Carbohydrate Homologation by the Use of 2-(Trimethylsilyl)thiazole. Preparative Scale Synthesis of Rare Sugars: L-Gulose, L-Idose, and the Disaccharide Subunit of Bleomycin A_2

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The well established one-carbon homologation method of protected monosaccharides employing 2-(trimethylsilyl)thiazole (2-TST) as a formyl anion equivalent has been used for high yield and multigram scale synthesis of the title rare hexoses from L-xylose. Thus, L-gulose has been obtained by stereoselective *anti*-addition of 2-TST to *aldehydo*-L-xylose diacetonide followed by thiazole to formyl conversion of the resulting alcohol. The inversion of configuration at C-1 of this alcohol by an oxidation−reduction sequence prior to the aldehyde releasing from thiazole led to L-idose. The same alcohol was readily elaborated into 1,3,4,6-tetra-*O*-acetyl-L-gulopyranose whose highly stereoselective glycosidation coupling with 3-*O*-carbamoyl-2,4,6-tri-*O*-acetyl-α-D-mannosyl diethyl phosphate afforded the same peracetylated disaccharide subunit employed by Boger and Honda in the total synthesis of the antibiotic bleomycin A_2.

While numerous common sugars are available in kilogram or ton quantities from natural products and therefore constitute a convenient source of starting materials for organic synthesis,[1] other special or rare sugars are the minor yet very important components of biologically active compounds. A significant example is given by L-gulose (**1**) which coupled with a 3-carbamoylmannose derivative (Figure 1) constitutes the disaccharide subunit of bleomycin A_2,[2] the major constituent of a family of glycopeptide antibiotics capable of mediating the cleavage of DNA and RNA by a metal-dependent oxidative process.[3] Quite recently the sugar **1** has been used as starting material in the synthesis of 1,3-oxathiolane pyrimidine and purine nucleosides that exhibit very potent antiviral activity against hepatitis B virus (HBV) and human immunodeficiency virus (HIV).[4] Also the C-2 epimer L-idose (**2**) is an interesting rare sugar. For instance quantities of suitable L-idopyranose derivatives were required in the synthesis of sensitive substrates for α-L-iduronidase.[5] Therefore simple synthetic routes that make rare sugars readily available at low cost[6] and on meaningful preparative scale are quite useful for the synthesis of carbohydrate-containing natural products and their analogues. Given the efficient thiazole-based one-carbon homologation of *aldehydo*-sugars that exploits 2-(trimethylsilyl)thiazole (**5**) as a formyl anion equivalent,[7] we have considered this method for rare monosaccharide synthesis. We report here a preparative scale synthesis of the hexoses **1** and **2** from the same pentose precursor L-xylose and the exploitation of a thiazole-bearing key intermediate for a concise synthesis of the disaccharide subunit of bleomycin A_2 suitably protected for the incorporation into the aglycone moiety. The method involves reactions which are operatively simple and which can be run for either centigram or gram scale preparations. Intermediates and final products were obtained in high yields and required few chromatographic purifications.

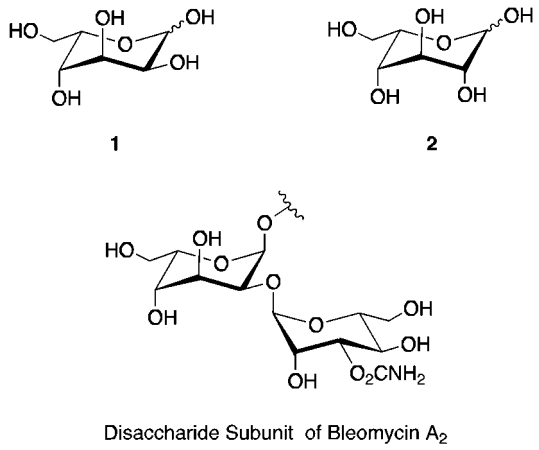


Figure 1.

Results and Discussion

Synthesis of L-Gulose (1) and L-Idose (2). A classical method of preparation of L-gulose (**1**) is that of

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) (a) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983. (b) Lichtenthaler, F. W. In *New Aspects of Organic Chemistry I*; Yoshida, Z., Shiba, T., Ohshiro, Y., Eds.; Kodansha: Tokyo, and VCH: Weinheim, 1989, p 351. (c) *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed., VCH: Weinheim, 1991. (d) *Carbohydrates as Organic Raw Materials II*; Descotes, G., Ed., VCH: Weinheim, 1993.

(2) (a) Umezawa, H. *Pure Appl. Chem.* **1971**, *28*, 665. (b) Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, A.; Umezawa, Y.; Naganawa, H.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 801.

(3) (a) Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383. (b) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107.

(4) (a) Kim, H. O.; Shanmuganathan, K.; Alves, A. J.; Jeong, L. S.; Beach, J. W.; Schinazi, R. F.; Chang, C.-N.; Cheng, Y.-C.; Chu, C. K. *Tetrahedron Lett.* **1992**, *33*, 6899. (b) Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217. (c) Jeong, L. S.; Schinazi, R. F.; Beach, J. W.; Kim, H. O.; Nampalli, S.; Shanmuganathan, K.; Alves, A. J.; McMillan, A.; Chu, C. K.; Mathis, R. *J. Med. Chem.* **1993**, *36*, 181.

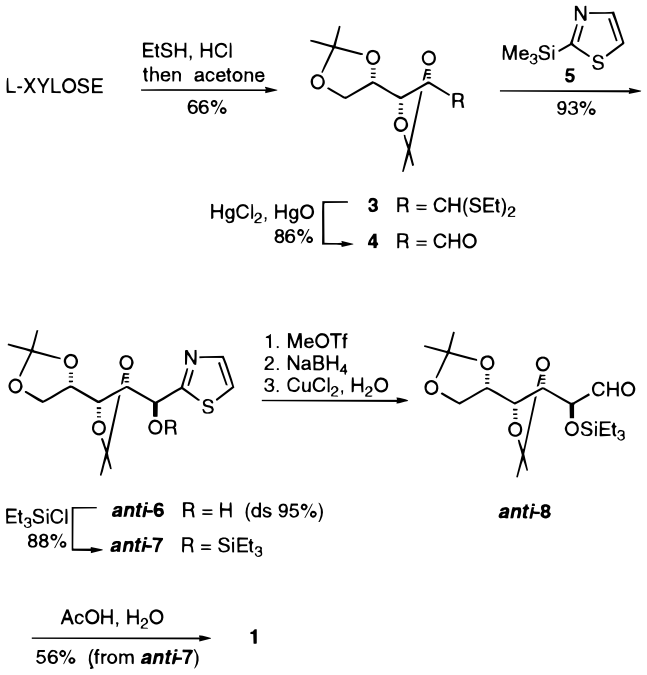
(5) (a) Stirling, J. L.; Robinson, D.; Fensom, A. H.; Benson, P. F.; Baker, J. E. *Lancet* **1978**, 147. (b) Hopwood, J. J.; Muller, V.; Smithson, A.; Baggett, N. *Clin. Chim. Acta* **1979**, *92*, 257.

(6) L-Gulose and L-idose cost *ca.* $200/100 mg.

(7) For overviews, see: (a) Dondoni, A. *Pure Appl. Chem.* **1990**, *62*, 643. (b) Dondoni, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992; p 377. (c) Dondoni, A. In *New Aspects of Organic Chemistry II*; Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo, and VCH: Weinheim, 1992; p 105. (d) Dondoni, A.; Marra, A. In *Preparative Carbohydrate Chemistry*, Hanessian, S., Ed., Marcel Dekker: New York, 1997; p 173.

