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Highly Stereoselective *de Novo* Synthesis of L-Hexoses

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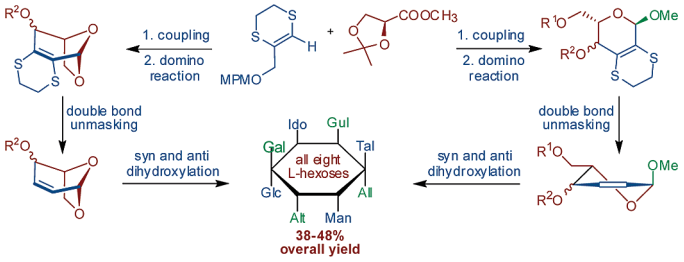

An efficient and general *de novo* synthetic route to enantiomerically pure L-hexoses has been accomplished starting from the heterocyclic homologating agent 5,6-dihydro-1,4-dithiin-2-yl[(4-methoxybenzyl)oxy]-methane and methyl α,β-isopropylidene-L-glycerate. The sugar scaffold was constructed by an acid-catalyzed domino reaction, which enabled selective preparation of either methyl 2,3-dideoxy-α-L-*threo*-hex-2-enopyranosides or 1,6-anhydro-2,3-dideoxy-β-L-*threo*-hex-2-enopyranose as key intermediates. The subsequent double bond functionalization by *syn* or *anti* dihydroxylation reactions allowed introduction of the remaining stereogenic centers, leading to desired orthogonally protected L-hexopyranosides with a high degree of diastereoselectivity and with very good overall yields. These and previous results (based on the use of the corresponding L-*erythro* epimers) contribute to make our approach general and place it among the few methods able to synthesize the whole series of the rare L-hexoses.

Introduction

Over the past decades, carbohydrates have been at the core of a huge body of investigations, given their abundance in nature and their importance in chemistry, biology, and medicine.[1] Indeed, carbohydrates play diverse and crucial roles in biological systems, as they are implicated in many life-essential metabolic processes, in signal transduction and in immune response.[2] Their involvement in health and disease events make them an attractive subject for chemical, pharmacological, and biological research.[3] In addition, in modern organic synthesis carbohydrates are both target molecules[3d] and sources of enantiopure building blocks,[4] chiral auxiliaries,[5] and catalysts.[6]

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As a consequence of the rapidly growing field of glycobiology and the development of carbohydrate-based pharmaceutical agents, innovative procedures for the selective construction of natural and unnatural carbohydrates have been developed.[7]

While the naturally occurring D-sugars are widely available and frequently used as chiral sources in the synthesis of complex natural products, the corresponding L-forms are rather rare in nature. This fact, coupled with practical difficulties in obtaining these compounds from inexpensive sources, has long delayed their entry into many aspects of organic and biomolecular chemistry. However, recent times have witnessed an emerging interest around "mirror image" carbohydrates,[8] as they have been often recognized as components of biologically relevant molecules. Indeed, L-hexoses are key constituents[9] of several bioactive oligosaccharides, antibiotics, glycopeptides, and terpene glycosides, as well as steroid glycosides and other clinically useful agents. Bleomycin A_2, a glycopeptide antibiotic with significant antitumor activity,[10] contains a carbohydrate moiety consisting of a $\alpha 1 \rightarrow 2$ linked 3-*O*-carbamoyl-D-mannopyranose with L-gulopyranose.[11] L-Guluronic acid moieties are found in alginate polysaccharides, which effect cytokine-inducing activities by binding to Toll-like receptors (TLRs) 2 and 4.[12,13] L-Glucose is contained in the natural product (−)-littoralisone, known as a bioactive agent for increased NGF-induced neurite outgrowth in PC12D cells.[14,15] L-Iduronic acid is a component of the disaccharide repeating unit of glycosaminoglycans[16] (GAG), such as the well-known heparin and heparan sulfate.[17] As a result of the interesting biological properties of unnatural carbohydrates and of the poor commercial and natural availability of almost all L-hexoses, several groups have shown interest in developing novel and efficient syntheses of these compounds. The successful approaches are divided into (a) *de novo* syntheses,[18] in which simple starting materials are manipulated *via* substrate-[19] or catalyst-controlled[20] methods, and (b) D-sugar elaboration methodologies by chemical[21] or enzymatic procedures.[22] Despite the wide range of synthetic studies reported in literature to date,[23] only a few strategies enable access to the whole series of rare L-sugars. Among them are noteworthy the total synthesis reported by Sharpless[19e] and the more recent efforts by Ogasawara,[20e] Izumori,[22] Sasaki[19a] and MacMillan.[20c,24]

In this context, for the past few years we have been working toward the *de novo* synthesis of polyhydroxylated compounds using our 1,2-bis-thioenol ether synthon **1** as three-carbon homologating agent with different chiral electrophiles[25] **2**−**4** (Figure 1). As a result, we successfully prepared uncommon monosaccharides,[19b,26] and more recently, we extended this methodology to the synthesis of L-polyhydroxylated piperidines[27] (i.e., L-iminosugars) and related nucleosides,[28] as well as to the synthesis of 1′,5′-anhydro-L-*arabino*-hexitol nucleic acids (L-HNA).[29]

Results and Discussion

In our preliminary communications[19b,26a] we reported a general and efficient route for the preparation of L-hexoses, starting from the 3-C homologating agent **1** (MPM = 4-methoxybenzyl) and the chiral building block 2,3-*O*-isopropylidene-L-glyceraldehyde (**3**), which provides the inherent

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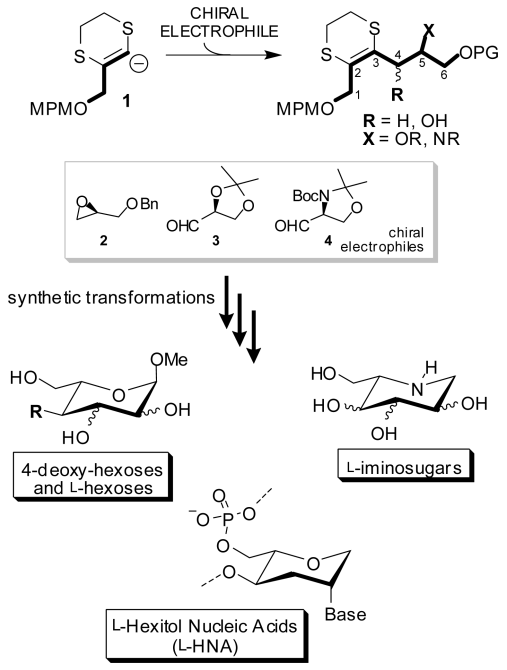

FIGURE 1. *De novo* synthesis of polyhydroxylated compounds by chain elongation of synthon **1**.

chirality at the C5 stereocenter of the final products (Figure 1). The aim of the project was to develop a general and stereoselective method that would be flexible enough to allow the synthesis of each epimer by minor variations of a common reaction scheme. Since this approach proved to be highly efficient when applied[19b] to the synthesis of four rare L-hexopyranoses with *gluco*-configuration, i.e., L-mannose, L-altrose, L-allose, and L-glucose, we have been particularly interested in extending our methodology to the preparation of the remaining four epimers with *galacto*-configuration. As shown in the retrosynthetic path (Scheme 1), the current strategy relies on the use of masked olefins **7** and **8**, in turn easily obtained through a stereoselective multistep process[30] starting from alcohols *syn*/*anti*-**6**. In particular, synthesis of L-hexoses belonging to the *galacto*-series, whose preparation will be herein discussed, involves the use of diastereomer *syn*-**6**, which provides the suitable configuration at the C4 position.

Critically evaluating the whole synthetic path, we realized that the first step of the synthesis was the weak point of our approach, as the coupling reaction of the *in situ* prepared C3 lithiated carbanion of **5** with aldehyde **3** (Scheme 2), while proceeding smoothly, yields the *syn*/*anti*-**6** diastereomers in a 6:4 dr. In a first attempt to overcome the low coupling stereoselection and selectively obtain the two secondary alcohols **6**, a two-step oxidation/reduction procedure was planned. While most of the widely used oxidizing conditions (PCC, TEMPO, Dess−Martin oxidation) were unsuccessful, the Swern oxidation of alcohols mixture **6** led to a mixture of ketone **9** (48%) and diene **10** (26%). Formation of the latter, which was at the core of some our previous synthetic investigations[19b] regarding the expeditious preparation of 4-deoxy-L-hexoses, has been already observed from *anti*-**6** under alkaline conditions.

On the basis of these findings, we decided to slightly change the nature of the chiral electrophile in the elongation step using methyl α,β-isopropylidene-L-glycerate (**11**). Thus, treatment of the lithiated carbanion of **5** with **11** smoothly afforded ketone **9** in 96% yield (Scheme 3). Then, the latter was stereoselectively reduced using $NaBH_4$, leading to the sole desired alcohol *syn*-**6** (98% yield). The complete diastereoselection observed could be easily explained assuming a borohydride attack to the less hindered face of the carbonyl of **9** in the nonchelated[31] conformation A (Felkin−Ahn−Houk model, Figure 2). In order to devise a more efficient route to alcohol *anti*-**6**, which represents the precursor of the already prepared L-hexoses having *gluco*-configuration,[26a] reduction of ketone **9** with a reverse stereoselectivity was next attempted. As shown in Table 1, although the reaction proved to be highly efficient in all of the tested conditions (>95% yield), only a slight stereoselection in favor of the *anti*-diastereomer (6:4, *anti*/*syn*) was observed in presence of *N*-Selectride (entry 5), *N*-Selectride/$ZnCl_2$ (entry 6), or DIBAL/$ZnCl_2$ (entry 7), according to the Cram chelate model[31] B (Figure 2).

