An Unexpected Rearrangement during Mitsunobu Epimerization Reaction of Sugar Derivatives

Rachel Persky and Amnon Albeck*

The Julius Spokojny Bioorganic Chemistry Laboratory, Department of Chemistry, Bar Ilan University, Ramat Gan 52900, Israel

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Mitsunobu reaction on the glucose derivative (3*S*,4*R*,5*R*,6*R*)-3,4,5,7-tetrabenzyloxy-6-hydroxy-1-heptene yielded an unexpected rearrangement major product. Its structure was determined as (3*R*,4*R*,5*R*,6*S*)-4,5,6,7-tetrabenzyloxy-3-hydroxy-1-heptene. The suggested rearrangement mechanism involves an initial intramolecular cyclization, followed by ring opening by the nucleophile *p*-nitrobenzoate. Product distribution of the Mitsunobu reaction was substrate-dependent, with the corresponding mannose derivative (the 3*R* epimer) giving less of the initial intramolecular reaction products and the corresponding galactose derivative (the 5*S* epimer) yielding almost exclusively the expected epimerization product. Varying the Mitsunobu reaction conditions (addition of base and using nonpolar solvent) led to the expected epimerization product of the glucose derivative.

Introduction

The Mitsunobu reaction is a useful way of activating alcohols for substitution reactions and for inversion of their stereochemistry (in the case of secondary alcohols).[1] The latter reaction is based on displacement of the activated hydroxyl group by a carboxylic acid, thus forming an ester of opposite absolute configuration. This is then followed by solvolysis of the ester, yielding an alcohol of the same chemical structure and opposite configuration. As part of our interest in the development of inhibitors and mechanistic probes for sugar-metabolizing enzymes,[2] we were involved in the synthesis of cyclic sugar analogues. In an attempt to utilize the Mitsunobu reaction to epimerize a secondary alcohol of a sugar derivative bearing benzyl protecting groups on the rest of the hydroxyls, an unexpected rearrangement product was isolated as the major product. Here, we describe the reaction, its stereochemical and mechanistic analysis, and its dependence on the substrate and the reaction conditions.

Results

(3*S*,4*R*,5*R*,6*R*)-3,4,5,7-Tetrabenzyloxy-6-hydroxy-1-heptene **1a** (glucose derivative)[3] was subjected to standard Mitsunobu reaction conditions (entry 1, Table 2)[4] to invert the stereochemistry of its C_6 (free hydroxy-bearing carbon) configuration. The reaction, stopped at the *p*-nitrobenzoate stage (prior to the solvolysis final step), yielded a mixture of three products. These were identified as a cyclization product **2a**, the expected epimerization product **3a**, and a rearrangement product **4a** (of unidentified stereochemistry) in a 1:2:10 molar ratio (Scheme 1 and Table 1). The cyclization product **2a** was identical to that obtained by Tf_2O activation of **1a**.[3]

Scheme 1

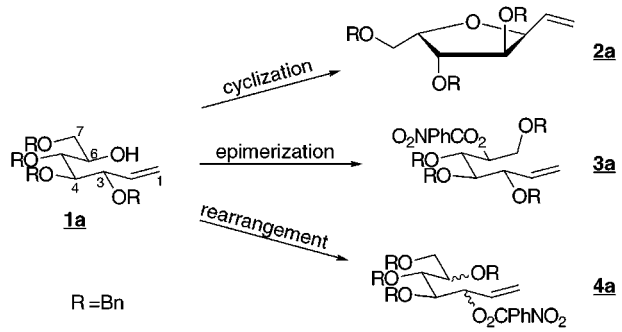

Table 1. Mitsunobu Reaction; Product Distribution as a Function of Substrate

	product distribution		
sugar derivative	**2** (cycl)	**3** (epi)	**4** (rearr)
gluco-**1a**	1	2	10
manno-**1b**	0−4	2.5	1
galacto-**1c**		9	1

The product distribution of the same reaction on other sugar analogues was examined (Table 1). The corresponding mannose derivative **1b** (3*R* epimer) yielded more of the expected epimerization product **3b** than rearrangement product **4b** (2.5:1 molar ratio) and variable amounts of cyclization product **2b** (0−40% of total products). The corresponding galactose derivative **1c** (5*S* epimer) gave primarily the desired epimerization product **3c** and the rearrangement **4c** product only as a minor side-product (9:1 molar ratio).

The Mitsunobu reaction on the glucose derivative **1a** was studied to maximize the epimerization product at the expense of the unexpected rearrangement product (Table 2). Changing the solvent and reactant ratio finally led to a 4:1 molar ratio in favor of the desired epimerization product **4a**. Under the same reaction conditions,

* Tel: 972-3-5318862. Fax: 972-3-5351250. E-mail: albecka@mail.biu.ac.il.

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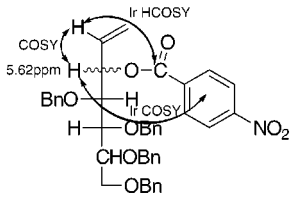
Table 2. Mitsunobu Reaction; Product Distribution as a Function of Reaction Conditions

	reactant molar ratio					product ratio	
alcohol[a]	Ph_3P	RCO_2H[b]	Et_3N	DEAD	solvent	**3a** (epi)	**4a** (rearr)
1	4	4		4	THF	1	5[c]
1	2	2	5	2	THF	2	1
1	2	10	25	2	THF	1	2
1	2	2	5	2	toluene	4	1
1	2	10	25	2	toluene	1	1

[a] Glucose derivative **1a**. [b] *p*-Nitrobenzoic acid. [c] Minor cyclization product was also obtained (see Table 1).



Ir COSY: ^1Hx^1H long-range COSY
Ir HCOSY: ^1Hx^{13}C long-range hetero-COSY (HMBC)

Figure 1. Determination by NMR analysis of the structure of the major product of Mitsunobu reaction on **1a**.

the mannose derivative **1b** yielded 3:1 epimerization: rearrangement products, while the cyclization side-product was not formed at all. The total yield was also improved significantly, from 37% to 67% for the glucose derivative and from 60% to 95% for the mannose derivative.

