C-Glycosidations of a 2-Ketohexosyl Bromide with Electrophilic, Radical, and Nucleophilic Anomeric Carbons[‡]

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The susceptibility of acylated 2-ketohexosyl halides to C-homologation is demonstrated with the easily accessible tri-*O*-benzoyl-α-D-*arabino*-hexos-ulosyl bromide **1** as the model compound. C-Glycosidation with an electrophilic anomeric carbon requires prior carbonyl protection, to avoid carbonyl addition by the C-nucleophile, for example, as the cyanohydrin. Silver triflate-promoted reaction with the silylenol ether of acetophenone then efficiently yields the β-phenacyl product. With thermal (AIBN) or photochemical induction, **1** smoothly generates an anomeric radical – comparatively electrophilic, due to its capto-dative substitution – which exclusively traps hydrogen in the presence of tributyltin and electron-deficient alkenes. With allyltributylstannanes, however, it reacts with high stereoselectivity to afford α-*C*-allyl glycosiduloses. The α-bromoketone functionality in ulosyl bromide **1** is susceptible to Reformatsky conditions: treatment with zinc-copper couple readily generates the 1,2-enolate, a most simple anomeric nucleophile, which effectively adds to aldehydes to give α-*C*-hydroxyalkyl glycosiduloses or α-*C*-disaccharides (with sugar aldehydes) with a high degree of double stereoselection.

Introduction

2-Ketohexosyl ("ulosyl") bromides of type VII have become readily accessible in large variety, as they can efficiently be prepared from the easily accessible 2-acyloxyglycals[2] (I) by either one of two ways: a high-yield, three-step procedure involving hydroxylaminolysis of the enediol ester group[3] (I → II), deoximation[3] (→ III), and photobromination at the push-pull-substituted anomeric center[6] (III → IV → VII) or, alternately, a straightforward, one-step process consisting simply of treatment of I with *N*-bromosuccinimide or bromine in the presence of methanol (Scheme 1).[5] Mechanistically, the direct conversion I → VII is thought to proceed by initial attack of the bromonium ion to form a 2-bromobenzoxonium salt intermediate of type V,[6] in which the 2-*O*-benzoyl group is captured by methanol, the resulting formation of methyl benzoate leaving the ion pair VI, which combines to form VII. The ease with which this conversion can be effected (30 min, room temperature) is as remarkable as the yields attainable (80−90%) and its applicability to essentially any blocking group pattern in the starting material, disaccharides included.

As Koenigs−Knorr glycosidation of these ulosyl bromides proceeds in an essentially β-specific manner − their nonparticipating, electron-withdrawing 2-keto groups favor direct S_N2 displacement of the bromine by O-nucleophiles[3d,5] – and since reduction of the β-D-hexosiduloses formed is highly *manno*-selective,[3d,5,7] this methodology has successfully been applied to the synthesis of various β-D-mannose-containing oligosaccharides up to the hexasaccharide level,[8,9] as well as to the generation of β-L-rhamnosidic linkages.[10]

As *C*-glycopyranosyl-containing natural products have been the focus of increasing biological, and hence synthetic, interest,[11] we were motivated to assess the reaction potential of ulosyl bromides of type VII for anomeric C-homologation: the synthesis of C-glycosid-2-uloses. This was deemed the more interesting as C-glycosidation would be expected to be feasible not only through the conventional electrophilic intermediates, as in VI, but also via the push-pull-substituted, hence readily generated, anomeric radicals of type IV, as well as via anomeric carbanions, since the α-bromoketone structural element in VII should be susceptible to Reformatsky-type conditions, a zinc 1,2-enolate then being the decisive intermediate. For exploration of these options the most readily accessible 3,4,5-tri-*O*-benzoyl-α-D-*arabino*-hexulosyl bromide (**1**) was used, the results being subject of this report.[12]

Results and Discussion

Electrophilic C-Glycosidation

Anomeric cyanation of an acylated glycosyl halide has undoubtedly been the most practical C-extension method

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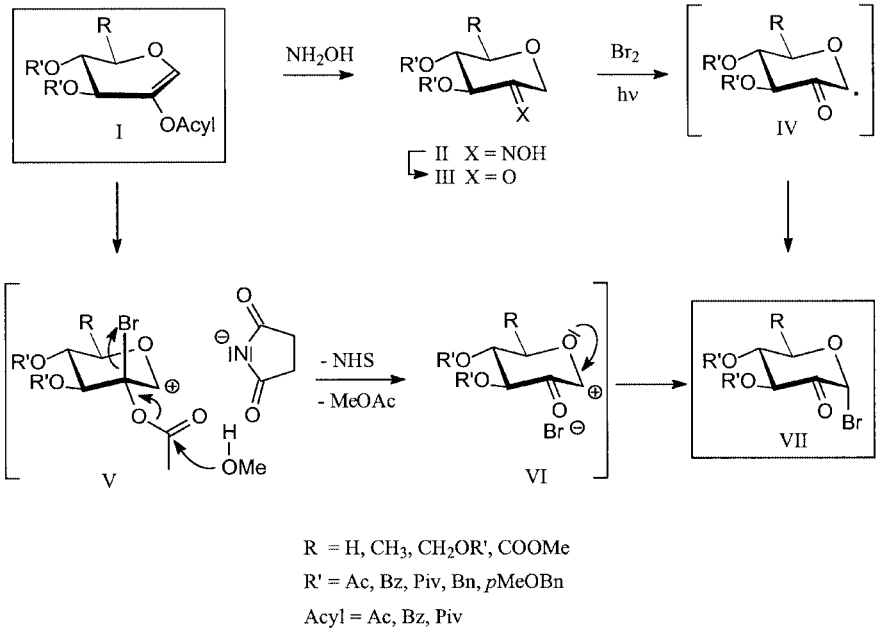
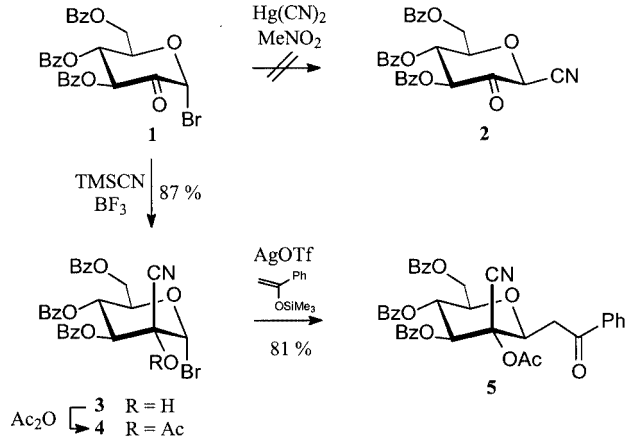


Scheme 1

in terms of simplicity of reagents, workup procedures, and yields.[13−15] However, treatment of ulosyl bromide **1** (Scheme 2) under the original Helferich cyanation conditions[13] (mercuric cyanide in nitromethane for 1−2 days at ambient temperature, a procedure that also worked well with hexulosyl bromides[14]) invariably resulted in complex product mixtures containing at best traces of the glycosylcyanide **2** (or its α-C anomer). More favorable conditions were found to be cyanation with trimethylsilyl cyanide/BF_3−diethyl ether.[15] Indeed, the reaction with **1** was instantaneous, but the anomeric bromine was not replaced by cyanide. The cyanohydrin **2**, isolable in crystalline form in 87% yield, was instead quantitatively formed (TLC). Thus, of the two electrophilic carbons that may be attacked by cyanide, involving displacement of bromine at C-1 or carbonyl addition at C-2, the latter is strongly preferred, obviously due to the electron-withdrawing effect of the 2-carbonyl, diminishing the polarity of the C−Br bond.

Anomeric C-extension in ulosyl bromides of type **1**, either by direct S_N2 displacement of the bromine by a C-nucleophile or in an bimolecular fashion through electrophilic intermediates of type VI, is thus unlikely to be effected directly. If the carbonyl group is protected, however − as the cyanohydrin **3** or its stable acetate **4**, for example − the reaction should proceed uniformly. Indeed, the silver triflate-promoted reaction between **4** and the trimethylsilylenol ether of acetophenone cleanly gives the 1-*C*-(β-D-glucosyl)acetophenone **5**.