In our search for a more convenient approach to *anti*-**6**, Mitsunobu inversion of the secondary hydroxyl group at the C4 position of *syn*-**6** was attempted. Hence, treatment of *syn*-**6** with PPh_3/DIAD/*p*-NO_2BzOH and subsequent alkaline hydrolysis of the resulting *p*-nitrobenzoate (Et_3N/MeOH) produced alcohol *anti*-**6** in a 75% overall yield (o.y.) (Scheme 3).

The synthesis of *galacto*-configured L-hexoses proceeded through cyclization of the main carbon chain starting from *syn*-**6**, by a similar route to that previously described[19b] (Scheme 4). This was accomplished by protection of the secondary hydroxyl function of *syn*-**6** with a benzyl (BnBr/NaH) or acetyl (Ac_2O/Py) group, affording **12a** (R = Bn) and **12b** (R = Ac) in almost quantitative yields. MPM group removal of **12a,b** (DDQ) and subsequent oxidation of the resulting primary alcohol of **13a,b** (PCC) provided aldehydes **14a,b** in very good yields (73−87% o.y. from **12**). Then, acetonide cleavage of **14a** (R = Bn) (Amberlyst 15 in MeOH) followed by direct acetylation of the crude residue (Ac_2O/Py) led to acetals **16a** (*via* alcohols **15a**) as an α/β (85:15) anomeric mixture (69% yield over two steps). On the other hand, treatment of anomeric mixture **15a** with Amberlyst 15 in $CHCl_3$ enabled efficient conversion to 1,6-anhydrocompound **17a** (85% yield). It should be pointed out that compound **15b** could not be easily isolated after reaction of **14b** with Amberlyst 15 or stoichiometric TMSOTf in MeOH, due to its rapid conversion to acetal **17b** (Scheme 4). Formation of the latter could be observed already in reaction medium or after common purification procedures. Alternatively, the bicyclic compound could be easily isolated under its acetylated form **16b**, by treatment of **14b** with catalytic TMSOTf in MeOH and immediate addition of Ac_2O/Py to the crude residue (91% over two steps).

In search for a more profitable approach to acetals **16a,b** and **17a,b**, we exploited the peculiar features of the DDQ reagent (Scheme 5). We have already discussed[26a] the aptitude by DDQ of (a) carrying out MPM group removal under diverse conditions,[32] leading to an alcohol or a formyl

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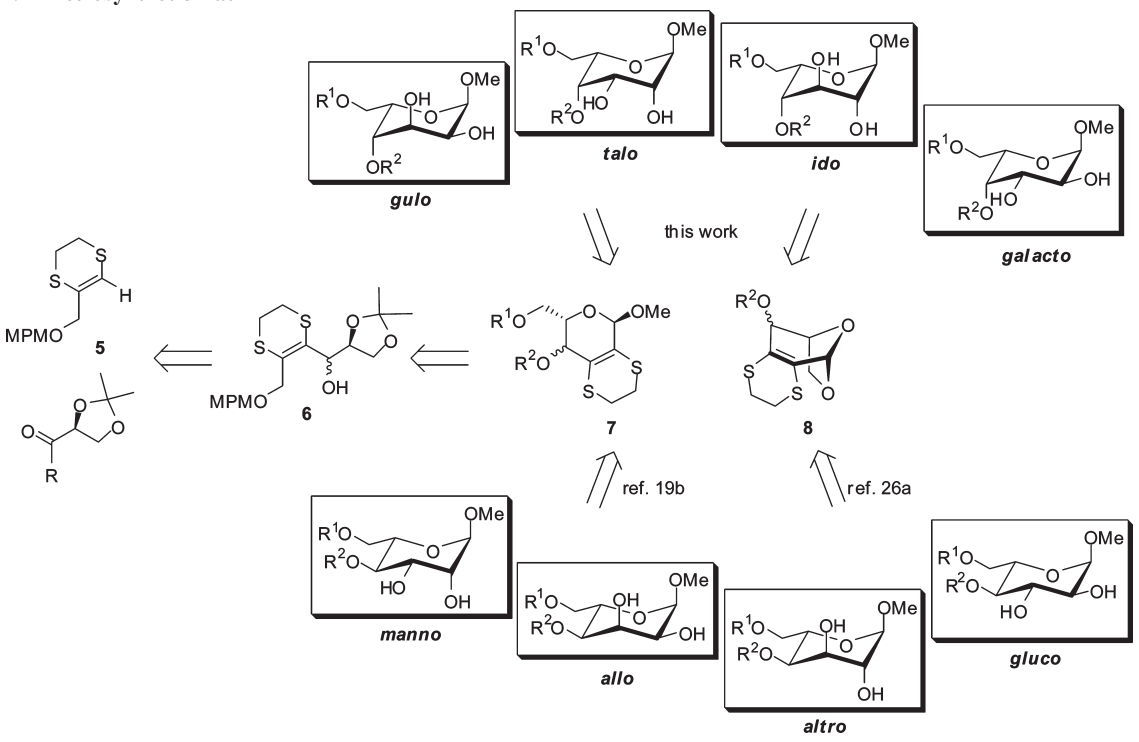
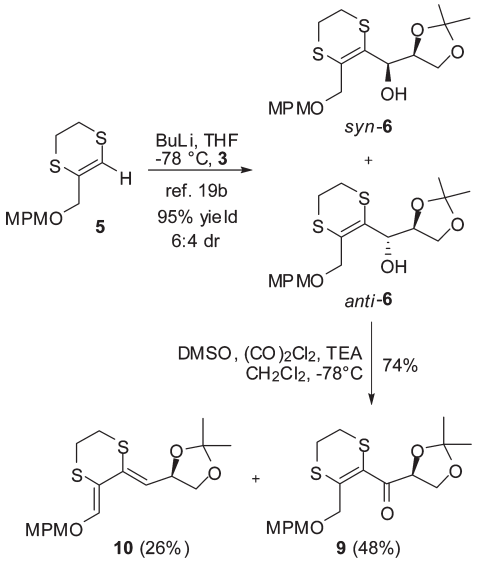
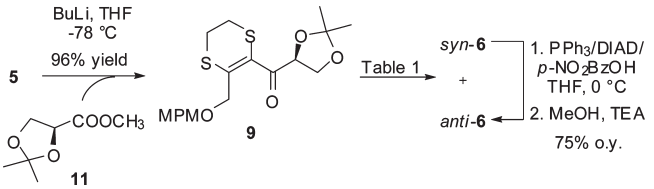
SCHEME 1. Retrosynthetic Path



SCHEME 2. Three-Carbon Homologation Reaction



SCHEME 3. Synthesis of *syn*/*anti*-6 by Homologation of L-Glycerate 11



function, and (b) evolving HCN, generating an acidic environment; such remarks led to the expeditious synthesis of 1,6-anhydrosugars by a domino process.[26a] Using the same

TABLE 1. Reduction of Ketone 9[a]

entry	reducing agent	*syn*/*anti*	yield (%)
1	$NaBH_4$[b,c]	>99:1	98
2	Red-Al[d,e]	80:20	96
3	$LiAlH_4$[d]	80:20	95
4	DIBALH[d]	60:40	97
5	*N*-Selectride[d]	40:60	97
6	*N*-Selectride/$ZnCl_2$[d]	40:60	97
7	DIBALH/$ZnCl_2$[d]	40:60	98

[a]THF used as solvent (unless otherwise stated). [b]Reaction was at −60 °C. [c]Reaction carried out in MeOH. [d]Reaction was at −78 °C. [e]Reaction was carried out in toluene.

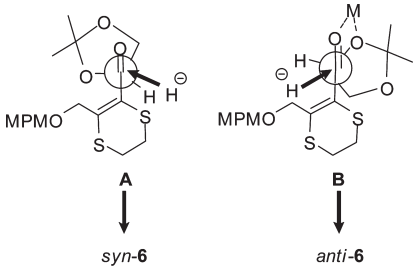
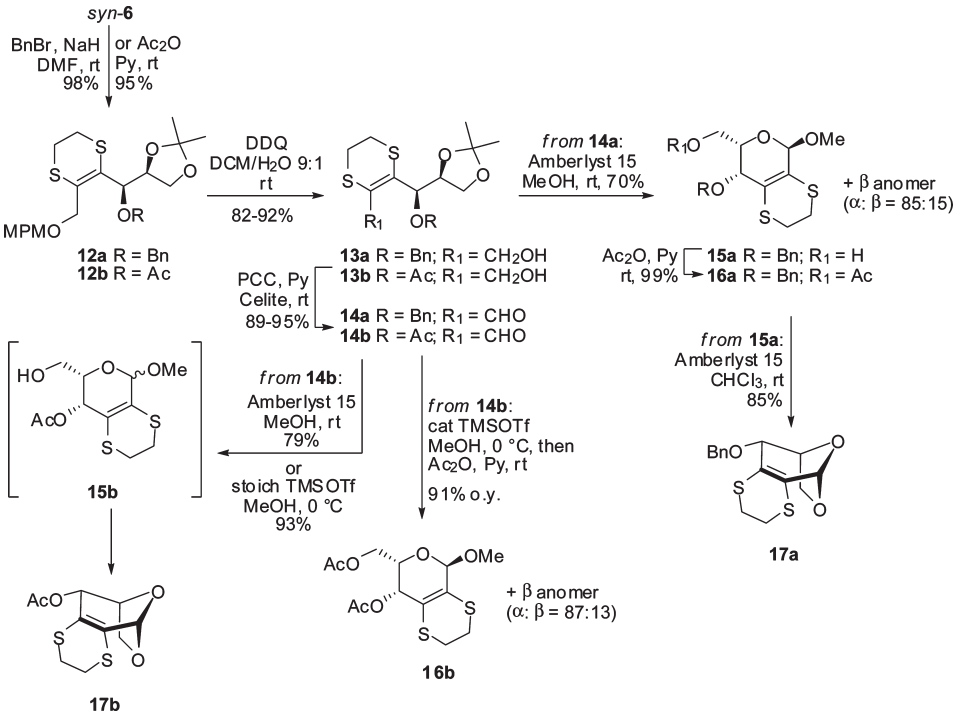