Discussion

Product Analysis. The Mitsunobu reaction on **1a** yielded a major product that seemed, at first glance, to be the expected epimerization product (at the *p*-nitrobenzoate stage); it had the correct mass (by MS analysis), and its ^1H and ^{13}C NMR spectra exhibited all of the expected resonances (with the expected integrations). Nevertheless, our curiosity was piqued by a ^1H resonance at 5.62 ppm, which seemed somewhat too low for the C6H ester proton. Indeed, further analysis identified the product as a rearrangement product on the basis of the following NMR data (Figure 1):

(1) ^1H COSY experiment showed that the 5.62 ppm resonance belongs to the allylic proton (C3H).

(2) $^1H-^1H$ long-range COSY experiment revealed a cross-peak (interaction) between the allylic proton (C3H) at 5.62 ppm and the aromatic protons of the *p*-nitrobenzoate at 7.9−8.0 ppm.

(3) $^1H-^{13}C$ long-range HCOSY experiment exhibited an interaction between the vinylic proton (C2H) at 6.00 ppm and the ester carbon at 163.3 ppm.

This set of experiments confirmed that the *p*-nitrobenzoate ester is on C_3, whereas C_6 bears a benzyl ether substituent. The absolute configuration of the two carbons involved in the rearrangement was not determined at this stage, nor was the mechanism of this rearrangement understood.

To determine the stereochemistry of the rearrangement product, the benzoate ester was hydrolyzed, and the resulting product **1e** was cyclized by activation of the hydroxy group as a triflate (Scheme 2).[3] This cyclization product was compared with the corresponding cyclization products (**2a,b,d**) of the original glucose derivative **1a**,

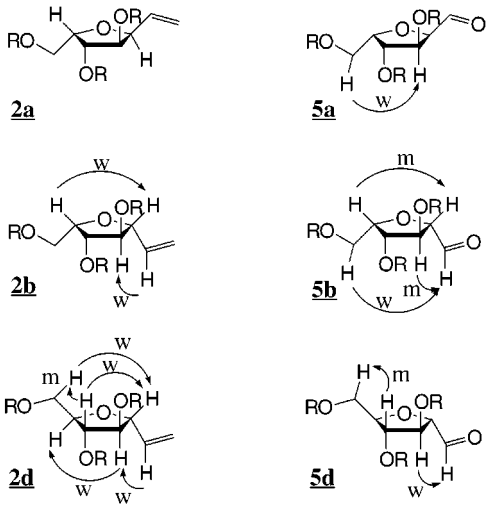


Figure 2. NOESY data for cyclic olefins **2** and aldehydes **5**. (Arrows indicate weak (w) or medium (m) interactions (cross-peaks in the 2-D spectrum) between sets of two protons).

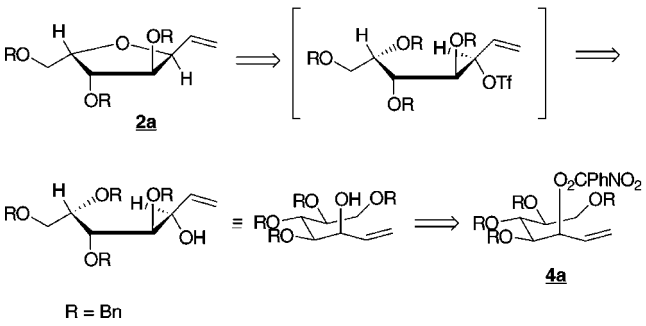
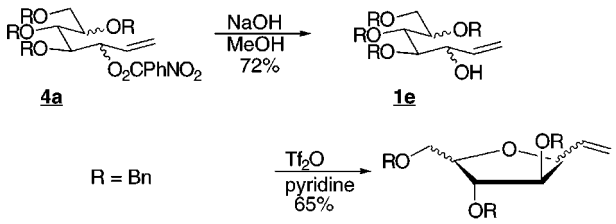


Figure 3. Retroanalysis of the stereochemistry of rearrangement product **4a**.

Scheme 2



the analogous mannose derivative **1b**, and its C_6 epimer **1d** (obtained by hydrolysis of the Mitsunobu epimerization product **3b**) (Scheme 3). The ^1H and ^{13}C NMR spectra of the cyclization product derived from **1e** were identical to those of the cyclization product **2a**, derived from the glucose derivative **1a**, confirming their identity.

The stereochemistry of cyclic compounds **2a,b,d** was confirmed by NOESY experiments of the cyclic olefins themselves and of their corresponding aldehydes **5a,b,d** (Figure 2). The latter were obtained by OsO_4, *N*-methyl morpholine-*N*-oxide followed by $NaIO_4$ oxidation.[5] Retroanalysis of the stereochemistry of the rearrangement product **4a**, based on the identification of its (Tf_2O-activated) cyclization product as **2a**, revealed that it underwent epimerization at both of the positions involved, C_3 and C_6 (Figure 3).

Mechanism. We considered three possible mechanisms for the rearrangement observed during the Mit-

