was stirred at rt for an additional 10 min, then diluted with acetone (1 mL), and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane-AcOEt to give 17 (696 mg, 95%) as a syrup. $[\alpha]_D$ –12.6 (*c* 1.1, CHCl₃); ¹H NMR (400 MHz) δ 7.36–7.24 (m, 15 H, 3 Ph), 4.77 and 4.67 (2 d, 2 H, *J* = 12.0 Hz, PhC*H*₂), 4.76 and 4.62 (2 d, 2 H, *J* = 11.8 Hz, PhC H_2), 4.65 and 4.51 (2 d, 2 H, J = 11.7 Hz, PhC H_2), 4.12 (ddd, 1 H, $J_{1a,2} = 7.8$ Hz, $J_{1b,2} = 4.8$ Hz, $J_{2,3} = 3.9$ Hz, H-2), 4.00 (dq, 1 H, $J_{5,6} = 3.5$ Hz, $J_{6,7} = 6.7$ Hz, H-6), 3.92-3.88 (m, 1 H, H-3), 3.81 (ddd, 1 H, $J_{1a,1b} = 11.6$ Hz, $J_{1a,OH} =$ 3.6 Hz, H-1a), 3.81-3.78 (m, 2 H, H-4, H-5), 3.69 (ddd, 1 H, $J_{1b,OH} = 8.7$ Hz, H-1b), 1.97 (dd, 1 H, OH), 1.30 (d, 3 H, 3 H-7). Anal. Calcd for C₂₈H₃₂O₅: C, 74.97; H, 7.19. Found: C, 74.81; H, 7.15.

(b) A mixture of 7 (1.60 g, 3.58 mmol), activated 4 Å powdered molecular sieves (3.0 g), and anhydrous CH_3CN (35 mL) was stirred at rt for 10 min, then methyl triflate (610 μ L, 5.37 mmol) was added. The suspension was stirred at rt for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of the crude N-methylthiazolium salt in CH₃OH (35 mL) was added NaBH₄ (331 mg, 8.95 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. To a vigorously stirred solution of the thiazolidines in CH₃CN (30 mL) was added dropwise H₂O (3 mL) and then AgNO₃ in one portion (912 mg, 5.37 mmol). The mixture was stirred at rt for 10 min, then NaBH₄ (397 mg, 10.74 mmol) was added. Stirring was continued for an additional 15 min, then the reaction mixture was diluted with acetone, filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give 17 (1.56 g, 97%).

2,6-Anhydro-3,4,5-tri-*O***-benzyl-1,7-dideoxy-1-iodo-L***glycero***-***D-gluco***-heptitol (18).** To a vigorously stirred solution of alcohol **17** (760 mg, 1.69 mmol), triphenylphosphine (1.11 g, 4.23 mmol), and imidazole (575 mg, 8.45 mmol) in anhydrous toluene (17 mL) was added iodine (1.07 g, 4.22 mmol). The mixture was stirred at 80 °C for 1 h, then cooled

to rt, filtered through a pad of Celite, and concentrated. A solution of the residue in Et₂O (200 mL) was washed with 5% aqueous Na₂S₂O₃ (2 × 50 mL), dried (Na₂SO₄), and concentrated. The residue was eluted from a column of silica gel with 11:1 cyclohexane–AcOEt to give **18** (880 mg, 93%) as a white solid. Mp 74–75 °C (MeOH); [α]_D–20.3 (*c* 0.8, CHCl₃); ¹H NMR (400 MHz) δ 7.37–7.24 (m, 15 H, 3 Ph), 4.74 and 4.63 (2 d, 2 H, *J* = 12.0 Hz, PhC*H*₂), 4.71 and 4.59 (2 d, 2 H, *J* = 11.9 Hz, PhC*H*₂), 4.62 and 4.53 (2 d, 2 H, *J* = 11.8 Hz, PhC*H*₂), 4.15 (dd, 1 H, *J*_{1a,2} = 5.7 Hz, *J*_{1b,2} = 8.9 Hz, *J*_{2,3} = 3.5 Hz, H-2), 3.94 (dd, 1 H, *H*-3, 4 = 6.5 Hz, H-3), 3.79 (dd, 1 H, *J*_{1a,1b} = 10.4 Hz, H-1a), 3.27 (dd, 1 H, H-1b), 1.34 (d, 3 H, 3 H-7). Anal. Calcd for C₂₈H₃₁IO₄: C, 60.22; H, 5.60. Found: C, 60.24; H, 5.35.

(2,6-Anhydro-3,4,5-tri-O-benzyl-1,7-dideoxy-L-glycero-D-gluco-heptitol-1-yl)triphenylphosphonium Iodide (19). A mixture of iodide 18 (830 mg, 1.48 mmol) and triphenylphosphine (2.20 g, 8.45 mmol) was stirred at 120 °C under a nitrogen atmosphere for 2 h, then cooled to ca. 80 °C, diluted with toluene (1 mL), transferred onto a column of silica gel, and eluted with toluene, then AcOEt, and finally 1:1 AcOEtacetone to give **19** (1.18 g, 97%) as a foam. $[\alpha]_{D}$ -34.7 (*c* 1.2, CHCl₃); ¹H NMR (400 MHz, acetone-d₆) δ 7.98-7.86, 7.79-7.73, and 7.41-7.26 (3 m, 30 H, 6 Ph), 4.80 (s, 2 H, PhCH₂), 4.79 and 4.67 (2 d, 2 H, J = 11.9 Hz, PhCH₂), 4.73 and 4.54 (2 d, 2 H, J = 11.6 Hz, PhCH₂), 4.44 (ddd, 1 H, $J_{1a,1b} = 15.3$ Hz, $J_{1a,2} = 11.0$ Hz, $J_{1a,P} = 21.7$ Hz, H-1a), 4.43–4.36 (m, 2 H, H-2, H-4), 4.11–4.04 (m, 2 H, H-3, H-6), 3.92 (dd, 1 H, $J_{4,5} = 3.0$ Hz, $J_{5,6} = 3.9$ Hz, H-5), 3.60 (ddd, 1 H, $J_{1b,2} = 2.0$ Hz, $J_{1b,P} =$ 15.5 Hz, H-1b), 0.60 (d, 3 H, $J_{6,7} = 6.5$ Hz, H-7); ³¹P NMR (162 MHz, acetone- d_6) δ 26.3. Anal. Calcd for C₄₆H₄₆IO₄P: C, 67.32; H, 5.65. Found: C, 67.55; H, 5.46.