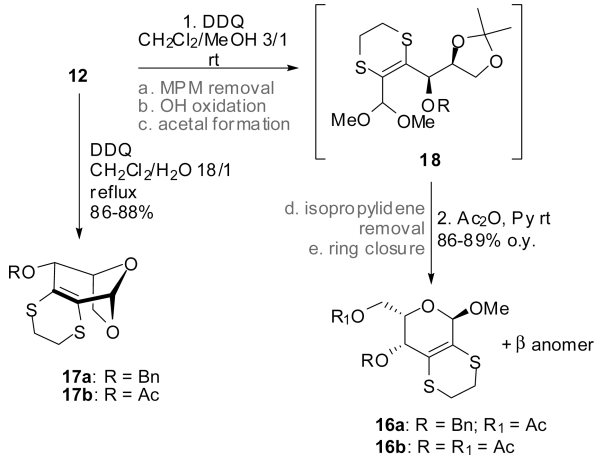
FIGURE 2. Nonchelated (A) and chelated (B) model in the reduction of ketone **9**.

methodology, treatment of **12a,b** (R = Bn or Ac) with an excess of DDQ (2.0 equiv) in a refluxing 18:1 CH_2Cl_2/H_2O emulsion afforded **17a,b** as single product, saving 3−4 steps (if R = Ac or Bn, respectively) with even better overall yields in comparison with the previous stepwise route (86−88% vs 52−68%). These results prompted us to use this domino procedure for the synthesis of bicycle acetals **16a,b** as well. In particular, we envisioned that replacement of water with methanol could easily lead to desired methyl glycoside

SCHEME 4. Ring Closure from *syn*-6 by Stepwise Route



SCHEME 5. Ring Closure from 12a,b by Domino Reaction



derivatives **16a,b**. Solvent change was not trivial: on one hand, the DDQ/CH_2Cl_2/MeOH system was slightly more acidic (pH ~2) compared to the DDQ/CH_2Cl_2/H_2O mixture (pH ~3); on the other hand, we observed a decrease of the reaction rate for the oxidative MPM group removal. Thus, use of a 18:1 CH_2Cl_2/MeOH solution caused isopropylidene group removal before formation of the formyl function, leading to undesired byproducts. Therefore, reaction conditions were tuned varying the CH_2Cl_2/MeOH ratios; best results were found treating **12a** with DDQ (1.2 equiv) in a 3:1 CH_2Cl_2/MeOH solution at rt for 24 h. Subsequent acetylation of the crude residue afforded desired bicycle **16a** in a gratifying 89% yield (Scheme 5). Reaction conditions were also compatible with acetyl group, as compound **12b** displayed similar reactivity (86% o.y.). Detection of dimethoxyacetals **18** as reaction intermediates suggests that the process proceeded across the following five steps: (a) MPM group removal, (b) oxidation of the resulting primary alcohol, (c) aldehyde dimethoxyacetalation, (d) isopropylidene group removal, and (e) ring closure by OH at the C5 position (Scheme 5).

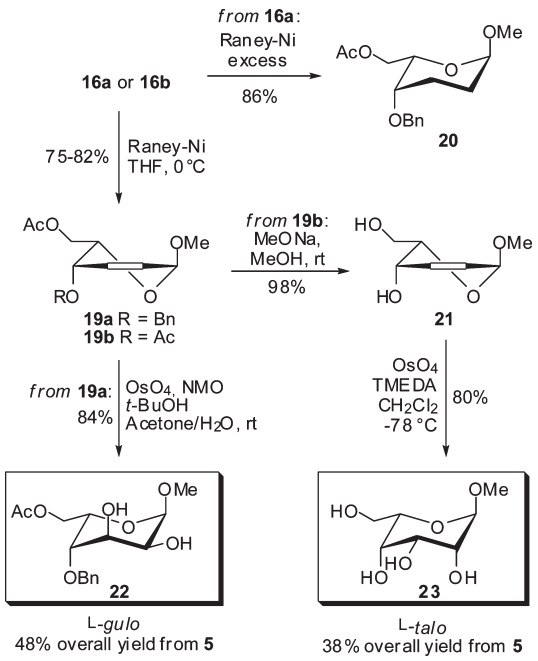
As underlined before, olefins **16a,b** and **17a,b** represent useful intermediates for complete L-hexoses synthesis. The double bond of **16a,b** was easily unmasked by dithioethylene bridge removal. Treating the most abundant α-epimer with Raney-Ni in THF afforded the unsaturated pyranosides **19a,b** (Scheme 6) in good yields (75−82%). A low temperature (0 °C) was strictly required to avoid formation of saturated pyranosides such as **20**, which could be obtained in satisfactory yield (86%) under stronger conditions (Raney-Ni excess at rt). Subsequent stereoselective double bond functionalization of olefins **19a,b** by *syn* dihydroxylation was explored, examining both Upjohn (catalytic OsO_4, NMO) and Donohoe's (stoichiometric OsO_4, TMEDA) reaction conditions (Scheme 6). The more hindered *syn* allylic ether **19a** was chosen for the dihydroxylation under Upjohn conditions; the osmylation reaction proceeded *anti* to the pseudoaxial benzyloxy group, thus yielding methyl 6-*O*-acetyl-4-*O*-benzyl-α-L-gulopyranoside[33,34] (**22**, 84% yield; 48% o.y. from **5**) On the other hand, osmylation under Donohoe's conditions of *syn* allylic alcohol **21**, obtained by Zemplen's deacetylation of **19a**, was highly *syn*-selective, smoothly yielding methyl α-L-talopyranoside[35] (**23**, 80% yield; 38% o.y. from **5**). The observed complementary stereoselectivity was explained by the hydrogen bond

(33) Less than 5% of the talose isomer was detected (^{1}H NMR analysis of the crude residue).

(34) Stereoelectronic preference for dihydroxylation *anti* to an allylic hydroxyl group has been recognized previously; see: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255. (b) Hodgston, R.; Majid, T.; Nelson, A. *J. Chem. Soc., Perkin Trans.1* **2002**, 1444–1454.

(35) In contrast to previous results reported on similar substrates (Harris, J. M.; Keränen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17–36.) no traces of the corresponding gulose isomer was herein detected.

SCHEME 6. ***Syn* Dihydroxylation of Olefins 19a,b**



formation between the *pseudo*-axial allylic hydroxyl group at the C4 position and the OsO_4/TMEDA complex, according to literature data.[36]

The *anti* dihydroxylation of olefin **19a** was next planned (Scheme 7) via double bond epoxidation. Early attempts employing *m*-CPBA were unsuccessful as a result of the extremely low reactivity of the reagent to our substrate. Then, olefin **19a** was subjected to Payne's epoxidation ($PhCN/H_2O_2/MeOH/NaHCO_3$), leading to the formation of both *gulo*- and *talo*-epoxides **24** and **25** (60% yield, 65:35 dr). However, even after prolonged reaction times a substantial amount of unreacted starting material was recovered (35%). Eventually, treatment of **19a** with *in situ* generated TFDO [methyl(trifluoromethyl)dioxirane], employing the oxone/trifluoroacetone system in CH_3CN/aq $NaHCO_3$, led to the mixture of epoxides **24** and **25** with the highest yield (79%). Good but reversed diastereoselectivity (dr 1:9) occurred under these conditions. As depicted in Scheme 7, ring opening of *talo*-epoxide **25** under alkaline conditions (refluxing 1 N KOH) afforded methyl 4-*O*-benzyl-α-L-idopyranoside (**26**) in quantitative yield (40% o.y. from **5**). On the other hand, treatment of epoxide **24** under the same conditions proceeded in a thoroughly stereoselective manner, but leading to the unexpected 3,6-anhydrosugar **27** (99% yield).

The regioselective outcome of these ring-opening processes deserves further comments. In the case of *gulo*-epoxide **24**, the exclusive formation of 3,6-anhydrosugar **27** could be explained by conjecturing that, under refluxing conditions, both $^{O}H_5$ and $^{5}H_O$ conformations exist. In the $^{5}H_O$ conformer, trans-diaxial opening should be prevented by the difficulty of ^{-}OH to reach the C2 position of the dihydropyrane ring from the same side of the endocyclic oxygen atom.[26b] Consequently, nucleophilic attack at the C3 position *via* the $^{O}H_5$ conformer became competitive with, and in fact dominated over, this process. However, if an entropically favored side reaction involving intramolecular attack by a deacetylated C6-OH function occurred, this would lead to anhydrosugar **27**. On the other hand, in the case of *talo*-epoxide **25**, *trans*-diaxial oxirane ring opening smoothly proceeded by preferred ^{-}OH attack at the relatively unhindered C3 position of the $^{5}H_O$ conformer (Scheme 7).