S0022-3263(97)00601-4 CCC: $14.00

Scheme 1



Sowden and Fischer via nitroaldol condensation of 2,4-*O*-benzylidene-L-xylose with nitromethane.[8] More recently, special chemical syntheses of **1** and derivatives in either the furanose or pyranose form have been reported starting from D-mannose[9] and D-glucose.[10] Noteworthy is the gram scale preparation of **1** by stereocontrolled ethylhydroborane reduction of D-glucurono-6,3-lactone.[11] Quite interestingly the sodium borohydride reduction of a derivative of the same sugar lactone followed by an inversion of configuration at C-5 are the key steps of a recommended synthesis [12] of the even more rare sugar L-idose (**2**). An enzymatic method leading to **1** and **2** based on transketolase-based condensation of hydroxypyruvic acid with hydroxy aldehydes has been also reported.[13]

Our synthesis of both **1** and **2** employs L-xylose as common starting material and relies on highly stereoselective organometallic addition and oxidation−reduction sequence for the construction of the new hydroxymethylene group in either *R* and *S* configuration. The *aldehydo*-L-xylose diacetonide **4** (Scheme 1) was easily prepared from L-xylose[14] in two steps through the corresponding diethyl dithioacetal **3**. The Hg(II)-promoted hydrolysis of **3** afforded the crude aldehyde **4** suitable for the reaction with 2-(trimethylsilyl)thiazole (**5**). Guided by earlier studies carried out in our laboratory,[15] the addition of **5** to **4** (5−6 g) was efficiently carried out in dichloromethane at 0 °C in about 1 h. Desilylative workup by treatment with tetrabutylammonium fluoride[16] gave a mixture of the expected alcohol *anti*-**6** and diastereomer *syn*-**6** (not shown) in 95:5 ratio (^{1}H NMR analysis) and 93% yield. The crystallization of this mixture from AcOEt-cyclohexane afforded the pure alcohol *anti*-**6** in 61% yield from dithioacetal **3**. The protection of the hydroxyl group of *anti*-**6** before proceeding to the formyl group unmasking from the thiazole ring was recommended by previous work as well.[17] Thus *anti*-**6** was converted into the triethylsilyl ether *anti*-**7** (88%), and this product was subjected to the standard thiazole-to-formyl deblocking protocol.[18] The resulting crude *aldehydo*-L-gulose derivative *anti*-**8** was converted into the free sugar **1** by treatment with aqueous acetic acid to remove the isopropylidene and silyl protective groups. The crude L-gulose (**1**) obtained in this way appeared to be pure enough as judged by ^{1}H NMR analysis and the optical rotation value (see Experimental Section). Purification by chromatography over silica gel and then Sephadex LH-20 gave analytically pure **1** (0.5 g) in 56% yield (20% from L-xylose).

The inversion of configuration at C-1 of the readily available alcohol *anti*-**6** by an oxidation−reduction sequence provided a tactically simple entry to L-idose (**2**). This method was developed in our laboratory in an earlier thiazole-based synthesis of all possible isomeric tetroses and pentoses starting from glyceraldehyde.[19] Therefore the crude 95:5 mixture of alcohols *anti*- and *syn*-**6** (1.6 g) formed by addition of **5** to *aldehydo*-L-xylose **4** was oxidized under Swern-type conditions to give the ketone **9** in nearly quantitative yield (Scheme 2). The reduction of **9** by sodium borohydride proceeded with good stereoselectivity to give a mixture (90%) of the same alcohols *anti*- and *syn*-**6** in 9:91 ratio (^{1}H NMR analysis). Because of the unsuccessful separation of these isomers by crystallization or chromatography, the above reaction mixture was silylated and purified by column chromatography on silica gel to afford the pure diastereomer *syn*-**7** in 82% yield. From this compound the synthesis followed a parallel line as in Scheme 1, i.e. cleavage of the thiazole ring to the formyl group to give the protected *aldehydo*-L-idose *syn*-**8** (87%) and removal of all protective groups by acid hydrolysis. The free L-idose, existing as a mixture of pyranoses (**2**) and furanoses (**2a**), proved to be a good quality product by ^{1}H NMR analysis and optical rotation (see Experimental Section). However, the chromatographic purification through a column of silica gel and then Sephadex LH-20 afforded the analytically pure product in 59% isolated yield (19% overall from L-xylose).

Synthesis of Peracetylated 2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose (13). The syn-

(8) (a) Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1945**, *67*, 1713. (b) Whistler, R. L.; BeMiller, J. N. *Methods Carbohydr. Chem.* **1962**, *1*, 137.

(9) (a) Evans, M. E.; Parrish, F. W. *Carbohydr. Res.* **1973**, *28*, 359. (b) Evans, M. E.; Parrish, F. W. *Methods Carbohydr. Chem.* **1980**, *8*, 173. (c) Oshitari, T.; Tomita, M.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 6493.

(10) (a) Santoyo González, F.; Baer, H. H. *Carbohydr. Res.* **1990**, *202*, 33. (b) Ding, X.; Kong, F. *Carbohydr. Res.* **1996**, *286*, 161.

(11) Dahlhoff, W. V.; Idelmann, P.; Köster, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 546.

(12) (a) Blanc-Muesser, M.; Defaye, J. *Synthesis* **1977**, 568. (b) Blanc-Muesser, M.; Defaye, J.; Horton, D.; Tsai, J.-H. *Methods Carbohydr. Chem.* **1980**, *8*, 177. For improvements, see: (c) Baggett, N.; Samra, A. K. *Carbohydr. Res.* **1984**, *127*, 149.

(13) Kobori, Y.; Myles, D. C.; Whitesides, G. M. *J. Org. Chem.* **1992**, *57*, 5899.

(14) L-Xylose costs *ca.* $400/100 g.

(15) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693 and 702.

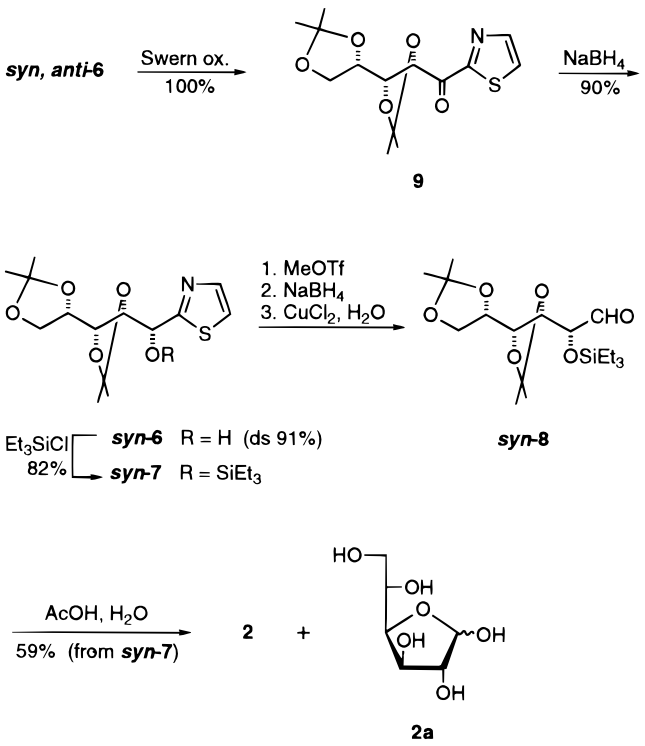
(16) Given a misleading statement that recently appeared in the literature (Parrain, J.-L.; Beaudet, I.; Cintrat, J.-C.; Duchêne, A.; Quintard, J.-P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 304), it is worth recalling here that the addition of the silylthiazole **5** to aldehydes does *not* require the activation by fluoride ions nor other catalysts. Treatment of the reaction mixture with *n*-Bu_4NF induces the desilylation of the *O*-silyl ether adduct into alcohol. A mechanistic explanation of this peculiar organosilane addition reaction has been provided, see: (a) Dondoni, A.; Douglas, A. W.; Shinkai, I. *J. Org. Chem.* **1993**, *58*, 3196. (b) Wu, Y.-D.; Lee, J. K.; Houk, K. N.; Dondoni, A. *J. Org. Chem.* **1996**, *61*, 1922.

(17) We have observed in several instances that the presence of the free hydroxyl group results in low yield of isolated aldehyde.

