JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

Glycosidase Inhibition by All 10 Stereoisomeric 2,5-Dideoxy-2,5-iminohexitols Prepared from the Enantiomers of Glucuronolactone

Benjamin J. Ayers,[†] Nigel Ngo,[†] Sarah F. Jenkinson,[†,‡] R. Fernando Martínez,[†] Yousuke Shimada,[§] Isao Adachi,[§] Alexander C. Weymouth-Wilson,[∥] Atsushi Kato,*[,§] and George W. J. Fleet*[,†,‡]

[†]Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

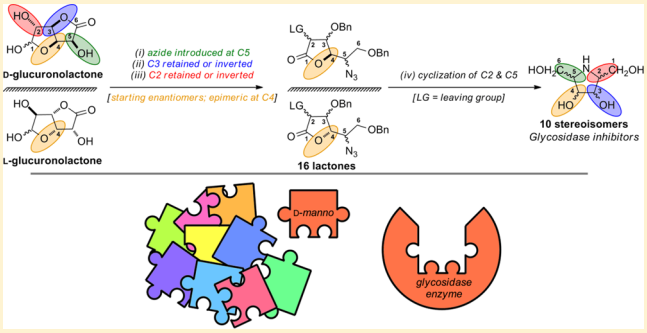
[‡]Oxford Glycobiology Institute, University of Oxford, South Parks Road, Oxford OX1 3QU, U.K.

[§]Department of Hospital Pharmacy, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan

[∥]Dextra Laboratories Ltd., The Science and Technology Centre, Whiteknights Road, Reading RG6 6BZ, U.K.

Supporting Information

ABSTRACT: The enantiomers of glucuronolactone are excellent chirons for the synthesis of the 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols by formation of the pyrrolidine ring by nitrogen substitution at C2 and C5, with either retention or inversion of configuration; the stereochemistry at C3 may be adjusted during the synthesis to give seven stereoisomers from each enantiomer. A definitive side-by-side comparison of the glycosidase inhibition of a panel of 13 glycosidases showed that 8 of the 10 stereoisomers showed significant inhibition of at least one glycosidase.



INTRODUCTION

The chemotherapeutic potential of iminosugars is due to the inhibition of glycosidases and interaction with other sugar receptors and metabolizing enzymes.[1−4] Glucuronolactone **1D** has been used as the starting material for many homochiral targets,[5−12] including iminosugars.[13] This paper reports the synthesis from the enantiomers of glucuronolactone of all 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols, three of which have been isolated from plants. Intermediates in the syntheses also allow access to any of 16 stereoisomeric lactones as precursors to a wide range of hydroxylated prolines and their derivatives. A side-by-side comparison showed that 8 of the 10 stereoisomers gave significant inhibition of varying glycosidases.

The strategy for the synthesis of the 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols is shown in Figure 1. There are four pairs of enantiomers and two *meso* forms. For all of them, the exocyclic primary alcohols result from reduction of C1 and C6 of glucuronolactone. The acetonide **1D** has a single unprotected hydroxyl group at C5 that allows introduction of nitrogen by azide at C5 with either inversion (***I5***) or retention (***R5***) of configuration. The stereochemistry at C3 (***R3***, ***I3***) and C2 can be adjusted, with subsequent nucleophilic displacement of leaving groups at C2 (***R2***, ***I2***), by nitrogen derived from the azide at C5 forming the pyrrolidine ring. Access to C4 is not possible; however, identical sequences starting from the acetonide of L-glucuronolactone **1L** allow access to epimers at C4.

Since the ring is formed by nucleophilic displacements at C2 and C5, the shortest synthesis is that of the D-*gluco* isomer (DGDP) **2D** with ***I5−R3−I2*** from the D-glucuronolactone **1D**. DGDP **2D** can also be formed by a longer sequence ***R5−R3−R2*** from the *same* acetonide, **1D**. This pyrrolidine is not available from the L-enantiomer **1L**. Similarly, the L-*gluco* enantiomer **2L** is accessible *via* identical sequences from the readily available acetonide of L-glucuronolactone **1L**.[14] In contrast, there is a single sequence for the syntheses from the acetonide **1D** of the two C_2-symmetric stereoisomers, D-*manno* (DMDP) **3D** [by ***R5−R3−I2***] and L-*ido* **4L** [***I5−R3−R2***]. The enantiomers L-*manno* (L-DMDP) **3L** [by ***R5−R3−I2***] and D-*ido* **4D** [***I5−R3−R2***] are thus identically available from the acetonide **1L**. The D-*altro* isomer **5D** is obtained in the same number of steps from either **1D** [***R5−I3−I2***] or from **1L** [***I5−I3−R2***]; the L-*altro* isomer **5L** is similarly accessible from both **1L** and **1D**. The *meso*-diastereomer *galacto* **6** [***I5−I3−I2***] was obtained in identical sequences from **1D** and **1L**. *meso-allo* **7** [***R5−I3−R2***] was similarly accessed from both enantiomers of acetonide **1**. Thus, the D-acetonide **1D** forms seven stereoisomers, whereas another seven are formed with the epimeric configuration at C4 from the L-enantiomer **1L**.

RESULTS AND DISCUSSION

The diols **8L** and **9D** are the key intermediates in the synthesis of all 2,5-dideoxy-2,5-iminohexitol stereoisomers. Compounds **8L** and **9D** are formed by the introduction of nitrogen as azide at C5 with inversion (***I5***) or retention (***R5***) of configuration,

Received: June 15, 2012

   dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

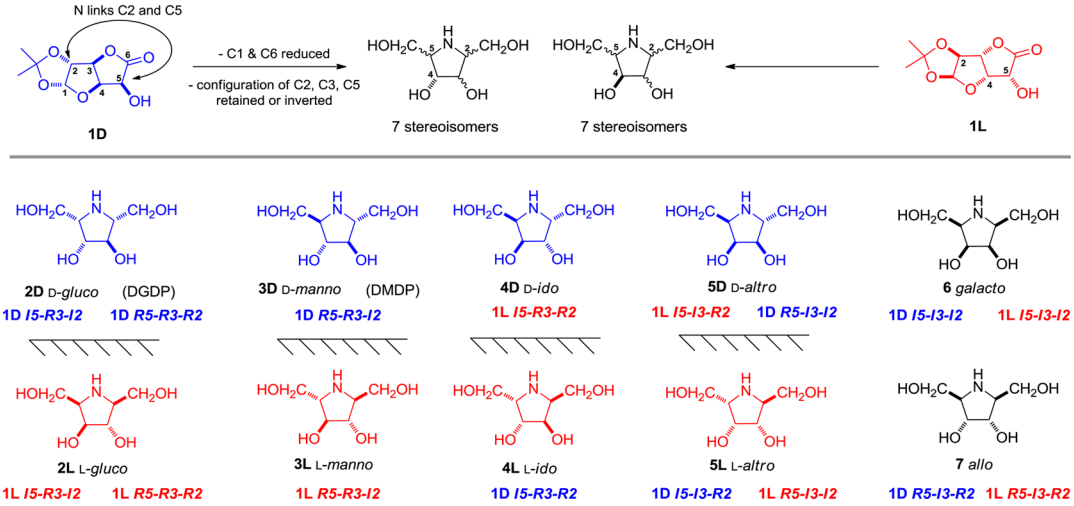
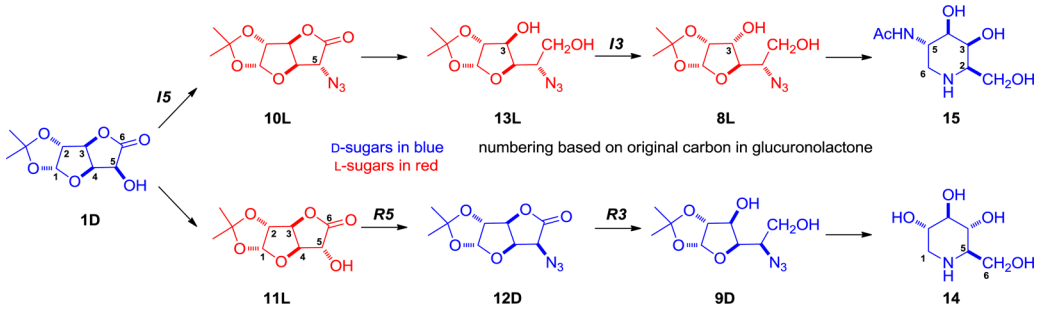


Figure 1. Ten stereoisomeric 2,5-dideoxy-2,5-iminohexitols showing the configurational changes *R* (retention) or *I* (inversion) required at C5−C3−C2 of the enantiomers of glucuronolactone acetonide **1D** and **1L**.

Scheme 1. Synthesis of Diols 8L and 9D as Key Intermediates for All 10 Stereoisomers of 2,5-Dideoxy-2,5-iminohexitols



reduction of C6 to a primary alcohol, and inversion (*I3*) or retention (*R3*) of the hydroxyl group at C3 (Scheme 1). The acetonide **1D**, with only the C5 OH group unprotected, is formed in 96% yield from D-glucuronolactone. Nucleophilic substitution α to a carbonyl group, even when β-oxygens are present, generally proceeds in high yield; thus, esterification of the free alcohol in **1D** with trifluoromethanesulfonic (triflic) anhydride affords the corresponding triflate ester, which on treatment with sodium azide in DMF forms the azido-lactone **10L** in 92% yield with inversion of configuration at C5 (*I5*).[15]

Reaction of the triflate of **1D** with trifluoroacetate as an oxygen nucleophile gives the epimeric *ido*-acetonide **11L** with inversion of configuration at C5.[16] Triflation of **11L** followed by azide displacement affords the azide **12D** with overall retention of configuration at C5 from **1D** (*R5*) in an overall yield of 84%.[17] Both of the epimeric azido-lactones **10L** and **12D** are stable, but highly base sensitive. Nonetheless, efficient two-step reductions of **10L** and **12D** by DIBALH followed by sodium borohydride afford the epimeric diols **13L** and **9D** in overall 70% and 71% yields, respectively, from D-glucurono-lactone acetonide **1D** on a multigram scale. The piperidine ring in a large scale synthesis of DNJ **14** was formed from reduction of the azide at C5 in the diol **9D** followed by intramolecular reductive amination with an aldehyde at C1.[17] The configuration at C3 in **13L** may be inverted by oxidation of C3 to the corresponding ketone followed by reduction with sodium borohydride to afford diol **8L** (*I3*).[18] Diol **8L** is a key intermediate in the scalable synthesis of the potent α-galactosaminidase inhibitor DGJNAc **15**,[19] in which the nitrogen at C5 forms the exocyclic NHAc group and the piperidine ring is formed by linking with nitrogen between C2 and C6.

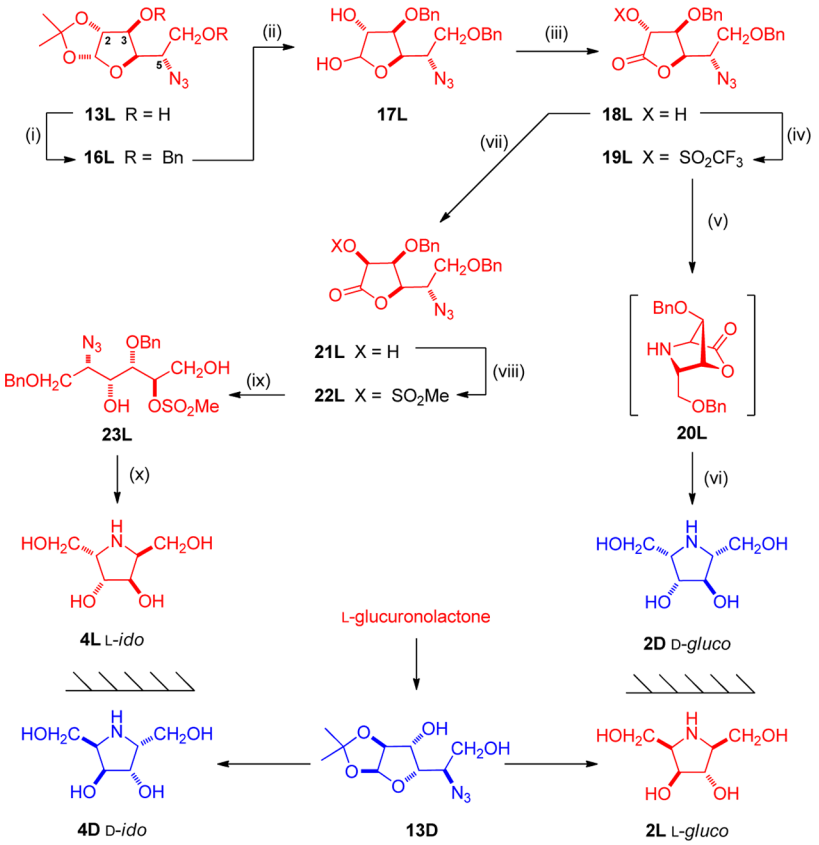
The diol **13L**, formed from **1D** in 70% yield by *I5-R3*, was converted into the triflate **19L** as a common intermediate for the synthesis of D-*gluco* (DGDP) **2D** and L-*ido* **4L** isomers (Scheme 2). Reaction of **13L** with benzyl bromide and sodium hydride in DMF gave the dibenzyl ether **16L** (73%). Hydrolysis of the acetonide **16L** with tosic acid in aqueous dioxane afforded the lactols **17L** (97%) which on oxidation with iodine in 2-methyl-2-propanol in the presence of potassium carbonate formed the lactone **18L** (72%). Esterification of the only free hydroxyl group in **18L** with triflic anhydride in the presence of pyridine in dichloromethane gave the stable triflate **19L** (95%). The overall yield of **19L** from **13L** was 48%.

The triflate α to the carbonyl group in **19L** is susceptible to easy intra- or intermolecular nucleophilic substitution. Thus, catalytic hydrogenation of the azide **19L** in ethanol in the presence of 10% palladium on charcoal gave the corresponding amine which spontaneously cyclized to the unstable bicyclic lactone **20L**; reduction of **20L** by sodium borohydride in ethanol, followed by further hydrogenation in the presence of hydrochloric acid, gave DGDP[20] **2D** in 80% yield [39% from diol **13L**, 27% from **1D**].

For the L-*ido* isomer **4L**, treatment of the triflate with sodium trifluoroacetate gave the inverted alcohol **21L** in 90% yield. Mesylation of **21L** with methanesulfonyl chloride in pyridine formed the mesylate **22L** (93%) which with sodium borohydride in ethanol/dioxane gave the open chain azido-

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of *ido*- and *gluco*-2,5-Dideoxy-2,5-iminohexitols from Diols 13 Derived from Glucuronolactone by *I5−R3*[a]



[a]Reagents and conditions: (i) NaH, $PhCH_2Br$, DMF, 73%; (ii) TsOH, dioxane/water, 7:1, 97%; (iii) I_2, K_2CO_3, *t*-BuOH, 72%; (iv) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 95%; (v) 10% Pd/C, H_2, EtOH; (vi) $NaBH_4$, EtOH, then 10% Pd/C, H_2, HCl, EtOH, 80% from **19L**; (vii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, then CF_3CO_2Na, DMF, 90%; (viii) MsCl, pyridine, 93%; (ix) $NaBH_4$, EtOH/dioxane, 8:1, 82%; (x) 10% Pd/C, H_2, CH_3CO_2Na, dioxane, then add HCl, 92%

mesylate **23L** (82%). Initial hydrogenation of **23L** in ethanol in the presence of 10% palladium and sodium acetate caused reduction to the amine, cyclization to the pyrrolidine, and partial removal of the benzyl groups; further hydrogenation with the addition of hydrochloric acid gave the L-*ido*[27] isomer **4L** (92%) in 32% overall yield from **13L** (23% from **1D**). The L-*gluco* **2L** and D-*ido* **4D** isomers were prepared by identical sequences from L-glucuronolactone **1L**.

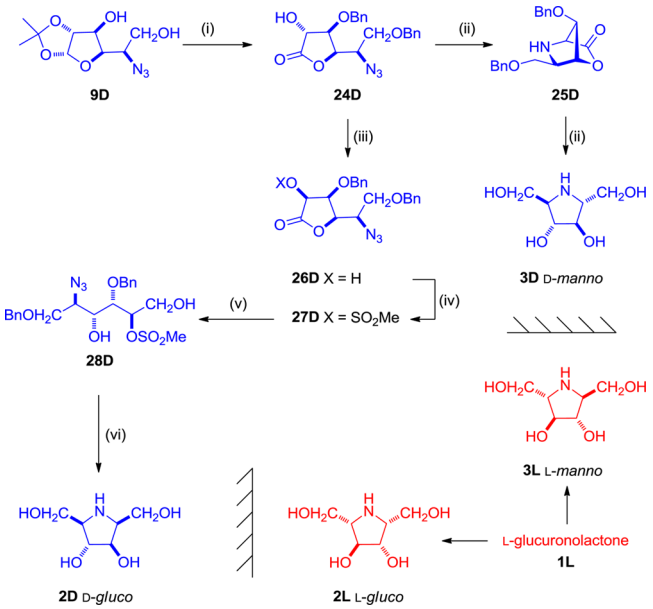
The synthesis of DGDP **2D** from **13L** in Scheme 2 required ***I5−R3−I2***. An alternative approach to **2D** from diol **9D**, with ***R5−R3−R2***, is shown in Scheme 3. The diol **9D** was first converted to the lactone **24D** as previously described in an overall yield of 70%.[17] Esterification of the C2 hydroxyl group α to the lactone carbonyl in **24D** gave the corresponding triflate which underwent a clean S_N2 reaction with sodium trifluoroacetate in DMF to afford the epimeric alcohol **26D** (85%). Treatment of **26D** with mesyl chloride formed the mesylate **27D** (99%) which on reduction with sodium borohydride in methanol gave the diol **28D** (50%). Catalytic hydrogenation of the azido-mesylate **28D** with 10% palladium in dioxane, initially in the presence of sodium acetate to ensure facile cyclization to the pyrrolidine, and subsequently in the presence of hydrochloric acid to hydrogenolyze the benzyl protecting groups, gave D-*gluco* **2D** (100%). The overall yield of **2D** was 29% from the diol **9D** and 21% from glucuronolactone **1D**.

The lactone **24D** was a divergent intermediate for both the synthesis of DGDP **2D** and DMDP[32] **3D**. **24D** was converted to DMDP **3D** via the relatively stable bicyclic lactone **25D** as previously reported[17] in an overall yield of 56% from the diol **9D** [40% from glucuronolactone **1D**]. The enantiomeric L-*gluco* **2L** and L-*manno* **3L** were similarly prepared from L-glucuronolactone **1L**.