Since ring opening of 2,3-anhydrosugar **24** in its $^{O}H_5$ conformation did not lead to the corresponding 2,3-*trans*-diequatorial diol[37] (i.e., the *galacto*-epimer), its preparation was envisaged starting from 1,6-anhydrosugar[38] derivative **17a** (Scheme 8). The masked olefin **17a** was treated with Raney-Ni in acetone,[39] to give the unsaturated derivative **28** in 78% yield. Stereoselective epoxidation with *in situ* generated TFDO from the less hindered face of olefin **28** led to 1,6:2,3-dianhydro-4-*O*-benzyl-β-L-*gulo*-pyranose (**29**) in 85% yield. 2,3-Oxirane ring opening[40] by means of a refluxing 6 N KOH solution enabled *trans*-diaxial installation of the C2 and C3 hydroxyl groups, the sugar chair being locked in a $^{4}C_1$ conformation (Scheme 8). Subsequent 1,6-ring cleavage by treatment of the crude dihydroxylated product **30** with catalytic TMSOTf in MeOH re-established the $^{1}C_4$ chair conformation, affording methyl 4-*O*-benzyl-α-L-galactopyranoside (**31**) as a single anomer and in excellent yield (90% over two steps; 48% o.y. from compound **5**).

Conclusion

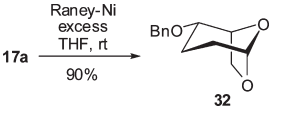
In summary, a highly stereoselective synthesis of enantiomerically pure L-hexoses belonging to the *galacto*-series (L-gulose, L-idose, L-galactose, and L-talose) has been accomplished, in very good overall yields (38−48%), starting from our 1,2-bis-thioenol ether synthon **5** and a suitable chiral electrophile, the methyl α,β-isopropylidene-L-glycerate (**11**). The core of the strategy relies on the development of a domino reaction, in which up to six synthetic transformations were carried out sequentially, with the advantage of increasing the efficiency of the entire process. In-depth investigation of the parameters involved in this reaction enabled us to selectively obtain the α-L-pyranoside **16** or the 1,6-anhydro-β-L-pyranoside **17**, depending on our synthetic requirements. Moreover, *syn* and *anti* dihydroxylation conditions were examined, affording each orthogonally protected L-hexopyranoside with high (in some cases with full) diastereoselectivity. These and previous results contribute to

(36) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946–7956.

(37) Acidic hydrolysis of epoxide **24** was also attempted (6% aq $HClO_4$); however, only C6 *O*-deacetylation occurred, even after prolonged reaction times.

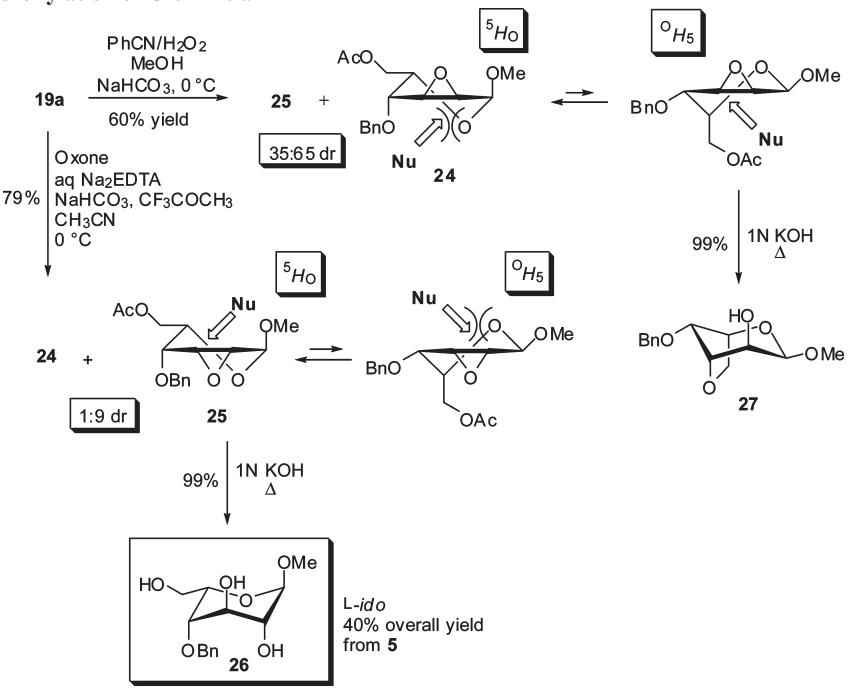
(38) Use of 1,6-anhydrosugars has been widely applied to the construction of rare sugars and oligosaccharides; see for example: Kulkarni, S. S.; Lee, J.-C.; Hung, S.-C. *Curr. Org. Chem.* **2004**, *8*, 475–509.

(39) Solvent substitution (acetone in place of THF) associated with a low temperature (0 °C) was necessary to partially deactivate the reagent, with the aim to prevent formation of **32**. Stronger reduction conditions yielded **32** in high yield (see Experimental Section for details).

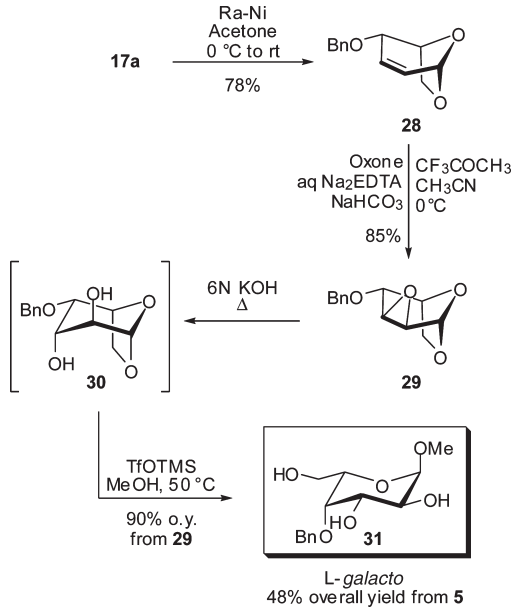


(40) It should be mentioned that very prolonged times were required to complete ring opening of **29**, as the C3 position was greatly hindered by both the C4 benzyl group and the C1−C6 bridge.

SCHEME 7. ***Anti*** **Dihydroxylation of Olefin 19a**



SCHEME 8. ***Anti*** **Dihydroxylation of Olefin 28**



make our approach general and place it among the few methods able to synthesize the whole series of the rare L-sugars. Ongoing efforts are currently focusing on the extension of our domino approach for the synthesis of more complex systems endowed with potential biological activity and will be published in due course.

Experimental Section

[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](3-[(4-methoxybenzyl)-oxy]methyl-5,6-dihydro-1,4-dithiin-2-yl)methanone (9). *n*-BuLi (1.6 M in hexane, 2.4 mL) was added dropwise to a stirred solution of **5** (2.0 g, 7.46 mmol) in anhydrous THF (15 mL) at −78 °C and under nitrogen atmosphere. After 10 min a solution of methyl α,β-isopropylidene-L-glycerate (**11**) (1.8 mL, 11.2 mmol) in the same solvent (8 mL) was added. The reaction mixture was stirred for 3 h at −78 °C, then carefully quenched with 10% aq NH_4Cl. The mixture was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a crude residue from which chromatography over silica gel column (hexane/acetone = 8:2) gave the pure **9** (2.8 g, 96% yield): oily, $[\alpha]^{25}_D$ −17.0 (*c* 0.18, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.47 (s, 3H), 3.06−3.15 (m, 2H), 3.27−3.31 (m, 2H), 3.80 (s, 3H), 4.03 (dd, *J* = 5.5, 8.5 Hz, 1H), 4.29 (dd, *J* = 7.4, 8.5 Hz, 1H), 4.42 (d, *J* = 14.8 Hz, 2H), 4.49 (d, *J* = 14.8 Hz, 2H), 5.02 (dd, *J* = 5.5, 7.7 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 25.8, 26.4, 30.3, 55.1, 66.7, 71.2, 72.4, 78.5, 111.0, 113.7, 122.0, 129.3, 129.5, 144.0, 159.2, 195.1. Anal. Calcd for $C_{19}H_{24}O_5S_2$: C 57.55, H 6.10, S 16.17. Found: C 57.67, H 6.09, S 16.12.

(*R*)-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](3-[(4-methoxybenzyl)oxy]methyl-5,6-dihydro-1,4-dithiin-2-yl)methanol (*syn*-6). To a stirred cold (−60 °C) solution of **9** (2.40 g, 6.06 mmol) in anhydrous methanol (60 mL) and under nitrogen atmosphere was added $NaBH_4$ (0.08 g, 2.02 mmol). The mixture, kept for 2 h at −60 °C, was then quenched with acetone and concentrated under reduced pressure. The residue was washed with saturated aq $NaHCO_3$ and extracted with Et_2O. The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure, to give a crude residue from which chromatography over silica gel (hexane/Et_2O = 7:3) gave the pure *syn*-**6** (2.36 g, 98% yield). All characterization data were identical to those reported in ref 19b. Anal. Calcd for $C_{19}H_{26}O_5S_2$: C 57.26, H 6.58, S 16.09. Found: C 57.12, H 6.60, S 16.13.

(*S*)-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](3-[(4-methoxybenzyl)oxy]methyl-5,6-dihydro-1,4-dithiin-2-yl)methanol (*anti*-6). To a solution of alcohol *syn*-**6** (0.10 g, 0.25 mmol) in anhydrous THF (1.1 mL) at 0 °C and under nitrogen atmosphere were added triphenylphosphine (0.12 g, 0.45 mmol), DIAD (0.04 mL, 0.45 mmol), and *p*-nitrobenzoic acid (0.08 g, 0.45 mmol). The reaction mixture was kept at 0 °C for 3 h, then it was diluted with

Et_2O and quenched with saturated $NaHCO_3$. The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. To a solution of crude residue in CH_3OH (0.57 mL) was added Et_3N (0.1 mL, 0.75 mmol). After 16 h the mixture was concentrated and purified by column chromatography (hexane/Et_2O = 7:3) to yield the pure *anti*-**6** (0.08 g, 75% overall yield). All characterization data were identical to those reported in ref 19b. Anal. Calcd for $C_{19}H_{26}O_5S_2$: C 57.26, H 6.58, S 16.09. Found: C 57.35, H 6.59, S 16.05.