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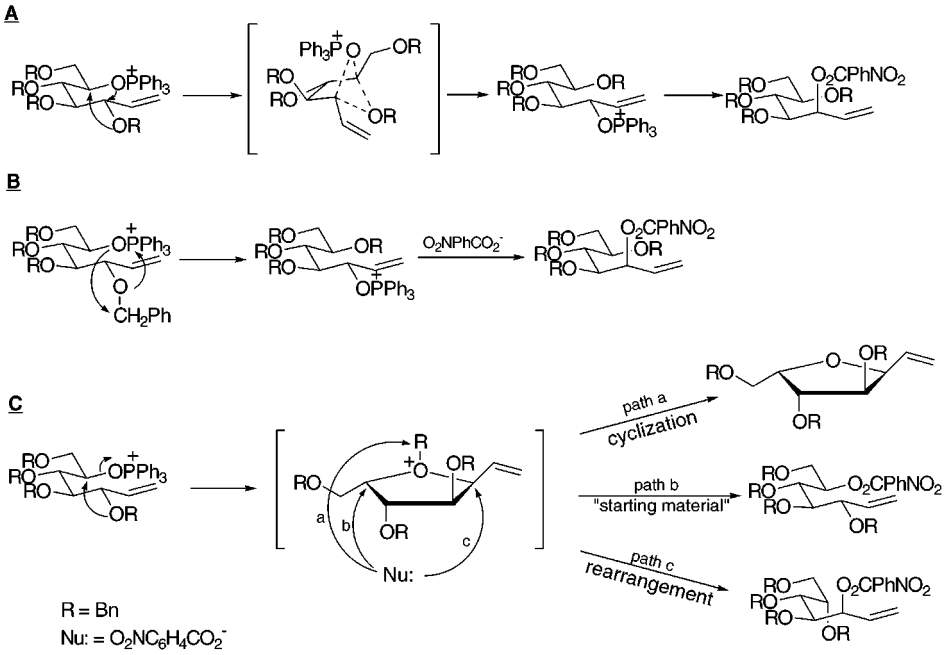
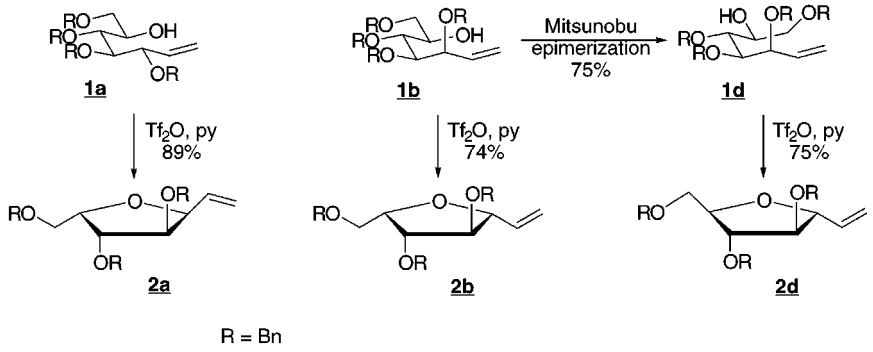


Figure 4. Possible mechanisms for the formation of the rearrangement product **4a** during the Mitsunobu reaction on **1a**.

Scheme 3



sunobu reaction (Figure 4). The first mechanism involves a concerted nucleophilic attack of the two oxygens (the C_3 benzylic oxygen and the C_6 phosphinoxy) on their counterpart "skeleton" carbons via a bicyclic transition state (Figure 4A). This is an "adjacent" substitution reaction (well-known in phosphorus chemistry[6]), leading to exchange of the two substituents (at C_3 and C_6) with retention of configuration at both stereogenic centers. Displacement of the triphenylphosphinoxy substitution at C_3 by *p*-nitrobenzoate completes the rearrangement reaction with an overall inversion of the configuration at C_3 and retention of configuration at C_6.

The second mechanism (Figure 4B) is based on nucleophilic attacks on the substituents rather than the skeleton carbons. Thus, the C_3 benzylic oxygen attacks the C_6 phosphorus, releasing a free alkoxide that can attack the C_3 benzylic carbon. This mechanism leaves the C_3 and C_6 oxygens in their original positions, with full retention of configuration. Therefore, completion of the reaction by *p*-nitrobenzoate displacement of the triphenylphosphinoxy leads to an overall inversion of configuration at C_3 and retention of configuration at the C_6 position.

These two mechanisms were ruled out since their stereochemical consequence does not match the observed stereochemistry of the rearrangement product **4a**.

Finally, the third mechanism (Figure 4C) involves an initial attack of the C_3 benzylic oxygen on the C_6 carbon, bearing the activated alcohol. This reaction is similar to the cyclization reaction, driven by triflate-activated alcohol, previously described by Martin and co-workers.[3] The common cyclic oxonium intermediate thus formed can interact with a common nucleophile, *p*-nitrobenzoate, in three different ways. The nucleophilic *p*-nitrobenzoate can attack the benzyl ring substituent, yielding the cyclization product **2** (path a in Figure 4C). Alternatively, it can attack at the (original) C_6 position, yielding the corresponding ester that, after solvolysis, will afford the starting material (path b in Figure 4C). The third possibility involves a similar attack at the C_3 position, yielding the rearrangement product **4** with inversion of configuration at both C_3 and C_6 positions (path c in Figure 4C). This stereochemistry coincides with that determined for the rearrangement product **4a**.

Therefore, only the third mechanism (Figure 4C) explains the formation of the observed rearrangement product **4a**. This mechanism also accounts for the observed cyclization side-product **2a**. It should be noted that two of the alternative routes of the third mechanism, path

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a and path c, involve nucleophilic attack at activated carbons (benzylic and allylic, respectively). Therefore they are much more favorable than path b. Indeed, the former two products were observed, in addition to the epimerization product, while the path b product was not observed in any of the sugar derivative Mitsunobu reactions.

Substrate Dependence. The outcome of the Mitsunobu reaction as a function of small variations of the substrate was studied (Table 1). A majority of 85% of the total product of the Mitsunobu reaction on the glucose derivative originated from the initial cyclization reaction (Figure 4C). Varying amounts of 25−70% of the product arose from this cyclization reaction when the corresponding mannose derivative was the substrate of the Mitsunobu reaction. Finally, only 10% of such products were observed for the galactose derivative. This can be explained on steric hindrance grounds. The initial cyclization reaction is strongly suppressed in reaction of the galactose analogue **1c** by steric repulsion between the C_5 benzyloxy and the C_6 triphenyl phosphinoxy substituents when properly oriented for displacement by the C_3 benzyloxy oxygen. This interaction is unique to the galactose derivative **1c** only, as a result of its 5*S* absolute configuration (in contrast to the 5*R* configuration of the glucose and the mannose derivatives, **1a** and **1b**, respectively).

