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Synthetic studies towards the tunicamycins and analogues based on diazo chemistry. Total synthesis of tunicaminyl uracil

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A synthetic approach to the tunicamycins, a complex family of nucleosides with potent antibiotic and antiviral activities is reported based on diazo chemistry. The corresponding precursors for the synthesis of tunicaminyl uracil derivatives, the non-stabilized diazo derived from **13** and the aldehyde derivative of uridine, compound **4**, were prepared efficiently from commercially available D-galactal and uridine, respectively. After a high yielding coupling reaction to obtain the ketone **14**, a stereoselective reduction provided the corresponding tunicaminyl uracil derivative **17a** and its C-7 epimer **17b**. The interconversion of the diazo and aldehyde functional groups in the requisite building blocks was similarly achieved to obtain the ketone **32**, which after reduction yielded the corresponding 7-deoxy-6-hydroxy tunicaminyl uracil analogs **33a** and **33b**.

Introduction

The tunicamycins isolated from *Streptomyces lysosuperficus*[1] represent an interesting and attractive family of natural complex nucleosides[2] possessing fascinating molecular architectures and intriguing antibiotic and antiviral activities.[3] Particularly, the biological action of the tunicamycins relies on their potent inhibition against the phospho-*N*-acetylmuramyl-pentapeptide translocase (translocase I) enzyme in bacteria[4,5] and UDP:GlcNAc:dolichyl phosphate *N*-acetylglucosaminyltransferase (IC_{50} = 7 nM), an essential enzyme involved in the biosynthesis of *N*-glycans in eukaryotic cells.[6] Due to the latter mechanism of action, the tunicamycins exhibit very high toxicity in mammals, thus making them unsuitable for use as therapeutic agents in humans. Exploring the structure of one of the most important members, tunicamycin V (**1**), it can be concluded that tunicamycin mimics the transition state of the substrate–enzyme intermediate **2** (Fig. 1) involved in *N*-glycosylation.[7] Despite their high toxicities, the tunicamycins represent suitable and useful tools for biochemical studies related to the biological role of *N*-glycans in recognition phenomena.[8,9] The structure is comprised of the undecose fragment tunicamine, which contains a C–C linkage between two sugar units, coupled with an *N*-acetylglucosamine unit through an intriguing α,β-trehalose linkage.[10] It is worthy of mention that other related complex nucleoside type antibiotics, such as streptovirudin[11] and corynetoxins,[12] contain the same undecose component.

So far, three total syntheses have been described[13–15] and numerous synthetic approaches have been reported[16] focusing mainly on the construction of the undecose tunicamine through the formation of the C–C bond between the 2-deoxy-2-galactosamine and uridine residues. As we reported in previous publications,[17,18] we have devised the use of non-stabilized diazo sugars as suitable reagents for the construction of *C*-disaccharides in a smooth and straightforward fashion under very mild conditions. Thus, according to the brief retrosynthetic analysis depicted in Scheme 1, the main two

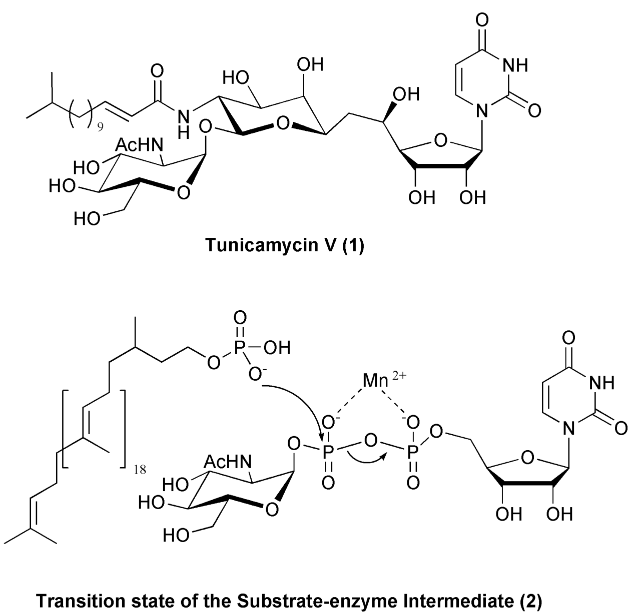
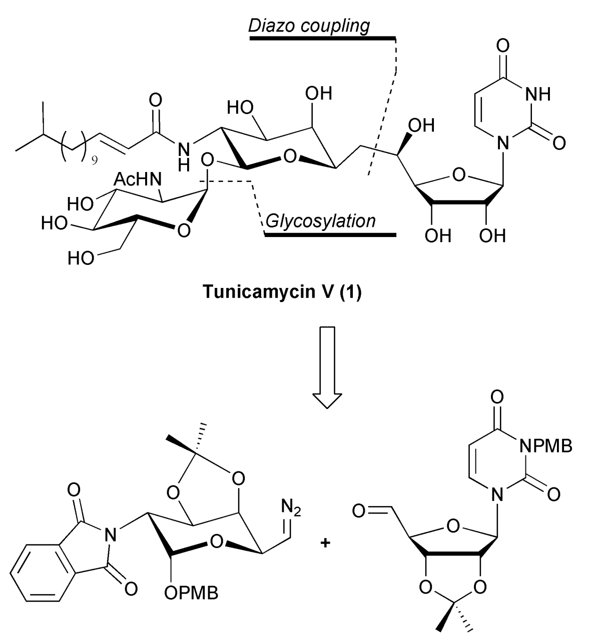


Fig. 1 Structures of tunicamycin V (**1**) and the transition state of the substrate–enzyme intermediate (**2**).



3 4

Scheme 1 Retrosynthetic analysis of tunicamycin (**1**) based on diazo chemistry (PMB = 4-methoxybenzyl).

† With the utmost respect and consternation, we regret to inform the scientific community of the passing of Professor López-Herrera.

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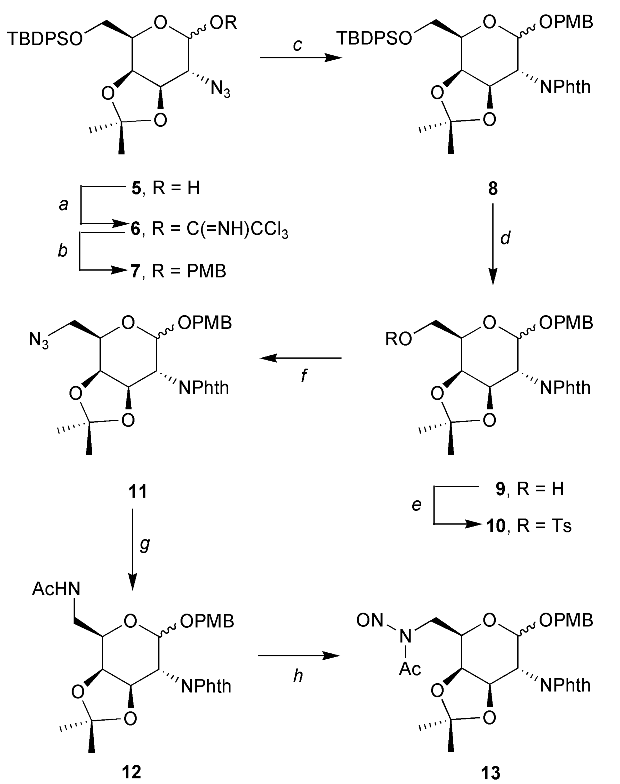
disconnections would be located at the glycosydic site of the α,β-trehalose unit and the C–C linkage contained in the undecose residue. Our initial synthetic studies directed towards the synthesis of the tunicamycins have focused on this undecose unit. According to the retrosynthetic analysis, we propose non-stabilized diazo **3** and aldehyde **4** as the key precursors required for the synthesis of the tunicaminyl uracil component of the tunicamycins.

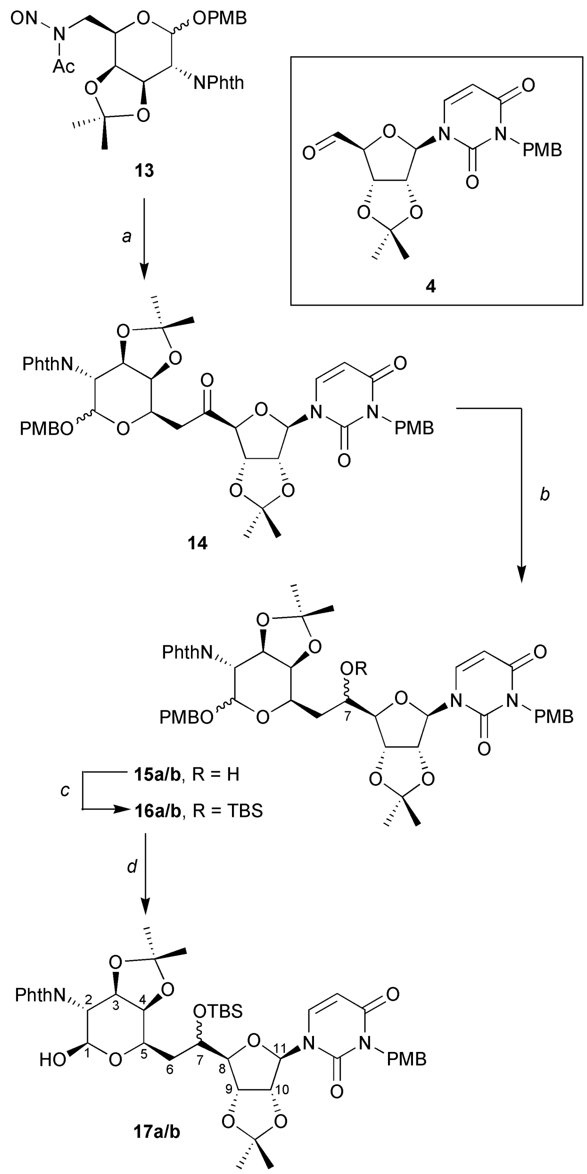
Results and discussion

The synthesis of the key fragment, diazo **3**, commenced from the 2-deoxy-2-azidogalactosyl derivative **5**, readily prepared from D-galactal according to the procedures described in the literature.[19–21] Thus, as it is outlined in Scheme 2, compound **5** was transformed into the corresponding trichloroacetimidate derivative **6**,[22] which was subjected to a glycosylation reaction with *p*-methoxybenzylalcohol mediated by a catalytic amount of trimethylsilyl trifluoromethylsulfonate (TMSOTf) to obtain **7** in 82.4% yield as a 4 : 1 mixture of α:β anomers. The *p*-methoxybenzyl glycoside **7** was then submitted to a sequential transformation of the azide functional group to the corresponding phthalimide **8** by treatment with PPh_3–H_2O[23] followed by reaction of the resulting amine with phthalic anhydride in refluxing DMF. After these functional group transformations, we proceeded with the installation of the diazo functional group at the C-6 position. Thus, silyl ether **8** was treated with TBAF, and the resulting alcohol **9** was transformed into the tosyl derivative **10**. Reaction of **10** with sodium azide in refluxing DMF furnished the 6-azido derivative **11** in 78% yield, which was then transformed to the *N*-nitroso-*N*-acetyl derivative **13** according to the procedure reported in earlier communications.[17]

With the diazo precursor **13** and aldehyde **4**[14] in hand, the key condensation was accomplished under the same conditions as previously reported.[17,18] Thus, the ketone **14** was obtained in 61% yield, with no detection of epoxide formation. Ketone **14** was reduced to the corresponding alcohol by the action of sodium borohydride in the presence of cerium trichloride[24] to obtain a 4 : 1 inseparable mixture of alcohols **15a/b**, whose major product was tentatively assigned the configuration, 7*R* according to previous theoretical and synthetic studies carried out in our laboratories with a model compound.[17] When this reduction was carried out with sodium borohydride alone, a 1 : 1 mixture of alcohols was obtained. Other attempts to improve the stereoselectivity of the reduction, through the use of bulky reductive reagents were unsuccessful. The mixture of alcohols was then submitted to a silylation reaction, and the resulting silyl ethers (**16a/b**) were treated with DDQ[25] in the presence of water to furnish compounds **17a** and **17b** as pure β-anomers in 85% combined yield, which were separated by flash column chromatography on silica gel (Scheme 3).