Ketone 9 and (4*R*)-4-[(3-(*Z*)-1-[(4-Methoxybenzyl)oxy]methylidene-1,4-dithian-2-yliden)methyl]-2,2-dimethyl-1,3-dioxolane (10). To a cooled (−78 °C), stirred solution of freshly distilled oxalyl chloride (0.05 mL, 0.56 mmol) in anhydrous CH_2Cl_2 (0.40 mL) was added dropwise a solution of freshly distilled DMSO (0.08 mL, 1.11 mmol) in the same solvent (0.40 mL). During addition, the internal temperature was kept below −70 °C and then allowed to reach −65 °C in 15 min. Hence, a solution of **6** (0.15 g, 0.38 mmol, *syn*/*anti* mixture) in CH_2Cl_2 (1.4 mL; internal temperature not exceeding −50 °C) was added dropwise. The mixture was stirred at −50 °C for 5 min and then diluted with anhydrous Et_3N (0.25 mL, 1.85 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. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give a crude residue from which chromatography over silica gel (hexane/Et_2O = 8:2) gave ketone **9** (0.07 g, 48% yield) and diene **10** (0.04 g, 26% yield). All characterization data regarding **9** and **10** were, respectively, identical to those reported above and in ref 19b.

(*R*)-(Benzyloxy)[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl](3-[(4-methoxybenzyl)oxy]methyl-5,6-dihydro-1,4-dithiin-2-yl)methane (12a). NaH (0.16 g, 4.24 mmol) was added to a solution of *syn*-**6** (1.30 g, 3.26 mmol) in anhydrous DMF (25 mL) at 0 °C under nitrogen atmosphere. After 10 min, BnBr (0.54 mL, 4.48 mmol) was added in one portion. The reaction mixture was warmed to room temperature, stirred for 2 h, then carefully quenched with 10% aq NH_4Cl. The mixture was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/Et_2O = 8:2) afforded the pure **12a** (1.56 g, 98% yield): oily, $[\alpha]^{25}_D$ +33.8 (*c* 0.47, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.36 (s, 3H), 3.06−3.11 (m, 1H), 3.12−3.20 (m, 2H), 3.21−3.27 (m, 1H), 3.80 (s, 3H), 3.81−3.84 (m, 1H), 3.86 (d, J = 11.7 Hz, 1H), 3.93−3.97 (m, 2H), 4.31−4.48 (m, 5H), 4.71 (d, J = 11.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.24−7.28 (m, 1H), 7.29−7.34 (m, 2H), 7.35−7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 26.5, 27.3, 29.1, 55.1, 65.6, 69.6, 69.7, 72.2, 77.8, 79.2, 109.7, 113.7, 127.1, 127.4, 127.6, 127.7, 127.8, 128.1, 129.4, 137.9, 159.2. Anal. Calcd for $C_{26}H_{32}O_5S_2$: C 63.91, H 6.60, S 13.12. Found: C 63.76, H 6.62, S 13.16.

(*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(3-[(4-methoxybenzyl)oxy]methyl-5,6-dihydro-1,4-dithiin-2-yl)methyl Acetate (12b). To a solution of *syn*-**6** (0.90 g, 2.26 mmol) in pyridine (6 mL) was added Ac_2O (0.42 mL, 4.5 mmol) at room temperature. After 10 h the mixture was concentrated under reduced pressure to give a crude residue from which chromatography over silica gel (hexane/EtOAc = 8:2) gave the pure **12b** (0.94 g, 95% yield): oily, $[\alpha]^{25}_D$ − 89.0 (*c* 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 6H), 2.11 (s, 3H), 3.06−3.10 (m, 2H), 3.14−3.22 (m, 2H), 3.79 (s, 3H), 3.86 (d, J = 11.8 Hz, 1H), 3.91 (dd, J = 6.4, 8.7 Hz, 1H), 3.96 (dd, J = 6.4, 8.7 Hz, 1H), 4.45−4.51 (m, 3H), 4.61 (d, J = 11.8 Hz, 1H), 5.73 (d, J = 6.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.0, 25.6, 26.4, 27.2, 29.3, 55.1, 65.5, 70.2, 72.2, 74.4, 76.3, 110.1, 113.7, 124.1, 128.9, 129.5, 129.7, 159.2, 169.9. Anal. Calcd for $C_{21}H_{28}O_6S_2$: C 57.25, H 6.41, S 14.56. Found: C 57.10, H 6.40, S 14.61.

(3-(*R*)-1-(Benzyloxy)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-methyl-5,6-dihydro-1,4-dithiin-2-yl)methanol (13a). To a stirred CH_2Cl_2/H_2O (9:1) emulsion (50 mL) containing the MPM ether **12a** (0.54 g, 1.11 mmol) was added DDQ (0.38 g, 1.68 mmol) in one portion at room temperature. After 3 h, H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/acetone = 9:1) gave the pure **13a** (0.39 g, 92% yield): oily, $[\alpha]^{25}_D$ +62.3 (*c* 0.33, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.40 (s, 3H), 2.70 (bs, 1H), 3.09−3.22 (m, 3H), 3.23−3.30 (m, 1H), 3.95 (dd, J = 6.3, 8.5 Hz, 1H), 4.04 (d, J = 12.9 Hz, 1H), 4.08 (dd, J = 6.3, 8.5 Hz, 1H), 4.14 (d, J = 12.9 Hz, 1H), 4.37−4.47 (m, 3H), 4.73 (d, J = 12.2 Hz, 1H), 7.22−7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4, 26.5, 27.7, 29.2, 62.9, 65.6, 70.5, 77.5, 78.5, 109.9, 125.4, 127.8, 127.9, 128.3, 130.4, 137.5. Anal. Calcd for $C_{18}H_{24}O_4S_2$: C 58.67, H 6.56, S 17.40. Found: C 58.48, H 6.59, S 17.48.

(*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-[3-(hydroxymethyl)-5,6-dihydro-1,4-dithiin-2-yl]methyl Acetate (13b). Under the same conditions reported for the preparation of alcohol **13a**, the pure **13b** was obtained (82% yield) starting from MPM ether **12b**: oily, $[\alpha]^{25}_D$ +12.0 (*c* 0.35, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.42 (s, 3H), 2.13 (s, 3H), 3.05−3.11 (m, 2H), 3.15−3.27 (m, 2H), 3.41 (dd, J = 3.7, 9.3 Hz, 1H), 3.81 (dd, J = 5.6, 8.8 Hz, 1H), 3.92−4.09 (m, 2H), 4.48−4.59 (m, 2H), 5.73 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 25.4, 26.6, 27.0, 29.3, 63.3, 65.5, 74.9, 75.9, 110.5, 122.7, 131.6, 170.0. Anal. Calcd for $C_{13}H_{20}O_5S_2$: C 48.73, H 6.29, S 20.01. Found: C 48.90, H 6.27, S 19.94.

3-(*R*)-1-(Benzyloxy)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-methyl-5,6-dihydro-1,4-dithiine-2-carbaldehyde (14a). A solution of alcohol **13a** (0.35 g, 0.95 mmol) in pyridine (3 mL) was added in one portion to a stirred suspension of PCC (0.28 g, 1.30 mmol) and Celite (0.28 g) in Py (8 mL) at room temperature. The resulting mixture was stirred for 8 h, diluted with 10 mL of anhydrous Et_2O, kept in an ultrasound bath for 30 min and filtered on a Celite pad. After solvent removal under reduced pressure, chromatography of the crude residue over silica gel (CH_2Cl_2) gave the pure **14a** (0.33 g, 95% yield): white crystals, mp 83.1−84.5 °C (MeOH), $[\alpha]^{25}_D$ +45.8 (*c* 0.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 6H), 3.04−3.10 (m, 1H), 3.15−3.21 (m, 1H), 3.25−3.32 (m, 2H), 3.95−4.01 (m, 2H), 4.40 (q, J = 6.1 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.70 (bs, 1H), 4.78 (d, J = 12.0 Hz, 1H), 7.28−7.36 (m, 5H), 9.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 25.7, 26.1, 29.7, 65.4, 71.5, 77.5, 79.0, 110.3, 128.0, 128.4, 128.7, 130.6, 130.7, 136.6, 184.6. Anal. Calcd for $C_{18}H_{22}O_4S_2$: C 58.99, H 6.05, S 17.50. Found: C 59.15, H 6.03, S 17.43.

(*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(3-formyl-5,6-dihydro-1,4-dithiin-2-yl)methyl Acetate (14b). Under the same conditions reported for the preparation of aldehyde **14a**, the pure **14b** was obtained (89% yield) starting from alcohol **13b**: white crystals, mp 132.0−134.5 °C (MeOH); $[\alpha]^{25}_D$ −37.0 (*c* 0.23 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.41 (s, 3H), 2.18 (s, 3H), 3.02−3.16 (m, 1H), 3.18−3.37 (m, 3H), 3.91 (dd, J = 4.5, 8.8 Hz, 1H), 4.05 (dd, J = 6.6, 8.8 Hz, 1H), 4.41−4.47 (m, 1H), 6.09 (d, J = 6.6 Hz, 1H), 10.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 25.2, 25.8, 26.3 29.5, 65.5, 73.1, 76.6, 110.8, 130.8, 145.9, 169.5, 183.7. Anal. Calcd for $C_{13}H_{18}O_5S_2$: C 49.04, H 5.70, S 20.14. Found: C 49.21, H 5.72, S 20.07.