The configuration at the tertiary C-2 of **3**, **4**, and **5** was inferred by analogy. Hydride addition to the carbonyl group of **1** has been shown to proceed from the β-side with high selectivity to give the corresponding glucosyl bromide, the configuration of which was readily established by ^1H NMR spectroscopy.[16] Attack of the more bulky cyanide would certainly not be expected to occur from the α-side (i.e., the side of the anomeric bromine), but should follow an analogous steric course.



Scheme 2

Radical C-Glycosidation

The most commonly used approach for C-extensions with glycosyl radicals is their generation from glycosyl bromides with tributyltin hydride and AIBN as initiators, and treatment with electron-deficient alkenes.[17] However, attempts to induce radical-induced coupling of ulosyl bromide **1** with acrylates or acrylonitrile under a variety of conditions failed, since the 2-oxoglycosyl radical **8**, generated by Bu_3SnH/hν or AIBN, is quantitatively trapped by hydrogen even in acrylonitrile as the solvent, to afford the known[3b,3c] 1,5-anhydro-D-fructose tribenzoate (**6**).

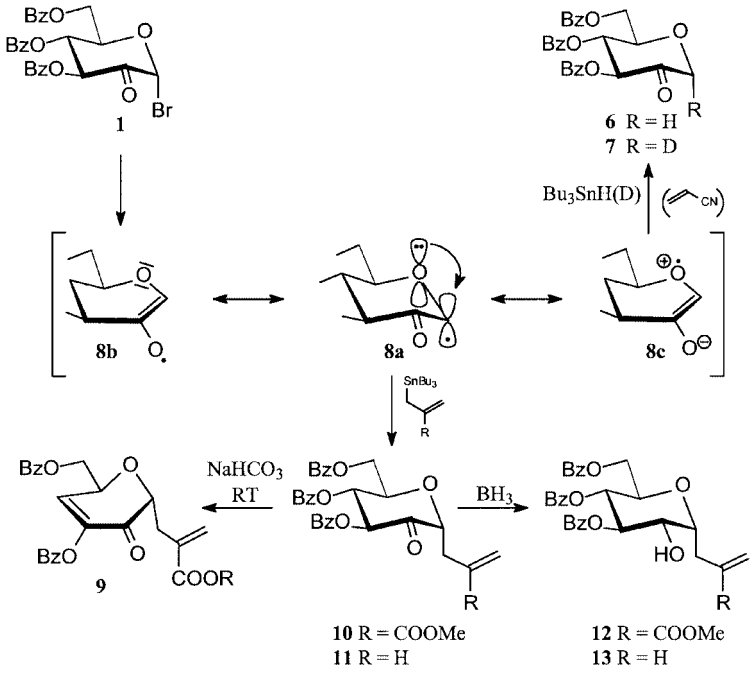
This course is in fact not unexpected, since even the prototype nucleophilic glucopyranosyl radical, generated from acetobromoglucose,[17] produces the hydrogen transfer product 1,5-anhydroglucose tetraacetate in a yield of over 20% on reaction with acrylonitrile,[17b] and the 2-oxoglycosyl radical **8** is clearly less nucleophilic, if not essentially electrophilic due to its push-pull − or capto-dative[18] − substitution: an electron-withdrawing group such as a carbonyl moiety next to a carbon radical entails a stabilization by some 10−12 kcal/mol in relation to a "pure" C-radical,[19] and the additional presence of a cycloalkoxy group allows for a variety of mesomeric forms (i.e., **8a** ⇄ **8b** ⇄ **8c**, Scheme 3). This is likely to result in a planar arrangement of O5−C1−C2−C3 (i.e., a $^4H_5$ half chair form rather than a mere $^4C_1$-type chair geometry as in **8a**). Nevertheless, hydrogen transfer (**8** → **6**) from the axial side is highly favored, as evidenced by treatment of **1** with Bu_3SnD, which gave the α-deuterated **7** with an 85:15 preference.

To avoid hydrogen trapping of the 2-oxoglycosyl radical **8**, inherent radical chain transfer reagents − allyltributylstannane and its 2-methoxycarbonyl analogue − were then tested for use in anomeric C-homologenation.[20] Indeed, ulosyl bromide **1**, on treatment with methyl 2-(tributylstannylmethyl)propenoate and catalytic amounts of AIBN, was converted into the 1-*C*-(α-D-2-ketoglycosyl)methylacrylate **10**, isolable in crystalline form (57%). The allyltributylstannane, though, reacted more sluggishly, giving, after carbonyl reduction with borane/pyridine,[7] 1-*C*-(α-D-glucosyl)-propene **13** in modest yield (26%). Thus, by use of the proper reagents, a "one-electron" C-extension may be effected even with electrophilic glycosyl radicals, although their more nucleophilic analogues appear to be preparatively more propitious towards this end.[21]

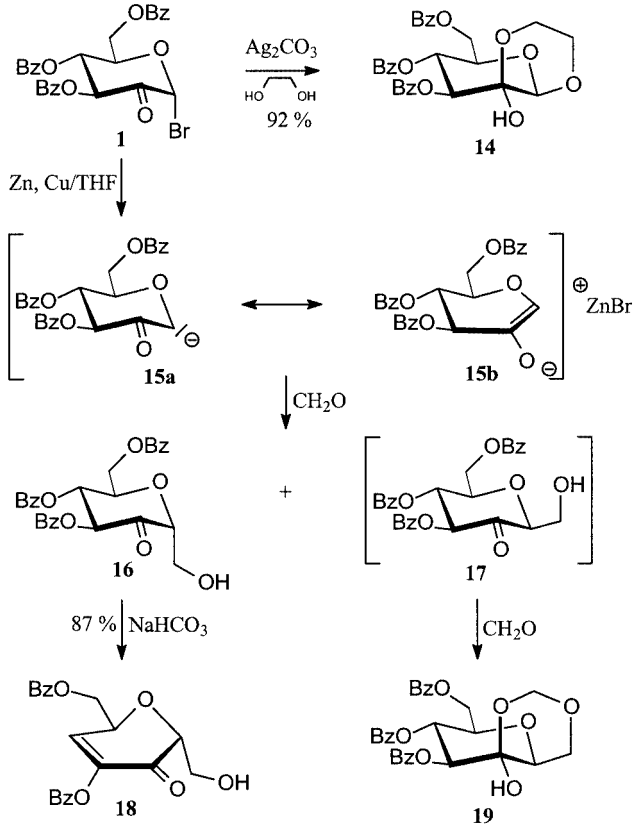
That the free radical-mediated C-glycosidations of ulosyl bromide **1** to **10** and **11** proceeded α-selectively, as already observed for the deuteration (→ **7**), followed most simply from their reduction products with BH_3/pyridine, **12** and **13**, which proved to have α-D-*gluco* configurations on the basis of their pyranoid ring $J_{1,2}$ couplings of 5.3−5.4 Hz, as usually found for α-*C*-alkyl or allyl glucosides.[17,22] Another preparatively useful ensuing reaction of C-glycosid-2-uloses of type **10** or **11** derives from their propensity to eliminate benzoic acid from the 3,4-positions. Simple treatment of **10** with, for example, sodium hydrogen carbonate in aqueous acetone at ambient temperature, smoothly afforded the enolone ester **9** (85% isol. yield), an enantiopure dihydropyranone building block with a particularly versatile array of functional groups.

Nucleophilic C-Glycosidations

Ulosyl bromide **1**, featuring an α-bromocarbonyl functionality, was expected to be susceptible to Reformatsky-type conditions, i. e. to generate enolate intermediate **15** on treatment with zinc in an inert solvent. Indeed, when **1** was treated with copper-activated zinc in THF, followed by addition of formaldehyde, a 1:1 mixture of α- and β-hydroxymethylation products was generated, of which the α isomer **16** was isolable (35%), but difficult to purify, since extensive 3,4-elimination of benzoic acid occurred on elution from a silica gel column to give the dihydropyranone **18** (Scheme 4). On brief treatment with $NaHCO_3$ in aqueous acetone, the conversion **16** → **18** can be effected quantitatively, thus smoothly affording a versatile enantiopure C_7-building block.