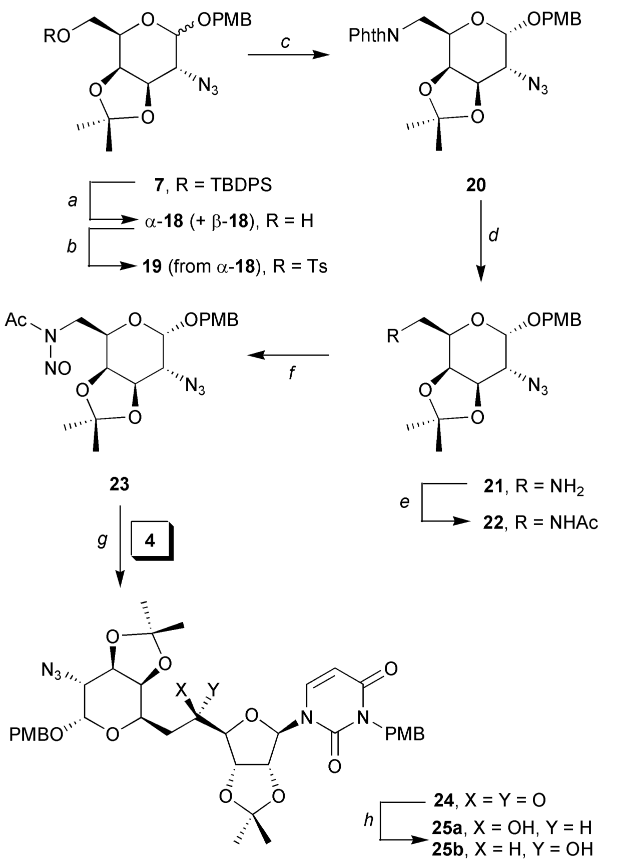


Scheme 2 Synthesis of the diazo precursor, *N*-nitroso derivative (**13**). *Reagents and conditions:* (a) 10.0 equiv. Cl_3CCN, 5.0 equiv. K_2CO_3, CH_2Cl_2, 0 ⟶ 25 °C, 12 h, 83% (4 : 1 mixture of β:α anomers). (b) 1.2 equiv. PMBOH, 0.5 equiv. TMSOTf, 4 Å mol. sieves, THF, −78 °C 1 h, then 0 °C 1 h, 82.4% (4 : 1 mixture of α:β anomers). (c) (1) 1.5 equiv. Ph_3P, 0 ⟶ 25 °C, 8 h, then H_2O, 2 h; (2) 2.0 equiv. PhthO, DMF, reflux, 48 h, 57% overall yield. (d) 1.5 equiv. TBAF, THF, 0° C, 1 h, 98%. (e) 3.0 equiv. TsCl, pyr., 0 ⟶ 25 °C, 8 h, 85%. (f) 20.0 equiv. NaN_3, DMF, reflux, 12 h, 78%. (g) (1) 2.5 equiv. Ph_3P, 0 ⟶ 25 °C, 1 h, then H_2O, 5 h; (2) 7.0 equiv. Ac_2O, pyr., 0 ⟶ 25 °C, 1.5 h. (h) 52.0 equiv. $NaNO_2$, Ac_2O:AcOH (5 : 1), −10 °C, 1 h, 85% overall yield.



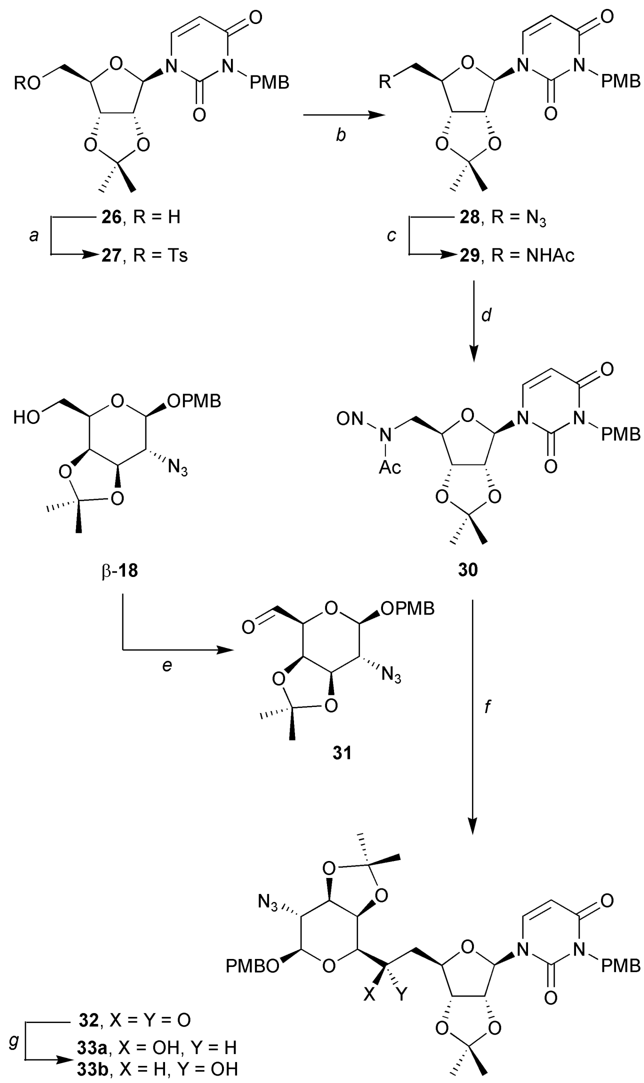
Scheme 3 Coupling of diazo (**3**) and aldehyde (**4**). Synthesis of tunicaminyl uracil derivatives **17a**:**17b**. *Reagents and conditions:* (a) 1.1 equiv. of **13**, 40% KOH, Et_2O/MeOH (10/1), 0 °C, 5 min.; then addition of 1.0 equiv. of **4**, Et_2O, 0 °C, 1 h, 61%. (b) 5.0 equiv. $CeCl_3$.7 × H_2O, 5.0 equiv. $NaBH_4$, MeOH, 0 °C, 0.5 h, 95%. (c) 1.5 equiv. TBDMSOTf, 2.0 equiv. 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 94%. (d) 1.5 equiv. DDQ, CH_2Cl_2–H_2O (10 : 1), 25 °C, 8 h, 68% for **17a**, 17% for **17b**.

Since the epoxide derivatives of these compounds represented very interesting products from both synthetic and biological points of view, we considered it of interest to explore other diazo substrates with the objective of obtaining such compounds. In this sense, the α,β anomeric mixture of azido derivative **7** was transformed into the tosylated compound **19** as the pure α-anomer, through the alcohols α-**18**/β-**18**, which were separated by flash column chromatography, in very good yields. The reaction of tosyl derivative **19** with potassium phthalimide led to the quantitative formation of the phthalimide derivative **20**, which was reacted with hydrazine to provide amine **21**. Acetylation of this amine, followed by *N*-nitrosation of the resulting acetamide **22** furnished the *N*-nitroso **23** as a new diazo precursor for a reaction with the uridinyl aldehyde **4**. The *in situ* formation of diazo compound according to previous protocols, followed by addition of aldehyde **4**, afforded ketone **24** in excellent yield (80%). Unfortunately, once again, no epoxide was detected in this reaction. Nevertheless, the interest of this synthetic alternative relied on the high yielding process of obtaining the undecose derivative **24**. In addition, reduction of **24** with sodium borohydride yielded alcohol **25** with a high stereoselectivity degree (8 : 1), however assignment of the configuration at C-7 has not been attempted (Scheme 4).



Scheme 4 Coupling of diazo derived from **23** with aldehyde (**4**). Synthesis of tunicaminyl uracil derivatives **25a**:**25b**. *Reagents and conditions:* (a) 1.2 equiv. TBAF, THF, 0 °C, 1.0 h, 45% for α-**18**, 30% for β-**18**. (b) 3.0 equiv. TsCl, pyr., 0 ⟶ 25 °C, 8 h, 88%. (c) 2.5 equiv. PhthNK, DMF, reflux, 48 h, 99%. (d) 1.5 equiv. NH_2NH_2, MeOH, 25 °C, 12 h. (e) 60.0 equiv. Ac_2O, pyr., 0 ⟶25 °C, 1.5 h, 99%. (f) 52.0 equiv. $NaNO_2$, Ac_2O:AcOH (5 : 1), −10 °C, 1 h, 82%. (g) 1.1 equiv. of **23**, 40% KOH, Et_2O/MeOH (10/1), 0 °C, 5 min.; then addition of 1.0 equiv. of **4**, Et_2O, 0 °C, 1 h, 80%. (h) 5.0 equiv. $NaBH_4$, MeOH, 0 °C, 15 min., 92%.

Finally, the feasibility of interchanging the functional groups in order to produce related compounds of interesting biological value, prompted us to prepare the non-stabilized diazo derivative of uridine, which would react with the corresponding aldehyde derivative of D-galactosamine. As is described in Scheme 5, the synthesis was performed starting from alcohol **26**,[26] which was transformed into *N*-nitroso-*N*-acetyl derivative



Scheme 5 Coupling of diazo derived from **30** with aldehyde (**31**). Synthesis of tunicamynil uracil analogues **33a**:**33b**. *Reagents and conditions:* (a) 3.0 equiv. TsCl, pyr., 0 ⟶ 25 °C, 5 h, 88%. (b) 30.0 equiv. NaN_3, DMF, 50 °C, 3 days, 77%. (c) (1) 2.5 equiv. Ph_3P, 0 ⟶ 25 °C, 1 h, then H_2O, 5 h; (2) 7.0 equiv. Ac_2O, pyr., 0 ⟶ 25 °C, 1.5 h. (d) 52.0 equiv. $NaNO_2$, Ac_2O:AcOH (5 : 1), −10 °C, 1 h, 76% overall yield. (e) 2.0 equiv. DMP, CH_2Cl_2, 25 °C, 1 h, 94%. (f) 1.1 equiv. of **30**, 40% KOH, Et_2O/MeOH (10/1), 0 °C, 5 min.; then addition of 1.0 equiv. of **31**, Et_2O, 0 °C, 1 h, 60%. (g) 5.0 equiv. $NaBH_4$, MeOH, 0 °C, 15 min., 98%.

30 through tosyl **27**, azide **28** and the *N*-acetyl derivative **29** in high yields. On the other hand, oxidation of alcohol β-**18** with DMP[27] furnished aldehyde **31** in 94% yield. Thus, the coupling reaction of the diazo derived from **30** with aldehyde **31** was undertaken according to the general procedure described previously, to give in a reasonable yield the ketone **32** (60%) as the sole product. The corresponding 5-deoxy-6-hydroxy analogue of tunicaminyl uracil was finally prepared by reduction of ketone **32** with sodium borohydride to obtain essentially one alcohol, compound **33**, whose configuration at C-6 remains to be assigned.

In conclusion, synthetic efforts carried out in our laboratories concerning the use of non-stabilized diazo sugars towards the synthesis of biologically active carbohydrates led us to target the tunicamycins as attractive synthetic targets. The present work demonstrates that the synthetic methodology based on diazo chemistry, established in earlier contributions, can be extended to more complex products such as the synthesis of tunicaminyl uracil and its epimer at C-7, as well as related compounds. Our future work includes the formation of the β,α-trehalose linkage present in the natural product, followed by the eventual completion of the total synthesis of tunicamycin V (**1**).