[(5*R*,7*S*,8*R*)-8-(Benzyloxy)-5-methoxy-3,5,7,8-tetrahydro-2*H*-[1,4]dithiino[2,3-*c*]pyran-7-yl]methanol (15a). Amberlyst 15 (3.5 g, previously washed with anhydrous MeOH) was added in one portion to a stirred solution of **14a** (0.22 g, 0.60 mmol) in

methanol (15 mL) at 0 °C. After 10 min, the suspension was warmed to room temperature and stirred for 1 h. Then the solid was filtered off and washed with MeOH. Pyridine was added until pH ~8, then the solvents were evaporated under reduced pressure to afford a crude residue from which chromatography over silica gel (hexane/AcOEt = 85:15) gave the pure dihydropyran **15a** (0.12 g, 59.5% yield), besides a minor amount of its β-anomer (0.02 g, 10.5% yield, 85:15 dr). Data for α-**15a**: white crystals, mp 78.9−80.2 °C (MeOH); $[\alpha]^{25}_D$ +55.2 (*c* 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 2.30−2.52 (m, 3H), 2.53−2.61 (m, 1H), 3.19 (s, 3H), 3.64 (d, *J* = 2.5 Hz, 1H), 3.68 (dd, *J* = 5.6, 11.3 Hz, 1H), 3.70 (dd, *J* = 7.6, 11.3 Hz, 1H), 4.16 (ddd, *J* = 2.5, 5.6, 7.6 Hz, 1H), 4.65 (d, *J* = 11.1 Hz, 1H), 4.81 (d, *J* = 11.1 Hz, 1H), 4.87 (s, 1H), 7.02−7.30 (m, 3H), 7.41 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 27.6, 28.1, 55.1, 62.1, 71.5, 72.3, 72.9, 98.6, 123.9 125.9, 127.7, 128.0, 128.3, 138.9. Anal. Calcd for $C_{16}H_{20}O_4S_2$: C 56.44, H 5.92, S 18.84. Found C 56.26, H 5.94, S 18.91.

[(5*R*,7*S*,8*R*)-8-(Benzyloxy)-5-methoxy-3,5,7,8-tetrahydro-2*H*-[1,4]dithiino[2,3-*c*]pyran-7-yl]methyl Acetate (16a). Method A (from 15a). To a stirred solution of the anomeric mixture of **15a** (0.12 g, 0.36 mmol) in pyridine (4 mL) was added Ac_2O (0.06 mL, 0.70 mmol) at room temperature. After 3 h, solvent removal under reduced pressure and chromatography of the crude residue over silica gel (CH_2Cl_2) afforded the pure α-**16a** (0.11 g, 84% yield) besides a minor amount of β-anomer (0.02 g, 15%, 85:15 dr).

Method B (Domino Reaction from 12a). To a stirred 3:1 CH_2Cl_2/MeOH solution (5 mL) containing the MPM ether **12a** (0.34 g, 0.70 mmol) was added DDQ (0.28 g, 1.30 mmol) in one portion at room temperature. The resulting mixture was stirred for 24 h at the same temperature. Then pyridine (10 mL) and Ac_2O (5 mL) were added carefully at rt. The resulting mixture was stirred at room temperature for 5 h, then H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/EtOAc = 8:2) gave the pure **16a**, besides a minor amount of its β-anomer (0.24 g, 89% overall yield; 85:15 dr): white crystals, mp 56.4−58.3 °C (MeOH); $[\alpha]^{25}_D$ +74.6 (*c* 0.93, C_6H_6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (s, 3H), 3.16−3.40 (m, 4H), 3.44 (s, 3H), 3.71 (d, *J* = 1.6 Hz, 1H), 4.26−4.37 (m, 3H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.76 (d, *J* = 11.0 Hz, 1H), 4.82 (s, 1H), 7.25−7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7, 27.7, 27.9, 55.3, 63.2, 69.4, 71.4, 71.9, 97.7, 123.3, 125.0, 127.7, 128.1, 128.2, 137.7, 170.4. Anal. Calcd for $C_{18}H_{22}O_5S_2$: C 56.52, H 5.80, S 16.77. Found: C 56.38, H 5.78, S 16.84.

(5*R*,7*S*,8*R*)-5-Methoxy-7-[(methylcarbonyloxy)methyl]-3,5,7,8-tetrahydro-2*H*-[1,4]dithiino[2,3-*c*]pyran-8-yl Acetate (16b). Method A (from 14b). TMSOTf (0.01 mL) was added dropwise to a stirred solution of aldehyde **14b** (0.19 g, 0.60 mmol) in anhydrous MeOH (12 mL) at 0 °C. The resulting mixture was stirred for 1 h at the same temperature. Then pyridine was added until pH ~8. MeOH was evaporated under reduced pressure and replaced by further pyridine (15 mL); Ac_2O was added to the solution (0.06 mL, 0.6 mmol) at room temperature. After 3 h, solvent removal under reduced pressure and chromatography of the crude residue over silica gel (CH_2Cl_2) afforded pure α-**16b** (0.16 g, 80% yield) in addition to a minor amount of its β-anomer (0.02 g, 11% yield; 87:13 dr).

Method B (Domino Reaction from 12b). Under the same conditions reported above for the preparation of the acetal **16a**, an anomeric mixture of **16b** (α/β = 85:15) was obtained starting from the MPM ether **12b** (86% yield). Data for α-**16b**: oily, $[\alpha]^{25}_D$ +52.0 (*c* 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.14 (s, 3H), 3.05−3.10 (m, 1H), 3.17−3.32 (m, 3H), 3.45 (s, 3H), 4.11 (dd, *J* = 7.3, 11.4 Hz, 1H), 4.18 (dd, *J* = 5.5, 11.4 Hz, 1H), 4.46 (ddd, *J* = 2.4, 5.5, 7.3 Hz, 1H), 4.82 (s, 1H), 5.19 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.6 (2C), 27.6, 27.9, 55.6, 62.0, 65.0, 67.3, 97.6, 122.2, 125.9, 170.3 (2C). Anal. Calcd for $C_{13}H_{18}O_6S_2$: C 46.69, H 5.43, S 19.18. Found: C 46.87, H 5.41, S 19.10.

Acetal 17a. Method A (from 15a). Amberlyst 15 (1.7 g, previously washed with anhydrous $CHCl_3$) was added in one portion to a stirred solution of an anomeric mixture of **15a** (0.12 g, 0.36 mmol) in $CHCl_3$ (8 mL) at 0 °C. After 10 min, the suspension was warmed to room temperature and further stirred for 1 h. Then the solid was filtered off and washed with $CHCl_3$ (100 mL), and the resulting solution was washed with saturated $NaHCO_3$ solution and brine. The organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/acetone = 95:5) gave the pure **17a** (0.09 g, 85% yield).

Method B (Domino Reaction from 12a). To a stirred 18:1 CH_2Cl_2/H_2O emulsion (5 mL) containing the MPM ether **12a** (0.54 g, 1.11 mmol) was added DDQ (0.38 g, 1.68 mmol) in one portion at room temperature. The resulting mixture was warmed to gentle reflux and further stirred for 24 h. Then H_2O was added to the reaction, and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/acetone = 95:5) gave the pure **17a** (0.32 g, 88% yield): oily, $[\alpha]^{25}_D$ +22.2 (*c* 0.83, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.07−3.31 (m, 4H), 3.78 (ddd, *J* = 1.7, 5.5, 7.6 Hz, 1H), 4.27 (dd, *J* = 1.7, 7.6 Hz, 1H), 4.45−4.51 (m, 2H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 5.14 (s, 1H), 7.30−7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 27.7, 62.6, 73.2, 73.3, 78.1, 99.1, 121.2, 123.4, 127.9, 128.0, 136.6. Anal. Calcd for $C_{15}H_{16}O_3S_2$: C 58.41, H 5.23, S 20.79. Found: C 58.24, H 5.25, S 20.88.

Acetal 17b. Method A (from 14b). Amberlyst 15 (3.4 g, previously washed with anhydrous MeOH) was added in one portion to a stirred solution of **14b** (0.25 g, 0.79 mmol) in MeOH (10 mL) at 0 °C. After 10 min, the suspension was warmed to room temperature and further stirred until TLC revealed the presence of a major spot, R_f ~0.2 (hexane/acetone = 8/2). Then the solid was filtered off and washed with $CHCl_3$ (100 mL), and the resulting solution was washed with satd $NaHCO_3$ solution and brine. The organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. During chromatography of the crude residue over silica gel (hexane/acetone = 95:5), cyclization of acetal **15b** occurred, giving **17b** as the major product (0.16 g, 79% yield).

Method B (from 14b). Acetal **17b** (0.05 g, 0.16 mmol) was obtained (93% yield) starting from aldehyde **14b** under the same conditions reported above, but replacing amberlyst 15 with stoich TMSOTf (0.02 mL, 0.16 mmol).

Method C (Domino Reaction from 12b). Under the same conditions reported for the preparation of **17a**, the pure **17b** was obtained starting from MPM ether **12b** (86% yield): oily, $[\alpha]^{25}_D$ +14.0 (*c* 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13 (s, 3H), 3.02−3.35 (m, 4H), 3.80 (ddd, *J* = 1.3, 5.8, 7.6 Hz, 1H), 4.18 (dd, *J* = 1.7, 7.6 Hz, 1H), 4.78 (ddd, *J* = 1.7, 4.8, 5.8 Hz, 1H), 5.20 (s, 1H), 5.75 (dd, *J* = 1.3, 4.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.6, 26.3, 27.8, 62.9, 72.4, 72.6, 99.3, 118.0, 126.1, 170.2. Anal. Calcd for $C_{10}H_{12}O_4S_2$: C 46.14, H 4.65, S 24.63. Found: C 46.29, H 4.64, S 24.55.

