JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

General Synthesis of Sugar-Derived Azepane Nitrones: Precursors of Azepane Iminosugars

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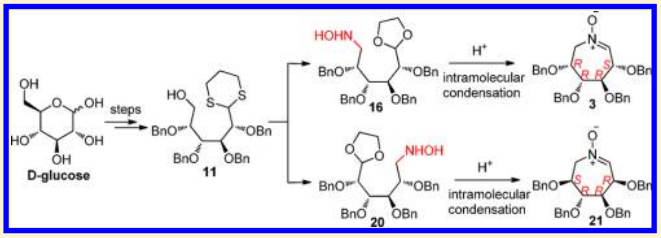
Supporting Information

ABSTRACT: A general and efficient method has been developed for the synthesis of sugar-derived azepane nitrones starting from aldohexoses, with an intramolecular condensation of aldehyde and hydroxylamine as the key step. Through this strategy, each aldohexose produced a pair of azepane nitrones, which are precursors of various azepane iminosugars.



INTRODUCTION

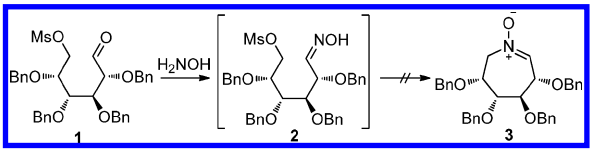
Because of their prominent biological activities, iminosugars have been extensively investigated for the past 30 years.[1] Compared to naturally occurring five- and six-membered iminosugars, their higher homologues, the polyhydroxylated azepanes or the azepane iminosugars, have been relatively less investigated. Azepane iminosugars were first synthesized by Paulsen in 1967.[2] Thirty years later, Wong[3] evaluated their bioactivities and found comparable outcomes with five- and six-membered iminosugars, which inspired more and more interest in this field.[4−9]

New azepane iminosugar family members also appeared. Seven-membered DNJ homologues[5] and 1-*N*-iminosugars[6] both showed good inhibitory activities, while acetylamino group substituted azepanes were inhibitors of *N*-acetyl-*β*-hexosaminidases.[7] Polyhydroxylated perhydroazaazulenes,[8] azepanes in bicyclic form, were synthesized, though no good bioactivities have been found yet. Several higher homologues of calystegine also showed promising inhibitory results.[9] However, few efficient synthetic strategies have been exploited to enable convenient structure modifications.

As powerful synthons, sugar-derived cyclic nitrones could greatly facilitate the molecular diversity-oriented iminosugar synthesis and the study of their structure−activity relationship.[10] Five-membered cyclic nitrones have been used widely for preparing pyrrolidine-based iminosugars,[10c−m] and six-membered cyclic nitrones for piperidine-based ones.[10m,n] To our knowledge, sugar-derived seven-membered cyclic nitrones or azepane nitrones have yet to be reported. On the basis of our ongoing projects[10j−m] on the synthesis and application of sugar-derived cyclic nitrones, herein we report the synthesis of azepane nitrones.

Intramolecular *N*-alkylation, the most widely used strategy in cyclic nitrone synthesis, was not applicable here. As shown in Scheme 1, D-glucose-derived aldehyde **1** gave oxime **2** when condensed with NH_2OH but failed to undergo subsequent intramolecular alkylation to give nitrone **3** under various conditions.[11] Other leaving groups such as -OTs and -I were also tried without success; intramolecular nucleophilic substitution to form seven-membered rings is less favorable than for five- and six-membered rings.

Scheme 1. Unsuccessful Intramolecular *N*-Alkylation Strategy



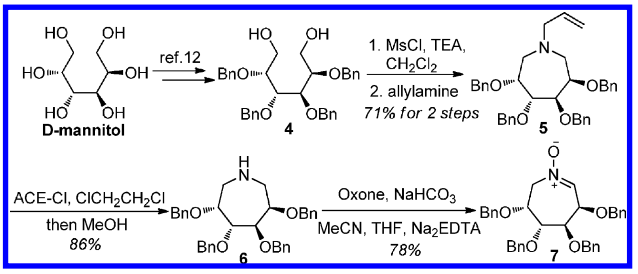
Received: January 21, 2013
Published: March 4, 2013

   dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

RESULTS AND DISCUSSION

Synthesis of Azepane Nitrones. To solve the problem mentioned above, the azepane ring may be formed first. Diol **4** was obtained from D-mannitol as described (Scheme 2).[12] After

Scheme 2. Synthesis of Azepane Nitrone 7 from D-Mannitol

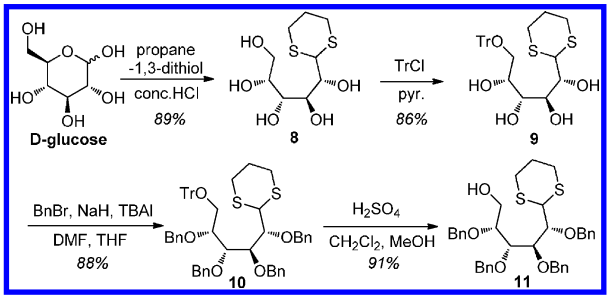


double mesylation of the two primary hydroxyl groups, the *N*-substituted azepane **5** was given by substitution with allylamine in 71% yield over two steps. Deallylation of **5** with 1-chloroethyl chloroformate[13] afforded secondary amine **6** in 86% yield. Using Busqué and Figueredo's protocol,[14] **6** was finally oxidized to nitrone **7** in 78% yield as the sole product.

The strategy is efficient only for the oxidation of C_2-symmetric azepanes since only a single nitrone can be produced; the oxidation of unsymmetrical azepanes, such as that derived from D-glucitol, showed little regioselectivity, giving a mixture of two nitrones in 1:3 ratio, which were difficult to separate. Oxidation of *meso*-azepanes gave racemic mixtures.

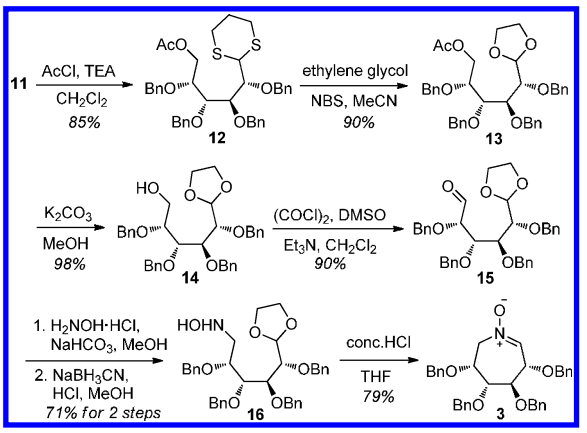
To both increase the ring formation activity and avoid the regioselectivity problem, we turned to a less used strategy in cyclic nitrone synthesis: the intramolecular condensation of a hydroxylamine and an aldehyde.[15] D-Glucose with propane-1,3-dithiol in concentrated hydrogen chloride[16] gave the open chain dithioacetal **8** in 89% yield. Successive tritylation of the primary hydroxyl group, benzylation of the other secondary hydroxyl groups in **9** and detritylation, furnished **11** in which only the C6 alcohol is unprotected (69% yield over three steps) (Scheme 3).

Scheme 3. Synthesis of Tetrabenzyloxylated Alcohol 11 from D-Glucose



With alcohol **11** in hand, the subsequent route divided into two independent paths. For path A (Scheme 4), after acetylation of the hydroxyl group of **11**, the dithioacetal **12** was transformed into acetal **13** with NBS in the presence of ethylene glycol. Subsequent deacetylation gave alcohol **14** in 73% yield over three steps. Direct change of dithioacetal to acetal without hydroxyl group protection gave a lower yield. Swern oxidation of **14** gave aldehyde **15** in 90% yield. Condensation of aldehyde **15** with NH_2OH, followed by

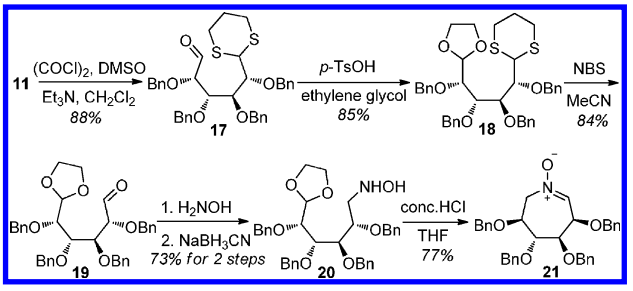
Scheme 4. Synthesis of Nitrone 3 through Path A



reduction of the resulting oxime with sodium cyanoborohydride gave hydroxylamine **16** in 71% yield over two steps. Acidic hydrolysis of the dioxolane afforded the desired nitrone **3** in 79% yield. It is necessary to switch the protecting group dithioacetal to acetal. All attempts to initiate a cascade hydrolysis of the dithioacetal and subsequent intramolecular condensation failed to give nitrone **3**. Path A introduced a hydroxylamine at C6 of D-glucose and then formed the nitrone by condensation on to C1.

For path B (Scheme 5), successive oxidation of alcohol **11**, protection of the aldehyde **17** with ethylene glycol and

Scheme 5. Synthesis of Nitrone 21 through Path B



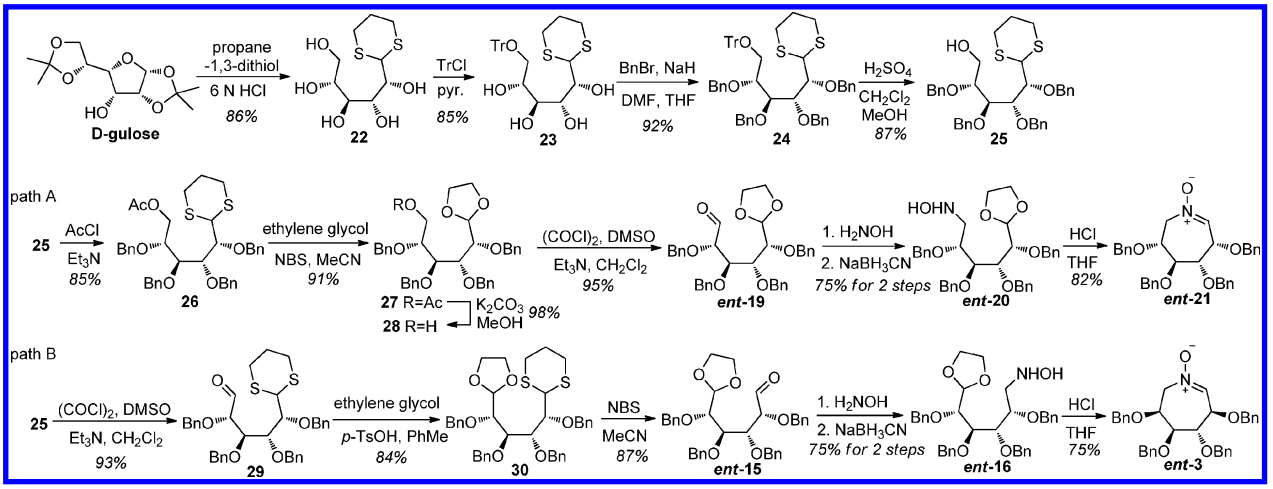
hydrolysis of the dithioacetal **18** with NBS afforded aldehyde **19** in 68% yield over three steps. Aldehyde **19** was then transformed to nitrone **21** through similar steps as path A in 51% yield. Path B yielded a nitrone from a hydroxylamine derived from C1 and an aldehyde derived from C6 of D-glucose. The two D-glucose-derived nitrones **3** and **21** were thus readily accessible.

To verify the generality of this condensation strategy, three other aldohexoses, D-gulose (Scheme 6), D-altrose (Scheme 7) and L-talose (Scheme 8), were all subjected to the same sequence described above. Eight azepane nitrones (four pairs of enantiomers) in all were obtained with yields of 20−44% from the intermediate tetrabenzyloxylated alcohols (Table 1). The instability of **40**, ***ent*-40**, **44** and ***ent*-44** led to lower yields in the intramolecular condensation step (Table 1, entries 3 and 4), which need careful workup and especially avoidance of high temperatures.

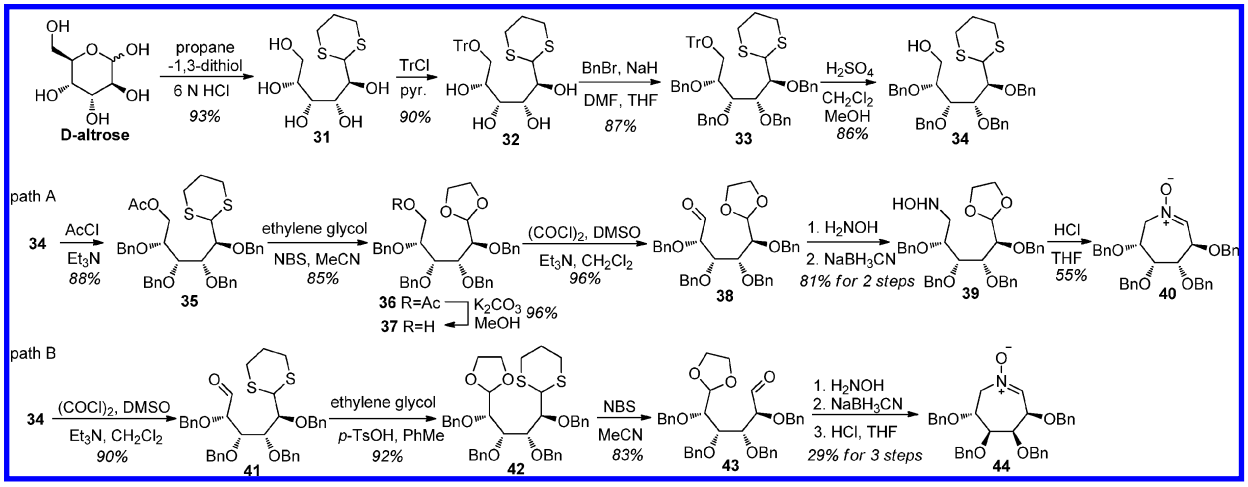
Synthesis of 2-*C*-Alkylated Azepane Iminosugars. The potential of the nitrones to prepare azepane iminosugars is illustrated by nucleophilic addition of organometallic reagents to nitrone **7**; diastereoselective addition formed hydroxylamines **54a−f** (Scheme 9). Grignard reagents gave good yields and

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

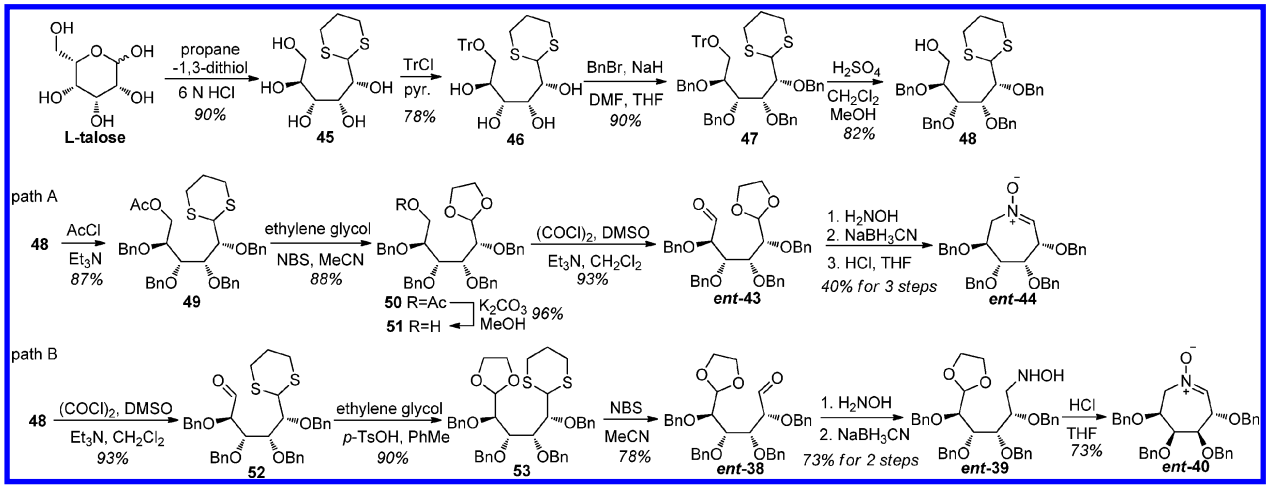
Scheme 6. Synthesis of D-Gulose-Derived Nitrones *ent*-3 and *ent*-21



