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Ceric Ammonium Nitrate / Acetic Anhydride: A Tunable System for the *O*-Acetylation and Mononitration of Diversely Protected Carbohydrates

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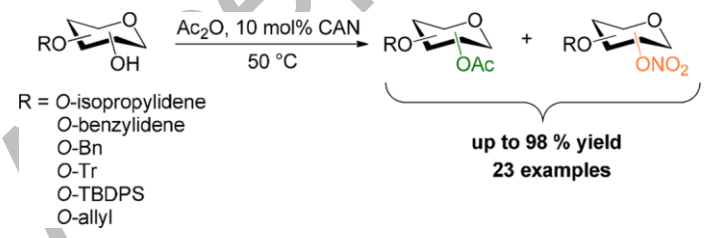
Abstract

Esterification of a wide range of partially protected carbohydrate derivatives was achieved using acetic anhydride and a catalytic amount of ceric ammonium nitrate. Compatibility with the commonly used protecting groups was demonstrated, with the esterified products being furnished in good yields. Apart from affording the *O*-acetylated products, their mononitrated counterparts were also produced depending upon the reactivity of the starting material. Decreasing the molar equivalents of CAN afforded the *O*-acetylated products exclusively, while increasing it favored the mononitrated derivatives.

Graphical Abstract



INTRODUCTION

The design and synthesis of any oligosaccharide requires careful selection of protecting groups employed throughout the scheme. Orthogonal compatibility of the different

groups utilized must be ensured: this encompasses both (1) tolerance to other groups present and any glycoside bonds, in the protecting and deprotection steps, and (2) general alignment with the glycosidation strategy required, for example, whether anchimeric assistance over the stereochemistry of the resulting glycoside bond is a necessity.[1]

A common class of protecting groups are the esters, with the most popular being the *O*-acetate group.[2] It is easily introduced and deprotected under a variety of mild conditions; which generally involve acetic anhydride as both solvent and reactant, and some other requisite catalyst/promoter. The single most popular means of introducing the *O*-acetate group employs pyridine as both co-solvent and base,[3] with or without a catalytic amount of DMAP.[4] However, the highly toxic nature and unpleasant smell of pyridine has led to an ongoing search for alternatives. Many such examples exist, which span the range from Lewis acids[5] such as I_2,[6] $In(OTf)_3$,[7] $Ce(OTf)_3$,[8] $BF_3.OEt_2$,[9] $Fe_2(SO_4)_3$,[10] $Er(OTf)_3$,[11] Me_3SiCl;[12] to solid supports involving Nafion-H,[13] molecular sieves,[14] Montmorillonite K-10,[15] as well as techniques involving microwave irradiation.[16] All of these excellent methods are quite effective at yielding the per-*O*-acetylated derivatives in near quantitative yield. However, many suffer from a lack of compatibility with other frequently employed groups; most notably causing the deprotection of *O*-benzyls and in some cases, many other popular protections such as *O*-trityl, *O*-silyl and *O*-benzylidenes. This has necessitated the reluctant utilization of the pyridine system, when the substrate is a derivatized sugar, as opposed to the free monosaccharide.

At the other end, the *O*-nitrate ester (-ONO_2) could lay claim to being the least popular of the esters and other classes in general; its use as a protecting group is completely absent from the modern literature.[17] This underutilization could be largely attributed to the inherent difficulty associated with controlled nitration.[18] It is generally observed that regardless of the reagent combination used, all free hydroxyls present in the carbohydrate will be nitrated. Such a global, non-specific, derivatization would be of little use in an extended synthetic sequence where it is often necessary to distinguish among different hydroxyls for reactivity purposes. As further deterrents, carbohydrates bearing multiple nitrate groups are frequently explosive,[19] and the reagents used for their synthesis (a common combination is a mixture of conc. HNO_3 and conc. H_2SO_4) present a difficult work-up procedure. In addition, the different reagents available are often not compatible with the range of protecting groups utilized in modern syntheses. While the combinations of conc. HNO_3/Ac_2O[20] or $N_2O_5/CHCl_3$,[21] will not cause significant deprotection of the acid-labile groups such as benzylidene, isopropylidene and trityl, most of the common nitrating mixtures will result in deprotection of any *O*-Bn groups present or nitration of their aromatic rings. Methods exist for the introduction of a nitrate group exclusively at the anomeric centre, starting from either anomeric chlorides or bromides.[22] However, mononitration at non-anomeric positions is traditionally a significantly more difficult endeavor, with the reported strategies involving the displacement of a previously installed triflate leaving group.[17a,23] The most recent approach towards the synthesis of nitrate esters utilized a $LiNO_3$ / $(CF_3CO)_2O$ system, this reagent combination furnished the nitrated derivatives in good yields, and showed compatibility with a variety of isopropylidene rings in different configurations and orientations.[24]