Methyl 6-*O*-Acetyl-4-*O*-benzyl-2,3-dideoxy-α-L-*threo*-hex-2-enopyranoside (19a). A solution of **16a** (0.25 g, 0.65 mmol) in THF (7 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (2.25 g, wet) in the same solvent (7 mL) at 0 °C. The suspension was stirred for 2 h, then the solid was filtered off and washed with THF. The filtrate was evaporated under reduced pressure to afford a crude residue from which chromatography over silica gel (hexane/acetone = 8/2) gave the pure

19a (0.16 g, 82% yield): oily, $[\alpha]^{25}_D$ +80.9 (*c* 0.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.43 (s, 3H), 3.69 (dd, J = 2.7, 5.1 Hz, 1H), 4.19 (dt, J = 2.7, 6.2 Hz, 1H), 4.37 (d, J = 6.2 Hz, 2H), 4.53 (d, J = 11.9 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.96 (d, J = 2.7 Hz, 1H), 6.01 (dd, J = 2.7, 10.2 Hz, 1H), 6.14 (ddd, J = 0.9, 5.1, 10.2 Hz, 1H), 7.27−7.38 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 55.4, 63.8, 66.9, 68.6, 70.8, 95.0, 126.6, 127.8, 128.4, 129.8, 138.1, 170.7. Anal. Calcd for $C_{16}H_{20}O_5$: C 65.74, H 6.90. Found: C 65.91, H 6.88.

Methyl 6-*O*-Acetyl-4-*O*-benzyl-2,3-dideoxy-α-L-*threo*-hexopyranoside (20). Treatment of **16a** (0.10 g, 0.26 mmol) with an excess of Raney-Ni (W2) (1.8 g, wet) afforded, after common workup and purification procedures, the pure **20** (0.07 g, 86% yield): oily, $[\alpha]^{25}_D$ −10.7 (*c* 0.14, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78−1.88 (m, 1H), 1.91−1.98 (m, 1H), 2.02 (s, 3H), 2.03−2.09 (m, 2H), 3.37 (s, 3H), 3.49 (bs, 1H), 3.96 (ddd, J = 1.5, 5.4, 6.9 Hz, 1H), 4.19 (dd, J = 5.4, 11.3 Hz, 1H), 4.22 (dd, J = 6.9, 11.3 Hz, 1H), 4.40 (d, J = 12.2 Hz, 1H), 4.67 (d, J = 12.2 Hz, 1H), 4.78 (d, J = 3.4 Hz, 1H), 7.25−7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.7, 23.9, 54.5, 64.6, 68.4, 70,3, 70.5, 97.9, 127.6, 127.8, 128.3, 138.1, 170.6. Anal. Calcd for $C_{16}H_{22}O_5$: C 65.29, H 7.53. Found: C 65.46, H 7.50.

Methyl 6-*O*-Acetyl-4-*O*-benzyl-α-L-gulopyranoside (22). To an ice-cooled solution of **19a** (0.05 g, 0.17 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added 4-methylmorpholine-*N*-oxide (0.04 g, 0.34 mmol) in one portion. After a few minutes, a catalytic amount of a 0.05 M OsO_4 solution in CH_2Cl_2 (0.3 mL, 0.015 mmol) was added. The resulting mixture was stirred overnight at room temperature; then the reaction was quenched with saturated aqNa_2SO_3 and evaporated under reduced pressure. Chromatography of the crude residue over silica gel (CH_2Cl_2) afforded the pure **22** (0.05 mmol, 84% yield): oily, $[\alpha]^{25}_D$ −15.8 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.50 (bs, 1H, D_2O exchange), 3.20 (bs, 1H, D_2O exchange), 3.46 (s, 3H), 3.65 (d, J = 3.1 Hz, 1H), 3.98 (bs, 1H), 4.05−4.10 (m, 1H), 4.11−4.16 (m, 2H), 4.28 (dd, J = 6.2, 10.2 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.67 (d, J = 11.8 Hz, 1H), 4.82 (d, J = 3.4 Hz, 1H), 7.28−7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 56.0, 63.1, 63.6, 65.2, 68.7, 72.5, 76.4, 100.8, 128.1, 128.5, 137.5, 169.6. Anal. Calcd for $C_{16}H_{22}O_7$: C 58.89, H 6.79. Found: C 59.05, H 6.77.

Methyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-L-*threo*-hex-2-enopyranoside (19b). A solution of **16b** (0.2 g, 0.60 mmol) in THF (5 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (2.0 g, wet) in the same solvent (5 mL) at 0 °C. The resulting mixture was stirred for 2 h at the same temperature, then the solid was filtered off and washed with THF. The filtrate was evaporated under reduced pressure to afford a crude residue from which chromatography over silica gel (hexane/acetone = 8/2) gave the pure **19b** (0.11 g, 75% yield): white solid, mp 60.5−61.5 °C (MeOH); $[\alpha]^{25}_D$ +173.3 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 6H), 3.43 (s, 3H), 4.23 (d, J = 5.7 Hz, 2H), 4.28−4.36 (m, 1H), 4.96 (d, J = 2.7 Hz, 1H), 5.02 (dd, J = 2.4, 5.4 Hz, 1H), 6.02 (dd, J = 2.7, 10.0 Hz, 1H), 6.10 (dd, J = 5.1, 10.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 20.7, 55.5, 62.8, 66.7, 76.5, 94.9, 125.2, 130.4, 171.3, 171.6. Anal. Calcd for $C_{11}H_{16}O_6$: C 54.09, H 6.60. Found: C 53.92, H 6.62.

Methyl 2,3-Dideoxy-α-L-*threo*-hex-2-enopyranoside (21). A methanolic 0.1 M MeONa solution (3 mL) was added to **19b** (0.1 g, 0.41 mmol). The resulting mixture was stirred for 4 h at room temperature, then it was neutralized with a few drops of acetic acid, and the solvents were evaporated under reduced pressure. Chromatography of the crude residue over silica gel ($CHCl_3$/CH_3OH = 9:1) gave the pure **21** (0.06 g, 98% yield): oily, $[\alpha]^{25}_D$ +69.7 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (bs, 1H, D_2O exchange), 2.30 (bs, 1H, D_2O exchange), 3.43 (s, 3H), 3.86−3.95 (m, 2H), 3.98 (dd, J = 5.8, 11.7 Hz, 1H), 4.03−4.08 (m, 1H), 4.96 (d, J = 3.0 Hz, 1H), 5.94 (dd, J = 3.0, 10.2 Hz, 1H), 6.15 (dd, J = 5.8, 10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 62.6, 62.8, 70.0, 95.2, 128.4, 129.2. Anal. Calcd for $C_7H_{12}O_4$: C 52.49, H 7.55. Found: C 52.30, H 7.58.

Methyl α-L-Talopyranoside (23). TMEDA (0.07 mL, 0.45 mmol) and an OsO_4 solution in anhydrous CH_2Cl_2 (0.45 mmol) were dropwise added to a stirred solution of olefin **21** (0.07 g, 0.45 mmol) in anhydrous CH_2Cl_2 (8 mL) at −78 °C and under nitrogen stream. The resulting mixture was stirred at the same temperature for 3 h, then ethylenediamine (0.07 mL, 1.0 mmol) was added. The solution was stirred for 48 h, until a dark brown precipitate was formed. The solution was then concentrated under reduced pressure. Chromatography of the crude residue over silica gel (CH_2Cl_2/MeOH = 8:2) afforded the pure **23** as single epimer (0.07 g, 80% yield): syrup, $[\alpha]^{25}_D$−101.0 (*c* 0.9, H_2O). ^{1}H NMR (500 MHz, D_2O): δ 3.39 (s, 3H), 3.74 (dd, J = 3.7, 11.0 Hz, 1H), 3.77−3.85 (m, 4H), 3.86−3.89 (m, 1H), 4.85 (s, 1H). ^{13}C NMR (125 MHz, D_2O): δ 55.1, 61.8, 65.6, 69.8, 70.2, 71.8, 101.8. Anal. Calcd for $C_7H_{14}O_6$: C 43.30, H 7.27. Found: C 43.19, H 7.29.

Methyl 6-*O*-Acetyl-4-*O*-benzyl-2,3-anhydro-α-L-gulopyranoside (24) and Methyl 6-*O*-Acetyl-4-*O*-benzyl-2,3-anhydro-α-L-talopyranoside (25). Method A. Hydrogen peroxide (0.12 mL, 50% aqueous solution) was added dropwise to a stirred suspension of olefin **19a** (0.05 g, 0.17 mmol), PhCN (0.11 mL, 1.11 mmol) and $NaHCO_3$ (0.05 g, 0.51 mmol) in MeOH (0.7 mL), cooled at 0 °C. The resulting suspension was warmed to room temperature and stirred for 48 h before dilution with brine and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/acetone = 8:2) gave the *gulo*-epoxide **24** along with a relevant amount of the *talo*-epoxide **25** (0.03 g, starting material recovered 0.02 g, 60% overall yield, 65:35 dr).