Reaction Condition Dependence. The distribution of rearrangement and epimerization products depends on the kinetics of intramolecular and intermolecular nucleophilic attacks on the 6-phosphinoxy intermediate, respectively. Initial attempts to increase the rate of the intermolecular reaction by the addition of 20 equiv of the carboxylic acid stopped all reactions entirely, and only starting material was isolated. This was probably due to diminishing even the small concentration of alkoxide necessary for the Mitsunobu reaction to proceed (step 3, Figure 5). Further analysis suggested addition of a base to increase the concentration of the nucleophilic carboxylate to accelerate the intermolecular nucleophilic attack (step 4, Figure 5).[7] This was tested for the Mitsunobu reaction on the glucose derivative **1a**. The results presented in Table 2 show that this indeed helped to improve the ratio of epimerization to rearrangement products. Hydrophobic solvent was also superior to polar solvent, probably because of better stabilization by the latter of the oxonium intermediate in the intramolecular initial cyclization reaction leading to the rearrangement product. The conditions affording the best epimerization: rearrangement ratio (entry 4, Table 2) also significantly improved the overall yield of the reaction.

Conclusions

In this work, sugar derivative **1a** was exposed to standard Mitsunobu epimerization reaction conditions. Surprisingly, the major product proved to be the result of a rearrangement involving substituents at the C_3 and C_6 positions. The suggested rearrangement mechanism implicates an initial intramolecular displacement of the C_6 activated hydroxyl by the C_3 benzyl ether oxygen. The common cyclic intermediate can further react in different ways to give the observed products. Such a participation

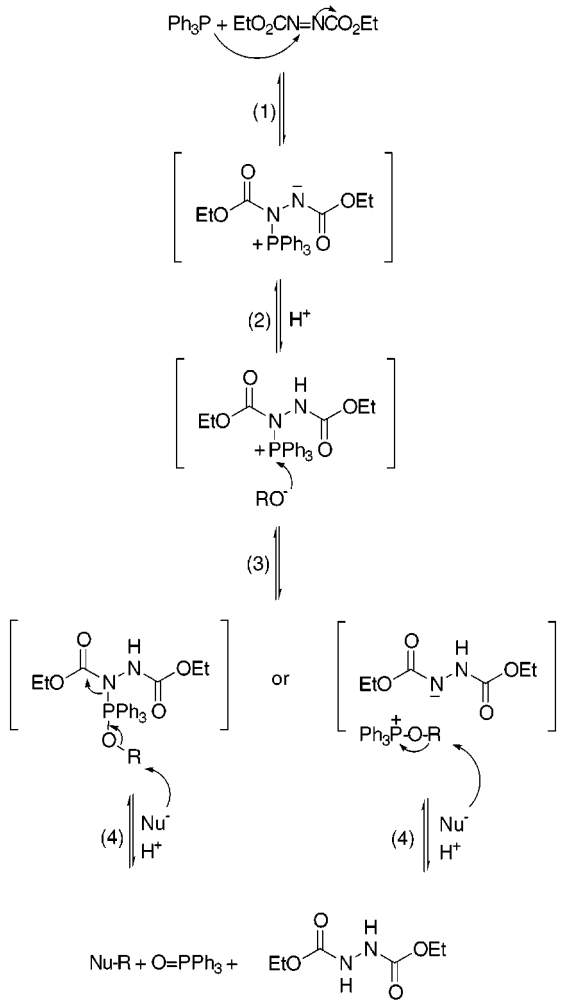

Figure 5. The Mitsunobu reaction mechanism.

of benzyl ether oxygen in nucleophilic cyclization reactions, either as a desired reaction or as a side reaction, is well documented.[3,8] In the present study we have demonstrated that, by varying the reaction conditions, we can shift from an intramolecular reaction, leading to the rearrangement product, to an intermolecular one, yielding the Mitsunobu epimerization product.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 600 and 150 MHz, respectively, in $CDCl_3$, with TMS as an internal standard. Multiplicity "d" refers to a doubletlike second-order peak. ^{1}H NMR assignments were supported by COSY experiments, and ^{13}C NMR assignments were supported by hetero COSY (HMQC and HMBC) experiments. Mass spectra were recorded in DCI mode with methane as the reagent gas. TLC was performed on E. Merck 0.2 mm precoated silica gel F-254 plates and viewed by UV, vanillin.[9] Chromatography refers to flash column chromatography,[10] carried out on silica gel 60

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(230−400 mesh ASTM, E. Merck). Anhydrous solvents were dried and freshly distilled (THF and toluene from sodium/benzophenone, pyridine and triethylamine from CaH_2, CH_2Cl_2 from $CaCl_2$, and DMF from 4 Å molecular sieves).

The linear olefins **1a−c** were synthesized according to Martin and co-workers[3] and purified by chromatography (eluted with either CH_2Cl_2 or ether/hexane 1:4).

The cyclic olefins **2a,b,d** were obtained by Tf_2O activation of the corresponding linear olefins **1a,b,d**, respectively, according to Martin and co-workers[3] and purified by chromatography (eluted with either CH_2Cl_2 or ether/hexane 1:4).

Mitsunobu Reaction. (a) The olefin **1** (2.69 g, 5 mmol), Ph_3P (5.24 g, 20 mmol), and *p*-nitrobenzoic acid (3.34 g, 20 mmol) were dissolved in dry THF at 0 °C. DEAD (3.15 mL, 20 mmol) was then added dropwise, and after 10 min the reaction mixture was allowed to warm to room temperature. After 5−18 h, the solvent was evaporated, and CH_2Cl_2 was added and extracted consecutively with 1 M HCl, saturated $NaHCO_3$, and H_2O. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. The product was chromatographed (ether/hexane 1:5), yielding a mixture of cyclization (**2**), epimerization (**3**), and rearrangement (**4**) products in overall 37%, 60%, and 40% yield for the glucose (**2a**−**4a**), mannose (**2b**−**4b**), and galactose (**2c**−**4c**) derivatives, respectively. (See Table 1 for product distribution).

