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Stereoselective Synthesis of (*E*)-Mannosylidene Derivatives Using the Wittig Reaction

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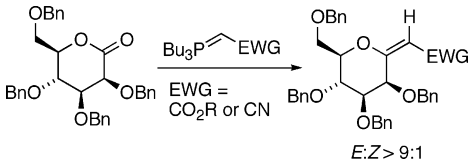
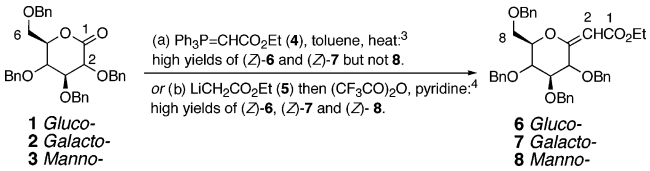


Stabilized ylides $Bu_3P{=}CH(EWG)$, where EWG is an ester or nitrile group, react with 2,3,4,6-tetra-*O*-benzylmannono-1,5-lactone giving high yields of mannosylidene derivatives; in contrast to the glucose and galactose analogues, the (*E*)-mannosylidenes are predominant (*E*:*Z* > 9:1), thus minimizing dipole−dipole repulsions in the Wittig reactions. NMR indicates chair-like conformations for solutions of the (*E*)-mannopyranosylidenes, but not for those (*Z*)-isomers where data are available (EWG = CN or CO_2Et). X-ray crystallography shows an approximately twist-boat conformation for the tetra-*O*-benzyl-protected (*Z*)-mannosylideneacetonitrile.

Glycosylidenes, also known as *exo*-glycals, are carbohydrate analogues containing an exocyclic C=C bond; their synthesis was reviewed recently.[1] Chapleur pioneered the use of Wittig reactions on sugar lactones to form glycosylidenes.[2] For example, reactions of $Ph_3P{=}CHCO_2Et$ and $Ph_3P{=}CHCN$ with isopropylidene-protected lactone derivatives of glucofuranose, mannofuranose, and mannopyranose occurred in good yields; although some of these reactions showed little stereoselectivity, the *E*-geometrical isomers of the products were often favored and *E*/*Z* ratios of up to 3.5:1 were reported. Xie obtained high yields of the (*Z*)-isomers from reactions between $Ph_3P{=}CHCO_2Et$ (**4**) and benzyl-protected gluco- or galactopyranolactones (Scheme 1); the corresponding mannonolactone **3** easily underwent β-elimination of benzyl alcohol, which limited the yield of glycosylidene product to 28%.[3] Lin showed that treatment of lactones **1**−**3** with the lithium enolate of ethyl acetate, followed by dehydration by trifluoroacetic anhydride−pyridine,

SCHEME 1. Routes to Glycosylidenes from Lactones (a) Using the Wittig Reaction[3] or (b) by Enolate Addition Then Dehydration[4]



1 *Gluco-*
2 *Galacto-*
3 *Manno-*

6 *Gluco-*
7 *Galacto-*
8 *Manno-*

gave high yields of (*Z*)-glycosylidene derivatives of all three sugars.[4] Lin's mannosylidene product had different physical properties from the one described by Xie; further investigation indicated that Xie's product was a glucose derivative, generated by epimerization at C-2 of mannose under the harsh conditions needed for the Wittig reaction.[4] We have shown that stabilized ylides derived from tri-*n*-butylphosphine react easily with the protected glucono- and galactonolactones **1** and **2** to give predominantly (*Z*)-glycosylidene products.[5] We now demonstrate that reaction of these ylides with the mannonolactone **3** avoids the epimerization experienced with $Ph_3P{=}CHCO_2Et$ and generates new (*E*)-mannosylidene derivatives, thus making our approach complementary to Lin's in the mannose series.