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

(19) Dondoni, A.; Orduna, J.; Merino, P. *Synthesis* **1992**, 201.

Scheme 2



thesis of the carbohydrate moiety of the bleomycin A_2 involves the assemblage through 1,2 *O*-glycosidic α-linkage of 3-*O*-carbamoyl-D-mannose (glycosyl donor) and L-gulose (glycosyl acceptor) and anomeric activation of the resulting disaccharide for the installation in the aglycone moiety of the antibiotic. Hence a suitably protected L-gulopyranose derivative with a free hydroxyl group at C-2 is required to start the synthesis. Evidently this problem goes beyond the preparation of the free L-gulose (**1**) as the multistep elaboration of this rare sugar[20] does not appear to be a convenient approach. Although a number of L-gulose derivatives that might serve as glycosyl acceptors at C-2 were prepared by Hecht and co-workers more than 10 years ago,[21] the synthesis of the target disaccharide and the completion of the total synthesis of bleomycin A_2 has been reported very recently by Boger and Honda.[22] The peracetylated key disaccharide intermediate **13** was obtained[22] by sequential debenzylation and acetylation of **12** that was in turn prepared by stereoselective *O*-glycosylation of the tetrabenzyl-L-gulose **10** with the tetraacetyl-D-mannopyranosyl diphenyl phosphate **11** (Figure 2). While **10** was prepared by inversion of the C-5 stereochemistry of D-mannose and through a series of protection-deprotection reactions (nine steps, 12% yield), we sought an alternative synthesis from the L-xylose−thiazole adduct *anti*-**6**. This readily available intermediate in the synthesis of L-gulose (**1**) appeared suitably tailored for the preparation of derivatives having the C-2 hydroxyl group differentially protected from the others. Thus, the alcohol *anti*-**6** was converted in nearly quantitative yield into the *tert*-butyldiphenylsilyl ether **14** (Scheme 3) from which the *aldehydo*-L-gulose **15** was obtained by thiazole-to-formyl cleavage in an exceptionally high yield (96%). As expected, the *tert*-butyldiphenylsilyl group could be taken

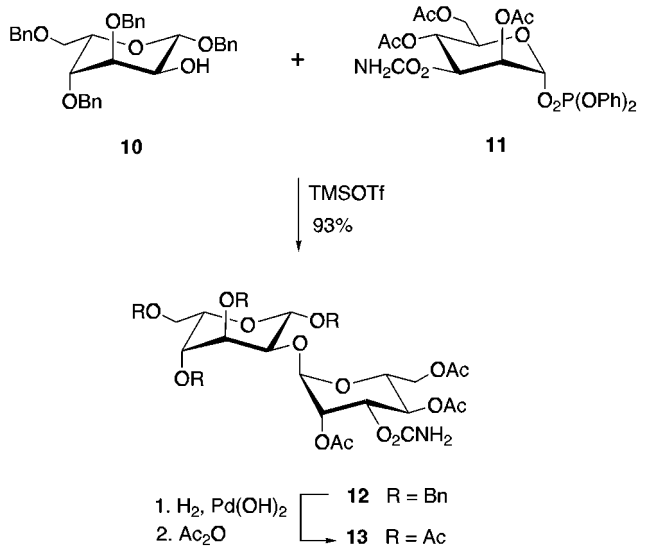
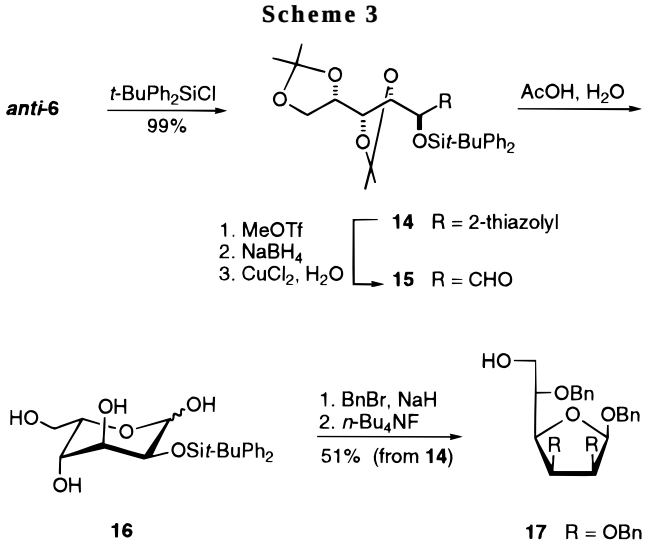


Figure 2. The Boger and Honda synthesis of the disaccharide subunit of bleomycin A_2 (ref 22).

Scheme 3



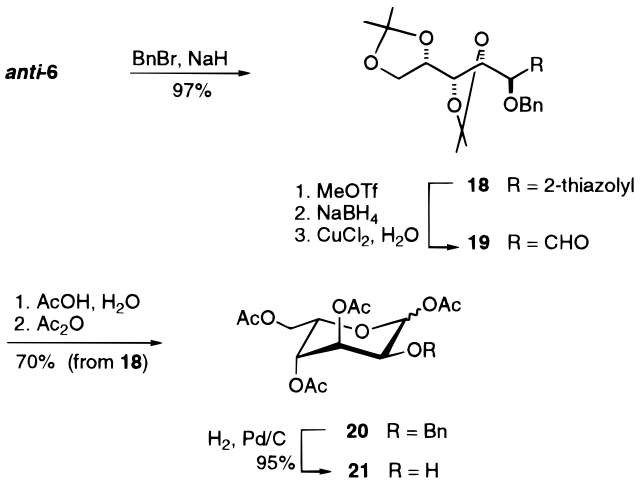
through the deacetonization of **15** by selective hydrolysis ($AcOH-H_2O$) to give, however, an inseparable 7:3 mixture of 2-*O*-silyl-L-gulose derivative[23] **16** together with regioisomers in ~100% overall yield. This detrimental silyl group migration[24] occurred under different conditions[25] of acid hydrolysis of **15**. Moreover, when crude **16** was subjected to benzylation followed by desilylation, the major product isolated (51%) was the L-gulofuranoside derivative[26] **17** that evidently precluded any further approach to the target tetrabenzylated L-gulopyranoside **10** by this route.

Therefore we decided to change the protective group strategy toward the synthesis of a suitable L-gulopyranoside derivative that could lead to the peracetylated disaccharide **13** by a more direct route avoiding the intermediacy of **12**. Thus, the alcohol *anti*-**6** was pro-

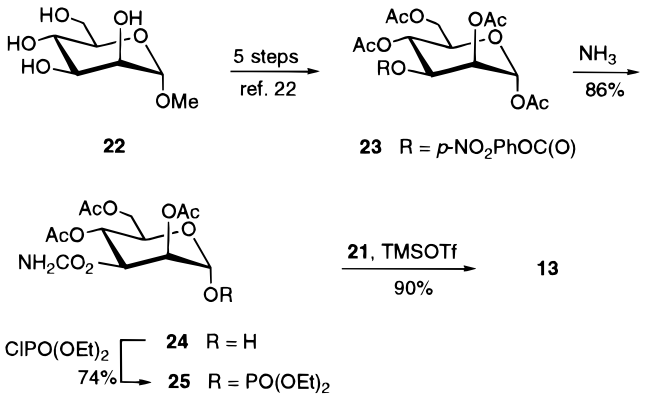
(20) Pozsgay, V.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 3761.
(21) Katano, K.; Chang, P.-I.; Millar, A.; Pozsgay, V.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1985**, *50*, 5807.
(22) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647.

(23) The structure of **16** was established by ^1H NMR analysis of the corresponding crude tetra-*O*-acetyl derivative.
(24) The so-called silicon dance is rather common in polyhydroxylated compounds, see: Arias-Pérez, M. S.; Santos, M. J. *Tetrahedron* **1996**, *52*, 10785.
(25) Other reaction conditions: 1:1 $CF_3CO_2H-H_2O$, 20 °C; 4:1 $CH_3CO_2H-H_2O$, 20 to 80 °C; 4:1 $CH_3CO_2H-CH_3OH$, 20 °C.
(26) The α-L-furanoside structure of **17** was proven by NOE experiments. Substantial enhancements of the H-1 and H-4 signals were observed in its ^1H NMR spectrum upon irradiation of H-2.