Scheme 7. Synthesis of D-Altrose-Derived Nitrones 40 and 44



Scheme 8. Synthesis of L-Talose-Derived Nitrones *ent*-40 and *ent*-44

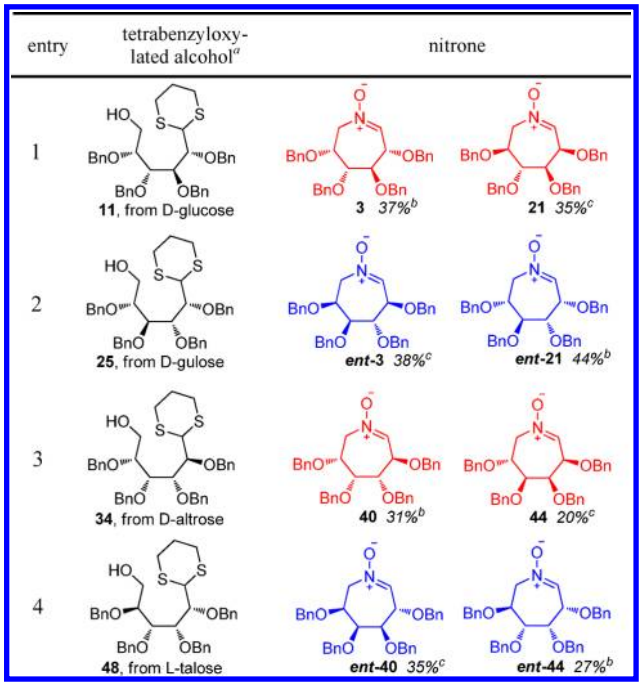


excellent d.r. (Scheme 9, entries 1 to 4); $MOMOCH_2Li$[17] gave a relatively lower yield and poorer d.r. (Scheme 9, entry 5); $TMSCF_3$ gave hydroxylamine **54f** along with unreacted nitrone **7** and also in excellent d.r. (Scheme 9, entry 6). After Pd/C catalyzed hydrogenolysis, 2-*C*-alkylated azepane iminosugars **55a–f** were obtained in high yields. This class of seven-membered iminosugar C-glycosides has been rarely reported in the literature.[18]

The configurations of the new chiral center at C-2 were determined by ^1H NMR spectroscopy. The coupling constants $J_{2,3}$ of the hydroxylamine **54a–d** were all between 7 to 8 Hz, which are consistent with 2,3-*trans* relative configuration. The fully deprotected 2-*C*-alkylated azepanes **55a–f** also showed

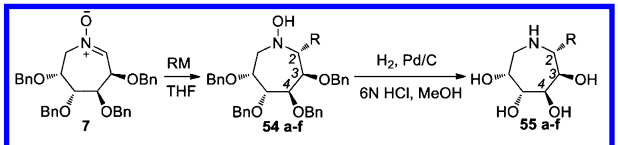
dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208–3221

Table 1. Aldohexose-Derived Azepane Nitrones



[a]Obtained from aldohexose after four steps. [b]Overall yield from tetrabenzyloxylated alcohol through path A. [c]Overall yield from tetrabenzyloxylated alcohol through path B.

Scheme 9. Synthesis of 2-*C*-Alkylated Azepane Iminosugars 55a–f from Nitrone 7



entry	RM	hydroxylamine	d.r.[a]	yield[b]	yield[c]
1	MeMgI	**54a**	> 95:5	84%	98%
2	^{n}BuMgI	**54b**	> 95:5	86%	92%
3	^{n}nonylMgBr	**54c**	> 95:5	87%	93%
4	PhMgBr	**54d**	> 95:5	88%	97%
5[d]	$MOMOCH_2Li$	**54e**	86:14	54%	93%
6	$TMSCF_3$	**54f**	> 95:5	70%	94%

[a]Determined by ^{1}H NMR analysis of a crude product. [b]Isolated yield of nucleophilic addition. [c]Yield of catalytic hydrogenation. [d]For **54e**, R= $-CH_2OMOM$; for **55e**, R= $-CH_2OH$.

relatively larger $J_{2,3}$ (5 to 8 Hz) and smaller $J_{3,4}$ (2 to 3 Hz), which further proved the same C-2 configurations of **54a–f**. The *trans* diastereoselective addition is consistent with a Felkin–Anh transition-state model.[19]

Glycosidase Inhibition. Azepane iminosugars **55a–f** were assayed as potential glycosidase inhibitors of a range of enzymes (Table 2). None of **55a,d–f** showed any inhibition toward the tested enzymes. However, compound **55b** showed weak inhibition against β-galactosidase (bovine liver, IC_{50} = 505 μM), while **55c** showed good inhibition against β-galactosidase (bovine liver, IC_{50} = 4.5 μM) and β-glucosidase (bovine liver, IC_{50} = 12 μM). The alkyl chain length appears to affect the glycosidase inhibition.

CONCLUSIONS

In summary, two efficient synthetic approaches toward azepane nitrones have been developed: (i) C_2-symmetric azepane initial formation of the seven-membered ring, and (ii) for unsymmetrical azepanes intramolecular condensation of aldehyde and hydroxylamine as the key step. Several 2-C-alkylated azepane iminosugars were prepared, and their glycosidase inhibition activities showed interesting results. Extension of these strategies to synthesize various azepane nitrones and their further applications in azepane iminosugar preparation are under investigation.

EXPERIMENTAL SECTION

General Methods. All reagents were used as received from commercial sources or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. Analytical TLC was performed with 0.20 mm silica gel 60F plates with 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent $\{(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, $H_2O\}$ or a solution of 0.5% ninhydrin in acetone. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230–400 mesh). Acidic ion exchange chromatography was performed on Amberlite IR-120 (H^+) or Dowex 50WX8–400, H^+ form. Melting points were determined using an electrothermal melting point apparatus. Infrared spectra were recorded on an FT-IR spectrometer. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or D_2O on a magnetic resonance spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on an LTQ/FT linear ion trap mass spectrometer. Polarimetry measurements were made at the sodium D-line with a 0.5 dm path length cell. Concentrations (c) are given in gram per 100 mL.

(3*R*,4*R*,5*R*,6*R*)-1-Allyl-3,4,5,6-tetrakis(benzyloxy)azepane (5). Methanesulfonyl chloride (460 mg, 4 mmol) was added dropwise to a solution of diol **4** (543 mg, 1.0 mmol) and triethylamine (606 mg, 6.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h. CH_2Cl_2 (20 mL) was added, and the solution was washed with H_2O (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was redissolved in allylamine (5 mL) and heated at reflux for 24 h. The solution was condensed in vacuo, and the residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 5:1) to afford tertiary amine **5** (398 mg, 71% for 2 steps) as a colorless oil: $[\alpha]_D^{20}$ = −16.7 (c 0.6, $CHCl_3$); IR (cm^{-1}) 3063, 3030, 2866, 1642, 1496, 1453, 1367, 1206, 1092, 1068, 1027, 920, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.23 (m, 20H), 5.93–5.80 (m, 1H), 5.18–5.11 (m, 1H), 4.71 (d, J = 12.3 Hz, 2H), 4.60–4.49 (m, 6H), 3.98 (dd, J = 2.4, 8.4 Hz, 2H), 3.90 (s, 2H), 3.16 (d, J = 6.3 Hz, 2H), 2.99 (dd, J = 5.6, 13.0 Hz, 2H), 2.73 (dd, J = 3.0, 13.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.8, 136.0, 128.6, 128.4, 128.3, 127.8, 127.7, 127.50, 127.48, 117.6, 79.9, 76.4, 73.4, 71.5, 61.5, 52.7; HRMS-ESI (m/z) calcd for $C_{37}H_{42}NO_4$ $[M + H]^+$ 564.3108, found 564.3104.

(3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)azepane (6). To a solution of tertiary amine **5** (605 mg, 1.07 mmol) in 1,2-dichloroethane (5 mL) was added 1-chloroethylchloroformate (307 mg, 2.14 mmol), and the resulting solution was stirred under reflux overnight. The solvent was removed in vacuo, and the residue was redissolved in MeOH (5 mL). The resulting solution was again heated at reflux overnight and then concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc, 1:1) to give azepane **6** (480 mg, 86%) as a white solid: mp 76–78 °C; $[\alpha]_D^{20}$ = −34.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3444, 3062, 3031, 2919, 1589, 1496, 1454, 1369, 1207, 1095, 1069, 1027, 909, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.16 (m, 20H), 4.72 (d, J = 12.0 Hz, 2H), 4.63–4.58 (m, 3H), 4.54–4.49 (m,

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208–3221

Table 2. Concentration of Iminosugars Giving 50% Inhibition of Various Glycosidases

	IC_{50} (μM)[a,b]					
enzyme	55a	55b	55c	55d	55e	55f
α-glucosidase						
yeast	NI (13.6%)	NI (5.7%)	539	NI (3.9%)	NI (4.1%)	NI (2.5%)
rice	NI (14.9%)	NI (5.5%)	NI (11.3%)	NI (7.1%)	NI (2.1%)	NI (14.2%)
rat intestinal maltase	NI (10.2%)	NI (21.0%)	NI (8.6%)	NI (5.6%)	NI (10.5%)	NI (20.3%)
β-glucosidase						
almond	NI (7.5%)	NI (39.7%)	591	NI (9.6%)	NI (6.9%)	NI (0.7%)
bovine liver	NI (27.8%)	NI (46.7%)	12	NI (15.5%)	NI (27.1%)	NI (9.3%)
α-galactosidase						
coffee beans	NI (19.4%)	NI (8.1%)	NI (34.2%)	NI (3.6%)	NI (9.7%)	NI (2.6%)
β-galactosidase						
bovine liver	NI (35.5%)	505	4.5	NI (14.3%)	NI (19.6%)	NI (6.9%)
α-mannosidase						
jack beans	NI (0%)	NI (2.2%)	NI (22.1%)	NI (0.9%)	NI (3.7%)	NI (5.9%)
β-mannosidase						
snail	NI (0.3%)	NI (6.7%)	NI (9.8%)	NI (0.8%)	NI (1.7%)	NI (2.4%)
α-L-fucosidase						
bovine kidney	NI (19.9%)	NI (7.7%)	581	NI (15.9%)	NI (10.4%)	NI (6.8%)
α,α-trehalase						
porcine kidney	NI (4.8%)	NI (3.4%)	NI (1.1%)	NI (1.1%)	NI (1.2%)	NI (0.7%)
amyloglucosidase						
Aspergillus niger	NI (1.5%)	NI (4.0%)	NI (8.3%)	NI (2.0%)	NI (0%)	NI (1.7%)
α-L-rhamnosidase						
Penicillium decumbens	NI (12.5%)	NI (5.7%)	NI (0.5%)	NI (2.8%)	NI (0%)	NI (2.0%)

[a]NI: No inhibition (less than 50% inhibition at 1000 μM). [b]Value in parentheses indicates inhibition % at 1000 μM.

3H), 4.09 (dd, J = 1.2, 8.4 Hz, 2H), 3.72 (s, 2H), 3.50−3.43 (m, 2H), 3.36−3.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.5, 128.42, 128.39, 127.8, 127.71, 127.66, 78.8, 77.8, 73.6, 71.9, 46.2; HRMS-ESI (m/z) calcd for $C_{34}H_{38}NO_4$ $[M + H]^+$ 524.2795, found 524.2790.

(3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (7). Oxone (7.38 g, 12.0 mmol) was added batchwise to the mixture of azepane **6** (5.23 g, 10.0 mmol) and $NaHCO_3$ (4.20 g, 5.0 mmol) in MeCN (40 mL)/THF (10 mL)/0.01 M Na_2EDTA (40 mL) at 0 °C. The resulting mixture was stirred for 3 h. EtOAc (100 mL) was added, and the resulting mixture was washed with brine (2 × 30 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 1:1) to afford nitrone **7** (4.27 g, 78%) as a yellow oil: $[\alpha]_D^{20}$ = −44.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3061, 3030, 2869, 1588, 1496, 1453, 1368, 1237, 1207, 1169, 1094, 912, 820, 738, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 20H), 7.04 (d, J = 4.7 Hz, 1H), 4.73−4.42 (m, 10H), 4.02−3.84 (m, 4H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.35−7.21 (m, 20H), 6.92 (s, 1H), 4.71−4.48 (m, 10H), 4.03−3.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.1, 137.9, 137.6, 137.0, 128.7, 128.6, 128.50, 128.47, 128.2, 128.0, 127.9, 127.8, 79.1, 77.4, 74.3, 74.0, 73.3, 73.1, 72.1, 71.7, 62.1; ^{13}C NMR (75 MHz, DMSO-d_6, 333 K) δ 139.5, 139.3, 139.0, 138.8, 135.5, 129.3, 129.23, 129.17, 128.6, 128.5, 79.9, 78.5, 74.8, 73.9, 73.6, 73.5, 72.3, 71.7, 63.4; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2592.

Typical procedure for the intramolecular condensation strategy to prepare azepane nitrones is represented by the synthesis of D-glucose-derived nitrones **3** and **21**.

D-Glucose propane-1,3-diyl dithioacetal (8). Propane-1,3-dithiol (5.6 mL, 0.055 mmol) was added dropwise into the solution of D-glucose (10.0 g, 0.055 mol) in concentrated HCl (10.0 mL). The resulting solution was stirred overnight at rt. The product was precipitated by adding EtOH (100 mL). The white solid was filtered and washed with EtOH to afford dithioacetal **8** (13.2 g, 89%): mp 134−135 °C; $[\alpha]_D^{20}$ = −8.0 (c 0.5, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 4.34 (d, J = 5.8 Hz, 1H), 4.16 (dd, J = 3.3, 5.3 Hz, 1H), 4.00 (t, J = 5.5 Hz, 1H), 3.89−3.76 (m, 3H), 3.73−3.65 (m, 1H), 3.06−2.89 (m, 4H), 2.20−2.10 (m, 1H), 1.94−1.80 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 73.5, 71.6, 71.1, 69.4, 62.8, 49.2, 29.0, 28.3, 25.3.

6-*O*-Trityl-D-glucose propane-1,3-diyl dithioacetal (9). The mixture of dithioacetal **8** (11.3 g, 42.0 mmol), trityl chloride (12.3 g, 44.0 mmol) and 4-dimethylamino-pyridine (51 mg, 0.42 mmol) in pyridine (150 mL) was stirred at 35 °C for 48 h and then concentrated in vacuo. H_2O (200 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried ($MgSO_4$) and condensed under reduced pressure. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH 100:1) to afford compound **9** (18.1 g, 86%) as a white solid: mp 68−71 °C; $[\alpha]_D^{20}$ = −4.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3432, 3058, 3032, 2932, 2900, 1651, 1635, 1597, 1491, 1448, 1422, 1266, 1221, 1076, 1032, 910, 766, 737, 706, 633; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (m, 15H), 4.29 (d, J = 6.6 Hz, 1H), 4.05−3.98 (m, 2H), 3.93−3.88 (m, 1H), 3.86−3.83 (m, 1H), 3.51 (s, 1H), 3.43 (d, J = 3.0 Hz, 1H), 3.36 (d, J = 5.1 Hz, 2H), 3.08 (d, J = 8.4 Hz, 1H), 2.92−2.81 (m, 3H), 2.64−2.59 (m, 2H), 2.08−1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 128.6, 128.0, 127.2, 87.0, 74.2, 73.5, 71.1, 68.1, 64.9, 46.7, 27.1, 26.4, 25.3; HRMS-ESI (m/z) calcd for $C_{28}H_{32}NaO_5S_2$ $[M + Na]^+$ 535.1583, found 535.1585.

2,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-D-glucose propane-1,3-diyl dithioacetal (10). To a solution of **9** (380 mg, 0.74 mmol) in DMF (10 mL) and tetrahydrofuran (10 mL) was added NaH (60% in oil, 163 mg, 4.08 mmol) batchwise. The resulting mixture was stirred at rt for 30 min. Then tetra-*n*-butylammonium iodide (5.5 mg, 0.015 mmol) was added. Benzyl bromide (0.44 mL, 3.70 mmol) was added dropwise at rt, and the resulting mixture was stirred overnight. H_2O (20 mL) was added to quench the reaction, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and condensed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 20:1) to afford compound **10** (567 mg, 88%) as a colorless oil: $[\alpha]_D^{20}$ = −10.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3060, 3030, 2929, 2896, 1495, 1450, 1212, 1090, 1065, 1028, 901, 736, 697, 633; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.05 (m, 35H), 4.85 (d, J = 11.1 Hz, 1H), 4.77−4.58 (m, 5H), 4.49 (d, J = 11.4 Hz, 1H), 4.41 (d, J =

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

12.0 Hz, 1H), 4.21 (d, J = 5.1 Hz, 1H), 4.11 (t, J = 5.4 Hz, 1H), 4.02−3.94 (m, 2H), 3.87−3.84 (m, 1H), 3.57 (dd, J = 2.4, 10.2 Hz, 1H), 3.39 (dd, J = 5.4, 10.2 Hz, 1H), 2.85−2.77 (m, 1H), 2.75−2.52 (m, 3H), 1.97−1.94 (m, 1H), 1.90−1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 138.9, 138.7, 138.49, 138.46, 128.9, 128.34, 128.25, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.43, 127.36, 127.0, 86.9, 81.9, 79.9, 79.8, 78.4, 75.1, 74.6, 73.8, 72.4, 63.4, 49.5, 30.0, 29.5, 26.2; HRMS-ESI (m/z) calcd for $C_{56}H_{56}NaO_5S_2$ [M + Na]$^+$ 895.3461, found 895.3467.