Despite these synthetic difficulties, the non-anomeric mononitrated carbohydrate derivatives present very attractive properties: (1) they are sufficiently stable to heat and shock;[19a] (2) they improve the acid stability of other groups present;[25] (3) they exhibit orthogonal compatibility towards conditions required for the removal of other common protecting groups, such as tolerance to dilute acids (for acetals and ketals)[26] and dilute bases (for acetates and benzoates);[27] and (4) their deprotection can be easily effected under a wide range of reductive conditions, such as: $Pd/CaCO_3$,[28] Pd/C,[17b] $LiAlH_4$,[29] or hydrazine,[23,30] any of which would convert the $–ONO_2$ to –OH; or a Zn/HCl/AcOH combination that can be used to transform the *O*-nitrate into an *O*-acetate.[31] Alternatively, removal of nitrates can also occur by photolysis, a mild protocol which is compatible with the common protecting groups.[17a,23] In addition to being easily deprotected, organic nitrates can undergo functional, synthetically useful, transformations into reactive alkoxy radicals in the presence of tributyltin hydride / AIBN.[17a,23,32]

Having already demonstrated the utility of the range of common lanthanide salts, in conjunction with Ac_2O, in effecting the synthesis of per-*O*-acetylated derivatives from the free monosaccharides in high yield,[33] we decided to investigate the applicability of ceric ammonium nitrate in acetylating differentially protected carbohydrate derivatives. CAN was chosen as the favoured Lanthanide salt due to its affordability and common use (and hence availability) in many synthetic transformations.[34] Presented herein are the results of this study, where the effect of temperature and stoichiometric ratio of the reagent system on the esterification efficiency were investigated. Interestingly, not only

does the CAN/Ac_2O afford the partially *O*-acetylated derivatives in high yield, but the system can be optimized to yield the mononitrated derivatives as well.

RESULTS AND DISCUSSION

A variety of carbohydrate derivatives with: (1) at least one free hydroxyl; and (2) which possessed the most commonly employed protecting groups, ranging from acid-labile constructs such as isopropylidene, benzylidene, silyl and trityl to other important groups such as benzyl and allyl functionalities, were examined. Substrates were chosen so as to exemplify and encompass the diversity of structures that may be encountered in synthetic routes, including pyranosides and furanosides. Examples include those where the *O*-Bn group was situated in a range of secondary positions and at the primary and anomeric centres; as well as where the *O*-benzylidene ring was present in cis, trans and 5-membered or 6-membered configurations.

Having previously reported that optimal results (reaction time and yield) were obtained by dissolving the free sugar in Ac_2O at 50 °C and then adding 0.1 equivalent CAN,[33] this protocol was extended to the partially protected derivatives. The results are shown in Table 1.

1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside (Entry 1) was the first to be examined, owing to its relative ease of synthesis in a single high-yielding step from D-galactose, as well as due to its possession of two acid–labile isopropylidene rings. After 20 minutes, there was complete consumption of starting material, accompanied by the

formation of a faster moving spot on the TLC plate that corresponded to that of an authentic sample of 6-*O*-acetate-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside, **1a**. Surprisingly, an even faster moving spot was also detected (R_f greater that of **1a**). Isolation and elucidation of this spot revealed it to be the nitrate ester equivalent, **1b**, of acetate **1a**.