Reaction of the protected mannonolactone **3** with the ylides **9a**−**9c** (2−3 equiv) in toluene at 80 °C (Scheme 2) required 12−24 h, as judged by the disappearance of the carbonyl stretch of the lactone **3** at 1771 cm^{-1}. ^1H NMR showed that each crude product comprised a main carbohydrate component **8**, with δ_H 5.6−5.7 (1H, s) for the C=CH group. These oily products were isolated by flash chromatography (84−91% yields). The ethyl ester product was *not* the isomer (*Z*)-**8b** that Lin had prepared by the enolate chemistry in Scheme 1 and for which the C=CH proton chemical shift is reported[4] to be 5.27. The relatively low field signals seen for the vinylic and allylic protons in all our ester products suggested that they were novel (*E*)-mannosylidenes (see refs 2a and 5 for discussion of the chemical shifts of glycosylidene geometrical isomers). NOESY spectra were obtained for the methyl and *tert*-butyl esters (*E*)-**8a** and (*E*)-**8c** and showed no correlations between the vinylic (H-2) and allylic (H-4) protons in either case, again supporting the assignment of *E*-geometry to these products. Evidence for the retention of the *manno*-configuration was provided by the magnitudes of the ^3J couplings between protons attached to the sugar ring and by nickel boride reduction of these esters to give predominantly β-mannosyl C-glycoside derivatives. Comparison with NMR data[4,5] for the isomeric (*E*)- and (*Z*)-glucosylidene derivatives excluded the possibility that any of the main products had arisen by epimerization of mannose to glucose. However, from the reaction with the *tert*-butyl ester **9c**, we were able to isolate a small amount (4% yield) of the glucosylidene (*Z*)-**6c**, which had been the main product when the ylide **9c** reacted with the protected gluconolactone **1**.[5]

$Bu_3P{=}CHCN$ (**9d**) is more nucleophilic than the esters **9a**−**9c**, and its reaction with lactone **3** was complete after 20 h reflux in dichloromethane. In this case, two geometrical isomers, (*E*)-**8d** and (*Z*)-**8d**, were formed in a 9:1 ratio as determined by ^1H

(1) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263−292.
(2) (a) Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 750−752. (b) Lakhrissi, Y.; Taillefumier, C.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 417−421.
(3) (a) Molina, A.; Czernecki, S.; Xie, J. *Tetrahedron Lett.* **1998**, *39*, 7507−7510. (b) Xie, J.; Molina, A.; Czernecki, S. *J. Carbohydr. Chem.* **1999**, *18*, 481−498.
(4) Yang, W.-B.; Yang, Y.-Y.; Gu, Y.-F.; Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem.* **2002**, *67*, 3773−3782.
(5) Gascón-López, M.; Motevalli, M.; Paloumbis, G.; Bladon, P.; Wyatt, P. B. *Tetrahedron* **2003**, *59*, 9349−9360.

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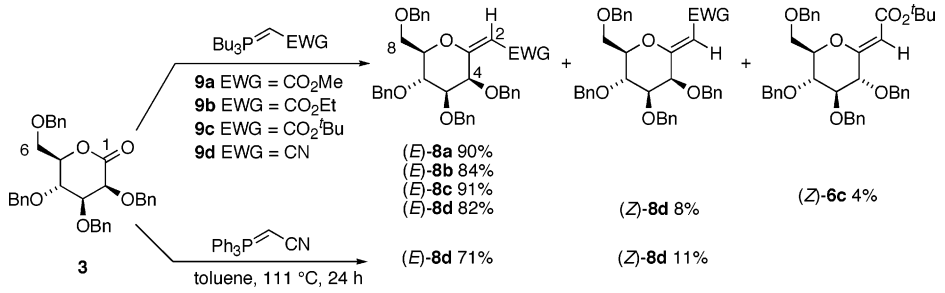
SCHEME 2. Reactions of Protected Mannonolactone 3 with Stabilized Ylides to Form Mainly (*E*)-Mannosylidenes (*E*)-8a−d