An inversion of configuration at C3 of **9D** was required for the synthesis of the lactone **35D** as a divergent intermediate in the synthesis of the D-*altro*[38] **5D** and *meso-allo*[41] **7** isomers (Scheme 4). Nucleophilic substitution of the secondary triflate from **29D**, which lacks an α-carbonyl group, was not efficient due to the steric hindrance of the isopropylidene protecting group being on the same side as the incoming nucleophile. Accordingly, the primary alcohol group in **9D** was selectively protected by reaction with *tert*-butyldimethylsilyl (TBDMS) chloride in pyridine to give the silyl ether **29D** (92%) which, on oxidation with Dess−Martin periodinane, gave the ketone **30D** (95%). Reduction of **30D** by sodium borohydride in ethanol was completely stereoselective, with hydride attack from the less hindered side, to give the epimeric silyl ether **31D** (93%). Removal of the silyl protecting group in **31D** with tetrabutylammonium fluoride (TBAF) in THF gave **32D** (98%); subsequent protection of both the C3 and C6 hydroxyl groups with benzyl bromide and sodium hydride in DMF afforded the dibenzyl ether **33D** (88%). Hydrolysis of the isopropylidene protecting group in **33D** by tosic acid in

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of *gluco*- and *manno*-2,5-Dideoxy-2,5-iminohexitols from Diols 9 Derived from Glucuronolactone by *R5*−*R3*[a]



[a]Reagents and conditions: (i) **24D** from **9D**, 70%;[17] (ii) **3D** from **9D**, 56%;[17] (iii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, then CF_3CO_2Na, DMF, 85% from **24D**; (iv) $MeSO_2Cl$, pyridine, 99%; (v) $NaBH_4$, EtOH/dioxane, 8:1, 50%; (vi) 10% Pd/C, H_2, CH_3CO_2Na, dioxane, then add HCl, 100%.

aqueous dioxane afforded the lactols **34D** (93%); C1 was then protected by oxidation with iodine in 2-methyl-2-propanol in the presence of potassium carbonate to give the lactone **35D** (79%); **35D**, a common intermediate for the synthesis of both targets **5D** and **7**, was prepared in overall yield of 52% from **9D**.

For the synthesis of D-*altro* **5D**, initial conversion of **35D** to the triflate **38D** (80%), followed by reduction of the azide to the amine, produced a complex mixture. Accordingly, esterification of **35D** by mesyl chloride in pyridine gave **36D** (70%); subsequent reduction with sodium borohydride in ethanol/dioxane formed **37D** (51%). Hydrogenation of **37D** in ethanol in the presence of 10% palladium and sodium acetate, followed by addition of hydrochloric acid to the hydrogenation mixture, produced the D-*altro* analogue **5D** (99%) in 18% overall yield from **9D** (13% from **1D**). Inversion of configuration at C2 of the lactone **35D** was necessary for access to the *meso-allo* isomer **7**. The triflate **38D**, formed by esterification with triflic anhydride, with sodium trifluoroacetate in DMF, gave the epimeric alcohol **39D** (75%). Mesylation of **39D** to give **40D** (84%) was followed by reduction by sodium borohydride to afford **41D** (93%); catalytic hydrogenation of **41D** formed *meso-allo* **7** (95%); the overall yield of **7** was 29% from the diol **9D** and 21% from **1D**. The L-*altro* **5L** and *meso-allo* **7** isomers were prepared by identical sequences from L-glucuronolactone **1L**.

The preceding synthesis of D-*altro* **5D** from **9D**, and of L-*altro* **5L** from **9L**, involves *R5*−*I3*−*I2*. An alternative strategy of *I5*−*I3*−*R2* leads to D-*altro* **5D** from **13D** and of L-*altro*-**5L** from **13L** and also to the *meso-galacto* analogue **6** from both enantiomers of **13** (Scheme 5).

For the synthesis of the lactone **44L**, a divergent intermediate in the synthesis of the L-*altro* **5L** and *meso-galacto*[45] **6** isomer, diol **13L** was converted to the C3 epimer **8L** in 66% yield as previously reported (*I5*−*I3*) (Scheme 5).[18] The diol **8L** with benzyl bromide and sodium hydride in DMF gave the dibenzyl ether **42L** (99%). Hydrolysis of the isopropylidene protecting group in **42L** by tosic acid in aqueous dioxane afforded the lactols **43L** (95%) in which C1 was protected by oxidation with iodine in 2-methyl-2-propanol in the presence of potassium carbonate to give the lactone **44L** (80%); **44L**, a common intermediate for the synthesis of both targets **5L** and **6**, was prepared in overall yield of 50% from **13L**.

For the synthesis of the *meso-galacto* isomer **6**, initial conversion of **44L** to the triflate **47L** (80%) followed by reduction of the azide to the amine produced a complex mixture. Accordingly, conversion of **44L** by mesyl chloride in pyridine to the mesylate **45L** (95%), followed by reduction with sodium borohydride in ethanol/dioxane formed **46L** (65%). Hydrogenation of **46L** in dioxane in the presence of 10% palladium and sodium acetate, followed by addition of hydrochloric acid to the hydrogenation mixture, gave the *meso-galacto* analogue **6** (91%) in 28% overall yield from **13L** (20% from **1D**). Inversion of configuration at C2 of the lactone **44L** was necessary for access to the L-*altro* isomer **5L**. The triflate **47L**, formed by esterification with triflic anhydride, with sodium trifluoroacetate in DMF gave the epimeric alcohol **48L** (72%). Mesylation of **48L** to give **49L** (78%), followed by reduction by sodium borohydride, afforded **50L** (89%) which on catalytic hydrogenation formed L-*altro* **5L** (92%); the overall yield of **5L** from the diol **13L** was 23% (16% from **1D**). The D-*altro* **5D** and *meso-galacto* **6** isomers were also prepared by identical sequences from L-glucuronolactone **1L**.

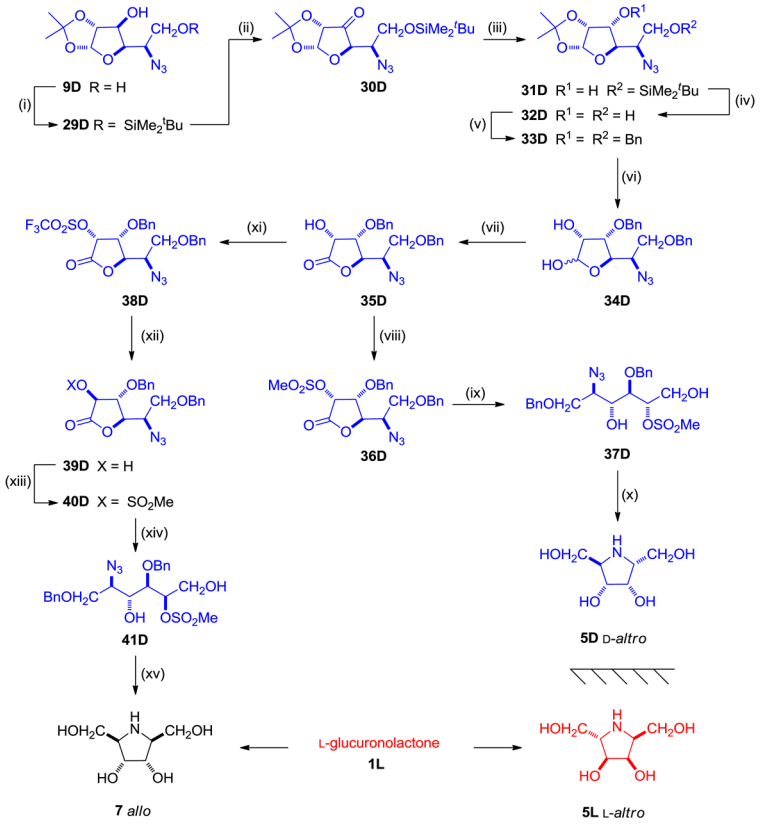
The overall number of steps and yields for the syntheses of seven DMDP stereoisomers from the azido-diols are summarized in Table 1; the epimeric diols **13L** and **9D** were prepared in overall 70% and 72% yields, respectively, from D-glucuronolactone acetonide **1D** on a multigram scale. The stereochemistry required (*R* or *I*) at C5, C3, and C2 for the individual synthetic routes are shown. The general procedures are scalable, robust and reliable for the synthesis of all the stereoisomers. While the yields for the different steps after the formation of diols **13L** and **9D** have not been optimized, the overall yields indicate that these are practicable sources of any stereoisomer. Both the ^{13}C NMR shifts and the specific rotations $[\alpha]_D$ of each diastereomer are also compared in Table 1; of the six diastereoisomers **2**−**7** only two (*gluco* **2** and *altro* **5**) have six nonequivalent ^{13}C signals. Full NMR analysis of each diastereomer is given in the experimental procedures.

Glycosidase inhibition. In piperidine pyranoside mimics (such as DNJ and DGJ), there is usually, but not always,[49] a good overlap between the structure of the glycoside and inhibition by the corresponding iminosugar mimic. Prediction of glycosidase inhibition by pyrrolidine analogues is far less reliable. A comparison of inhibition of a panel of glycosidases by all 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols was obtained by assays as previously described (Table 2).[50] Three of the stereoisomers are natural products. DGDP **2D** was isolated from the Thai traditional crude drug "Non tai yak" (*Stemona tuberosa*),[51] D-*altro* **5D** was extracted from the roots of *Adenophora triphylla*[52] and DMDP **3D** is the most widely naturally occurring iminosugar.[53]

Both DGDP **2D** and DMDP **3D** are modest α-glucosidase inhibitors; DMDP is a much more potent inhibitor of β-glucosidase[54,55] and β-galactosidase. DGDP **2D**, but not DMDP **3D**, is an inhibitor of xylose isomerase.[56] Enantiomers

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 4. Synthesis of *meso-allo-* and *altro*-2,5-Dideoxy-2,5-iminohexitols from Diols 9 Derived from Glucuronolactone by *R5*–*I3*[a]



[a]Reagents and conditions: (i) *t*-BuMe$_2$SiCl, pyridine, 92%; (ii) Dess–Martin periodinane, CH_2Cl_2, 95%; (iii) $NaBH_4$, EtOH, 93%; (iv) TBAF, THF, 98%; (v) NaH, $PhCH_2Br$, DMF, 88%; (vi) TsOH, dioxane/water, 7:1, 93%; (vii) I_2, K_2CO_3, *t*-BuOH, 79%; (viii) $MeSO_2Cl$, pyridine, 70%; (ix) $NaBH_4$, EtOH/dioxane, 8:1, 51%; (x) 10% Pd/C, H_2, CH_3CO_2Na, EtOH, then add HCl, 99%; (xi) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 80%; (xii) CF_3CO_2Na, DMF, 75% from **35D**; (xiii) $MeSO_2Cl$, pyridine, 84%; (xiv) $NaBH_4$, EtOH/dioxane, 8:1, 93%; (xv) 10% Pd/C, H_2, CH_3CO_2Na, dioxane, then add HCl, 95%.

of iminosugars frequently inhibit the *same* enzymes as the natural product.[57−62] Thus, L-*gluco* **2L** is a better, and more specific, α-glucosidase inhibitor than the natural product DGDP **2D**. L-*manno* **3L** shows potent α-glucosidase and trehalase inhibition. The *meso-galacto* **6** is an excellent inhibitor of both α-D-galactosidase and α-L-fucosidase; **6** contains both D-*galacto* and L-*fuco* motifs (Figure 2); the equivalence of α-D-galactosidase and α-L-fucosidase inhibition is well established.[63,64] The natural product D-*altro* **5D** is a good inhibitor of α-galactosidase and a weak inhibitor of β-glucosidase; **5D** has shown promise as a pharmacological chaperone alternative to DGJ for the treatment of Fabry's disease. The L-*altro* enantiomer **5L** is a moderate inhibitor of both α-galactosidase and α-L-rhamnosidase and a weak inhibitor of α-L-fucosidase (Table 2). *meso-allo* **7** is also good inhibitor of α-galactosidase. Neither of the *ido* **4** enantiomers showed any significant inhibition of any glycosidase. None of the stereoisomers showed any significant inhibition of β-mannosidase or of β-glucuronidases.

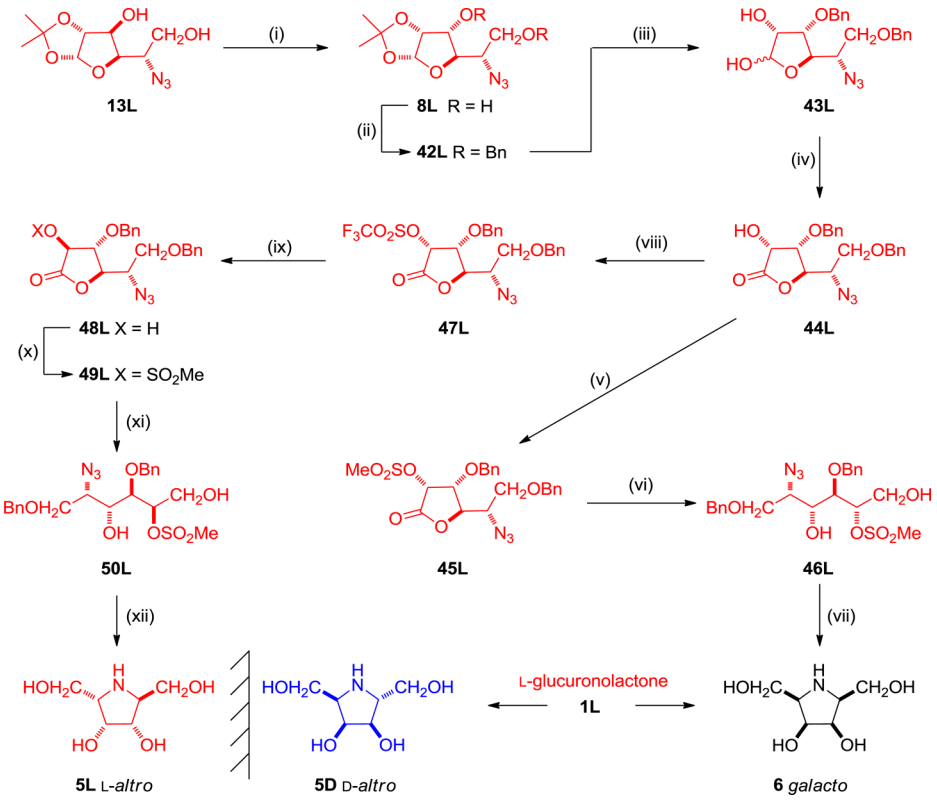
A recent paper reported that L-*gluco* **2L**, L-*manno* **3L**, L-*altro* **5L**, and *meso-allo* **7**, synthesized from chiral tri-*O*-benzyl cyclic nitrones,[33] are all good inhibitors of Jack bean α-mannosidase with IC_{50} values of 98, 88, 94, and 52 μM, respectively. In our present study, none of these stereoisomers caused 50% inhibition for the same Jack bean α-mannosidase even at concentrations as high as 1000 μM. Of all 10 iminohexitols, only D-*altro* **5D** showed modest inhibition against α-mannosidase with IC_{50} value of 421 μM (Table 2), whereas its enantiomer L-*altro* **5L** gave good inhibition of α-L-rhamnosidase (IC_{50} 91 μM) but *no* inhibition of Jack bean α-mannosidase; pyrrolidine mimics of D-mannofuranose inhibit α-mannosidase,[65,66] whereas pyrrolidine mimics of L-mannofuranose inhibit α-L-rhamnosidase.[67]

■ CONCLUSION

The synthesis of all 10 stereoisomers of 2,5-dideoxy-2,5-iminohexitols from the enantiomers of glucuronolactone shows the versatility of the acetonides **1D** and **1L** as chirons. Of the 10 2,5-dideoxy-2,5-iminohexitol stereoisomers, eight are good inhibitors of varying glycosidases, with only the *ido* enantiomers **4D** and **4L** failing to significantly inhibit at least one glycosidase (IC_{50} >100 μM). The main features of the inhibition are as follows. (a) The natural products DGDP **2D** and DMDP **3D** are weak—and their enantiomers **2L** and L-DMDP **3L** more specific and potent—inhibitors of α-glucosidases; the other six stereoisomers show no inhibition of α-glucosidases; (b) both *meso* isomers (*meso-galacto* **6** and *meso-allo* **7**) and D-*altro* **5D** are excellent inhibitors of α-galactosidase; (c) DMDP **3D** is the only isomer that exhibits good inhibition of β-glucosidases; (d) none of the stereoisomers show any significant inhibition of α-mannosidase. Biological properties, including glycosidase

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 5. Synthesis of *altro*- and *meso-galacto*-2,5-Dideoxy-2,5-iminohexitols from Diols 13 Derived from Glucuronolactone by *I5−I3*[a]



[a]Reagents and conditions: (i) **8L** from **13L**, 66%;[18] (ii) NaH, $PhCH_2Br$, DMF, 99%; (iii) TsOH, dioxane/water, 7:1, 95%; (iv) I_2, K_2CO_3, *t*-BuOH, 80%; (v) $MeSO_2Cl$, pyridine, 95%; (vi) $NaBH_4$, EtOH/dioxane, 8:1, 65%; (vii) 10% Pd/C, H_2, CH_3CO_2Na, dioxane, then add HCl, 91%; (viii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 80%; (ix) CF_3CO_2Na, DMF, 72% from **44L**; (x) $MeSO_2Cl$, pyridine, 78%; (xi) $NaBH_4$, EtOH/dioxane, 8:1, 89%; (xii) 10% Pd/C, H_2, CH_3CO_2Na, dioxane, then add HCl, 92%.