Method B. Na_2EDTA (4.0×10^{-4} M, 1.0 mL) and CF_3COCH_3 (0.18 mL, 2.0 mmol) were added to a solution of **19a** (0.05 g, 0.17 mmol) in CH_3CN (1.5 mL) at 0 °C. After a few minutes, a mixture of $NaHCO_3$ (0.13 g, 1.6 mmol) and Oxone (0.61 g, 1.9 mmol) was added over 1 h. The resulting suspension was stirred for 48 h at the same temperature. Then the reaction was diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/acetone = 8:2) afforded the *talo*-epoxide **25** in addition to a minor amount of its *gulo* epimer **24** (0.04 g, 79% overall yield, 9:1 dr). Data for *gulo*-epoxide **24**: oily, $[\alpha]^{25}_D$ −12.0 (*c* 0.3, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6): δ 1.63 (s, 3H), 2.88−2.94 (m, 2H), 3.24 (s, 3H), 3.40 (bs, 1H), 4.10−4.26 (m, 4H), 4.42−4.45 (m, 1H), 4.62 (d, J = 2.8 Hz, 1H), 7.08−7.30 (m, 5H). ^{13}C NMR (125 MHz, C_6D_6): δ 20.3, 49.9, 51.4, 54.8, 64.0, 66.4, 71.5, 73.0, 95.1, 127.4, 128.5, 128.6, 138.2, 169.7. Anal. Calcd for $C_{16}H_{20}O_6$: C 62.33, H 6.54. Found: C 62.18, H 6.56. Data for *talo*-epoxide **25**: oily, $[\alpha]^{25}_D$ +43.0 (*c* 0.3, C_6H_6). ^{1}H NMR (400 MHz, C_6D_6): δ 1.65 (s, 3H), 2.76−2.82 (m, 2H), 3.13 (s, 3H), 3.18 (appt, J = 3.5, 4.5 Hz, 1H), 3.79−3.85 (m, 1H), 4.26 (d, J = 12.0 Hz, 1H), 4.37 (dd, J = 4.3, 11.6 Hz, 1H), 4.42 (dd, J = 7.9, 11.6 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.70 (s, 1H), 7.10−7.40 (m, 5H). ^{13}C NMR (100 MHz, C_6D_6): δ 20.9, 48.8, 49.6, 54.7, 63.1, 66.0, 67.7, 70.1, 95.9, 127.5, 128.2, 128.3, 138.0, 169.7. Anal. Calcd for $C_{16}H_{20}O_6$: C 62.33, H 6.54. Found: C 62.20, H 6.56.

Methyl 4-*O*-Benzyl-α-L-idopyranoside (26). A solution of the *talo*-epoxide **25** (0.05 g, 0.16 mmol) was refluxed for 12 h in a 1 N aq KOH solution (3 mL). Then the reaction mixture was cooled to 0 °C, and 1 N HCl was carefully added until neutrality. The white solid was filtered off and washed with AcOEt. Solvent removal under reduced pressure, and chromatography of the resulting crude residue (CH_2Cl_2/MeOH = 9:1) afforded the pure **26** (0.05 g, 99% yield): oily, $[\alpha]^{25}_D$ −40.0 (*c* 0.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (t, J = 7.5 Hz, 1H, D_2O exchange), 3.46 (s, 3H), 3.57−3.60 (m, 1H), 3.65 (dd, J = 4.6, 11.9 Hz, 1H), 3.68−3.72 (m, 1H), 3.92 (dd, J = 7.5, 11.9 Hz, 1H), 4.06−4.15 (m, 2H), 4.52 (d, J = 11.9 Hz, 1H), 4.78 (d, J = 11.9 Hz, 1H), 4.85 (s, 1H), 7.28−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 62.5, 65.5, 66.2, 67.7, 72.7, 75.9, 102.1, 128.3, 128.4, 128.7, 128.9, 136.5. Anal. Calcd for $C_{14}H_{20}O_6$: C 59.14, H 7.09. Found: C 59.32, H 7.06.

Methyl 3,6-Anhydro-4-*O*-benzyl-α-L-galactopyranoside (27). As discussed in the previous section, ring opening of the *gulo*-epoxide **24** (0.02 g, 0.07 mmol) with refluxing 1 N KOH (0.5 mL) for 12 h provided, after common purification procedures, the pure **27** (0.02 g, 99% yield) as the sole product: oily, $[\alpha]^{25}_D$ −12.0 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (s, 3H), 3.96 (dd, J = 2.5, 5.3 Hz, 1H), 4.03 (dd, J = 2.2, 10.0 Hz, 1H), 4.06 (d, J = 10.0 Hz, 1H), 4.34 (bs, 1H), 4.38 (d, J = 1.8 Hz, 1H), 4.50 (d, J = 5.3 Hz, 1H), 4.55 (d, J = 11.9 Hz, 1H), 4.65 (d, J = 11.9 Hz, 1H), 4.72 (d, J = 2.5 Hz, 1H), 7.27−7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.1, 69.4, 70.2, 71.3, 75.3, 77.5, 78.3, 99.7, 127.7, 127.9, 128.4, 138.2. Anal. Calcd for $C_{14}H_{18}O_5$: C 63.15, H 6.81. Found: C 63.34, H 6.79.

4-*O*-Benzyl-1,6-anhydro-2,3-dideoxy-β-L-*threo*-hex-2-enopyranose (28). A solution of **17a** (0.30 g, 0.97 mmol) in acetone (10 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (3.0 g, wet) in the same solvent (10 mL) at 0 °C. The suspension was stirred for 2 h at room temperature, then the solid was filtered off and washed with further acetone. The filtrate was evaporated under reduced pressure to afford a crude residue from which chromatography over silica gel (hexane/acetone = 9:1) gave the pure **28** (0.17 g, 78% yield): oily, $[\alpha]^{25}_D$ +10.0 (c 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85−3.88 (m, 1H), 4.26 (d, J = 8.0 Hz, 1H), 4.51−4.56 (m, 2H), 4.57 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 5.49 (d, J = 2.9 Hz, 1H), 5.80 (d, J = 9.8 Hz, 1H), 5.88 (dd, J = 2.9, 9.8 Hz, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.7, 71.2, 73.6, 74.8, 95.9, 127.2, 127.5, 128.2, 128.4, 129.7, 136.8. Anal. Calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47. Found: C 71.65, H 6.45.

4-*O*-Benzyl-1,6-anhydro-2,3-dideoxy-β-L-*threo*-pyranose (32). Treatment of **17a** (0.05 g, 0.16 mmol) with an excess of Raney-Ni (W2) (1.0 g, wet) in THF (1 mL) at room temperature afforded, after common workup and purification procedures, the pure **32** (0.03 g, 90% yield): oily; $[\alpha]^{25}_D$ +30.4 (c 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58−1.78 (m, 3H), 1.95−2.02 (m, 1H), 3.68−3.73 (m, 2H), 4.19 (d, J = 7.8 Hz, 1H), 4.47 (bt, J = 3.9 Hz, 1H), 4.53 (d, J = 12.2 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 5.48 (s, 1H), 7.26−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.8, 30.8, 65.1, 70.5, 73.1, 73.9, 100.9, 127.5, 127.7, 128.4, 138.3. Anal. Calcd for $C_{13}H_{16}O_3$: C 70.89, H 7.32. Found: C 71.01, H 7.29.

4-*O*-Benzyl-1,6:2,3-dianhydro-β-L-gulopyranose (29). Na_2EDTA (4.0×10^{-4} M, 4.0 mL) and CF_3COCH_3 (0.70 mL, 7.8 mmol) were added to a solution of **28** (0.15 g, 0.69 mmol) in CH_3CN (8.0 mL) at 0 °C. After a few minutes, a mixture of $NaHCO_3$ (0.5 g, 5.9 mmol) and Oxone (2.0 g, 6.5 mmol) was added over 1 h, and the resulting mixture was stirred for 12 h at the same temperature. Then the reaction was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the crude residue over silica gel (hexane/acetone = 8:2) afforded the pure **29** (0.14 g, 85% yield) as single diastereoisomer: white solid, mp 74.0−76.0 °C (MeOH); $[\alpha]^{25}_D$ +10.0 (c 0.7, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.02 (dd, J = 0.8, 3.8 Hz, 1H), 3.12 (dd, J = 2.2, 3.8 Hz, 1H), 3.75 (dd, J = 6.2, 8.0 Hz, 1H), 3.97 (dd, J = 0.8, 5.0 Hz, 1H), 4.16 (dd, J = 2.0, 8.0 Hz, 1H), 4.32−4.42 (m, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 5.56 (s, 1H), 7.30−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.4, 50.9, 63.4, 70.4, 71.9 (2C), 96.9, 127.6, 128.1, 128.5, 137.8. Anal. Calcd for $C_{13}H_{14}O_4$: C 66.66, H 6.02. Found C 66.50, H 6.04.

Methyl 4-*O*-Benzyl-α-L-galactopyranoside (31). Epoxide **29** (0.14 g, 0.60 mmol) was refluxed for 72 h in a 6 N aq KOH solution (5 mL). Then the reaction mixture was cooled to 0 °C, and 1 N HCl was carefully added until neutrality. The white solid was filtered off and washed with AcOEt, and the solvent was removed under reduced pressure. The resulting crude residue was dissolved in anhydrous MeOH (5 mL), then a catalytic amount of TMSOTf (10 μL, 0.06 mmol) was added at room temperature. The reaction mixture was stirred at 50 °C for 48 h. Then solid $NaHCO_3$ was added, and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (CH_2Cl_2/MeOH = 9:1) gave the pure **31** (0.15 g, 90% yield) as single anomer: white crystals, mp 84.0−86.0 °C (EtOAc); $[\alpha]^{25}_D$ −90.6 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (bs, 2H, D_2O exchange), 2.34 (bs, 1H, D_2O exchange), 3.42 (s, 1H), 3.56−3.70 (m, 2H), 3.72−3.94 (m, 4H), 4.72 (d, J = 11.7 Hz, 1H), 4.84 (d, J = 11.7 Hz, 1H), 4.85 (d, J = 3.2 Hz, 1H), 7.26−7.42 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.5, 62.2, 70.1, 70.7, 71.9, 74,9, 76.4, 99.4, 128.1, 128.2, 128.4, 137.9. Anal. Calcd for $C_{14}H_{20}O_6$: C 59.14, H 7.09. Found: C 59.30, H 7.07.

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