NMR. These products were then separated by flash chromatography, and the structure of the crystalline minor isomer was confirmed by X-ray diffraction (Figure 1). ^{1}H NMR spectra supported the assigned geometries: only the minor isomer (*Z*)-**8d** showed a NOE between the vinylic (H-2) and allylic (H-4) protons. Both the vinylic and allylic protons of the (*E*)-**8d** appear further downfield than their counterparts in the (*Z*)-isomer [for (*E*)-**8d** $\delta_{H-2} = 4.98$ and $\delta_{H-4} = 4.60$, whereas for (*Z*)-**8d** $\delta_{H-2} = 4.84$ and $\delta_{H-4} = 4.24$]. $Ph_3P{=}CHCN$ reacted much more slowly than $Bu_3P{=}CHCN$ with lactone **3** (>22 h in toluene at 111 °C was required for consumption of **3**, despite using a 3-fold excess of ylide), but the major (*E*)- and minor (*Z*)-mannosylidene products **8d** were again isolated. Thus, significant epimerization during Wittig reactions of lactone **3** with stabilized ylides has only been seen for $Ph_3P{=}CHCO_2Et$,[4] where the combination of triphenylphosphonium ylide with an ester substituent leads to particularly low nucleophilicity. The mechanism of this process is likely to involve base-induced enolization of lactone **3**.[6]

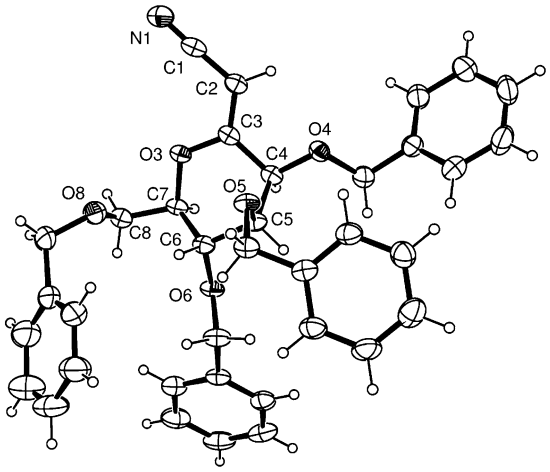


FIGURE 1. Molecular structure of the (*Z*)-mannosylidene nitrile (*Z*)-**8d** (ellipsoids at 50% probability).

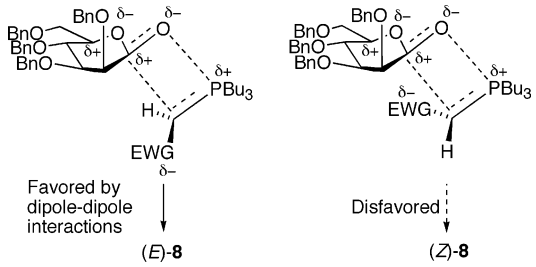


FIGURE 2. Competing pathways leading to (*E*)- and (*Z*)-mannosylidene derivatives.

The change in the favored geometry of the Wittig product from *Z* in the glucose and galactose series to *E* in the case of mannose derivatives must clearly arise from the different configuration at C-2 of mannose. It has been suggested that the formation of (*Z*)-glycosylidenes from protected gluconolactones and galactonolactones avoids steric repulsions between the ester or nitrile substituent from the ylide and equatorial C-2 benzyloxy substituents.[3b] Similarly, Lin has proposed that the dehydration of lactols, noted in Scheme 1, leads to (*Z*)-glycosylidene derivatives in the glucose, galactose, and mannose series because this minimizes the development of 1,3-allylic strain with the C-2 substituent during the deprotonation of intermediate oxonium ions.[4] It has been recognized that strong dipole−dipole interactions are present during Wittig reactions.[7] We consider that if Wittig reactions on lactones are kinetically controlled[8] then dipolar repulsion will tend to maximize the separation between the pyranose ring oxygen and the electron-withdrawing group on the ylide, thus favoring the transition state leading to the (*E*)-glycosylidene (Figure 2). However, steric effects favor the (*Z*)-isomer, so when these effects are relatively large, they may explain the outcome of the reactions on lactones **1** and **2** as noted previously. The C-2 configuration of mannose could make the development of 1,3-allylic strain less important in determining the stereochemical outcome of Wittig reactions on lactone **3**, so allowing electrostatic effects to favor the formation of products with the *E*-configuration. Another significant difference between lactones **1**, **2**, and **3** is that, as a result of steric effects, the mannose derivative **3** is most likely to undergo nucleophilic attack on its α-face.