Table 1. ^{13}C NMR, $[\alpha]^{25}_D$, Overall Yields, and Number of Steps from Diols 9D and 13L Derived from D-Glucuronolactone Acetonide 1D for 2,5-Dideoxy-2,5-iminohexitols

					δ_C (ppm)						
2,5-dideoxy-2,5-iminohexitol		from diol	steps	yield (%)	C1	C2	C3	C4	C5	C6	$[\alpha]^{25}_D$ (H_2O)
D-*gluco* **2D**	***I5−R3−I2***	**13L**	6	39	57.4	63.7	75.0	76.5	67.3	59.8	+22.2 (*c* 1.2)
D-*gluco* **2D**	***R5−R3−R2***	**9D**	8	29							
D-*manno* **3D**	***R5−R3−I2***	**9D**	6	56	62.5	62.2	78.3				+50.4[a] (c 0.9)
L-*ido* **4L**	***I5−R3−R2***	**13L**	8	32	57.9	63.4	75.1				+7.25 (*c* 0.3)
D-*altro* **5D**	***R5−I3−I2***	**9D**	10	18	58.0	62.8	70.6	71.7	62.2	58.6	+31.0 (*c* 1.1)
L-*altro* **5L**	***I5−I3−R2***	**13L**	12	23							−25.5 (*c* 0.9)
meso-galacto **6**	***I5−I3−I2***	**13L**	10	28	60.4	60.5	71.9				0 (*c* 1.5)
meso-allo **7**	***R5−I3−R2***	**9D**	12	29	58.5	64.5	71.0				0 (*c* 1.0)

[a]$[\alpha]^{21}_D$.

inhibition, are likely to lead to commercial exploitation of stereoisomers of DMDP.

EXPERIMENTAL SECTION

General Experimental Procedures. All commercial reagents were used as supplied. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with 60 F_{254} silica. Plates were visualized using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2 M aqueous sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotation concentrations are quoted in g·100 mL^{-1}. ^1H and ^{13}C NMR spectra were assigned by utilizing 2D COSY and HSQC spectra. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference, except in the case of deuterium oxide, where acetonitrile was used as the reference. HRMS measurements were made using a time-of-flight (TOF) mass analyzer.

*5-Azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-β-L-ido-furanose (**16L**).* Sodium hydride (60% min oil suspension, 118 mg, 4.89 mmol) was added portionwise to a solution of diol **13L** (410 mg, 1.67 mmol) and benzyl bromide (0.60 mL, 4.89 mmol) in DMF (5 mL) at −10 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 17 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.07) and the formation of a major product (R_f 0.68). The reaction was quenched with methanol (0.5 mL), diluted with ethyl acetate (60 mL), and washed with a 1:1 brine/water

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Concentration of 2,5-Dideoxy-2,5-iminohexitols Giving 50% Inhibition (IC_{50}) of Various Glycosidases

	IC_{50} (μM)								
									
Enzyme	D-*gluco* **2D** (DGDP)	L-*gluco* **2L**	D-*manno* **3D** (DMDP)	L-*manno* **3L**	*meso-galacto* **6**	D-*ido* **4D**	L-*ido* **4L**	D-*altro* **5D**	L-*altro* **5L**
α-Glucosidase									
Rice	131	60	214	5.8	NI (38.9%)	792	NI (36.7%)	NI (24.1%)	NI (35.7%)
Yeast	167	NI (16.0%)	NI (15.6%)	NI (34.9%)	NI (0%)	NI (4.1%)	NI (29.4%)	NI (26.5%)	NI (35.1%)
Rat intestinal maltase	138	48	290	1.2	NI (44.2%)	654	NI (37.6%)	NI (31.8%)	754
β-Glucosidase									
Almond	256	NI (32.4%)	10	NI (12.1%)	597	NI (44.4%)	650	126	NI (15.9%)
Bovine liver	523	NI (5.4%)	9.7	NI (4.6%)	NI (44.5%)	NI (41.2%)	NI (34.7%)	759	NI (10.3%)
α-Galactosidase									
Coffee beans	NI[a] (38.4%)[b]	216	NI (10.5%)	NI (13.78%)	0.19	419	229	5.2	120
β-Galactosidase									
Bovine liver	361	NI (12.0%)	3.3	NI (0%)	NI (48.2%)	655	NI (43.1%)	358	NI (5.9%)
α-Mannosidase									
Jack beans	NI (13.3%)	NI (0%)	NI (31.5%)	NI (17.3%)	NI (10.2%)	NI (0%)	NI (22.3%)	421	NI (37.6%)
β-Mannosidase									
Snail	NI (14.6%)	NI (0%)	721	NI (12.6%)	NI (0%)	NI (9.5%)	NI (0.5%)	NI (0%)	NI (3.7%)
α-L-Rhamnosidase									
Penicillium decumbens	NI (3.3%)	NI (16.1%)	NI (24.1%)	NI (45.6%)	550	NI (12.2%)	NI (9.8%)	NI (13.4%)	91
α-L-Fucosidase									
Bovine kidney	NI (37.2%)	NI (0.3%)	NI (37.2%)	NI (0%)	41	NI (10.1%)	NI (15.8%)	NI (38.0%)	205
β-Glucuronidase									
E. coli	NI (5.1%)	NI (1.4%)	NI (0.4%)	NI (0.8%)	NI (21.3%)	NI (3.6%)	NI (2.1%)	NI (6.3%)	NI (2.0%)
Trehalase									
Porcine kidney	379	NI (40.1%)	200	48	NI (8.4%)	NI (13.1%)	NI (30.5%)	NI (4.3%)	1000

[a] *NI : No inhibition (less than 50% inhibition at 1000 μM).*
[b] *( ) : inhibition % at 1000 μM*

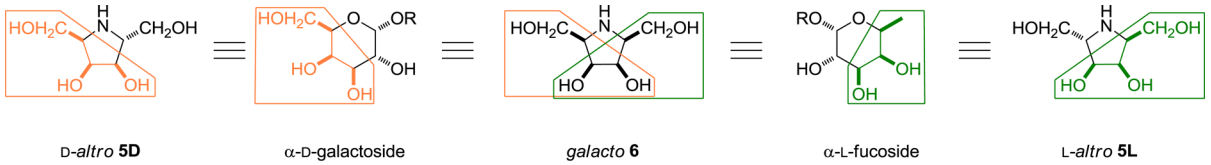


Figure 2. D-*galacto*- and L-*fuco*-stereochemical motifs in *altro*-**5D** and **5L** and in *meso-galacto* **6**.

solution (5 × 60 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (24:1 to 1:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **16L** (519 mg, 73%) as a yellow oil: $[\alpha]^{25}_D$ −30.7 (*c* 0.93, $CHCl_3$); ν_{max} (thin film) 2097 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 1.34, 1.51 (2 × 3H, s, $C(CH_3)_2$), 3.38 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 10.0), 3.45 (1H, dd, H6′, $J_{6',5}$ 3.3, $J_{6',6}$ 10.0), 3.81 (1H, d, H3, $J_{3,4}$ 3.3), 3.92 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.8, $J_{5,4}$ 8.9), 4.25 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.27 (1H, dd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 8.9), 4.39 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.51 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.60 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.62 (1H, d, H2, $J_{2,1}$ 3.8), 5.97 (1H, d, H1, $J_{1,2}$ 3.8), 7.24−7.38 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 26.3, 26.8 ($C(CH_3)_2$), 60.8 (C5), 69.2 (C6), 71.6, 73.4 (OCH_2Ph), 79.9 (C4), 81.5 (C3), 81.9 (C2), 104.8 (C1), 112.0 ($C(CH_3)_2$), 127.8, 127.9, 128.0, 128.2, 128.5, 128.6 (ArCH), 136.8, 137.6 (ArCC); LRMS (ESI +ve) 448 (34, M + Na^+), 873 (100, 2M + Na^+); HRMS (ESI +ve) found 448.1827 [M + Na^+], $C_{23}H_{27}N_3NaO_5$ requires 448.1843.

For the enantiomer **16D**: $[\alpha]^{25}_D$ +38.2 (*c* 1.00, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-*L*-idofuranose (17L).* *p*-Toluenesulfonic acid (1.04 g, 5.5 mmol) was added to a solution of isopropylidene-protected **16L** (1.05 g, 2.5 mmol) in 7:1 1,4-dioxane/water (6.4 mL) at 80 °C. Water (2 mL) was added over 30 min to maintain a homogeneous reaction mixture. The reaction was stirred for 2.5 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.68) and the formation of a major product (R_f 0.07). The reaction mixture was allowed to cool to rt, quenched with saturated aqueous sodium bicarbonate (32 mL), and extracted with ethyl acetate (3 × 32 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford lactol **17L** (917 mg, 97%) as a yellow oil, in an anomeric mixture (A:B, 3:1). Lactol **17L** was reacted without further purification: $[\alpha]^{25}_D$ +23.2 (*c* 0.83, $CHCl_3$); ν_{max} (thin film) 2101 (s, N_3), 3417 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 3.48 (1H, dd, $H6^A$, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.1), 3.51−3.56 (3H, m, $H6^B$, $H6'^A$, $H6'^B$), 3.84 (1H, td, $H5^A$, $J_{5,6'}$ 4.2, $J_{5,6}$ = $J_{5,4}$ 6.6), 3.88−3.91 (2H, m, $H3^B$, $H5^B$), 3.93 (1H, dd, $H3^A$, $J_{3,2}$ 3.3, $J_{3,4}$ 5.0), 4.30 (1H, dd, $H2^A$, $J_{2,3}$ 3.3, $J_{2,1}$ 4.9), 4.33−4.35 (2H, m, $H2^B$, $H4^B$), 4.36 (1H, d, OCH_2Ph^B, J_{gem} 11.6), 4.38 (1H, dd, $H4^A$, $J_{4,3}$ 5.0, $J_{4,5}$ 6.6), 4.38 (1H, d, OCH_2Ph^A, J_{gem} 11.6), 4.45 (1H, d, OCH_2Ph^A, J_{gem} 11.9), 4.46 (1H, d, OCH_2Ph^B, J_{gem} 11.9), 4.52 (1H, d, OCH_2Ph^A, J_{gem} 11.9), 4.54 (1H, d, OCH_2Ph^B, J_{gem} 11.9), 4.62 (1H, d, OCH_2Ph^B, J_{gem} 11.6), 4.70 (1H, d, OCH_2Ph^A, J_{gem} 11.6), 5.15 (1H, d, $H1^B$, $J_{1,2}$ 10.6), 5.53 (1H, d, $H1^A$, $J_{1,2}$ 4.6), 7.28−7.39 (20H, m, ArH^A, ArH^B); δ_C ($CDCl_3$, 100 MHz) 60.9 ($C5^A$), 61.8 ($C5^B$), 69.4 ($C6^B$), 69.8 ($C6^A$), 71.9, 73.4 (OCH_2Ph^A), 72.6, 73.5 (OCH_2Ph^B), 75.4 ($C2^A$), 77.6 ($C4^A$), 78.5 ($C2^B$), 80.4 ($C4^B$), 82.4 ($C3^B$), 82.9 ($C3^A$), 95.7 ($C1^A$), 103.5 ($C1^B$), 127.8, 127.9, 128.0, 128.0, 128.2, 128.5, 128.5, 128.7 ($ArCH^A$, $ArCH^B$), 137.2 ($ArCC^B$), 137.6 ($ArCC^A$); LRMS (ESI +ve) 403 (59, M + NH_4^+), 408 (73, M + Na^+), 739 (100, 2M + Na^+); HRMS (ESI +ve) found 408.1520 [M + Na^+], $C_{20}H_{23}N_3NaO_5$ requires 408.1530.

For the enantiomer **17D**: $[\alpha]^{25}_D$ −34.6 (*c* 0.95, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-*L*-idono-1,4-lactone (18L).* Potassium carbonate (337 mg, 2.44 mmol) and iodine (620 mg, 2.44 mmol) were added to a solution of lactol **17L** (464 mg, 1.20 mmol) in 2-methyl-2-propanol (5 mL) at 100 °C. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated complete consumption of the starting material (R_f 0.33) and the formation of a major product (R_f 0.60). The reaction mixture was allowed to cool to rt and diluted with ethyl acetate (35 mL). Saturated aqueous sodium thiosulfate (15 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 35 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **18L** (317 mg, 72%) as a yellow oil: $[\alpha]^{25}_D$ +39.1 (*c* 1.26, $CHCl_3$); ν_{max} (thin film) 1794 (s, C═O), 2116 (s, N_3), 3424 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 3.21 (1H, br s, OH2), 3.62 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 9.5), 3.69 (1H, dd, H6′, $J_{6',5}$ 7.6, $J_{6',6}$ 9.5), 4.07 (1H, ddd, H5, $J_{5,4}$ 1.5, $J_{5,6}$ 6.6, $J_{5,6'}$ 7.6), 4.41 (1H, dd, H3, $J_{3,2}$ 7.8, $J_{3,4}$ 8.2), 4.55 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.59 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.65 (1H, dd, H4, $J_{4,5}$ 1.5, $J_{4,3}$ 8.2), 4.67 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.84 (1H, dd, H2, $J_{2,OH}$ 2.5, $J_{2,3}$ 7.8), 4.88 (1H, d, OCH_2Ph, J_{gem} 11.9), 7.32−7.39 (10H, m, ArH); δ_C ($CDCl_3$, 100

dx.doi.org/10.1021/jo301243s | *J. Org. Chem.* XXXX, XXX, XXX−XXX

MHz) 59.4 (C5), 69.4 (C6), 72.0 (C2), 72.8, 73.6 (OCH_2Ph), 76.1 (C4), 79.7 (C3), 127.7, 128.0, 128.2, 128.5, 128.6 (ArCH), 136.8, 137.3 (ArCC), 174.8 (C1); LRMS (ESI +ve) 401 (15, M + NH_4^+), 406 (100, M + Na^+), 438 (28, M + MeOH + Na^+), 789 (74, 2M + Na^+); (ESI −ve) 418 (100, M + $^{35}Cl^-$), 420 (39, M + $^{37}Cl^-$); HRMS (ESI +ve) found 406.1360 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **18D**: $[\alpha]^{25}_D$ −35.2 (*c* 1.15, $CHCl_3$).

5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-trifluoromethanesulfonyl-L-idono-1,4-lactone (19L). Trifluoromethanesulfonic anhydride (0.13 mL, 0.76 mmol) was added dropwise to a solution of lactone **18L** (220 mg, 0.58 mmol) and pyridine (0.14 mL, 1.74 mmol) in dichloromethane (2.5 mL) at −40 °C under argon. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated complete consumption of the starting material (R_f 0.39) and the formation of a major product (R_f 0.59). The reaction was diluted with dichloromethane (11 mL), washed with 2 M aqueous hydrochloric acid (3 × 11 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 to 4:1, cyclohexane/ethyl acetate) to afford the triflate **19L** (280 mg, 95%) as a yellow oil: $[\alpha]^{25}_D$ +56.9 (*c* 0.84, $CHCl_3$); ν_{max} (thin film) 1813 (s, C═O), 2119 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 3.60 (1H, dd, H6, $J_{6,5}$ 6.7, $J_{6,6'}$ 9.5), 3.69 (1H, dd, H6′, $J_{6',5}$ 7.4, $J_{6',6}$ 9.5), 4.01 (1H, dd, H5, $J_{5,6}$ 6.7, $J_{5,6'}$ 7.4), 4.53 (1H, d, OCH_2Ph, J_{gem} 11.8), 4.57 (1H, d, OCH_2Ph, J_{gem} 11.3), 4.58 (1H, d, H3, $J_{3,2}$ 8.0), 4.59 (1H, d, H4, $J_{4,2}$ 5.3), 4.60 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.84 (1H, d, OCH_2Ph, J_{gem} 11.8), 5.82 (1H, dd, H2, $J_{2,4}$ 5.3, $J_{2,3}$ 8.0), 7.30−7.42 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 58.9 (C5), 68.9 (C6), 73.8, 73.8 (OCH_2Ph), 76.2 (C3), 76.7 (C4), 81.4 (C2), 127.8, 128.1, 128.2, 128.6, 128.9 (ArCH), 135.5, 137.0 (ArCC), 165.7 (C1); LRMS (ESI +ve) 456 (100), 538 (18, M + Na^+), 570 (54, M + MeOH + Na^+); HRMS (ESI +ve) found 538.0858 [M + Na^+], $C_{21}H_{20}F_3N_3NaO_7S$ requires 538.0866.

For the enantiomer **19D**: $[\alpha]^{25}_D$ −63.4 (*c* 0.98, $CHCl_3$).

2,5-Dideoxy-2,5-imino-D-glucitol (2D). Palladium (10% on C, 28 mg) was added to a solution of triflate **19L** (106 mg, 0.21 mmol) in ethanol (1.2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material (R_f 0.59) and the formation of a major product (R_f 0.19). The reaction mixture was filtered through glass microfiber (GF/B) to afford the bicyclic lactone **20L**. LRMS indicated the absence of a peak corresponding to the triflate **19L** (*m*/*z* 538 [M + Na^+]) and the presence of a peak corresponding to the bicyclic lactone **20L** (*m*/*z* 340 [M + H^+]). The crude bicyclic lactone **20L** was reacted without further purification.

Partial data for bicyclic lactone **20L**: ν_{max} (thin film) 1822 (s, C═O); δ_H ($CDCl_3$, 500 MHz) 3.78 (1H, dd, H6, $J_{6,5}$ 7.6, $J_{6,6'}$ 10.1), 3.85 (1H, dd, H6′, $J_{6',5}$ 7.0, $J_{6',6}$ 10.1), 4.36 (1H, d, H3 or H4, *J* 2.2), 4.39 (1H, dd, H5, $J_{5,6'}$ 7.0, $J_{5,6}$ 7.6), 4.51 (1H, d, OCH_2Ph, J_{gem} 12.0), 4.54 (1H, d, OCH_2Ph, J_{gem} 12.0), 4.58 (1H, d, OCH_2Ph, J_{gem} 11.7), 4.78 (2H, m, H2, H3 or H4), 4.84 (1H, d, OCH_2Ph, J_{gem} 12.0), 7.25−7.37 (10H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 59.4 (C5), 60.3 (C2), 63.9 (C6), 72.9, 73.7 (OCH_2Ph), 79.1, 79.5 (C3 or C4), 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8 (ArCH), 135.4, 136.9 (ArCC), 165.5 (C1); LRMS (ESI +ve) 362 (60, M + Na^+), 394 (100, M + MeOH + Na^+), 701 (24, 2M + Na^+).