5,9-Anhydro-6,7,8-tri-O-benzyl-2-tert-butoxycarbonylamino-2,3,4,10-tetradeoxy-1,2-N,O-isopropylidene-Lthreo-D-gulo- and -D-ido-dec-3-(Z,E)-enitol (21). A mixture of phosphonium salt 19 (195 mg, 0.24 mmol), activated 4-Å powdered molecular sieves (0.24 g), anhydrous THF (1.6 mL), and anhydrous HMPA (1.6 mL) was stirred at room temperature for 10 min, then cooled to -20 °C. The stirred mixture was treated with *n*-butyllithium (180 μ L, 0.28 mmol of a 1.6 M solution in hexanes), warmed to 0 °C, stirred for an additional 30 min, and then cooled to -20 °C. To the stirred mixture was added a solution of 20 (92 mg, 0.40 mmol) in anhydrous THF (1.6 mL) over a 10-min period. The mixture was allowed to reach 0 °C in 2.5 h, stirred at 0 °C for an additional 60 min, then diluted with Et₂O (150 mL), and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3 \times 30 mL), dried (Na₂SO₄), and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 8:1 to 4:1, containing 0.3% of Et_3N) to give syrupy **21** (106 mg, 70%) as a 3:1 E,Z mixture. ¹H NMR (300 MHz, DMSO-d₆, 120 °C) (selected data) δ 5.86 (dd, 1 H, J = 4.4, 15.9 Hz, CH=), 5.83 (dd, J = 6.1, 11.0 Hz, CH=), 5.77 (ddd, J = 0.8, 5.8, 15.9 Hz, CH=), 5.71 (ddd, J = 1.5, 5.0, 11.0 Hz, CH=), 5.56 (ddd, J = 1.5, 8.2, 11.3 Hz, CH=), 1.21 (d, J_{9,10} = 6.3 Hz, H-10), 1.18 (d, $J_{9,10} = 6.3$ Hz, H-10), 1.16 (d, $J_{9,10} = 6.3$ Hz, H-10); MALDI-TOF MS (643.83) 665.6 (M^+ + Na), 681.7 (M^+ + K). Anal. Calcd for C₃₉H₄₉NO₇: C, 72.76; H, 7.67; N, 2.18. Found: C, 72.58; H, 7.52; N, 2.31.

6,7,8-Tri-O-acetyl-5,9-anhydro-2-*tert***-butoxycarbonylamino-2,3,4,10-tetradeoxy-1,2-***N,O***-isopropylidene-L-***threo***-D-gulo-** and -D-*ido*-decitol (22). A vigorously stirred mixture of **21** (90 mg, 0.14 mmol), 20% palladium hydroxide on carbon (31 mg), and 1:1 CH₃OH–AcOEt (4 mL) was degassed under vacuum and saturated with hydrogen (by a H₂-filled balloon) three times. The suspension was stirred at rt for 1 h under a positive pressure of hydrogen (5 bar), then filtered through a plug of cotton and concentrated. A solution of the crude triol in pyridine (1 mL) and freshly distilled acetic anhydride (1 mL) was kept at rt for 20 h, then concentrated. The residue was eluted from a column of silica gel with cyclohexane–AcOEt (from 2:1 to 1:1) to give **22** (51 mg, 73%) as a syrup. ¹H NMR (300 MHz, DMSO- d_6 , 120 °C) (selected data) δ 5.22–5.03 (m, 3 H, H-6, H-7, H-8), 4.08–3.64 (m, 5 H, 2 H-1, H-2, H-5, H-9), 2.11, 2.02, and 1.97 (3 s, 9 H, 3 Ac), 1.46 (s, 9 H, *t*-Bu); MALDI-TOF MS (501.58) 524.3 (M⁺ + Na), 540.5 (M⁺ + K). Anal. Calcd for C₂₄H₃₉NO₁₀: C, 57.47; H, 7.84; N, 2.79. Found: C, 57.20; H, 7.63; N, 2.88.

Methyl 6,7,8-Tri-O-acetyl-5,9-anhydro-2-tert-butoxycarbonylamino-2,3,4,10-tetradeoxy-L-threo-D-gulo- and -D-ido-deconate (23). To a stirred, cooled (0 °C) solution of 22 (91 mg, 0.16 mmol) in acetone (3 mL) was added freshly prepared 1 M Jones' reagent (480 µL, 0.48 mmol). The mixture was allowed to warm to rt in 30 min, stirred at rt for an additional 2.5 h, diluted with 2-propanol (~0.5 mL), then with brine (10 mL), and extracted with CH_2Cl_2 (3 \times 30 mL). The combined organic phases were dried (Na₂SO₄) and concentrated. Treatment of a solution of crude acid in 1:1 Et_2O -MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (1:1 cyclohexane–AcOEt), 23 (55 mg, 70%) as a ca. 3:2 mixture of C-2 epimers. ¹H NMR (300 MHz) (selected data) δ 5.32 (dd, 1 H, $J_{5,6} = 5.6$ Hz, $J_{6,7} = 10.2$ Hz, H-6), 5.28 (dd, 1 H, $J_{7,8} = 3.3$ Hz, J_{8.9} = 1.6 Hz, H-8), 5.18 (dd, 0.4 H, H-7), 5.17 (dd, 0.6 H, H-7), 4.22-4.12 (m, 1 H, H-5), 3.92 (dq, 0.4 H, $J_{9,10} = 6.5$ Hz, H-9), 3.90 (dq, 0.6 H, $J_{9,10} = 6.5$ Hz, $\hat{H-9}$), 3.77 (s, 3 H, OMe), 1.47 (s, 1.8 H, t-Bu), 1.46 (s, 1.2 H, t-Bu), 1.17 (d, 3 H, 3 H-10); MALDI-TOF MS (489.53) 512.3 (M^+ + Na), 528.3 (M^+ + K). Anal. Calcd for C₂₂H₃₅NO₁₁: C, 53.98; H, 7.21; N, 2.86. Found: C, 53.66; H, 7.17; N, 2.98.