Applying these same reaction conditions, the overall trend was that those derivatives bearing the acid-labile groups (Entries 1-10) all gave product (s) in which their previously installed protecting groups were unaffected. More importantly, those substrates in which *O*-Bn groups were present (Entries 9-23) were also preserved, with the aromatic rings not undergoing any nitration. The tetra-*O*-Bn derivative (Entry 23) did however undergo partial acetolysis of the different *O*-Bn groups to give a complex mixture of di-*O*-Ac-tri-*O*-Bn products. In the majority of cases, the corresponding nitrated esters were also formed, with the total yield of products [acetylated, **a**, and nitrated, **b**] almost always exceeding 90 %. It should be noted that only the mononitrated products were isolated, multiple nitrations of the same molecule did not occur. As with **1a** and **1b**, the nitrated derivatives always had a higher R_f, and hence were generally easy to separate via column chromatography, from their acetylated counterparts. In addition, for those substrates bearing a free anomeric hydroxyl (Entries 2, 5, 6, 9, 14, 16, 17 and 23), no nitration of this centre was observed. Where multiple non-anomeric hydroxyls were available for esterification, the isomeric mononitrated products were usually obtained. Apart from entries 19 and 20, the acetylated product was always obtained in higher yield than that of the corresponding mononitrated isomers. The product

distribution observed for those substrates bearing free non-anomeric hydroxyls warrant closer examination.

For silylated derivative (Entry 3), a mixture of mononitrated products was obtained, with the nitrate group being present on either the 2, 3 or 4 positions, in a distribution ratio of 1:1.6:1, respectively. This suggests that nitration at the 3-OH position is most facile, likely due to steric factors encountered at the 2 (axial) and 4 (proximity to the bulky *O*-TBDPS group) positions.

For tritylated derivative (Entry 4), no mononitrated product was observed, however this may be due to the pseudo-axially oriented 2 and 3-OHs not presenting a favourable reacting centre for nitration.

Nitration vs acetylation appears to be controlled by electronic factors, with product distribution of the resulting mononitrated isomers being governed by sterically accessible centres.

With 4,6-*O*-benzylidene mannopyranose (Entry 5), no 2-*O*-NO_2 isomer was detected; only the more sterically accessible equatorial 3-OH being nitrated, albeit in low yield. For the analogous 4,6-*O*-benzylidene galactopyranose (Entry 6), no nitrated products were isolated. For all of the other entries, the ratio of nitrated isomers to each other can be explained sterically, with the more reactive hydroxyl being more likely to be nitrated than the others.[35]

For those examples where a free anomeric hydroxyl was available for esterification (entries 2, 5, 6, 9, 14, 16, 17, 23) the α:β ratios generally exhibited a preference for the α-anomer, the only exception being the 4,6-*O*-benzylidene mannopyranose derivative (Entry 5), which favoured the β-product. This can be attributed to the influence of the 4,6-*O*-benzylidene ring on the anomeric equilibrium of mannopyranose.[36]

CAN in combination with a variety of wet solvents, most commonly acetonitrile, has been used for the deprotection of many groups, including: trityl,[37] silyl,[38] acetals,[39] ketals,[40] as well as hydrolysis of disaccharides.[41] That such deprotection is not observed in the present reaction is suggestive of the critical role played by water in these synthetic protocols.

Tanemura and co-workers showed that a mixture of 0.1 mol eq. CAN in Ac_2O was effective in cleaving the 2-methoxyethoxymethyl and methoxymethyl protecting groups.[42] The mechanism was proposed to involve the production of acetyl nitrate from the reaction between CAN and Ac_2O. The acetyl nitrate would then generate the CH_3COO^- and NO_2^+ ions in a reversible reaction. However, for the nitration reaction reported in this present work, if only 1 molecule of acetyl nitrate is generated per molecule of CAN, then at a 0.1 mol eq. CAN, the maximum yield of nitrated derivative would be 10 %, much less than the yields reported with some substrates (entries 1, 7, 8, 11, 13, 18-21). In Tanemura's reaction, the NO_2^+ generated was acting as a catalyst, thereby maintaining equilibrium between CH_3COONO_2 and $CH3COO^-/NO_2^+$. Acetyl

nitrate has been shown to act as a mild nitrating agent for a variety of substrates,[43] and it is likely that it is also the active source of NO_2^+ in the present reaction. In this case however, nucleophilic attack of a reactive hydroxyl on the NO_2^+, followed by subsequent deprotonation by CH_3COO^- (Scheme 1), drives the equilibrium forward, favouring the complete, but sequential replacement of all the nitrate ions of CAN by acetate anions (Scheme 2). Such a mechanism would allow for a maximum yield of 60 % with 0.1 mol eq. CAN.

