# *Articles*

## Reaction of *O*-Benzyl- and 4,6-*O*-Benzylidene-D-Gluco- and D-Galactopyranose Derivatives with Amide-Stabilized Sulfur Ylides: Stereoselectivity and Reactivity

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The reaction of *N*,*N*-diethyl-2-(dimethylsulfuranylidene)acetamide (**1**) with protected monosaccharides has been extended to several *O*-benzyl- and 4,6-*O*-Benzylidene-D-gluco- and -D-galactopyranose derivatives. When the monosaccharide is 2,3,4,6-tetra-*O*-benzyl-D-glucose (**6**) or D-galactose (**9**), elimination of the 3-benzyloxy substituent occurs, to give the unsaturated epoxyamides **7** and **10**, respectively, in reasonable yields and poor stereoselectivity. On the other hand, the reaction of **1** with the 4,6-*O*-benzylidene-D-glucopyranose derivatives **11**, **14**, and **17** yielded the corresponding epoxyamides **12**, **15a:15b**, and **18a:18b** in good yields and variable stereoselectivity. In accordance with previous studies concerning the configurational assignments for the epoxide derivatives **3**, **5a**, and **21**,[6] obtained from **2**, **4**, and **20**, respectively, the present article confirms the role of the hydroxyl group at C-2 on the stereselectivity of the reaction. Thus, when the C-2 OH is unprotected (**4**, **11**, **20**), the major epoxide formed has the configuration 2*S*, 3*R* (epoxyamides **5a**, **12**, and **21**). Conversely, derivatives with the hydroxyl group protected at C-2, or 2-deoxy sugars (**2**, **14**, and **17**), yield as the major epoxides the corresponding 2*R*, 3*S* isomers (**3**, **15b**, and **18b**).

### Introduction

Highly functionalized acyclic monosaccharide derivatives are products of interest in organic synthesis with utility as building blocks[1] for the synthesis of bioactive compounds.[2] The elongation of the monosaccharide chain with the incorporation of an epoxide group is especially interesting, taking into account the diverse synthetic possibilities that this functional group offers.[3] In addition, the stereochemistry of the epoxide ring is an important factor for the synthesis of bioactive products. Recently, we reported the reaction of *N*,*N*-diethyl 2-(dimethylsulfuranylidene)acetamide (**1**) with acyclic aldehydosugars,[4] furanose,[5] and pyranose[6,7] derivatives to give acyclic epoxyamides in good yields and high stereoselectivity. These results encouraged further studies using other pyranose derivatives. It is worthy to note that these preliminary studies revealed the influence of the protecting group at the C-2 hydroxyl of the starting sugars on the yield and stereoselectivity for the resulting epoxyamide. These results also aimed to correlate the absolute configuration of the major resulting *trans*-epoxyamides with the presence or absence of a protecting group of the C-2 hydroxyl. It was shown that the reaction of ylide **1** with compound **2** by the two-phase method[8] produced only the stereoisomer **3** in a quantitative yield and with a configuration (2*R*,3*S*) opposite to that of the major product **5a** (2*S*,3*R*) obtained in a lower yield from **4**.

To demonstrate the correlation between stereoselectivity and OH protection at C-2, in this article we report new reactions of **1** with different monosaccharide derivatives. In this investigation, we have selected *O*-benzyl ethers and 4,6-*O*-benzylidene pyranose derivatives of D-glucose and D-galactose.

### Results and Discussion

Initially, we considered the reactions of the perbenzyl derivatives, taking into account that benzyl ethers are valuable protecting groups widely used in carbohydrate chemistry. However, it is known that benzyl monosaccharides are sometimes unstable under basic conditions,

(1) Lichtenthaler, F. W. *Pure Appl. Chem.* **1978**, *50*, 1342. (b) Vasella, A. *Chiral Building Blocks in Enantiomer Synthesis-ex Sugars*. In *Modern Synthetic Methods*; Scheffold, R., Ed.; 1980, p 174. (c) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161. (d) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3−30.

(2) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon: New York, 1983. (b) Fraser-Reid, B.; Anderson, R. C. *Carbohydrate Derivatives in the Asymmetric Synthesis of Natural Products, Fortschr. Chem. Org. Naturst.* Springer-Verlag: Wien, **1980**, p 1. (c) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677−1716.

(3) (a) Seebach, D.; Weidmann, B.; Wilder, L. *Modern Synthetic Methods 1983*, Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, **1983**, p 323. (b) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885−8927.

(4) Valpuesta-Fernández, M.; Durante Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1990**, *46*, 7911−7922.

(5) Valpuesta-Fernández, M.; Durante Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1993**, *49*, 9547−9560.

(6) López-Herrera, F. J.; Heras-López, A.; Pino-González, M. S.; Sarabia-García, F. *J. Org. Chem.* **1996**, *61*, 8839−8848.