Experimental

General techniques

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and ethyl ether (ether) were distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2), benzene (PhH), and toluene from calcium hydride. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50 or 1 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on a Bruker Advanced-400 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. IR spectra were recorded on a Beckman Aculab IV spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a Kratos MS 80 RFA mass spectrometer under fast atom bombardment (FAB) conditions.

2-Azido-2-deoxy-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-α,β-D-galactopyranosyl trichloroacetimidate 6

A solution of hemiacetal **5** (9.3 g, 19.23 mmol, 1.0 equiv.) in CH_2Cl_2 (300 mL) was treated with trichloroacetonitrile (19.3 mL, 192.3 mmol, 10.0 equiv.) and K_2CO_3 (13.3 g, 96.15 mmol, 5.0 equiv.) at 0°C. Then, the reaction was allowed to reach room temperature and after 12 h, the resulting mixture was filtered, and the filtrate concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% EtOAc in hexanes) provided pure trichloroacetimidate **6** (10.1 g, 83%) as a 4 : 1 mixture of β:α anomers and as a foamed solid: R_f = 0.57 (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3448 (*w*, NH), 3342 (*w*, NH), 2931 (*m*, CH), 2860 (*m*, CH), 2108 (*s*, N_3), 1725 (*m*, C=NH), 1672 (*m*), 1460 (*w*), 1425 (*w*), 1284 (*m*) and 1108 (*s*); δ_H (400 MHz, $CDCl_3$) 8.82 (1H, s, C=NH), 7.86–7.75 (5H, m, SiPh), 7.57–7.30 (5H, m, SiPh), 6.35 (1H, d, *J* = 2.9, H–C(1), α-anomer), 5.65 (1H, d, *J* = 8.9, H–C(1), β-anomer), 4.57–4.54 (1H, m), 4.48 (1H, dd, *J* = 5.4 and 2.4, α-anomer), 4.38 (1H, *J* = 5.2 and 1.8 Hz, β-anomer), 4.19–4.12 (2H, m), 4.06–3.94 (2H, m), 3.76–3.69 (1H, m, CHN_3), 1.63 and 1.43 (6H, 2 s, $C(CH_3)_2$, β-anomer), 1.59 and 1.45 (6H, 2 s, $C(CH_3)_2$, α-anomer), 1.11 (9H, s, $SiC(CH_3)_3$, α-anomer), 1.10 (9H, s, $SiC(CH_3)_3$, β-anomer); δ_C (100 MHz, $CDCl_3$) (β anomer)‡ 161.2 (C=NH), 135.8, 135.7, 133.5, 133.4, 130.0, 128.3, 128.2, 128.1, 127.9, 110.8 ($C(CH_3)_2$), 96.7 (C-1), 77.6, 74.6, 72.6 (C-3, C-4, C-5), 65.0 (C-6), 62.5 (C-2), 60.9 (CCl_3), 28.5 ($C(CH_3)_2$), 27.1 ($SiC(CH_3)_3$), 26.4 ($C(CH_3)_2$), 19.5 ($SiC(CH_3)_3$).

‡ The ^{13}C-NMR spectra obtained for compound **6** corresponds to the α,β-anomeric mixture and contains the signals of both anomers, but only the signals corresponding to the major anomer have been reported. Similarly, the same was done in the description of the ^1H and ^{13}C NMR spectra for compounds **7**–**14**.

p-Methoxybenzyl 2-azido-2-deoxy-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-α,β-D-galactopyranoside 7. Reaction of trichloroacetimidate 6 with *p*-methoxybenzyl alcohol

To a solution of trichloroacetimidate **6** (10.0 g, 16.00 mmol, 1.0 equiv.), *p*-methoxybenzyl alcohol (2.4 mL, 19.29 mmol, 1.2 equiv.) and 4 Å molecular sieves (30 g) in THF (500 mL) were added dropwise TMSOTf (1.45 mL, 8.04 mmol, 0.5 equiv.) at −78°C. After being stirred for 1 h, the solution was allowed to warm to 0 °C for an additional 1 h. After this time, Et_3N (1.12 mL, 8.04 mmol, 0.5 equiv.) was added and the crude mixture was filtered through silica gel. After dilution with EtOAc, the organic solution was washed with water, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by flash column chromatography (silica gel, 25% EtOAc in hexanes) to provide glycoside **7** (8.0 g, 82.4%) as a 4 : 1 inseparable mixture of α:β anomers: R_f = 0.67 (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3060 (*w*, CH), 2919 (*m*, CH), 2860 (*m*, CH), 2096 (*s*, N_3), 1613 (*w*), 1507 (*m*), 1460 (*m*), 1425 (*m*), 1372 (*m*), 1243 (*s*) and 1108 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.84–7.80 (5H, m, SiPh), 7.58–7.35 (5H, m, SiPh), 7.31 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 6.87 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 4.94 (1H, d, *J* = 3.3, H–C(1)), 4.69 (1H, d, *J* = 11.7, *p*-$CH_2C_6H_4OCH_3$), 4.51 (1H, d, *J* = 11.7, *p*-$CH_2C_6H_4OCH_3$), 4.44 (1H, dd, *J* = 8.6 and 5.2, H–C(3)), 4.33 (1H, dd, *J* = 5.1 and 2.4, H–C(4)), 4.20 (1H, ddd, *J* = 11.9, 5.2 and 2.4, H–C(5)), 4.02 (1H, dd, *J* = 12.0 and 6.2, CH_2OTPS), 3.93 (1H, dd, *J* = 9.8 and 6.4, CH_2OTPS), 3.84 (3H, s, –OCH_3), 3.34 (1H, dd, *J* = 8.8 and 3.3, H–C(2)), 1.53 and 1.38 (6H, 2 s, $C(CH_3)_2$), 1.13 (9H, s, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (α anomer) 159.4, 135.5, 135.4, 133.5, 133.3, 129.8, 129.6, 127.9, 127.8, 127.6, 113.8, 109.5 ($C(CH_3)_2$), 96.1 (C-1), 73.4, 72.7, 69.1 (C-3, C-4, C-5), 68.3 (C-6), 62.8 (C-2), 61.3 (–OCH_2–), 55.1 (–OCH_3), 28.3 ($C(CH_3)_2$), 26.7 ($SiC(CH_3)_3$), 26.1 ($C(CH_3)_2$), 19.1 ($SiC(CH_3)_3$); MALDI-FTMS (NBA) *m*/*z* 626.2658, M + Na^+ calcd for $C_{33}H_{41}N_3O_6Si$: 626.2662.

p-Methoxybenzyl 6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3,4-*O*-isopropylidene-2-*N*-phthalimido-α,β-D-galactopyranoside 8

A solution of azido **7** (6.0 g, 9.94 mmol, 1.0 equiv., 4 : 1 mixture of anomers) in THF (50 mL) was treated with triphenylphosphine (3.91 g, 14.91 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at 25 °C for 8 h. After this time, H_2O (50 mL) was added and after vigorous stirring for 2 h, the organic layer was separated. The aqueous phase was extracted with Et_2O (2 × 50 mL), and the combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was subjected to the next step without further purification. Thus, the crude amine was dissolved in DMF (200 mL) and treated with phthalic anhydride (2.94 g, 19.88 mmol, 2.0 equiv.). After 48 h under reflux conditions, the crude mixture was diluted with ether and washed with water. The aqueous phase was extracted with Et_2O (2 × 50 mL), and the combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided *N*-phthalimide **8** (4.0 g, 57% overall yield) as a yellow oil: R_f = 0.37 (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3060 (*m*, CH), 2931 (*s*, CH), 2872 (*s*, CH), 1848 (*m*), 1772 (*s*, C=O), 1713 (*s*, C=O), 1607 (*m*), 1507 (*s*), 1460 (*s*), 1378 (*s*), 1243 (*s*) and 1102 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.87–7.79 (2H, m, NPhth), 7.75–7.72 (5H, m, SiPh), 7.69–7.67 (2H, m, NPhth), 7.44–7.36 (5H, m, SiPh), 7.07 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 6.63 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 5.78 (1H, dd, *J* = 9.5 and 5.2, H–C(3)), 4.86 (1H, d, *J* = 3.5, H–C(1)), 4.69 (1H, d, *J* = 12.3, *p*-$CH_2C_6H_4OCH_3$), 4.50 (1H, dd, *J* = 9.5 and 3.5, H–C(2)), 4.47 (1H, d, *J* = 12.3, *p*-$CH_2C_6H_4OCH_3$), 4.45

(1H, dd, $J = 5.2$ and 2.3, H–C(4)), 4.37–4.34 (1H, m), 4.10–4.03 (1H, m), 3.97 (1H, dd, $J = 10.0$ and 6.6, CH_2OTPS), 3.67 (3H, s, $–OCH_3$), 1.50 and 1.33 (6H, 2 s, $C(CH_3)_2$), 1.08 (9H, s, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) (α anomer) 168.3 (C=O), 158.9, 135.6, 133.7, 131.8, 129.7, 129.1, 127.7, 127.6, 123.5, 113.5, 109.5 ($C(CH_3)_2$), 96.3 (C-1), 72.8, 68.9, 68.7, 68.3 (C-3, C-4, C-5, C-6), 63.1 ($–OCH_2–$), 55.1 ($–OCH_3$), 54.6 (C-2), 28.3 ($C(CH_3)_2$), 26.7 ($SiC(CH_3)_3$), 26.4 ($C(CH_3)_2$), 19.2 ($SiC(CH_3)_3$); MALDI-FTMS (NBA) *m*/*z* 730.2885, M + Na^+ calcd for $C_{41}H_{45}NO_8Si$: 730.2812.

p-Methoxybenzyl 2-deoxy-3,4-*O*-isopropylidene-2-*N*-phthalimido-α,β-D-galactopyranoside 9. Treatment of *N*-phthalimide 8 with tetrabutylammonium fluoride

A solution of silyl ether **8** (3.0 g, 4.24 mmol, 1.0 equiv.) in THF (20 mL) at 0 °C was treated with TBAF (6.36 mL, 1 M solution in THF, 6.36 mmol, 1.5 equiv.). After stirring for 1 h, the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous solution was extracted with Et_2O (2 × 20 mL) and the combined organic phase was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to provide alcohol **9** (1.95 g, 98%) as a 4 : 1 mixture of anomers: $R_f = 0.23$ (silica gel, 50% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3497 (*s*, OH), 2971 (*s*, CH), 2916 (*s*, CH), 1771 (*s*, C=O), 1710 (*s*, C=O), 1609 (*s*), 1508 (*s*), 1458 (*s*), 1380 (*s*), 1240 (*s*) and 1061 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.80–7.77 (2H, m, NPhth), 7.70–7.67 (2H, m, NPhth), 7.07 (2H, d, $J = 8.6$, *p*-$CH_2C_6H_4OCH_3$), 6.61 (2H, d, $J = 8.6$, *p*-$CH_2C_6H_4OCH_3$), 5.76 (1H, dd, $J = 9.7$ and 5.3, H–C(3)), 4.89 (1H, d, $J = 3.5$, H–C(1)), 4.63 (1H, d, $J = 12.2$, *p*-$CH_2C_6H_4OCH_3$), 4.44 (1H, dd, $J = 9.6$ and 3.5, H–C(2)), 4.37 (1H, d, $J = 12.2$, *p*-$CH_2C_6H_4OCH_3$), 4.32 (1H, dd, $J = 5.2$ and 2.5, H–C(4)), 4.29 (1H, dd, $J = 9.0$ and 8.9, CH_2OH), 4.25–4.23 (1H, m, H–C(5)), 4.04–3.98 (1H, m, CH_2OH), 3.66 (3H, s, $–OCH_3$), 2.26 (1H, bs, OH), 1.49 and 1.32 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (α anomer) 168.3 (C=O), 159.1, 133.9, 131.7, 129.4, 129.0, 123.2, 113.6, 109.9 ($C(CH_3)_2$), 96.5 (C-1), 74.1, 69.4, 68.8 (C-3, C-4, C-5), 67.8 (C-6), 62.9 ($–OCH_2–$), 55.1 ($–OCH_3$), 54.4 (C-2), 28.3 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$); MALDI-FTMS (NBA) *m*/*e* 492.1631, M + Na^+ calcd for $C_{25}H_{27}NO_8$: 492.1629.