Scheme 4



Scheme 5



tected as the *O*-benzyl ether **18** (97%) by benzylation (BnBr, NaH, DMF) at 0 °C (Scheme 4). We noticed that the isolation of this compound, particularly in gram scale runs, required some simple operations to avoid the formation of considerable amounts of side products.[27] Then compound **18** was converted quite easily into the tetra-*O*-acetyl-2-*O*-benzyl-L-gulopyranoside **20** (70%) through a one-pot sequence of transformations involving the cleavage of the thiazole ring into the formyl group by the standard protocol,[18] the removal of the isopropylidene protective groups by acid hydrolysis, and finally the exhaustive acetylation. Compound **20** proved to be a mixture of β-L and α-L anomers in ca. 80:20 ratio by ^{1}H NMR analysis, contaminated by ca. 3% of furanosides. The formation of furanosides could not be suppressed under different conditions of acetylation nor were these compounds removable by chromatography. Therefore **20** was subjected to debenzylation by hydrogenolysis over Pd to give cleanly 1,3,4,5-tetra-*O*-acetyl-L-gulopyranose (**21**) as a ca. 80:20 mixture of β-L and α-L anomers. Without deliberate purification of this compound,[28] the glycosidation coupling (TMSOTf, 0 °C, CH_2Cl_2, 10 min) with the mannosyl diethyl phosphate **25** (Scheme 5) afforded the peracetylated α-D-linked disaccharide **13** in a rewarding 90% isolated yield.[29] The NMR data for **13** were in agreement with those reported.[22] The exclusive formation of the α-D-linkage in this glycosidation as well can be attributed to the neighboring acetyl group participation in the addition of **21** to the oxycarbenium ion intermediate derived from **25**. The calculated overall yield of **13** from L-xylose was 23.4% (nine steps). It is worth noting that this route to **13** features also an improved synthesis of the 3-*O*-carbamoylmannopyranosyl donor **25** since its precursor **24** was prepared in one step (86% yield) by ammonolysis of the tetraacetyl carbonate derivative **23**.

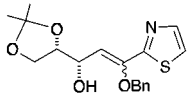
In conclusion the thiazole-based homologation of L-xylose set the basis not only for the preparative scale synthesis of the rare monosaccharides L-gulose (**1**) and L-idose (**2**) but also for an expeditious approach to the important disaccharide **13**. A key intermediate in these syntheses is the sugar−thiazole adduct *anti*-**6** whose free hydroxyl group can be manipulated in different ways while the other protected hydroxyl groups remain unaffected. Hence this stereoselective one-carbon chain-elongation of sugars offers the advantage over multicarbon processes[30] to permit a differentiation of the hydroxyl groups. It is worth noting that *anti*-**6** is conceptually similar to the allyl alcohol derivative employed as masked L-gulose glycosyl acceptor in a recent synthetic approach[31] to the disaccharide moiety of bleomycin A_2 via glycosylation with an activated 3-*O*-carbamoylmannopyranose derivative. This suggests the use of *anti*-**6** in this approach as well.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[32] and freshly distilled prior to use. Commercially available powdered 4-Å molecular sieves (50 μm average particle size) were used without further activation. Flash column chromatography[33] was performed on silica gel 60 (230−400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^{1}H (300 MHz), ^{13}C (75 MHz), and ^{31}P (121 MHz) NMR were recorded at rt for $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments.

2,3:4,5-Di-*O*-isopropylidene-L-xylose Diethyl Dithioacetal (3). To a suspension of L-xylose (5.00 g, 33.3 mmol) in concentrated HCl (2.0 mL) was added, with vigorous magnetic stirring, ethanethiol (7.4 mL, 99.9 mmol). Stirring was continued at room temperature until the two-layer mixture gave an homogeneous solution (usually after 15 min) which was diluted with acetone (100 mL). After 5 h, the solution was neutralized with 28% aqueous NH_4OH and coevaporated under high vacuum several times with toluene in order to remove water and most of acetone diethyl dithioketal. The residue was eluted from a column of silica gel with cyclohexane−CH_2Cl_2 (from 3:1 to 1:1) to give **3** (7.40 g, 66%) as a syrup:

(27) It is recommended to draw out DMF by repeated washing with water of Et_2O solutions. The evaporation of DMF from the basic reaction medium under vacuum at 50−60 °C induced deacetonization with elimination to an allyl alcohol derivative such as:



(28) Crude **21** upon flash chromatography over silica gel gave a complex mixture of products arising from intramolecular transesterification reactions.

(29) Our product contained 5% of the α-anomer at the L-gulose moiety. Since the acceptor **21** was used as a 80:20 mixture of β-L and α-L anomers, this result indicates that considerable anomerization of the L-gulose unit took place during the TMSOTf-promoted glycosylation.

(30) Oshitari, T.; Kobayashi, S. *Tetrahedron Lett.* **1995**, *36*, 1089.

(31) For a remarkable synthesis of L-sugars by a two-carbon chain elongation method see: Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.

(32) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

$[\alpha]_D = +51.3$ (*c* 1.8, C_6H_6); lit.[34] for the D-isomer: $[\alpha]_D = -51.25$ (*c* 2.99, C_6H_6). ^{1}H NMR (C_6D_6): δ 4.71 (dd, 1 H, $J_{1,2} = 4.5$, $J_{2,3} = 7.5$ Hz, H-2), 4.31 (ddd, 1 H, $J_{3,4} = 2.5$, $J_{4,5a} = J_{4,5b} = 7.5$ Hz, H-4), 4.21 (dd, 1 H, H-3), 4.02 (dd, 1 H, $J_{5a,5b} = 7.5$ Hz, H-5a), 3.94 (d, 1 H, H-1), 3.77 (dd, 1 H, H-5b), 2.78−2.48 (m, 4 H, 2 CH_3CH_2), 1.49, 1.45, 1.43, and 1.33 (4 s, 12 H, 4 CH_3), 1.10 and 1.08 (2 t, 6 H, $J = 7.5$ Hz, 2 CH_3CH_2). ^{13}C NMR selected data: δ 110.0 and 109.5 (2 OCO), 27.3, 27.1, 26.1, 25.6, 25.3, and 24.9 (4 CH_3, 2 CH_3CH_2), 14.3 and 14.2 (2 CH_3CH_2).

2,3:4,5-Di-*O*-isopropylidene-*aldehydo*-L-xylose (4). A stirred solution of **3** (6.00 g, 17.8 mmol) in acetone (60 mL) was diluted with H_2O (6.0 mL) and treated with yellow mercury(II) oxide (8.88 g, 41.0 mmol) and mercury(II) chloride (8.71 g, 32.1 mmol). The mixture was stirred at 55 °C for 2 h and then cooled to room temperature, filtered through a pad of Celite, and concentrated. The residue was suspended in CH_2Cl_2 (3 × 100 mL) and filtered through a pad of Celite. The solution was washed with 1 M aqueous KI (100 mL), dried (Na_2SO_4), and concentrated to give almost pure aldehyde **4** (3.53 g, ∼86%): $[\alpha]_D = +26.1$ (*c* 1.9, EtOH); lit.[35] $[\alpha]_D = +25.6$ (*c* 3.2, EtOH). ^{1}H NMR: δ 9.79 (s, 1 H, H-1), 4.25 (ddd, 1 H, $J_{3,4} = 5.0$, $J_{4,5a} = J_{4,5b} = 6.8$ Hz, H-4), 4.24 (d, 1 H, $J_{2,3} = 7.1$ Hz, H-2), 4.14 (dd, 1 H, H-3), 4.08 (dd, 1 H, $J_{5a,5b} = 8.6$ Hz, H-5a), 3.88 (dd, 1 H, H-5b), 1.53, 1.45, 1.42, and 1.39 (4 s, 12 H, 4 CH_3).