(7) López-Herrera, F. J.; Sarabia-García, F.; Heras-López, A.; Pino-González, M. S. *J. Org. Chem.* **1997**, *62*, 6056−6059.

(8) López-Herrera, F. J.; Pino-González, M. S.; Sarabia-García, F.; Heras-López, A.; Ortega-Alcántara, J. J.; Pedraza-Cebrián, M. G. *Tetrahedron: Asymmetry* **1996**, *7*, 2065−2071 and refs cited therein.

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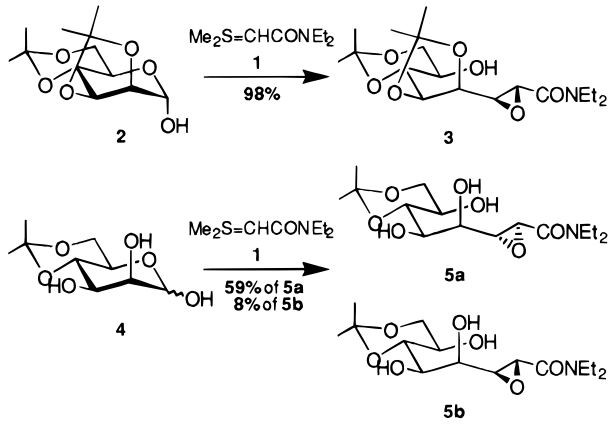
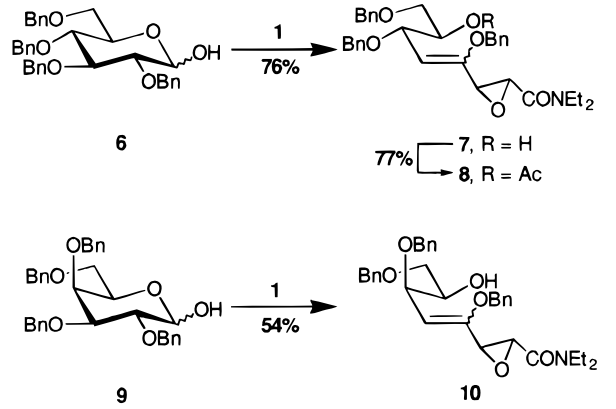
**Scheme 1**




**Scheme 2**




affording elimination products. Thus, reactions of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6**) and 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**9**) with the ylide **1** yielded the corresponding $\gamma,\delta$-unsaturated-$\alpha,\beta$-*trans*-epoxyamides **7** and **10**, respectively, as a result of the elimination of benzyl alcohol at C-3 of **6** and **9** and subsequent condensation with **1**. Attempts to avoid this elimination were in all cases unsuccessful. A possible explanation for this observation is that the basic medium generated by the presence of the ylide caused abstraction of the proton at the $\alpha$ position adjacent to the carbonyl group of the starting sugar, giving the corresponding $\alpha,\beta$-unsaturated aldehyde, which reacted with **1**. Similar benzylic eliminations have been previously reported for the Wittig reaction of several tetra-*O*-benzyl-D-glucopyranoses with ethoxycarbonylmethylene triphenylphosphorane.[9] This elimination was likewise observed in reactions of **6** with methylene dimethylsulfurane and oxosulfurane.[10]

In light of these discouraging results, we decided to study the reaction of **1** with the 3-*O*-benzyl- and 2-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**11**)[11] and (**14**),[12] respectively. These sugars were chosen to avoid the elimination at C-3 and also to introduce some conformational restriction to the open oxo-form of these derivatives by the presence of the 4,6-*O*-benzylidene ring, to influence the stereoselectivity of the ylide addition process.

**Table 1. Reaction of Ylide 1 with Derivatives 6, 9, 11, 14, and 17**

| starting sugar | solvent | equiv of **1** | reaction time (h) | yield (%) | product (ratio) |
|---|---|---|---|---|---|
| **6** | MeCN/THF[a] (7:1) | 1.0 | 72 | 76 | **7** (1:1.4)[c] |
| **6** | $CH_2Cl_2/H_2O$[b] | 2.0 | 23 | 67 | **7** (1:1.3)[c] |
| **9** | $CH_2Cl_2/H_2O$[b] | 1.0 | 7 | 54 | **10** (1:1) |
| **11** | THF[a] | 4.0 | 12 | 54 | **12** (100:0) |
| **14** | THF[a] | 8.0 | 21 | 93 | **15a:15b** (1:2) |
| **17** | THF[a] | 2.0 | 12 | 30 | **18a:18b** (1:1.6) |

[a] Reaction with ylide **1**. [b] Two-phase method. [c] *Z*, *E* assignments were not made.