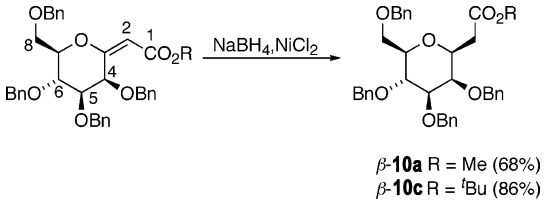
X-ray and solution phase NMR show that some benzyl-protected glucosylidenes and galactosylidenes, such as the (*Z*)-galactosylidene nitrile (*Z*)-**7d**, adopt chair-like conformations but that this is not the case for glucose derivatives or for compounds where the exocyclic double bond had the *E*-geometry.[5] Conjugation of the ring oxygen with an electron-withdrawing group on the double bond and 1,3-allylic strain can disfavor chair-like arrangements, and the latter effect is particularly significant for the (*E*)-isomers.

(6) This might be caused by basic contaminants rather than the basicity of the ylide itself; Xie has noted in ref 3b that epimerizations of other lactones occurred only when ylides were not adequately washed free of base.

(7) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 13468−13469.

(8) Isomerization of enol ethers with electron-withdrawing substituents occurs relatively easily, and 2-(ethoxycarbonylmethylene)tetrahydropyran isomerizes spontaneously on standing: (a) Sauvé, G.; Deslongchamps, P. *Synth. Commun.* **1985**, *15*, 201−212. We found that (*E*)-**8d** and (*Z*)-**8d** did *not* interconvert when heated in toluene (111 °C, 24 h). Wittig reactions on cyclic anhydrides often proceed via acyclic acylphosphorane intermediates to yield enol lactone products of *E*-geometry, even though the (*Z*)-isomers are more stable: (b) Abell, A. D.; Massy-Westropp, R. A. *Aust. J. Chem.* **1982**, *35*, 2077−2087.

SCHEME 3. Nickel Boride Reduction of Mannosylidene Esters



X-ray crystallography on the (*Z*)-mannosylidene nitrile (*Z*)-**8d** (Figure 1) reveals a similar conformation to the *gluco*-analogue, intermediate between a boat and a twist-boat.[9] For a comparison of crystallographically determined torsion angles for the three nitriles (*Z*)-**6d**, (*Z*)-**7d,** and (*Z*)-**8d**, see the Supporting Information. The C(7)−O(3)−C(3)═C(2) torsion angle in (*Z*)-**8d** is 170°, which is consistent with the ring oxygen atom being sp^2-hybridized, allowing overlap of a lone pair in an oxygen p-orbital with the π-system of the C═C−C≡N unit.

^{1}H NMR coupling constant data show that the solution phase conformations of the ethyl ester (*Z*)-**8b** and the nitrile (*Z*)-**8d** are not chairs and may resemble that adopted by (*Z*)-**8d** within the crystal.[10] For both these compounds, the conjugation between the vinyl ether unit and the attached electron-withdrawing group appears to determine the conformation of the ring. On the other hand, the esters (*E*)-**8a**−**c** and the nitrile (*E*)-**8d** have coupling constants consistent with chair-like conformations; such arrangements are not seen for the analogous (*E*)-glucosylidenes and galactosylidenes because the presence of an equatorial benzyloxy group at C-4 leads to greater 1,3-allylic strain.[5]

The hydrogenation of glycosylidene derivatives has been investigated by Xie and co-workers.[3b] These authors found that the glucosylidene derivative (*Z*)-**6b**, which bears a CO_2Et substituent on the C═C bond, could be reduced by the combination of nickel chloride and sodium borohydride ("nickel boride") in methanol to give predominantly the α-C-glucoside without cleavage of the *O*-benzyl protecting groups, whereas the galactosylidene analogue (*Z*)-**7b** underwent reduction under these conditions to give mainly the β-C-galactoside. We have found that similar reductions of the mannosylidene esters (*E*)-**8a** and (*E*)-**8c** gave the β-C-mannosides β-**10a**, a known compound,[11,12] and β-**10c** in 68 and 86% yields, respectively (Scheme 3). Reduction of the ethyl ester (*E*)-**8b** gave a 75% combined yield of two diastereoisomeric reduction products, which were considered on the basis of ^{1}H NMR to be the known[4,12] C-glycosides β-**10b** and α-**10b** in a 93:7 ratio. This consistent preference for β-product in the reduction of mannosylidene derivatives indicates that the presence of the 2-benzyloxy substituent on the β-face in the mannose series directs the delivery of hydrogen to the α-face.