p-Methoxybenzyl 2-deoxy-3,4-*O*-isopropylidene-2-*N*-phthalimido-6-*O*-*p*-toluenesulfonyl-α,β-D-galactopyranoside 10. Treatment of alcohol 9 with *p*-toluenesulfonylchloride

To a solution of alcohol **9** (1.95 g, 4.15 mmol, 1.0 equiv.) in pyridine (50 mL) was added portionwise tosyl chloride (2.37 g, 12.46 mmol, 3.0 equiv.) at 0 °C. After stirring for 15 min, the solution was allowed to warm to 25 °C, and after 8 h at room temperature, the reaction mixture was diluted with Et_2O (50 mL) and washed with aqueous HCl (20 mL, 1 M solution). The aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic solution was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ⟶ 50% EtOAc in hexanes) furnished tosylate **10** (2.2 g, 85%) as a 4 : 1 mixture of anomers: $R_f = 0.34$ (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 2989 (*m*, CH), 2931 (*m*, CH), 1772 (*m*, C=O), 1713 (*s*, C=O), 1607 (*m*), 1508 (*m*), 1455 (*s*), 1372 (*s*, SO_2), 1249 (*s*), 1172 (*s*, SO_2) and 1038 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.81 (2H, d, $J = 8.5$, *p*-$OSO_2C_6H_4CH_3$), 7.78–7.76 (2H, m, NPhth), 7.70–7.67 (2H, m, NPhth), 7.33 (2H, d, $J = 8.5$, *p*-$OSO_2C_6H_4CH_3$), 7.04 (2H, d, $J = 8.4$, *p*-$CH_2C_6H_4OCH_3$), 6.61 (2H, d, $J = 8.4$, *p*-$CH_2C_6H_4OCH_3$), 5.66 (1H, dd, $J = 9.2$ and 5.2, H–C(3)), 4.77 (1H, d, $J = 3.7$, H–C(1)), 4.56 (1H, d, $J = 12.1$, *p*-$CH_2C_6H_4OCH_3$), 4.40–4.36 (2H, m), 4.32–4.29 (2H, m), 4.23–4.21 (1H, m), 4.13–4.11 (1H, m), 3.67 (3H, s, $–OCH_3$), 2.43 (3H, s, *p*-$OSO_2C_6H_4CH_3$), 1.42 and 1.25 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (α anomer) 168.2 (C=O), 159.1, 144.9, 133.9, 132.9, 131.7, 131.6, 129.9, 129.8, 129.5, 127.7, 123.2, 113.6, 109.8 ($C(CH_3)_2$), 96.0 (C-1), 72.5, 69.3, 69.2 (C-3, C-4, C-5), 68.7 (C-6), 66.0 ($–OCH_2–$), 55.1 ($–OCH_3$), 53.9 (C-2), 28.1 ($C(CH_3)_2$), 26.4 ($C(CH_3)_2$), 21.6 ($–CH_3$); MALDI-FTMS (NBA) *m*/*z* 646.1710, M + Na^+ calcd for $C_{32}H_{33}NO_{10}S$: 646.1717.

p-Methoxybenzyl 6-azido-2,6-dideoxy-3,4-*O*-isopropylidene-2-*N*-phthalimido-α,β-D-galactopyranoside 11. Reaction of tosylate 10 with sodium azide

To a solution of tosylate **10** (2.2 g, 3.53 mmol, 1.0 equiv.) in DMF (30 mL) was added NaN_3 (4.6 g, 70.6 mmol, 20.0 equiv.) in one portion at 25 °C. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (*ca* 12 h). The crude mixture was then poured into saturated aqueous NH_4Cl solution (30 mL), diluted with Et_2O (50 mL) and the layers separated. The aqueous solution was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided azide **11** (1.37 g, 78%) as a 4 : 1 mixture of anomers: $R_f = 0.48$ (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 2987 (*s*, CH), 2871 (*s*, CH), 2097 (*s*, N_3), 1773 (*s*, C=O), 1715 (*s*, C=O), 1608 (*m*), 1511 (*m*), 1458 (*m*), 1385 (*s*), 1255 (*s*), 1153 (*s*) and 1028 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.79–7.77 (2H, m, NPhth), 7.71–7.63 (2H, m, NPhth), 7.07 (2H, d, $J = 8.5$, *p*-$CH_2C_6H_4OCH_3$), 6.59 (2H, d, $J = 8.5$, *p*-$CH_2C_6H_4OCH_3$), 5.72 (1H, dd, $J = 9.4$ and 5.2, H–C(3)), 4.86 (1H, d, $J = 3.6$, H–C(1)), 4.65 (1H, d, $J = 12.1$, *p*-$CH_2C_6H_4OCH_3$), 4.43 (1H, dd, $J = 9.4$ and 3.6, H–C(2)), 4.39 (1H, d, $J = 12.1$, *p*-$CH_2C_6H_4OCH_3$), 4.33–4.29 (1H, m, H–C(5)), 4.24 (1H, dd, $J = 5.2$ and 2.4, H–C(4)), 3.67 (3H, s, $–OCH_3$), 3.64 (1H, dd, $J = 13.0$ and 8.3, CH_2N_3), 3.43 (1H, dd, $J = 13.0$ and 4.6, CH_2N_3), 1.49 and 1.29 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (α anomer) 168.2 (C=O), 159.1, 133.9, 131.7, 129.5, 129.1, 128.8, 123.2, 113.6, 109.8 ($C(CH_3)_2$), 96.2 (C-1), 73.3, 69.4, 68.7 (C-3, C-4, C-5), 67.3 ($–OCH_2–$), 55.1 ($–OCH_3$), 54.2 (C-2), 51.3 (C-6), 28.2 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$); MALDI-FTMS (NBA) *m*/*z* 517.1675, M + Na^+ calcd for $C_{25}H_{26}N_4O_7$: 517.1694.

p-Methoxybenzyl 6-acetamido-2,6-dideoxy-3,4-*O*-isopropylidene-2-*N*-phthalimido-α,β-D-galactopyranoside 12. Reduction of Azide 11 and acetylation

To a stirred solution of azide **11** (1.37 g, 2.77 mmol, 1.0 equiv.) in THF (30 mL) was added Ph_3P (1.81 g, 6.93 mmol, 2.5 equiv.). After being stirred for 1 h at 25 °C, H_2O (30 mL) was added and the mixed system was vigorously stirred for an additional 5 h at room temperature. After that time, the reaction mixture was poured into brine (30 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated. The resulting residue was dissolved in pyridine (10 mL), followed by addition of Ac_2O (1.83 mL, 19.39 mmol, 7.0 equiv.) at 0 °C. After stirring for 30 min, the reaction mixture was allowed to warm to 25 °C and was stirred for 1 h at this temperature. The crude mixture was diluted with CH_2Cl_2 (30 mL) and the resulting solution was washed with aqueous HCl (30 mL, 1 M solution). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were sequentially washed with saturated aqueous Na_2CO_3 solution (30 mL) and brine (30 mL), followed by drying over $MgSO_4$, filtration and concentration under reduced pressure. The resulting crude mixture was used for the next step without further purification: $R_f = 0.13$ (silica gel, 50% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3366 (*s*, NH), 3072 (*s*, CH), 2720 (*s*, CH), 1760 (*s*, C=O), 1696 (*s*, C=O), 1549 (*s*), 1513 (*s*), 1384 (*s*) and 915 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.83–7.78 (2H, m, NPhth), 7.49–7.40 (2H, m, NPhth), 7.09 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 6.65 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 5.80 (1H, dd, *J* = 9.6 and 5.0, H–C(3)), 4.89 (1H, d, *J* = 3.5, H–C(1)), 4.64 (1H, d, *J* = 12.1, *p*-$CH_2C_6H_4OCH_3$), 4.47 (1H, dd, *J* = 9.6 and 3.5, H–C(2)), 4.39 (1H, d, *J* = 12.1, *p*-$CH_2C_6H_4$-OCH_3), 4.36–4.31 (2H, m), 3.93–3.87 (1H, m), 3.71 (3H, s, –OCH_3), 3.50–3.47 (1H, m), 2.07 (3H, s, $NHCOCH_3$), 1.55 and 1.37 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (α anomer) 170.7 (CH_3C=O), 168.2 (C=O), 158.9, 133.8, 131.7, 129.7, 129.2, 128.9, 123.9, 113.5, 109.5 ($C(CH_3)_2$), 96.3 (C-1), 73.8, 69.3, 68.6 (C-3, C-4, C-5), 65.9 (–OCH_2–), 54.9 (–OCH_3), 54.2 (C-2), 40.5 (C-6), 28.2 ($C(CH_3)_2$), 26.3 ($C(CH_3)_2$), 22.9 (O=CCH_3); MALDI-FTMS (NBA) *m*/*z* 533.1882, M + Na^+ calcd for $C_{27}H_{30}N_2O_8$: 533.1894.

_p_-Methoxybenzyl 6-(_N_-nitroso)-acetamido-2,6-dideoxy-3,4-_O_-isopropylidene-2-_N_-phthalimido-α,β-D-galactopyranoside 13. Treatment of acetamide 12 with sodium nitrite

To a stirred solution of acetamide **12** (*ca* 2.77 mmol, 1.0 equiv.) in a mixed solvent system of Ac_2O : AcOH (5 : 1, 36 mL) was added in small portions $NaNO_2$ (9.94 g, 144.04 mmol, 52.0 equiv.) at −10 °C. The reaction mixture was stirred for 1 h, before being poured into an ice–water mixture and extracted with Et_2O (3 × 30 mL). The combined ethereal solution was washed with a 5% sodium hydrogen carbonate several times until removal of acetic acid was complete. Finally, the organic solution was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ⟶ 50% EtOAc in hexanes) afforded *N*-nitroso derivative **13** (1.27 g, 85% overall yield from **11**) as a 4 : 1 mixture of anomers: R_f = 0.57 (silica gel, 50% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 2989 (*m*, CH), 2919 (*m*, CH), 1772 (*m*, C=O), 1713 (*s*, C=O), 1607 (*m*), 1507 (*s*, N=O), 1378 (*s*), 1243 (*s*), 1126 (*s*), 1072 (*s*) and 1032 (*s*); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.79–7.77 (2H, m, NPhth), 7.68–7.65 (2H, m, NPhth), 6.97 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 6.59 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 5.62 (1H, dd, *J* = 9.3 and 5.0, H–C(3)), 4.72 (1H, d, *J* = 3.7, H–C(1)), 4.51 (1H, dd, *J* = 14.2 and 8.8, CH_2N(N=O)Ac), 4.39 (1H, dd, *J* = 9.2 and 3.7, H–C(2)), 4.38 (1H, d, *J* = 12.0, *p*-$CH_2C_6H_4OCH_3$), 4.25 (1H, dd, *J* = 9.0 and 8.9, CH), 4.21–4.19 (1H, m), 4.14 (1H, d, *J* = 12.0, *p*-$CH_2C_6H_4OCH_3$), 3.85 (1H, ddd, *J* = 13.8, 3.7 and 3.4, H–C(5)), 3.66 (3H, s, –OCH_3), 2.78 (3H, s, N(N=O)$COCH_3$), 1.48 and 1.27 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (α anomer) 174.2 (O=CCH_3), 168.2 (C=O), 159.1, 133.9, 131.7, 129.4, 129.0, 128.6, 123.2, 113.6, 109.8 ($C(CH_3)_2$), 96.3 (C-1), 73.2, 69.2, 68.7 (C-3, C-4, C-5), 64.6 (–OCH_2–), 55.1 (–OCH_3), 53.9 (C-2), 38.9 (C-6), 28.2 ($C(CH_3)_2$), 26.4 ($C(CH_3)_2$), 22.5 ($OCCH_3$); MALDI-FTMS (NBA) *m*/*z* 539.1898, M^+ calcd for $C_{27}H_{29}N_3O_9$: 539.1904.