Thus, the reaction of **11** with **1**, with the presence of a free hydroxyl group at C-2, should (i) lead to the preferential formation of the epoxyamide **12**, and (ii) protect the proton at C-2 against abstraction due to the higher acidity of the OH group. In accord with these assumptions, and as it is shown in Table 1, epoxyamide **12** was obtained as the only product. The configurational assignment at C-2 and C-3 was confirmed by benzylation of **12** to the corresponding tri-*O*-benzyl derivative **13**, the same product obtained by benzylation of **21**, and stereochemistry has previously been established.[6]

For 2-*O*-benzyl derivative **14**, its reaction with **1** should furnish the *trans*-epoxyamide with the opposite configuration at C-2 and C-3 with regard to **12**. In fact, this reaction provided epoxyamide **15b** as the major product but in rather lower stereoselectivity (see Table 1). Similarly, the stereochemistry for the major isomer **15b** was established by benzylation of a pure sample of the minor isomer **15a**, obtaining **13**.

The disappointing yields obtained in the reactions in which the OH at C-2 of the starting sugar is free can be ascribed to a Payne rearrangement[13] of the resulting epoxyamide to produce a 3,4-epoxyamide. Subsequent intramolecular cyclizations of 3,4-epoxyamides should give C-furanosides as we have previously reported for **20**.[6] For the case in which the OH is protected at C-2, such as the glucopyranose derivative **14**, epoxyamides were obtained in very high yield (95%), although with low stereoselectivity. This poor stereoselectivity may be the result of two competitive electrostatic and dipolar repulsions between the carbonyl group in the open-chain form of **14**, and the partial oxyanions generated at C-3 or C-5, of which the latter appears to be dominant.

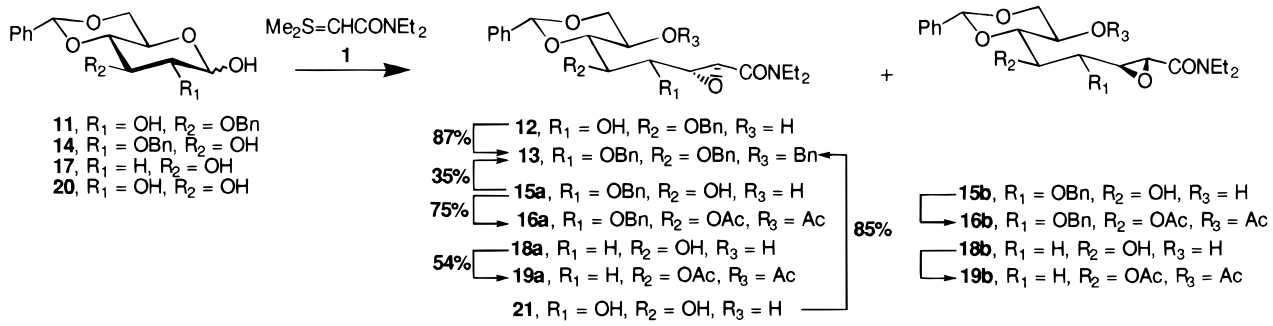
Finally, the reaction was extended to other C-2 modified 4,6-*O*-benzylidene-D-glucopyranoses. Thus, 2-deoxy-D-glucopyranose derivative **17**[14] was reacted with **1** to obtain a mixture of the corresponding *trans*-epoxyamides **18a** and **18b** in low yield (30%) and stereoselectivity (1:1.6). We attribute this low stereoselectivity to the absence of a C-2 hydroxyl and the accompanying higher conformational flexibility around the C1−C2 and C2−C3 bonds in the open form of the sugar. This flexibility allows an increased separation of the carbonyl group and the oxyanions generated at C-3 or C-5.

## Conclusion

The present study confirms the crucial role of the protecting group at the hydroxyl on C-2 of the starting

(9) Nicotra, F.; Ronchetti, F.; Russo, G.; Toma, L. *Tetrahedron Lett.* **1984**, *49*, 5697−5700.
(10) Fréchou, C.; Dheilly, L.; Beaupère, D.; Uzan, R.; Demailly, G. *Tetrahedron Lett.* **1992**, *33*, 5067−5070.
(11) Prentice, N.; Cuendet, L. S.; Smith, F. *J. Am. Chem. Soc.* **1956**, *78*, 4439−4440.
(12) Lubineau, A.; Queuneau, Y. *Tetrahedron* **1989**, *45*, 6697−6712.
(13) Payne, G. B. *J. Org. Chem.* **1962**, 3819−3822.
(14) Overend, W. G.; Stacey, M.; Stanek, J. *J. Chem. Soc.* **1949**, 2841−2845.

**Scheme 3**




4,6-*O*-benzylidene-D-glucopyranose. Furthermore, the size of the substituent at C-2 and the presence of a 4,6-*O*-benzylidene group were shown to be important factors in determining the yield and stereoselectivity for these reactions.