Scheme 3

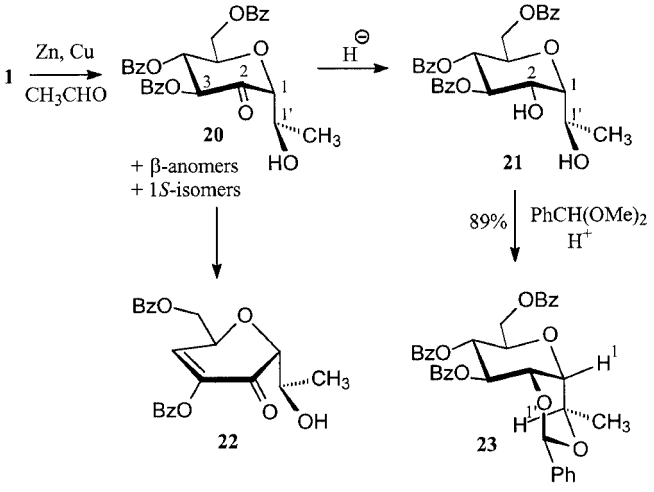


Scheme 4

The β anomer **17** cannot be isolated as such, but is obtained as the crystalline 1,3-*O*-methylene-bridged cycloacetal **19** (29%), since − unlike the α anomer **17** − this compound reacts in situ with another formaldehyde molecule.

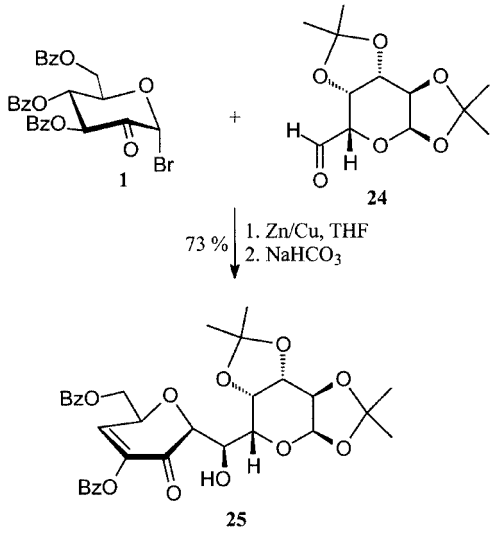
The anomeric configurations of the two *C*-glycosiduloses were inferred from the near identity of the ^{1}H NMR chemical shifts and coupling patterns for the pyranoid hydrogens (except for 1-H) of **19** with those of the isomeric cycloacetal *O*-glycosidulose **14**, formed nearly quantitatively on treatment with Ag_2CO_3/glycol, in conjunction with the established fact that *O*-glycosidations of **1** always proceed in an essentially β-specific manner.[5,8] Additional evidence was provided by the significantly small coupling constants between the anomeric proton (1′-H) and the two hydrogens of the introduced hydroxymethyl group in **19** ($J_{1,1'}$ = 0.5, 1.6 Hz), since the alternative *cis*-annelated cycloacetal derived from α-*C*-glycoside **16** through elaboration of a methylene bridge would be expected to show one diaxial 1-H/1′-H coupling in the 8−10 Hz range.

Use of acetaldehyde as the electrophile to react with the zinc enolate **15** gave an approximately 2:1 α/β mixture of 1-*C*-(hydroxyethyl)glycosid-2-ulose (^{1}H NMR), in which the α-(1*R*) isomer **20** predominated (Scheme 5). It was not isolated as such, but in the form of ensuing products: elimination of benzoic acid by treatment with $NaHCO_3$ in aqueous acetone gave a dihydropyranone mixture from which **22** crystallized (48%, based on ulosyl bromide **1**), whereas reduction with $NaBH_3CN$ afforded the 1-*C*-(hydroxyethyl)-glucoside **21**, also in crystalline form (43%). Its α configuration clearly followed from the coupling of the anomeric 1-H ($J_{1,2}$ = 4.3 Hz), whilst the *R* configuration in the hydroxyethyl moiety was ascertained from the coupling patterns of the benzylidene derivative **23**, obtained on cycloacetalization of **21** with benzaldehyde dimethyl acetal (89%): its anomeric 1-H showed − apart from a $J_{1,2}$ of 4.5 Hz − a large coupling of 10.6 Hz for $J_{1,1'}$, only compatible with an *anti* arrangement of 1-H and 1′-H (i.e., the 1*R* configuration in **23**, and hence in **20**−**23**).



Scheme 5

Trapping of the ulosyl bromide-derived enolate **15** with carbohydrate-based aldehydes would be expected to generate *C*-disaccharides. Treatment of **1** with the diacetonegalactose-6-aldehyde **24**, for example, smoothly gave an approximately 8:1 mixture of two addition products (^{1}H NMR),[23] which, because of difficulties in separating the mixture on silica gel, was directly subjected to $NaHCO_3$ treatment in aqueous acetone to induce β-elimination of benzoate. This resulted in the isolation of the beautifully crystalline *galacto*-dihydropyranone **25** (yield as high as 73%). Configurational evidence for the α-linkage of the dihydropyranone and galactose portions in **25** could already be derived from chiroptical data, as the long-wave Cotton effect for the exciton split enone-R-band is negative ($\Delta\varepsilon_{max}$ = −0.48 at 335 nm) as usually observed for 2,6-*trans* substitution for dihydropyranones of this type[24] as well as for the acetaldehyde addition-derived **22** ($\Delta\varepsilon_{max}$ = −0.15 at 349 nm). In contrast, 2,6-*cis*-substituted enantiopure analogues consistently exhibit positive enone-R-Cotton effects. The (*R*) configuration at the carbon linking the two pyranoid residues, however, could only be derived from X-ray structural analysis,[25] which unequivocally established the configurations of the two newly formed chiral centers as shown in Scheme 6.



Scheme 6

As the zinc−copper-mediated reaction between **1** and aldehyde **24** can give rise to four isomeric products, the generation of a single one, **25**, in 73% yield shows a remarkable double stereoselectivity with a strong preference for α-C-glycosidation of the ulosyl bromide together with elaboration of the (*R*) configuration for the CHOH group linking the pyranoid moieties (Scheme 6). This double stereoselection is undoubtedly due to the sterically demanding isopropylidene-protected galactosyl aldehyde.

Conclusion

A series of novel C-glycosides bearing keto groups at C-2 have been synthesized from the readily available α-D-*arabino*-2-ketohexosyl bromide **1**, which features the unique capability to undergo C-extension through the straightforward generation of electrophilic, radical, and nucleophilic anomeric carbons. The availability of these C-homologated α-ketoglycosides not only provides novel candidates for evaluation as glycosidase inhibitors, but also expands − most notably with the enantiopure 2,6-disubstituted dihydropyranones − the pool of easily accessible sugar-derived building blocks for the synthesis of noncarbohydrate natural products.

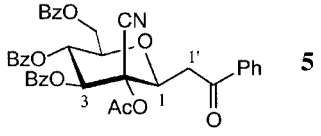
Experimental Section

General Remarks: All solvents were of reagent grade and were further dried. All other reagents were used as received. Melting points are uncorrected and were measured on a Büchi SMP-20. Optical rotations were measured with a Perkin−Elmer 241 polarimeter at 20 °C in a cell of 1 dm path length. Mass spectra were recorded with Varian MAT 311 and MAT 212 spectrometers. Microanalyses were determined with a Perkin−Elmer 240 Elemental Analyzer. Analytical thin layer chromatography (TLC) was performed with precoated Merck plastic sheets (0.2 mm silica gel 60-F_{254}) with detection by UV (254 nm) and/or by spraying with H_2SO_4 (50%) and heating. Column chromatography was carried out on Fluka silica gel 60 (70−230 mesh); eluents are given in brackets. ^1H and ^{13}C NMR spectra were recorded with Bruker WM 300, and AVANCE 500 spectrometers. Chemical shifts are reported relative to Me_4Si as internal reference. Coupling constants are listed separately if an assignment was possible. In the listings of ^1H and ^{13}C NMR spectroscopic data for the individual compounds, signals from blocking groups, such as those originating from benzoyl moieties, are omitted if well separated from the hexopyranoid hydrogen and carbon signals.