3-tert-Butoxycarbonylamino-2,3-dideoxy-3,4-N,O-isopropylidene-aldehydo-D-glycero-tetrose (24). A mixture of (S)-N-tert-butoxycarbonyl-4-(2-hydroxyethyl)-2,2-dimethyloxazolidine^{58,59} (500 mg, 2.04 mmol; crystallized from cyclohexane, mp 73–75 °C), activated 4 Å powdered molecular sieves (2.0 g), and anhydrous CH₂Cl₂ (10 mL) was stirred at rt for 10 min, and then pyridinium chlorochromate (2.15 g, 10.0 $\,$ mmol) was added. The suspension was vigorously stirred for 40 min, then diluted with Et₂O (10 mL) and cyclohexane (10 mL), stirred for an additional 5 min, and filtered through a short pad of silica gel (7 \times 2 cm, d \times h) placed in a syntherized glass filter and previously conditioned in 1:1 Et₂O-cyclohexane. Further elution with 1:1 Et₂O-cyclohexane (ca. 200 mL) gave pure 24 (390 mg, 79%) as a white solid that could not be recrystallized (mp <40 °C). $[\alpha]_D$ +34.0 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, DMSO- d_6 , 100 °C) δ 9.70 (dd, 1 H, $J_{1,2a} = 2.2$ Hz, $J_{1,2b} = 1.8$ Hz, H-1), 4.25 (dddd, 1 H, $J_{2a,3} = 5.3$ Hz, $J_{2b,3} = 7.0$ Hz, $J_{3,4a} = 6.0$ Hz, $J_{3,4b} = 2.2$ Hz, H-3), 4.04 (dd, 1 H, $J_{4a,4b} = 9.2$ Hz, H-4a), 3.73 (dd, 1 H, H-4b), 2.75 (ddd, 1 H, $J_{2a,2b} =$ 16.0 Hz, H-2a), 2.66 (ddd, 1 H, H-2b), 1.51 and 1.45 (2 s, 6 H, 2 Me), 1.44 (s, 9 H, *t*-Bu). Anal. Calcd for C₁₂H₂₁NO₄: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.02; H, 8.63; N, 5.85.

6,10-Anhydro-7,8,9-tri-O-benzyl-2-tert-butoxycarbonylamino-2,3,4,5,11-pentadeoxy-1,2-N,O-isopropylidene-L-threo-D-ido-undec-4-(Z)-enitol (25). A mixture of phosphonium salt 19 (760 mg, 0.92 mmol), activated 4-Å powdered molecular sieves (0.90 g), anhydrous THF (7.1 mL), and anhydrous HMPA (4.7 mL) was stirred at room temperature for 10 min, then cooled to -20 °C. The stirred mixture was treated with *n*-butyllithium (580 µL, 0.92 mmol of a 1.6 M solution in hexanes), warmed to 0 °C, stirred for an additional 30 min, and then cooled to -20 °C. To the stirred mixture was added a solution of 24 (336 mg, 1.37 mmol) in anhydrous THF (7.1 mL) over a 15-min period. The mixture was allowed to reach 0 °C in 2.5 h, stirred at 0 °C for an additional 60 min, then diluted with Et₂O (200 mL), and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3 \times 30 mL), dried (Na₂SO₄), and concentrated. The residue was eluted from a column of silica gel with 5:1 cyclohexane-AcOEt to give 25 (457 mg, 75%) as a syrup. [α]_D -1.1 (*c* 1.4, CHCl₃); ¹H NMR (300 MHz, DMSO-11.5 Hz, CH=), 5.69-5.60 (m, 1 H, CH=), 4.78 and 4.58 (2 d,

2 H, J = 11.9 Hz, PhC H_2), 4.76 and 4.71 (2 d, 2 H, J = 11.5 Hz, PhC H_2), 4.63 and 4.57 (2 d, 2 H, J = 11.7 Hz, PhC H_2), 1.50 and 1.44 (2 s, 6 H, 2 Me), 1.44 (s, 9 H, *t*-Bu), 1.19 (d, 3 H, $J_{10,11} = 6.4$ Hz, 3 H-11). Anal. Calcd for C₄₀H₅₁NO₇: C, 73.03; H, 7.81; N, 2.13. Found: C, 72.78; H, 7.72; N, 2.29.

7,8,9-Tri-*O***-acetyl-6,10-anhydro-2***-tert***-butoxycarbo-nylamino-2,3,4,5,11-pentadeoxy-1,2***-N,O***-isopropylidene-**L-*threo***-***ido***-undecitol (27).** The alkene **25** (190 mg, 0.28 mmol) was hydrogenated and acetylated as described for the preparation of **22** to give, after column chromatography on silica gel (2.5:1 cyclohexane–AcOEt), first **27** (82 mg, 55%) as a syrup. $[\alpha]_D - 45.4$ (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, DMSO- d_6 , 120 °C) δ 5.22–5.15 (m, 2 H, H-8, H-9), 5.10 (dd, 1 H, $J_{6,7} = 5.3$ Hz, $J_{7,8} = 9.3$ Hz, H-7), 4.09–4.01 (m, 2 H, H-6, H-10), 3.93 (dd, 1 H, $J_{1a,1b} = 8.8$ Hz, $J_{1a,2} = 6.0$ Hz, H-1a), 3.80 (dddd, 1 H, $J_{1b,2} = 1.9$ Hz, $J_{2,3a} = 4.0$ Hz, $J_{2,3b} = 8.0$ Hz, H-2), 3.68 (dd, 1 H, H-1b), 2.10, 2.03, and 1.96 (3 s, 9 H, 3 Ac), 1.51 and 1.44 (2 s, 6 H, 2 Me), 1.46 (s, 9 H, *t*-Bu), 1.09 (d, 3 H, $J_{10,11} = 6.5$ Hz, 3 H-11). Anal. Calcd for C₂₅H₄₁NO₁₀: C, 58.24; H, 8.02; N, 2.72. Found: C, 58.02; H, 7.91; N, 2.73.