3-(4-Methoxybenzyl)-1-[_p_-methoxybenzyl (11_R_)-2,6-dideoxy-3,4:9,10-di-_O_-isopropylidene-7-keto-2-_N_-phthalimido-L-_ribo_-α,β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]-uracil 14. Reaction of aldehyde 4 with diazo derived from 13

To a solution of *N*-nitroso acetamide **13** (1.20 g, 2.22 mmol, 1.1 equiv.) in Et_2O (20 mL) was added MeOH (2 mL), cooled to 0 °C and protected from the light. Under these conditions, a 40% aqueous solution of KOH (4 mL) was added and after stirring for 5 min, the crude mixture was diluted with H_2O (15 mL), the layers were separated and the aqueous phase was extracted with Et_2O (1 × 20 mL). The combined organic extracts were washed with brine (20 mL) and the resulting solution was immediately treated with a solution of aldehyde **4** (0.81 g, 2.02 mmol, 1.0 equiv.) in Et_2O (5 mL) at 0 °C. After stirring for 1 h, the solvent was removed by concentration under reduced pressure and the resulting residue was subjected to purification by flash column chromatography (silica gel, 50% EtOAc in hexanes) to obtain ketone **14** (1.05 g, 61%) as a white solid and a 4 : 1 mixture of anomers: R_f = 0.43 (silica gel, 60% EtOAc in hexanes); δ_H (400 MHz, $CDCl_3$) (α anomer) 7.79–7.77 (2H, m, NPhth), 7.69–7.67 (2H, m, NPhth), 7.32 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 7.23 (1H, d, *J* = 8.0, C*H*=CH), 7.11 (2H, d, *J* = 8.2, *p*-$CH_2C_6H_4OCH_3$), 6.77 (2H, d, *J* = 8.2, *p*-$CH_2C_6H_4$-OCH_3), 6.60 (2H, d, *J* = 8.4, *p*-$CH_2C_6H_4OCH_3$), 5.80 (1H, d, *J* = 8.0, CH=C*H*), 5.72 (1H, dd, *J* = 9.6 and 5.3, H–C(3)), 5.52 (1H, s, C(O)H–N), 5.08 (1H, d, *J* = 5.9, H–C(11)), 5.03–4.96 (2H, m), 4.89 (1H, dd, *J* = 14.1 and 13.8, CH), 4.72 (1H, d, *J* = 3.2, H–C(1)), 4.65 (1H, d, *J* = 11.8, *p*-$CH_2C_6H_4OCH_3$), 4.61 (1H, d, *J* = 11.8, *p*-$CH_2C_6H_4OCH_3$), 4.45–4.34 (3H, m), 4.24–4.22 (1H, m), 3.71 (3H, s, –OCH_3), 3.66 (3H, s, –OCH_3), 3.01 (1H, dd, *J* = 17.1 and 9.0, H–C(6)), 2.66 (1H, dd, *J* = 17.1 and 4.4, H′–C(6)), 1.57, 1.55, 1.37 and 1.29 (12H, 4 s, 2 × $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (α anomer) 203.2 (C-7), 168.3 (C=O), 162.4 (C=O), 159.1 (C=O), 159.0 (C=O), 151.2, 141.3, 133.9, 131.7, 130.5, 128.8, 128.4, 123.2, 113.7, 113.5, 109.4 ($C(CH_3)_2$), 102.6 ($C(CH_3)_2$), 98.5 (C-11), 96.1 (C-1), 94.5, 84.5, 82.7 (C-8, C-9, C-10), 74.5, 69.1, 68.6 (C-3, C-4, C-5), 63.5 (–OCH_2–), 55.2 (–OCH_3), 55.1 (–OCH_3), 54.3 (C-2), 43.6 (–NCH_2–), 39.7 (C-6), 28.4 ($C(CH_3)_2$), 26.7 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 25.1 ($C(CH_3)_2$); MALDI-FTMS (NBA) *m*/*z* 876.2959, M + Na^+ calcd for $C_{45}H_{47}N_3O_{14}$: 876.2956.

3-(4-Methoxybenzyl)-1-[_p_-methoxybenzyl (11_R_)-2,6-dideoxy-3,4:9,10-di-_O_-isopropylidene-2-_N_-phthalimido-L-_allo_-α,β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 15a and L-_altro_-α,β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 15b. Reduction of ketone 14

A solution of ketone **14** (0.5 g, 0.58 mmol, 1.0 equiv.) in MeOH (10 mL) was sequentially treated with $CeCl_3$. 7 × H_2O (1.1 g, 2.93 mmol, 5.0 equiv.) and $NaBH_4$ (110 mg, 2.93 mmol, 5.0 equiv.) at 0 °C. After stirring for 0.5 h at 0 °C, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NH_4Cl solution (20 mL). The aqueous solution was extracted with EtOAc (3 × 10 mL) and the combined organic phase was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 66% EtOAc in hexanes) provided alcohols **15a/b** (0.47 g, 95%) as an inseparable mixture of diastereoisomers.

3-(4-Methoxybenzyl)-1-[_p_-methoxybenzyl (11_R_)-7-_O_-_tert_-butyldimethylsilyl-2,6-dideoxy-3,4:9,10-di-_O_-isopropylidene-2-_N_-phthalimido-L-_allo_-α,β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 16a and L-_altro_-α,β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 16b. Silylation of alcohols 15a/b

A solution of alcohols **15a/b** (154 mg, 0.180 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was treated, at 0 °C, with 2,6-lutidine (43 µL, 0.360 mmol, 2.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethansulfonate (62 µL, 0.269 mmol, 1.5 equiv.). After stirring for 1 h, saturated aqueous NH_4Cl solution (10 mL) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic solution was washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 10% EtOAc in hexanes) provided silyl ethers **16a/b** (165 mg, 94%) as an inseparable mixture of diastereoisomers.

3-(4-Methoxybenzyl)-1-[(11_R_)-7-_O_-_tert_-butyldimethylsilyl-2,6-dideoxy-3,4:9,10-di-_O_-isopropylidene-2-_N_-phthalimido-L-_allo_-β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 17a and L-_altro_-β-D-_galacto_-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 17b. Reaction of silyl ethers 16a/b with DDQ

To a solution of silyl ethers **16a/b** (141 mg, 0.145 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added H_2O (0.5 mL) and

DDQ (50 mg, 0.217 mmol, 1.5 equiv.) at 25 °C. After stirring for 8 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and the resulting organic solution was washed with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic solution was washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) provided pure hemiacetals **17a** (84 mg, 68%) and **17b** (21 mg, 17%) as white solids and as pure enantiomers. Hemiacetal **17a**: R_f = 0.26 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{22}_D$ +34.2 (*c* 1.4 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.78–7.76 (2H, m, NPhth), 7.66–7.64 (2H, m, NPhth), 7.38 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 7.15 (1H, d, *J* = 8.1, C*H*=CH), 6.76 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 5.81 (1H, d, *J* = 3.2, H–C(11)), 5.72 (1H, d, *J* = 8.1, CH=C*H*), 5.16 (1H, d, *J* = 8.5, H–C(1)), 5.02 (1H, d, *J* = 13.6, *p*-$CH_2C_6H_4OCH_3$), 4.93 (1H, d, *J* = 13.6, *p*-$CH_2C_6H_4OCH_3$), 4.81–4.76 (2H, m, H–C(3), H–C(9)), 4.64 (1H, dd, *J* = 6.9 and 3.3, H–C(10)), 4.12 (1H, dd, *J* = 8.9 and 8.5, H–C(2)), 4.01–3.98 (3H, m, H–C(5), H–C(7), H–C(8)), 3.90 (1H, dd, *J* = 5.0 and 3.8, H–C(4)), 3.69 (3H, s, –OCH_3), 2.11 (1H, ddd, *J* = 14.5, 9.2 and 4.7, H–C(6)), 1.83 (1H, ddd, *J* = 14.5, 8.0 and 3.9, H′–C(6)), 1.56, 1.52, 1.28 and 1.25 (12H, 4 s, 2 × $C(CH_3)_2$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.06 and 0.01 (6H, 2 s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 162.4 (C=O), 159.1, 150.6, 138.7, 134.1, 131.8, 130.8, 128.8, 123.7, 123.4, 113.7, 110.2 (*C*$(CH_3)_2$), 102.4 (*C*$(CH_3)_2$), 92.4 (C-11), 91.1 (C-1), 87.6, 83.6, 78.9 (C-8, C-9, C-10), 75.4, 73.6, 69.2, 68.0 (C-3, C-4, C-5, C-7), 56.8 (–OCH_3), 55.2 (C-2), 43.7 (–NCH_2–), 35.5 (C-6), 28.0 ($C(CH_3)_2$), 27.3 ($C(CH_3)_2$), 26.4 ($C(CH_3)_2$), 25.9 ($SiC(CH_3)_3$), 25.4 ($C(CH_3)_2$), 18.1 (Si*C*$(CH_3)_3$), −4.1 ($Si(CH_3)_2$), −4.5 ($Si(CH_3)_2$); FAB (NBA) *m*/*z* 872.3402, M + Na^+ calcd for $C_{43}H_{55}N_3O_{13}Si$: 872.3402. Hemiacetal **17b**: R_f = 0.31 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{22}_D$ +36.1 (*c* 0.4 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.77–7.75 (3H, m), 7.65–7.63 (2H, m, NPhth), 7.39 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 6.75 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 6.05 (1H, d, *J* = 3.6, H–C(11)), 5.69 (1H, d, *J* = 8.2, CH=C*H*), 5.16 (1H, dd, *J* = 8.2 and 8.0, H–C(1)), 5.03 (1H, d, *J* = 13.5, *p*-$CH_2C_6H_4OCH_3$), 4.92 (1H, d, *J* = 13.5, *p*-$CH_2C_6H_4OCH_3$), 4.74 (1H, dd, *J* = 9.1 and 5.0, H–C(3)), 4.68 (1H, dd, *J* = 6.2 and 1.9 Hz, H–C(9)), 4.56 (1H, dd, *J* = 6.0 and 3.6, H–C(10)), 4.34 (1H, d, *J* = 1.9, H–C(8)), 4.16 (1H, ddd, *J* = 9.8, 4.4 and 2.2, H–C(5)), 4.11 (1H, dd, *J* = 9.0 and 8.2, H–C(2)), 3.99 (1H, dd, *J* = 5.0 and 2.0, H–C(4)), 3.94 (1H, ddd, *J* = 10.3 and 1.9, H–C(7)), 3.70 (3H, s, –OCH_3), 3.34 (1H, d, *J* = 7.7, OH), 2.20 (1H, ddd, *J* = 14.6, 10.7 and 4.5, H–C(6)), 1.90 (1H, ddd, *J* = 14.6, 9.5 and 2.5, H′–C(6)), 1.56, 1.55, 1.28 and 1.25 (12H, 4 s, 2 × $C(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 0.09 and 0.06 (6H, 2 s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 162.5 (C=O), 159.0, 150.9, 138.3, 134.0, 131.8, 130.8, 128.9, 123.4, 113.9, 113.6, 110.4 (*C*$(CH_3)_2$), 102.3 (*C*$(CH_3)_2$), 92.6 (C-11), 92.0 (C-1), 85.7, 84.8, 81.6 (C-8, C-9, C-10), 75.3, 73.5, 70.2, 69.9 (C-3, C-4, C-5, C-7), 56.8 (–OCH_3), 55.2 (C-2), 43.6 (–NCH_2–), 34.5 (C-6), 28.0 ($C(CH_3)_2$), 27.3 ($C(CH_3)_2$), 26.4 ($C(CH_3)_2$), 25.8 ($SiC(CH_3)_3$), 25.2 ($C(CH_3)_2$), 17.9 (Si*C*$(CH_3)_3$), −4.2 ($Si(CH_3)_2$), −4.8 ($Si(CH_3)_2$); FAB (NBA) *m*/*z* 872.3398, M + Na^+ calcd for $C_{43}H_{55}N_3O_{13}Si$: 872.3402.