Nomenclature: For simplicity, the anomerically C-extended products described here are designated as C-glycosides rather than as heptos-3-ulose (**16**, **17**), octulose (**20**), or nonulosonic acid (**10**) derivatives, as officially allowed.[26] Accordingly, the C-aglycon residue (with prime numbering) is considered to be substituted by a C-hexopyranosyl moiety (standard numbering, C-1 to C-6). The pyranoid enolone esters **18**, **22** and **25**, however, being dihydropyranones, follow pyran ring numbering starting at the ring oxygen.

3,4,6-Tri-*O*-benzoyl-2*S*-cyano-α-D-glucopyranosyl Bromide (3): Trimethylsilyl cyanide (1.7 mL, 1.5 molar equiv.) was added to a solution of ulosyl bromide **1** (5.00 g, 9 mmol) in CH_2Cl_2 (50 mL), and the solution was stirred at ambient temperature for 4 h. The reaction mixture was diluted with $CHCl_3$ form (100 mL), washed with satd. aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). Concentration in vacuo gave a syrup, which was dissolved in EtOAc and filtered through a short column of silica gel. The filtrate was concentrated to a crystalline solid, which was recrystallized from $CHCl_3$/*n*-hexane to afford **3** (4.58 g, 87%) as colorless crystals of m.p. 178−180 °C; $[\alpha]_D^{20}$ = +81.4 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.49 (dd, 1 H, 6-H_a), 4.66 (m, 3 H, 5-H, 6-H_b, OH), 5.94 (d, 1 H, 3-H), 6.08 (t, 1 H, 4-H), 6.64 (s, 1 H, 1-H) ppm; $J_{3,4}$ = 9.7, $J_{4,5}$ = 9.7, $J_{5,6a}$, = 4.4, $J_{6,6}$ = 13.2 Hz. MS (FD): *m*/*z* = 580 [M^+], 581 [M +1]. $C_{28}H_{22}BrNO_8$ (580.40): calcd. C 57.94, H 3.82, N 2.41; found C 57.88, H 3.75, N 2.35.

2-*O*-Acetyl-3,4,6-tri-*O*-benzoyl-2*S*-cyano-α-D-glucopyranosyl Bromide (4): A few drops of BF_3−diethyl ether were added to a suspension of cyanohydrin **3** (1.00 g, 1.7 mmol) in acetic anhydride (10 mL), followed by stirring of the mixture at ambient temperature for 3 h. The reaction mixture was then poured with stirring into cold aqueous $NaHCO_3$ solution. The precipitated solids were filtered off and dissolved in diethyl ether, from which an amorphous solid precipitated upon addition of *n*-hexane. After standing at 5 °C, filtration and drying afforded **4** (1.00 g, 93%) as a uniform solid of R_f = 0.45 (hexane/EtOAc, 2:1). M.p. 157−158 °C;$[\alpha]_D^{20}$ = +43.9 (*c* = 1.1, $CHCl_3$). MS (FD): *m*/*z* = 622 [M^+]. $C_{30}H_{24}BrO_9N$ (622.44): calcd. C 57.89, H 3.87, N 2.25; found C 57.80, H 3.80, N 2.23.



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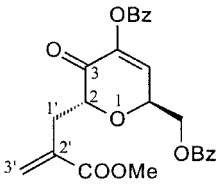
1′-*C*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzoyl-2*S*-cyano-β-D-glucopyranosyl)acetophenone (5): 1-Phenyl-1-trimethylsilyloxy-ethene (1 mL, 3 molar equiv.) and silver triflate (870 mg, 3.2 mmol) were added to a solution of cyanohydrin bromide **4** (1.0 g, 1.6 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred in the dark for 7 h, after which **4** had disappeared (TLC, *n*-hexane/EtOAc, 2:1). The reaction mixture was filtered, and the filtrate was diluted with

$CHCl_3$ and washed with satd. aqueous $NaHCO_3$ solution and water, followed by drying (Na_2SO_4), and concentration to a syrup, which solidified on trituration with benzene/*n*-hexane. Purification by elution from a silica gel column (1.5 × 20 cm) with *n*-hexane/EtOAc (2:1), collection of the appropriate fraction, and concentration in vacuo afforded **5** (750 mg, 81%) as a syrup;$[\alpha]_D^{20} = -41$ (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, Ac), 3.55 and 3.78 (2d, J = 16.1 Hz, 1 H each, phenacyl-CH_2), 4.46 (m, 1 H, 5-H), 4.55 and 4.65 (2 dd, 1 H each, 6-H_2), 5.57 (dd, 1 H, 4-H), 5.90 (d, 1 H, 3-H), 6.17 (s, 1 H, 1-H) ppm; $J_{3,4}$ = 3.4, $J_{4,5}$ = 7.7, $J_{5,6}$ = 4.8 and 3.2, $J_{6,6}$ = 12.1, $J_{1,1'} > 0.3$, $J_{1',1'}$ = 16.1 Hz. MS (FD): m/z = 661 [M^+], 662 [M +1]. $C_{38}H_{31}NO_{10}$ (661.68): calcd. C 68.98, H 4.72, N 2.12; found C 68.90, H 4.66, N 2.11.

3,4,6-Tri-*O*-benzoyl-1,5-anhydro-D-fructose (6): A solution of ulosyl bromide **1** (2.20 g, 4 mmol) and tributyltin hydride (1.45 g, 5 mmol) in diethyl ether (20 mL) was kept at reflux by irradiation with a high-pressure mercury lamp for 4 h, and subsequently taken to dryness. The residue was dissolved in acetonitrile (50 mL), followed by extraction with *n*-pentane (3 × 20 mL) and removal of the solvent. The resulting syrup crystallized on trituration with CH_2Cl_2/*n*-hexane to afford **6** (1.40 g, 74%) as colorless crystals of m.p. 126−127 °C and $[\alpha]_D^{20} = -29$ (c = 1, $CHCl_3$); ref.[3b][3c] m.p. 126−127 °C and $[\alpha]_D^{20} = -29.2$ (c = 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, C_6D_6): δ = 3.44 (d, 1 H, 1-H_a), 3.74 (ddd, 1 H, 5-H), 3.94 (d, 1 H, 1-H_e), 4.36 and 4.61 (2 dd, 1 H each, 6-H_2), 5.92 (d, 1 H, 3-H), 6.05 (t, 1 H, 4-H) ppm; $J_{1,1}$ = 15.1, $J_{3,4}$ = 10.1, $J_{4,5}$ = 9.8, $J_{5,6}$ = 2.8 and 5.0, $J_{6,6}$ = 12.3 Hz. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.27 and 4.39 (2d, 1 H each, 1-H_2), 4.40 (m, 1 H, 5-H), 4.54 and 4.72 (2 dd, 1 H each, 6-H_2), 5.92 (m, 2 H, 3-H, 4-H) ppm; $J_{1,1}$ = 15.3, $J_{5,6}$ = 2.7 and 5.4, $J_{6,6}$ = 12.3 Hz. $C_{27}H_{22}O_8$ (474.45): calcd. C 70.73, H 4.84; found C 70.69, H 4.80.

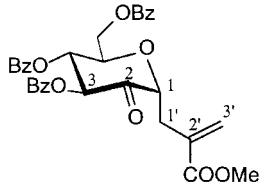
The presence of a fivefold molar excess either of acrylonitrile or methyl acrylate in the reaction mixture, or even of the conduction of the reaction in acrylonitrile as solvent, inevitably resulted in reductive debromination to **6**, with only traces of the products detectable by TLC. The same course was observed when radical formation was initiated with AIBN in refluxing benzene.