Our studies in the mannose series have further demonstrated the synthetic value of ester- and nitrile-stabilized tributylphosphonium ylides for transforming sugar lactones into glycosylidene derivatives. It is pleasing both that the epimerization of mannose, previously observed when using a related triphenylphosphonium ylide, is minimized and that the high selectivity for the *E*-product geometry complements the *Z*-selectivity reported for other approaches to mannosylidenes.

Experimental Section

Representative Wittig Procedure: (*E*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-*manno*-oct-2-enonic acid, methyl ester (*E*)-8a. $Bu_3P{=}CHCO_2Me$ (360 mg, 1.31 mmol) and 2,3,4,6-tetra-*O*-benzyl-D-mannono-1,5-lactone[13] (**3**) (330 mg, 0.61 mmol) were heated together in toluene (1.5 mL) at 80 °C for 15 h, after which IR showed the consumption of the starting lactone and the appearance of the title compound. The solvent was evaporated to leave a residue which was purified by flash chromatography (petrol−diethyl ether, 5:1) to give (*E*)-**8a** (326 mg, 90%) as a colorless oil: $[\alpha]^{24}_D$ +76 (*c* 1, CH_2Cl_2); ν_{max} (film)/cm^{-1} 1717 (C═O) and 1653 (C═C); δ_H (400 MHz, $CDCl_3$) 3.66 (1H, dd, *J* = 9.0, 2.7 Hz, H-5), 3.67 (3H, s, OMe), 3.74−3.81 (3H, m, H-7, H-8a, H-8b), 4.30 (1H, t, *J* = 9.0 Hz, H-6), 4.53 (2H, d, *J* = 11.8 Hz, 2 × PhC*H*), 4.53 (1H, d, *J* = 12.3 Hz, PhC*H*), 4.57 (1H, d, *J* = 12.3 Hz, PhC*H*), 4.64 (1H, d, *J* = 12.1 Hz, PhC*H*), 4.68 (1H, d, *J* = 12.0 Hz, PhC*H*), 4.73 (1H, d, *J* = 11.9 Hz, PhC*H*), 4.92 (1H, d, *J* = 10.9 Hz, PhC*H*), 5.70 (1H, s, H-2), 5.78 (1H, d, *J* = 2.7 Hz, H-4), 7.17−7.37 (20H, m, 4 × Ph); δ_C (101 MHz, $CDCl_3$, assignments supported by HSQC) 51.4 (OMe), 69.0, 69.3, 71.1, 71.3, 73.4, 73.7, 75.1 (Ph*C*), 80.7 (C-5), 81.3 (C-7 or C-8), 105.0 (C-2), 127.4, 127.7, 127.7, 127.77, 127.81, 128.09, 128.18, 128.40, 128.43, 138.0, 138.1, 138.3, 138.5, 166.3 (C-3 or C-1), 167.2 (C-1 or C-3); *m*/*z* (ESI) M + H$^+$ 595.2690 [$C_{37}H_{39}O_7$ requires 595.2691].