Eluted second was **26** (22 mg, 15%) as a syrup. $[\alpha]_D - 48.9$ (*c* 0.8, CHCl₃); ¹H NMR (300 MHz) δ 5.32 (dd, 1 H, $J_{6,7} = 5.7$ Hz, $J_{7,8} = 10.2$ Hz, H-7), 5.27 (dd, 1 H, $J_{8,9} = 3.2$ Hz, $J_{9,10} = 1.7$ Hz, H-9), 5.21 (dd, 1 H, H-8), 4.53 (bd, 1 H, $J_{2,NH} = 8.5$ Hz, NH), 4.19 (ddd, 1 H, $J_{5a,6} = 3.1$ Hz, $J_{5b,6} = 11.4$ Hz, H-6), 4.14–4.01 (m, 2 H), 3.93 (dq, 1 H, $J_{10,11} = 6.4$ Hz, H-10), 3.91–3.82 (m, 1 H), 2.18, 2.09, 2.08, and 2.02 (4 s, 12 H, 4 Ac), 1.43 (s, 9 H, *t*-Bu), 1.16 (d, 3 H, 3 H-11). Anal. Calcd for C₂₄H₃₉NO₁₁: C, 55.69; H, 7.60; N, 2.71. Found: C, 55.41; H, 7.48; N, 2.85.

Methyl 7,8,9-Tri-*O***-acetyl-6,10-anhydro-2***- tert***-butoxy-carbonylamino-2,3,4,5,11-pentadeoxy-L***- threo***-D***- ido***-undeconate (28).** Compound **27** (100 mg, 0.19 mmol) was oxidized and methylated as described for the preparation of **23** to give, after column chromatography on silica gel (2:1 cyclohexane–AcOEt), **28** (71 mg, 73%) as a foam. [α]_D – 52.6 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz) δ 5.28 (dd, 1 H, $J_{6,7} = 5.7$ Hz, $J_{7,8} = 10.2$ Hz, H-7), 5.24 (dd, 1 H, $J_{8,9} = 3.4$ Hz, $J_{9,10} = 1.8$ Hz, H-9), 5.17 (dd, 1 H, H-8), 5.01 (bd, 1 H, $J_{2,NH} = 8.5$ Hz, NH), 4.30 (ddd, 1 H, $J_{2,3a} = 4.7$ Hz, $J_{2,3b} = 7.8$ Hz, H-2), 4.16 (ddd, 1 H, $J_{5a,6} = 3.2$ Hz, $J_{5b,6} = 11.5$ Hz, H-6), 3.90 (dq, 1 H, $J_{10,11} = 6.5$ Hz, H-10), 3.74 (s, 3 H, OMe), 2.15, 2.05, and 2.00 (3 s, 9 H, 3 Ac), 1.43 (s, 9 H, *t*-Bu), 1.13 (d, 3 H, 3 H-11). Anal. Calcd for C₂₃H₃₇NO₁₁: C, 54.86; H, 7.41; N, 2.78. Found: C, 54.63; H, 7.30; N, 2.86.

2,6-Anhydro-3,4,5-tri-O-benzyl-7-deoxy-1-C-phenyl-aldehydo-L-glycero-D-manno-heptose (31). To a cooled (-60 °C), stirred solution of β -1 (290 mg, 0.64 mmol) in anhydrous THF (6.4 mL) was added dropwise a solution of commercially available phenylmagnesium bromide (430 μ L, 1.29 mmol, of a 3.0 M solution in Et₂O) over a 15-min period. The solution was allowed to warm to $-35\ ^\circ C$ in 1.5 h, then poured into 20 mL of a 1 M phosphate buffer at pH 7, and extracted with Et₂O (2 \times 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. A mixture of the crude alcohols, activated 4-Å powdered molecular sieves (0.6 g), and anhydrous CH₂Cl₂ (9 mL) was stirred at rt for 10 min, and then pyridinium chlorochromate (0.69 g, 3.20 mmol) was added. The suspension was vigorously stirred for 60 min, then diluted with Et₂O (40 mL) and cyclohexane (20 mL), stirred for an additional 5 min, and filtered through a short pad of silica gel (3 \times 1 cm, d \times h) placed in a syntherized glass filter and previously conditioned in 1:1 Et₂O-cyclohexane. Further elution with 1:1 Et₂Ocyclohexane (ca. 100 mL) gave crude 31 (0.30 g). The residue was eluted from a column of silica gel with 6:1 cyclohexane-AcOEt to give **31** (225 mg, 67% from β -**1**) as a white solid. Mp 142–143 °C (cyclohexane); [α]_D –16.8 (*c* 1.0, CHCl₃); ¹H NMR (400 MHz) δ 8.15–8.11 (m, 2 H, 2 H_{ortho} of Ph), 7.53 (tt, 1 H, *J* = 1.2, 7.4 Hz, H_{para} of Ph), 7.43–7.28, 7.20–7.16, and 7.10– 7.07 (3 m, 17 H, År), 5.08 and 4.73 (2 d, 2 H, J = 11.6 Hz, PhCH₂), 4.81 and 4.77 (2 d, 2 H, J = 11.9 Hz, PhCH₂), 4.76 and 4.56 (2 d, 2 H, J = 10.2 Hz, PhCH₂), 4.47-4.44 (m, 2 H), 3.78-3.72 (m, 2 H), 3.67 (dq, 1 H, $J_{5,6} = 0.6$ Hz, $J_{6,7} = 6.4$ Hz,

H-6), 1.24 (d, 3 H, 3 H-7). Anal. Calcd for $C_{34}H_{34}O_5{:}$ C, 78.14; H, 6.56. Found: C, 77.83; H, 6.43.