## Experimental Section

**General Techniques.** All reactions were carried out under a dry argon atmosphere using freshly distilled solvents unless otherwise noted. Reactions were monitored by TLC on E. Merck silica gel plates (0.25 mm) and visualized using UV light (254 nm) or heating with *p*-anisaldehyde solution (340 mL of ethanol, 9.2 mL of *p*-anisaldehyde, 12.5 mL of sulfuric acid, and 3.75 mL of acetic acid). Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040−0.063 mm). Melting points are given uncorrected. NMR spectra were recorded at 200 MHz on a Bruker WP200SY spectrometer at ambient temperature. Chemical shifts are reported relative to the residual solvent peak. Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (bs). Coupling constants are expressed as *J* values in Hertz units. Mass spectra were recorded on a Hewlett-Packard 5988A instrument. Microanalyses were performed by the "Servicio de Microanálisis" of the University of Málaga. Exact masses were recorded on a Kratos MS 80 RFA instrument of the University of Seville. Specific rotations were measured with a Perkin-Elmer 241 polarimeter.

***N,N*-Diethyl-2,3-anhydro-5-deoxy-4,6,8-tri-*O*-benzyl-D-*altro*- and D-*gluco*-oct-4-enonamides (7). Method A (one phase):** To a solution of **6**[15] (0.5 g, 0.92 mmol) in 20 mL of $CH_3CN$/THF (7:1 v/v) was added portionwise **1** (0.2 g, 1.03 mmol). After 3 days, TLC ($CH_2Cl_2$:MeOH:hexanes, 10:1:2) showed the depletion of **6** and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 25% AcOEt in hexanes) followed by purification on preparative TLC furnished an inseparable mixture of epoxyamides **7** (1:1.4) (383 mg, 76%) as a colorless oil. **Method B (two phases):** To a cooled solution of **6** (0.5 g, 0.92 mmol) in $CH_2Cl_2$ (20 mL) was sequentially added *N,N*-diethylcarbamoylmethyl dimethylsulfonium chloride (0.5 g, 2.31 mmol) and sodium hydroxide (2.5 mL, 50% w/v) with vigorous stirring. After 22−23 h at room temperature, the reaction mixture was diluted with water (20 mL). The organic phase was separated and the aqueous phase was extracted with *tert*-butyl methyl ether (4 × 20 mL). The combined organic solution was dried ($Na_2SO_4$), filtered, and the solvents removed under vacuum. Flash column chromatography (silica gel, 25% AcOEt in hexanes) furnished an inseparable mixture of epoxyamides **7a and 7b** (1:1.4) (331 mg, 67%): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.30−7.10 (m, 15 H), 5.25 and 5.20 (2 d, two isomers, $J$ = 9.6 Hz and $J'$ = 9.3 Hz, 1 H), 4.94−4.74 (2 d, 2 H), 4.56−4.28 (m, 5 H), 3.91−3.80 (m, 1 H), 3.67 (2d, $J$ = 1.9 Hz and $J'$ = 2.0 Hz, 1 H), 3.65 and 3.55 (2d, $J$ = 1.9 Hz and $J'$ = 2.0 Hz, 1 H), 3.54−3.33 (m, 6 H), 2.37 and 2.30 (2d, $J$ = 4.7 Hz, and $J'$ = 4.9 Hz, 1 H), 1.25−1.05 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 165.4, 165.3, 153.3, 152.5, 138.0, 137.8, 137.7, 136.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.1, 113.6, 113.1, 74.4, 73.5, 73.1, 72.6, 72.1, 71.8, 70.7, 70.6, 70.2, 70.0, 56.1, 53.1, 52.8, 41.3, 40.6, 14.6, 12.7; FAB HRMS (NBA/CsI) *m/e* 678.1848, M + $Cs^+$ calcd for $C_{33}H_{39}O_6N$ 678.1832.

***N,N*-Diethyl-7-*O*-acetyl-2,3-anhydro-5-deoxy-4,6,8-tri-*O*-benzyl-D-*altro* and D-*gluco*-oct-4-enonamides (8).** Epoxyamide **7** (95 mg, 0.17 mmol) was dissolved in pyridine (2 mL) and treated with acetic anhydride (0.06 mL, 0.57 mmol) at 0 °C. After 12 h at room temperature, the crude mixture was diluted with $CH_2Cl_2$ (5 mL), washed with 10% aqueous HCl (5 mL), and the organic layer was separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 × 5 mL) and the combined organic solution was dried ($Na_2SO_4$), filtered, and concentrated. The crude mixture was purified by preparative TLC (silica gel, AcOEt) to afford an irresoluble mixture of two isomers of **8** (79 mg, 77%) as a colorless oil: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.31−7.18 (m, 15 H), 5.30−5.05 (m, 2 H), 4.90−4.70 (2 × 2d, 2 H), 4.69−4.50 (m, 1 H), 4.48−4.19 (m, 4 H), 3.72−3.50 (m, 4 H), 3.50−3.25 (m, 4 H), 2.02 (s, 3 H), 1.15 (q, $J$ = 7.3 Hz, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 170.2, 170.0, 165.4, 165.3, 153.6, 152.8, 137.9, 137.8, 136.7, 136.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 113.5, 112.0, 74.8, 73.3, 73.1, 72.9, 71.7, 70.9, 70.4, 70.3, 68.3, 68.2, 56.0, 55.5, 53.3, 52.8, 41.4, 40.7, 21.0, 14.7, 12.7.