Representative Reduction: Methyl (2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)acetate β-10a. A mixture of (*E*)-**8a** (104 mg, 0.171 mmol) and $NiCl_2{\cdot}6H_2O$ (20.7 mg, 0.087 mmol) in methanol (3 mL) was cooled to 0 °C and treated with $NaBH_4$ (120 mg, 3.17 mmol) in small portions over 1 h. After a further 1 h, acetic acid (0.1 mL) was added, followed by CH_2Cl_2 (15 mL). The mixture was filtered and the filtrate concentrated, then flash chromatography (petrol−Et_2O, gradient from 3:1 to 2:1) gave β-**10a** (71 mg, 68%) as a colorless oil: $[\alpha]^{24}_D$ +9.7 (*c* 1.28, $CHCl_3$) {lit[11] $[\alpha]^{20}_D$ +8.0 (*c* 1, $CHCl_3$), lit[12] $[\alpha]^{20}_D$ +8.5 (*c* 1, $CHCl_3$)}; ν_{max} (film)/cm^{-1} 1738 (C═O); δ_H (400 MHz, $CDCl_3$, assignments supported by COSY) 2.59 (1H, dd, *J* = 16.4, 7.3 Hz, C*H*CO), 2.70 (1H, dd, *J* = 16.4, 6.1 Hz, C*H*CO), 3.47 (1H, ddd, *J* = 9.7, 5.5, 1.9 Hz, H-5), 3.59 (3H, s, CO_2Me), 3.61−3.70 (2H, m, H-2, H-6a), 3.73 (1H, dd, *J* = 11.1, 1.9 Hz, H-6b), 3.79 (1H, "t", *J* = 6.7 Hz, H-1), 3.89−3.90 (1H, m, H-3), 3.90 (1H, t, *J* = 9.6 Hz, H-4), 4.53 (1H, d, *J* = 12.1 Hz, PhC*H*), 4.56 (1H, d, *J* = 10.8 Hz, PhC*H*), 4.60 (1H, d, *J* = 11.7 Hz, PhC*H*), 4.63 (1H, d, *J* = 11.6 Hz, PhC*H*), 4.74 (1H, d, *J* = 11.7 Hz, PhC*H*), 4.80 (1H, d, *J* = 11.7 Hz, PhC*H*), 4.87 (1H, d, *J* = 10.8 Hz, PhC*H*), 5.00 (1H, d, *J* = 11.7 Hz, PhC*H*), 7.16−7.39 (20H, m, 4 × Ph); δ_C (101 MHz, $CDCl_3$) 36.0, 51.6, 69.6, 72.7, 73.4, 74.4, 74.55, 74.64, 75.18, 75.19, 79.9, 85.1, 127.4, 127.57, 127.62, 127.69, 127.9, 128.0, 128.28, 128.33, 128.5, 138.35, 138.38, 138.50, 138.56, 171.6; *m*/*z* (ESI) M + NH_4^+ 614.3113 [$C_{38}H_{44}NO_7$ requires 614.3112].

Acknowledgment. We thank Mrs. B. Stein and the staff of the EPSRC National Mass Spectrometry Service Centre, Swansea. We appreciate the helpful advice of Drs. Christine and Peter Bladon.

Supporting Information Available: Comparison of selected crystallographic torsion angles (degrees) for the (*Z*)-mannosylidene

(9) Bérces, A.; Whitfield, D. M.; Nukada, T. *Tetrahedron* **2001**, *57*, 477−491. The conformation of a six-membered ring can be expressed in spherical polar coordinates such that *d* indicates the amount of puckering; $\theta = 0$ or 180° corresponds to a chair; $\theta = 90°$, $\phi = 60n$ (where $n = 0, 1, 2, ...$) corresponds to a boat, and $\theta = 90°$, $\phi = 60(n + 0.5)$ corresponds to a twist-boat. (*Z*)-**8d** gives $d = 0.96$; $\phi = 74°$; $\theta = 88°$.

(10) *J* values for (*Z*)-**8b** are available from ref 4.

(11) Dheilly, L.; Fréchou, C.; Beaupère, D.; Uzan, R.; Demailly, G. *Carbohydr. Res.* **1992**, *224*, 301−306.

(12) Allevi, P.; Ciuffreda, P.; Colombo, D.; Monti, D.; Speranza, G.; Manitto, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1281−1283.

(13) Prepared by DMSO−Ac_2O oxidation of the corresponding hemiacetal according to Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron* **1994**, *50*, 4215−4224.

nitrile (*Z*)-**8d** with the analogous glucosylidene (*Z*)-**6d** and galactosylidene (*Z*)-**7d** nitriles. Experimental procedures and characterization data for new compounds not included in the Experimental Section. ^{1}H and ^{13}C spectra for all new compounds, HPLC traces for mannosylidenes **8a**−**8d**, and crystallographic data for (*Z*)-**8d** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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