(1R)-2,6-Anhydro-3,4,5-tri-O-benzyl-7-deoxy-1-C-phenyl-1-C-(2-thiazolyl)-L-glycero-D-manno-heptitol (32). To a cooled (-78 °C), stirred solution of *n*BuLi (600 μ L, 0.95 mmol of a 1.6 M solution in hexane) in anhydrous Et₂O (1.3 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (85 µL, 0.92 mmol) in anhydrous Et₂O (0.5 mL) over a 15-min period. The yellow solution was stirred at -75 °C for 30 min, then a solution of ketone **31** (190 mg, 0.36 mmol) in anhydrous THF (1 mL) was added slowly (10 min). After an additional 30 min at -75 °C the mixture was allowed to warm to -65 °C in 40 min and then poured into 20 mL of a 1 M phosphate buffer at pH 7. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 \times 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 4:1 to 2:1) to give 32 (165 mg, 75%) as a syrup. $[\alpha]_D$ –69.9 (c 1.0, CHCl₃); ¹H NMR (400 MHz) δ 7.85–7.81 (m, 2 H, Ar), 7.74 and 7.17 (2 d, 2 H, J = 3.3 Hz, Th), 7.39-7.18 and 7.15-7.07 (2 m, 16 H, Ar), 6.78-6.74 (m, 2 H, Ar), 4.99 and 4.63 (2 d, 2 H, J = 11.6 Hz, PhCH₂), 4.80 (s, 1 H, OH), 4.68 and 4.55 (2 d, 2 H, J = 11.5 Hz, PhCH₂), 4.62 (d, 1 H, $J_{2,3} = 8.9$ Hz, H-2), 4.50 and 3.51 (2 d, 2 H, J = 10.6Hz, PhCH₂), 4.10 (dd, 1 H, J_{3,4} = 8.9 Hz, H-3), 3.72 (dd, 1 H, J_{4,5} = 2.6 Hz, H-4), 3.67-3.61 (m, 2 H, H-5, H-6), 1.05 (d, 3 H, $J_{6,7} = 6.4$ Hz, 3 H-7). Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.14; N, 2.30. Found: C, 72.86; H, 6.08; N, 2.45.

3,7-Anhydro-2,4,5,6-tetra-O-benzyl-8-deoxy-2-C-phenyl-aldehydo-L-threo-D-gulo-octose (33). To a stirred solution of 32 (110 mg, 0.18 mmol) in DMF (0.6 mL) was added NaH (15 mg, 0.36 mmol of a 60% dispersion in oil) and, after 15 min, benzyl bromide (27 μ L, 0.23 mmol). The mixture was stirred at rt for 3.5 h, then treated with CH₃OH (0.5 mL), stirred for an additional 10 min, diluted with H₂O (10 mL), and extracted with Et₂O (2×40 mL). The combined organic phases were dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane-AcOEt to give (1R)-2,6-anhydro-1,3,4,5-tetra-O-benzyl-7-deoxy-1-Cphenyl-1-C-(2-thiazolyl)-L-glycero-D-manno-heptitol (32-Bn) as a syrup (123 mg). ¹H NMR (300 MHz, CDCl₃, 55 °C) δ 7.78 (d, 1 H, J = 3.2 Hz, Th), 7.74–7.69 (m, 2 H, Ar), 7.42–7.00 (m, 22 H, Ar, Th), 6.51-6.46 (m, 2 H, Ar), 5.26 and 4.84 (2 d, 2 H, J = 12.4 Hz, PhCH₂), 5.02 and 4.63 (2 d, 2 H, J = 11.4 Hz, PhCH₂), 4.88 (d, 1 H, $J_{2,3} = 9.2$ Hz, H-2), 4.70 and 4.60 (2 d, 2 H, J = 11.8 Hz, PhCH₂), 4.56 and 4.19 (2 d, 2 H, J = 11.2Hz, PhC H_2), 4.29 (dd, 1 H, $J_{3,4} = 8.8$ Hz, H-3), 3.83 (dq, 1 H, $J_{5,6} = 0.8$ Hz, $J_{6,7} = 6.5$ Hz, H-6), 3.77 (dd, 1 H, $J_{4,5} = 2.8$ Hz, H-4), 3.75 (dd, 1 H, H-5), 1.30 (d, 3 H, 3 H-7). A solution of 32-Bn (123 mg, 0.17 mmol) and methyl triflate (29 μ L, 0.25 mmol) in anhydrous CH₃CN (1.7 mL) was kept at rt for 10 min, then concentrated. To a stirred suspension of the crude N-methylthiazolium salt in CH₃OH (1.7 mL) was added NaBH₄ (16 mg, 0.42 mmol). The mixture was stirred at rt for an additional 45 min, diluted with acetone, filtered through a pad of Celite, and concentrated. A solution of the residue in CH₂Cl₂ (50 mL) was washed with 1 M phosphate buffer at pH 7 (10 mL), dried (Na₂SO₄), and concentrated. To a vigorously stirred solution of the thiazolidines in CH₃CN (2 mL) was added dropwise H₂O (0.2 mL) and then AgNO₃ in one portion (43 mg, 0.25 mmol). The mixture was stirred at rt for 10 min, then diluted with 1 M phosphate buffer at pH 7 (5 mL) and partially concentrated to remove CH₃CN (bath temperature not exceeding 40 °C). The suspension was extracted with Et₂O (50 mL) and then CH₂Cl₂ (50 mL), and the combined organic phases were dried (Na₂SO₄) and concentrated to give a vellow syrup. A solution of the residue in Et₂O (ca. 50 mL) was filtered through a pad of Celite (1 \times 3 cm, h \times d) and concentrated to give 33 (58 mg, 50% from 32) as a colorless syrup ca. 95% pure by ¹H NMR analysis. ¹H NMR (300 MHz) δ 9.70 (s, 1 H, H-1), 7.75-7.70 (m, 2 H, Ar), 7.43-7.24 (m, 18 H, Ar), 7.14-7.01 (m, 3 H, Ar), 6.42-6.37 (m, 2 H, Ar), 5.25 and 5.08 (2 d, 2 H,