Sodium borohydride (50 mg, 1.31 mmol) was added portionwise to a solution of the bicyclic lactone **20L** in ethanol (2 mL) and the reaction stirred at rt for 16 h. Aqueous hydrochloric acid (2 M, 1.5 mL) and palladium (10% on C, 50 mg) were added to the reaction mixture. The reaction vessel was evacuated and flushed with hydrogen and stirred for 20 h. The reaction mixture was filtered through glass microfiber (GF/B) and the filtrate concentrated to approximately 1 mL. This was loaded onto a short column of Dowex 50W-X8 (H^+ form) and the pyrrolidine **2D** liberated with 2 M aqueous ammonia. The ammoniacal fractions were concentrated in vacuo to afford pyrrolidine **2D** (26 mg, 80% over three steps) as a yellow oil: $[\alpha]^{25}_D$ +22.2 (*c* 1.18, H_2O) [lit.[68] $[\alpha]^{25}_D$ +26.1 (*c* 1.2, H_2O)]; ν_{max} (thin film) 3332 (br s, NH/OH); δ_H (D_2O, 400 MHz) 3.52 (1H, ddd, H5, $J_{5,4}$ 3.5, $J_{5,6'}$ 4.8, $J_{5,6}$ 8.3), 3.82 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 12.1), 3.87 (1H, dd, H2, $J_{2,3}$ 3.7, *J* 7.6), 3.88 (1H, dd, H6′, $J_{6',5}$ 4.8, $J_{6',6}$ 12.1), 3.85−3.93 (2H, m, H1, H1′), 4.07 (1H, dd, H4, $J_{4,3}$ 2.3, $J_{4,5}$ 3.5), 4.24 (1H, dd, H3, $J_{3,4}$ 2.3, $J_{3,2}$ 3.7); δ_C (D_2O, 100 MHz) 57.4 (C1), 59.8 (C6), 63.7 (C2), 67.3 (C5), 75.0 (C3), 76.5 (C4); LRMS (ESI +ve) 164 (100, M + H^+); (ESI −ve) 162 (100, [M − H]$^-$), 325 (57, [2M − H]$^-$); HRMS (ESI +ve) found 162.0765 [M − H]$^-$, $C_6H_{12}NO_4$ requires 162.0772.

For the enantiomer **2L**: $[\alpha]^{25}_D$ −19.1 (*c* 1.80, H_2O).

5-Azido-3,6-di-O-benzyl-5-deoxy-L-gulono-1,4-lactone (21L). Trifluoromethanesulfonic anhydride (0.35 mL, 2.07 mmol) was added dropwise to a solution of lactone **18L** (610 mg, 1.59 mmol) and pyridine (0.39 mL, 4.77 mmol) in dichloromethane (6 mL) at −40 °C under argon. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.39) and the formation of a major product (R_f 0.59). The reaction mixture was diluted with dichloromethane (8 mL), washed with 2 M aqueous hydrochloric acid (3 × 8 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate **19L** as a yellow oil. The crude triflate **19L** was reacted on without further purification.

Sodium trifluoroacetate (362 mg, 2.66 mmol) was added to a solution of crude triflate **19L** in DMF (3 mL) at rt under argon. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.59) and the formation of a major product (R_f 0.27). The reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (30 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the organic fractions were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 2:1, cyclohexane/ethyl acetate) to afford lactone **21L** (444 mg, 90%) as a yellow oil: $[\alpha]^{25}_D$ +11.7 (*c* 0.81, $CHCl_3$); ν_{max} (thin film) 1785 (s, C═O), 2099 (s, N_3), 3410 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.42 (1H, dd, H6, $J_{6,5}$ 5.6, $J_{6,6'}$ 10.4), 3.54 (1H, dd, H6′, $J_{6',5}$ 2.9, $J_{6',6}$ 10.4), 3.94 (1H, ddd, H5, $J_{5,6'}$ 2.9, $J_{5,6}$ 5.6, $J_{5,4}$ 9.1), 4.09 (1H, br d, OH2, $J_{OH,2}$ 6.1), 4.20 (1H, dd, H3, $J_{3,4}$ 3.3, $J_{3,2}$ 4.4), 4.37 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.39 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.44 (1H, dd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 9.1), 4.47 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.63 (1H, br dd, H2, $J_{2,3}$ 4.8, $J_{2,OH}$ 6.1), 4.88 (1H, d, OCH_2Ph, J_{gem} 11.4), 7.30−7.39 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 61.8 (C5), 69.2 (C6), 72.9 (C2), 74.0, 74.9 (OCH_2Ph), 77.3 (C3), 79.3 (C4), 128.9, 129.0, 129.2, 129.5 (ArCH), 138.8, 139.0 (ArCC), 175.5 (C1); LRMS (ESI +ve) 406 (70, [M + Na]$^+$), 789 (100, [2M + Na]$^+$); HRMS (ESI +ve) found 406.1362 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **21D**: $[\alpha]^{25}_D$ −11.2 (*c* 0.95, $CHCl_3$).

5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-gulono-1,4-lactone (22L). Methanesulfonyl chloride (133 μL, 1.72 mmol) was added dropwise to a solution of lactone **21L** (444 mg, 1.15 mmol) in pyridine (2 mL) at 0 °C under argon. The reaction was allowed to warm to rt and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.27) and the formation of a major product (R_f 0.55). The reaction mixture was concentrated in vacuo and coevaporated with toluene (3 × 5 mL). The crude residue was purified by flash chromatography (9:1 to 2:1, cyclohexane/ethyl acetate) to afford mesylate **22L** (494 mg, 93%) as a yellow oil: $[\alpha]^{25}_D$ +2.52 (*c* 0.45, $CHCl_3$); ν_{max} (thin film) 1178 (s, SO_2), 1361 (s, SO_2), 1801 (s, C═O), 2102 (s, N_3); δ_H (CD_3CN, 400 MHz) 3.30 (3H, s, SO_2CH_3), 3.44 (1H, dd, H6, $J_{6,5}$ 5.2, $J_{6,6'}$ 10.5), 3.55 (1H, dd, H6′, $J_{6',5}$ 2.8, $J_{6',6}$ 10.5), 3.99 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.3, $J_{5,4}$ 8.3), 4.40 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.42 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.47 (1H, dd, H3, $J_{3,4}$ 3.3, $J_{3,2}$ 4.6), 4.49 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.61 (1H, dd, H4, $J_{4,3}$ 3.0, $J_{4,5}$ 9.1), 4.78 (1H, d, OCH_2Ph, J_{gem} 11.6), 5.58 (1H, d, H2, $J_{2,3}$ 4.6), 7.30−7.40 (10H, m, ArH); δ_C (CD_3CN, 100 MHz); 39.7 (SO_2CH_3), 61.3 (C5), 69.1 (C6), 74.0, 75.1 (OCH_2Ph), 76.5 (C3), 77.1 (C2), 80.4 (C4), 129.0, 129.1, 129.3, 129.4, 129.5, 129.6 (ArCH), 138.0, 138.9 (ArCC), 170.7 (C1); LRMS (ESI +ve) 484 (38, M + Na^+), 516 (100, M + MeOH + Na^+), 945 (70, [2M + Na]$^+$); HRMS

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

(ESI +ve) found 484.1144 [M + Na^+], $C_{21}H_{23}N_3NaO_7S$ requires 484.1149.

For the enantiomer **22D**: $[\alpha]^{25}_D$ −1.54 (*c* 0.65, $CHCl_3$).

5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-gulitol (23L). Sodium borohydride (41 mg, 1.08 mmol) was added portionwise to a solution of lactone **22L** (100 mg, 0.22 mmol) in 8:1 ethanol/1,4-dioxane (5 mL) at −30 °C under argon. The reaction was stirred for 4 h, with the internal temperature rising to −15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the partial consumption of the starting material (R_f 0.55) and the formation of a major product (R_f 0.42). Further sodium borohydride (41 mg, 1.08 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 6 h, TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.55) and the major product (R_f 0.42). The reaction mixture was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 1:4, cyclohexane/ethyl acetate) to afford diol **23L** (83 mg, 82%) as a yellow oil: $[\alpha]^{25}_D$ +4.76 (*c* 0.48, $CHCl_3$); ν_{max} (thin film) 1172 (s, SO_2), 1336 (s, SO_2), 2098 (s, N_3), 3490 (br s, OH); δ_H (CD_3OD, 400 MHz) 3.13 (3H, s, SO_2CH_3), 3.43 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.4), 3.55 (1H, dd, H6′, $J_{6',5}$ 3.5, $J_{6',6}$ 10.4), 3.63 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,4}$ 6.3, $J_{5,6}$ 6.6), 3.84 (1H, dd, H4, $J_{4,3}$ 3.8, $J_{4,5}$ 6.3), 3.84 (1H, dd, H1, $J_{1,2}$ 6.8, $J_{1,1'}$ 12.7), 3.92 (1H, t, H3, $J_{3,4}$ = $J_{3,2}$ 3.8), 4.05 (1H, dd, H1′, $J_{1',2}$ 3.0, $J_{1',1}$ 12.7), 4.45 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.52 (1H, d, OCH_2Ph, J_{gem} 9.5), 4.55 (1H, d, OCH_2Ph, J_{gem} 9.5), 4.76 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.85 (1H, m, H2), 7.30−7.36 (10H, m, ArH); δ_C (CD_3OD, 100 MHz) 38.6 (SO_2CH_3), 61.8 (C1), 65.0 (C5), 70.1 (C6), 72.2 (C4), 74.5, 75.3 (OCH_2Ph), 80.1 (C3), 85.9 (C2), 129.0, 129.1, 129.2, 129.6, 129.6 (ArCH), 139.3, 139.3 (ArCC); LRMS (ESI +ve) 488 (60, M + Na^+), 953 (100, 2M + Na^+); HRMS (ESI +ve) found 488.1462 [M + Na^+], $C_{21}H_{27}N_3NaO_7S$ requires 488.1448.

For the enantiomer **23D**: $[\alpha]^{25}_D$ −4.54 (*c* 0.50, $CHCl_3$).

2,5-Dideoxy-2,5-imino-L-iditol (4L). Palladium (10% on carbon, 32 mg) and sodium acetate (29 mg, 0.35 mmol) were added to a solution of mesylate **23L** (81 mg, 0.17 mmol) in 1,4-dioxane (4 mL). The reaction vessel was evacuated, flushed with hydrogen, and stirred for 24 h. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.42) and the formation of a major product (baseline). Aqueous hydrochloric acid (2 M, 1 mL) was added and the reaction vessel evacuated and flushed with hydrogen and the reaction stirred for 16 h. The reaction mixture was filtered through glass microfiber (GF/A), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (4 mL), and loaded onto a short column of Dowex 50W-X8 (H^+ form). The product was liberated with 2 M aqueous ammonia, and the ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **4L** (26 mg, 92%) as a yellow oil: $[\alpha]^{25}_D$ +7.25 (*c* 0.30, H_2O) [lit.[28] $[\alpha]^{25}_D$ +14.0 (*c* 1.0, H_2O)]; ν_{max} (thin film) 3347 (br s, NH/OH); δ_H (D_2O, 400 MHz) 3.79 (1H, dd, H1, $J_{1,2}$ 6.6, $J_{1,1'}$ 10.4), 3.80−3.84 (1H, m, H2), 3.89 (1H, dd, H1′, $J_{1',2}$ 6.8, $J_{1',1}$ 10.4), 4.10 (1H, d, H3, $J_{3,2}$ 2.5); δ_C (D_2O, 100 MHz) 57.9 (C1), 63.4 (C2), 75.1 (C3); LRMS (ESI +ve) 164 (100, M + Na^+); HRMS (ESI +ve) found 164.0912 [M + H^+], $C_6H_{14}NO_4$ requires 164.0917.

For the enantiomer **4D**: $[\alpha]^{25}_D$ −8.11 (*c* 0.45, H_2O).

5-Azido-3,6-di-O-benzyl-5-deoxy-D-mannono-1,4-lactone (26D). Trifluoromethanesulfonic anhydride (0.21 mL, 1.27 mmol) was added dropwise to a solution of lactone **24D** (0.405 g, 1.06 mmol) and pyridine (0.21 mL, 2.64 mmol) in dichloromethane (4 mL) at −30 °C under argon. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.40) and the formation of a major product (R_f 0.55). The reaction was diluted with dichloromethane (20 mL), washed with 2 M aqueous hydrochloric acid (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate as a yellow oil. The crude triflate was reacted on without further purification.

Sodium trifluoroacetate (0.29 g, 2.11 mmol) was added portionwise to a solution of crude triflate in DMF (6 mL) at rt under argon. The reaction was stirred for 17 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.55) and the formation of a major product (R_f 0.29). The reaction mixture was partitioned between ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic fractions were washed with a 1:1 brine/water solution (2 × 20 mL), dried ($MgSO_4$), and concentrated . The crude residue was purified by flash chromatography (4:1, cyclohexane/ethyl acetate) to afford the lactone **26D** (344 mg, 85%) as a white solid: $[\alpha]^{25}_D$ −41.2 (*c* 0.89, $CHCl_3$) [lit.[69] $[\alpha]^{25}_D$ −42.0 (*c* 0.5, CH_2Cl_2)]; mp 115−117 °C; ν_{max} (thin film) 1790 (s, C═O), 2102 (s, N_3) 3424 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 2.85 (1H, d, OH2, $J_{OH,2}$ 7.6), 3.79 (1H, dd, H6′, $J_{6,5}$ 5.6, $J_{6,6'}$ 10.4), 3.93 (1H, br d, H6′, $J_{6',6}$ 10.4), 3.98 (1H, m, H5), 4.38 (2H, m, H3, H4), 4.50 (1H, m, H2), 4.61 (2H, a-s, 2 × OCH_2Ph), 4.78 (1H, d, OCH_2Ph, J_{gem} 10.8), 4.87 (1H, d, OCH_2Ph, J_{gem} 10.8), 7.32 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 57.9 (C5), 69.1 (C6), 71.4 (C2), 73.6, 75.0 (OCH_2Ph), 76.1 (C3), 76.4 (C4), 127.7, 127.9, 128.2, 128.4, 128.5, 128.6 (ArCH), 136.8, 137.4 (ArCC), 174.5 (C1); LRMS (ESI +ve) 406 (100, M + Na^+), 789 (83, 2M + Na^+); HRMS (ESI +ve) found 406.1362 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **26L**: $[\alpha]^{20}_D$ +44.9 (*c* 0.52, $CHCl_3$); mp 114−116 °C.

5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-mannono-1,4-lactone (27D). Methanesulfonyl chloride (0.09 mL, 1.17 mmol) was added dropwise to a solution of alcohol **26D** (300 mg, 0.78 mmol) in pyridine (3 mL) at 0 °C under argon. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.67) and the formation of a major product (R_f 0.83). The reaction was mixture was concentrated in vacuo, and the crude residue was purified by flash chromatography (3:1, cyclohexane/ethyl acetate) to afford the mesylate **27D** (358 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ −40.0 (*c* 1.3, $CHCl_3$); ν_{max} (thin film) 1178 (s, SO_2), 1362 (s, SO_2), 1802 (s, C═O), 2103 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 3.33 (3H, s, SO_2CH_3), 3.76 (1H, dd, H6, $J_{6,5}$ 5.2, $J_{6,6'}$ 10.4), 3.90 (1H, dd, H6′, $J_{6',5}$ 2.2, $J_{6',6}$ 10.4), 4.00 (1H, ddd, H5, $J_{5,6'}$ 2.2, $J_{5,6}$ 5.2, $J_{5,4}$ 11.0), 4.44 (1H, dd, H4, $J_{4,3}$ 3.0, $J_{4,5}$ 11.0), 4.52 (1H, dd, H3, $J_{3,4}$ 3.0, $J_{3,2}$ 4.5), 4.60 (2H, a-s, OCH_2Ph), 4.70 (1H, d, OCH_2Ph J_{gem} 10.8), 4.94 (1H, d, OCH_2Ph, J_{gem} 10.8), 5.40 (1H, d, H2, $J_{2,3}$ 4.5), 7.36 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 39.9 (SO_2CH_3), 57.7 (C5), 68.8 (C6), 73.6, 74.9 (OCH_2Ph), 75.1 (C3), 75.7 (C2), 76.7 (C4), 127.8, 127.9, 128.4, 128.4, 128.5, 128.5 (ArCH), 136.4, 137.3 (ArCC), 169.2 (C1); LRMS (ESI +ve) 484 (50, M + Na^+), 516 (71, M + MeOH + Na^+), 945 (100, 2M + Na^+); HRMS (ESI +ve) found 516.1413 [M + MeOH + Na^+], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **27L**: $[\alpha]^{20}_D$ +29.8 (*c* 0.90, $CHCl_3$).

5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-mannitol (28D). Sodium borohydride (52 mg, 1.37 mmol) was added portionwise to a solution of lactone **27D** (0.13 g, 0.27 mmol) in 8:1 ethanol/1,4-dioxane (6 mL) at −30 °C under argon. The reaction mixture was stirred for 4 h, with the internal temperature rising to −20 °C, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.83) and the formation of a major product (R_f 0.43). The reaction mixture was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (30 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (3:1, cyclohexane/ethyl acetate) to afford the diol **28D** (63 mg, 50%) as a pale yellow oil: $[\alpha]^{25}_D$ −45.4 (*c* 0.55, methanol); ν_{max} (thin film) 2106 (s, N_3), 3375 (br s, OH); δ_H (CD_3OD, 400 MHz) 3.14 (3H, s, SO_2CH_3), 3.64 (2H, m, H4, H5),

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

3.75 (1H, dd, H6, $J_{6,5}$ 6.4, $J_{6,6'}$ 10.4), 3.87 (1H, dd, H1, $J_{1,2}$ 5.6, $J_{1,1'}$ 12.8), 3.96 (1H, dd, H6′, $J_{6',5}$ 2.2, $J_{6',6}$ 10.4), 4.10 (2H, m, H1′, H3), 4.58 (2H, a-s, 2 × OCH_2Ph), 4.66 (1H, d, OCH_2Ph, J_{gem} 11.2), 4.83 (2H, m, OCH_2Ph, H2), 7.34 (10H, m, ArH); δ_C (CD_3OD, 100 MHz) 38.7 (SO_2CH_3), 61.9 (C1), 63.1 (C5), 70.6 (C4), 71.8 (C6), 74.5, 75.9 (OCH_2Ph), 78.4 (C3), 84.8 (C2), 128.9, 128.9, 129.2, 129.5, 129.6 (ArCH), 139.4, 139.6 (ArCC); LRMS (ESI +ve) 488 (67, M + Na^+), 953 (100, 2M + Na^+); HRMS (ESI +ve) found 488.1455 [M + Na^+], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **28L**: $[\alpha]^{20}_D$ +42.6 (*c* 0.63, MeOH).