p-Methoxybenzyl 2-azido-2-deoxy-3,4-*O*-isopropylidene-α,β-D-galactopyranoside 18. Desilylation of 7

A solution of silyl ether **7** (1.7 g, 2.82 mmol, 1.0 equiv.), as a 4 : 1 mixture of anomers, in THF (15 mL) at 0 °C was treated with TBAF (3.38 mL, 1 M solution in THF, 3.38 mmol, 1.2 equiv.). After stirring for 1 h, the reaction mixture was diluted with Et_2O (30 mL) and washed with saturated aqueous NH_4Cl solution (30 mL). The aqueous solution was extracted with Et_2O (2 × 15 mL) and the combined organic phase was washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to provide the corresponding alcohols in form of pure α and β anomers α-**18** (0.47 g, 45%) and β-**18** (0.31 g, 30%) respectively, as colorless oils. Alcohol α-**18**: R_f = 0.46 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ +134.9 (*c* 0.6 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 6.88 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 4.97 (1H, d, *J* = 3.3, H–C(1)), 4.66 (1H, d, *J* = 11.6, *p*-$CH_2C_6H_4OCH_3$), 4.51 (1H, d, *J* = 11.6, *p*-$CH_2C_6H_4OCH_3$), 4.42 (1H, dd, *J* = 8.7 and 5.3, H–C(3)), 4.23 (1H, dd, *J* = 5.3 and 2.6, H–C(4)), 4.11–4.08 (1H, m, H–C(5)), 3.94 (1H, dd, *J* = 11.8 and 6.5, C*H*$_2$OH), 3.83 (1H, dd, *J* = 11.8 and 4.4, C*H*$_2$OH), 3.79 (3H, s, –OCH_3), 3.33 (1H, dd, *J* = 8.7 and 3.3, H–C(2)), 2.45 (1H, bs, OH), 1.51 and 1.35 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 159.4, 129.6, 128.4, 113.8, 109.8 (*C*$(CH_3)_2$), 96.4 (C-1), 73.6, 73.5, 69.5 (C-3, C-4, C-5), 67.9 (C-6), 62.4 (C-2), 61.1 (–OCH_2–), 55.1 (–OCH_3), 28.2 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$); FAB (NBA) *m*/*z* 365.1597, M^+ calcd for $C_{17}H_{23}N_3O_6$: 365.1587. Alcohol β-**18**: R_f = 0.29 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ +53.3 (*c* 0.3 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 6.84 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 4.82 (1H, d, *J* = 11.6, *p*-$CH_2C_6H_4OCH_3$), 4.61 (1H, d, *J* = 11.6, *p*-$CH_2C_6H_4OCH_3$), 4.22 (1H, d, *J* = 8.4, H–C(1)), 4.02 (1H, dd, *J* = 5.3 and 1.6, H–C(4)), 3.93 (1H, dd, *J* = 11.6 and 7.3, C*H*$_2$OH), 3.84 (1H, dd, *J* = 8.0 and 5.3, H–C(3)), 3.79 (1H, dd, *J* = 11.6 and 4.4, C*H*$_2$OH), 3.75 (3H, s, –OCH_3), 3.75–3.72 (1H, m, H–C(5)), 3.39 (1H, dd, *J* = 8.4 and 8.2, H–C(2)), 2.47 (1H, bs, OH), 1.48 and 1.29 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 159.4, 129.7, 128.4, 113.8, 110.6 (*C*$(CH_3)_2$), 99.7 (C-1), 77.2, 73.3, 72.9 (C-3, C-4, C-5), 70.5 (C-6), 65.0 (C-2), 62.1 (–OCH_2–), 55.1 (–OCH_3), 28.0 ($C(CH_3)_2$), 26.1 ($C(CH_3)_2$); FAB (NBA) *m*/*z* 365.1590, M^+ calcd for $C_{17}H_{23}N_3O_6$: 365.1587.

p-Methoxybenzyl 2-azido-2-deoxy-3,4-*O*-isopropylidene-6-*p*-toluenesulfonyl-α-D-galactopyranoside 19. Tosylation of α-18

Tosylate **19** (585 mg, 88%) was prepared from alcohol α-**18** (470 mg, 1.28 mmol) according to the procedure described above for **10**. **19:** colorless oil; R_f = 0.28 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ +100.9 (*c* 1.3 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.2, *p*-$OSO_2C_6H_4CH_3$), 7.29 (2H, d, *J* = 8.2, *p*-$OSO_2C_6H_4CH_3$), 7.21 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 6.83 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 4.81 (1H, d, *J* = 3.4, H–C(1)), 4.54 (1H, d, *J* = 11.5, *p*-$CH_2C_6H_4OCH_3$), 4.38 (1H, d, *J* = 11.5, *p*-$CH_2C_6H_4OCH_3$), 4.31 (1H, dd, *J* = 8.5 and 5.3, H–C(3)), 4.23–4.17 (3H, m), 3.75 (3H, s, –OCH_3), 3.20 (1H, dd, *J* = 8.5 and 3.4, H–C(2)), 2.39 (3H, s, –CH_3), 1.38 and 1.23 (6H, 2 s, $C(CH_3)_2$); δ_C (50.3 MHz, $CDCl_3$) 159.5, 144.9, 129.8, 127.9, 113.9, 110.1 (*C*$(CH_3)_2$), 96.1 (C-1), 73.4, 72.4, 69.6 (C-3, C-4, C-5), 68.8 (C-6), 66.1 (–OCH_2–), 60.8 (C-2), 55.3 (–OCH_3), 28.1 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 21.6 (–CH_3); FAB (NBA) *m*/*z* 519.1679, M^+ calcd for $C_{24}H_{29}N_3O_8S$: 519.1675.

p-Methoxybenzyl 2-azido-2,6-dideoxy-3,4-*O*-isopropylidene-*N*-phthalimido-α-D-galactopyranoside 20. Treatment of tosylate 19 with potassium phthalimide

To a solution of tosylate **19** (90 mg, 0.173 mmol, 1.0 equiv.) in DMF (5 mL) was added potassium phthalimide (80 mg, 0.433 mmol, 2.5 equiv.). The reaction mixture was then heated at reflux for 48 h with complete depletion of starting material according to TLC. The crude mixture was allowed to reach 25 °C and was diluted with Et_2O (10 mL) and washed with saturated aqueous NH_4Cl solution (15 mL). The aqueous solution was extracted with Et_2O (2 × 10 mL) and the combined organic phase was washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) furnished *N*-phthalimide **20** (85 mg, 99%) as a white solid: R_f = 0.33 (silica gel, 50% EtOAc in hexanes); δ_H (400 MHz, $CDCl_3$) 7.84–7.78 (2H, m, NPhth), 7.69–7.67 (2H, m, NPhth), 7.01 (2H, d, *J* = 8.5, *p*-CH_2C_6*H_4*OCH_3), 6.70 (2H, d, *J* = 8.5, *p*-CH_2C_6*H_4*OCH_3), 4.80 (1H, d, *J* = 3.4, *C**H*–OCH_2-$C_6H_4OCH_3$), 4.42 (1H, ddd, *J* = 9.6, 2.8 and 2.7 Hz, CH), 4.33–4.29 (2H, m), 4.26–4.15 (3H, m), 3.77 (1H, dd, *J* = 14.2 and 3.1, CH_2NPhth), 3.69 (3H, s, –OCH_3), 3.29 (1H, dd, *J* = 8.5 and 3.4, CHN_3), 1.47 and 1.29 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 168.1 (C=O), 159.4, 134.2, 134.1, 131.8, 129.8, 128.1, 123.3, 113.8, 110.0 (*C*$(CH_3)_2$), 96.1 (C-1), 73.6, 73.1, 69.3 (C-3, C-4, C-5), 65.1 (C-2), 60.9 (–OCH_2–), 55.2 (–OCH_3), 38.8 (C-6), 28.2 (C(*C*$H_3)_2$), 26.2 (C(*C*$H_3)_2$); FAB (NBA) *m*/*z* 494.1809, M^+ calcd for $C_{25}H_{26}N_4O_7$: 494.1802.

p-Methoxybenzyl 6-acetamido-2-azido-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-galactopyranoside 22. Hydrazinolysis of *N*-phthalimide 20 and acetylation of amine 21

To a stirred solution of *N*-phthalimide **20** (85 mg, 0.172 mmol, 1.0 equiv.) in MeOH (3 mL) was added NH_2NH_2 (273 µL, 1.0 M solution in THF, 0.273 mmol, 1.5 equiv.). After being stirred for 12 h at 25 °C, the reaction mixture was diluted with EtOAc (5 mL) and H_2O (5 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phase was dried ($MgSO_4$), filtered and concentrated. The resulting amine **21**, practically pure, was dissolved in pyridine (5 mL), followed by addition of Ac_2O (1.0 mL, 10.59 mmol, 60.0 equiv.) at 0 °C. After stirring for 30 min, the reaction mixture was allowed to warm to 25 °C and was stirred for 1 h at this temperature. The crude mixture was diluted with CH_2Cl_2 (5 mL) and the resulting solution was washed with aqueous HCl (5 mL, 1 M solution). The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were sequentially washed with saturated aqueous Na_2CO_3 solution (10 mL) and brine (10 mL). Finally, the organic solution was dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The resulting acetamide **22** (74 mg, 99% for two steps) was practically pure according to its NMR spectra and did not require further purification.

p-Methoxybenzyl 6-(*N*-nitroso)-acetamido-2-azido-2,6-dideoxy-3,4-*O*-isopropylidene-α-D-galactopyranoside 23. Treatment of acetamide 22 with sodium nitrite

N-nitroso acetamide **23** was prepared from acetamide **22** (74 mg, 0.182 mmol, 1.0 equiv.) by treatment with sodium nitrite and acetic acid according to the same procedure described above for the preparation of **13**, to obtain pure *N*-nitroso **23** (65 mg, 82%) as a pale yellow solid: R_f = 0.57 (silica gel, 50% EtOAc in hexanes); δ_H (400 MHz, $CDCl_3$) 7.11 (2H, d, *J* = 8.6, *p*-CH_2C_6-*H_4*OCH_3), 6.81 (2H, d, *J* = 8.6, *p*-CH_2C_6*H_4*OCH_3), 4.75 (1H, d, *J* = 3.4, H–C(1)), 4.44 (1H, dd, *J* = 13.9 and 9.2 Hz, CH_2-N(N=O)Ac), 4.32 (1H, d, *J* = 11.3, *p*-*C**H_2*$C_6H_4OCH_3$), 4.27 (1H, dd, *J* = 8.6 and 5.3, H–C(3)), 4.23 (1H, d, *J* = 11.3, *p*-*C**H_2*$C_6H_4OCH_3$), 4.06 (1H, dd, *J* = 5.3 and 2.5, H–C(4)), 4.01 (1H, ddd, *J* = 9.2, 3.3 and 2.8, H–C(5)), 3.75 (3H, s, –OCH_3), 3.72 (1H, dd, *J* = 13.9 and 3.3, CH_2N(N=O)Ac), 3.25 (1H, dd, *J* = 8.6 and 3.4, H–C(2)), 2.75 (3H, s, –N(N=O)$COCH_3$), 1.46 and 1.29 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 169.5 (C=O), 129.7, 113.8, 109.9 (*C*$(CH_3)_2$), 96.1 (C-1), 73.4, 72.9, 69.4 (C-3, C-4, C-5), 64.4 (–OCH_2–), 60.6 (C-2), 55.1 (–OCH_3), 38.5 (C-6), 28.1 (C(*C*$H_3)_2$), 26.1 (C(*C*$H_3)_2$), 22.4 (C(O)*C*H_3); FAB (NBA) *m*/*z* 436.1840, M + H^+ calcd for $C_{19}H_{25}N_5O_7$: 436.1832.