(2*S*,3*R*,4*R*,5*S*)-1,2:3,4-Di-*O*-isopropylidene-5-*C*-(2-thiazolyl)pentane-1,2,3,4,5-pentol (*anti*-6). To a cooled (−20 °C), stirred solution of crude **4** (3.53 g, ∼15.3 mmol) in anhydrous CH_2Cl_2 (60 mL) was added 2-(trimethylsilyl)thiazole (**5**, 3.2 mL, 19.9 mmol) during 15 min. The solution was stirred at 0 °C for an additional 1 h and then concentrated. A solution of the residue in anhydrous THF (60 mL) was treated with *n*-$Bu_4NF{\cdot}3H_2O$ (4.84 g, 15.3 mmol) at room temperature for 30 min and then concentrated. The residue was dissolved in CH_2Cl_2 (300 mL), washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated to give **6** (4.50 g, 80% from **3**, *anti*/*syn* = 95:5) as a white solid. Repeated crystallization of this mixture with AcOEt−cyclohexane afforded pure *anti*-**6** (3.42 g, 61% from **3**): mp 146−148 °C; $[\alpha]_D = +18.5$ (*c* 1.1, $CHCl_3$). ^{1}H NMR: δ 7.79 and 7.38 (2 d, 2 H, $J = 3.2$ Hz, Th), 5.13 (dd, 1 H, $J_{1,OH} = 4.0$, $J_{1,2} = 6.0$ Hz, H-1), 4.33 (dd, 1 H, $J_{2,3} = 7.5$ Hz, H-2), 4.20 (dd, 1 H, $J_{3,4} = 3.8$ Hz, H-3), 3.90 (dd, 1 H, $J_{4,5a} = 6.5$, $J_{5a,5b} = 7.5$ Hz, H-5a), 3.85 (ddd, 1 H, $J_{4,5b} = 6.5$ Hz, H-4), 3.73 (dd, 1 H, H-5b), 3.55 (d, 1 H, OH), 1.48, 1.46, 1.42, and 1.34 (4 s, 12 H, 4 CH_3). Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found: C, 53.43; H, 6.73; N, 4.43.

(2*S*,3*R*,4*S*,5*S*)-1,2:3,4-Di-*O*-isopropylidene-5-*C*-(2-thiazolyl)-5-*O*-(triethylsilyl)pentane-1,2,3,4,5-pentol (*anti*-7). To a stirred solution of *anti*-**6** (2.00 g, 6.34 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.20 g, 1.64 mmol) in pyridine (15 mL) was added triethylsilyl chloride (3.2 mL, 19.0 mmol). The mixture was stirred at room temperature for an additional 30 min, diluted with CH_3OH (2 mL), and, after 30 min, concentrated. The residue was suspended in CH_2Cl_2 (200 mL), washed with H_2O (30 mL), dried (Na_2SO_4), and concentrated. The residue was filtered through a short column (5 × 8 cm, d × h) of silica gel with 4:1 cyclohexane−Et_2O (containing 0.3% of Et_3N) to give *anti*-**7** (2.40 g, 88%) as a syrup: $[\alpha]_D = -9.9$ (*c* 1.1, $CHCl_3$). ^{1}H NMR: δ 7.78 and 7.34 (2 d, 2 H, $J = 3.2$ Hz, Th), 5.22 (d, 1 H, $J_{1,2} = 4.0$ Hz, H-1), 4.42 (dd, 1 H, $J_{2,3} = 7.0$ Hz, H-2), 4.17−4.13 (m, 1 H, H-3), 3.83−3.79 (m, 1 H, H-5a), 3.69−3.61 (m, 2 H, H-4, H-5b), 1.42, 1.39, 1.35, and 1.30 (4 s, 12 H, 4 CH_3), 0.94 (t, 9 H, $J = 7.2$ Hz, 3 CH_3CH_2), 0.64 (q, 6 H, 3 CH_3CH_2). Anal. Calcd for $C_{20}H_{35}NO_5SSi$: C, 55.91; H, 8.21; N, 3.26. Found: C, 56.07; H, 8.23; N, 3.25.

3,4:5,6-Di-*O*-isopropylidene-2-*O*-(triethylsilyl)-*aldehydo*-L-gulose (*anti*-8). A mixture of *anti*-**7** (2.15 g, 5.0 mmol), activated 4-Å powdered molecular sieves (10.0 g), and anhydrous CH_3CN (50 mL) was stirred at room temperature for 10 min, and then methyl triflate (0.74 mL, 6.5 mmol) was added. The suspension was stirred at room temperature for 15 min and then concentrated to dryness. To a cooled (0 °C), stirred suspension of the crude *N*-methylthiazolium salt in CH_3OH (50 mL) was added $NaBH_4$ (0.42 g, 11.0 mmol). The mixture was stirred at room temperature for an additional 5 min, diluted with acetone (5 mL), filtered through a pad of Celite, and concentrated. A solution of the crude mixture of diastereomeric thiazolidines in CH_3CN (45.5 mL) and H_2O (4.5 mL) was treated, under vigorous stirring, with CuO (3.18 g, 40.0 mmol) and then $CuCl_2{\cdot}2H_2O$ (0.85 g, 5.0 mmol). The mixture was stirred at room temperature for 15 min and then filtered through a pad of Celite and concentrated to remove acetonitrile and most of the water (bath temperature not exceeding 40 °C); the brown residue was triturated with Et_2O (4 × 50 mL), and the liquid phase was pipetted and filtered through a pad (6 x 1.5 cm, d × h) of Florisil (100−200 mesh) to afford a colorless solution. After a further washing of Florisil with AcOEt (50 mL), the combined organic phases were concentrated to yield almost pure (NMR analysis) aldehyde *anti*-**8** (1.65 g, ∼88%) as a syrup. ^{1}H NMR: δ 9.67 (d, 1 H, $J_{1,2} = 1.6$ Hz, H-1), 4.23−3.85 (m, 6 H), 1.42, 1.41, and 1.37 (3 s, 12 H, 4 CH_3), 0.98 (t, 9 H, $J = 7.2$ Hz, 3 CH_3CH_2), 0.65 (q, 6 H, 3 CH_3CH_2).

L-Gulose (1). A solution of crude *anti*-**8** (1.65 g, ∼4.4 mmol) in AcOH (24 mL) and H_2O (6 mL) was stirred at 100 °C for 1 h and then concentrated by coevaporation with toluene to give **1** slightly contaminated by uncharacterized byproducts: $[\alpha]_D$ after 3 h = +21.2 (*c* 1.1, H_2O). This mixture was eluted from a column of silica gel with 85:15 AcOEt−CH_3OH and then, in order to remove contaminating colloidal silica, from a column of Sephadex LH-20 (2 × 60 cm) with 2:1 CH_3OH−CH_2Cl_2 to afford pure **1** (0.50 g, 56% from *anti*-**7**) as an amorphous solid: $[\alpha]_D$ after 3 h = +23.4 (*c* 1.1, H_2O); lit.[11] $[\alpha]_D = +23.3$ (*c* 1.6, H_2O).