***N,N*-Diethyl-2,3-anhydro-5-deoxy-4,6,8-tri-*O*-benzyl-D-*threo*-L-*ido* and L-*galacto*-oct-4-enonamides (10).** To a stirred solution of **9**[15] (50 mg, 0.09 mmol) in $CH_2Cl_2$ (2 mL) was added *N,N*-diethylcarbamoylmethyl dimethylsulfonium chloride (22 mg, 0.10 mmol) and aqueous NaOH (0.5 mL, 50% w/v) at 0 °C. After 1 h at 0 °C, the reaction mixture was allowed to stir at room temperature for 7 h. Water (4 mL) was added, the organic phase was separated, and the aqueous phase extracted with *tert*-butyl methyl ether (2 × 4 mL). The combined organic solution was dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude oil thus obtained was subjected to preparative TLC (silica gel, 10:1:2 $HCCl_3$/MeOH/hexanes) to obtain an irresoluble mixture of the epoxyamides **10a** and **10b** (25 mg, 54%) as a colorless oil: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.35−7.20 (m, 15 H), 5.19 and 5.15 (2d, $J$ and $J'$ = 9.7 Hz, 1 H), 4.93−4.69 (m, 2 H), 4.57−4.18 (m, 6 H), 3.70 (m, 1 H), 3.69 and 3.55 (2d, $J$ = 2.1 Hz and $J'$ = 2.0 Hz, 1 H), 3.55−3.33 (m, 6 H), 2.68 and 2.66 (2 d, $J$ and $J'$ = 4.2 Hz, 1 H), 1.30−1.17 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 166.1, 165.9, 153.1, 138.1, 137.0, 128.5−126.9, 113.4, 112.9, 74.5, 72.9, 72.6, 68.4, 56.1, 55.8, 53.6, 53.2, 41.5, 40.8, 14.9, 14.8, 12.9; FAB HRMS (NBA/CsI) *m/e* 678.1847, M + $Cs^+$ calcd for $C_{33}H_{39}O_6N$ 678.1832.

**3-*O*-Benzyl-4,6-*O*-benzylidene-D-glucopyranose (11).** Powdered zinc chloride (2.3 g) was added portionwise to a mixture of benzaldehyde (25 mL) and 3-*O*-benzyl-D-glucose[11] (4.6 g, 17.0 mmol). The reaction mixture was stirred magnetically at 25 °C for 5 h and the resulting suspension was poured into an Erlenmeyer flask containing ice-water (50 mL) and hexanes (50 mL) to separate a yellow oil. After cooling for several hours, the precipitate was filtered and washed with cold water and hexanes. The residue was dissolved in methanol/water and neutralized with sodium bicarbonate. The crude product obtained after evaporation was poured into water (50

(15) Compounds **6** and **9** were purchased from Sigma Aldrich.

mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic layer was washed with cold water (1 × 25 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate/diethyl ether as a white solid (3.2 g, 53% yield): $[\alpha]^{25}_D$ +19.0° (c 2.3, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.50−7.20 (m, 10 H), 5.57 (s, 1 H), 5.29 (d, $J$ = 3.1 Hz, 1 H), 5.02−4.72 (m, 3 H), 4.40−4.25 (m, 1 H), 4.08 (dd, $J$ = 4.3, 9.8 Hz, 1 H), 3.92−3.41 (m, 3 H), 2.50 (d, $J$ = 5.4 Hz, 1 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 138.3, 138.1, 137.3, 137.1, 129.0−126.0, 101.3, 101.2, 97.1, 92.9, 82.0, 81.4, 80.3, 78.3, 75.2, 74.9, 74.4, 72.2, 69.0, 68.6, 66.5, 62.7; Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19; found: C, 67.52; H, 6.48.