2,3,4,5-Tetra-*O*-benzyl-D-glucose propane-1,3-diyl dithioacetal (11). To a solution of compound **10** (26.2 g, 0.03 mol) in MeOH (150 mL) and CH_2Cl_2 (150 mL) was added concentrated H_2SO_4 (5 mL) dropwise. The resulting mixture was stirred overnight at rt. The pH value was adjusted to 8 with NH_4OH solution, and the resulting mixture was extracted with EtOAc (3 × 200 mL). The combined organic layer was dried ($MgSO_4$) and condensed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 6:1) to afford tetrabenzyloxylated alcohol **11** (17.2 g, 91%) as a yellow oil: $[\alpha]_D^{20}$ = −2.4 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3464, 3062, 3030, 2927, 2897, 1496, 1454, 1209, 1099, 1065, 1028, 909, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 20H), 4.90 (d, J = 11.1 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), 4.74−4.66 (m, 4H), 4.51 (d, J = 11.7 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 4.5 Hz, 1H), 4.02 (dd, J = 4.8, 6.0 Hz, 1H), 3.97−3.80 (m, 4H), 3.67 (dd, J = 4.4, 8.9 Hz, 1H), 2.88−2.75 (m, 2H), 2.71−2.61 (m, 2H), 2.20 (t, J = 6.1 Hz, 1H), 2.03−1.98 (m, 1H), 1.91−1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 138.2, 138.1, 128.5, 128.37, 128.35, 128.3, 128.1, 127.9, 127.81, 127.77, 127.7, 127.6, 81.8, 80.4, 79.8, 78.6, 75.3, 74.4, 74.1, 71.8, 61.1, 49.5, 30.4, 29.8, 26.1; HRMS-ESI (m/z) calcd for $C_{37}H_{42}NaO_5S_2$ [M + Na]$^+$ 653.2366, found 653.2365.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-D-glucose propane-1,3-diyl dithioacetal (12). To a solution of tetrabenzyloxylated alcohol **11** (6.31 g, 10.0 mmol) and triethylamine (2.08 mL, 15.0 mmol) in CH_2Cl_2 (60 mL) was added acetyl chloride (0.85 mL, 12.0 mmol) dropwise at 0 °C, and the resulting mixture was stirred at rt for 1h. The reaction mixture was washed with H_2O (2 × 30 mL), and the organic phase was dried ($MgSO_4$). After concentration under reduced pressure the residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 10:1) to afford ester **12** (5.72 g, 85%) as a yellow oil: $[\alpha]_D^{20}$ = +4.0 (c 1.5, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2931, 2898, 1739, 1496, 1454, 1366, 1236, 1092, 1065, 1028, 910, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 20H), 4.89 (d, J = 11.1 Hz, 1H), 4.79−4.68 (m, 5H), 4.56−4.51 (m, 2H), 4.42 (d, J = 12.0 Hz, 1H), 4.25 (dd, J = 6.3, 12.0 Hz, 1H), 4.19 (d, J = 5.1 Hz, 1H), 4.04−3.95 (m, 3H), 3.83−3.79 (m, 1H), 2.88−2.75 (m, 2H), 2.69−2.60 (m, 2H), 2.05−1.99 (m, 4H), 1.92−1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.6, 138.3, 138.19, 138.15, 128.52, 128.45, 128.40, 128.35, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.62, 127.59, 81.2, 80.1, 78.7, 78.6, 75.5, 74.1, 73.9, 72.0, 63.9, 48.9, 30.0, 29.5, 26.1, 21.1; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ [M + Na]$^+$ 695.2472, found 695.2467.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-D-glucose ethylene acetal (13). *N*-Bromo succinimide (3.97 g, 22.3 mmol) was added batchwise to the solution of ester **12** (5.00 g, 7.4 mmol) in acetonitrile (50 mL) and ethylene glycol (5 mL), and the resulting solution was stirred at rt for 1 h. The pH value was adjusted to 8 with saturated $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and condensed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 8:1) to afford acetal **13** (4.21 g, 90%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2885, 1739, 1496, 1454, 1367, 1236, 1092, 1069, 1028, 737, 698, 605; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 20H), 5.16 (d, J = 4.5 Hz, 1H), 4.87 (d, J = 11.7 Hz, 1H), 4.80−4.64 (m, 4H), 4.57 (d, J = 11.7 Hz, 1H), 4.51−4.39 (m, 3H), 4.23 (dd, J = 6.6, 12.0 Hz, 1H), 4.06 (dd, J = 4.2, 6.6 Hz, 1H), 3.98−3.94 (m, 1H), 3.93−3.85 (m, 3H), 3.81−3.78 (m, 2H), 3.65 (t, J = 4.5 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.8, 138.7, 138.5, 138.4, 128.30, 128.25, 128.10, 128.08, 128.0, 127.6, 127.5, 104.0, 79.8, 79.5, 78.3, 75.3, 74.7, 74.0, 71.8, 65.3, 64.8, 64.0, 21.0; HRMS-ESI (m/z) calcd for $C_{38}H_{42}NaO_8$ [M + Na]$^+$ 649.2772, found 649.2769.

2,3,4,5-Tetra-*O*-benzyl-D-glucose ethylene acetal (14). K_2CO_3 (1.76 g, 12.8 mmol) was added to the solution of acetal **13** (4.00 g, 6.4 mmol) in methanol (50 mL), and the resulting mixture was stirred at rt for 3 h. After filtration, the filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 5:1) to afford alcohol **14** (3.64 g, 98%) as a light yellow oil: $[\alpha]_D^{20}$ = +20.0 (c 0.5, $CHCl_3$); IR (cm^{-1}) 3465, 3062, 3031, 2925, 2884, 1496, 1454, 1210, 1089, 1067, 1028, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.24 (m, 20H), 5.13 (d, J = 3.9 Hz, 1H), 4.85 (d, J = 11.4 Hz, 1H), 4.80−4.67 (m, 4H), 4.62 (d, J = 14.4 Hz, 1H), 4.48−4.39 (m, 2H), 4.04−3.79 (m, 8H), 3.65−3.61 (m, 2H), 2.30 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.5, 128.5, 128.43, 128.36, 128.3, 128.2, 127.7, 127.6, 104.1, 80.2, 79.71, 79.68, 79.6, 75.3, 74.8, 74.2, 71.5, 65.4, 64.9, 61.3; HRMS-ESI (m/z) calcd for $C_{36}H_{40}NaO_7$ [M + Na]$^+$ 607.2666, found 607.2668.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-D-glucose ethylene acetal (15). To a solution of oxalyl dichloride (0.34 mL, 4.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise DMSO (0.43 mL, 6.0 mmol) at −70 °C, and the resulting solution was stirred for 20 min. A solution of alcohol **14** (1.17 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −70 °C, and the resulting solution was stirred for 20 min. Then triethylamine (1.38 mL, 10.0 mmol) was added, and the resulting solution was stirred at −70 °C for 15 min and at rt for another 1 h. The resulting miture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (3 × 20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford aldehyde **15** (1.08 g, 90%) as a colorless oil, which was pure enough to use into the next step: $[\alpha]_D^{20}$ = +6.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3087, 3063, 3031, 2883, 1733, 1496, 1454, 1397, 1355, 1210, 1122, 1086, 1067, 1028, 945, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, J = 1.5 Hz, 1H), 7.29−7.23 (m, 20H), 5.12 (d, J = 3.6 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.75−4.70 (m, 2H), 4.66−4.56 (m, 4H), 4.38 (d, J = 12.0 Hz, 1H), 4.16 (dd, J = 2.7, 6.3 Hz, 1H), 4.02−3.91 (m, 4H), 3.89−3.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 138.5, 138.4, 138.1, 137.5, 128.4, 128.3, 128.2, 128.11, 128.09, 127.9, 127.8, 127.64, 127.61, 127.57, 103.7, 84.5, 80.8, 79.5, 79.1, 75.2, 74.08, 74.05, 72.5, 65.4, 64.9; HRMS-ESI (m/z) calcd for $C_{36}H_{38}NaO_7$ [M + Na]$^+$ 605.2510, found 605.2507.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-hydroxylamino-D-glucose ethylene acetal (16). General Method to Transform An Aldehyde to Hydroxylamine. To a solution of aldehyde **15** (1.05 g, 1.8 mmol) in MeOH (10 mL) was added hydroxylamine chloride (621 mg, 9.0 mmol) and $NaHCO_3$ (1.21 g, 14.4 mmol). The resulting mixture was stirred at rt overnight and then concentrated in vacuo. H_2O (20 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was redissolved in methanol (20 mL), and sodium cyanoborohydride (227 mg, 3.6 mmol) was added. Two drops of methyl orange was added as the indicator. The resulting solution was carefully treated with concentrated HCl/methanol (v/v = 1/10) to maintain the pH value between 3 and 4 at rt. After the completion of the reaction, the resulting solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with 1 N NaOH (1 × 20 mL) and then brine (2 × 20 mL). After dried ($MgSO_4$) and condensed under reduced pressure, the crude product was purified by flash chromatography (silica gel, petroleum ether/EtOAc 3:1 to 1:1) to afford hydroxylamine **16** (767 mg, 71% for 2 steps) as a colorless oil: $[\alpha]_D^{20}$ = +32.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3268, 3062, 3030, 2925, 2885, 1496, 1454, 1399, 1360, 1210, 1122, 1087, 1066, 1028, 944, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.23 (m, 20H), 5.15 (dd, J = 2.1, 4.5 Hz, 1H), 4.94 (dd, J = 2.4, 11.7 Hz, 1H), 4.83−4.66 (m, 4H), 4.60 (dd, J = 1.5, 11.7 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 4.33 (d, J = 11.7 Hz, 1H), 4.18−4.15 (m, 1H), 3.97−3.73 (m, 6H), 3.58 (d, J = 2.7 Hz, 1H), 3.17 (d, J = 5.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.78, 138.76, 138.5 (2C), 128.4, 128.30, 128.26, 128.21, 128.15, 128.1, 127.6, 127.54, 127.49, 127.4, 104.0, 80.1, 79.8, 79.4,

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

76.7, 75.3, 74.8, 73.8, 71.7, 65.3, 64.7, 53.8; HRMS-ESI (m/z) calcd for $C_{36}H_{42}NO_7$ $[M + H]^+$ 600.2956, found 600.2960.

(3*S*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (3). General Method of The Intramolecular Condensation. To a solution of hydroxylamine **16** (600 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added concentrated HCl (2 mL), and the resulting solution was stirred at room temperature for 2 h. The solution was diluted with EtOAc (50 mL) and then washed with H_2O (2 × 20 mL) and saturated $NaHCO_3$ solution (1 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH 100:1) to afford nitrone **3** (426 mg, 79%) as a white solid: mp 129−131 °C; $[\alpha]_D^{20}$ = −18.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2920, 2873, 1608, 1496, 1454, 1393, 1362, 1209, 1119, 1107, 1087, 1029, 909, 859, 735, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.20 (m, 20H), 7.14 (d, J = 4.8 Hz, 1H), 4.85 (d, J = 12.3 Hz, 1H), 4.70−4.58 (m, 8H), 4.09 (dd, J = 4.8, 8.1 Hz, 1H), 3.95−3.88 (m, 3H), 3.62 (dd, J = 2.4, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.9, 137.5, 137.1, 136.3, 128.6, 128.5, 128.43, 128.39, 128.0, 127.91, 127.89, 127.86, 127.7, 82.0, 77.9, 75.6, 75.0, 73.7, 73.1, 71.9, 71.7, 62.8; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2580.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-D-glucose propane-1,3-diyl dithioacetal (17). To a solution of oxalyl dichloride (254 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise DMSO (234 mg, 3.0 mmol) at −70 °C, and the resulting solution was stirred for 20 min. A solution of alcohol **11** (631 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −70 °C, and the resulting solution was stirred for 20 min. Then triethylamine (0.69 mL, 5.0 mmol) was added dropwise, and the resulting solution was stirred at −70 °C for 15 min and at rt for another 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford aldehyde **17** (553 mg, 88%) as a colorless oil, which was pure enough to be used directly into the next step: $[\alpha]_D^{20}$ = −6.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3087, 3062, 3031, 2897, 2868, 1732, 1496, 1454, 1397, 1347, 1277, 1210, 1103, 1027, 910, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.38−7.22 (m, 20H), 4.88 (d, J = 11.1 Hz, 1H), 4.76−4.58 (m, 6H), 4.39 (d, J = 12.0 Hz, 1H), 4.13−4.05 (m, 3H), 4.02−4.00 (m, 2H), 2.87−2.77 (m, 2H), 2.68−2.55 (m, 2H), 1.99−1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 138.3, 138.0, 137.5, 137.3, 128.6, 128.50, 128.44, 128.40, 128.3, 128.0, 127.9, 127.8, 127.6, 84.8, 82.2, 79.9, 79.7, 75.2, 74.4, 73.2, 72.8, 49.1, 30.2, 29.7, 26.1; HRMS-ESI (m/z) calcd for $C_{37}H_{40}NaO_5S_2$ $[M + Na]^+$ 651.2209, found 651.2203.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-D-glucose propane-1,3-diyl dithioacetal (18). The mixture of aldehyde **17** (3.0 g, 4.77 mmol), ethylene glycol (2 mL) and *p*-toluenesulfonic acid (45 mg, 0.26 mmol) in toluene (30 mL) was stirred under reflux for 1 h, and H_2O (50 mL) was added. The resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then purified by flash chromatography (silica gel, petroleum ether/EtOAc 10:1) to afford compound **18** (2.73 g, 85%) as a colorless oil: $[\alpha]_D^{20}$ = −8.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3089, 3062, 3030, 2894, 1496, 1454, 1396, 1341, 1210, 1089, 1067, 1028, 909, 736, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, 20H), 5.30 (d, J = 3.6 Hz, 1H), 4.87 (d, J = 11.1 Hz, 1H), 4.82−4.69 (m, 6H), 4.42 (d, J = 11.7 Hz, 1H), 4.33 (d, J = 5.7 Hz, 1H), 4.25 (t, J = 5.4 Hz, 1H), 4.00−3.83 (m, 6H), 3.77 (t, J = 4.5 Hz, 1H), 2.87−2.61 (m, 4H), 2.06−1.92 (m, 1H), 1.89−1.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.7, 138.6, 138.4, 128.6, 128.30, 128.27, 128.24, 128.19, 128.1, 127.7, 127.62, 127.55, 127.5, 127.40, 127.35, 127.0, 104.0, 81.0, 80.1, 79.7, 79.5, 75.2, 74.4, 73.9, 73.5, 65.2, 65.1, 49.2, 30.1, 29.7, 26.1; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ $[M + Na]^+$ 695.2472, found 695.2469.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-D-glucose (19). To the solution of compound **18** (1.35 g, 2.0 mmol) in acetonitrile (20 mL) and H_2O (5 mL) was added *N*-bromo succinimide (712 mg, 4.0 mmol) batchwise. The resulting mixture was stirred at rt for 20 min, and then the pH value was adjusted to 8 with aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then purified by flash chromatography (silica gel, petroleum ether/EtOAc 10:1) to afford aldehyde **19** (981 mg, 84%) as a colorless oil: $[\alpha]_D^{20}$ = +4.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3089, 3063, 3031, 2883, 1729, 1496, 1454, 1397, 1210, 1093, 1069, 1028, 735, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.31−7.16 (m, 20H), 5.26 (d, J = 1.8 Hz, 1H), 4.86 (d, J = 11.7 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.63−4.44 (m, 6H), 4.16 (dd, J = 3.3, 5.1 Hz, 1H), 4.06−3.85 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 138.7, 138.0, 137.8, 137.4, 128.5, 128.44, 128.35, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.50, 127.47, 104.0, 80.6, 80.0, 77.91, 77.86, 74.3, 73.8, 73.5, 73.0, 65.6, 65.3; HRMS-ESI (m/z) calcd for $C_{36}H_{38}NaO_7$ $[M + Na]^+$ 605.2510, found 605.2509.