*2,5-Dideoxy-2,5-imino-D-glucitol (**2D**).* Palladium (10% on C, 25 mg) and sodium acetate (17 mg, 0.20 mmol) were added to a solution of diol **28D** (63 mg, 0.14 mmol) in 1,4-dioxane (2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 16 h. TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material (R_f 0.43) and the formation of a major product (baseline). Aqueous hydrochloric acid (2 M, 0.4 mL) was added, and the reaction vessel was evacuated and flushed with hydrogen and the reaction stirred for 24 h. The reaction mixture was filtered through glass microfiber (GF/B) and concentrated in vacuo. The crude residue was dissolved in 2 M aqueous hydrochloric acid and loaded onto a short column of Dowex 5W-X80 (H^+ form). The product was liberated with 2 M aqueous ammonia, the ammoniacal fractions combined and concentrated in vacuo to afford the pyrrolidine **2D** (22.1 mg, quant) as a yellow oil.[70]

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**29D**).* *tert*-Butyldimethylsilyl chloride (5.90 g, 38.5 mmol) was added to a solution of diol **9D** (6.30 g, 25.7 mmol) in pyridine (60 mL) at rt under argon. The reaction was stirred for 20 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.19) and the formation of a major product (R_f 0.52). The reaction was diluted with ethyl acetate (500 mL), washed with 2 M aqueous hydrochloric acid (3 × 150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (39:1 to 4:1, cyclohexane/ethyl acetate) to afford silyl ether **29D** (8.50 g, 92%) as a colorless oil: $[\alpha]^{25}_D$ −23.1 (*c* 1.30, $CHCl_3$); ν_{max} (thin film) 2099 (s, N_3), 3458 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 0.11, 0.11 (2 × 3H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.32, 1.49 (2 × 3H, s, $C(CH_3)_2$), 2.42 (1H, d, OH3, $J_{3,OH}$ 4.3), 3.74 (1H, ddd, H5, $J_{5,6'}$ 3.2, $J_{5,6}$ 5.8, $J_{5,4}$ 8.1), 3.84 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 10.6), 4.03 (1H, dd, H6′, $J_{6',5}$ 3.2, $J_{6',6}$ 10.6), 4.14 (1H, dd, H4, $J_{4,3}$ 2.8, $J_{4,5}$ 8.1), 4.31 (1H, dd, H3, $J_{3,4}$ 2.8, $J_{3,OH}$ 4.3), 4.53 (1H, d, H2, $J_{2,1}$ 3.7), 5.94 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz) −5.6 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 26.2, 26.7 ($C(CH_3)_2$), 60.9 (C5), 63.8 (C6), 75.2 (C3), 78.4 (C4), 84.9 (C2), 104.9 (C1), 111.9 ($C(CH_3)_2$); LRMS (ESI +ve) 382 (95, M + Na^+), 741 (100, 2M + Na^+); (ESI −ve) 358 (10, [M − H]$^-$), 394 (25, M + $^{35}Cl^-$), 396 (10, M + $^{37}Cl^-$), 717 (100, [2M − H]$^-$); HRMS (ESI +ve) found 382.1767 [M + Na^+], $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769.

For the enantiomer **29L**: $[\alpha]^{25}_D$ +29.9 (*c* 0.90, $CHCl_3$).

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (**30D**).* Dess−Martin periodinane (15.1 g, 35.5 mmol) was added to a solution of alcohol **29D** (8.50 g, 23.6 mmol) in dichloromethane (90 mL) at 0 °C under argon. After 15 min, the reaction was allowed to warm to rt. After 18 h, TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.52) and the formation of a major product (R_f 0.23 streaking to R_f 0.67). The reaction mixture was diluted with ethyl acetate (450 mL) and washed with a saturated aqueous sodium bicarbonate/sodium thiosulfate solution (400 mL, 2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (83:17 to 5:1, cyclohexane/ethyl acetate) to afford ketone **30D** (8.00 g, 95%) as a clear oil: $[\alpha]^{25}_D$ +93.5 (*c* 1.40, $CHCl_3$); ν_{max} (thin film) 1775 (s, C═O), 2106 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 0.08 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.44, 1.48 (2 × 3H, s, $SiC(CH_3)_2$), 3.78−3.83 (3H, m, H5, H6, H6′), 4.41 (1H, dd, H2, *J* 1.0, $J_{2,1}$ 4.3), 4.52 (1H, br s, H4), 6.10 (1H, d, H1, $J_{1,2}$ 4.3); δ_C ($CDCl_3$, 100 MHz) −5.5, −5.5 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 27.2, 27.5 ($C(CH_3)_2$), 60.7 (C6), 64.2 (C5), 76.7 (C2), 78.7 (C4), 103.7 (C1), 114.4 ($C(CH_3)_2$), 207.5 (C3); LRMS (ESI +ve) 412 (75, M + MeOH + Na^+), 801 (100, M + 2MeOH + Na^+); HRMS (ESI +ve) found 412.1870 [M + MeOH + Na^+], $C_{16}H_{31}N_3NaO_6Si$ requires 412.1874.

For the enantiomer **30L**: $[\alpha]^{25}_D$ −96.9 (*c* 0.92, $CHCl_3$).

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**31D**).* Sodium borohydride (847 mg, 22.4 mmol) was added portionwise to a solution of ketone **30D** (8.00 g, 22.4 mmol) in ethanol (80 mL) at 0 °C under argon. The reaction was stirred at 0 °C for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.23 streaking to R_f 0.67) and the formation of a major product (R_f 0.47). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (500 mL) and washed with saturated aqueous sodium bicarbonate (3 × 100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 to 3:2, cyclohexane/ethyl acetate) to afford alcohol **31D** (7.48 g, 93%) as a clear oil: $[\alpha]^{25}_D$ +19.9 (*c* 1.05, $CHCl_3$); ν_{max} (thin film) 2099 (s, N_3), 3479 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 0.11 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.37, 1.58 (2 × 3H, s, $C(CH_3)_2$), 3.14 (1H, d, OH3, $J_{OH,3}$ 7.3), 3.80−3.83 (2H, m, H5, H6), 3.87−3.92 (1H, m, H6′), 3.96 (1H, dd, H4, $J_{4,5}$ 3.7, $J_{4,3}$ 8.4), 4.09 (1H, ddd, H3, $J_{3,2}$ 4.9, $J_{3,OH}$ 7.3, $J_{3,4}$ 8.4), 4.63 (1H, dd, H2, $J_{2,1}$ 3.6, $J_{2,3}$ 4.9), 5.81 (1H, d, H1, $J_{1,2}$ 3.6); δ_C ($CDCl_3$, 100 MHz) −5.6, −5.6 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 26.4, 26.6 ($C(CH_3)_2$), 63.2 (C6), 63.5 (C5), 71.4 (C3), 79.2 (C2), 79.9 (C4), 103.8 (C1), 113.0 ($C(CH_3)_2$); LRMS (ESI +ve) 382 (85, M + Na^+), 741 (100, 2M + Na^+); (ESI −ve) 358 (45, [M − H]$^-$), 394 (30, M + $^{35}Cl^-$), 396 (10, M + $^{37}Cl^-$), 717 (100, [2M − H]$^-$); HRMS (ESI +ve) found 382.1769 [M + Na^+], $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769.

For the enantiomer **31L**: $[\alpha]^{25}_D$ −21.7 (*c* 1.34, $CHCl_3$).

*5-Azido-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**32D**).* Tetrabutylammonium fluoride (1 M in THF, 26 mL, 26.0 mmol) was added to a solution of silyl ether **31D** (7.48 g, 20.8 mmol) in THF (75 mL) under argon. The reaction was stirred at rt for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.47) and the formation of a major product (R_f 0.19). The reaction was concentrated in vacuo and purified by flash chromatography (1:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford diol **32D** (5.0 g, 98%) as a white crystalline solid: $[\alpha]^{25}_D$ +50.1 (*c* 1.20, acetone) [lit.[71] $[\alpha]^{25}_D$ +47.6 (*c* 1.0, $CHCl_3$)]; mp 82−84 °C [lit.[71] mp 82−83 °C]; ν_{max} (thin film) 2098 (s, N_3), 3382 (br s, OH); δ_H (($CD_3)_2CO$, 400 MHz) 1.31, 1.47 (2 × 3H, s, $C(CH_3)_2$), 3.71 (1H, dd, H6, $J_{6,5}$ 7.3, $J_{6,6'}$ 11.9), 3.80 (1H, dd, H6′, $J_{6',5}$ 3.8, $J_{6',6}$ 11.9), 3.87 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.8, $J_{5,6}$ 7.3), 4.00 (1H, dd, H4, $J_{4,5}$ 3.2, $J_{4,3}$ 8.6), 4.05 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.6), 4.61 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 3.9), 5.78 (1H, d, H1, $J_{1,2}$ 3.5); δ_C (($CD_3)_2CO$, 100 MHz) 26.8, 27.0 ($C(CH_3)_2$), 62.3 (C6), 65.8 (C5), 72.4 (C3), 80.4 (C2), 80.5 (C4), 104.9 (C1), 113.1 ($C(CH_3)_2$); LRMS (ESI −ve) 244 (100, [M − H]$^-$), 489 (82, [2M − H]$^-$); HRMS (ESI +ve) found 268.0901 [M + Na^+], $C_9H_{15}N_3NaO_5$ requires 268.0904.

For the enantiomer **32L**: $[\alpha]^{25}_D$ −55.3 (*c* 1.12, acetone), mp 84−86 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**33D**).* Sodium hydride (60% min oil suspension, 2.50 g, 61.2 mmol) was added portionwise to a solution of diol **32D** (5.00 g, 20.4 mmol) and benzyl bromide (7.30 mL, 61.2 mmol) in DMF (75 mL) at 0 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 18 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.19) and the formation of a major product (R_f 0.68). The reaction was quenched with methanol (10 mL), diluted with ethyl acetate (600 mL), and washed with a 1:1 brine/water solution (3 × 150 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (99:1 to 1:1, cyclohexane/ethyl acetate) to afford

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

dibenzyl ether **33D** (7.61 g, 88%) as a colorless oil: $[\alpha]^{25}_{D}$ +58.3 (*c* 1.25, $CHCl_3$); ν_{max} (thin film) 2099 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 1.37, 1.59 (2 × 3H, s, $C(CH_3)_2$), 3.52 (1H, dd, H6, $J_{6,5}$ 9.1, $J_{6,6'}$ 10.1), 3.62 (1H, dd, H6′, $J_{6',5}$ 4.0, $J_{6',6}$ 10.1), 3.90 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.6), 4.03 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.5, $J_{5,6}$ 8.6), 4.17 (1H, dd, H4, $J_{4,5}$ 3.0, $J_{4,3}$ 8.6), 4.53 (2H, a-d, 2 × OCH_2Ph, *J* 11.6), 4.55 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 4.1), 4.56 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.72 (1H, d, OCH_2Ph, J_{gem} 11.6), 5.75 (1H, d, H1, $J_{1,2}$ 3.8), 7.31−7.39 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 26.5, 26.8 ($C(CH_3)_2$), 62.1 (C5), 69.4 (C6), 72.1, 73.3 (OCH_2Ph), 77.4 (C2), 77.5 (C3), 77.8 (C4), 104.1 (C1), 113.2 ($C(CH_3)_2$), 127.7, 127.7, 128.1, 128.1, 128.4, 128.4 (ArCH), 137.1, 137.6 (ArCC); LRMS (ESI +ve) 443 (25, M + NH_4^+), 448 (70, M + Na^+), 873 (100, 2M + Na^+); HRMS (ESI +ve) found 448.1838 [M + Na^+], $C_{23}H_{27}N_3NaO_5$ requires 448.1843.

For the enantiomer **33L**: $[\alpha]^{25}_{D}$ −63.4 (*c* 1.23, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-allofuranose (**34D**).* *p*-Toluenesulfonic acid (7.30 g, 39.3 mmol) was added to a solution of isopropylidene-protected **33D** (7.60 g, 17.9 mmol) in 7:1 1,4-dioxane/water (40 mL) and heated to 80 °C. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.68) and the formation of a major product (R_f 0.16). The reaction mixture was allowed to cool to rt, diluted with ethyl acetate (600 mL) and quenched with saturated aqueous sodium bicarbonate (250 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 350 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford lactol **34D** (6.39 g, 93%) as a yellow oil, in an anomeric mixture (A:B, 2:1). Lactol **34D** was reacted without further purification: $[\alpha]^{25}_{D}$ +12.0 (*c* 1.50, $CHCl_3$); ν_{max} (thin film) 2099 (s, N_3), 3411 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 3.47 (1H, dd, $H6^A$, $J_{6,5}$ 7.3, $J_{6,6'}$ 10.0), 3.53 (1H, dd, $H6^B$, $J_{6,5}$ 8.2, $J_{6,6'}$ 10.1), 3.61 (1H, dd, $H6'^A$, $J_{6',5}$ 4.0, $J_{6',6}$ 10.1), 3.68−3.74 (2H, m, $H5^A$, $H6'^B$), 3.81 (1H, ddd, $H5^B$, $J_{5,6'}$ 3.3, $J_{5,4}$ 6.3, $J_{5,6}$ 8.2), 3.99 (1H, dd, $H3^A$, $J_{3,4}$ 3.9, $J_{3,2}$ 5.7), 4.02 (1H, br d, $H3^B$, $J_{3,4}$ 4.7), 4.07−4.11 (2H, m, $H2^A$, $H2^B$), 4.19 (1H, a-t, $H4^A$, $J_{4,3} = J_{4,5}$ 4.0), 4.29 (1H, a-t, $H4^B$, $J_{4,5} = J_{4,3}$ 5.0), 4.52 (2H, a-d, 2 × OCH_2Ph^B, *J* 12.1), 4.54−4.57 (2H, m, 2 × OCH_2Ph^A), 4.58 (2H, a-d, 2 × OCH_2Ph^A, *J* 11.9), 4.62 (2H, a-d, 2 × OCH_2Ph^B, *J* 11.7), 5.26−5.27 (2H, m, $H1^A$, $H1^B$), 7.30−7.39 (20H, m, ArH^A, ArH^B); δ_C ($CDCl_3$, 100 MHz) 62.5 ($C5^A$), 63.3 ($C5^B$), 67.0 ($C6^A$), 69.7 ($C6^B$), 70.6 ($C2^A$), 73.0, 73.5 (OCH_2Ph^B), 73.0, 73.5 (OCH_2Ph^A), 73.7 ($C3^B$), 77.5 ($C3^A$), 79.0 ($C4^B$), 80.2 ($C2^B$), 80.4 ($C4^A$), 97.0 ($C1^A$), 102.3 ($C1^B$), 127.6, 127.8, 127.9, 128.2, 128.2, 128.4, 128.5, 128.5, 128.7 ($ArCH^A$, $ArCH^B$), 136.6, 136.6, 137.4, 137.5 ($ArCC^A$, $ArCC^B$); LRMS (ESI +ve) 408 (60, M + Na^+), 793 (100, 2M + Na^+); (ESI −ve) 769 (100, $[2M - H]^-$), HRMS (ESI +ve) found 408.1526 [M + Na^+]; $C_{20}H_{23}N_3NaO_5$ requires 408.1530.