**2-*O*-Benzyl-4,6-*O*-benzylidene-D-glucopyranose (14).** To a solution of 2-*O*-benzyl-D-glucose[12] (4.9 g, 18.1 mmol) in DMF (25 mL) was added benzaldehyde dimethyl acetal (6.0 mL, 40.0 mmol) and *p*-toluenesulfonic acid (35 mg, 0.18 mmol) at 50 °C. After 9 h, DMF was removed under reduced pressure and the residue purified on column chromatography (silica gel, 10:1:8 $CHCl_3$:MeOH:hexanes). The obtained product was crystallized from ethyl ether to obtain pure **14** (1.5 g, 23% yield, 1:1 mixture of $\alpha$:$\beta$ anomers) as a white solid: $R_f$ = 0.81 (silica gel, 10:1:2 $HCCl_3$:MeOH:hexanes); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.60−7.22 (m, 10 H), 5.49 (s, 1 H), 5.22 (dd, $J$ = 3.5, 12.0 Hz, 0.5 H), 5.00−4.74 (m, 2.5 H), 4.40−4.18 (m, 1 H), 4.05 (dd, $J$ = 3.8, 8.8 Hz, 1 H), 3.84−3.22 (m, 4 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 137.9, 137.3, 136.8, 136.7, 129.6−126.0, 101.8, 101.6, 97.3, 91.5, 82.6, 80.9, 80.2, 79.3, 73.1, 72.9, 70.1, 68.7, 68.4, 65.7, 62.0.

**4,6-*O*-Benzylidene-2-deoxy-D-glucopyranose (17).** Compound **17** was prepared from 2-desoxi-D-*arabino*-hexose[14] (3.0 g, 18.3 mmol) by treatment with benzaldehyde dimethyl acetal (9.0 mL, 60.0 mmol) and *p*-toluenesulfonic acid (68 mg, 0.36 mmol) according to the procedure described above for the preparation of **14**, obtaining pure **17** (2.1 g, 46%) as a white solid: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.62−7.35 (m, 5 H), 5.56 (s, 0.5 H), 5.54 (s, 0.5 H), 5.34 (s, 0.5 H), 4.86 (m, 0.5 H), 4.35−4.13 (m, 2 H), 4.09−3.94 (m, 1 H), 3.93−3.28 (m, 4 H), 2.85−2.60 (m, 1 H), 2.40−2.15 (m, 1 H), 1.82−1.52 (m, 1 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 137.2, 137.1, 129.1−126.2, 101.9, 101.8, 94.4, 92.4, 84.0, 83.7, 69.0, 68.6, 67.9, 66.3, 65.2, 62.6, 37.7, 36.5.

***N,N*-Diethyl-2,3-anhydro-5-*O*-benzyl-6,8-*O*-benzylidene-D-*erythro*-L-*galacto*-octonamide (12).** A solution of 3-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**11**) (1.0 g, 2.8 mmol) in THF (40 mL) was cooled to 0 °C and then *N*,*N*-diethylsulfuranylidene acetamide (**1**) was added dropwise (2.0 g, 11.4 mmol). The mixture was allowed to stir at room temperature for 12 h. After this time, the reaction mixture was neutralized with 0.1 N HCl and the solvents were concentrated. The crude product was extracted with $CHCl_3$ (3 × 100 mL) and the combined organic layer was dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10:1:8 $HCCl_3$:MeOH:hexanes) provided pure epoxyamide **12** (0.7 g, 54% yield) as a white solid. Recrystallization was performed from $CHCl_3$/$Et_2O$: $[\alpha]^{25}_D$ +13.7° (c 1.8, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.55−7.22 (m, 10 H), 5.48 (s, 1 H), 4.78 (s, 2 H), 4.29 (dd, $J$ = 4.3, 11.0 Hz, 1 H), 4.25−3.92 (m, 4 H), 3.70 (d, $J$ = 2.4 Hz, 1 H), 3.59 (dd, $J$ = 9.8, 10.4 Hz, 1 H), 3.54−3.23 (m, 6 H), 3.15 (d, $J$ = 5.4 Hz, 1 H), 1.11 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 166.5, 137.8, 137.6, 128.8−126.1, 100.8, 81.1, 79.9, 74.7, 70.9, 69.3, 62.4, 58.4, 50.7, 41.4, 40.7, 14.4, 12.8; FAB HRMS (NBA/NaI) *m/e* 494.2146, M + $Na^+$ calcd for $C_{26}H_{33}O_7N$ 494.2155.