(b) The olefin **1** (2.69 g, 5 mmol), Ph_3P (2.62 g, 10 mmol), *p*-nitrobenzoic acid (1.67 or 8.35 g, 10 or 50 mmol), and Et_3N (3.5 or 17.5 mL, 25 or 125 mmol) were dissolved in dry THF or dry toluene at 0 °C. DEAD (1.6 mL, 10 mmol) was then added dropwise, and after 10 min the reaction mixture was allowed to warm to room temperature. After 5−18 h, the solvent was evaporated, and the reaction mixture worked up as above, affording the glucose derivative products in 67% yield and the mannose derivatives in 95% yield. (See Table 2 for conditions and product distribution).

Gluco-epimerized ester 3a: ^{1}H NMR δ 3.504 (dd, J = 10.6, 5.9 Hz, 1H, C7H$_2$), 3.554 (dd, J = 10.5, 3.7 Hz, 1H, C7H$_2$), 3.558 (t, J = 5.1 Hz, 1H, C4H), 4.031 (t, J = 5.2 Hz, 1H, C5H), 4.044 (dd, J = 7.4, 5.0 Hz, 1H, C3H), 4.241 (d, J = 12.0 Hz, 1H, CH$_2$Ph (C7)), 4.308 (d, J = 12.0 Hz, 1H, CH$_2$Ph (C7)), 4.517 (d, J = 11.8 Hz, 1H, CH$_2$Ph (C5)), 4.550 (d, J = 11.7 Hz, 1H, CH$_2$Ph (C6)), 4.580 (d, J = 11.6 Hz, 1H, CH$_2$Ph (C3)), 4.631 (d, J = 11.6 Hz, 1H, CH$_2$Ph (C3)), 4.638 (d, J = 11.6 Hz, 1H CH$_2$Ph (C6)), 4.658 (d, J = 12.0 Hz, 1H, CH$_2$Ph (C5)), 5.177 (ddd, J = 17.2, 1.7, 0.9 Hz, 1H, C1H$_2$), 5.191 (ddd, J = 10.6, 1.7, 0.9 Hz, 1H, C1H$_2$), 5.441 (q, J = 5.1 Hz, 1H, C6H), 5.789 (ddd, J = 17.2, 10.5, 7.4 Hz, 1H, C2H), 7.06−7.19 (m, 20H, Ph), 7.981 ("d", J = 9.0 Hz, 2H, Ph-NO$_2$), 8.072 ("d", J = 9.0 Hz, 2H, Ph-NO$_2$); ^{13}C NMR δ 68.12 (C7), 72.86 (CH$_2$Ph(C7)), 74.08 (CH$_2$Ph(C3)), 74.23 (CH$_2$Ph(C6), C6), 74.66 (CH$_2$Ph(C5)), 77.30 (C5), 80.22 (C3), 80.54 (C4), 119.00 (C1), 123.29, 127.43−128.21, 130.65 (Ph), 135.02 (C2), 135.41, 137.72−138.22, 150.32 (Ph), 163.96 (CO$_2$).

Gluco-rearranged ester 4a: ^{1}H NMR δ 3.549 (dd, J = 10.1, 5.4 Hz, 1H, C7H$_2$), 3.593 (dd, J = 10.1, 4.3 Hz, 1H, C7H$_2$), 3.696 (dd, J = 6.4, 4.5 Hz, 1H, C5H), 3.748 (dt, J = 5.4, 4.5 Hz, 1H, C6H), 3.913 (dd, J = 6.4, 3.8 Hz, 1H, C4H), 4.226 (d, J = 11.7 Hz, 1H, CH$_2$Ph (C4)), 4.300 (d, J = 11.9 Hz, 1H, CH$_2$-Ph (C7)), 4.329 (d, J = 12.0 Hz, 1H, CH$_2$Ph (C7)), 4.485 (d, J = 11.7 Hz, 1H, CH$_2$Ph (C4)), 4.509 (d, J = 11.8 Hz, 1H, CH$_2$-Ph (C6)), 4.530 (d, J = 12.0 Hz, 1H, CH$_2$Ph (C5)), 4.575 (d, J = 11.3 Hz, 1H, CH$_2$Ph (C5)), 4.643 (d, J = 11.6 Hz, 1H, CH$_2$-Ph (C6)), 5.248 (dt, J = 10.5, 1.1 Hz, 1H, C1H$_2$), 5.286 (dt, J = 17.3, 1.2 Hz, 1H, C1H$_2$), 5.616 (ddt, J = 6.9, 3.8, 1.0 Hz, 1H, C3H), 6.001 (ddd, J = 17.4, 10.5, 6.9 Hz, 1H, C2H), 7.06−7.19 (m, 20H, Ph), 7.890 ("d", J = 9.0 Hz, 2H, Ph-NO$_2$), 8.009 ("d", J = 9.0 Hz, 2H, Ph-NO$_2$); ^{13}C NMR δ 69.49 (C7), 70.60 (CH$_2$Ph(C4)), 72.71 (CH$_2$Ph(C6)), 73.19 (CH$_2$Ph(C7)), 74.52 (CH$_2$Ph(C5)), 76.26 (C3), 77.69 (C6), 78.36 (C5), 80.23 (C4), 119.78 (C1), 123.07, 127.43−128.21, 130.59 (Ph), 132.40 (C2), 135.41, 137.72−138.22, 150.32 (Ph), 163.28 (CO$_2$).

HRMS (for the **3a**:**4a** mixture) calcd for $C_{42}H_{42}NO_8$ (MH^+) 688.2910, found 688.29.40.