For the enantiomer **34L**: $[\alpha]^{25}_{D}$ −11.5 (*c* 1.20, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-allono-1,4-lactone (**35D**).* Potassium carbonate (4.94 mg, 35.7 mmol) and iodine (9.07 g, 35.7 mmol) were added to a solution of lactol **34D** (6.39 g, 16.7 mmol) in 2-methyl-2-propanol (80 mL) at 100 °C. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.16) and the formation of a major product (R_f 0.32). The reaction mixture was allowed to cool to rt and diluted with ethyl acetate (500 mL). Saturated aqueous sodium thiosulfate (250 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford lactone **35D** (5.1 g, 79%) as a colorless oil: $[\alpha]^{25}_{D}$ −20.3 (*c* 1.50, $CHCl_3$); ν_{max} (thin film) 1789 (s, C═O), 2104 (s, N_3), 3434 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.62 (1H, dd, H6, $J_{6,5}$ 7.1, $J_{6,6'}$ 10.4), 3.71 (1H, dd, H6′, $J_{6',5}$ 4.0, $J_{6',6}$ 10.4) 3.77 (1H, d, OH2, $J_{OH,2}$ 8.6), 3.94 (1H, ddd, H5, $J_{5,6'}$ 4.0, $J_{5,4}$ 6.0, $J_{5,6}$ 7.1), 4.19 (1H, dd, H3, $J_{3,4}$ 0.8, $J_{3,2}$ 5.8), 4.45 (1H, dd, H4, $J_{4,3}$ 0.8, $J_{4,5}$ 6.0), 4.54 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.57 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.59 (1H, dd, H2, $J_{2,3}$ 5.8, $J_{2,OH}$ 8.6), 4.61 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.65 (1H, d, OCH_2Ph, J_{gem} 11.6), 7.30−7.39 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 61.9 (C5), 69.0 (C2), 70.3 (C6), 73.1, 74.1 (OCH_2Ph), 75.9 (C3), 81.8 (C4), 128.8, 128.8, 129.0, 129.1, 129.5 (ArCH), 138.6, 139.0 (ArCC), 175.8 (C1); LRMS (ESI +ve) 789 (100, 2M + Na^+); HRMS (ESI +ve) found 406.1369 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **35L**: $[\alpha]^{25}_{D}$ +20.5 (*c* 1.40, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-trifluoromethanesulfonyl-D-allono-1,4-lactone (**38D**).* Trifluoromethanesulfonic anhydride (0.06 mL, 0.35 mmol) was added dropwise to a solution of lactone **35D** (100 mg, 0.27 mmol) and pyridine (0.07 mL, 0.81 mmol) in dichloromethane (1.0 mL) at −40 °C under argon. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.32) and the formation of a major product (R_f 0.63). The reaction was diluted with dichloromethane (5 mL), washed with 2 M aqueous hydrochloric acid (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 to 4:1, cyclohexane/ethyl acetate) to afford triflate **38D** (108 mg, 80%) as a yellow oil, which crystallized on standing: $[\alpha]^{25}_{D}$ −5.7 (*c* 1.06, $CHCl_3$); mp 66−68 °C; ν_{max} (thin film) 1808 (s, C═O), 2125 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 3.53−3.54 (2H, m, H6, H6′), 3.94 (1H, ddd, H5, *J* 5.8, *J* 5.6, $J_{5,4}$ 3.0), 4.35 (1H, d, H3, $J_{3,2}$ 5.7), 4.51 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.52 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.55 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.62 (1H, d, H4, $J_{4,5}$ 3.0), 4.66 (1H, d, OCH_2Ph, J_{gem} 11.9), 5.52 (1H, d, H2, $J_{2,3}$ 5.7), 7.26−7.42 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 61.2 (C5), 68.4 (C6), 73.0 (C3), 73.2, 73.9 (OCH_2Ph), 76.5 (C2), 82.9 (C4), 127.8, 128.2, 128.4, 128.6, 128.7, 128.7 (ArCH), 135.8, 136.6 (ArCC), 166.7 (C1); LRMS (ESI +ve) 565 (38, M + MeOH + NH_4^+), 570 (100, M + MeOH + Na^+); HRMS (ESI +ve) found 570.1127 [M + MeOH + Na^+], $C_{22}H_{24}F_3N_3NaO_8S$ requires 570.1128.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-allono-1,4-lactone (**36D**).* Methanesulfonyl chloride (29 μL, 0.37 mmol) was added dropwise to a solution of alcohol **35D** (90 mg, 0.24 mmol) in pyridine (1.0 mL) at 0 °C under argon. The reaction was stirred at 0 °C for 15 min, allowed to warm to rt, and stirred for a further 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.32) and the formation of a major product (R_f 0.52). The reaction mixture was concentrated in vacuo and coevaporated with toluene (3 × 3 mL). The crude residue was purified by flash chromatography (19:1 to 3:1, cyclohexane/ethyl acetate) to afford mesylate **36D** (76 mg, 70%) as a colorless oil: $[\alpha]^{25}_{D}$ +26.2 (*c* 1.00, $CHCl_3$); ν_{max} (thin film) 1178 (s, SO_2), 1365 (s, SO_2), 1801 (s, C═O), 2109 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 3.31 (3H, s, SO_2CH_3), 3.47 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.1), 3.52 (1H, dd, H6′, $J_{6',5}$ 4.9, $J_{6',6}$ 10.1), 3.92 (1H, ddd, H5, $J_{5,4}$ 3.5, $J_{5,6'}$ 4.9, $J_{5,6}$ 6.6), 4.30 (1H, d, H3, $J_{3,2}$ 6.1), 4.51−4.55 (3H, m, 3 × OCH_2Ph), 4.58 (1H, d, H4, $J_{4,5}$ 3.5), 4.76 (1H, d, OCH_2Ph, J_{gem} 11.9), 5.50 (1H, d, H2, $J_{2,3}$ 6.1), 7.30−7.40 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 39.8 (SO_2CH_3), 61.3 (C5), 68.6 (C6), 73.1 (C2) 73.1, (C3), 73.3, 73.7 (OCH_2Ph), 83.3 (C4), 127.8, 128.2, 128.3, 128.4, 128.6, 128.7 (ArCH), 136.4, 136.7 (ArCC), 169.8 (C1); LRMS (ESI +ve) 484 (24, M + Na^+), 516 (21, M + MeOH + Na^+), 945 (100, 2M + Na^+); (ESI −ve) 352 (100), 496 (76, M + $^{35}Cl^-$), 498 (32, M + $^{37}Cl^-$); HRMS (ESI +ve) found 516.1407 [M + MeOH + Na^+], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **36L**: $[\alpha]^{25}_{D}$ −22.7 (*c* 1.15, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-allitol (**37D**).* Sodium borohydride (90 mg, 2.40 mmol) was added portionwise to a solution of lactone **36D** (101 mg, 0.22 mmol) in 8:1 ethanol/1,4-dioxane (6 mL) at −30 °C under argon. The reaction was stirred for 6 h, with the internal temperature rising to −20 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.52) and the formation of a major product (R_f 0.05). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (40 mL) and washed with saturated aqueous sodium bicarbonate (25 mL) and the aqueous layer extracted with ethyl acetate (2 × 40 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford diol **37D** (52 mg, 51%) as a yellow oil: $[\alpha]^{25}_{D}$ +12.1 (*c* 0.90, $CHCl_3$); ν_{max} (thin film) 1173 (s, SO_2), 1339 (s, SO_2), 2102 (s, N_3), 3449 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 3.08 (3H, s, SO_2CH_3), 3.58 (1H, dd, H6, $J_{6,5}$ 5.7, $J_{6,6'}$ 10.1), 3.66 (1H, dd, H6′, $J_{6',5}$ 3.4, $J_{6',6}$ 10.1), 3.75 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,4}$ 4.5, $J_{5,6}$ 5.7), 3.83 (1H, dd, H3, $J_{3,2}$ 2.3, $J_{3,4}$ 7.7), 3.92 (1H, dd, H4, $J_{4,5}$ 4.5, $J_{4,3}$ 7.7), 3.96 (1H, dd, H1, $J_{1,2}$ 6.5, $J_{1,1'}$ 12.9), 4.01 (1H, dd, H1′, $J_{1',2}$ 4.1, $J_{1',1}$ 12.9), 4.46 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.47 (1H, d, OCH_2Ph, J_{gem} 11.1), 4.53 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.75 (1H, d, OCH_2Ph, J_{gem} 11.1), 5.14 (1H, ddd, H2, $J_{2,3}$ 2.3, $J_{2,1'}$ 4.1, $J_{2,1}$ 6.5), 7.29–7.39 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 38.5 (SO_2CH_3), 61.3 (C1), 61.4 (C5), 69.4 (C6), 71.4 (C4), 73.4, 73.7 (OCH_2Ph), 79.2 (C3), 82.8 (C2), 127.9, 128.1, 128.3, 128.5, 128.6, 128.6 (ArCH), 136.8, 137.0 (ArCC); LRMS (ESI +ve) 953 (100, 2M + Na^+); HRMS (ESI +ve) found 488.1460 [M + Na^+], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **37L**: $[\alpha]^{25}_{D}$ −8.5 (*c* 1.00, $CHCl_3$).

*2,5-Dideoxy-2,5-imino-D-altritol (**5D**).* Palladium (10% on C, 60 mg) and sodium acetate (54 mg, 0.65 mmol) were added to a solution of diol **37D** (152 mg, 0.33 mmol) in 1,4-dioxane (10 mL). The reaction vessel was evacuated and flushed with hydrogen and the reaction stirred for 4 h. TLC analysis (3:7, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.64) and the formation of a major product (R_f 0.02). LRMS indicated the absence of a peak corresponding to the diol **37D** (*m*/*z* 488 [M + Na^+]) and the presence of a peak corresponding to the dibenzyl pyrrolidine intermediate (*m*/*z* 344 [M + H^+]). Aqueous hydrochloric acid (2 M, 0.5 mL) was added, the reaction vessel evacuated and flushed with hydrogen, and the reaction stirred for 19 h. LRMS indicated the absence of a peak corresponding to dibenzylpyrrolidine intermediate (*m*/*z* 344 [M + H^+]) and the presence of a peak corresponding to the pyrrolidine **5D** (*m*/*z* 164 [M + H^+]). The reaction was filtered through glass microfiber (GF/B), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (1 mL), and loaded onto a short column of Dowex 50W-X8 (H^+ form). The product was liberated with 2 M aqueous ammonia. The ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **5D** (53 mg, 99%) as a colorless oil: $[\alpha]^{25}_{D}$ +31.0 (*c* 1.10, H_2O) [lit.[52] $[\alpha]^{25}_{D}$ +34.2 (*c* 0.83, H_2O)]; ν_{max} (thin film) 3283 (br s, NH/OH); δ_H (D_2O, 400 MHz) 3.57 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,6}$ 5.8, $J_{5,4}$ 9.1), 3.68 (1H, ddd, H2, $J_{2,3}$ 3.3, $J_{2,1'}$ 5.3, $J_{2,1}$ 8.1), 3.77 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 12.6), 3.82 (1H, dd, H1, $J_{1,2}$ 8.1, $J_{1,1'}$ 12.1), 3.89 (1H, dd, H6′, $J_{6',5}$ 3.5, $J_{6',6}$ 12.6), 3.92 (1H, dd, H1′, $J_{1',2}$ 5.3, $J_{1',1}$ 12.1), 4.19 (1H, dd, H4, $J_{4,3}$ 3.8, $J_{4,5}$ 9.1), 4.26 (1H, dd, H3, $J_{3,2}$ 3.3, $J_{3,4}$ 3.8); δ_C (D_2O, 100 MHz) 58.0 (C1), 58.6 (C6), 62.2 (C5), 62.8 (C2), 70.6 (C3), 71.7 (C4); LRMS (ESI +ve) 164 (100, M + Na^+), 250 (38, M + 2MeOH + Na^+); HRMS (ESI +ve) found 186.0736 [M + Na^+], $C_6H_{13}NNaO_4$ requires 186.0737.

For the enantiomer **5L**: $[\alpha]^{25}_{D}$ −25.5 (*c* 0.90, H_2O).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-altrono-1,4-lactone (**39D**).* Trifluoromethanesulfonic anhydride (2.9 mL, 17.3 mmol) was added dropwise to a solution of lactone **35D** (5.1 g, 13.3 mmol) and pyridine (3.2 mL, 39.9 mmol) in dichloromethane (60 mL) at −40 °C under argon. The reaction was stirred for 1 h, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.32) and the formation of a major product (R_f 0.63). The reaction was diluted with dichloromethane (250 mL), washed with 2 M aqueous hydrochloric acid (3 × 250 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate **38D**. The crude triflate **38D** was reacted on without further purification.

Sodium trifluoroacetate (3.62 g, 26.6 mmol) was added portionwise to a solution of the crude triflate **38D** in DMF (30 mL) at −30 °C under argon. The reaction was allowed to warm to rt and stirred for 16 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.63) and the formation of a major product (R_f 0.45). The reaction mixture was partitioned between ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate (150 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3 × 250 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (49:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **39D** (3.80 g, 75%) as a white crystalline solid: $[\alpha]^{25}_{D}$ +37.1 (*c* 1.97, $CHCl_3$); mp 121–123 °C; ν_{max} (thin film) 1799 (s, C═O), 2115 (s, N_3), 3175 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.54 (1H, dd, H6, $J_{6,5}$ 8.1, $J_{6,6'}$ 10.2), 3.65 (1H, dd, H6′, $J_{6',5}$ 4.0, $J_{6',6}$ 10.2), 4.09 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.0, $J_{5,6}$ 8.1), 4.19 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.6), 4.24 (1H, br d, OH2, $J_{OH,2}$ 6.1), 4.33 (1H, dd, H4, $J_{4,5}$ 4.2, $J_{4,3}$ 7.5), 4.51 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.54 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.59 (1H, dd, H2, $J_{2,OH}$ 6.1, $J_{2,3}$ 7.6), 4.61 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.79 (1H, d, OCH_2Ph, J_{gem} 11.6), 7.29–7.38 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 62.7 (C5), 69.8 (C6), 72.9, 73.9 (OCH_2Ph), 75.1 (C2), 78.1 (C4), 81.2 (C3), 128.8, 129.0, 129.3, 129.5 (ArCH), 138.6, 139.1 (ArCC), 174.4 (C1); LRMS (ESI +ve) 406 (100, M + Na^+), 789 (60, 2M + Na^+); HRMS (ESI +ve) found 406.1369 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **39L**: $[\alpha]^{25}_{D}$ −31.9 (*c* 2.00, $CHCl_3$), mp 120–122 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-altrono-1,4-lactone (**40D**).* Methanesulfonyl chloride (1.20 mL, 15.6 mmol) was added dropwise to a solution of alcohol **39D** (3.99 g, 10.4 mmol) in pyridine (40 mL) at 0 °C under argon. After 10 min, the reaction was allowed to warm to rt and stirred for a further 2 h. After which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.45) and the formation of a major product (R_f 0.60). The reaction mixture was concentrated in vacuo and coevaporated with toluene (2 × 25 mL) and dichloromethane (2 × 25 mL). The crude residue was purified by flash chromatography (47:3 to 3:2, cyclohexane/ethyl acetate) to afford the mesylate **40D** (4.04 g, 84%) as a clear oil: $[\alpha]^{25}_{D}$ +40.5 (*c* 2.40, $CHCl_3$); ν_{max} (thin film) 1178 (s, SO_2), 1369 (s, SO_2), 1803 (s, C═O), 2110 (s, N_3); δ_H (CD_3CN, 400 MHz) 3.29 (3H, s, SO_2CH_3), 3.56 (1H, dd, H6, $J_{6,5}$ 7.8, $J_{6,6'}$ 10.2), 3.67 (1H, dd, H6′, $J_{6',5}$ 4.5, $J_{6',6}$ 10.2), 4.10 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.0, $J_{5,6}$ 7.8), 4.48–4.56 (4H, m, H3, H4, OCH_2Ph × 2), 4.61 (1H, d, OCH_2Ph, J_{gem} 11.0), 4.78 (1H, d, OCH_2Ph, J_{gem} 11.0), 5.59 (1H, d, H2, $J_{2,3}$ 6.8), 7.31–7.40 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 40.3 (SO_2CH_3), 62.2 (C5), 69.6 (C6), 73.4, 74.0 (OCH_2Ph), 79.0, 79.2 (C3, C4), 81.0 (C2), 128.8, 128.8, 129.3, 129.5, 129.5, 129.6 (ArCH), 137.8, 139.0 (ArCC), 169.6 (C1); LRMS (ESI +ve) 484 (56, M + Na^+), 516 (100, M + MeOH + Na^+), 945 (48, 2M + Na^+); HRMS (ESI +ve) found 516.1406 [M + MeOH + Na^+], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **40L**: $[\alpha]^{25}_{D}$ −35.6 (*c* 2.05, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-altritol (**41D**).* Sodium borohydride (205 mg, 5.42 mmol) was added portionwise to a solution of mesylate **40D** (500 mg, 1.08 mmol) in 8:1 ethanol/1,4-dioxane (24 mL) at −30 °C under argon. The reaction was stirred for 1 h, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material (R_f 0.60) and the formation of a major product (R_f 0.18). Further sodium borohydride (205 mg, 5.42 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 3 h, TLC analysis indicated the complete consumption of the starting material (R_f 0.60) and the major product (R_f 0.18). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 7:3, cyclohexane/ethyl acetate) to afford the diol **41D** (468 mg, 93%) as a pale yellow oil: $[\alpha]^{25}_{D}$ +5.7 (*c* 0.91, $CHCl_3$); ν_{max} (thin film) 1171 (s, SO_2), 1334 (s, SO_2), 2100 (s, N_3), 3500 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.07 (3H, s, SO_2CH_3), 3.67 (1H, dd, H1 or H6, *J* 7.7, *J* 10.2), 3.77–3.89 (8H, m, H1 or H6, H1′, H3, H4, H5, H6′, OH1, OH4), 4.50 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.54 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.60 (1H, d, OCH_2Ph, J_{gem} 11.1), 4.64 (1H, d, OCH_2Ph, J_{gem} 11.1), 4.85 (1H, td, H2, *J* 3.4, *J* 5.5, *J* 5.5), 7.29–7.38 (10H, m, ArH); δ_C (CD_3CN, 100

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX–XXX

MHz) 38.9 (SO_2CH_3), 61.8 (C1 or C6), 64.0, 70.7 (C1 or C6), 71.5, 73.9 (OCH_2Ph), 75.0 (OCH_2Ph), 78.8, 83.7 (C2), 128.7, 128.8, 128.9, 129.2, 129.4, 129.4 (ArCH), 139.0, 139.3 (ArCC); LRMS (ESI +ve) 488 (85, M + Na^+), 953 (100, 2M + Na^+); (ESI −ve) 929 (100, [2M − H]$^-$); HRMS (ESI +ve) found 488.1463 [M + Na^+], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **41L**: $[\alpha]^{25}_D$ −7.1 (*c* 1.05, $CHCl_3$).

*2,5-Dideoxy-2,5-iminoallitol (**7**).* Palladium (10% on C, 180 mg) and sodium acetate (160 mg, 1.94 mmol) were added to a solution of diol **41D** (450 mg, 0.97 mmol) in 1,4-dioxane (16 mL). The reaction vessel was evacuated and flushed with hydrogen. The reaction was stirred at rt for 4 h under hydrogen, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.38) and the formation of a single product (baseline). LRMS indicated the absence of a peak corresponding to the diol **41D** (*m*/*z* 488 [M + Na^+]) and the presence of a peak corresponding to the dibenzyl pyrrolidine intermediate (*m*/*z* 344 [M + H^+]). Aqueous hydrochloric acid (2 M, 4 mL) was added, the reaction vessel evacuated and flushed with hydrogen, and the reaction stirred for 16 h. LRMS indicated the absence of a peak corresponding to the dibenzylpyrrolidine intermediate (*m*/*z* 344 [M + H^+]) and the presence of a peak corresponding to the pyrrolidine **7** (*m*/*z* 164 [M + H^+]). The reaction was filtered through glass microfiber (GF/B), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (1 mL), and loaded onto a short column of Dowex 50W-X8 (H^+ form). The product was liberated with 2 M aqueous ammonia, and the ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **7** (150 mg, 95%) as a colorless oil: HRMS (ESI +ve) found 164.0919 [M + H^+]; $C_6H_{14}NO_4$ requires 164.0917; $[\alpha]^{25}_D$ 0.0 (*c* 1.00, H_2O); ν_{max} (thin film) 3450 (br s, OH/NH); δ_H (D_2O, 400 MHz) 3.61 (1H, a-q, H2, $J_{2,1} = J_{2,1'} = J_{2,3}$ 4.9), 3.73 (1H, dd, H1, $J_{1,2}$ 5.8, $J_{1,1'}$ 12.4), 3.82 (1H, dd, H1′, $J_{1',2}$ 4.0, $J_{1',1}$ 12.4), 4.11 (1H, d, H3, $J_{3,2}$ 4.0); δ_C (D_2O, 100 MHz) 58.5 (C1), 64.5 (C2), 71.0 (C3); LRMS (ESI +ve) 164 (100, M + H^+).