3,4,6-Tri-*O*-benzoyl-1*S*-monodeuterio-1,5-anhydro-D-fructose (7): A solution of **1** (550 mg, 1 mmol) and tributyltin deuteride (320 mg, 1.1 mmol) in diethyl ether (10 mL) was irradiated as described above. The resulting syrup, which had partially crystallized, was subjected to ^{1}H NMR in C_6D_6 (rather than $CDCl_3$, due to better resolution of the signals), indicating it to be an 85:15 mixture of the α-(**7**, major) and 1-β-deuterated isomers as shown by the signal intensities of 1-H_a (δ = 3.42 ppm) and 1-H_e (δ = 3.92 ppm).



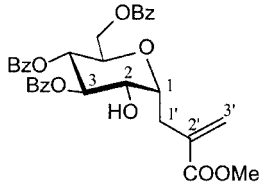
9

(2*R*,6*S*)-4-Benzoyloxy-2-benzoyloxymethyl-2-[2′-(methoxycarbonyl)propen-1′-yl]-3,6-dihydro-2*H*-pyran-3-one (9): Sodium hydrogen carbonate (1.0 g, 8 mmol) was added to a solution of C-uloside **10** (510 mg, 0.89 mmol) in acetone (15 mL) and water (1.5 mL), and the mixture was stirred at ambient temperature for 3 h. Filtration, dilution with CH_2Cl_2 (100 mL), washing with water (3 × 15 mL), drying ($MgSO_4$), and evaporation to dryness in vacuo left a syrup, which was purified by elution from a short silica gel column with cyclohexane/EtOAc (4:1). Evaporation of the appropriate fraction afforded of dihydropyranone **9** (340 mg, 85%) as a colorless syrup of $[\alpha]_D^{20} = -15.8$ (c = 0.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85, 2.94 (2 dd, 1 H each, 1′-H_2), 3.70 (s, 3 H, OCH_3), 4.49, 4.68 (2 dd, 1 H each, CH_2OBz), 4.78 (dd, 1 H, 2-H), 5.14 (ddd, 1 H, 6-H), 5.75, 6.28 (2 d, 1 H each, 3′-H_2), 6.81 (d, 1 H, 5-H) ppm; $J_{2,1'}$ = 4.7 and 9.8, $J_{5,6}$ = 2.8, J_{6,CH_2} = 4.1 and 6.5, $J_{1',1'}$ = 14.8, $J_{1',2}$ = 4.7, 9.6 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.1 (C-1′), 52.1 (OCH_3), 64.3 (CH_2OBz), 69.2 (C-6), 77.7 (C-1), 128.3−134.5 (2 C_6H_5), 128.7 (C-3′), 135.6 (C-2′), 143.1 (C-4), 164.1, 166.2, 167.0 (2 × C_6H_5CO, COOMe), 188.7 (C-3) ppm. $C_{25}H_{22}O_8$ (450.44): calcd. C 66.66, H 4.92; found C 66.48, H 4.83.



10

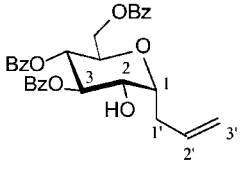
1′-*C*-(3,4,6-Tri-*O*-benzoyl-α-D-hexopyranosyl-2-ulosyl)-2′-(methoxycarbonyl)propene (10): A solution of ulosyl bromide **1** (2.2 g, 4.0 mmol), methyl 2-(tri-*n*-butylstannylmethyl)propenoate[27] (1.6 g, 4.1 mmol), and AIBN (25 mg, 0.13 mmol) in benzene (50 mL) was heated at reflux under dry N_2. After 6 h another portion of AIBN (25 mg) was added and heating was continued for 2 h. Evaporation of the solvent gave a crystalline solid, which was dissolved in acetonitrile (60 mL) and washed with *n*-hexane (4 × 10 mL) and pentane (4 × 10 mL). The acetonitrile layer was concentrated to dryness, and the crystalline residue was recrystallized from benzene/*n*-hexane (15 mL, 2:1) to afford **10** (1.20 g, 52%) as colorless needles; concentration of the mother liquor furnished additional **10** (120 mg, 5%). M.p. 159−161 °C; $[\alpha]_D^{20} = +50.9$ (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 (dd, 1 H, 1′-H_a), 2.99 (dd, 1 H, 1′-H_b), 3.72 (s, 3 H, OCH_3), 4.62−4.73 (m, 4 H, 1-H, 5-H, 6-H_2), 5.78 and 6.29 (2d, 1 H each, 3′-H_2), 5.84 (dd, 1 H, 4-H), 6.14 (d, 1 H, 3-H) ppm; $J_{1',1'}$ = 14.4, $J_{1'a,1}$ = 5.3, $J_{1'b,1}$ = 9.5, $J_{3,4}$ = 10.1, $J_{4,5}$ = 7.9 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.3 (C-1′), 52.1 (OCH_3), 63.3 (C-6), 70.6 (C-4), 72.3 (C-5), 75.7 (C-3), 79.5 (C-1), 128.4−134.4 (3 C_6H_5), 129.1 (C-3′), 134.4 (C-2′), 165.0, 165.4, 166.1, 166.7 (3 C_6H_5CO, 2′-COOMe), 199.8 (C-2) ppm. MS (FD, 20 mA): m/z = 572 [M^+]. $C_{32}H_{28}O_{10}$ (572.57): calcd. C 67.07, H 4.89; found C 66.97, H 4.74.



12

1′-*C*-(3,4,6-Tri-*O*-benzoyl-α-D-hexopyranosyl)-2′-(methoxycarbonyl)propene (12): A solution of ulosyl bromide **1** (1.1 g, 2 mmol), methyl 2-(tri-*n*-butylstannylmethyl)propenoate[27] (0.9 g, 2.3 mmol), and AIBN (30 mg, 0.15 mmol) in benzene (25 mL) was heated at reflux for 7 h under dry N_2. The solvent was removed in vacuo, and the remaining residue was dissolved in THF (10 mL) and cooled to −78 °C. A solution of BH_3/pyridine (1.0 mL, 10 mmol) in THF was added dropwise over 10 min and stirring was continued for 30 min. The mixture was warmed up to room temp.,

stirred for another hour, and quenched with water (5 mL). Evaporation of the solvent in vacuo afforded a syrup, which was dissolved in acetonitrile (40 mL) and extracted with pentane (3 × 10 mL). Reextraction of the pentane phase with acetonitrile (5 mL) and concentration of the collected acetonitrile layers gave a residue, which was subjected to chromatographic purification (silica gel, 3 × 35 cm) with toluene/EtOAc (20:1) as the eluent. Evaporation of the appropriate fraction to dryness left a syrup, which was crystallized from diisopropyl ether to afford **12** (675 mg, 59%) as colorless crystals of m.p. 103−104 °C; $[\alpha]_D^{20} = +39.9$ (c = 0.9, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.90 (dd, 3 H, 1′-H_2, 2′-OH), 3.71 (s, 3 H, OCH_3), 4.16 (dd, 1 H, 2-H), 4.37(ddd, 1 H, 5-H), 4.49 (m, 3 H, 1-H, 6-H_2), 5.49 (dd, 1 H, 4-H), 5.60 (dd, 1 H, 3-H), 5.79 and 6.23 (2d, 2 H, 3′-H_2) ppm; $J_{1,2}$ = 5.3, $J_{2,3}$ = 8.3, $J_{3,4}$ = 8.2, $J_{4,5}$ = 8.1, $J_{5,6a}$ = 5.9, $J_{5,6b}$ = 3.7 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.5 (C-1′), 52.1 (OCH_3), 63.3 (C-6), 69.4 (C-4), 70.0 (C-5), 70.3 (C-2), 74.2 (C-1, C-3), 128.1 (C-3′), 128.4−136.5 (3 × C_6H_5, C-2′), 165.5, 166.3, 167.0, 167.5 (3 × C_6H_5CO, 2′-$COOMe$) ppm. MS (FD, 20 mA): m/z = 574 [M^+]. $C_{32}H_{30}O_{10}$ (574.58): calcd. C 66.89, H 5.26; found C 66.91, H 5.10.