J = 12.0 Hz, PhC H_2), 5.07 and 4.67 (2 d, 2 H, J = 11.3 Hz, PhC H_2), 4.74 and 4.66 (2 d, 2 H, J = 11.6 Hz, PhC H_2), 4.63 (d, 1 H, $J_{3,4} = 9.2$ Hz, H-3), 4.51 and 4.20 (2 d, 2 H, J = 10.2 Hz, PhC H_2), 4.26 (dd, 1 H, $J_{4,5} = 9.5$ Hz, H-4), 3.76–3.70 (m, 2 H, H-5, H-6), 3.66 (dq, 1 H, $J_{6,7} = 0.6$ Hz, $J_{7,8} = 6.4$ Hz, H-7), 1.32 (d, 3 H, 3 H-8).

Methyl 3,7-Anhydro-2,4,5,6-tetra-O-benzyl-8-deoxy-2-C-phenyl-L-threo-D-gulo-octonate (34). To a stirred, cooled (0 °C) solution of **33** (43 mg, 0.07 mmol) in acetone (1.2 mL) was added freshly prepared 1 M Jones' reagent (210 μ L, 0.21 mmol). The mixture was allowed to warm to rt in 30 min, stirred at rt for an additional 3 h, diluted with 2-propanol (~ 0.2 mL), then with brine (10 mL), and extracted with AcOEt (3 imes25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated. Treatment of a solution of crude acid in 1:1 Et₂O–MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (3:1 cyclohexane-AcOEt), **34** (32 mg, 72%) as syrup. $[\alpha]_D$ -74.3 (c 0.7, CHCl₃); ¹H NMR (400 MHz) & 7.84-7.80 (m, 2 H, Ar), 7.41-7.16 (m, 18 H, Ar), 7.09-6.97 (m, 3 H, Ar), 6.36-6.32 (m, 2 H, Ar), 5.26 and 5.12 (2 d, 2 H, J = 12.1 Hz, PhCH₂), 5.04 and 4.63 (2 d, 2 H, J = 11.1 Hz, PhCH₂), 4.70 and 4.62 (2 d, 2 H, J = 11.6 Hz, PhCH₂), 4.60 (d, 1 H, $J_{3,4} = 9.2$ Hz, H-3), 4.40 and 4.03 (2 d, 2 H, J = 10.2 Hz, PhCH₂), 4.17 (dd, 1 H, J_{4,5} = 8.8 Hz, H-4), 3.72-3.67 (m, 2 H, H-5, H-6), 3.67 (s, 3 H, OMe), 3.61 (dq, 1 H, $J_{6,7} = 0.6$ Hz, $J_{7,8} = 6.4$ Hz, H-7), 1.28 (d, 3 H, 3 H-8). Anal. Calcd for $C_{43}H_{44}O_7$: C, 76.76; H, 6.59. Found: C, 76.68; H, 6.50.

2,6-Anhydro-3,4,5-tri-O-benzyl-7-deoxy-1-C-(2-thiazolyl)aldehydo-L-glycero-D-manno-heptose (36). To a stirred solution of β -1 (826 mg, 1.85 mmol) in anhydrous CH₂Cl₂ (9.2 mL) was added dropwise 2-TST 35 in three portions (350 μ L, 2.20 mmol, each) every 12 h. The solution was kept at rt for an additional 24 h, then concentrated. To a solution of the crude silyl ethers in freshly distilled DMSO (33 mL) was added freshly distilled acetic anhydride (7 mL). The solution was kept at rt for an additional 50 h, then diluted with saturated aqueous NaHCO₃ until pH 7 (ca. 50 mL), and extracted with Et₂O (200 mL). The organic phase was dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane-AcOEt to give 36 (703 mg, 72%) as a white solid. Mp 102–104 °C (cyclohexane); $[\alpha]_D$ +17.8 (c 1.1, CHCl₃); ¹H NMR (400 MHz) δ 8.04 and 7.70 (2 d, 2 H, J = 3.0Hz, Th), 7.41-7.28 (m, 10 H, 2 Ph), 7.18-7.14 and 6.99-6.96 (2 m, 5 H, Ph), 5.13 (d, 1 H, $J_{2,3} = 9.6$ Hz, H-2), 5.03 and 4.75 (2 d, 2 H, J = 12.0 Hz, PhCH₂), 4.85 and 4.55 (2 d, 2 H, J =11.8 Hz, PhCH₂), 4.79 and 4.76 (2 d, 2 H, J = 11.9 Hz, PhCH₂), 4.41 (dd, 1 H, $J_{3,4} = 9.6$ Hz, H-3), 3.81 (dd, 1 H, $J_{4,5} = 2.8$ Hz, H-4), 3.75-3.69 (m, 2 H, H-5, H-6), 1.20 (d, 3 H, $J_{6,7} = 6.3$ Hz, 3 H-7). Anal. Calcd for C₃₁H₃₁NO₅S: C, 70.30; H, 5.90; N, 2.64. Found: C, 70.25; H, 5.78; N, 2.71.