(2*S*,3*R*,4*S*)-2,3,4,5-Tetrahydroxy-2,3:4,5-di-*O*-isopropylidene-1-*C*-(2-thiazolyl)-1-pentanone (9). To a cooled (−78 °C), stirred solution of freshly distilled oxalyl chloride (0.64 mL, 7.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise a solution of freshly distilled DMSO (1.06 mL, 15.0 mmol) in anhydrous CH_2Cl_2 (5 mL). During the addition the internal temperature was kept below −70 °C and then allowed to reach −65 °C in 15 min. To this solution was added dropwise a solution of **6** (1.58 g, 5.0 mmol, 95:5 *anti*/*syn* mixture) in anhydrous CH_2Cl_2 (15 mL) (internal temperature not exceeding −50 °C). The mixture was stirred at −50 °C for 5 min, and then diluted with anhydrous Et_3N (3.48 mL, 25.0 mmol), stirred for an additional 5 min, warmed to 0 °C in 10 min, poured into a 1 M phosphate buffer (pH = 7), and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated to give almost pure **9** (1.57 g, ∼100%) suitable for the next step. An analytical sample was obtained by column chromatography (4:1 cyclohexane−AcOEt): $[\alpha]_D = +40.9$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (C_6D_6): δ 7.35 and 6.49 (2 d, 2 H, $J = 3.2$ Hz, Th), 5.88 (d, 1 H, $J_{2,3} = 6.5$ Hz, H-2), 4.42 (ddd, 1 H, $J_{3,4} = 3.2$, $J_{4,5a} = J_{4,5b} = 7.0$ Hz, H-4), 4.32 (d, 1 H, H-3), 3.97 (dd, 1 H, $J_{5a,5b} = 8.5$ Hz, H-5a), 3.78 (dd, 1 H, H-5b), 1.54, 1.53, 1.44, and 1.35 (4 s, 12 H, 4 CH_3). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.55; H, 6.08; N, 4.46.

The oxidation of a ca. 1:1 *anti*/*syn*-**6** mixture led to similar results.

(2*S*,3*R*,4*R*,5*R*)-1,2:3,4-Di-*O*-isopropylidene-5-*C*-(2-thiazolyl)pentane-1,2,3,4,5-pentol (*syn*-6). To a cooled (−78 °C), stirred solution of crude **9** (1.57 g, ∼5.0 mmol) in CH_3OH (25 mL) was added $NaBH_4$ (208 mg, 5.5 mmol). The mixture was stirred at −78 °C for an additional 40 min and then diluted with acetone (2 mL), warmed to room temperature, and concentrated. The residue was suspended in CH_2Cl_2 (150 mL), washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated to give a 91:9 mixture of *syn*-**6** and *anti*-**6** (1.42 g, 90%). ^{1}H NMR: δ 7.78 and 7.36 (2 d, 2 H, $J = 3.2$ Hz, Th), 5.03 (dd, 1 H, $J_{1,OH} = 7.2$, $J_{1,2} = 3.9$ Hz, H-1), 4.47 (dd, 1 H, $J_{2,3} = 7.8$ Hz, H-2), 4.21 (dd, 1 H, $J_{3,4} = 4.0$ Hz, H-3), 4.07 (ddd, 1 H, $J_{4,5a} = J_{4,5b} = 6.5$ Hz, H-4), 4.01 (dd, 1 H, $J_{5a,5b} = 8.1$ Hz, H-5a), 3.81 (dd, 1 H, H-5b), 3.49 (d, 1 H, OH), 1.48, 1.46, 1.42, and 1.35 (4 s, 12 H, 4 CH_3).

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(2*S*,3*R*,4*S*,5*R*)-1,2:3,4-Di-*O*-isopropylidene-5-*C*-(2-thiazolyl)-5-*O*-(triethylsilyl)pentane-1,2,3,4,5-pentol (*syn*-7). A 91:9 *syn*/*anti*-**6** mixture (1.26 g, 4.0 mmol) was silylated as described for the preparation of *anti*-**7**. Column chromatography of the residue (85:15 cyclohexane−Et_2O) gave first a 2:1 *anti*/*syn*-**7** mixture (0.30 g). Eluted second was pure *syn*-**7** (1.29 g, 82%) as a syrup: $[\alpha]_D = +50.1$ (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 7.78 and 7.34 (2 d, 2 H, J = 3.2 Hz, Th), 5.18−5.12 (m, 1 H, H-1), 4.24−4.18 (m, 2 H, H-2, H-3), 3.93 (dd, 1 H, $J_{4,5a}$ = 6.6, $J_{5a,5b}$ = 7.8 Hz, H-5a), 3.83−3.76 (m, 1 H, H-4), 3.70 (dd, 1 H, $J_{4,5b}$ = 7.8 Hz, H-5b), 1.42, 1.39, 1.35, and 1.30 (4 s, 12 H, 4 CH_3), 0.94 (t, 9 H, J = 7.5 Hz, 3 CH_3CH$_2$), 0.65 and 0.64 (2 q, 6 H, 3 CH$_3$CH_2). Anal. Calcd for $C_{20}H_{35}NO_5SSi$: C, 55.91. H, 8.21; N, 3.26. Found: C, 55.91; H, 8.20; N, 3.25.

3,4:5,6-Di-*O*-isopropylidene-2-*O*-(triethylsilyl)-*aldehydo*-L-idose (*syn*-8). Treatment of *syn*-**7** (1.29 g, 3.0 mmol) as described for the preparation of *anti*-**8** afforded almost pure aldehyde *syn*-**8** (0.98 g, ∼87%) as a syrup. ^{1}H NMR: δ 9.72 (s, 1 H, CHO), 4.27 (dd, 1 H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 7.9 Hz, H-3), 4.23 (ddd, 1 H, $J_{4,5}$ = 4.3, $J_{5,6a}$ = 6.7, $J_{5,6b}$ = 7.0 Hz, H-5), 4.14 (dd, 1 H, H-4), 4.13 (d, 1 H, H-2), 4.04 (dd, 1 H, $J_{6a,6b}$ = 8.2 Hz, H-6a), 3.87 (dd, 1 H, H-6b), 1.43, 1.42, 1.41, and 1.36 (4 s, 12 H, 4 CH_3), 0.97 (t, 9 H, J = 7.2 Hz, 3 CH_3CH$_2$), 0.64 (q, 6 H, 3 CH$_3$CH_2).

L-Idopyranose and L-Idofuranose (2 and 2a). Aldehyde *syn*-**8** (0.98 g, ∼2.6 mmol) was treated with 80% AcOH as described for the synthesis of **1** to afford **2** and **2a** contaminated by trace amounts of uncharacterized byproducts: $[\alpha]_D$ after 3 h = −13.9 (*c* 0.9, H_2O). Similar chromatographic purification gave pure **2** and **2a** (0.32 g, 59% from *syn*-**7**) as an amorphous solid: $[\alpha]_D$ after 3 h = −15.8 (*c* 1.1, H_2O); lit.[12a] $[\alpha]_D$ = −13.0 (*c* 1.4, H_2O); lit.[12c] $[\alpha]_D$ = −21.0 (*c* 1.0, H_2O); lit.[36] for the D-isomer $[\alpha]_D = +16 \pm 1$ (*c* 2.3, H_2O).

(2*S*,3*R*,4*S*,5*S*)-1,2:3,4-Di-*O*-isopropylidene-5-*O*-(*tert*-butyldiphenylsilyl)-5-*C*-(2-thiazolyl)pentane-1,2,3,4,5-pentol (14). To a warmed (80 °C), stirred solution of *anti*-**6** (630 mg, 2.00 mmol) and imidazole (817 mg, 12.00 mmol) in anhydrous DMF (5 mL) was added *tert*-butyldiphenylsilyl chloride (15.4 mL, 6.00 mmol). The mixture was stirred at 80 °C for 18 h and then cooled to room temperature, treated with CH_3OH (1 mL), stirred for an additional 30 min, diluted with H_2O (20 mL), and extracted with Et_2O (2 × 125 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane−Et_2O (4:1 and then 1.5:1) to give **14** (1.095 g, 99%) as a syrup: $[\alpha]_D = +1.7$ (*c* 1.7, $CHCl_3$). ^{1}H NMR: δ 7.80−7.74, 7.68−7.65, 7.60−7.54, and 7.52−7.26 (4 m, 12 H, 2 Ph and Th), 5.11 (d, 1 H, $J_{1,2}$ = 3.0 Hz, H-1), 4.24 (dd, 1 H, $J_{2,3}$ = 8.0 Hz, H-2), 4.02 (dd, 1 H, $J_{3,4}$ = 4.2 Hz, H-3), 3.68−3.46 (m, 3 H, H-4, H-5a, H-5b), 1.36, 1.33, 1.29, and 1.05 (4 s, 12 H, 4 CH_3), 1.11 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{30}H_{39}NO_5SSi$: C, 65.07; H, 7.10; N, 2.53. Found: C, 65.24; H, 7.11; N, 2.51.