13

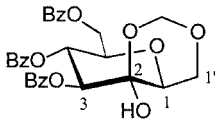
1′-*C*-(3,4,6-Tri-*O*-benzoyl-α-D-hexopyranosyl)propene (13): A mixture of ulosyl bromide **1** (1.6 g, 2.9 mmol), allyltributylstannane[20b] (4.5 mL, 15 mmol), and AIBN (40 mg, 0.2 mmol) in benzene (30 mL) was heated at reflux under dry N_2 for 4 h. Additional AIBN (40 mg) was added and heating was continued for another 3 h. The mixture was concentrated to a syrup, dissolved in THF (30 mL), cooled to −78 °C, and subjected to reduction with BH_3/pyridine (1.4 mL, 14 mmol) in THF (3 mL) for 30 min. The solution was then warmed to room temp., and was quenched with water (5 mL), followed by removal of the solvents in vacuo. The remaining syrup was dissolved in CH_2Cl_2 (50 mL), washed successively with HCl (2 N, 2 × 15 mL) and satd. aq. $NaHCO_3$ (10 mL), and dried (Na_2SO_4). Evaporation of the solvent gave a syrup, which was purified by chromatography on silica gel (4 × 20 cm) with cyclohexane/EtOAc (4:1) as eluent. Fractions with R_f = 0.16 (TLC in eluent), on evaporation to dryness, left a syrup, which was crystallized from diisopropyl ether to afford **13** (390 mg, 26%). M.p. 164−165 °C; $[\alpha]_D^{20} = +13.3$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (dd, 2 H, 1′-H_2), 2.81 (d, 1 H, 2-OH), 4.12 (ddd, 1 H, 2-H), 4.26−4.32 (m, 2 H, 1-H, 5-H), 4.50 and 4.57 (2 dd, 1 H each, 6-H_2), 5.05 (ddd, 1 H, H-3′$_a$), 5.21 (ddd, 1 H, H-3′$_b$), 5.47 (dd, 1 H, 3-H), 5.56 (dd, 1 H, 4-H), 5.86 (ddt, 1 H, 2′-H) ppm; $J_{1,2}$ = 5.2, $J_{2,3}$ = 8.0, $J_{2,OH}$ = 6.3, $J_{3,4}$ = 8.0, $J_{4,5}$ = 8.0, $J_{5,6}$ = 3.6 and 6.6, $J_{6,6}$ = 11.9, $J_{1',1'}$ = 1.4, $J_{1',3'}$ = 3.0, $J_{1',1}$ = 7.3, $J_{1',2'}$ = 7.1, $J_{2',3'a}$ = 10.2, $J_{2',3'b}$ = 17.1 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.3 (C-1′), 62.9 (C-6), 69.1 (C-3), 69.7, 73.8 (C-1, C-5), 70.0 (C-2), 74.0 (C-4), 117.4 (C-3′), 128.1−133.6 (3 C_6H_5, C-2′) ppm. $C_{30}H_{28}O_8$ (516.55): calcd. C 69.76, H 5.46; found C 69.63, H 5.43.

Zn/Cu-Mediated Addition of Ulosyl Bromide 1 to Aldehydes

Preparation of Zinc-Copper Couple: (adapted from ref.[16]): Zinc dust (392 mg, 6 mmol) was added to a hot (80 °C), well stirred solution of $Cu(OAc)_2 \cdot H_2O$ (22.4 mg, 0.1 mmol) in glacial acetic acid (1 mL). After about 30 sec the solution became colorless due to the deposition of the copper on the zinc. The silt-like couple was allowed to settle for about 1 min, followed by careful decantation of as much of the acetic acid as possible without loss of the deposits. The dark red-gray couple was then washed with a 1 mL portion of acetic acid and thrice with 1 mL of diethyl ether, followed by drying in a stream of nitrogen and subsequent suspension in dry THF (5 mL).

The Zn/Cu couple resulting from this procedure was used for reactions with 1 mmol of **1**. The procedure can readily be scaled up tenfold.

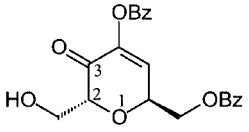
3,4,6-Tri-*O*-benzoyl-1,2-*O*-ethylene-β-D-*arabino*-hexopyranos-2-uloside (2*S*)-Cyclohemiketal (14): Glycol (0.7 mL, 12 mmol) was added to a suspension of Ag_2CO_3 (3.30 g, 12 mmol) and molecular sieves (4 Å, 3 g) in CH_2Cl_2 (100 mL), followed, after stirring at ambient temperature for 15 min, by the addition of ulosyl bromide **1** (5.53 g, 10 mmol). Stirring was continued for 5 h with exclusion of light, the mixture was filtered, and the solvent was removed in vacuo. The crystalline residue was recrystallized from EtOAc to give **14** (4.90 g, 92%). M.p. 181−182 °C; $[\alpha]_D^{20} = -7.1$ (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.57 and 4.33 (2m, 2 H each, 2 OCH_2), 4.10 (ddd, 1 H, 5-H), 4.50 and 4.67 (2dd, 1 H each, 6-H_2), 4.85 (s, 1 H, 1-H), 5.24 (d, 1 H, 3-H), 5.25 (s, 1 H, OH), 5.86 (dd, 1 H, 4-H) ppm; $J_{3,4}$ = $J_{4,5}$ = 10.0, $J_{5,6}$ = 2.9 and 5.0, $J_{6,6}$ = 12.1 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 59.1 and 59.4 (2 × OCH_2), 63.2 (C-6), 67.9 (C-4), 71.8 (C-5), 79.1 (C-3), 90.9 (C-2), 95.3 (C-1) ppm. MS (FD, 14 mA): m/z = 534 [M^+]. $C_{29}H_{26}O_{10}$ (534.5): calcd. C 66.17, H 4.90; found C 64.89, H 4.91.



19

Addition of 1 to Formaldehyde: *C*-(3,4,6-Tri-*O*-benzoyl-β-D-*arabino*-hexopyranos-2-ulosyl)methanol (1′,2*R*)-*O*-Methylene Cyclohemiacetal (19): Zn-Cu pair, prepared from $Cu(OAc)_2$ monohydrate (224 mg, 1 mmol) and zinc dust (3.92 g, 60 mmol), was suspended in dry THF (50 mL) and cooled to −35 °C. A solution of ulosyl bromide **1** (5.50 g, 10 mmol) in dry THF (50 mL) was added dropwise, while gaseous formaldehyde, generated by pyrolysis of paraformaldehyde (10 g, 110 mmol), was bubbled through the stirred mixture. Stirring was continued for 1 h at −35 °C, and the solution was then warmed to room temp., filtered, and poured into water (100 mL). After dilution with CH_2Cl_2 (500 mL), HCl (2 N) was added until clearness, and the organic layer was washed with satd. aq. $NaHCO_3$ (50 mL) and water (50 mL), followed by drying (Na_2SO_4) and evaporation of the solvents in vacuo, which resulted in a crystalline mass. Collection of the crystals and recrystallization from diethyl ether at −30 °C afforded **19** (1.5 g, 29%). M.p. 139−140 °C; $[\alpha]_D^{20} = -47.8$ (c = 1.1, $CHCl_3$); R_f = 0.47 (CH_2Cl_2/EtOAc, 10:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.51 (dd, 1 H, 1-H), 4.10 (m, 2 H, 1′-H_a, 5-H), 4.25 (dd, 1 H, 1′-H_b), 4.54 (dd, 1 H, 6-H_a), 4.64 (dd, 1 H, 6-H_b), 4.87, 5.26 (2d, J = 6 Hz, 1 H each, OCH_2O), 5.11 (d, 1 H, 3-H), 5.78 (s, 1 H, 2-OH), 5.90 (dd, 1 H, 4-H) ppm; J_{OCH_2O} = 6.0, $J_{1',1'}$ = 12.3, $J_{1'a,1}$ = 0.5, $J_{1'b,1}$ = 1.6, $J_{3,4}$ = 9.8, $J_{4,5}$ = 10.0, $J_{5,6a}$ = 5.9, $J_{5,6b}$ = 3.3 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 63.4 (C-1′), 64.6 (C-6), 69.0 (C-3), 72.3 (C-4), 74.3 (C-5), 76.1 (C-1), 85.6 (OCH_2O), 92.3 (C-2) ppm. MS (FD, 12 mA): m/z = 534 [M^+], 504 [M^+ − HCHO], 383 [M^+ − OBz]. $C_{29}H_{26}O_{10}$ (534.52): calcd. C 65.16, H 4.91; found C 65.12, H 4.83.