2,3,4,5-Tetra-*O*-benzyl-1,6-dideoxy-6,6-(ethylene-1,2-dioxy)-1-hydroxylamino-D-glucose (20). Following the general method to transform an aldehyde to hydroxylamine, aldehyde **19** (1.17 g, 2.0 mmol) gave hydroxylamine **20** (875 mg, 73% for 2 steps) as a colorless oil: $[\alpha]_D^{20}$ = −8.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3269, 3086, 3062, 2885, 1496, 1454, 1396, 1361, 1209, 1091, 1069, 1028, 736, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.23 (m, 20H), 5.27 (d, J = 3.0 Hz, 1H), 4.82−4.75 (m, 2H), 4.73−4.61 (m, 4H), 4.55 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.02−3.81 (m, 8H), 3.16 (dd, J = 3.9, 13.5 Hz, 1H), 2.93 (dd, J = 7.5, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.53, 128.45, 128.4, 128.3, 128.14, 128.12, 128.0, 127.7, 127.60, 127.58, 127.5, 104.2, 79.3, 78.8, 78.7, 75.7, 74.2, 74.1, 74.0, 73.0, 65.3, 65.2, 54.4; HRMS-ESI (m/z) calcd for $C_{36}H_{42}NO_7$ $[M + H]^+$ 600.2956, found 600.2967.

(3*R*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (21). Following the general method of intramolecular condensation, hydroxylamine **20** (200 mg, 0.33 mmol) gave nitrone **21** (138 mg, 77%) as a yellow oil: $[\alpha]_D^{20}$ = −18.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3087, 3063, 3031, 2868, 1577, 1496, 1455, 1362, 1207, 1188, 1095, 1068, 1028, 910, 737, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 20H), 7.04 (d, J = 5.4 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), 4.69−4.57 (m, 7H), 4.53 (d, J = 12.0 Hz, 1H), 4.26 (d, J = 4.8 Hz, 1H), 4.09 (d, J = 13.5 Hz, 1H), 3.99 (t, J = 7.2 Hz, 1H), 3.72−3.67 (m, 1H), 3.62 (d, J = 6.6 Hz, 1H); ^1H NMR (300 MHz, DMSO-d_6) δ 7.36−7.24 (m, 20H), 6.98 (d, J = 5.1 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.68−4.51 (m, 8H), 4.36−4.30 (m, 1H), 4.24−4.20 (m, 1H), 3.94 (t, J = 5.9 Hz, 1H), 3.81−3.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.9, 137.5, 136.9, 134.6, 128.7, 128.53, 128.47, 128.3, 128.01, 127.97, 127.94, 127.92, 127.86, 127.8, 81.1, 79.8, 76.6, 75.1, 73.6, 72.7, 72.2, 63.3; ^{13}C NMR (75 MHz, DMSO-d_6, 373 K) δ 138.2, 138.1, 137.9, 137.7, 133.0, 128.0, 127.9, 127.80, 127.79, 127.3, 127.2, 127.1, 127.0, 79.2, 78.8, 75.1, 73.2, 73.1, 72.1, 71.30, 71.25, 62.6; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2583.

D-Gulose-derived azepane nitrones ***ent*-3** and ***ent*-21** were synthesized following the typical procedure except for special instructions.

D-Gulose propane-1,3-diyl dithioacetal (22). The mixture of D-gulose diacetonide[20] (17.1 g, 0.0658 mol) and propane-1,3-dithiol (32.3 mL, 0.329 mol) in 6 N HCl (100 mL) was stirred overnight. The reaction mixture was diluted with H_2O (500 mL) and washed with CH_2Cl_2 (3 × 100 mL). The aqueous layer was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to afford dithioacetal **22** (15.2 g, 86%) as a brown oil: $[\alpha]_D^{20}$ = +10.0 (*c* 1.0, MeOH); IR (cm^{-1}) 3376, 2932, 2900, 1420, 1278, 1081, 1045, 792; ^1H NMR (300 MHz, D_2O) δ 4.57 (d, J = 2.1 Hz, 1H), 3.94 (dd, J = 2.1, 9.3 Hz, 1H), 3.84−3.71 (m, 4H), 3.65−3.56 (m, 1H), 3.14−3.04 (m, 1H), 3.02−2.92 (m, 3H), 2.19−2.11 (m, 1H), 1.86−1.71 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 73.2, 73.0, 70.2, 69.2, 50.9, 30.2, 29.4, 25.6; HRMS-ESI (m/z) calcd for $C_9H_{18}NaO_5S_2$ $[M + Na]^+$ 293.0488, found 293.0487.

6-*O*-Trityl-D-gulose propane-1,3-diyl dithioacetal (23). Dithoacetal **22** (14.5 g, 0.0537 mol) afforded compound **23** (23.5 g, 85%) as a white solid: mp 158−160 °C; $[\alpha]_D^{20}$ = +10.0 (*c* 1.8,

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

$CHCl_3$); IR (cm^{-1}) 3419, 3057, 3030, 2925, 1491, 1448, 1266, 1218, 1077, 1032, 902, 737, 705, 633; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.21 (m, 15H), 4.34 (d, J = 4.8 Hz, 1H), 4.00−3.96 (m, 2H), 3.94−3.87 (m, 2H), 3.39−3.35 (m, 2H), 3.37 (dd, J = 5.7, 9.9 Hz, 1H), 3.06 (d, J = 5.7 Hz, 1H), 3.01 (d, J = 3.9 Hz, 1H), 2.97−2.70 (m, 5H), 2.14−2.04 (m, 1H), 2.00−1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 128.7, 128.0, 127.2, 87.1, 74.1, 73.2, 72.7, 69.6, 64.9, 49.9, 29.6, 28.9, 25.8; HRMS-ESI (m/z) calcd for $C_{28}H_{32}NaO_5S_2$ $[M + Na]^+$ 535.1583, found 535.1582.

2,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-D-gulose propane-1,3-diyl dithioacetal (24). Compound **23** (23.0 g, 0.0448 mol) afforded **24** (36.1 g, 92%) as a light yellow oil: $[\alpha]_D^{20}$ = −8.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3060, 3031, 2932, 2894, 1495, 1450, 1211, 1089, 1072, 1028, 901, 735, 698, 646; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.10 (m, 20H), 5.00 (d, J = 11.1 Hz, 1H), 4.69−4.46 (m, 7H), 4.40 (d, J = 11.1 Hz, 1H), 4.04 (dd, J = 4.2, 5.4 Hz, 1H), 3.95−3.87 (m, 3H), 3.41 (dd, J = 3.3, 9.9 Hz, 1H), 3.24 (dd, J = 5.4, 9.9 Hz, 1H), 2.76−2.54 (m, 4H), 1.99−1.94 (m, 1H), 1.87−1.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 138.9 (2C), 138.8, 138.3, 128.9, 128.4, 128.33, 128.25, 128.1, 127.9, 127.8, 127.6, 127.5, 127.42, 127.40, 127.0, 86.8, 82.6, 79.7, 79.0, 78.5, 74.6, 74.0, 73.7, 73.2, 63.5, 51.3, 32.3, 30.5, 26.5; HRMS-ESI (m/z) calcd for $C_{56}H_{57}O_5S_2$ $[M + H]^+$ 873.3642, found 873.3632.

2,3,4,5-Tetra-*O*-benzyl-D-gulose propane-1,3-diyl dithioacetal (25). Compound **24** (36.0 g, 0.0412 mol) afforded tetrabenzyloxylated alcohol **25** (22.6 g, 87%) as a yellow oil: $[\alpha]_D^{20}$ = −1.5 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3466, 3062, 3030, 2931, 2895, 1496, 1454, 1395, 1351, 1209, 1092, 1028, 908, 735, 697, 606; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 20H), 5.02 (d, J = 11.1 Hz, 1H), 4.77 (s, 2H), 4.63−4.62 (m, 4H), 4.58 (d, J = 2.4 Hz, 1H), 4.42 (d, J = 11.1 Hz, 1H), 4.00 (dd, J = 3.6, 6.9 Hz, 1H), 3.91 (dd, J = 2.7, 6.9 Hz, 1H), 3.85 (dd, J = 3.9, 5.4 Hz, 1H), 3.76−3.68 (m, 2H), 3.61−3.54 (m, 1H), 2.84−2.62 (m, 4H), 2.09−1.97 (m, 2H), 1.93−1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (2C), 138.3, 138.0, 128.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.79, 127.76, 127.72, 127.68, 82.2, 79.7, 79.1, 77.6, 74.5, 74.0, 73.6, 73.1, 62.1, 51.2, 32.2, 30.4, 26.4; HRMS-ESI (m/z) calcd for $C_{37}H_{42}NaO_5S_2$ $[M + Na]^+$ 653.2366, found 653.2361.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-D-gulose propane-1,3-diyl dithioacetal (26). Tetrabenzyloxylated alcohol **25** (6.31 g, 10.0 mmol) afforded ester **26** (5.74 g, 85%) as a light yellow oil: $[\alpha]_D^{20}$ = −1.6 (c 3.7, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2932, 2897, 1740, 1496, 1455, 1366, 1235, 1093, 1028, 909, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.23 (m, 20H), 5.02 (d, J = 11.4 Hz, 1H), 4.81 (d, J = 11.7 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.66−4.58 (m, 4H), 4.54 (d, J = 2.4 Hz, 1H), 4.40 (d, J = 11.1 Hz, 1H), 4.26 (dd, J = 4.2, 11.7 Hz, 1H), 4.12 (dd, J = 6.0, 11.7 Hz, 1H), 3.99 (dd, J = 4.2, 7.5 Hz, 1H), 3.90−3.83 (m, 2H), 3.81−3.78 (m, 1H), 2.84−2.59 (m, 4H), 2.08−2.03 (m, 1H), 1.90−1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 138.5, 138.4, 138.2, 138.0, 128.9, 128.5, 128.39, 128.35, 128.29, 128.26, 128.2, 127.9, 127.8, 127.7, 127.64, 127.61, 82.5, 78.2, 77.7, 77.6, 74.4, 73.9, 73.8, 73.4, 64.2, 51.2, 32.2, 30.4, 26.5, 20.9; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ $[M + Na]^+$ 695.2472, found 695.2466.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-D-gulose ethylene acetal (27). Compound **26** (5.50 g, 8.17 mmol) afforded **27** (4.66 g, 91%) as a light yellow oil: $[\alpha]_D^{20}$ = +2.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2885, 1739, 1496, 1454, 1368, 1232, 1090, 1072, 1028, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.23 (m, 20H), 5.26 (d, J = 3.6 Hz, 1H), 4.77 (d, J = 11.7 Hz, 2H), 4.71−4.61 (m, 4H), 4.56 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.28 (dd, J = 4.5, 11.7 Hz, 1H), 4.17 (dd, J = 6.0, 11.7 Hz, 1H), 4.03−3.98 (m, 2H), 3.96−3.82 (m, 5H), 3.75 (dd, J = 3.6, 5.4 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 138.8, 138.6, 138.5, 138.3, 128.4, 128.33, 128.30, 128.23, 128.15, 128.1, 127.8, 127.60, 127.58, 127.52, 127.45, 104.0, 79.2 (2C), 78.1, 77.0, 74.4, 74.1, 74.0, 72.8, 65.3, 65.2, 64.2, 21.0; HRMS-ESI (m/z) calcd for $C_{38}H_{42}NaO_8$ $[M + Na]^+$ 649.2772, found 649.2765.

2,3,4,5-Tetra-*O*-benzyl-D-gulose ethylene acetal (28). Compound **27** (4.60 g, 7.34 mmol) afforded alcohol **28** (4.20 g, 98%) as a light yellow oil: $[\alpha]_D^{20}$ = +4.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3479, 3062, 3031, 2884, 1496, 1454, 1395, 1350, 1209, 1092, 1067, 1028, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.24 (m, 20H), 5.26 (d, J = 3.6 Hz, 1H), 4.81−4.76 (m, 2H), 4.71−4.55 (m, 5H), 4.48 (d, J = 11.7 Hz, 1H), 4.01−3.80 (m, 7H), 3.76−3.68 (m, 2H), 3.58 (dd, J = 4.8, 11.1 Hz, 1H), 2.07 (t, J = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.50, 138.46, 138.4, 128.5, 128.41, 128.36, 128.33, 128.25, 128.1, 128.0, 127.8, 127.71, 127.66, 127.6, 127.5, 104.1, 79.1, 79.03 (2C), 79.00, 74.4, 74.0, 73.9, 72.5, 65.3, 65.2, 62.1; HRMS-ESI (m/z) calcd for $C_{36}H_{40}NaO_7$ $[M + Na]^+$ 607.2666, found 607.2662.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-D-gulose ethylene acetal (*ent*-19). Alcohol **28** (4.20 g, 7.18 mmol) afforded aldehyde ***ent*-19** (3.98 g, 95%) as a yellow oil: $[\alpha]_D^{20}$ = −2.0 (c 2.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2885, 1729, 1496, 1455, 1210, 1093, 1072, 1028, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s,1H), 7.32−7.16 (m, 20H), 5.26 (d, J = 2.1 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.63−4.45 (m, 6H), 4.16 (dd, J = 3.6, 5.4 Hz, 1H), 4.05−3.85 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 138.8, 138.0, 137.8, 137.4, 128.6, 128.5, 128.4, 128.3, 128.24, 128.17, 128.1, 128.0, 127.60, 127.56, 127.5, 104.1, 80.6, 80.1, 78.0, 77.9, 74.4, 73.9, 73.5, 73.1, 65.6, 65.3; HRMS-ESI (m/z) calcd for $C_{36}H_{38}NaO_7$ $[M + Na]^+$ 605.2510, found 605.2505.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-hydroxylamino-D-gulose ethylene acetal (*ent*-20). Aldehyde ***ent*-19** (3.80 g, 6.52 mmol) afforded hydroxylamine ***ent*-20** (2.94 g, 75% for 2 steps) as a light yellow oil: $[\alpha]_D^{20}$ = +10.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3269, 3062, 3030, 2885, 1496, 1454, 1395, 1359, 1209, 1090, 1067, 1028, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.22 (m, 20H), 5.27 (d, J = 3.0 Hz, 1H), 4.82−4.75 (m, 2H), 4.73−4.61 (m, 4H), 4.55 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.02−3.82 (m, 8H), 3.16 (dd, J = 4.2, 13.5 Hz, 1H), 2.94 (dd, J = 7.2, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.5, 128.4, 128.34, 128.32, 128.11, 128.09, 128.0, 127.7, 127.58, 127.55, 127.5, 104.2, 79.3, 78.73, 78.69, 75.7, 74.2, 74.1, 74.0, 73.0, 65.3, 65.2, 54.4; HRMS-ESI (m/z) calcd for $C_{36}H_{42}NO_7$ $[M + H]^+$ 600.2956, found 600.2964.