(1S)-2,6-Anhydro-3,4,5-tri-O-benzyl-7-deoxy-1-C-phenyl-1-C-(2-thiazolyl)-L-glycero-D-manno-heptitol (37). To a cooled (-50 °C), stirred solution of **36** (330 mg, 0.62 mmol) in anhydrous THF (6.2 mL) was added dropwise a solution of commercially available phenylmagnesium bromide (510 μ L, 1.55 mmol of a 3.0 M solution in Et₂O) over a 15-min period. The solution was allowed to warm to -30 °C in 1 h, stirred for an additional 1 h at -30 °C, then poured into 20 mL of a 1 M phosphate buffer at pH 7, and extracted with Et₂O (2 \times 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane-AcOEt to give 37 (375 mg, 99%) as a white solid. Mp 158-159 °C (AcOEt-cyclohexane); [a]_D -63.2 (c 0.9, CHCl₃); ¹H NMR (400 MHz) δ 7.98-7.94 (m, 2 H, Ar), 7.70 (d, 1 H, J = 3.2 Hz, Th), 7.39-7.24 (m, 16 H, Ar, Th), 7.14-7.10 (m, 3 H, Ar), 5.11 (s, 1 H, OH), 4.99 and 4.59 (2 d, 2 H, J = 11.6 Hz, PhCH₂), 4.83 and 4.04 (2 d, 2 H, J =10.6 Hz, PhC H_2), 4.74 and 4.63 (2 d, 2 H, J = 11.7 Hz, PhC H_2), 4.21 (d, 1 H, $J_{2,3} = 9.4$ Hz, H-2), 4.10 (dd, 1 H, $J_{3,4} = 9.2$ Hz, H-3), 3.77 (dd, 1 H, $J_{4,5} = 2.5$ Hz, H-4), 3.68 (dd, 1 H, $J_{5,6} =$ 0.6 Hz, H-5), 3.53 (dq, 1 H, J_{6,7} = 6.1 Hz, H-6), 1.13 (d, 3 H, 3

H-7). Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.14; N, 2.30. Found: C, 72.88; H, 6.05; N, 2.42.

3,7-Anhydro-2,4,5,6-tetra-O-benzyl-8-deoxy-2-C-phenyl-aldehydo-L-threo-D-ido-octose (38). To a stirred solution of 37 (320 mg, 0.52 mmol) in DMF (1.7 mL) was added NaH (44 mg, 1.05 mmol of a 60% dispersion in oil) and, after 15 min, benzyl bromide (120 μ L, 0.67 mmol). The mixture was stirred at rt for 1 h, then treated with CH₃OH (1 mL), stirred for an additional 10 min, diluted with H₂O (50 mL), and extracted with Et₂O (2 \times 100 mL). The combined organic phases were dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane-AcOEt to give (1.S)-2,6-anhydro-1,3,4,5-tetra-O-benzyl-7-deoxy-1-Cphenyl-1-C-(2-thiazolyl)-L-glycero-D-manno-heptitol (37-Bn) as a syrup (330 mg). ¹H NMR (400 MHz) δ 7.54–7.51 (m, 2 H, Ar), 7.46 (d, 1 H, J = 3.3 Hz, Th), 7.41–7.09 (m, 21 H, Ar, Th), 6.77–6.73 (m, 3 H, Ar), 5.19 and 4.75 (2 d, 2 H, J = 12.9Hz, PhCH₂), 5.12 (d, 1 H, J_{2,3} = 9.4 Hz, H-2), 5.02 and 4.60 (2 d, 2 H, J = 11.2 Hz, PhC H_2), 4.80 and 4.46 (2 d, 2 H, J = 11.6Hz, PhCH₂), 4.69 and 4.60 (2 d, 2 H, J = 11.7 Hz, PhCH₂), 4.33 (dd, 1 H, $J_{3,4} = 9.4$ Hz, H-3), 3.86 (dd, 1 H, $J_{4,5} = 2.6$ Hz, H-4), 3.74 (dd, 1 H, $J_{5,6} = 0.5$ Hz, H-5), 3.71 (dq, 1 H, $J_{6,7} =$ 6.4 Hz, H-6), 1.24 (d, 3 H, 3 H-7). A solution of 37-Bn (330 mg, 0.47 mmol) and methyl triflate (80 μ L, 0.70 mmol) in anhydrous CH₃CN (4.7 mL) was kept at rt for 10 min, then concentrated. To a warmed (60 °C), stirred suspension of the crude N-methylthiazolium salt in CH₃CH₂OH (4.7 mL) was added NaBH₄ (52 mg, 1.41 mmol). The mixture was stirred at 60 °C for an additional 15 min, then cooled to rt, diluted with acetone, and concentrated. To a vigorously stirred solution of the thiazolidines in CH₂Cl₂ (0.2 mL) and CH₃CN (9 mL) was added dropwise H₂O (0.4 mL) and then AgNO₃ in one portion (120 mg, 0.70 mmol). The mixture was stirred at rt for 15 min, then diluted with 1 M phosphate buffer at pH 7 (20 mL), partially concentrated to remove CH₃CN (bath temperature not exceeding 40 °C), and extracted with Et₂O (2 \times 50 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to give a yellow syrup. A solution of the residue in Et₂O (ca. 100 mL) was filtered through a pad of Celite (1 \times 3 cm, h \times d), and concentrated to give $\boldsymbol{38}$ (237 mg, 70% from 37) as a white solid ca. 95% pure by ¹H NMR analysis. ¹H NMR (300 MHz) δ 9.36 (s, 1 H, H-1), 7.45–7.20 (m, 25 H, 5 Ph), 5.06 and 4.66 (2 d, 2 H, J = 11.3 Hz, PhCH₂), 5.05 and 4.56 (2 d, 2 H, J = 12.1 Hz, PhCH₂), 4.96 and 4.74 (2 d, 2 H, J = 11.0 Hz, PhC H_2), 4.81 and 4.73 (2 d, 2 H, J = 11.6 Hz, PhC H_2), 4.43 (d, 1 H, $J_{3,4} = 9.5$ Hz, H-3), 4.36 (dd, 1 H, $J_{4,5} = 8.8$ Hz, H-4), 3.84 (dd, 1 H, $J_{5,6} = 2.7$ Hz, H-5), 3.77 (dd, 1 H, $J_{6,7} =$ 0.5 Hz, H-6), 3.64 (dq, 1 H, $J_{7,8} = 6.4$ Hz, H-7), 1.26 (d, 3 H, 3 H-8).