Manno-epimerized ester 3b: ^{1}H NMR δ 3.568 (dd, J = 10.7, 5.7 Hz, 1H, C7H$_2$), 3.683 (dd, J = 10.7, 4.2 Hz, 1H, C7H$_2$), 3.743 (dd, J = 5.7, 4.7 Hz, 1H, C4H), 4.094 (dd, J = 8.0, 5.7 Hz, 1H, C3H), 4.112 (dd, J = 5.6, 4.7 Hz, 1H, C5H), 4.237 (d, J = 11.7 Hz, 1H, CH$_2$Ph(C3)), 4.362 (d, J = 12.3 Hz, 1H, CH$_2$-Ph(C7)), 4.469 (d, J = 12.1 Hz, 1H, CH$_2$Ph(C7)), 4.542 (d, J = 11.3 Hz, 1H, CH$_2$Ph(C4)), 4.565 (d, J = 11.6 Hz, 1H, CH$_2$Ph-(C5)), 4.597 (d, J = 11.8 Hz, 1H, CH$_2$Ph(C3)), 4.697 (d, J = 11.3 Hz, 1H, CH$_2$Ph(C5)), 4.794 (d, J = 11.3 Hz, 1H, CH$_2$Ph-(C4)), 5.410 (dt, J = 10.4, 1 Hz, 1H, C1H$_2$), 5.417 (ddd, J = 17.1, 1.6, 0.9 Hz, 1H, C1H$_2$), 5.580 (td, J = 5.7, 4.2 Hz, 1H, C6H), 5.975 (ddd, J = 17.1, 10.5, 8.1 Hz, 1H, C2H), 7.177−7.287 (m, 20H, Ph), 8.097 ("d", J = 8.9 Hz, 2H, Ph-NO$_2$), 8.212 ("d", J = 8.9 Hz, 2H, Ph-NO$_2$); ^{13}C NMR δ 68.14 (C7), 69.92 (CH$_2$Ph(C3)), 72.96 (CH$_2$Ph(C7)), 73.70 (CH$_2$Ph(C4)), 74.33 (C6), 75.0 (CH$_2$Ph(C5)), 77.67 (C5), 80.38 (C3), 80.63 (C4), 120.08 (C1), 123.35, 127.43−128.31, 130.76 (Ph), 135.47 (C2), 135.49, 138.14, 138.19, 138.24, 138.27, 150.40 (Ph), 164.07 (CO$_2$).

Manno-rearranged ester 4b: ^{1}H NMR δ 3.593 (dd, J = 10.2, 5.2 Hz, 1H, C7H$_2$), 3.675 (dd, J = 10.2, 4.4 Hz, 1H, C7H$_2$), 3.813 (q, J = 4.7 Hz, 1H, C6H), 3.854 (t, J = 5 Hz, 1H, C5H), 3.927 (t, J = 5.3 Hz, 1H, C4H), 4.376 (d, J = 12 Hz, 1H, CH$_2$-Ph(C7/C5)), 4.382 (d, J = 12 Hz, 1H, CH$_2$Ph(C7/C5)), 4.532 (d, J = 11.9 Hz, 1H, CH$_2$Ph(C6)), 4.657 (d, J = 11.1 Hz, 2H, CH$_2$Ph(C4,C7/C5)), 4.709 (d, J = 11.4 Hz, 1H, CH$_2$Ph(C5/C7)), 4.722 (d, J = 11.4 Hz, 1H, CH$_2$Ph(C4)), 4.728 (d, J = 11.8 Hz, 1H, CH$_2$Ph(C6)), 5.211 (bt, J = 10.5 Hz, 1H, C1H$_2$), 5.229 (bd, J = 17.3, 1H, C1H$_2$), 5.663 (t, J = 5.8 Hz, 1H, C3H), 5.869 (ddd, J = 17.2, 10.5, 6.5 Hz, 1H, C2H), 7.177−7.287 (m, 20H, Ph), 8.101 ("d", J = 8.9 Hz, 2H, Ph-NO$_2$), 8.176 ("d", J = 8.9 Hz, 2H, Ph-NO$_2$); ^{13}C NMR δ 69.31 (C7), 69.92 (CH$_2$Ph(C3)), 72.65 (CH$_2$Ph(C7/C5)), 73.16 (CH$_2$Ph(C5/C7)), 74.40 (C4), 74.56 (CH$_2$Ph(C6)), 76.14 (C3), 77.48 (C6), 78.03 (C5), 80.06 (C4), 118.59 (C1), 123.39, 127.56−128.24, 130.60 (Ph), 133.04 (C2), 135.49, 137.75−138.11, 150.40 (Ph), 163.61 (CO$_2$).

HRMS (for the **3b**:**4b** mixture) calcd for $C_{42}H_{42}NO_8$ (MH^+) 688.2910, found 688.2960; calcd for $C_{35}H_{34}NO_7$ (MH^+ − BnOH) 580.2335, found 580.2290.

Galacto-epimerized ester 3c: ^{1}H NMR δ 3.736 (t, J = 5.4 Hz, 1H, C4H), 3.886 (dd, J = 11.1, 6.7 Hz, 1H, C7H$_2$), 3.914 (dd, J = 11.2, 3.5 Hz, 1H, C7H$_2$), 4.069 (dd, J = 5.6, 3.5 Hz, 1H, C5H), 4.120 (dd, J = 7.7, 5.1 Hz, 1H, C3H), 4.329 (d, J = 11.9 Hz, 1H, CH$_2$Ph(C3)), 4.382 (d, J = 12.1 Hz, 1H, CH$_2$Ph-(C7)), 4.459 (d, J = 11.3 Hz, 1H, CH$_2$Ph(C5)), 4.493 (d, J = 12.0 Hz, 1H, CH$_2$Ph(C7)), 4.593 (d, J = 11.7 Hz, 1H, CH$_2$Ph-(C5)), 4.613 (d, J = 12.3 Hz, 1H, CH$_2$Ph(C3)), 4.720 (d, J = 11.4 Hz, 1H, CH$_2$Ph(C4)), 4.790 (d,J = 11.4 Hz, 1H, CH$_2$Ph-(C4)), 5.336 (ddd, J = 10.4, 1.6, 0.7 Hz, 1H, C1H$_2$), 5.383 (ddd, J = 17.3, 1.5, 1.1 Hz, 1H, C1H$_2$), 5.800 (dt, J = 6.8, 3.5 Hz, 1H, C6H), 5.919 (ddd, J = 17.4, 10.4, 7.6 Hz, 1H, C2H), 7.22−7.32 (m, 20H, Ph), 8.069 ("d", J = 8.9 Hz, 2H, Ph-NO$_2$), 8.227 ("d", J = 8.9 Hz, 2H, Ph-NO$_2$); ^{13}C NMR δ 68.66 (C7), 70.48 (CH$_2$Ph(C3)), 72.87 (CH$_2$Ph(C7)), 73.14 (CH$_2$Ph(C5)),74.47 (CH$_2$Ph(C4)), 74.63 (C6), 78.69 (C5), 80.66 (C3), 81.60 (C4), 119.16 (C1), 123.43, 127.47−128.33, 130.70 (Ph), 135.55 (C2), 137.92−138.22, 150.41 (Ph), 163.78 (CO$_2$).