(3*S*,4*S*,5*S*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (*ent*-21). Hydroxylamine ***ent*-20** (600 mg, 1.0 mmol) afforded nitrone ***ent*-21** (440 mg, 82%) as a yellow oil: $[\alpha]_D^{20}$ = +22.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2867, 1583, 1496, 1454, 1362, 1308, 1238, 1208, 1188, 1099, 1028, 912, 738, 698, 610; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 20H), 7.04 (d, J = 5.1 Hz, 1H), 4.78 (d, J = 11.4 Hz, 1H), 4.69−4.57 (m, 7H), 4.52 (d, J = 12.0 Hz, 1H), 4.27 (d, J = 5.1 Hz, 1H), 4.09 (d, J = 13.5 Hz, 1H), 3.98 (t, J = 7.2 Hz, 1H), 3.72−3.66 (m, 1H), 3.62 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.9, 137.5, 137.0, 134.8, 128.7, 128.5, 128.4, 128.3, 128.03, 127.98, 127.95, 127.93, 127.86, 80.8, 79.7, 76.4, 75.1, 73.6, 72.7, 72.2, 63.2; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2584.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-D-gulose propane-1,3-diyl dithioacetal (29). Tetrabenzyloxylated alcohol **25** (6.31 g, 10.0 mmol) afforded aldehyde **29** (5.85 g, 93%) as a light yellow oil: $[\alpha]_D^{20}$ = −8.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2932, 2896, 2866, 1728, 1496, 1454, 1326, 1210, 1115, 1072, 1028, 909, 735, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s,1H), 7.36−7.14 (m, 20H), 5.11 (d, J = 11.1 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.56−4.49 (m, 3H), 4.44−4.39 (m, 2H), 4.08−4.01 (m, 2H), 3.95 (dd, J = 1.5, 7.8 Hz, 1H), 3.89 (d, J = 5.1 Hz, 1H), 2.83−2.56 (m, 4H), 2.08−2.02 (m, 1H), 1.92−1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 138.3, 138.1, 137.8, 137.4, 128.6, 128.51, 128.45, 128.4, 128.23, 128.19, 128.1, 128.0, 127.90, 127.72, 127.68, 81.9, 81.0, 80.0, 77.5, 74.2, 74.0, 73.9, 73.3, 51.3, 32.6, 30.4, 26.4; HRMS-ESI (m/z) calcd for $C_{37}H_{40}NaO_5S_2$ $[M + Na]^+$ 651.2209, found 651.2208.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-D-gulose propane-1,3-diyl dithioacetal (30). Aldehyde **29** (5.50 g, 8.74 mmol) afforded **30** (4.93 g, 84%) as a light yellow oil: $[\alpha]_D^{20}$ = −6.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2936, 2892, 1496, 1454, 1210, 1120, 1089, 1067, 1028, 908, 736, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 20H), 5.16 (d, J = 7.2 Hz, 1H), 5.02 (d, J = 11.1 Hz, 1H), 4.86−4.80 (m, 2H), 4.73−4.63 (m, 4H), 4.53 (d, J = 2.1

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

Hz, 1H), 4.41 (d, J = 11.1 Hz, 1H), 4.05−4.01 (m, 1H), 3.97 (t, J = 5.1 Hz, 1H), 3.86−3.81 (m, 3H), 3.77−3.73 (m, 1H), 3.67 (t, J = 5.7 Hz, 1H), 2.83−2.68 (m, 3H), 2.65−2.55 (m, 1H), 2.07−2.02 (m, 1H), 1.91−1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.9, 138.7, 138.1, 128.44, 128.39, 128.30, 128.25, 128.21, 128.19, 128.0, 127.9, 127.6, 127.5, 127.3, 104.3, 83.2, 80.3, 79.6, 77.8, 75.2, 74.6, 73.94, 73.91, 65.0, 64.8, 51.3, 32.2, 30.4, 26.5; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ [M + Na]$^+$ 695.2472, found 695.2466.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-D-gulose (*ent*-15). Compound **30** (4.80 g, 7.13 mmol) afforded aldehyde ***ent*-15** (3.63 g, 87%) as a light yellow oil: $[\alpha]_D^{20}$ = −4.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2884, 1731, 1496, 1455, 1210, 1120, 1090, 1069, 1028, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, J = 1.5 Hz, 1H), 7.34−7.22 (m, 20H), 5.12 (d, J = 3.6 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.75−4.70 (m, 2H), 4.66−4.56 (m,4H), 4.38 (d, J = 12.0 Hz, 1H), 4.12 (dd, J = 3.0, 6.6 Hz, 1H), 4.01−3.91 (m, 4H), 3.88−3.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 138.5, 138.4, 138.1, 137.5, 128.5, 128.3, 128.2, 128.13, 128.11, 127.9, 127.8, 127.7, 127.63, 127.59, 103.8, 84.5, 80.8, 79.5, 79.1, 75.2, 74.09, 74.07, 72.5, 65.4, 64.9; HRMS-ESI (m/z) calcd for $C_{36}H_{38}NaO_7$ [M + Na]$^+$ 605.2510, found 605.2507.

2,3,4,5-Tetra-*O*-benzyl-1,6-dideoxy-6,6-(ethylene-1,2-dioxy)-1-hydroxylamino-D-gulose (*ent*-16). Aldehyde ***ent*-15** (3.50 g, 6.0 mmol) afforded hydroxylamine ***ent*-16** (2.69 g, 75% for 2 steps) as a light yellow oil: $[\alpha]_D^{20}$ = −28.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3272, 3063, 3031, 2884, 1496, 1455, 1397, 1360, 1210, 1120, 1086, 1067, 1028, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (m, 20H), 5.14 (d, J = 4.8 Hz, 1H), 4.91 (d, J = 11.7 Hz, 1H), 4.83−4.66 (m, 4H), 4.60 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.33 (d, J = 11.7 Hz, 1H), 4.16 (dd, J = 5.4, 7.2 Hz, 1H), 3.99−3.86 (m, 4H), 3.84−3.75 (m, 2H), 3.57 (t, J = 4.2 Hz, 1H), 3.17 (d, J = 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.99, 138.96, 138.7, 138.6, 128.5, 128.44, 128.37, 128.35, 128.24, 128.20, 128.1, 127.7, 127.64, 127.56, 104.2, 80.4, 79.9, 79.7, 76.8, 75.5, 75.0, 73.9, 71.8, 65.4, 64.8, 54.1; HRMS-ESI (m/z) calcd for $C_{36}H_{42}NO_7$ [M + H]$^+$ 600.2956, found 600.2955.

(3*R*,4*S*,5*S*,6*S*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (*ent*-3). Hydroxylamine ***ent*-16** (600 mg, 1.0 mmol) afforded nitrone ***ent*-3** (406 mg, 75%) as a white solid: mp 134−137 °C; $[\alpha]_D^{20}$ = +18.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3061, 3031, 2904, 2871, 1612, 1496, 1454, 1362, 1207, 1107, 1058, 1028, 909, 738, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.22 (m, 20H), 7.15 (d, J = 4.8 Hz, 1H), 4.86 (d, J = 12.3 Hz, 1H), 4.71−4.59 (m, 8H), 4.09 (dd, J = 4.8, 8.1 Hz, 1H), 3.96−3.88 (m, 3H), 3.61 (dd, J = 1.8, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 137.5, 137.1, 136.3, 128.6, 128.5, 128.44, 128.39, 128.1, 127.89, 127.86, 127.7, 82.0, 77.9, 75.7, 75.0, 73.7, 73.1, 71.8, 71.6, 62.8; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ [M + H]$^+$ 538.2588, found 538.2584.

D-Altrose-derived azepane nitrones **40** and **44** were synthesized following the typical procedure except for special instructions.

D-Altrose propane-1,3-diyl dithioacetal (31). Following the method to prepare **22**, D-altrose (5.0 g, 0.0278 mol) and propane-1,3-dithiol (4.2 mL, 0.0417 mol) afforded dithioacetal **31** (6.95 g, 93%) as a brown oil: $[\alpha]_D^{20}$ = +0.2 (c 5.0, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 4.21 (d, J = 9.3 Hz, 1H), 4.14−4.08 (m, 2H), 4.00−3.95 (m, 1H), 3.88−3.82 (m, 2H), 3.72 (dd, J = 7.5, 11.7 Hz, 1H), 3.06−2.94 (m, 2H), 2.91−2.82 (m, 2H), 2.16−2.06 (m, 1H), 1.99−1.86 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 72.8, 71.6, 70.1, 70.0, 62.0, 47.6, 27.7, 27.3, 25.2.

6-*O*-Trityl-D-altrose propane-1,3-diyl dithioacetal (32). Dithioacetal **31** (6.87 g, 0.0254 mol) afforded compound **32** (11.8 g, 90%) as a white solid: mp 155−158 °C; $[\alpha]_D^{20}$ = −0.6 (c 3.3, $CHCl_3$); IR (cm^{-1}) 3395, 3059, 3030, 2933, 1491, 1448, 1266, 1225, 1059, 1033, 1001, 903, 737, 705, 633; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.21 (m, 15H), 4.24 (d, J = 9.6 Hz, 1H), 4.13 (brs, 1H), 3.95−3.88 (m, 2H), 3.83−3.77 (m, 1H), 3.51 (dd, J = 3.9, 9.9 Hz, 1H), 3.38 (dd, J = 5.1, 9.9 Hz, 2H), 3.22 (d, J = 6.6 Hz, 1H), 3.14 (brs, 1 H), 3.00−2.85 (m, 3H), 2.63−2.53 (m, 2H), 2.02−1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 128.6, 128.0, 127.3, 87.4, 73.6, 71.9, 70.5, 69.2, 65.4, 46.2, 26.3, 25.8, 25.2; HRMS-ESI (m/z) calcd for $C_{28}H_{32}NaO_5S_2$ [M + Na]$^+$ 535.1583, found 535.1577.

2,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-D-altrose propane-1,3-diyl dithioacetal (33). Compound **32** (11.8 g, 0.023 mol) afforded **33** (17.4 g, 87%) as a light yellow oil: $[\alpha]_D^{20}$ = −6.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3060, 3030, 2932, 2895, 1496, 1449, 1212, 1093, 1067, 1028, 908, 736, 697, 633; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.06 (m, 35H), 4.74−4.64 (m, 5H), 4.60 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 11.4 Hz, 1H), 4.36 (d, J = 3.9 Hz, 1H), 4.16 (dd, J = 3.6, 6.3 Hz, 1H), 4.10−4.05 (m, 2H), 4.00−3.96 (m, 1H), 3.54 (dd, J = 2.4, 10.2 Hz, 1H), 3.32 (dd, J = 4.8, 10.2 Hz, 1H), 2.93−2.71 (m, 4H), 2.05−1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 139.1, 138.8, 138.5, 138.4, 128.9, 128.3, 128.2, 128.1, 128.0, 127.9, 127.84, 127.78, 127.7, 127.4, 127.3, 127.2, 126.9, 86.7, 83.2, 81.2, 79.1, 78.5, 74.93, 74.85, 72.7, 72.4, 63.2, 50.9, 30.6, 30.1, 26.2; HRMS-ESI (m/z) calcd for $C_{56}H_{56}NaO_5S_2$ [M + Na]$^+$ 895.3461, found 895.3450.

2,3,4,5-Tetra-*O*-benzyl-D-altrose propane-1,3-diyl dithioacetal (34). Compound **33** (17.2 g, 0.0197 mol) afforded tetrabenzyloxylated alcohol **34** (10.7 g, 86%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3468, 3062, 3030, 2932, 2897, 1496, 1454, 1209, 1094, 1070, 1028, 908, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.24 (m, 20H), 4.81−4.78 (m, 3H), 4.70−4.68 (m, 3H), 4.60 (s, 2H), 4.21 (d, J = 3.6 Hz, 1H), 4.16 (dd, J = 3.3, 6.9 Hz, 1H), 3.97 (dd, J = 3.6, 6.9 Hz, 1H), 3.90−3.83 (m, 2H), 3.78−3.76 (m, 2H), 2.97−2.78 (m, 2H), 2.74−2.66 (m, 2H), 2.22 (brs, 1H), 2.09−1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.6, 138.0 (2C), 128.5, 128.32, 128.26, 128.2, 128.13, 128.05, 128.0, 127.9, 127.6, 127.5, 83.1, 80.6, 79.5, 78.7, 75.1 (2C), 72.9, 72.1, 61.4, 50.5, 30.5, 30.0, 26.1; HRMS-ESI (m/z) calcd for $C_{37}H_{42}NaO_5S_2$ [M + Na]$^+$ 653.2366, found 653.2366.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-D-altrose propane-1,3-diyl dithioacetal (35). Tetrabenzyloxylated alcohol **34** (2.52 g, 4.0 mmol) afforded ester **35** (2.36 g, 88%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.4 (c 1.1, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2927, 2897, 1739, 1496, 1454, 1366, 1237, 1098, 1067, 1028, 908, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.23 (m, 20H), 4.82−4.56 (m, 8H), 4.46 (dd, J = 2.4, 12.0 Hz, 1H), 4.25−4.18 (m, 2H), 4.16−4.11 (m, 1H), 4.02−3.97 (m, 2H), 3.85 (t, J = 4.8 Hz, 1H), 2.96−2.81 (m, 2H), 2.75−2.63 (m, 2H), 2.07−1.86 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.7, 138.6, 138.1, 138.0, 128.4, 128.24, 128.19, 128.13, 128.08, 128.0, 127.9, 127.70, 127.68, 127.4, 83.0, 80.0, 78.9, 77.0, 74.9, 74.8, 72.8, 72.4, 63.9, 50.3, 30.3, 29.9, 26.1, 21.0; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ [M + Na]$^+$ 695.2472, found 695.2470.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-D-altrose ethylene acetal (36). Ester **35** (2.30 g, 3.42 mmol) afforded acetal **36** (1.82 g, 85%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2886, 1739, 1496, 1455, 1384, 1366, 1236, 1090, 1071, 1028, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.23 (m, 20H), 5.16 (d, J = 4.5 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.76 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 11.4 Hz, 2H), 4.62 (s, 2H), 4.55 (d, J = 11.4 Hz, 1H), 4.46−4.39 (m, 2H), 4.19 (dd, J = 6.0, 12.0 Hz, 1H), 4.07−4.03 (m, 1H), 4.02−3.83 (m, 6H), 3.79−3.73 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.9, 138.7, 138.3 (2C), 128.32, 128.30, 128.2, 128.0, 127.93, 127.87, 127.60, 127.58, 127.4, 104.2, 80.0, 79.3, 78.1, 77.4, 74.5, 74.4, 72.9, 72.3, 65.3, 65.0, 64.2, 21.0; HRMS-ESI (m/z) calcd for $C_{38}H_{42}NaO_8$ [M + Na]$^+$ 649.2772, found 649.2770.

2,3,4,5-Tetra-*O*-benzyl-D-altrose ethylene acetal (37). Compound **36** (1.73 g, 2.76 mmol) afforded alcohol **37** (1.55 g, 96%) as a light yellow oil: $[\alpha]_D^{20}$ = +3.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3470, 3063, 3031, 2884, 1496, 1454, 1395, 1333, 1210, 1090, 1070, 1028, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.21 (m, 20H), 5.08 (d, J = 4.2 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.79−4.68 (m, 3H), 4.65−4.55 (m, 3H), 4.51 (d, J = 11.4 Hz, 1H), 4.05−3.90 (m, 4H), 3.88−3.76 (m, 6H), 2.28 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.6, 138.3, 138.2, 128.5, 128.4, 128.29, 128.26, 128.01, 127.96, 127.9, 127.74, 127.72, 127.6, 127.5, 104.0, 80.1, 79.7, 79.2, 78.8, 74.7, 74.6, 73.0, 72.1, 65.4, 65.1, 61.6; HRMS-ESI (m/z) calcd for $C_{36}H_{40}NaO_7$ [M + Na]$^+$ 607.2666, found 607.2664.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-D-altrose ethylene acetal (38). Alcohol **37** (2.03 g, 1.94 mmol) afforded aldehyde

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

38(1.94 g, 96%) as a yellow oil: $[\alpha]_D^{20}$ = −10.8 (*c* 1.3, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2883, 1731, 1496, 1455, 1395, 1333, 1210, 1094, 1072, 1028, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.34−7.17 (m, 20H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.91 (d, *J* = 11.7 Hz, 1H), 4.76−4.62 (m, 4H), 4.51−4.44 (m, 2H), 4.22 (d, *J* = 11.4 Hz, 1H), 4.18−4.06 (m, 3H), 4.01−3.85 (m, 3H), 3.82−3.77 (m, 1H), 3.65 (dd, *J* = 2.4, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 138.8, 138.4, 137.8, 137.6, 128.5, 128.4, 128.31, 128.27, 128.00, 127.98, 127.9, 127.8, 127.5, 127.4, 104.4, 82.5, 80.8, 79.1, 77.8, 74.0, 73.6, 73.2, 72.2, 65.2, 64.9; HRMS-ESI (*m*/*z*) calcd for $C_{36}H_{38}NaO_7$ $[M + Na]^+$ 605.2510, found 605.2506.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-hydroxylamino-D-altrose ethylene acetal (39). Aldehyde **38** (1.93 g, 3.31 mmol) afforded hydroxylamine **39** (1.61 g, 81% for 2 steps) as a light yellow oil: $[\alpha]_D^{20}$ = +16.0 (*c* 0.5, $CHCl_3$); IR (cm^{-1}) 3268, 3063, 3031, 2886, 1496, 1454, 1396, 1330, 1210, 1090, 1070, 1028, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 20H), 5.17 (d, *J* = 5.4 Hz, 1H), 4.90 (d, *J* = 11.4 Hz, 1H), 4.79−4.68 (m, 4H), 4.56−4.51 (m, 2H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.20−4.16 (m, 1H), 4.08 (dd, *J* = 2.7, 7.5 Hz, 1H), 4.01−3.98 (m, 1H), 3.95−3.80 (m, 4H), 3.75 (dd, *J* = 3.6, 5.4 Hz, 1H), 3.25−3.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.6, 138.50, 138.46, 128.4, 128.33, 128.28, 128.26, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 104.4, 79.8, 79.1, 78.3, 76.2, 74.5, 74.1, 73.1, 72.2, 65.3, 64.9, 54.1; HRMS-ESI (*m*/*z*) calcd for $C_{36}H_{42}NO_7$ $[M + H]^+$ 600.2956, found 600.2953.