The ethereal mother liquor remaining after isolation of **19** still contained small amounts of **19** (ca. 5% by TLC, R_f = 0.47), together with **1′-*C*-(3,4,6-Tri-*O*-benzoyl-α-D-hexopyranos-2-ulosyl)methanol (16)** as the major product (R_f range 0.3−0.4 in CH_2Cl_2/EtOAc (10:1) due to the presence of keto and monohydrate forms on the TLC plate). Evaporation to dryness left crude **16** (2.1 g, 35%) as a foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (br. s, 1 H, 1′-OH), 4.09 (m, 2 H, 1′-H_2), 4.49 (t, 1 H, 1-H), 4.69 and 4.76 (2 dd, 1 H each, 6-H_2), 4.89 (ddd, 1 H, 5-H), 5.83 (dd, 1 H, 4-H), 6.17 (d, 1 H, 3-H) ppm; $J_{1',1}$ = 4.1, $J_{3,4}$ = 9.6, $J_{4,5}$ = 9.8, $J_{5,6}$ = 3.2, 5.5 Hz. MS (FD, 10 mA): *m*/*z* = 504 [M$^+$].

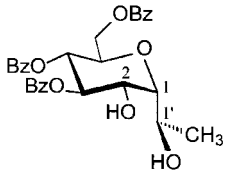


18

(2*R*,6*S*)-4-Benzoyloxy-6-benzoyloxymethyl-2-hydroxymethyl-3,6-dihydro-2*H*-pyran-3-one (18): Solid $NaHCO_3$ (0.5 g) was added to a solution of crude **16** (1.5 g, 3 mmol), as obtained above on workup of the mother liquor of **19**, in acetone (10 mL), and the mixture was stirred overnight at ambient temperature. Filtration, dilution of the filtrate with CH_2Cl_2 (50 mL), washing with water (20 mL), and evaporation of the organic phase to dryness left a syrup, which crystallized from methanol/water to afford **18** (0.99 g, 87%) as colorless crystals of m.p. 89−91 °C. $[\alpha]_D^{20}$ = −19.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (br. s, 1 H, OH), 4.00 and 4.11 (2dd, 1 H each, C*H*$_2$OH), 4.55 and 4.79 (2dd, 1 H each, CH_2OBz), 4.67 (dd, 1 H, 2-H), 5.25 (ddd, 1 H, 6-H), 6.84 (d, 1 H, 5-H) ppm; J_{2,CH_2} = 3.7 and 4.7, $J_{5,6}$ = 3.5, J_{6,CH_2} = 4.0, 6.1 Hz. MS (FD): *m*/*z* = 383 [M$^+$], 352 [M$^+$ − CH_2OH]. $C_{21}H_{18}O_7$ (382.4): calcd. C 65.96, H 4.75; found C 65.92, H 4.69.

Addition of 1 to Acetaldehyde: 1′-*C*-(3,4,6-Tri-*O*-benzoyl-α/β-D-*arabino*-hexopyranos-2-ulosyl)ethanol (20 + Isomers): A suspension of Zn-Cu couple in THF (50 mL, tenfold scale of the procedure given above) was cooled to −35 °C, and a solution of ulosyl bromide **1** (5.50 g, 10 mmol) and acetaldehyde (3.4 mL, 60 mmol) in THF (50 mL) was added dropwise. Stirring at −35 °C for 30 min, filtration, pouring of the filtrate into water (150 mL) containing HCl (2 N, 5 mL), extraction with CH_2Cl_2 (2 × 150 mL), washing of the combined extracts with satd. $NaHCO_3$ solution (100 mL) and water (100 mL), drying (Na_2SO_4), and evaporation in vacuo gave a foamy syrup (4.42 g, 85%), consisting of an approximate 2:1 mixture of hydroxyethyl α/β-C-ulosides in which **20** predominated. The mixture was directly used for carbonyl reduction (→ **21**) and elimination of benzoic acid (→ **23**).

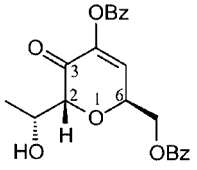
On standing for 2 d, partial crystallization occurred, but the crystals, isolated by filtration with cold methanol, of m.p. 154−155 °C still proved to be a mixture, not separable by fractional crystallization. Attempted separation by silica gel chromatography caused elimination of benzoic acid to produce dihydropyranones, of which **22** was obtained in crystalline form (vide infra).



21

(1′*R*)-(3,4,6-Tri-*O*-benzoyl-α-D-glucopyranosyl)ethanol (21): $NaBH_3CN$ (850 mg, 5 mmol) and Amberlite IR 120 (H^+-form, 2.5 g) were added to a solution of the α/β-hydroxyethyl C-uloside mixture obtained above (2.6 g, 5 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred overnight at room temperature. Filtration, pouring of the filtrate into satd. $NaHCO_3$ solution (100 mL), addition of CH_2Cl_2 (100 mL), separation of the organic phase, drying (Na_2SO_4), and evaporation to dryness left a syrup consisting of two main components (TLC). This was placed on a silica gel column (2 × 30 cm) and eluted with CH_2Cl_2/EtOAc (10:1). The fraction with R_f = 0.18 contained pure octitol **21**, which crystallized upon removal of the solvents in vacuo and trituration with EtOAc (1.10 g, 43%); m.p. 172−173 °C; $[\alpha]_D^{20}$ = −9.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, 3 H, CH_3), 3.00 (br. s, 1 H, OH), 3.90 (dd, 2 H, OH, 1-H), 4.31 (m, 2 H, 2-H, 5-H), 4.40 (dq, 1 H, EtC*H*), 4.47 and 4.67 (2dd, 1 H each, 6-H_2), 5.46 (dd, 1 H, 4-H), 5.63 (dd, 1 H, 3-H) ppm; $J_{1',2'}$ = 6.3, $J_{1',1}$ = 7.8, $J_{1,2}$ = 4.3, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 7.1, $J_{5,6}$ = 3.5 and 7.3, $J_{6,6}$ = 12.0 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.6 (*C*H_3), 62.8 (*C*H_2), 66.8, 68.8, 70.1, 72.1, 74.0, 75.4 (C-2′, C-1, C-2, C-3, C-4, C-5) ppm. MS (FD, 14 mA): *m*/*z* = 521 [M$^+$], 503 [M − H_2O], 475 [M − EtOH]. $C_{29}H_{28}O_9$ (520.6): calcd. C 66.91, H 5.43; found C 66.86, H 5.39.

Further eluates from the silica gel column proved, upon evaporation to dryness, to be syrupy mixtures of **21** with its β anomer and a minor product (TLC, ^{1}H NMR), which were not further characterized.



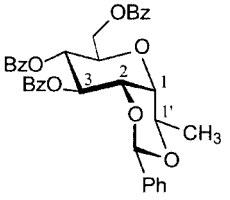
22

(2*R*,6*S*)-4-Benzoyloxy-6-benzoyloxymethyl-2-[(1*R*)-hydroxyethyl]-3,6-dihydro-2*H*-pyran-3-one (22): A solution of α/β-C-uloside mixture (3.65 g, 7 mmol), consisting of **20** and isomers, in acetone (70 mL) was stirred with $NaHCO_3$ (590 mg) at room temperature overnight, followed by filtration, dilution of the filtrate with CH_2Cl_2 (150 mL), washing with water, and evaporation to dryness in vacuo. The resulting syrupy mixture of dihydropyranones was subjected to chromatography (2.5 × 25 cm) with CH_2Cl_2/EtOAc (10:1).