Galacto-rearranged ester 4c: ^{1}H NMR δ 5.272 (dt, J = 17.3, 1.3 Hz, 1H, C1H$_2$), 5.303 (dt, J = 10.5, 1.2 Hz, 1H, C1H$_2$), 5.933 (ddt, J = 7.2, 2.8, 1.0 Hz, 1H, C3H), 6.052 (ddd, J = 17.2, 10.5, 7.2 Hz, 1H, C2H); ^{13}C NMR δ 77.46 (C3), 119.80 (C1).

Methanolysis. To the ester (**3** and **4**, a mixture from the Mitsunobu reaction) in methanol were added 10 equiv of NaOH (solid). After 1 h, the solvent was partially removed under reduced pressure. CH_2Cl_2 was added and extracted twice with water. The organic phase was dried over $MgSO_4$, filtered, and evaporated to dryness. Chromatography (ether/hexane 1:3) afforded the clean product (as a mixture of isomers derived from **3** and **4**).

Manno-epimerized alcohol 1d: 79% yield from **3b**; ^{1}H NMR δ 3.389 (dd, J = 9.6, 6.0 Hz, 1H, C7H$_2$), 3.429 (dd, J = 9.5, 6.2 Hz, 1H, C7H$_2$), 3.721 (dd, J = 6.1, 3.0 Hz, 1H, C5H), 3.831 (dd, J = 6.1, 5.1 Hz, 1H, C4H), 3.921 (ddd, J = 6.2, 6.0, 3.0 Hz, 1H, C6H), 4.036 (ddd, J = 7.9, 5.0, 0.7 Hz, 1H, C3H), 4.306 (d, J = 11.8 Hz, 1H, CH$_2$Ph(C3)), 4.380 (d, J = 11.9 Hz, 1H, CH$_2$Ph(C7)), 4.423 (d, J = 11.9 Hz, 1H, CH$_2$Ph(C7)), 4.451

(d, J = 11.3 Hz, 1H, CH_2Ph(C5)), 4.583 (d, J = 11.1 Hz, 1H, CH_2Ph(C4)), 4.597 (d, J = 11.8 Hz, 1H, CH_2Ph(C3)), 4.684 (d, J = 11.1 Hz, 1H, CH_2Ph(C5)), 4.731 (d, J = 11.1 Hz, 1H, CH_2-Ph(C4)), 5.329 (ddd, J = 17.5, 1.7, 0.8 Hz, 1H, C1H_2), 5.354 (ddd, J = 10.4, 1.6, 0.8 Hz, 1H, C1H_2), 5.962 (ddd, J = 17.5, 10.4, 7.9 Hz, 1H, C2H), 7.218−7.280 (m, 20H, Ph); ^{13}C NMR δ 70.14 (C6/CH_2Ph(C3)), 70.17 (C6/CH_2Ph(C3)), 71.21 (C7), 73.19 (CH_2Ph(C7)), 74.32 (CH_2Ph(C4)), 74.87 (CH_2Ph(C5)), 78.64 (C5), 81.12 (C3), 81.75 (C4), 119.61 (C1), 127.48−129.56 (Ph), 135.53 (C2), 138.05−138.45 (Ph); HRMS calcd for $C_{35}H_{39}O_5$ (MH^+) 539.2798, found 539.2841; MS m/z 539 (MH^+, 8), 431 (22), 323 (19), 91 (84).

Gluco-rearranged alcohol 1e: 72% yield from **4a**; ^{1}H NMR δ 3.202 (d, J = 5.2 Hz, 1H, OH), 3.522 (dd, J = 10.3, 5.1 Hz, 1H, C7H_2), 3.568 (dd, J = 5.2, 4.1 Hz, 1H, C4H), 3.642 (dd, J = 10.4, 3.7 Hz, 1H, C7H_2), 3.884 (dd, J = 5.4, 4.0 Hz, 1H, C5H), 3.907 (qd, J = 5.2, 3.7 Hz, 1H, C6H), 4.35 (m, 1H, C3H), 4.383 (d, J = 12.1 Hz, 1H, CH_2Ph(C7)), 4.433 (d, J = 12.2 Hz, 1H, CH_2Ph(C7)), 4.475 (d, J = 11.5 Hz, 1H, CH_2Ph-(C4)), 4.601 (d, J = 11.7 Hz, 1H, CH_2Ph(C6)), 4.625 (d, J = 11.2 Hz, 1H, CH_2Ph(C5)), 4.642 (d, J = 11.5 Hz, 1H, CH_2Ph-(C4)), 4.681 (d, J = 11.2 Hz, 1H, CH_2Ph(C5)), 4.717 (d, J = 11.7 Hz, 1H, CH_2Ph(C6)), 5.206 (dt, J = 10.5, 1.7 Hz, 1H, C1H_2), 5.348 (dt, J = 17.2, 1.7 Hz, 1H, C1H_2), 5.883 (ddd, J = 17.2, 10.6, 5.3 Hz, 1H, C2H), 7.248−7.31 (m, 20H, Ph); ^{13}C NMR δ 69.55 (C7), 71.94 (C3), 72.46 (CH_2Ph(C5)), 72.72 (CH_2-Ph(C7)), 73.07 (CH_2Ph(C6)), 74.04 (CH_2Ph(C4)), 78.14 (C6), 78.65 (C5), 79.34 (C4), 116.04 (C1), 127.5−128.3 (Ph), 137.59 (C2), 137.7−138.2 (Ph); HRMS calcd for $C_{35}H_{39}O_5$ (MH^+) 539.2798, found 539.2800; MS m/z 539 (MH^+, 35), 521 (20), 431 (22), 361 (16.5).