(3*R*,4*S*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (40). Hydroxylamine **39** (300 mg, 0.5 mmol) afforded nitrone **40** (147 mg, 55%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.7 (*c* 1.2, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2870, 1587, 1496, 1454, 1361, 1209, 1098, 1027, 738, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 20H), 7.04 (d, *J* = 4.5 Hz, 1H), 4.88−4.79 (m, 3H), 4.75−4.58 (m, 6H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.11 (d, *J* = 1.2 Hz, 1H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 9.6 Hz, 1H), 3.54 (dd, *J* = 2.1, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 138.5, 138.2, 137.4, 137.2, 128.5, 128.4, 128.2, 128.01, 127.98, 127.93, 127.87, 127.74, 127.69, 127.63, 127.60, 79.8, 79.6, 75.8, 75.2, 74.3, 73.7, 73.4, 71.3, 61.2; HRMS-ESI (*m*/*z*) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2584.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-D-altrose propane-1,3-diyl dithioacetal (41). Tetrabenzyloxylated alcohol **34** (3.16 g, 0.5 mmol) afforded aldehyde **41** (2.85 g, 90%) as a light yellow oil: $[\alpha]_D^{20}$ = +1.7 (*c* 1.2, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2897, 2866, 1730, 1496, 1454, 1209, 1107, 1067, 1028, 909, 737, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.36−7.20 (m, 20H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 2H), 4.73−4.63 (m, 2H), 4.61−4.52 (m, 2H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 6.0 Hz, 1H), 4.21 (dd, *J* = 4.5, 7.5 Hz, 1H), 4.15 (d, *J* = 2.1 Hz, 1H), 4.08 (dd, *J* = 2.7, 7.5 Hz, 1H), 3.91 (dd, *J* = 4.8, 5.4 Hz, 1H), 2.90−2.78 (m, 2H), 2.75−2.61 (m, 2H), 2.04−1.98 (m, 1H), 1.94−1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 138.4, 138.3, 137.5, 137.4, 128.6, 128.5, 128.30, 128.28, 128.13, 128.06, 128.0, 127.9, 127.7, 127.6, 127.5, 82.2, 81.9, 81.4, 78.0, 74.8, 73.9, 73.3, 72.3, 49.9, 30.3, 29.9, 26.1; HRMS-ESI (*m*/*z*) calcd for $C_{37}H_{40}NaO_5S_2$ $[M + Na]^+$ 651.2209, found 651.2206.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-D-altrose propane-1,3-diyl dithioacetal (42). Aldehyde **41** (2.75 g, 4.37 mmol) afforded compound **42** (2.71 g, 92%) as a light yellow oil: $[\alpha]_D^{20}$ = −4.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2893, 1496, 1454, 1210, 1164, 1102, 1067, 1028, 908, 736, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 20H), 5.27 (d, *J* = 3.0 Hz, 1H), 4.87−4.64 (m, 8H), 4.28−4.24 (m, 2H), 4.03−3.90 (m, 5H), 3.88−3.79 (m, 2H), 2.96−2.80 (m, 2H), 2.77−2.64 (m, 2H), 2.05−1.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.8, 138.6, 138.5, 128.3, 128.20, 128.15, 127.94, 127.92, 127.88, 127.8, 127.5, 127.4, 127.3, 104.3, 83.2, 80.8, 79.9, 78.8, 74.7, 74.4, 72.8, 65.33, 65.25, 50.0, 30.2, 29.8, 26.1; HRMS-ESI (*m*/*z*) calcd for $C_{39}H_{44}NaO_6S_2$ $[M + Na]^+$ 695.2472, found 695.2465.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-D-altrose (43). Compound **42** (2.55 g, 3.79 mmol) afforded aldehyde **43** (1.83 g, 83%) as a light yellow oil: $[\alpha]_D^{20}$ = −20.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2882, 1729, 1496, 1454, 1328, 1210, 1093, 1028, 737, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.5 Hz, 1H), 7.34−7.23 (m, 20H), 5.18 (d, *J* = 4.5 Hz, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.67−4.54 (m, 5H), 4.51−4.44 (m, 2H), 4.26 (dd, *J* = 4.5, 5.7 Hz, 1H), 4.07−4.00 (m, 2H), 3.96−3.79 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 138.7, 138.0, 137.8, 137.3, 128.6, 128.5, 128.33, 128.31, 128.30, 128.26, 128.1, 128.00, 127.95, 127.71, 127.66, 127.6, 127.4, 103.9, 84.2, 79.5, 79.2, 79.0, 74.0, 73.44, 73.39, 73.3, 65.1, 65.0; HRMS-ESI (*m*/*z*) calcd for $C_{36}H_{38}NaO_7$ $[M + Na]^+$ 605.2510, found 605.2509.

(3*R*,4*R*,5*S*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (44). Aldehyde **43** (640 mg, 1.10 mmol) gave a hydroxylamine that was not stable on the silica gel and used into the next step without further purification to afford nitrone **44** (172 mg, 29% for 3 steps) as a white solid: mp 155−157 °C; $[\alpha]_D^{20}$ = −40.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2881, 1601, 1496, 1454, 1377, 1227, 1117, 1098, 1027, 839, 742, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.21 (m, 20H), 7.09 (d, *J* = 4.5 Hz, 1H), 4.77−4.67 (m, 5H), 4.59 (d, *J* = 13.2 Hz, 2H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 13.5 Hz, 1H), 4.14 (d, *J* = 4.8 Hz, 1H), 4.10−4.04 (m, 2H), 3.89 (dd, *J* = 10.2, 13.2 Hz, 1H), 3.46 (dd, *J* = 2.4, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.11, 138.06, 137.5 (2C), 136.6, 128.7, 128.5, 128.4, 128.24, 128.21, 128.00, 127.99, 127.82, 127.77, 127.7, 127.6, 83.4, 78.8, 76.0, 74.1, 73.7, 73.6, 73.4, 72.1, 64.6; HRMS-ESI (*m*/*z*) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2591.

L-Talose-derived azepane nitrones ***ent*-40** and ***ent*-44** were synthesized following the typical procedure except for special instructions.

L-Talose propane-1,3-diyl dithioacetal (45). Following the method to prepare **22**, L-talose (1.80 g, 0.01 mol) and propane-1,3-dithiol (1.5 mL, 0.015 mol) afforded dithioacetal **45** (2.42 g, 90%) as a white solid: mp 123−124 °C; $[\alpha]_D^{20}$ = +1.4 (*c* 2.5, MeOH); IR (cm^{-1}) 3373, 2922, 2898, 1456, 1418, 1122, 1105, 1040, 1013, 983; ^1H NMR (300 MHz, D_2O) δ 4.55 (d, *J* = 3.3 Hz, 1H), 4.01−3.92 (m, 3H), 3.83 (dd, *J* = 2.1, 6.3 Hz, 1H), 3.71−3.60 (m, 2H), 3.08−2.91 (m, 4H), 2.18−2.08 (m, 1H), 1.87−1.72 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 74.5, 71.3, 70.7, 70.6, 62.9, 50.1, 29.8, 29.0, 25.5; HRMS-ESI (*m*/*z*) calcd for $C_9H_{18}NaO_5S_2$ $[M + Na]^+$ 293.0488, found 293.0488.

6-*O*-Trityl-L-talose propane-1,3-diyl dithioacetal (46). Dithioacetal **45** (1.80 g, 0.0067 mol) afforded **46** (2.66 g, 78%) as a white solid: mp 65−69 °C; $[\alpha]_D^{20}$ = −12.0 (*c* 0.7, $CHCl_3$); IR (cm^{-1}) 3419, 3057, 2932, 2901, 1491, 1448, 1266, 1220, 1075, 736, 705, 633; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44−7.20 (m, 15H), 4.42 (d, *J* = 3.6 Hz, 1H), 4.08 (dd, *J* = 4.8, 10.2 Hz, 1H), 4.03−3.98 (m, 1H), 3.91 (dd, *J* = 6.6, 13.5 Hz, 1H), 3.82 (t, *J* = 6.0 Hz, 1H), 3.43−3.22 (m, 5H), 3.06 (d, *J* = 5.7 Hz, 1H), 2.97−2.72 (m, 4H), 2.09−2.01 (m, 1H), 1.97−1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 128.6, 128.0, 127.3, 87.3, 75.4, 73.1, 71.8, 69.7, 65.9, 49.6, 29.5, 28.8, 25.8; HRMS-ESI (*m*/*z*) calcd for $C_{28}H_{32}NaO_5S_2$ $[M + Na]^+$ 535.1583, found 535.1583.

2,3,4,5-Tetra-*O*-benzyl-6-*O*-trityl-L-talose propane-1,3-diyl dithioacetal (47). Compound **46** (16.0 g, 0.0312 mol) afforded **47** (24.4 g, 90%) as a light yellow oil: $[\alpha]_D^{20}$ = +22.9 (*c* 0.7, $CHCl_3$); IR (cm^{-1}) 3060, 3030, 2895, 1495, 1450, 1214, 1106, 1065, 1028, 735, 697, 633; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.18 (m, 35H), 4.94−4.85 (m, 2H), 4.73 (d, *J* = 11.1 Hz, 1H), 4.61−4.56 (m, 2H), 4.49−4.37 (m, 4H), 4.33 (dd, *J* = 2.7, 6.6 Hz, 1H), 4.02 (dd, *J* = 3.6, 7.2 Hz, 1H), 3.87 (dd, *J* = 2.7, 7.2 Hz, 1H), 3.77−3.72 (m, 1H), 3.38 (dd, *J* = 3.3, 10.2 Hz, 1H), 3.11 (dd, *J* = 3.9, 10.2 Hz, 1H), 2.82−2.68 (m, 3H), 2.58−2.50 (m, 1H), 2.04−1.98 (m, 1H), 1.90−1.78 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 139.2, 138.9, 138.6, 138.3, 128.8, 128.3, 128.2, 128.13, 128.12, 128.06, 127.90, 127.85, 127.6, 127.40, 127.36, 127.33, 127.27, 127.2, 126.9, 86.7, 82.0, 80.3 (2C), 79.2, 75.0, 74.3, 72.9, 72.5, 63.3, 50.6, 31.1, 29.9, 26.3; HRMS-ESI (*m*/*z*) calcd for $C_{56}H_{57}O_5S_2$ $[M + H]^+$ 873.3642, found 873.3630.

2,3,4,5-Tetra-*O*-benzyl-L-talose propane-1,3-diyl dithioacetal (48). Compound **47** (24.0 g, 0.0275 mol) afforded tetrabenzyloxylatd alcohol **48** (14.3 g, 82%) as a yellow oil: $[\alpha]_D^{20}$ = +18.0 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3447, 3062, 3030, 2931, 2896, 1496, 1454, 1395, 1210, 1104, 1063, 1028, 908, 737, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.19 (m, 20H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.84 (d, *J* = 11.4 Hz,

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

1H), 4.73−4.68 (m, 2H), 4.64−4.60 (m, 2H), 4.57−4.53 (m, 2H), 4.43 (d, J = 11.4 Hz, 1H), 4.05−4.03 (m, 3H), 3.73−3.62 (m, 3H), 2.89−2.76 (m, 3H), 2.67−2.58 (m, 1H), 2.08−2.04 (m, 2H), 1.95−1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.6, 138.2, 138.1, 128.5, 128.42, 128.35, 128.32, 128.28, 128.0, 127.9, 127.8, 127.7, 127.5, 81.7, 81.0, 80.5, 78.9, 74.5 (2C), 73.1, 72.9, 61.6, 51.4, 31.8, 30.3, 26.5; HRMS-ESI (m/z) calcd for $C_{37}H_{42}NaO_5S_2$ [M + Na]$^+$ 653.2366, found 653.2368.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-L-talose propane-1,3-diyl dithioacetal (49). Tetrabenzyloxylated alcohol **48** (4.70 g, 7.45 mmol) afforded ester **49** (4.36 g, 87%) as a yellow oil: $[\alpha]_D^{20}$ = +14.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2932, 2897, 1742, 1496, 1454, 1365, 1236, 1104, 1028, 908, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.19 (m, 20H), 5.01 (d, J = 11.1 Hz, 1H), 4.83 (d, J = 11.1 Hz, 1H), 4.71−4.55 (m, 5H), 4.51−4.43 (m, 2H), 4.32 (dd, J = 3.6, 12.0 Hz, 1H), 4.15 (dd, J = 5.1, 12.0 Hz, 1H), 4.03−4.01 (m, 3H), 3.82 (dd, J = 4.8, 9.0 Hz, 1H), 2.86−2.78 (m, 3H), 2.67−2.57 (m, 1H), 2.07−1.99 (m, 4H), 1.91−1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 138.7, 138.4, 138.2, 138.1, 128.5, 128.32, 128.29, 128.27, 128.2, 128.1, 127.9, 127.7, 127.6, 127.54, 127.52, 81.7, 79.8, 78.9, 78.4, 74.6, 74.5, 73.1, 73.0, 63.9, 51.0, 31.6, 30.2, 26.4, 21.0; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ [M + Na]$^+$ 695.2472, found 695.2468.

6-*O*-Acetyl-2,3,4,5-tetra-*O*-benzyl-L-talose ethylene acetal (50). Ester **49** (3.0 g, 4.46 mmol) afforded acetal **50** (2.47 g, 88%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2886, 1741, 1496, 1455, 1367, 1234, 1163, 1099, 1028, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.23 (m, 20H), 5.29 (d, J = 3.3 Hz, 1H), 4.87−4.78 (m, 2H), 4.70−4.47 (m, 6H), 4.29 (dd, J = 4.2, 11.7 Hz, 1H), 4.18 (dd, J = 5.4, 11.7 Hz, 1H), 4.02−3.81 (m, 8H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 138.70, 138.67, 138.5, 138.3, 128.4, 128.3, 128.0, 127.92, 127.85, 127.60, 127.57, 127.5, 127.4, 104.2, 79.6, 79.5, 78.8, 78.1, 74.4, 74.3, 73.1, 73.0, 65.4, 65.3, 64.0, 21.0; HRMS-ESI (m/z) calcd for $C_{38}H_{42}NaO_8$ [M + Na]$^+$ 649.2772, found 649.2764.

2,3,4,5-Tetra-*O*-benzyl-L-talose ethylene acetal (51). Compound **50** (2.47 g, 3.94 mmol) afforded alcohol **51** (2.22 g, 96%) as a light yellow oil: $[\alpha]_D^{20}$ = +22.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3466, 3063, 3031, 2884, 1496, 1454, 1395, 1210, 1164, 1100, 1028, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 20H), 5.31 (s, 1H), 4.86−4.78 (m, 2H), 4.72−4.64 (m, 4H), 4.58 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.02−3.81 (m, 7H), 3.74−3.36 (m, 3H), 2.24 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.7, 138.6, 138.2, 128.40, 128.38, 128.3, 128.0, 127.93, 127.91, 127.73, 127.67, 127.51, 127.46, 104.3, 80.6, 80.4, 79.7, 78.4, 74.5, 74.2, 73.3, 72.9, 65.5, 65.3, 61.6; HRMS-ESI (m/z) calcd for $C_{36}H_{40}NaO_7$ [M + Na]$^+$ 607.2666, found 607.2659.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-L-talose ethylene acetal (*ent*-43). Alcohol **51** (2.00 g, 3.42 mmol) afforded aldehyde ***ent*-43** (1.86 g, 93%) as a light yellow oil: $[\alpha]_D^{20}$ = +22.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3438, 3063, 3031, 2882, 1731, 1496, 1455, 1394, 1329, 1210, 1104, 1028, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, J = 1.5 Hz, 1H), 7.29−7.23 (m, 20H), 5.19 (d, J = 4.2 Hz, 1H), 4.82 (d, J = 11.7 Hz, 1H), 4.67−4.53 (m, 5H), 4.51−4.44 (m, 2H), 4.22 (dd, J = 4.5, 6.0 Hz, 1H), 4.07−4.01 (m, 2H), 3.96−3.79 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 138.7, 138.0, 137.8, 137.3, 128.5, 128.38, 128.35, 128.3, 128.1, 128.04, 128.01, 127.8, 127.70, 127.66, 127.5, 103.9, 84.2, 79.5, 79.1, 79.0, 74.0, 73.4 (2C), 73.3, 65.14, 65.08; HRMS-ESI (m/z) calcd for $C_{36}H_{38}NaO_7$ [M + Na]$^+$ 605.2510, found 605.2507.