2-*O*-(*tert*-Butyldiphenylsilyl)-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-L-gulose (15). Treatment of **14** (1.00 g, 1.81 mmol) as described for the preparation of *anti*-**8** gave almost pure aldehyde **15** (0.85 g, ∼96%) as a syrup. ^{1}H NMR: δ 9.60 (s, 1 H, H-1), 7.75−7.68, 7.67−7.60, and 7.51−7.35 (3 m, 10 H, 2 Ph), 4.23 (dd, 1 H, $J_{2,3}$ = 3.2, $J_{3,4}$ = 8.0 Hz, H-3), 4.11 (d, 1 H, H-2), 3.77 (dd, 1 H, $J_{4,5}$ = 3.6 Hz, H-4), 3.83 (ddd, 1 H, $J_{5,6a}$ = 6.4, $J_{5,6b}$ = 7.8 Hz, H-5), 3.71 and 3.66 (2 dd, 2 H, $J_{6a,6b}$ = 8.2 Hz, H-6a, H-6b), 1.39, 1.37, and 1.34 (3 s, 12 H, 4 CH_3), 1.14 (s, 9 H, *t*-Bu).

2-*O*-(*tert*-Butyldiphenylsilyl)-L-gulopyranose (16). Aldehyde **15** (800 mg, ∼1.64 mmol) was treated with 80% AcOH as described for the synthesis of **1** to give a ∼7:3 mixture of **16** and regioisomers (686 mg, ∼100%). ^{1}H NMR (acetone-d_6 + D_2O) selected data: δ 5.05 (d, 0.5 H, $J_{1,2}$ = 8.2 Hz, H-1βp), 4.82 (d, 0.5 H, $J_{1,2}$ = 3.6 Hz, H-1αp).

Benzyl 2,3,5-Tri-*O*-benzyl-α-L-gulofuranoside (17). To a cooled (0 °C), stirred solution of crude **16** and regioisomers (686 mg, ∼1.64 mmol) in DMF (10 mL) were added portionwise NaH (393 mg, 9.84 mmol, of a 60% dispersion in oil) and, after 30 min, benzyl bromide (935 μL, 7.87 mmol). The mixture was stirred at room temperature for 30 min and then treated with CH_3OH (1 mL), stirred for an additional 10 min, diluted with H_2O (30 mL), and extracted with Et_2O (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. A solution of the crude tetrabenzyl derivative in anhydrous THF (20 mL) was treated with *n*-$Bu_4NF{\cdot}3H_2O$ (517 mg, 1.64 mmol) at room temperature for 1.5 h and then concentrated. The residue was dissolved in CH_2Cl_2 (80 mL), washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated to give crude **17**. The residue was eluted from a column of silica gel with 9:1 cyclohexane−AcOEt to afford **17** (443 mg, 51% from **14**) as a syrup: $[\alpha]_D = -0.8$ (*c* 0.4, $CHCl_3$). ^{1}H NMR (C_6D_6): δ 7.50−7.05 (m, 20 H, 4 Ph), 5.13 and 4.37 (2 d, 2 H, J = 10.6 Hz, PhCH_2), 5.09 (d, 1 H, $J_{1,2}$ = 4.6 Hz, H-1), 4.96 and 4.51 (2 d, 2 H, J = 12.1 Hz, PhCH_2), 4.89 and 4.49 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.55 and 4.28 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.18 (dd, 1 H, $J_{3,4}$ = 4.2, $J_{4,5}$ = 8.5 Hz, H-4), 4.07 (ddd, 1 H, $J_{5,6a}$ = 3.3, $J_{5,6b}$ = 4.1 Hz, H-5), 3.80 (dd, 1 H, $J_{6a,6b}$ = 11.6 Hz, H-6a), 3.79 (dd, 1 H, $J_{2,3}$ = 4.5 Hz, H-3), 3.67 (dd, 1 H, H-6b), 3.56 (dd, 1 H, H-2), 2.00 (bs, 1 H, OH). ^{1}H NMR (C_6D_6 + $Cl_3CC(O)NCO$) selected data: δ 8.00 (s, 1 H, NH), 4.99 (d, 1 H, $J_{1,2}$ = 4.6 Hz, H-1), 4.50 (dd, 1 H, $J_{5,6a}$ = 2.1, $J_{6a,6b}$ = 11.6 Hz, H-6a), 4.41 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, H-6b), 4.15 (dd, 1 H, $J_{3,4}$ = 4.4, $J_{4,5}$ = 8.5 Hz, H-4), 4.10 (ddd, 1 H, H-5), 3.84 (dd, 1 H, $J_{2,3}$ = 4.6 Hz, H-3), 3.49 (dd, 1 H, H-2). Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.76; H, 6.79.

(1*S*,2*R*,3*R*,4*S*)-1-*O*-Benzyl-2,3:4,5-di-*O*-isopropylidene-1-*C*-(2-thiazolyl)pentane-1,2,3,4,5-pentol (18). To a cooled (0 °C), stirred solution of *anti*-**6** (1.58 g, 5.0 mmol) in DMF (15 mL) were added portionwise NaH (0.40 g, 10.0 mmol, of a 60% dispersion in oil) and, after 30 min, benzyl bromide (0.89 mL, 7.5 mmol). The mixture was stirred at room temperature for 30 min and then treated with CH_3OH (1 mL), stirred for an additional 10 min, diluted with H_2O (30 mL), and extracted with Et_2O (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 9:1 toluene−AcOEt to give **18** (1.97 g, 97%) as a white solid: mp 80−81 °C (from *i*-Pr_2O−cyclohexane); $[\alpha]_D = -32.3$ (*c* 1.1, $CHCl_3$). ^{1}H NMR: δ 7.83 and 7.42 (2 d, 2 H, J = 3.2 Hz, Th), 7.38−7.29 (m, 5 H, Ph), 4.88 (d, 1 H, $J_{1,2}$ = 4.8 Hz, H-1), 4.71 and 4.52 (2 d, 2 H, J = 12.1 Hz, PhCH_2), 4.42 (dd, 1 H, $J_{2,3}$ = 7.0 Hz, H-2), 4.04 (dd, 1 H, $J_{3,4}$ = 4.5 Hz, H-3), 3.98 (ddd, 1 H, $J_{4,5a}$ = 6.2, $J_{4,5b}$ = 7.3 Hz, H-4), 3.87 (dd, 1 H, $J_{5a,5b}$ = 8.2 Hz, H-5a), 3.75 (dd, 1 H, H-5b), 1.42, 1.38, 1.35, and 1.28 (4 s, 12 H, 4 CH_3). Anal. Calcd for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.37; H, 6.72; N, 3.44.