3-(4-Methoxybenzyl)-1-[*p*-methoxybenzyl (11*R*)-2-azido-2,6-dideoxy-3,4:9,10-di-*O*-isopropylidene-7-keto-L-*ribo*-α-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 24. Reaction of aldehyde 4 with diazo derived from 23

A solution of diazo derived from *N*-nitroso acetamide **23** (20 mg, 0.046 mmol, 1.1 equiv.), prepared in exactly the same way as described above for **13**, in Et_2O (5 mL) was reacted with aldehyde **4** (17 mg, 0.042 mmol, 1.0 equiv.) according to the same procedure for the preparation of **14**, to afford ketone **24** (27 mg, 80%) as a white solid: R_f = 0.45 (silica gel, 20% EtOAc in hexanes); δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* = 8.6, *p*-CH_2-C_6*H_4*OCH_3), 7.24 (2H, d, *J* = 8.7, *p*-CH_2C_6*H_4*OCH_3), 7.18 (1H, d, *J* = 8.0, C*H*=CH), 6.81 (2H, d, *J* = 8.6, *p*-CH_2C_6*H_4*OCH_3), 6.71 (2H, d, *J* = 8.7, *p*-CH_2C_6*H_4*OCH_3), 5.76 (1H, d, *J* = 8.0, CH=C*H*), 5.45 (1H, s, H–C(11)), 5.33 (1H, dd, *J* = 6.1 and 2.2, H–C(9)), 5.07 (1H, d, *J* = 6.1, H–C(10)), 4.93 (1H, d, *J* = 13.8, *p*-*C**H_2*$C_6H_4OCH_3$), 4.80 (1H, d, *J* = 13.8, *p*-*C**H_2*$C_6H_4OCH_3$), 4.73 (1H, d, *J* = 3.3, H–C(1)), 4.63 (1H, d, *J* = 11.2, *p*-*C**H_2*C_6-H_4OCH_3), 4.55 (1H, d, *J* = 2.2, H–C(8)), 4.44 (1H, ddd, *J* = 8.9, 3.4 and 3.0, H–C(5)), 4.35 (1H, d, *J* = 11.2, *p*-*C**H_2*$C_6H_4OCH_3$), 4.30 (1H, dd, *J* = 8.7 and 5.2, H–C(3)), 3.98 (1H, dd, *J* = 5.2 and 2.5, H–C(4)), 3.74 (3H, s, –OCH_3), 3.62 (3H, s, –OCH_3), 3.14 (1H, dd, *J* = 8.7 and 3.3, H–C(2)), 2.90 (1H, dd, *J* = 17.0 and 9.1, H–C(6)), 2.56 (1H, dd, *J* = 17.0 and 4.1, H′–C(6)), 1.50, 1.44, 1.33 and 1.27 (12H, 4 s, 2 × $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 202.9 (C-7), 162.2 (C=O), 158.9, 141.4, 129.9, 128.4, 113.8, 113.7, 109.5 (*C*$(CH_3)_2$), 102.5 (*C*$(CH_3)_2$), 98.7 (C-11), 95.8 (C-1), 94.6, 84.3, 82.6 (C-8, C-9, C-10), 74.3, 73.3, 69.2 (C-3, C-4, C-5), 63.1 (–OCH_2–), 60.8 (C-2), 55.1 (–OCH_3), 54.9 (–OCH_3), 43.5 (–NCH_2–), 39.3 (C-6), 28.2 (C(*C*$H_3)_2$), 26.5 (C(*C*$H_3)_2$), 25.5 (C(*C*$H_3)_2$), 24.8 (C(*C*$H_3)_2$); FAB (NBA) *m*/*z* 750.2990, M + H^+ calcd for $C_{37}H_{43}N_5O_{12}$: 750.2986.

3-(4-Methoxybenzyl)-1-[*p*-methoxybenzyl (11*R*)-2-azido-2,6-dideoxy-3,4:9,10-di-*O*-isopropylidene-L-*allo*-α-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 25a and –L-*altro*-α-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 25b. Reduction of ketone 24

A solution of ketone **24** (20 mg, 0.026 mmol, 1.0 equiv.) in MeOH (2 mL) was treated with $NaBH_4$ (4.8 mg, 0.13 mmol, 5.0 equiv.) at 0 °C for 15 min. The solution was diluted with Et_2O (5 mL) and then saturated aqueous NH_4Cl solution (5 mL) was carefully added. The aqueous solution was extracted with Et_2O (2 × 5 mL) and the combined organic phase was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 66% EtOAc in hexanes) gave alcohols **25a/b** (18 mg, 92%) as an inseparable mixture in a 8 : 1 proportion: R_f = 0.30 (silica gel, 20% EtOAc in hexanes); δ_H (400 MHz, $CDCl_3$) (major isomer) 7.49 (2H, d, *J* = 8.7, *p*-CH_2C_6*H_4*OCH_3), 7.38 (2H, d, *J* = 8.6, *p*-CH_2C_6*H_4*OCH_3), 7.23 (1H, d, *J* = 8.0, C*H*=CH), 6.82 (2H, d, *J* = 8.6, *p*-CH_2-C_6*H_4*OCH_3), 6.76 (2H, d, *J* = 8.7, *p*-CH_2C_6*H_4*OCH_3), 5.77 (1H, d, *J* = 3.3, H–C(11)), 5.72 (1H, d, *J* = 8.0, CH=C*H*), 5.32 (1H, d, *J* = 3.1, H–C(10)), 5.07 (1H, d, *J* = 13.7, *p*-*C**H_2*$C_6H_4OCH_3$), 4.96 (1H, bs, CH), 4.93 (1H, d, *J* = 13.7, *p*-*C**H_2*$C_6H_4OCH_3$), 4.88–4.84 (2H, m), 4.78 (1H, dd, *J* = 6.5 and 3.3, H–C(9)), 4.58 (1H, d, *J* = 11.7, *p*-*C**H_2*$C_6H_4OCH_3$), 4.46 (1H, d, *J* = 11.7, *p*-*C**H_2*$C_6H_4OCH_3$), 4.33 (1H, dd, *J* = 8.7 and 5.2, H–C(3)), 4.08–4.04 (1H, m), 3.91–3.87 (1H, m), 3.75 (3H, s, –OCH_3), 3.69 (3H, s, –OCH_3), 3.26 (1H, dd, *J* = 8.8 and 3.3, H–C(2)), 1.89–1.95 (1H, m, C*H_2*CH(OH)), 1.64 (1H, ddd, *J* = 12.8, 7.4 and 3.8, C*H_2*CH(OH)), 1.53, 1.51, 1.31 and 1.29 (12H, 4 s, 2 × $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) (major isomer) 162.4 (C=O), 159.5, 139.5, 130.9, 130.7, 129.6, 113.8, 113.7, 110.8 (*C*$(CH_3)_2$), 102.3 (*C*$(CH_3)_2$), 96.4 (C-11), 94.2 (C-1), 88.1, 83.7, 80.8 (C-8, C-9, C-10), 75.6, 74.3, 73.2, 70.1, 69.8 (C-3, C-4, C-5, C-7), 66.9 (–OCH_2–), 60.8 (C-2), 55.1 (–OCH_3), 55.0 (–OCH_3), 43.5 (–NCH_2–), 33.7 (C-6), 28.2 (C(*C*$H_3)_2$), 27.2 (C(*C*$H_3)_2$), 25.4 (C(*C*$H_3)_2$), 24.8 (C(*C*$H_3)_2$); FAB (NBA) *m*/*z* 752.3139, M + H^+ calcd for $C_{37}H_{45}N_5O_{12}$: 752.3143.

1-(2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranosyl)-3-(4-methoxybenzyl)uracil 27. Tosylation of alcohol 26

Tosylate **27** (0.86 g, 88%) was prepared from alcohol **26** (0.71 g, 1.75 mmol) according to the procedure described above for **10**.

19: white solid; R_f = 0.27 (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3060 (*m*, CH), 2978 (*s*, CH), 2884 (*m*, CH), 1719 (*s*, C=O), 1666 (*s*, C=O), 1507 (*s*), 1455 (*s*), 1367 (*s*), 1255 (*s*), 1108 (*s*) and 979 (*s*); δ_H (400 MHz, $CDCl_3$) 7.71 (2H, d, *J* = 8.3, *p*-$OSO_2C_6H_4CH_3$), 7.40 (2H, d, *J* = 8.3, *p*-$OSO_2C_6H_4CH_3$), 7.27 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 7.11 (1H, d, *J* = 8.1, C*H*=CH), 6.79 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 5.70 (1H, d, *J* = 8.1, CH=C*H*), 5.60 (1H, bs, H–C(1)), 5.00 (1H, d, *J* = 13.6, *p*-$CH_2C_6H_4OCH_3$), 4.90 (1H, d, *J* = 13.6, *p*-$CH_2C_6H_4OCH_3$), 4.85 (1H, ddd, *J* = 6.4 and 1.8, H–C(4)), 4.78 (1H, dd, *J* = 6.4 and 3.5, H–C(3)), 4.33–4.30 (1H, m), 4.26–4.22 (2H, m), 3.76 (3H, s, –OCH_3), 2.41 (3H, s, *p*-$OSO_2C_6H_4CH_3$), 1.51 and 1.31 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 162.3 (C=O), 159.2, 150.6, 145.2, 139.6, 132.6, 130.8, 129.9, 128.6, 127.9, 114.5, 113.7, 102.3 (*C*$(CH_3)_2$), 95.5 (C-1), 84.9, 84.5, 80.9 (C-2, C-3, C-4), 69.2 (C-5), 55.2 (–OCH_3), 43.5 (–NCH_2–), 27.0 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 21.6 (–CH_3); MALDI-FTMS (NBA) *m*/*z* 581.1568, M + Na^+ calcd for $C_{27}H_{30}N_2O_9S$: 581.1564.