(3*S*,4*S*,5*R*,6*S*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (*ent*-44). Aldehyde ***ent*-43** (1.86 g, 3.19 mmol) gave a hydroxylamine that was not stable on the silica gel and used into the next step without further purification to afford nitrone ***ent*-44** (687 mg, 40% for 3 steps) as a white solid: mp 150−152 °C; $[\alpha]_D^{20}$ = +44.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2881, 1602, 1496, 1454, 1377, 1227, 1188, 1116, 1098, 1027, 907, 742, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.22 (m, 20H), 7.10 (d, J = 4.5 Hz, 1H), 4.78−4.68 (m, 5H), 4.62−4.58 (m, 2H), 4.46 (d, J = 12.0 Hz, 1H), 4.25 (d, J = 13.8 Hz, 1H), 4.14 (d, J = 4.5 Hz, 1H), 4.11−4.05 (m, 2H), 3.90 (dd, J = 10.5, 13.8 Hz, 1H), 3.46 (dd, J = 2.7, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.11, 138.06, 137.5 (2C), 136.6, 128.7, 128.5, 128.4, 128.3, 128.2, 128.02, 127.99, 127.84, 127.79, 127.7, 127.6, 83.4, 78.7, 76.0, 74.1, 73.7, 73.6, 73.4, 72.1, 64.6; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ [M + H]$^+$ 538.2588, found 538.2585.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6-oxo-L-talose propane-1,3-diyl dithioacetal (52). Tetrabenzyloxylated alcohol **48** (5.50 g, 8.72 mmol) afforded aldehyde **52** (5.12 g, 93%) as a yellow oil: $[\alpha]_D^{20}$ = +22.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2897, 1730, 1496, 1454, 1210, 1097, 1027, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.36−7.21 (m, 20H), 4.92 (d, J = 11.1 Hz, 1H), 4.65−4.51 (m, 7H), 4.45 (d, J = 12.0 Hz, 1H), 4.22 (t, J = 4.5 Hz, 1H), 4.11 (t, J = 5.1 Hz, 1H), 4.04−4.01 (m, 2H), 2.81−2.68 (m, 3H), 2.61−2.52 (m, 1H), 2.04−1.95 (m, 1H), 1.90−1.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 138.3, 137.9, 137.7, 137.2, 128.52, 128.46, 128.4, 128.30, 128.27, 128.2, 128.1, 127.8, 127.7, 127.5, 83.8, 81.3, 80.3, 79.0, 74.5, 73.64, 73.55, 73.3, 50.6, 31.3, 30.0, 26.3; HRMS-ESI (m/z) calcd for $C_{37}H_{40}NaO_5S_2$ [M + Na]$^+$651.2209, found 651.2208.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-L-talose propane-1,3-diyl dithioacetal (53). Aldehyde **52** (5.0 g, 7.95 mmol) afforded **53** (4.80 g, 90%) as a light yellow oil: $[\alpha]_D^{20}$ = +16.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3030, 2894, 1496, 1454, 1396, 1210, 1162, 1095, 1070, 1028, 736, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.21 (m, 20H), 5.19 (d, J = 3.3 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 4.83 (d, J = 11.1 Hz, 1H), 4.75−4.66 (m, 3H), 4.57−4.49 (m, 4H), 4.13−3.98 (m, 4H), 3.95−3.77 (m, 4H), 2.85−2.73 (m, 3H), 2.62−2.53 (m, 1H), 2.05−1.95 (m, 1H), 1.91−1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 139.1, 138.4, 138.3, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 127.34, 127.29, 104.0, 81.8, 80.8, 80.6, 78.6, 74.9, 74.8, 74.7, 72.4, 65.5, 65.2, 50.9, 31.4, 30.1, 26.4; HRMS-ESI (m/z) calcd for $C_{39}H_{44}NaO_6S_2$ [M + Na]$^+$ 695.2472, found 695.2465.

2,3,4,5-Tetra-*O*-benzyl-6-deoxy-6,6-(ethylene-1,2-dioxy)-L-talose (*ent*-38). Compound **53** (4.80 g, 7.13 mmol) afforded aldehyde ***ent*-38** (3.26 g, 78%) as a light yellow oil: $[\alpha]_D^{20}$ = +14.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3063, 3031, 2888, 1731, 1496, 1454, 1332, 1210, 1092, 1072, 1028, 737, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.35−7.17 (m, 20H), 5.14 (d, J = 6.3 Hz, 1H), 4.91 (d, J = 11.7 Hz, 1H), 4.76−4.63 (m, 4H), 4.51−4.44 (m, 2H), 4.21 (d, J = 11.4 Hz, 1H), 4.17−4.06 (m, 3H), 4.02−3.87 (m, 3H), 3.84−3.80 (m, 1H), 3.65 (dd, J = 2.4, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 138.8, 138.4, 137.8, 137.6, 128.6, 128.5, 128.4, 128.30, 128.25, 128.2, 127.98, 127.96, 127.9, 127.7, 127.6, 127.5, 127.4, 127.0, 104.4, 82.5, 80.8, 79.0, 77.8, 74.0, 73.6, 73.2, 72.2, 65.2, 64.8; HRMS-ESI (m/z) calcd for $C_{36}H_{38}NaO_7$ [M + Na]$^+$ 605.2510, found 605.2507.

2,3,4,5-Tetra-*O*-benzyl-1,6-dideoxy-6,6-(ethylene-1,2-dioxy)-1-hydroxylamino-L-talose (*ent*-39). Aldehyde ***ent*-38** (3.20 g, 5.49 mmol) afforded hydroxylamine ***ent*-39** (2.42 g, 73% for 2 steps) as a light yellow oil: $[\alpha]_D^{20}$ = −13.0 (c 0.7, $CHCl_3$); IR (cm^{-1}) 3271, 3063, 3031, 2885, 1496, 1454, 1396, 1330, 1210, 1090, 1070, 1028, 735, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.22 (m, 20H), 5.17 (d, J = 5.7 Hz, 1H), 4.90 (d, J = 11.7 Hz, 1H), 4.79−4.66 (m, 4H), 4.57−4.52 (m, 2H), 4.35 (d, J = 11.4 Hz, 1H), 4.20−4.15 (m, 1H), 4.08 (dd, J = 2.7, 7.5 Hz, 1H), 4.03−3.99 (m, 1H), 3.97−3.82 (m, 4H), 3.75 (dd, J = 3.6, 5.4 Hz, 1H), 3.25−3.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.6, 138.5, 138.4, 128.4, 128.30, 128.25, 128.2, 128.1, 127.93, 127.87, 127.8, 127.7, 127.53, 127.50, 127.4, 104.4, 79.7, 79.1, 78.2, 76.2, 74.4, 74.1, 73.1, 72.2, 65.2, 64.9, 54.1; HRMS-ESI (m/z) calcd for $C_{36}H_{42}NO_7$ [M + H]$^+$ 600.2956, found 600.2946.

(3*S*,4*R*,5*S*,6*S*)-3,4,5,6-Tetrakis(benzyloxy)-3,4,5,6-tetrahydro-7*H*-azepine 1-oxide (*ent*-40). Hydroxylamine ***ent*-39** (200 mg, 0.33 mmol) afforded nitrone ***ent*-40** (130 mg, 73%) as a yellow oil: $[\alpha]_D^{20}$ = −18.0 (c 1.0, $CHCl_3$); IR (cm^{-1}) 3062, 3031, 2870, 1586, 1496, 1454, 1361, 1209, 1097, 1072, 1028, 910, 737, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.23 (m, 20H), 7.05 (d, J = 4.5 Hz, 1H), 4.89−4.79 (m, 3H), 4.77−4.58 (m, 6H), 4.53 (d, J = 12.0 Hz, 1H), 4.11 (d, J = 0.9 Hz, 1H), 3.87 (d, J = 12.9 Hz, 1H), 3.67 (d, J = 9.6 Hz, 1H), 3.54 (dd, J = 2.1, 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 138.5, 138.2, 137.3, 137.2, 128.6, 128.4, 128.3, 128.03, 127.99, 127.94, 127.88, 127.8, 127.69, 127.65, 127.6, 79.7, 79.6, 75.8, 75.3, 74.3, 73.7,

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

73.4, 71.3, 61.2; HRMS-ESI (m/z) calcd for $C_{34}H_{36}NO_5$ $[M + H]^+$ 538.2588, found 538.2584.

Typical procedure for the addition of Grignard reagent to azepane nitrone 7 is represented by the synthesis of hydroxylamin **54a**.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-2-methylazepan-1-ol (54a). To a solution of nitrone 7 (269 mg, 0.50 mmol) in THF (5 mL) under Ar atmosphere was added MeMgI (3 M in ether, 0.33 mL, 1.0 mmol) dropwise at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. Saturated NH_4Cl (20 mL) was added to quench the reaction, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and condensed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 5:1) to afford hydroxylamine **54a** (233 mg, 84%) as a light yellow oil: $[\alpha]_D^{20} = -16.0$ (c 1.0, $CHCl_3$); IR (cm^{-1}) 3254, 3063, 3030, 2906, 2869, 1496, 1454, 1369, 1206, 1092, 1069, 1028, 911, 737, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.21 (m, 20H), 4.72 (d, J = 12.0 Hz, 1H), 4.68−4.61 (m, 2H), 4.57−4.49 (m, 3H), 4.41 (s, 2H), 4.08 (d, J = 8.4 Hz, 1H), 3.85 (s, 2H), 3.66 (d, J = 7.8 Hz, 1H), 3.49−3.39 (m, 2H), 3.25 (dd, J = 1.8, 14.4 Hz, 1H), 1.23 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.6, 138.2, 138.1, 128.40, 128.36, 127.92, 127.89, 127.8, 127.71, 127.66, 80.4, 77.2, 73.8, 73.5, 73.3, 72.7, 71.7, 62.5, 54.2, 17.6; HRMS-ESI (m/z) calcd for $C_{35}H_{40}NO_5$ $[M + H]^+$ 554.2907, found 554.2901.

Hydroxylamines **54b−d** were obtained following the typical procedure.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-2-butylazepan-1-ol (54b). Nitrone 7 (350 mg, 0.65 mmol) and Grignard reagent ^{n}BuMgI (produced by n-butyl iodide and magnisum in ether, 3.25 mmol) gave hydroxylamine **54b** (334 mg, 86%) as a colorless oil: $[\alpha]_D^{20} = -16.0$ (c 1.0, $CHCl_3$); IR (cm^{-1}) 3365, 3063, 3030, 2954, 2927, 2869, 1496, 1454, 1370, 1261, 1206, 1092, 1068, 1028, 911, 803, 736, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.16 (m, 20H), 6.57 (brs, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.70−4.62 (m, 2H), 4.59−4.50 (m, 3H), 4.44−4.36 (m, 2H), 4.15 (d, J = 7.5 Hz, 1H), 3.88 (s, 2H), 3.74 (d, J = 7.5 Hz, 1H), 3.37−3.23 (m, 2H), 3.17−3.13 (m, 1H), 1.48−1.26 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 (2C), 138.2, 137.6, 128.5, 128.40, 128.38, 128.0, 127.8, 127.72, 127.70, 127.6, 127.0, 80.8, 77.2, 76.5, 74.1, 73.5, 72.7, 72.5, 71.8, 68.2, 52.8, 32.4, 28.9, 22.9, 14.1; HRMS-ESI (m/z) calcd for $C_{38}H_{46}NO_5$ $[M + H]^+$ 596.3371, found 596.3373.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-2-*n*-nonylazepan-1-ol (54c). Nitrone 7 (269 mg, 0.50 mmol) and Grignard reagent (produced by n-nonyl bromide and magnisum in THF, 1.50 mmol) gave hydroxylamine **54c** (290 mg, 87%) as a colorless oil: $[\alpha]_D^{20} = -10.0$ (c 1.0, $CHCl_3$); IR (cm^{-1}) 3365, 3063, 3030, 2924, 2854, 1496, 1456, 1362, 1205, 1094, 1069, 1028, 735, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.16 (m, 20H), 6.45 (brs, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.70−4.63 (m, 2H), 4.58−4.51 (m, 3H), 4.44−4.35 (m, 2H), 4.15 (d, J = 9.0 Hz, 1H), 3.88 (s, 2H), 3.74 (d, J = 7.8 Hz, 1H), 3.38−3.22 (m, 2H), 3.17−3.13 (m, 1H), 1.49−1.21 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.2, 137.8, 128.5, 128.42, 128.40, 128.00, 127.98, 127.9, 127.8, 127.7, 127.6, 80.7, 77.2, 76.7, 74.1, 73.5, 72.8, 72.5, 71.9, 68.1, 53.2, 32.6, 32.0, 29.9, 29.7 (2C), 29.5, 26.8, 22.8, 14.2; HRMS-ESI (m/z) calcd for $C_{43}H_{56}NO_5$ $[M + H]^+$ 666.4153, found 666.4158.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-2-phenylazepan-1-ol (54d). Nitrone 7 (350 mg, 0.65 mmol) and Grignard reagent PhMgBr (produced by phenyl bromide and magnisum in THF, 3.25 mmol) gave hydroxylamine **54d** (352 mg, 88%) as a light yellow oil: $[\alpha]_D^{20} = -2.0$ (c 1.0, $CHCl_3$); IR (cm^{-1}) 3430, 3062, 3029, 2916, 2868, 1496, 1454, 1359, 1206, 1097, 1069, 1028, 911, 737, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.18 (m, 23H), 6.90−6.88 (m, 2H), 5.41 (brs, 1H), 4.75−4.53 (m, 6H), 4.41 (d, J = 7.2 Hz, 1H), 4.19 (d, J = 11.7 Hz, 1H), 4.12−4.09 (m, 1H), 3.97 (d, J = 6.0 Hz, 1H), 3.92 (dd, J = 2.1, 6.0 Hz, 1H), 3.87 (d, J = 7.2 Hz, 1H), 3.75 (dd, J = 8.4, 15.3 Hz, 1H), 3.37 (d, J = 15.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 138.9, 138.8, 138.5, 138.0, 128.4, 128.3, 128.2, 128.1, 127.9, 127.80, 127.77, 127.7, 127.6, 127.54, 127.53, 127.4, 127.0, 79.3, 77.9, 77.5, 73.5, 73.2, 73.0, 72.7, 71.43, 71.35, 55.5; HRMS-ESI (m/z) calcd for $C_{40}H_{42}NO_5$ $[M + H]^+$ 616.3058, found 616.3053.

(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-2-((methoxymethoxy)methyl)azepan-1-ol (54e). n-Butyllithium (2.5 M in hexane, 1.02 mL, 2.55 mmol) was slowly added under Ar atmosphere to a cooled (−80 °C) solution of the tributyl-((methoxymethoxy)methyl)stannane (0.930 g, 2.55 mmol) in anhydrous THF (10 mL). The resulting solution was stirred for 15 min, and then nirone 7 (457 mg, 0.85 mmol) in THF (2 mL) was added dropwise. After 30 min at −80 °C the reaction was quenched with sat. NH_4Cl, and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and condensed under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 3:1) to afford the major diastereomer hydroxylamine **54e** (282 mg, 54%) as a colorless oil: $[\alpha]_D^{20} = -15.0$ (c 1.0, $CHCl_3$); IR (cm^{-1}) 3379, 3063, 3030, 2928, 2881, 1496, 1454, 1362, 1208, 1150, 1109, 1060, 1028, 918, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.17 (m, 20H), 6.45 (brs, 1H), 4.78−4.49 (m, 8H), 4.39 (s, 2H), 4.10 (d, J = 9.5 Hz, 1H), 3.95 (d, J = 8.6 Hz, 1H), 3.90−3.79 (m, 3H), 3.65 (dd, J = 5.8, 9.7 Hz, 1H), 3.56−3.44 (m, 2H), 3.35−3.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.7, 138.1, 138.0, 128.54, 128.49, 128.44, 128.38, 127.93, 127.89, 127.85, 127.8, 127.74, 127.72, 127.67, 127.6, 97.0, 77.2, 76.5, 76.2, 73.7, 73.3, 72.7, 72.5, 71.6, 68.8, 66.6, 55.4, 54.5; HRMS-ESI (m/z) calcd for $C_{37}H_{44}NO_7$ $[M + H]^+$ 614.3112, found 614.3113.