CAN as a viable source of the nitronium ion has also been demonstrated in the widespread synthetic application of Lemieux's azidonitration protocol, in which a CAN/NaN_3 mixture when reacted with a 1,2-glycal, affords a pyranoside derivative bearing an anomeric nitro group and an azide at the 2-position.[44] Interestingly, under these same conditions, 1,2-anhydrosugars furnished the anomeric azide, with a free 2-OH.[45]

It is also possible that the acetyl nitrate is acting as the active acetylating agent, regenerating CAN in the process. The relatively electron rich acetyl portion of this reactant may explain the greater tendency of relatively more sterically accessible and/or reactive hydroxyls to undergo acetylation, while the less nucleophilic hydroxyls favour nitration (Scheme 3). However, the pathway involving activation of the carbonyl carbon of Ac_2O to nucleophilic attack, as a result of Ce^{IV} coordination to the acyl oxygen, cannot be discounted as an alternative and competing acetylation mechanism.[46] The existence of two acetylation pathways would account for the absence of a clearly defined

relationship between acetylated:nitrated product distribution ratio and structural / electronic features of the available free hydroxyls.

^{13}C NMR analysis (Table 2) proved very useful in quickly establishing which hydroxyl had undergone nitration as opposed to acetylation. The carbon of the sugar ring, bonded to a nitrate, experienced an average downfield chemical shift of 7 ppm, compared to its acetylated counterpart; corroborating the greater electron withdrawing, and hence deactivating, nature of a nitrate group as compared to an acetate. The proton attached to the aforementioned carbon generally experienced a downfield shift, but not to any diagnostically significant extent.

Next, having established the versatility of the CAN / Ac_2O system for protecting group compatible esterifications, we decided to optimize both acetylation and nitration yields respectively. Choosing 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside as the test substrate, esterifications were carried out under various conditions of equivalents of CAN, temperature, and order of addition of reactants (Table 3).

Firstly, conducting the reaction at room temperature (entries 1-5), showed a direct relation between the yield of acetylated:nitrated product distribution ratio and the stoichiometric equivalents of CAN used. At 0.001 mol eq. CAN, no mononitrated product was detected; indicating that this combination of Ac_2O / CAN can be used to yield exclusively the acetylated derivatives in yields comparable to that obtained with the traditional pyridine / Ac_2O protocol. Having demonstrated that the method can afford

exclusively the partially acetylated, differentially protected derivatives, we then turned our attention to maximizing the yield of the nitrated derivatives. Increasing the mol eq. of CAN from 0.1 to 1.0 (entry 4) resulted in a sizeable increase in the yield of the mononitrated derivative, **1b**, though the acetylated derivative, **1a**, was still the favoured product. Increasing further the mol eq. CAN to 3.0 (entry 5) did not result in any appreciable increase in the yield of **1b**. However, increasing the temperature (entries 6-9) did result in an increase in the yield of **1b**, though **1a** was still marginally dominant. Whilst the highest ratios favouring **1b** were obtained at 80 °C (entries 8 and 9), the absolute yield of the product was decreased, attributed to deprotection of the isopropylidene rings, as per-*O*-acetylated galactopyranoside was recovered. At 50 °C (entry 6) and 60 °C (entry 7), there was a visible amount of CAN that remained undissolved in the Ac_2O, even after the reaction had gone to completion. Reasoning that maximization of the yield of the nitrated derivative would require a large concentration of NO_2^+ species present in solution, so as to effectively compete with the activated Ac_2O species, the order of addition of the reactants was altered.