1-(5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(4-methoxybenzyl)uracil 28. Reaction of tosylate 27 with sodium azide

To a solution of tosylate **27** (0.85 g, 1.53 mmol, 1.0 equiv.) in DMF (5 mL) was added NaN_3 (2.9 g, 45.81 mmol, 30.0 equiv.) in one portion at 25 °C. The reaction mixture was heated at 50 °C for 3 days. There was no detection after this time of the starting tosylate by TLC. The crude mixture was then poured into saturated aqueous NH_4Cl solution (20 mL), diluted with Et_2O (20 mL) and the layers separated. The aqueous solution was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided azide **28** (0.51 g, 77%) as a colorless oil: R_f = 0.35 (silica gel, 25% EtOAc in hexanes); ν_{max}/cm^{-1} (thin film) 3084 (*w*, CH), 2955 (*m*, CH), 2096 (*s*, N_3), 1707 (*s*, C=O), 1666 (*s*, C=O), 1507 (*s*), 1455 (*s*), 1384 (*s*), 1343 (*s*), 1255 (*s*), 1085 (*s*) and 908 (*s*); δ_H (400 MHz, $CDCl_3$) 7.38 (2H, d, *J* = 8.8, *p*-$CH_2C_6H_4OCH_3$), 7.20 (1H, d, *J* = 8.0, C*H*=CH), 6.80 (2H, d, *J* = 8.8, *p*-$CH_2C_6H_4OCH_3$), 5.75 (1H, d, *J* = 8.0, CH=C*H*), 5.63 (1H, d, *J* = 1.8, H–C(1)), 5.00 (2H, s, *p*-$CH_2C_6H_4OCH_3$), 4.94 (1H, dd, *J* = 6.3 and 1.8, H–C(2)), 4.78 (1H, dd, *J* = 6.6 and 4.0, H–C(3)), 4.20 (1H, q, *J* = 4.0, H–C(4)), 3.77 (3H, s, –OCH_3), 3.55 (2H, bs, CH_2N_3), 1.56 and 1.32 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 162.3 (C=O), 159.1, 150.6, 139.8, 130.5, 114.6, 113.7, 102.4 (*C*$(CH_3)_2$), 95.3 (C-1), 85.7, 84.5, 81.4 (C-2, C-3, C-4), 55.2 (–OCH_3), 52.3 (C-5), 43.5 (–NCH_2–), 27.1 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$); MALDI-FTMS (NBA) *m*/*z* 452.1540, M + Na^+ calcd for $C_{20}H_{23}N_5O_6$: 452.1546.

1-(5-Acetamido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(4-methoxybenzyl)uracil 29. Reduction of azide 28 and acetylation

The treatment of azide **28** (505 mg, 1.17 mmol, 1.0 equiv.) with Ph_3P (460 mg, 1.75 mmol, 1.5 equiv.) and subsequent acetylation with acetic anhydride were carried out exactly as described above for **12** and yielded acetamide **29** (440 mg, 84%) which was used for the next step without purification.

1-(5-(*N*-Nitroso)-acetamido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-3-(4-methoxybenzyl)uracil 30. Treatment of acetamide 29 with sodium nitrite

N-Nitroso acetamide **30** was prepared from acetamide **29** (350 mg, 0.78 mmol, 1.0 equiv.) by treatment with sodium nitrite and acetic acid according to the same procedure as described above for the preparation of **13**, to obtain pure *N*-nitroso **30** (281 mg, 76%) as a pale yellow solid: R_f = 0.56 (silica gel, 25% EtOAc in hexanes); $[\alpha]^{22}_D$ +76.3 (*c* 0.6 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 7.05 (1H, d, *J* = 8.0, C*H*=CH), 6.78 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 5.76 (1H, d, *J* = 8.0, CH=C*H*), 5.36 (1H, bs, H–C(1)), 5.08 (1H, d, *J* = 13.5, *p*-$CH_2C_6H_4OCH_3$), 5.05 (1H, bs, H–C(2)), 5.02 (1H, d, *J* = 13.5, *p*-$CH_2C_6H_4OCH_3$), 4.77 (1H, dd, *J* = 6.3 and 3.5, H–C(3)), 4.21 (1H, dd, *J* = 13.4 and 8.2, CH_2N(N=O)Ac), 4.06 (1H, ddd, *J* = 8.4, 4.9 and 3.5, H–C(4)), 3.95 (1H, dd, *J* = 13.4 and 4.9, CH_2N(N=O)Ac), 3.74 (3H, s, –OCH_3), 2.71 (3H, s, N(N=O)$COCH_3$), 1.46 and 1.29 (6H, 2 s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 174.3 (C=O), 162.5 (C=O), 159.0, 150.8, 140.8, 130.5, 128.7, 114.2, 113.6, 102.5 (*C*$(CH_3)_2$), 96.8 (C-1), 84.6, 84.4, 82.7 (C-2, C-3, C-4), 55.2 (–OCH_3), 43.6 (–NCH_2–), 40.1 (C-5), 26.9 ($C(CH_3)_2$), 25.2 ($C(CH_3)_2$), 22.5 (–$COCH_3$); FAB (NBA) *m*/*z* 497.1639, M + Na^+ calcd for $C_{22}H_{26}N_4O_8$: 497.1648.

p-Methoxybenzyl 2-azido-2-deoxy-3,4-*O*-isopropylidene-β-D-galacto-hexonodialdo-1,5-pyranoside 31. Oxidation of alcohol β-18

To a solution of alcohol β-**18** (244 mg, 0.67 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (566 mg, 1.33 mmol, 2.0 equiv.) in one portion at 25 °C. After stirring at this temperature for 1 h, the crude mixture was then poured into saturated aqueous $NaHCO_3$ solution (20 mL), diluted with Et_2O (20 mL) and the layers were separated. The aqueous solution was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided aldehyde **31** (230 mg, 94%) as a colorless oil.

3-(4-Methoxybenzyl)-1-[*p*-methoxybenzyl (11*R*)-2-azido-2,7-dideoxy-3,4:9,10-di-*O*-isopropylidene-6-keto-L-*ribo*-β-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 32. Reaction of aldehyde 31 with diazo derived from 30

A solution of diazo derived from *N*-nitroso acetamide **30** (225 mg, 0.474 mmol, 1.01 equiv.), prepared under the same conditions as the diazo derived from **13**, in Et_2O (5 mL) was reacted with aldehyde **31** (170 mg, 0.468 mmol, 1.0 equiv.) according to the same procedure as for the preparation of **14**, to afford ketone **32** (210 mg, 60%) as a white solid: R_f = 0.40 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ +3.5 (*c* 1.0 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 7.24 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 7.21 (1H, d, *J* = 8.0, C*H*=CH), 6.82 (2H, d, *J* = 8.6, *p*-$CH_2C_6H_4OCH_3$), 6.75 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 5.72 (1H, d, *J* = 8.0, CH=C*H*), 5.71 (1H, d, *J* = 3.7, H–C(11)), 4.98 (1H, d, *J* = 13.7, *p*-$CH_2C_6H_4OCH_3$), 4.93 (1H, d, *J* = 13.8, *p*-$CH_2C_6H_4OCH_3$), 4.90 (1H, dd, *J* = 6.8 and 3.2, H–C(9)), 4.81 (1H, d, *J* = 11.6, *p*-$CH_2C_6H_4OCH_3$), 4.73 (1H, dd, *J* = 6.6 and 3.6, H–C(10)), 4.59 (1H, d, *J* = 11.6, *p*-$CH_2C_6H_4OCH_3$), 4.45 (1H, ddd, *J* = 5.0, H–C(8)), 4.23 (1H, dd, *J* = 5.3 and 2.5, H–C(4)), 4.18 (1H, d, *J* = 8.4, H–C(1)), 3.99 (1H, d, *J* = 2.5, H–C(5)), 3.86 (1H, dd, *J* = 7.7 and 5.4, H–C(3)), 3.73 (3H, s, –OCH_3), 3.68 (3H, s, –OCH_3), 3.42 (1H, dd, *J* = 8.4 and 8.1, H–C(2)), 3.17 (1H, dd, *J* = 18.7 and 4.9, H–C(7)), 3.02 (1H, dd, *J* = 18.7 and 5.7, H′–C(7)), 1.53, 1.43, 1.29 and 1.23 (12H, 4 s, 2 × $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 204.2 (C-6), 163.8 (C=O), 159.6, 158.9, 150.7, 139.5, 130.6, 129.8, 129.7, 128.7, 128.4, 113.9, 113.7, 110.8 (*C*$(CH_3)_2$), 102.4 (*C*$(CH_3)_2$), 99.6 (C-1), 93.8 (C-11), 84.4, 83.2, 81.8 (C-8, C-9, C-10), 77.9, 77.0, 73.1, (C-3, C-4, C-5), 70.8 (C-2), 64.5 (–OCH_2–), 55.2 (–OCH_3), 55.1 (–OCH_3), 43.6 (–NCH_2–), 42.3 (C-7), 28.1 ($C(CH_3)_2$), 27.2 ($C(CH_3)_2$), 25.9 ($C(CH_3)_2$), 25.1 ($C(CH_3)_2$); FAB (NBA) *m*/*z* 772.2789, M + Na^+ calcd for $C_{37}H_{43}N_5O_{12}$: 772.2806.

3-(4-Methoxybenzyl)-1-[*p*-methoxybenzyl (11*R*)-2-azido-2,7-dideoxy-3,4:9,10-di-*O*-isopropylidene-L-*ribo*-D-*glycero*-β-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 33a and L-*ribo*-L-*glycero*-β-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil 33b. Reduction of ketone 32

Alcohol **33** was prepared from ketone **32** (80 mg, 0.107 mmol, 1.0 equiv.) by treatment with sodium borohydride according to the same procedure as described above for the preparation of **25**, to obtain alcohol **33** (79 mg, 98%) as a white solid: R_f = 0.39 (silica gel, 50% EtOAc in hexanes); δ_H (400 MHz, $CDCl_3$) 7.34 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4OCH_3$), 7.23 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 7.15 (1H, d, *J* = 8.0, C*H*=CH), 6.83 (2H, d, *J* = 8.5, *p*-$CH_2C_6H_4OCH_3$), 6.75 (2H, d, *J* = 8.7, *p*-$CH_2C_6H_4$-OCH_3), 5.71 (1H, d, *J* = 8.0, CH=C*H*), 5.60 (1H, d, *J* = 2.5, H–C(11)), 4.97 (1H, d, *J* = 13.6, *p*-$CH_2C_6H_4OCH_3$), 4.92 (1H, d, *J* = 13.6, *p*-$CH_2C_6H_4OCH_3$), 4.86 (1H, dd, *J* = 6.6 and 2.5, H–C(10)), 4.78 (1H, d, *J* = 11.7, *p*-$CH_2C_6H_4OCH_3$), 4.75 (1H, dd, *J* = 6.8 and 4.6, H–C(9)), 4.59 (1H, d, *J* = 11.7, *p*-$CH_2C_6H_4$-OCH_3), 4.27 (1H, ddd, *J* = 6.4 and 6.2, H–C(8)), 4.18 (1H, d, *J* = 8.5, H–C(1)), 4.15–4.12 (1H, m, H–C(6)), 3.98 (1H, dd, *J* = 5.3 and 2.1, H–C(4)), 3.81 (1H, dd, *J* = 8.0 and 5.4, H–C(3)), 3.74 (3H, s, –OCH_3), 3.69 (3H, s, –OCH_3), 3.45 (1H, dd, *J* = 5.9 and 2.0, H–C(5)), 3.37 (1H, dd, *J* = 8.5 and 8.2, H–C(2)), 2.90 (1H, s, OH), 1.98–1.94 (1H, m, H–C(7)), 1.83–1.76 (1H, m, H′–C(7)), 1.52, 1.47, 1.29 and 1.26 (12H, 4 s, 2 × $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 162.4 (C=O), 159.5, 159.1, 150.6, 139.7, 130.5, 129.7, 128.7, 113.9, 113.7, 110.8 (*C*$(CH_3)_2$), 102.4 (*C*$(CH_3)_2$), 99.8 (C-1), 94.5 (C-11), 84.1, 84.0, 83.8 (C-8, C-9, C-10), 77.5, 74.9, 73.2, 70.7 (C-3, C-4, C-5, C-6), 68.6 (C-2), 64.8 (–OCH_2–), 55.2 (–OCH_3), 55.1 (–OCH_3), 43.5 (–NCH_2–), 35.0 (C-7), 28.1 ($C(CH_3)_2$), 27.2 ($C(CH_3)_2$), 26.1 ($C(CH_3)_2$), 25.3 ($C(CH_3)_2$); FAB (NBA) *m*/*z* 774.2945, M + Na^+ calcd for $C_{37}H_{45}N_5O_{12}$: 774.2962.

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References and notes

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