Oxidation. To the cyclic olefin (**2a,b,d**) (4.3 g, 10 mmol) in H_2O/THF (50 mL, 1:1 v/v) was added *N*-methyl morpholine-*N*-oxide (2.34 g, 20 mmol), followed by the addition of a catalytic amount (0.04 mmol) of OsO_4. After 2−18 h, $NaIO_4$ (5.8 g, 30 mmol) and methanol (50 mL) were added. After 2 h, the organic solvents were removed under reduced pressure, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). This organic phase was dried over $MgSO_4$, filtered, and evaporated. The product was purified by chromatography, using CH_2Cl_2 as eluent.

Gluco-cyclic aldehyde 5a: 44% yield; ^{1}H NMR δ 3.742 (dd, J = 10.8, 6.1 Hz, 1H, C6H_2), 3.765 (dd, J = 10.8, 6.1 Hz, 1H, C6H_2), 4.022 (dd, J = 3.6, 1.3 Hz, 1H, C4H), 4.314 (dd, J = 4.8, 1.3 Hz, 1H, C3H), 4.372 (d, J = 12.0 Hz, 1H, CH_2Ph(C3)), 4.416 (d, J = 12.1 Hz, 1H, CH_2Ph(C4)), 4.432 (d, J = 12.0 Hz, 1H, CH_2Ph(C3)), 4.480 (d, J = 12.1 Hz, 1H, CH_2Ph(C4)), 4.487 (dd, J = 4.8, 2.0 Hz, 1H, C2H), 4.533 (d, J = 12.0 Hz, 1H, CH_2Ph(C6)), 4.575 (td, J = 6.1, 3.6 Hz, 1H, C5H), 4.629 (d, J = 12.0 Hz, 1H, CH_2Ph(C6)), 7.2−7.4 (m, 15H, Ph), 9.673 (d, J = 2.0 Hz, 1H, C1HO); ^{13}C NMR δ 67.97 (C6), 72.35 (CH_2Ph-(C4)), 72.41 (CH_2Ph(C3)), 73.53 (CH_2Ph(C6)), 80.89 (C4), 81.06 (C5), 83.71 (C3), 84.72 (C2), 127.54−128.49, 136.87, 137.35, 137.97 (Ph), 201.88 (C1); HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.2000; MS m/z 433 (MH^+, 1), 341 (13), 107 (50), 91 (100).

Manno-cyclic aldehyde 5b: 48% yield;^{1}H NMR δ 3.772 (dd, J = 10, 5.5 Hz, 1H, C6H_2), 3.791 (dd, J = 10, 6.5 Hz, 1H, C6H_2), 3.973 (dd, J = 3.4, 1.4 Hz, 1H, C4H), 4.194 (dd, J = 1.3, 1.1 Hz, 1H, C3H), 4.299 (d, J = 11.8 Hz, 1H, CH_2Ph(C4)), 4.368 (dd, J = 1.4, 0.9 Hz, 1H, C2H), 4.443 (d, J = 11.8 Hz, 1H, CH_2Ph(C4)), 4.495 (ddd, J = 6.5, 5.5, 3.4 Hz, 1H, C5H), 4.504 (d, J = 11.7 Hz, 1H, CH_2Ph(C6)), 4.532 (d, J = 12.0 Hz, 1H, CH_2Ph(C3)), 4.614 (d, J = 12.0 Hz, 1H, CH_2Ph(C3)), 4.614 (d, J = 12.0 Hz, 1H, CH_2Ph(C6)), 7.25−7.35 (m, 15H, Ph), 9.588 (d, J = 0.9 Hz, 1H, C1HO); ^{13}C NMR δ 68.28 (C6), 71.67 (CH_2-Ph(C4)), 71.76 (CH_2Ph(C3)), 73.51 (CH_2Ph(C6)), 80.19 (C4), 81.11 (C5), 84.87 (C3), 87.16 (C2), 127.62−128.49, 137.00, 137.06, 137.95 (Ph), 203.33 (C1); HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.1978; MS m/z 433 (MH^+, 2), 341 (51), 313 (54), 163 (80).

Manno-epimerized cyclic aldehyde 5d: 76% yield; ^{1}H NMR δ 3.585 (dd, J = 9.9, 6.3 Hz, 1H, C7H_2), 3.646 (dd, J = 9.9, 6.4 Hz, 1H, C7H_2), 4.023 (dd, J = 2.4, 1.7 Hz, 1H, C4H), 4.199 (t, J = 1.8 Hz, 1H, C3H), 4.401 (td, J = 6.4, 2.3 Hz, 1H, C5H), 4.422 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.453 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.462 (dd, J = 2.4, 0.9 Hz, 1H, C2H), 4.464 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.523 (d, J = 12.1 Hz, 1H, CH_2-Ph), 4.570 (d, J = 11.8 Hz, 1H, CH_2Ph), 4.586 (d, J = 12.1 Hz, 1H, CH_2Ph), 7.255−7.942 (m, 15H, Ph), 9.679 (d, J = 1.0 Hz, 1H, C1HO); ^{13}C NMR δ 69.87 (C6), 71.45 (CH_2Ph), 71.90 (CH_2-Ph), 73.35 (CH_2Ph), 82.60 (C4), 83.90 (C5), 84.75 (C3), 87.56 (C2), 127.70−128.52, 136, 137.11, 137.97 (Ph), 202.60 (C1); HRMS calcd for $C_{27}H_{29}O_5$ (MH^+) 433.2015, found 433.2028.

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Supporting Information Available: Figures showing ^{1}H NMR and NOESY spectra of cyclic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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