*5-Azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-β-L-talofuranose (**42L**).* Sodium hydride (60% mineral oil suspension, 2.2 g, 55.1 mmol) was added portionwise to a solution of diol **8L** (4.50 g, 18.4 mmol) and benzyl bromide (6.55 mL, 55.1 mmol) in DMF (70 mL) at 0 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 19 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.13) and the formation of a major product (R_f 0.73). The reaction was quenched with methanol (2 mL), diluted in ethyl acetate (200 mL) and washed with a 1:1 brine/water solution (3 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (20:1 to 10:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **42L** (7.73 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +122.0 (*c* 1.5, $CHCl_3$); ν_{max} (thin film) 2098 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 1.37, 1.58 (2 × 3H, s, $C(CH_3)_2$), 3.70 (1H, ddd, H5, $J_{5,4}$ 2.3, $J_{5,6}$ 3.8, $J_{5,6'}$ 9.1), 3.75 (1H, dd, H6, $J_{6,5}$ 3.8, $J_{6,6'}$ 10.1), 3.80 (1H, dd, H6′, $J_{6',5}$ 9.1, $J_{6',6}$ 10.1), 3.90 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.8), 4.08 (1H, dd, H4, $J_{4,5}$ 2.3, $J_{4,3}$ 8.8), 4.56 (1H, d, OC*H*$_2$Ph, J_{gem} 11.6), 4.57−4.59 (1H, m, H2), 4.57 (1H, d, OC*H*$_2$Ph, J_{gem} 11.7), 4.62 (1H, d, OC*H*$_2$Ph, J_{gem} 11.9), 4.79 (1H, d, OC*H*$_2$Ph, J_{gem} 11.9), 5.74 (1H, d, H1, $J_{1,2}$ 3.5), 7.29−7.42 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 26.4, 26.8 ($C(CH_3)_2$), 60.0 (C5), 70.8 (C6), 72.3, 73.4 (OCH_2Ph), 77.0 (C2), 77.6 (C4), 77.9 (C3), 104.3 (C1), 113.3 ($C(CH_3)_2$), 127.7, 127.8, 128.1, 128.3, 128.5, 128.6 (ArCH), 137.2, 137.7 (ArCC); LRMS (ESI +ve) 448 (100, M + Na^+), 464 (25, M + K^+), 873 (100, 2M + Na^+); HRMS (ESI +ve) found 448.1831 [M + Na^+], $C_{23}H_{27}N_3NaO_5$ requires 448.1843.

For the enantiomer **42D**: $[\alpha]^{25}_D$ −138.4 (*c* 1.60, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-talofuranose (**43L**).* *p*-Toluenesulfonic acid (6.0 g, 36.7 mmol) was added to a solution of isopropylidene-protected **42L** (7.1 g, 16.7 mmol) in 7:1 1,4-dioxane/water (40 mL) and heated to 50 °C for 2 h. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.73) and the formation of a major product (R_f 0.24). The reaction mixture was allowed to cool to rt, quenched with saturated aqueous sodium bicarbonate (350 mL), and extracted with ethyl acetate (3 × 350 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (7:3 to 1:1, cyclohexane/ethyl acetate) to afford lactol **43L** (6.0 g, 95%) as a colorless oil, in an anomeric mixture (A:B, 3:2): $[\alpha]^{25}_D$ +66.8 (*c* 2.4, $CHCl_3$); ν_{max} (thin film) 2100 (s, N_3), 3422 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 2.59 (1H, br s, OH2^B), 2.93 (1H, br s, OH2^A), 3.13 (1H, br s, OH1^B), 3.49 (1H, ddd, H5^A, $J_{5,4}$ 2.8, $J_{5,6}$ 4.4, $J_{5,6'}$ 8.2), 3.58 (1H, a-dt, H5^B, $J_{5,4} = J_{5,6}$ 4.0, $J_{5,6'}$ 8.0), 3.68 (1H, dd, H6^B, $J_{6,5}$ 4.4, $J_{6,6'}$ 10.1), 3.68 (1H, dd, H6^A, $J_{6,5}$ 4.4, $J_{6,6'}$ 9.9), 3.72 (1H, dd, H6′^{B}, $J_{6',5}$ 8.0, $J_{6',6}$ 10.1), 3.74 (1H, dd, H6′^{A}, $J_{6',5}$ 8.2, $J_{6',6}$ 9.9), 3.88 (1H, br s, OH1^A), 4.01 (1H, a-t, H3^A, $J_{3,2} = J_{3,4}$ 5.6), 4.03 (1H, d, H2^B, $J_{2,3}$ 3.9), 4.05 (1H, dd, H4^B, $J_{4,5}$ 3.5, $J_{4,3}$ 7.1), 4.11 (1H, dd, H4^A, $J_{4,5}$ 2.8, $J_{4,3}$ 5.3), 4.11−4.13 (1H, m, H2^A), 4.29 (1H, dd, H3^B, $J_{3,2}$ 4.0, $J_{3,4}$ 7.1), 4.53 (1H, d, OC*H*$_2$Ph^B, J_{gem} 11.5), 4.62 (1H, d, OC*H*$_2$Ph^B, J_{gem} 11.5), 4.54 (1H, d, OC*H*$_2$Ph^A, J_{gem} 11.7), 4.56 (1H, d, OC*H*$_2$Ph^A, J_{gem} 11.7), 4.59 (1H, d, OC*H*$_2$Ph^B, J_{gem} 11.6), 4.65 (1H, d, OC*H*$_2$Ph^B, J_{gem} 11.6), 4.60 (1H, d, OC*H*$_2$Ph^A, J_{gem} 11.6), 4.68 (1H, d, OC*H*$_2$Ph^A, J_{gem} 11.6), 5.27 (1H, s, H1^B), 5.30 (1H, br s, H1^A), 7.29−7.43 (20H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 61.1 (C5^A), 62.0 (C5^B), 69.7 (C2^A), 70.1 (C6^A), 70.5 (C6^B), 73.1, 73.5 (OCH_2Ph^B), 73.4, 73.6 (OCH_2Ph^A), 73.4 (C2^B), 78.1 (C3^A), 78.8 (C3^B), 79.7 (C4^A), 80.4 (C4^B), 97.3 (C1^A), 102.3 (C1^B), 127.7, 127.8, 127.9, 127.9, 128.2, 128.5, 128.6, 128.7, 128.8 (ArCH), 136.7, 136.7, 137.5, 137.5 (ArCC); LRMS (ESI +ve) 408 (100, M + Na^+), 793 (73, 2M + Na^+); (ESI −ve) 384 (20, [M − H]$^-$), 420 (25, M + $^{35}Cl^-$), 422 (10, M + $^{37}Cl^-$), 769 (100, [2M − H]$^-$); HRMS (ESI +ve) found 408.1528 [M + Na^+], $C_{20}H_{23}N_3NaO_5$ requires 408.1530.

For the enantiomer **43D**: $[\alpha]^{25}_D$ −80.8 (*c* 2.00, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-talono-1,4-lactone (**44L**).* Potassium carbonate (1.98 g, 14.33 mmol) and iodine (3.64 g, 14.33 mmol) were added to a warm solution of lactol **43L** (2.76 g, 7.17 mmol) in 2-methyl-2-propanol (30 mL) at 100 °C. The reaction was stirred for 90 min, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.40) and the formation of a major product (R_f 0.68). The reaction was allowed to cool to rt and diluted with ethyl acetate (200 mL). Saturated aqueous sodium thiosulfate (100 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 200 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (17:3 to 1:1, cyclohexane/ethyl acetate) to afford lactone **44L** (2.20 g, 80%) as a clear oil: $[\alpha]^{25}_D$ +110.3 (*c* 1.25, $CHCl_3$); ν_{max} (thin film) 1790 (s, C═O), 2112 (s, N_3), 3447 (br s, OH); δ_H ($CDCl_3$, 400 MHz) 3.04 (1H, br s, OH2), 3.68−3.78 (3H, m, H5, H6, H6′), 4.15 (1H, dd, H3, $J_{3,4}$ 0.9, $J_{3,2}$ 6.2), 4.45 (1H, br s, H4), 4.54 (1H, d, OC*H*$_2$Ph, J_{gem} 11.9), 4.59 (1H, d, OC*H*$_2$Ph, J_{gem} 11.9), 4.66 (1H, d, OC*H*$_2$Ph, J_{gem} 11.6), 4.67 (1H, d, H2, $J_{2,3}$ 6.2), 4.72 (1H, d, OC*H*$_2$Ph, J_{gem} 11.9), 7.31−7.41 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 61.1 (C5), 67.8 (C2), 69.5 (C6), 73.1, 73.8 (OCH_2Ph), 75.9 (C3), 80.9 (C4), 127.9, 128.1, 128.1, 128.6, 128.6, 128.8 (ArCH), 136.3, 137.0 (ArCC), 174.7 (C1); LRMS (ESI +ve) 406 (45, M + Na^+), 438 (40, M + MeOH + Na^+), 789 (60, 2M + Na^+), 821 (63, 2M + MeOH + Na^+), 853 (100, 2M + 2MeOH + Na^+); HRMS (ESI +ve) found 406.1365 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **44D**; $[\alpha]^{25}_D$ −102.2 (*c* 1.30, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-trifluoromethanesulfonyl-L-talono-1,4-lactone (**47L**).* Trifluoromethanesulfonic anhydride (0.14 mL, 0.85 mmol) was added dropwise to a solution of alcohol **44L** (250 mg, 0.65 mmol) and pyridine (0.16 mL, 1.96 mmol) in dichloromethane (3 mL) at −40 °C under argon. The reaction was stirred for 90 min, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.38) and the formation of a major product (R_f 0.71). The reaction was diluted with dichloromethane (20 mL), washed with 2 M aqueous hydrochloric acid (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (49:1 to 9:1, cyclohexane/ethyl acetate) to afford triflate **47L** (270 mg, 80%) as a

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

pale yellow oil: $[\alpha]^{25}_{D}$ +63.2 (*c* 1.25, $CHCl_3$); ν_{max} (thin film) 1808 (s, C═O), 2115 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 3.69−3.78 (3H, m, H5, H6, H6′), 4.32 (1H, dd, H3, $J_{3,4}$ 1.8, $J_{3,2}$ 6.1), 4.52−4.53 (1H, m, H4), 4.54 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.59 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.60 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.79 (1H, d, OCH_2Ph, J_{gem} 11.6), 5.56 (1H, d, H2, $J_{2,3}$ 6.1), 7.32−7.43 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 60.2 (C5), 69.1 (C6), 73.5, 73.8 (OCH_2Ph), 74.6 (C3), 76.3 (C2), 81.8 (C4), 127.9, 128.2, 128.3, 128.6, 128.9 (ArCH), 135.6, 136.8 (ArCC), 166.6 (C1); LRMS (ESI +ve) 554 (95, M + K^+), 570 (100, M + MeOH + Na^+); HRMS (ESI +ve) found 570.1112 [M + MeOH + Na^+], $C_{22}H_{24}F_3N_3NaO_8S$ requires 570.1128.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-talono-1,4-lactone (**45L**).* Methanesulfonyl chloride (90 μL, 1.06 mmol) was added to a solution of alcohol **44L** (340 mg, 0.89 mmol) in pyridine (3.5 mL) at 0 °C under argon. After 10 min, the reaction was allowed to warm to rt and stirred for a further 90 min. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.38) and the formation of a major product (R_f 0.50). The reaction mixture was concentrated in vacuo and coevaporated with toluene (2 × 5 mL). The crude residue was purified by flash chromatography (47:3 to 3:1, cyclohexane/ethyl acetate) to afford mesylate **45L** (390 mg, 95%) as a clear oil: $[\alpha]^{25}_{D}$ +106.6 (*c* 1.27, $CHCl_3$); ν_{max} (thin film) 1180 (s, SO_2), 1455 (s, SO_2), 1801 (s, C═O), 2117 (s, N_3); δ_H ($CDCl_3$, 400 MHz) 3.30 (3H, s, SO_2CH_3), 3.71 (1H, dd, H6, $J_{6,5}$ 6.5, $J_{6,6'}$ 9.7), 3.74 (1H, dd, H6′, $J_{6',5}$ 6.5, $J_{6',6}$ 9.7), 3.82 (1H, td, H5, $J_{5,4}$ 1.9, $J_{5,6}$ = $J_{5,6'}$ 6.5), 4.30 (1H, dd, H3, $J_{3,4}$ 1.4, $J_{3,2}$ 6.0), 4.55 (1H, d, OCH_2Ph, J_{gem} 11.8), 4.55 (1H, a-t, H4, $J_{4,3}$ = $J_{4,5}$ 1.7), 4.59 (1H, d, OCH_2Ph, J_{gem} 11.8), 4.60 (1H, d, OCH_2Ph, J_{gem} 11.8), 4.86 (1H, d, OCH_2Ph, J_{gem} 11.8), 5.57 (1H, d, H2, $J_{2,3}$ 6.0), 7.32−7.41 (10H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 39.7 (SO_2CH_3), 60.6 (C5), 69.4 (C6), 72.9 (C2), 73.6, 73.8 (OCH_2Ph), 75.1 (C3), 82.5 (C4), 127.8, 128.2, 128.2, 128.5, 128.6, 128.7 (ArCH), 136.3, 136.9 (ArCC), 169.8 (C1); LRMS (ESI +ve) 484 (27, M + Na^+), 516 (100, M + MeOH + Na^+), 945 (25, 2M + Na^+), 977 (34, 2M + MeOH + Na^+); HRMS (ESI +ve) found 516.1408 [M + MeOH + Na^+], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **45D**: $[\alpha]^{25}_{D}$ −96.3 (*c* 1.25, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-talitol (**46L**).* Sodium borohydride (41 mg, 1.08 mmol) was added portionwise to a solution of lactone **45L** (100 mg, 0.217 mmol) in 8:1 ethanol/1,4-dioxane (9 mL) at −30 °C under argon. The reaction was stirred for 2.5 h, with the internal temperature rising to −15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the partial consumption of the starting material (R_f 0.50) and the formation of a major product (R_f 0.11). Further sodium borohydride (41 mg, 1.08 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 2 h, TLC analysis indicated the complete consumption of the starting material R_f 0.50) and the major product (R_f 0.11). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in ethyl acetate (20 mL) and washed with saturated aqueous sodium bicarbonate (6 mL) and the aqueous phase extracted with ethyl acetate (2 × 20 mL). The organic fractions were combined, washed with brine (6 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 0:1, cyclohexane/ethyl acetate) to afford the diol **46L** (65 mg, 65%) as a clear oil: $[\alpha]^{25}_{D}$ +63.5 (*c* 1.25, $CHCl_3$); ν_{max} (thin film) 1173 (s, SO_2), 1337 (s, SO_2), 2104 (s, N_3), 3484 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.09 (3H, s, SO_2CH_3), 3.27 (1H, t, OH6, $J_{OH,6}$ = $J_{OH,6'}$ 5.7), 3.58 (1H, d, OH3, $J_{OH,3}$ 6.8), 3.73−3.77 (4H, m, H1, H1′, H5, H3), 3.82−3.85 (3H, m, H4, H6, H6′), 4.54 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.56 (1H, d, OCH_2Ph, J_{gem} 11.0), 4.58 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.80 (1H, d, OCH_2Ph, J_{gem} 11.0), 5.06 (1H, ddd, H2, *J* 1.5, *J* 4.8, *J* 6.3), 7.28−7.39 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 39.0 (SO_2CH_3), 61.4 (C1), 62.0, 70.8 (C4, C5), 71.5 (C6), 74.0, 74.5 (OCH_2Ph), 80.6 (C3), 85.7 (C2), 128.8, 128.8, 129.0, 129.4, 129.5 (ArCH), 139.0, 139.3 (ArCC); LRMS (ESI +ve) 488 (45, M + Na^+), 504 (100, M + K^+), 953 (15, 2M + Na^+), 969 (10, 2M + K^+); (ESI −ve) 464 (10, [M − H]$^-$), 500 (50, M + $^{35}Cl^-$), 502 (22, M + $^{37}Cl^-$), 510, (100, M + $HCOO^-$), 929 (41, [2M − H]$^-$); HRMS (ESI +ve) found 488.1445 [M + Na^+], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **46D**: $[\alpha]^{25}_{D}$ −60.7 (*c* 1.20, $CHCl_3$).

*2,5-Dideoxy-2,5-iminogalactitol (**6**).* Palladium (10% on carbon, 6 mg) and sodium acetate (11 mg, 0.13 mmol) were added to a solution of diol **46L** (30 mg, 0.06 mmol) in 1,4-dioxane (2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h. TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material (R_f 0.88) and the formation of a major product (R_f 0.08). LRMS also indicated the absence of a peak corresponding to the starting material **46L** (*m*/*z* 488 [M + Na^+]) and the formation of a peak corresponding to the amino intermediate (*m*/*z* 440 [M + H^+]). After a further 4 h, LRMS indicated the absence of the amino diol intermediate (*m*/*z* 440 [M + H^+]) and the presence of a peak corresponding to the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + H^+]). Aqueous hydrochloric acid (2 M, 0.4 mL) was added and the reaction vessel evacuated, flushed with hydrogen and stirred for 16 h. LRMS indicated the absence of the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + H^+]) and presence of a peak corresponding to the fully deprotected pyrrolidine **6** (*m*/*z* 164 [M + H^+]). The reaction mixture was filtered through a glass microfiber (GF/A), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (1 mL), and loaded onto a short column of Dowex 50W-X8 (H^+ form). The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated in vacuo to afford the pyrrolidine **6** (9.5 mg, 91%) as a yellow oil: $[\alpha]^{25}_{D}$ 0.0 (*c* 1.50, H_2O); ν_{max} (thin film) 3319 (br s, OH, NH); δ_H (D_2O, 500 MHz) 3.25 (1H, q, H2, $J_{2,1}$ = $J_{2,1'}$ = $J_{2,3}$ 5.7), 3.59 (1H, dd, H1, $J_{1,2}$ 5.7, $J_{1,1'}$ 11.4), 3.70 (1H, dd, H1′, $J_{1',2}$ 5.7, $J_{1',1}$ 11.4), 4.21 (1H, d, H3, $J_{3,2}$ 5.7); δ_C (D_2O, 125 MHz) 60.4 (C1), 60.5 (C2), 71.9 (C3); LRMS (ESI +ve) 164 (55, M + H^+), 186 (85, M + Na^+), 327 (100, 2M + H^+); (ESI −ve) 162 (100, [M − H]$^-$); HRMS (ESI +ve) found 186.0743 [M + Na^+], $C_6H_{13}NNaO_4$ requires 186.0737.

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-galactono-1,4-lactone (**48L**).* Trifluoromethanesulfonic anhydride (0.30 mL, 1.75 mmol) and pyridine (0.33 mL, 4.05 mmol) were added to a solution of lactone **44L** (517 mg, 1.35 mmol) in dichloromethane (5 mL) at −40 °C under argon. The reaction was stirred for 90 min, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.38) and the formation of a major product (R_f 0.71). The reaction was diluted with dichloromethane (150 mL), washed with 2 M aqueous hydrochloric acid (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude triflate **47L** as a yellow oil. The crude triflate **47L** was reacted on without further purification.