***N,N*-Diethyl-2,3-anhydro-4,5,7-tri-*O*-benzyl-6,8-*O*-benzylidene-D-*erythro*-L-*galacto*-octonamide (13).** To a cooled solution (0 °C) of epoxyamide **12** (100 mg, 0.21 mmol) in THF (2 mL) was added NaH (32 mg, 0.80 mmol, 60% in mineral oil). The reaction mixture was stirred at 0 °C for 30 min and then tetrabutylammonium bromide (9 mg, 0.03 mmol) and benzyl bromide (0.03 mL, 0.27 mmol) were sequentially added. The resulting mixture was allowed to stir at 25 °C for 2 days. After this time, MeOH (0.25 mL) was carefully added at 0 °C, then ether (5 mL) and saturated aqueous $NH_4Cl$ solution (5 mL) were sequentially added and the organic layer was separated. The aqueous phase was extracted with ether (2 × 5 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% EtOAc in hexanes) provided pure tri-*O*-benzyl epoxyamide **13** (120 mg, 87%). Similarly, compound **13** (145 mg, 85%) was prepared from epoxyamide **21** (100 mg, 0.26 mmol) according to the procedure described above. **[13]**: $[\alpha]^{25}_D$ +4.5° (q 2.3, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.53−7.22 (m, 20 H), 5.53 (s, 1 H), 4.92−4.33 (m, 8 H), 4.19 (dd, $J$ = 1.2, 9.2 Hz, 1 H), 4.07 (dd, $J$ = 1.8, 6.1 Hz, 1 H), 3.97 (m, 1 H), 3.69 (t, $J$ = 10.4 Hz, 1 H), 3.62 (t, $J$ = 4.9 Hz, 1 H), 3.49−3.27 (m, 3 H), 2.98−2.81 (m, 2 H), 0.95 (t, $J$ = 6.7 Hz, 3 H), 0.78 (t, $J$ = 6.7 Hz, 3 H); 13C NMR (50.3 MHz, $CDCl_3$) $\delta$ 166.7, 137.9, 137.7, 137.3, 128.6−125.9, 101.1, 79.0, 78.7, 76.8, 74.1, 72.4, 71.3, 69.4, 68.0, 54.8, 50.7, 41.1, 40.4, 14.1, 12.9; FAB HRMS (NBA/CsI) *m/e* 784.7091, M + $Cs^+$ calcd for $C_{40}H_{45}O_7N$ 784.7079.

***N,N*-Diethyl-2,3-anhydro-4-*O*-benzyl-6,8-*O*-benzylidene-D-erythro-L-*galacto* and L-*ido*-octonamides (15a and 15b).** Epoxyamides **15a** and **15b** (1.35 g, 93%) were prepared from 2-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**14**) (1.1 g, 3.1 mmol) by treatment with *N*,*N*-diethylcarbamoylmethyl dimethyl sulfonium (4.2 g, 23.96 mmol) in THF (50 mL) according to the procedure described above for **12**. Purification by flash column chromatography (silica gel, 50% AcOEt in hexanes) provided pure epoxyamide **15b** (250 mg) and a 1:1 mixture of **15a**:**15b** (1.1 g, total yield 93%) as colorless oils. **[15b]**: $[\alpha]^{25}_D$ −3.8° (c 7.1, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.54−7.24 (m, 10 H), 5.51 (s, 1 H), 4.90 and 4.63 (2d, 2 H), 4.28 (dd, $J$ = 4.3, 10.4 Hz, 1 H), 4.11 (m, 1 H), 4.05−3.00 (m, 12 H), 1.12 (q, $J$ = 6.7 Hz, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 166.4, 137.6, 137.5, 128.6−125.9, 100.7, 80.8, 80.1, 72.6, 70.8, 69.4, 60.7, 57.5, 50.6, 41.2, 40.6, 14.4, 12.7; FAB HRMS (NBA/CsI) *m/e* 494.2147, M + $Cs^+$ calcd for $C_{26}H_{33}O_7N$ 494.2155.

**15a (from a mixture with 15b):** $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 166.7, 137.7, 137.5, 128.7−125.8, 100.8, 81.4, 80.0, 72.2, 60.0, 57.7, 50.3, 41.2, 40.7, 14.4, 12.7.

***N,N*-Diethyl-2,3-anhydro-4,5,7-tri-*O*-benzyl-6,8-*O*-benzylidene-D-*erythro*-L-*galacto*-octonamide (13) from 15a.** A solution of **15a** (90 mg, 0.19 mmol) in THF (2 mL) was treated with NaH (27 mg, 0.70 mmol, in 60% mineral oil), tetrabutylammonium bromide (11 mg, 0.03 mmol), and benzyl bromide (0.04 mL, 0.27 mmol) at 0 °C according to the procedure described above for **13** from **12**. Purification by TLC (silica gel, 25% EtOAc in hexanes) provided pure **13** (44 mg, 35%), the spectroscopic and physical properties of which were identical to **13** obtained above.

***N,N*-Diethyl-2,3-anhydro-5,7-di-*O*-acetyl-4-*O*-benzyl-6,8-*O*-benzylidene-D-*erythro*-L-*galacto* and L-*ido*-octonamides (16a and 16b).** Acetylation of a mixture of **15a** and **15b** (157 mg, 0.33 mmol) was accomplished with acetic anhydride (0.64 mL, 6.66 mmol) in pyridine (1.3 mL) by the same procedure described above for **7**, to obtain, after purification by flash column chromatography (silica gel, 20% EtOAc in hexanes), pure **16b** (21 mg) and a 1:1 mixture of **16a**:**16b** (104 mg, 75% overall).