3,7-Anhydro-4,5,6-tri-O-benzyl-8-deoxy-2-C-phenyl-aldehydo-L-threo-D-ido-octose (40). A solution of 37 (140 mg, 0.23 mmol) and methyl triflate (40 μ L, 0.35 mmol) in anhydrous CH₂Cl₂ (0.5 mL) and CH₃CN (1.8 mL) was kept at rt for 15 min, then concentrated. To a solution of the crude Nmethylthiazolium salt in CH3CH2OH (4 mL) was added NaBH4 (25 mg, 0.69 mmol). The mixture was stirred at rt for an additional 15 min, then diluted with acetone, and concentrated. A solution of the residue in CH₂Cl₂ (50 mL) was washed with 1 M phosphate buffer at pH 7 (2 \times 10 mL), dried (Na₂SO₄), and concentrated. To a vigorously stirred solution of the thiazolidines in CH₂Cl₂ (0.5 mL) and CH₃CN (1.8 mL) was added dropwise H₂O (0.2 mL) and then AgNO₃ in one portion (58 mg, 0.34 mmol). The mixture was stirred at rt for 15 min, then diluted with 1 M phosphate buffer at pH 7 (50 mL), partially concentrated to remove CH₃CN (bath temperature not exceeding 40 °C), and extracted with CH_2Cl_2 (2 \times 50 mL). The combined organic phases were dried (Na₂SO₄) and concentrated to give a yellow syrup. The residue was eluted from a column of silica gel with 30:1 CH₂Cl₂-Et₂O to give 40 (103 mg, 81%) as a foam. $[\alpha]_D$ –122.4 (*c* 0.9, CHCl₃); ¹H NMR (300 MHz) & 9.54 (s, 1 H, H-1), 7.59-7.54 (m, 2 H, 2 H_{ortho} of Ph), 7.42–7.24 (m, 18 H, Ar), 4.99 and 4.72 (2 d, 2 H, J=11.9 Hz, PhC H_2), 4.92 and 4.34 (2 d, 2 H, J = 10.3 Hz, PhC H_2), 4.80 and 4.67 (2 d, 2 H, J = 11.7 Hz, PhC H_2), 4.20 (dd, 1 H, $J_{3,4} = 9.4$ Hz, $J_{4,5} = 9.2$ Hz, H-4), 4.10 (d, 1 H, H-3), 3.77 (dd, 1 H, $J_{5,6} = 2.6$ Hz, H-5), 3.68 (dd, 1 H, $J_{6,7} = 0.6$ Hz, H-6), 3.47 (dq, 1 H, $J_{7,8} = 6.4$ Hz, H-7), 1.09 (d, 3 H, 3 H-8). Anal. Calcd for C₃₅H₃₆O₆: C, 76.06; H, 6.57. Found: C, 75.81; H, 6.46.

Methyl 3,7-Anhydro-4,5,6-tri-*O***-benzyl-8-deoxy-2-***C***phenyl-L***-threo*-D-*ido***-octonate (41).** To a vigorously stirred solution of **40** (83 mg, 0.15 mmol) in CCl₄ (0.5 mL) and CH₃OH (2.5 mL) was added solid KOH (42 mg, 0.75 mmol) and, after 20 min, iodine (142 mg, 1.12 mmol). One more portion of iodine (142 mg) was added after 45 min. Stirring was continued for an additional 45 min, then the resulting purple suspension was treated with solid KOH (42 mg, 0.75 mmol). After 20 min of stirring the reaction mixture turned a pale yellow, thus iodine was added portionwise (2×142 mg, 1.12 mmol) after 45 and 90 min. Stirring was continued for an additional 45 min, then the reaction mixture was treated with solid NH₄Cl until pH 8 and concentrated. A suspension of the residue in AcOEt (100 mL) was washed with saturated aqueous NH₄Cl (30 mL), then 20% aqueous Na₂S₂O₃ (2×30 mL), dried (Na₂SO₄), and concentrated. The residue was eluted from a column of silica gel with CHCl₃–Et₂O (from 30:1 to 15:1) to give **41** (61 mg, 70%) as a white solid. Mp 167–169 °C (cyclohexane); [α]_D –56.4 (*c* 1.2, CHCl₃); ¹H NMR (300 MHz) δ 7.64–7.59 (m, 2 H, 2 H_{ortho} of Ph), 7.40–7.23 (m, 18 H, Ar), 5.09 and 4.53 (2 d, 2 H, *J* = 10.5 Hz, PhCH₂), 4.96 and 4.70 (2 d, 2 H, *J* = 12.0 Hz, PhCH₂), 4.80 and 4.71 (2 d, 2 H, *J* = 11.6 Hz, PhCH₂), 4.35 (dd, 1 H, J_{3,4} = 9.3 Hz, J_{4,5} = 9.5 Hz, H-4), 4.23 (d, 1 H, H-3), 4.04 (br s, 1 H, OH), 3.82 (dd, 1 H, J_{5,6} = 2.8 Hz, H-5), 3.70 (dd, 1 H, J_{6,7} = 1.0 Hz, H-6), 3.48 (dq, 1 H, J_{7,8} = 6.4 Hz, H-7), 3.28 (s, 3 H, OMe), 1.02 (d, 3 H, 3 H-8). Anal. Calcd for C₃₆H₃₈O₇: C, 74.21; H, 6.57. Found: C, 74.40; H, 6.43.

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