Sodium trifluoroacetate (370 mg, 2.70 mmol) was added portionwise to a solution of the crude triflate **47L** in DMF (10 mL) at −30 °C under argon. The reaction was allowed to warm to rt and stirred for 20 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.71) and the formation of a major product (R_f 0.50). The reaction mixture was partitioned between ethyl acetate (150 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (49:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **48L** (403 mg, 78% over two steps) as a pale yellow oil, which crystallized on standing to form a white crystalline solid: $[\alpha]^{25}_{D}$ +99.8 (*c* 1.25, CH_3Cl); mp 62−64 °C; ν_{max} (thin film) 1793 (s, C═O), 2104 (s, N_3), 3423 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.70 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 10.1), 3.76 (1H, dd, H6′, $J_{6',5}$ 4.3, $J_{6',6}$ 10.1), 3.83 (1H, a-dt, H5, $J_{5,4}$ = $J_{5,6'}$ 3.8, $J_{5,6}$ 8.0), 4.19 (1H, a-t, H3, $J_{3,2}$ = $J_{3,4}$ 7.6), 4.22 (1H, d, OH2, $J_{OH,2}$ 5.6), 4.25 (1H, dd, H4, $J_{4,5}$ 3.5, $J_{4,3}$ 7.8), 4.53 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.56 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.57 (1H, dd, H2, $J_{2,OH}$ 5.6, $J_{2,3}$ 7.6), 4.64 (1H, d, OCH_2Ph, J_{gem} 11.6), 4.82 (1H, d, OCH_2Ph, J_{gem} 11.6), 7.29−7.41 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 61.9 (C5), 70.5 (C6), 73.1, 74.0 (OCH_2Ph), 74.8 (C2), 78.3 (C4), 81.8 (C3), 128.8, 129.1, 129.2, 129.5, 129.5 (ArCH), 138.8,

dx.doi.org/10.1021/jo301243s | J. Org. Chem. XXXX, XXX, XXX−XXX

139.1 (ArCC), 174.2 (C1); LRMS (ESI +ve) 484 (18, M + Na^+), 516 (100, M + MeOH + Na^+); HRMS (ESI +ve) found 406.1364 [M + Na^+], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **48D**: $[\alpha]^{25}_D$ −104.0 (*c* 1.40, $CHCl_3$), mp 62−64 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-galactono-1,4-lactone (**49L**).* Methanesulfonyl chloride (0.10 mL, 1.29 mmol) was added dropwise to a solution of alcohol **48L** (330 mg, 0.861 mmol) in pyridine (4 mL) at 0 °C under argon. After 10 min, the reaction mixture was allowed to warm to rt and stirred for 90 min. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (R_f 0.50) and the formation of a major product (R_f 0.65). The reaction mixture was concentrated in vacuo, coevaporated with toluene (3 × 10 mL) and the crude residue purified by flash chromatography (47:3 to 4:1, cyclohexane/ethyl acetate) to afford the mesylate **49L** (310 mg, 78%) as a clear oil: $[\alpha]^{25}_D$ −99.9 (*c* 1.35, $CHCl_3$); ν_{max} (thin film) 1173 (s, SO_2), 1363 (s, SO_2), 1801 (s, C═O), 2107 (s, N_3); δ_H (CD_3CN, 400 MHz) 3.27 (3H, s, SO_2CH_3), 3.71 (1H, dd, H6, $J_{6,5}$ 8.1, $J_{6,6'}$ 10.1), 3.77 (1H, dd, H6′, $J_{6',5}$ 4.3, $J_{6',6}$ 10.1), 3.86 (1H, ddd, H5, $J_{5,4}$ 3.3, $J_{5,6'}$ 4.3, $J_{5,6}$ 8.1), 4.43 (1H, dd, H4, $J_{4,5}$ 3.3, $J_{4,3}$ 7.6), 4.54 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.7), 4.55 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.56 (1H, d, OCH_2Ph, J_{gem} 12.1), 4.65 (1H, d, OCH_2Ph, J_{gem} 11.4), 4.81 (1H, d, OCH_2Ph, J_{gem} 11.4), 5.56 (1H, d, H2, $J_{2,3}$ 7.8), 7.30−7.41 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 40.2 (SO_2CH_3), 61.2 (C5), 70.3, 73.6 (OCH_2Ph), 79.3 (C4), 79.4 (C3), 80.5 (C2), 128.8, 128.8, 129.4, 129.5, 129.6 (ArCH), 138.0, 139.0 (ArCC), 169.4 (C1); LRMS (ESI +ve) 484 (100, M + Na^+), 516 (73, M + MeOH + Na^+); HRMS (ESI +ve) found 516.1414 [M + MeOH + Na^+], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **49D**: $[\alpha]^{25}_D$ +105.8 (*c* 1.32, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-galactitol (**50L**).* Sodium borohydride (80 mg, 2.11 mmol) was added portionwise to a solution of lactone **49L** (150 mg 0.325 mmol) in 8:1 ethanol/1,4-dioxane (4 mL) at −30 °C under argon. The reaction was stirred for 90 min, with the internal temperature rising to −15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material (R_f 0.65) and the formation of a major product (R_f 0.24). Further sodium borohydride (80 mg, 2.11 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 4 h, TLC analysis indicated the complete consumption of the starting material (R_f 0.65) and the major product (R_f 0.24). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in ethyl acetate (80 mL) and washed with saturated aqueous sodium bicarbonate (40 mL). The aqueous phase was extracted with ethyl acetate (2 × 80 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 3:7, cyclohexane/ethyl acetate) to afford the diol **50L** (134 mg, 89%) as a white, crystalline solid: $[\alpha]^{25}_D$ +44.5 (*c* 0.97, $CHCl_3$); mp 80−81 °C; ν_{max} (thin film) 1169 (s, SO_2), 1333 (s, SO_2), 2102 (s, N_3), 3484 (br s, OH); δ_H (CD_3CN, 400 MHz) 3.10 (3H, s, SO_2CH_3), 3.28 (1H, t, OH1, $J_{OH,1} = J_{OH,1'}$ 5.8), 3.42 (1H, d, OH4, $J_{OH,4}$ 6.3), 3.75−3.91 (7H, m, H1, H1′, H3, H4, H5, H6, H6′), 4.55 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.59 (1H, d, OCH_2Ph, J_{gem} 11.9), 4.62 (1H, d, OCH_2Ph, J_{gem} 11.1), 4.69 (1H, d, OCH_2Ph, J_{gem} 11.1), 4.89 (1H, ddd, H2, *J* 2.0, *J* 6.1, *J* 6.8), 7.29−7.39 (10H, m, ArH); δ_C (CD_3CN, 100 MHz) 38.9 (SO_2CH_3), 61.5 (C5), 61.8 (C6), 70.7, 78.3 (C3, C4), 71.5 (C1), 73.9, 75.8 (OCH_2Ph), 83.2 (C2), 128.8, 128.8, 129.0, 129.2, 129.5, 129.5 (ArCH), 139.0, 139.3 (ArCC); LRMS (ESI +ve) 488 (45, M + Na^+), 953 (100, 2M + Na^+); (ESI −ve) 929 (100, [2M − H]$^-$); HRMS (ESI +ve) found 488.1461 [M + Na^+], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **50D**: $[\alpha]^{25}_D$ −52.2 (*c* 1.00, $CHCl_3$); mp 80−81 °C.

*2,5-Dideoxy-2,5-imino-L-altritol (**5L**).* Palladium (10% on carbon, 54 mg) and sodium acetate (48 mg, 0.576 mmol) were added to a solution of diol **50L** (134 mg, 0.29 mmol) in 1,4-dioxane (5 mL). The reaction flask was evacuated and flushed with hydrogen and the reaction stirred for 1 h. After which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material (R_f 0.24) and the formation of a major product (R_f 0.08). LRMS indicated the absence of a peak corresponding to the starting material **50L** (*m*/*z* 488 [M + Na^+]) and the formation of a peak corresponding to the amino intermediate (*m*/*z* 440 [M + H^+]). After a further 4 h, LRMS indicated the absence of the amino intermediate (*m*/*z* 440 [M + H^+]) and the formation of peak corresponding to the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + H^+]). Aqueous hydrochloric acid (2 M, 1.0 mL) was added, the reaction vessel evacuated and flushed with hydrogen, and the reaction stirred for 16 h. LRMS indicated the absence of the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + H^+]) and the formation a peak corresponding to the fully deprotected pyrrolidine **5L** (*m*/*z* 164 [M + H^+]). The reaction mixture was filtered through glass microfiber (GF/B) and concentrated in vacuo, and the residue dissolved in 2 M aqueous hydrochloric acid (1 mL) and loaded onto a short column of Dowex 50W-X8 (H^+ form). The product was liberated with 2 M aqueous ammonia, and the ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **5L** (43 mg, 92%) as a yellowish oil.[72]

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: george.fleet@chem.ox.ac.uk; kato@med.u-toyama.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Newton Abraham Research Fund (B.J.A.), Fundación Ramón Areces (R.F.M.), and a Grant-in-Aid for Scientific Research (C) (No. 23590127) (A.K.) from the Japanese Society for the Promotion of Science (JSPS).

■ REFERENCES

(1) Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discovery Today* **2011**, *16*, 107−118.

(2) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645−651.

(3) Compain, P.; Martin, O. R. *Iminosugars From Synthesis to Therapeutic Applications*; Wiley-VCH: New York, 2007.

(4) Martinez-Montero, S.; Fernandez, S.; Sanghvi, Y. S.; Chattopadhyaya, J.; Ganesan, M.; Ramesh, N. G.; Gotor, V.; Ferrero, M. *J. Org. Chem.* **2012**, *77*, 4671−4678.

(5) Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131−1146.

(6) Goddard-Borger, E. D.; Ghisalberti, E. L.; Stick, R. V. *Eur. J. Org. Chem.* **2007**, 3925−3934.

(7) Matsuura, D.; Mitsui, T.; Sengoku, T.; Takahashi, M.; Yoda, H. *Tetrahedron* **2008**, *64*, 11686−11696.

(8) Xu, D. D.; Waykole, L.; Calienni, J. V.; Ciszewski, L.; Lee, G. T.; Liu, W.; Szewczyk, J.; Vargas, K.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 856−865.

(9) Ke, W.; Whitfield, D. M.; Gill, M.; Larocque, S.; Yu, S.-H. *Tetrahedron Lett.* **2003**, *44*, 7767−7770.

(10) Le Manach, C.; Baron, A.; Guillot, R.; Vauzeilles, B.; Beau, J.-M. *Tetrahedron Lett.* **2011**, *52*, 1462−1465.

(11) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *J. Org. Chem.* **1995**, *60*, 3121−3130.

(12) Kitahara, T.; Ogawa, T.; Naganuma, T.; Matsui, M. *Agric. Biol. Chem.* **1974**, *38*, 2189−2190.

(13) Kalamkar, N. B.; Kasture, V. M.; Chavan, S. T.; Sabharwal, S. G.; Dhavale, D. D. *Tetrahedron* **2010**, *66*, 8522−8526.

(14) Weymouth-Wilson, A. C.; Clarkson, R. A.; Jones, N. A.; Best, D.; Wilson, F. X.; Pino-González, M.-S.; Fleet, G. W. J. *Tetrahedron Lett.* **2009**, *50*, 6307−6310.
(15) Bashyal, B. P.; Chow, H. F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205−3208.
(16) Bell, A. A.; Pickering, L.; Finn, M.; de la Fuente, C.; Krulle, T. M.; Davis, B. G.; Fleet, G. W. J. *Synlett* **1997**, 1077−1078.
(17) Best, D.; Wang, C.; Weymouth-Wilson, A. C.; Clarkson, R. A.; Wilson, F. X.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2010**, *21*, 311−319.
(18) Best, D.; Chairatana, P.; Glawar, A. F. G.; Crabtree, E.; Butters, T. D.; Wilson, F. X.; Yu, C.-Y.; Wang, W.-B.; Jia, Y.-M.; Adachi, I.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2010**, *51*, 2222−2224.
(19) Glawar, A. F. G.; Best, D.; Ayers, B. J.; Miyauchi, S.; Nakagawa, S.; Aguilar-Moncayo, M.; García Fernández, J. M.; Mellet, C. O.; Crabtree, E. V.; Butters, T. D.; Wilson, F. X.; Kato, A.; Fleet, G. W. J. *Chem.—Eur. J.* **2012**, *18*, 9341−9359.
(20) Example syntheses of the enantiomers of *gluco* **2**.[21−26]
(21) Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2009**, *7*, 2310−2321.
(22) Malle, B. M.; Lundt, I.; Wrodnigg, T. M. *Org. Biomol. Chem.* **2008**, *6*, 1779−1786.
(23) Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem.* **2008**, *6*, 3896−3898.
(24) Izquierdo, I.; Plaza, M. T.; Yáñez, V. *Tetrahedron* **2006**, *63*, 1440−1447.
(25) García-Moreno, M. I.; Aguilar, M.; Mellet, C. O.; Fernandez, J. M. G. *Org. Lett.* **2006**, *8*, 297−299.
(26) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203−7214.
(27) Example syntheses of the enantiomers of *ido* **4**.[28−31]
(28) Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352−8353.
(29) Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877−1885.
(30) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Eur. J. Med. Chem.* **2005**, *40*, 1255−1261.
(31) Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349−6352.
(32) Example syntheses of the enantiomers of *manno* **3**.[25,26,33−37]
(33) Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93−100.
(34) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929−2947.
(35) Behr, J.-B.; Guillerm, G. *Tetrahedron Lett.* **2007**, *48*, 2369−2372.
(36) Shing, T. K. M. *Tetrahedron* **1988**, 7261−7264.
(37) Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891−893.
(38) Example syntheses of the enantiomers of *altro*-**5**.[26,31,39,40]
(39) Chikkanna, D.; Han, H. *Synlett* **2004**, 2311−2314.
(40) Saotome, C.; Kanie, Y.; Kanie, O.; Wong, C. H. *Bioorg. Med. Chem.* **2000**, *8*, 2249−2261.
(41) Example syntheses of *meso-allo* **7**.[26,42−44]
(42) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Franco, F.; Martos, A. *Tetrahedron* **2005**, *61*, 11697−11704.
(43) Moreno-Vargas, A. J.; Robina, I.; Petricci, E.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 4487−4491.
(44) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999−1002.
(45) Example syntheses of *meso-galacto* **6**.[21,28,31,33,46−48]
(46) Calderón, F.; Doyagüez, E. G.; Cheong, P. H.-Y.; Férnandez-Mayoralas, A.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 7916−7920.
(47) Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Tamayo, J. A.; Martos, A. *Tetrahedron* **2006**, *62*, 2693−2697.
(48) Wang, Y.-F.; Takaoka, Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1994**, *33*, 1242−1244.
(49) Davis, B. G.; Hull, A.; Smith, C.; Nash, R. J.; Watson, A. A.; Winkler, D. A.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2947−2960.
(50) Hakansson, A. E.; van Ameijde, J.; Guglielmini, L.; Horne, G.; Nash, R. J.; Evinson, E. L.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 282−289.
(51) Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238−1242.
(52) Kato, A.; Yamashita, Y.; Nakagawa, S.; Koike, Y.; Adachi, I.; Hollinshead, J.; Nash, R. J.; Ikeda, K.; Asano, N. *Bioorg. Med. Chem.* **2010**, *18*, 3790−3794.
(53) Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393−426.
(54) Wrodnigg, T. M.; Stuetz, A. E.; Tarling, C. A.; Withers, S. G. *Carbohydr. Res.* **2006**, *341*, 1717−1722.
(55) Wrodnigg, T. M.; Withers, S. G.; Stuetz, A. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1063−1064.
(56) Collyer, C. A.; Goldberg, J. D.; Viehmann, H.; Blow, D. M.; Ramsden, N. G.; Fleet, G. W. J.; Montgomery, F. J.; Grice, P. *Biochemistry* **1992**, *31*, 12211−12218.
(57) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473−505.
(58) Jenkinson, S. F.; Fleet, G. W. J.; Nash, R. J.; Koike, Y.; Adachi, I.; Yoshihara, A.; Morimoto, K.; Izumori, K.; Kato, A. *Org. Lett.* **2011**, *13*, 4064−4067.
(59) Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Boomkamp, S. D.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *ChemMedChem* **2009**, *4*, 378−392.
(60) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036−2044.
(61) Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2005**, *16*, 223−229.
(62) Clinch, K.; Evans, G. B.; Fleet, G. W. J.; Furneaux, R. H.; Johnson, S. W.; Lenz, D. H.; Mee, S. P. H.; Rands, P. R.; Schramm, V. L.; Taylor, R. E. A.; Tyler, P. C. *Org. Biomol. Chem.* **2006**, *4*, 1131−1139.
(63) Blériot, Y.; Gretzke, D.; Kruelle, T. M.; Butters, T. D.; Dwek, R. A.; Nash, R. J.; Asano, N.; Fleet, G. W. J. *Carbohydr. Res.* **2005**, *340*, 2713−2718.
(64) Winchester, B.; Barker, C.; Baines, S.; Jacob, G. S.; Namgoong, S. K.; Fleet, G. W. J. F. *Biochem. J.* **1990**, *265*, 277−282.
(65) Winchester, B.; Al-Daher, S. S.; Carpenter, N. C.; Dibello, I. C.; Choi, S. S.; Fairbanks, A. J.; Fleet, G. W. J. *Biochem. J.* **1993**, *290*, 743−749.
(66) Myerscough, P. M.; Fairbanks, A. J.; Jones, A. H.; Bruce, I.; Choi, S. S.; Fleet, G. W. J.; Al-Daher, S. S.; Dibello, I. C.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177−10190.
(67) Mercer, T. B.; Jenkinson, S. F.; Bartholomew, B.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2009**, *20*, 2368−2373.
(68) Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stuetz, A. E. *Carbohydr. Res.* **1993**, *250*, 67−77.
(69) Berger, A.; Ebner, M.; Stuetz, A. E. *Tetrahedron Lett.* **1995**, *36*, 4989−4990.
(70) Data for D-*gluco* **2D** is quoted earlier in the experimental procedures.
(71) Lee, C. K.; Jiang, H. *J. Carbohydr. Chem.* **1995**, *14*, 407−416.
(72) Data for L-*altro* **5L** is quoted earlier in the experimental procedures.