**[16b]:** $[\alpha]^{25}_D$ −5.2° (c 1.2, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.45−7.23 (m, 10 H), 5.35 (dd, $J$ = 1.8 Hz, 1 H), 5.33 (s, 1 H), 4.89−4.54 (m, 3 H), 4.54 (dd, $J$ = 4.9, 10.4 Hz, 1 H), 4.37 (m, 1 H), 4.16 (dd, $J$ = 2.5, 9.8 Hz, 1 H), 3.74 (dd, $J$ = 6.7, 9.2 Hz, 1 H), 3.57 (t, $J$ = 10.4 Hz, 1 H), 3.55−3.24 (m, 6 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 1.15−1.10 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 169.6, 169.8, 165.3, 136.8, 128.9−125.8, 101.1, 76.5, 75.1, 72.9, 68.2, 67.8, 61.5, 57.9, 50.7, 41.2, 40.5, 20.5, 14.6, 12.6; FAB HRMS (NBA/CsI) *m/e* 688.1543, M + $Cs^+$ calcd for $C_{30}H_{37}O_9N$ 688.1523. **16a (from a mixture with 16b):** $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.51−7.21 (m, 10 H), 5.53 (s, 1 H), 5.21 (dd, $J$ = 1.8 Hz, 1 H), 4.96−4.36 (m, 4 H), 4.54 (m, 1 H), 4.24−3.20 (m, 8 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 1.24−1.07 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 170.0, 165.6, 163.7, 129.0−125.9, 101.2, 75.8, 72.3, 71.4, 70.3, 69.2, 61.7, 56.2, 49.3, 41.2, 40.5, 20.5, 14.4, 12.6.

***N,N*-Diethyl-2,3-anhydro-4-deoxy-6,8-*O*-benzylidene-D-*glycero*-D-*ido* and D-*galacto*-octonamides (18a and 18b).** Epoxyamides **18a** and **18b** (1.11 g, 69%, 1:1.6 mixture) were prepared from **17** (1.1 g, 4.3 mmol) by treatment with *N*,*N*-

diethylcarbamoylmethyl dimethyl sulfonium (1.5 g, 8.5 mmol) in THF (40 mL) according to the procedure described above for **12**. Epoxyamides **18a:18b** could not be separated by purification by flash column chromatography (silica gel, 10:3:4 $HCCl_3$:MeOH:hexanes). Mixture **18a:18b** (1:1.6): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.50−7.12 (m, 5 H), 5.47 (s, 1 H), 4.45−3.11 (m, 11 H), 2.34−2.06 (m, 2 H), 1.27−1.05 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 167.1, 137.6, 137.5, 128.8−126.1, 100.8, 83.6, 83.0, 71.0, 67.1, 66.5, 61.1, 60.8, 56.3, 56.0, 53.8, 53.0, 41.5, 40.8, 35.4, 34.3, 14.5, 12.8; FAB HRMS (NBA/NaI) *m/e* 366.1922, M + $H^+$ calcd for $C_{19}H_{28}O_6N$ 366.1917.

***N,N*-Diethyl-2,3-anhydro-4-deoxy-5,7-di-*O*-acetyl-6,8-*O*-benzylidene-D-*glycero*-D-*ido* and D-*galacto*-octonamides (19a and 19b).** Acetylation of a mixture of **18a** and **18b** (73 mg, 0.33 mmol) was accomplished with acetic anhydride (1.90 mL, 6.66 mmol) in pyridine (3.8 mL) by the same procedure described above for **7**, to obtain, after purification by flash column chromatography (silica gel, 20% EtOAc in hexanes), a mixture of **19a** and **19b** (48 mg, 54%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.54−7.20 (m, 5 H), 5.55 and 5.53 (2s, two isomers, 1H), 5.47 (m, 1 H), 4.98 (m, 1 H), 4.38 (dd, $J$ = 5.3, 10.5 Hz, 1 H), 4.05 (m, 1 H), 3.77−3.56 (m, 2H, H-3, H-8a), 3.56−3.18 (m, 6 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 1.27−1.05 (m, 6 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 170.3, 169.6, 166.1, 136.8, 130.7−126.0, 101.3, 78.5, 78.2, 67.7, 67.6, 67.1, 61.9, 61.8, 54.5, 54.4, 53.3, 53.1, 41.3, 40.6, 31.8, 31.6, 20.7, 20.5, 14.6, 14.5, 12.6; FAB HRMS (NBA/NaI) *m/e* 472.1938, M + $Na^+$ calcd for $C_{23}H_{31}O_8N$ 472.1947.

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**Supporting Information Available:** Experimental procedures and $^{13}$C NMR spectra (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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