2-*O*-Benzyl-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-L-gulose (19). Treatment of **18** (1.63 g, 4.0 mmol) as described for the preparation of *anti*-**8** gave almost pure aldehyde **19** (1.26 g, ∼90%) as a syrup. ^{1}H NMR: δ 9.71 (d, 1 H, $J_{1,2}$ = 2.0 Hz, H-1), 7.44−7.26 (m, 5 H, Ph), 4.76 and 4.59 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.26 (dd, 1 H, $J_{2,3}$ = 5.2, $J_{3,4}$ = 7.5 Hz, H-3), 4.12 (ddd, 1 H, $J_{4,5}$ = 4.1, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, H-5), 4.03 (dd, 1 H, H-4), 3.96 (dd, 1 H, $J_{6a,6b}$ = 7.9 Hz, H-6a), 3.85 (dd, 1 H, H-2), 3.83 (dd, 1 H, H-6b), 1.43, 1.41, 1.38, and 1.37 (4 s, 12 H, 4 CH_3).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-benzyl-L-gulopyranose (20). A solution of crude **19** (1.26 g, ∼3.6 mmol) in AcOH (20 mL) and H_2O (5 mL) was stirred at 100 °C for 40 min and then concentrated by coevaporation with toluene to give crude 2-*O*-benzyl-L-gulose as a 79:17:4 mixture of β-pyranose, α-pyranose, and furanose forms. ^{1}H NMR (D_2O) selected data: δ 7.33−7.06 (m, Ph), 5.21 (d, $J_{1,2}$ = 4.0 Hz, H-1f), 5.06 (d, $J_{1,2}$ = 3.8 Hz, H-1αp), 4.78 (d, $J_{1,2}$ = 8.2 Hz, H-1βp), 4.56 and 4.52 (2 d, J = 11.0 Hz, PhC$H_2\beta$p), 3.99 (dd, $J_{2,3}$ = 3.2, $J_{3,4}$ = 3.4 Hz, H-3βp), 3.82 (ddd, $J_{5,4}$ = 1.0, $J_{5,6a}$ = $J_{5,6b}$ = 6.3 Hz, H-5βp), 3.61 (dd, H-4βp), 3.55 (d, 2 H-6βp), 3.36 (dd, H-2βp). A solution of the residue and 4-(*N*,*N*-dimethylamino)pyridine (0.44 g, 3.6 mmol) in pyridine (9 mL) and acetic anhydride (9 mL) was kept at room temperature for 6 h and then concentrated. The residue was eluted from a column of silica gel with 85:15 toluene−AcOEt to give **20** (1.22 g, 70% from **18**) as a 77:20:3 mixture of β-pyranose, α-pyranose, and furanose forms. ^{1}H NMR selected data: δ 7.36−7.25 (m, Ph), 6.26 (d, $J_{1,2}$ = 3.8 Hz, H-1αp), 6.23 (d, $J_{1,2}$ = 2.4 Hz, H-1f), 5.93 (d, $J_{1,2}$ = 8.5 Hz, H-1βp), 5.49 (dd, $J_{2,3}$ = 3.5, $J_{3,4}$ = 3.8 Hz, H-3βp), 4.99 (dd,

$J_{4,5}$ = 1.4 Hz, H-4βp), 4.67 and 4.53 (2 d, J = 11.9 Hz, PhC$H_2\beta$p), 4.32 (ddd, $J_{5,6a}$ = 5.8, $J_{5,6b}$ = 7.0 Hz, H-5βp), 4.15 (dd, $J_{6a,6b}$ = 11.0 Hz, H-6aβp), 4.09 (dd, H-6bβp), 3.88 (dd, H-2βp), 2.15, 2.11, 2.09, and 2.05 (4 s, 4 $CH_3\beta$p). ^{13}C NMR selected data: δ 91.4 (C-1βp), 91.0 and 89.4 (C-1αp, C-1f). Anal. Calcd for $C_{21}H_{26}O_{10}$: C, 57.53; H, 5.98. Found: C, 57.68; H, 5.98.

When the acetylation of crude 2-*O*-benzyl-L-gulose was carried out without 4-(*N*,*N*-dimethylamino)pyridine the furanose tetraacetates were formed at a larger extent. Also other acetylation procedures (THF, Ac_2O, Et_3N, rt; Ac_2O, AcONa, 130 °C) gave appreciable amounts of acetylated L-gulofuranoses.

1,3,4,6-Tetra-*O*-acetyl-L-gulopyranose (21). A vigorously stirred mixture of **20** (1.32 g, 3.0 mmol), 10% palladium on activated carbon (0.66 g), and AcOEt (20 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at room temperature for 2 h under a slightly positive pressure of H_2 (balloon) and then filtered through a pad of Celite and concentrated to afford **21** (0.99 g, 95%) as 77:20:3 mixture of β-pyranose, α-pyranose, and furanose forms. ^{1}H NMR selected data: δ 6.21 (d, $J_{1,2}$ = 3.9 Hz, H-1αp), 6.16 (bs, H-1f), 5.86 (d, $J_{1,2}$ = 8.5 Hz, H-1βp), 5.35 (dd, $J_{2,3}$ = 4.9, $J_{3,4}$ = 4.6 Hz, H-3βp), 5.03 (dd, $J_{4,5}$ = 1.4 Hz, H-4βp), 4.30 (ddd, $J_{5,6a}$ = 5.8, $J_{5,6b}$ = 7.0 Hz, H-5βp), 4.18 (dd, $J_{6a,6b}$ = 11.0 Hz, H-6aβp), 4.11 (dd, H-6bβp), 3.98 (dd, H-2βp), 2.34 (bs, OH), 2.18, 2.13, 2.12, and 2.04 (4 s, 4 $CH_3\beta$p). ^{13}C NMR selected data: δ 92.3 (C-1βp), 90.6 (C-1αp). Anal. Calcd for $C_{14}H_{20}O_{10}$: C, 48.28; H, 5.79. Found: C, 48.15; H, 5.78.

2,4,6-Tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranose (24). Ammonia was bubbled at room temperature through a solution of **23** (315 mg, 0.62 mmol) in anhydrous THF (12 mL) until the TLC analysis (9:1 CH_2Cl_2−acetone) revealed that the starting material and the 1,2,4,6-tetra-*O*-acetyl-3-*O*-carbamoyl derivative intermediate had disappeared (usually 40 min). The solution was concentrated, and the residue was eluted by a column of silica gel with 6:4 cyclohexane−AcOEt to give **24** (186 mg, 86%) as a colorless syrup. The ^{1}H NMR data for **24** were in agreement with those reported.[22]

Prolonged treatment with ammonia (~1.5 h) led to lower yields of **24** due to further cleavage of acetyl groups.

2,4,6-Tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl Diethyl Phosphate (25). To a cooled (−78 °C), stirred solution of hemiacetal **24** (254 mg, 0.73 mmol) in anhydrous THF (20 mL) was added *n*-BuLi (0.6 mL, 0.87 mmol of a 1.6 M solution in hexanes). The solution was stirred at −78 °C for 10 min before the addition of freshly distilled diethyl chlorophosphate (126 μL, 0.87 mmol). The reaction mixture was stirred at −78 °C for an additional 10 min and then poured into a mixture of AcOEt (8 mL) and saturated aqueous $NaHCO_3$ (5 mL) with vigorous stirring. The organic layer was separated, washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 6:4 AcOEt−cyclohexane (containing 5% of Et_3N) to give **25** (261 mg, 74%) as a white solid: mp 121−122 °C (from AcOEt−cyclohexane); $[\alpha]_D$ = +0.3 (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ 5.64 (dd, 1 H, $J_{1,2}$ = 1.8, $J_{1,P}$ = 6.8 Hz, H-1), 5.38−5.24 (m, 3 H), 4.73 (bs, 2 H, NH_2), 4.31 (dd, 1 H, J = 4.8, J = 11.9 Hz, H-6a), 4.25−4.07 (m, 6 H), 2.17, 2.09, and 2.07 (3 s, 9 H, 3 CH_3), 1.36 (t, 6 H, J = 7.0 Hz, 2 CH_3CH$_2$). ^{31}P NMR: δ −3.14. Anal. Calcd for $C_{17}H_{28}NO_{13}P$: C, 42.07; H, 5.81; N, 2.89. Found: C, 42.06; H, 5.81; N, 2.88.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl)-β-L-gulopyranose (13). To a cooled (0 °C), stirred solution of **21** (50 mg, 0.14 mmol) and **25** (82 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (1 mL) was added TMSOTf (47 μL, 0.26 mmol). The mixture was stirred at 0 °C for 10 min and then poured into a mixture of AcOEt (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) with vigorous stirring. The organic layer was separated, washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 7:3 AcOEt−cyclohexane to give a 95:5 mixture of **13** and its α-L-anomer (86 mg, 90%) as a colorless foam. The NMR data for **13** were in agreement with those reported.[22] ^{1}H NMR selected data for the α-L-anomer: δ 6.29 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1).

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