(2*S*,3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrakis(benzyloxy)-2-(trifluoromethyl)azepan-1-ol (54f). To a solution of nitrone 7 (200 mg, 0.37 mmol) and trifluoromethyltrimethylsilane (159 mg, 1.12 mmol) in THF (5 mL) was added tetrabutylammonium floride (582 mg, 2.23 mmol) batchwise at 0 °C. The resulting mixture was stirred at rt for 1 h. EtOAc (30 mL) was added, and the organic layer was washed with H_2O (3 × 20 mL). After dried ($MgSO_4$) and condensed under reduced pressure, the residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc 15:1) to afford hydroxylamine **54f** (157 mg, 70%) as a colorless oil: $[\alpha]_D^{20} = -30.0$ (c 1.0, $CHCl_3$); IR (cm^{-1}) 3384, 3063, 3031, 2917, 2872, 1496, 1455, 1364, 1268, 1207, 1165, 1138, 1091, 1028, 912, 843, 737, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.12 (m, 20H), 6.26 (s, 1H), 4.76−4.67 (m, 2H), 4.62 (d, J = 12.0 Hz, 1H), 4.52−4.43 (m, 4H), 4.25 (d, J = 11.1 Hz, 1H), 4.10−3.92 (m, 3H), 3.83 (d, J = 5.7 Hz, 1H), 3.76 (d, J = 5.7 Hz, 1H), 3.47 (dd, J = 9.6, 15.5 Hz, 1H), 3.35 (d, J = 15.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.6, 137.7, 137.6, 128.7, 128.62, 128.56, 128.5, 128.2, 128.10, 128.08, 128.0, 127.9, 127.8, 126.5 (q, J = 280.9 Hz), 77.2, 75.6, 75.2, 73.9, 73.7, 73.0, 72.0, 71.6, 68.3 (q, J = 25.1 Hz), 53.7; HRMS-ESI (m/z) calcd for $C_{35}H_{37}F_3NO_5$ $[M + H]^+$ 608.2618, found 608.2623.

Typical procedure for the hydrogenlysis of the hydroxylamines is represented by the synthesis of azepane iminosugar **55a**.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2-Methylazepane-3,4,5,6-tetraol (55a). To a solution of hydroxylamine **54a** (92 mg, 0.166 mmol) in MeOH (5 mL) and 6 N HCl (1 mL) was added 10% Pd/C (15 mg), and the resulting mixture was stirred under H_2 atmosphere overnight. The catalyst was filtered out, and the filtrate was concentrated at reduced pressure. The residue was dissolved in MeOH and neutralized with aqueous ammonium solution, concentrated in vacuo. The above procedure was repeated for three times to ensure complete neutralization. The residue was then purified by an acidic ion exchanger column (Dowex 5WX8−400, H^+ form, Aldrich), eluting with distilled water (50 mL) and then 1 N NH_4OH (50 mL), affording azepane iminosugar **55a** (29 mg, 98%) as a yellow oil: $[\alpha]_D^{20} = -20.0$ (c 1.0, MeOH); IR (cm^{-1}) 3364, 2961, 2925, 1457, 1050; ^1H NMR (300 MHz, D_2O) δ 4.06−4.01 (m, 2H), 3.94 (dd, J = 2.7, 8.7 Hz, 1H), 3.80 (dd, J = 2.7, 6.1 Hz, 1H), 3.02 (dd, J = 5.4, 14.7 Hz, 1H), 2.88−2.77 (m, 2H), 1.21 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 75.6, 70.7, 69.7, 69.6, 56.2, 48.1, 19.2; HRMS-ESI (m/z) calcd for $C_7H_{16}NO_4$ $[M + H]^+$ 178.1074, found 178.1074.

Azepane iminosugars **55b−f** were obtained following the typical procedure.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2-Butylazepane-3,4,5,6-tetraol (55b). Hydroxylamine **54b** (112 mg, 0.188 mmol) gave azepane iminosugar

dx.doi.org/10.1021/jo400130p | J. Org. Chem. 2013, 78, 3208−3221

55b (38 mg, 92%) as a yellow oil: $[\alpha]_D^{20}$ = −26.0 (*c* 1.0, MeOH); IR (cm^{-1}) 3365, 2956, 2929, 2871, 1457, 1065; ^1H NMR (300 MHz, D_2O) δ 4.05−3.99 (m, 2H), 3.95−3.87 (m, 2H), 3.08 (dd, *J* = 4.8, 14.4 Hz, 1H), 2.89 (dd, *J* = 1.8, 14.4 Hz, 1H), 2.73−2.67 (m, 1H), 1.67−1.30 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 74.3, 70.4, 69.13, 69.08, 61.3, 48.4, 32.8, 27.4, 21.9, 13.2; HRMS-ESI (*m*/*z*) calcd for $C_{10}H_{22}NO_4$ $[M + H]^+$ 220.1543, found 220.1542.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2-*n*-Nonylazepane-3,4,5,6-tetraol (55c). Hydroxylamine **54c** (67 mg, 0.10 mmol) gave azepane iminosugar **55c** (27 mg, 93%) as a yellow oil: $[\alpha]_D^{20}$ = −18.0 (*c* 1.0, MeOH); IR (cm^{-1}) 3339, 2884, 2853, 1457, 1119, 1065; ^1H NMR (300 MHz, CD_3OD) δ 3.98−3.90 (m, 3H), 3.83 (dd, *J* = 2.0, 5.1 Hz, 1H), 3.03 (dd, *J* = 4.8, 14.1 Hz, 1H), 2.89 (dd, *J* = 2.1, 14.1 Hz, 1H), 1.66−1.34 (m, 16H), 0.94 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 76.4, 72.6, 71.6, 71.3, 63.0, 49.8, 35.6, 33.1, 31.0, 30.8 (2C), 30.5, 27.4, 23.8, 14.5; HRMS-ESI (*m*/*z*) calcd for $C_{15}H_{32}NO_4$ $[M + H]^+$ 290.2326, found 290.2322.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2-Phenylazepane-3,4,5,6-tetraol (55d). Hydroxylamine **54d** (125 mg, 0.203 mmol) gave azepane iminosugar **55d** (47 mg, 97%) as a yellow oil: $[\alpha]_D^{20}$ = −24.0 (*c* 1.0, MeOH); IR (cm^{-1}) 3357, 2909, 1450, 1068, 1031, 763, 703; ^1H NMR (300 MHz, D_2O) δ 7.46−7.34 (m, 5H), 4.27 (dd, *J* = 3.3, 8.1 Hz, 1H), 4.21 (dd, *J* = 3.3, 8.1 Hz, 1H), 4.11−4.08 (m, 1H), 4.05 (dd, *J* = 2.4, 8.1 Hz, 1H), 3.68 (d, *J* = 8.1 Hz, 1 H), 3.09 (dd, *J* = 5.4, 14.4 Hz, 1H), 2.94 (dd, *J* = 2.7, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 142.5, 128.9, 127.8, 127.2, 74.2, 71.3, 70.4, 70.0, 64.9, 49.9; HRMS-ESI (*m*/*z*) calcd for $C_{12}H_{18}NO_4$ $[M + H]^+$ 240.1230, found 240.1228.

(2*R*,3*R*,4*R*,5*R*,6*R*)-2-(Hydroxymethyl)azepane-3,4,5,6-tetraol (55e). Hydroxylamine **54e** (120 mg, 0.195 mmol) gave azepane iminosugar **55e** (35 mg, 93%) as a yellow oil: $[\alpha]_D^{20}$ = −22.0 (*c* 1.0, MeOH); IR (cm^{-1}) 3366, 2925, 1416, 1106, 1076, 1030; ^1H NMR (300 MHz, D_2O) δ 4.09−4.05 (m, 2H), 3.98−3.91 (m, 2H), 3.78 (dd, *J* = 3.9, 11.4 Hz, 1H), 3.60 (dd, *J* = 7.5, 11.4 Hz, 1H), 3.15 (dd, *J* = 5.4, 14.4 Hz, 1H), 2.89−2.76 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 71.0, 70.5, 69.8, 69.7, 62.9, 62.6, 49.1; HRMS-ESI (*m*/*z*) calcd for $C_7H_{16}NO_5$ $[M + H]^+$ 194.1023, found 194.1023.

(2*S*,3*R*,4*R*,5*R*,6*R*)-2-(Trifluoromethyl)azepane-3,4,5,6-tetraol (55f). Hydroxylamine **54f** (112 mg, 0.203 mmol) gave azepane iminosugar **55f** (40 mg, 94%) as a yellow oil: $[\alpha]_D^{20}$ = −20.0 (*c* 1.0, MeOH); IR (cm^{-1}) 3364, 2933, 1387, 1263, 1146, 1068; ^1H NMR (300 MHz, D_2O) δ 4.35 (dd, *J* = 2.4, 6.6 Hz, 1H), 4.15 (dd, *J* = 2.1, 8.4 Hz, 1H), 4.04−4.00 (m, 2H), 3.47−3.36 (m, 1H), 3.10 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.84 (dd, *J* = 2.1, 15.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 126.1 (q, *J* = 279.8 Hz), 71.0, 70.3, 70.2, 68.5, 61.8 (q, *J* = 26.3 Hz), 47.6; HRMS-ESI (*m*/*z*) calcd for $C_7H_{13}F_3NO_4$ $[M + H]^+$ 232.0791, found 232.0791.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by The National Basic Research Program of China (No. 2012CB822101 and No. 2011CB808603), The National Natural Science Foundation of China (No. 21102149), Grant-in-Aid for Scientific Research (C) (No: 23590127) (AK) from the Japanese Society for the Promotion of Science (JSPS) and Summit PLC (UK).

■ REFERENCES

(1) (a) Compain, P.; Martin, O. *Iminosugars: From Synthesis to Therapeutic Applications*; Wiley-VCH: Weinheim, 2007. (b) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999. (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (d) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

(2) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 512.

(3) Morís-Varas, F.; Qian, X. H.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647.

(4) (a) Andreana, P. R.; Sanders, T.; Janczuk, A.; Warrick, J. I.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 6525. (b) Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F. *Tetrahedron* **2002**, *58*, 6907. (c) Fuentes, J.; Gasch, C.; Olano, D.; Pradera, M. Á.; Repetto, G.; Sayago, F. J. *Tetrahedron: Asymmetry* **2002**, *13*, 1743. (d) Tilekar, J. N.; Patil, N. T.; Jadhav, H. S.; Dhavale, D. D. *Tetrahedron* **2003**, *59*, 1873. (e) Dhavale, D. D.; Chaudhari, V. D.; Tilekar, J. N. *Tetrahedron Lett.* **2003**, *44*, 7321. (f) Painter, G. F.; Eldridge, P. J.; Falshaw, A. *Bioorg. Med. Chem.* **2004**, *12*, 225. (g) Moutel, S.; Shipman, M.; Martin, O. R.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2005**, *16*, 487 and references cited therein.

(5) (a) Li, H. Q.; Blériot, Y.; Chantereau, C.; Mallet, J. M.; Sollogoub, M.; Zhang, Y. M.; Rodríguez-García, E.; Vogel, P.; Jiménez-Barbero, J.; Sinaÿ, P. *Org. Biomol. Chem.* **2004**, *2*, 1492. (b) Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; PrakashaReddy, J. *J. Org. Chem.* **2004**, *69*, 4760. (c) Li, H. Q.; Schütz, C.; Favre, S.; Zhang, Y. M.; Vogel, P.; Sinaÿ, P.; Blériot, Y. *Org. Biomol. Chem.* **2006**, *4*, 1653.

(6) (a) Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2002**, *43*, 331. (b) Li, H. Q.; Zhang, Y. M.; Vogel, P.; Sinaÿ, P.; Blériot, Y. *Chem. Commun.* **2007**, 183. (c) Jabgunde, A. M.; Kalamkar, N. B.; Chavan, S. T.; Sabharwal, S. G.; Dhavale, D. D. *Bioorg. Med. Chem.* **2011**, *19*, 5912. (d) Deschamp, J.; Mondon, M.; Nakagawa, S.; Kato, A.; Alonzi, D. S.; Butters, T. D.; Zhang, Y. M.; Sollogoub, M.; Blériot, Y. *Bioorg. Med. Chem.* **2012**, *20*, 641.

(7) (a) Li, H. Q.; Marcelo, F.; Bello, C.; Vogel, P.; Butters, T. D.; Rauter, A. P.; Zhang, Y. M.; Sollogoub, M.; Blériot, Y. *Bioorg. Med. Chem.* **2009**, *17*, 5598. (b) Marcelo, F.; He, Y.; Yuzwa, S. A.; Nieto, L.; Jiménez-Barbero, J.; Sollogoub, M.; Vocadlo, D. J.; Davies, G. D.; Blériot, Y. *J. Am. Chem. Soc.* **2009**, *131*, 5390.

(8) (a) Bande, O. P.; Jadhav, V. H.; Puranik, V. G.; Dhavale, D. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1176. (b) Bande, O. P.; Jadhav, V. H.; Puranik, V. G.; Dhavale, D. D. *Synlett* **2009**, 1959. (c) Lindsay, K. B.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 4173. (d) Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *Org. Biomol. Chem.* **2006**, *4*, 2549. (e) Torres-Sánchez, M. I.; Borrachero, P.; Cabrera-Escribano, F.; Gómez-Guillén, M.; Angulo-Álvarez, M.; Diánez, M. J.; Estrada, M. D.; López-Castro, A.; Pérez-Garrido, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3897.

(9) Chagnault, V.; Compain, P.; Lewinski, K.; Ikeda, K.; Asano, N.; Martin, O. R. *J. Org. Chem.* **2009**, *74*, 3179.

(10) For reviews of cyclic nitrone, see: (a) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485. (b) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem.—Eur. J* **2009**, *15*, 7808. For recent synthesis and applications of cyclic nitrone, see: (c) D'Adamio, G.; Goti, A.; Parmeggiani, C.; Moreno-Clavijo, E.; Robina, I.; Cardona, F. *Eur. J. Org. Chem.* **2011**, 7155. (d) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *J. Org. Chem.* **2011**, *76*, 4139. (e) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (f) Gilles, P.; Py, S. *Org. Lett.* **2012**, *14*, 1042. (g) Wu, S.-F.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *Tetrahedron* **2010**, *66*, 1653. (h) Tsou, E.-L.; Chen, S.-Y.; Yang, M.-H.; Wang, S.-C.; Cheng, T.-R. R.; Cheng, W.-C. *Bioorg. Med. Chem.* **2008**, *16*, 10198. (i) Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93. (j) Yu, C.-Y.; Huang, M.-H. *Org. Lett.* **2006**, *8*, 3021. (k) Hu, X.-G.; Bartholomew, B.; Nash, R. J.; Wilson, F. X.; Fleet, G. W. J.; Nakagawa, S.; Kato, A.; Jia, Y.-M.; van Well, R.; Yu, C.-Y. *Org. Lett.* **2010**, *12*, 2562. (l) Zhang, W.; Sato, K.; Kato, A.; Jia, Y.-M.; Hu, X.-G.; Wilson, F. X.; van Well, R.; Horne, G.; Fleet, G. W. J.; Nash, R. J.; Yu, C.-Y. *Org. Lett.* **2011**, *13*, 4414. (m) Wang, W.-B.;

Huang, M.-H.; Li, Y.-X.; Rui, P.-X.; Hu, X.-G.; Zhang, W.; Su, J.-K.; Zhang, Z.-L.; Zhu, J.-S.; Xu, W.-H.; Xie, X.-Q.; Jia, Y.-M.; Yu, C.-Y. *Synlett* **2010**, 488. (n) Chan, T.-H.; Chang, Y.-F.; Hsu, J.-J.; Cheng, W.-C. *Eur. J. Org. Chem.* **2010**, 5555.

(11) Using the general alkylation conditions described in ref 10, no reaction occurred when **2** was heated in THF, MeOH or DMF with excess of $NH_2OH{\cdot}HCl$ and bases; gradually elevating the temperature to reflux in DMF only led to the decomposition of **2**.

(12) Ackermann, L.; El Tom, D.; Furstner, A. *Tetrahedron* **2000**, *56*, 2195.

(13) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

(14) Gella, C.; Ferrer, È.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6365.

(15) (a) Chackalamannil, S.; Wang, Y. G. *Tetrahedron* **1997**, *53*, 11203. (b) Oppolzer, W.; Deerberg, J.; Tamura, O. *Helv. Chim. Acta* **1994**, *77*, 554. (c) Gracias, V.; Zeng, Y. B.; Desai, P.; Aubé, J. *Org. Lett.* **2003**, *5*, 4999.

(16) Kölln, O.; Redlich, H.; Frank, H. *Synthesis* **1995**, 1383.

(17) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806.

(18) (a) Tite, T.; Tsimilaza, A.; Lallemand, M. C.; Tillequin, F.; Leproux, P.; Libot, F.; Husson, H. P. *Eur. J. Org. Chem.* **2006**, 863. (b) Mondon, M.; Fontelle, N.; Désiré, J.; Lecornué, F.; Guillard, J.; Marrot, J.; Blériot, Y. *Org. Lett.* **2012**, *14*, 870.

(19) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776.

(20) Raju, R.; Castillo, B. F.; Richardson, S. K.; Thakur, M.; Severins, R.; Kronenberg, M.; Howell, A. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4122.