The fraction eluted first (R_f = 0.33 in CH_2Cl_2/EtOAc, 10:1), upon removal of the solvents and trituration of the residue with methanol, gave **22** (1.56 g, 56% based on C-uloside mixture, 48% based on ulosyl bromide **1**) as colorless crystals. M.p. 105−106 °C; $[\alpha]_D^{20}$ = −37.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, 3 H, CH_3), 3.10 (br. s, 1 H, OH), 4.30 (ddd, 1 H, MeC*H*), 4.42 (d, 1 H, 2-H), 4.54 and 4.78 (2dd, 1 H each, CH_2OBz), 5.23 (ddd, 1 H, 6-H), 6.82 (d, 1 H, 5-H) ppm; $J_{2,CHMe}$ = 5.3, $J_{5,6}$ = 3.5, J_{6,CH_2} = 4.0, 6.2 Hz. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.1 (*C*H_3), 64.4 (*C*H_2OBz), 68.9 (C-6), 71.3 (CH_3*C*), 81.5 (C-2), 128.6−134.0 (m, C-5, 2 C_6H_5), 143.9 (C-4), 189.2 (C-3). CD (MeOH): $\Delta\varepsilon_{max}$ = −5.2 (242 nm), −0.15 (349 nm) ppm. MS (FD): *m*/*z* = 397 [M$^+$ +1]. $C_{22}H_{20}O_7$ (396.4): calcd. C 66.65, H 5.10; found C 66.68, H 5.06.

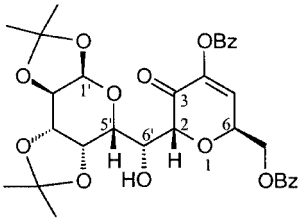
The fraction eluted second (R_f = 0.16), on evaporation in vacuo, gave an isomeric dihydropyranone (450 mg, 16%) as a syrup of $[\alpha]_D^{20}$ = −17.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 3 H, CH_3), 3.10 (br. s, 1 H, OH), 4.15 (dd, 1 H, 2-H), 4.29 (ddd, 1 H, CH_3C*H*), 4.55 and 4.64 (2dd, 1 H each, C*H*$_2$OBz), 5.04

(dddd, 1 H, 6-H), 6.91 (d, 1 H, 5-H) ppm; $J_{2,CHMe}$ = 6.2, $J_{2,6}$ = 2.2, $J_{5,6}$ = 1.7, $J_{6,CH2}$ = 5.1, 5.6 Hz. MS (FD, 7 mA): *m*/*z* = 397 [M^+ +1].



23

1′,2-*O*-Benzylidene Cycloacetal of (1*R*)-(3,4,6-Tri-*O*-benzoyl-α-D-glucopyranosyl)ethanol (23): Benzaldehyde dimethylacetal (150 mg, 1 mmol) and *p*-toluenesulfonic acid (1 mg) were added to a solution of α-hydroxyethyl C-glucoside **21** (520 mg, 1 mmol) in DMF (1 mL), and the mixture was heated to 60 °C for 4 h with stirring and application of a slight vacuum (ca. 20 Torr) to remove the water formed. Subsequent pouring into satd. $NaHCO_3$ solution (10 mL), extraction with CH_2Cl_2 (2 × 25 mL), washing of the organic phase with water (20 mL), drying (Na_2SO_4), and removal of the solvent in vacuo left a syrup, which was purified by elution from a silica gel column (2 × 20 cm) with CCl_4/EtOAc (13:1). Taking the eluates containing **23** to dryness resulted in crystallization (542 mg, 89%). M.p. 170−171 °C; $[\alpha]_D^{20}$ = +15.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, 3 H, C*H*$_3$), 4.07 (dd, 1 H, 1-H), 4.21 (ddd, 1 H, 5-H), 4.41 and 4.56 (2dd, 1 H each, 6-H$_2$), 4.52 (dd, 1 H, 2-H), 4.59 (dd, 1 H, 1′-H), 5.60 (dd, 1 H, 4-H), 6.20 (s, 1 H, C_6H_5C*H*), 6.44 (dd, 1 H, 3-H) ppm; $J_{1',2'}$ = 6.2, $J_{1',1}$ = 10.6, $J_{1,2}$ = 4.5, $J_{2,3}$ = 10.0, $J_{3,4}$ = 10.0, $J_{4,5}$ = 10.0, $J_{5,6}$ = 2.9 and 5.8, $J_{6,6}$ = 12.0 Hz. MS (FD, 12 mA): *m*/*z* = 608 [M^+]. $C_{36}H_{32}O_9$ (608.7): calcd. C 71.03, H 5.31; found C 70.94, H 5.34.



25

4-Benzoyloxy-6*S*-benzoyloxymethyl-2*R*-[6′*R*-(1′,2′:3′,4′-di-*O*-isopropylidene-α-D-galactopyranosyl)]-3,6-dihydro-2*H*-pyran-3-one (25): A suspension of Zn-Cu couple in THF (50 mL, tenfold scale of the procedure given above) was cooled to −35 °C and a solution of ulosyl bromide **1** (1.65 g, 3 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdopyranose[28] (**24**, 0.78 g, 3 mmol) in THF (10 mL) was added dropwise over the course of 15 min with stirring, which then was continued for another 30 min at −35 °C. The mixture was subsequently filtered, and the filtrate was poured into HCl (20 mL, 0.2 N), and then extracted with CH_2Cl_2 (2 × 15 mL), followed by washing of the combined extracts with satd. $NaHCO_3$ solution (10 mL) and water (20 mL), drying (Na_2SO_4), and evaporation in vacuo to afford a foamy syrup (2.3 g), consisting of two products of R_f = 0.59 and 0.48 (TLC in CH_2Cl_2/EtOAc 10:1) in an 8:1 ratio (^{1}H NMR). Because of the propensity of ulosides to eliminate benzoic acid in contact with silica gel, separation of the products was best achieved after elimination, effected by stirring of the mixture with $NaHCO_3$ in moist acetone (250 mg in 25 mL, containing a few drops of water) at ambient temperature overnight. Filtration and evaporation to dryness left a partially crystalline residue that was placed on a silica gel column (35 × 4 cm) and eluted with CH_2Cl_2/EtOAc (10:1).

The fraction eluted first (R_f = 0.33 in CH_2Cl_2/EtOAc, 10:1), once taken to dryness in vacuo, gave **25** (1.39 g, 73%) as well formed crystals of M. p. 189−190 °C; $[\alpha]_D^{20}$ = −48.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): (i) dihydropyranone part: δ = 4.56 and 4.65 (2 dd, 1 H each, C*H*$_2$OBz), 4.69 (d, 1 H, 2′-H), 5.55 (m, 2 H, 6-H, Gal-1-H), 6.87 (d, 1 H, 5-H) ppm; $J_{2,6'}$ = 3.6, $J_{5,6}$ = 2.8, $J_{6,CH2}$ = 4.8, 5.0 Hz; (ii) galactose part: δ = 1.30, 1.31, 1.45, 1.51 (4 s, 3 H each, 4 CH_3), 2.81 (s, 1 H, 6′-OH), 3.92 (dd, 1 H, 5′-H), 4.34 (dd, 1 H, 2′-H), 4.41 (dd, 1 H, 6′-H), 4.44 (dd, 1 H, 4′-H), 4.59 (dd, 1 H, 3′-H) ppm; $J_{1',2'}$ = 5.0, $J_{2',3'}$ = 2.5, $J_{3',4'}$ = 7.9, $J_{4',5'}$ = 1.9, $J_{5'',6'}$ = 7.9 Hz. MS (FD, 10 mA): *m*/*z* = 610 [M^+]. CD (MeOH): $\Delta\varepsilon_{max}$ = −0.48 (335 nm), −9.9 (230 nm). $C_{32}H_{34}O_{12}$ (610.7): calcd. C 62.93, H 5.62; found C 62.94, H 5.61.

The fraction eluted second (R_f = 0.14) afforded 160 mg (8%) of a colorless syrup with ^{1}H NMR spectroscopic data very similar to those listed for **25** (differences, e.g., 6′-H as ddd at δ = 5.06 ppm and $J_{5',6'}$ = 1.7 Hz, as compared to δ = 5.55 ppm and 2.2 Hz for **25**), hence an isomer of **25**, conceivably the 2′-β anomer.

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