The CAN was added to the Ac_2O and allowed to fully dissolve (entries 10-17), before the carbohydrate substrate was added. The effect of these "pre-mixing" conditions is significant: for those pairs of experiments conducted at the same temperature and mol eq. CAN (entries 6 and 11; entries 7 and 12; entries 9 and 17) there was an inverse in the product distribution, with the desired nitrated derivative **1b**, now being favoured over that of its acetylated counterpart, **1a**. While the best ratios favouring **1b** (0.5:1) were obtained with both 3.0 mol eq. CAN / 50 °C (entry 11) and 1.5 eq. CAN / 80 °C (entry 17), the

higher temperature again resulted in lower yields of the desired product, with per-*O*-acetylated galactopyranoside being recovered.

Under the pre-mixing conditions, an increase in the yield of **1b** was observed by increasing either temperature or mol eq. CAN. Increasing temperature up to 80 °C increased the distribution ratio favouring **1b**, but at temperatures above 90 °C, evolution of NO_2 was observed. At 105 °C (entry 13), only when no more brown fumes of NO_2 were visible, was the sugar added to the reaction mixture. While no per-*O*-acetylation was observed, the yield of nitrated product was also negligible. This suggests that a fine balance must exist between the amount of NO_2^+ allowed in solution (favouring nitration) and the removal of protecting groups (favoured by high mol eq. of CAN and elevated temperatures).

Reasoning that higher temperatures would increase the susceptibility of aromatic rings to undergo nitration or cause the deprotection of benzyl / benzylidene groups, the conditions of entry 11 (3.0 mol eq. CAN per free non-anomeric hydroxyl/50 °C) were selected so as to determine the maximum yields of the nitrated product that could be obtained with selected *O*-TBDPS, *O*-Bn, and *O*-benzylidene protected derivatives (Table 4). In all cases examined, the ratio of nitrated product (**b**):acetylated derivative (**a**) was increased. However, for the *O*-Bn and *O*-benzylidene derivatives, this was accompanied by formation of complex mixtures of acetolyzed products, indicating that deprotection of these Lewis acid-labile groups is a competing side reaction at high concentrations of CAN. For those derivatives in which multiple isomeric mononitration products were

synthesized (entries 1 and 3), the distribution ratios of the nitrated isomers were identical to those obtained with 0.1 mol eq. CAN (entries 3 and 7 respectively, Table 1).

CONCLUSION

We have demonstrated the versatility and utility of the ceric ammonium nitrate / acetic anhydride system for the acetylation of partially protected carbohydrate derivatives, proceeding in high yield at low catalytic loading of CAN. Unlike most other acetylation methods however, this system, as with the pyr / Ac_2O combination, affords compatibility with the range of commonly utilized protecting groups. Crucially however, it avoids toxic and noxious chemicals, and possesses a straightforward work-up and purification protocol.

As added evidence of enhanced versatility, it provides access to a range of mononitrated carbohydrate derivatives, hitherto inaccessible. It is hoped that this body of work will serve to stimulate interest and research in a long forgotten, but versatile carbohydrate protecting group, the nitrate ester. The low yield of these shock and thermal stable mononitrated products, is compensated for by the alternative routes for their synthesis, especially in those derivatives possessing aromatic rings, being virtually non-existent. Furthermore, it has been demonstrated that organic nitrates function as NO donors, and are postulated to be a viable source of NO-mimetic targeted drugs.[47] This represents a possible medicinal application for these nitrated carbohydrate derivatives.

EXPERIMENTAL

All chemicals used were reagent grade and used as purchased unless otherwise stated. ^{1}H, ^{13}C, COSY, HSQC, HMBC and TOCSY NMR experiments were recorded on Bruker 600, 400 or 300 NMR spectrometers in the deuterated solvents stated. Chemical shifts are stated in ppm. Multiplicities are stated as either s (singlet), bs (broad singlet), d (doublet), apptd (apparent doublet), t (triplet), apptt (apparent triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), apptdd (apparent doublet of doublets), apptqd (apparent quartet of doublets), ABq (AB quartet), m (multiplet) or *p*dd (pseudo doublet of doublets). High-resolution mass spectral (HRMS) analyses were obtained using a Bruker Daltonics micrOToF-Q instrument in the electron spray ionization mode. Optical rotations were measured on a Bellingham & Stanley ADP 220 polarimeter at 24.6 °C. TLC was performed using pre-coated silica gel 60 F_{254} plates; compounds were visualized using acidic ammonium molybdate solution (ammonium molybdate (VI) tetrahydrate (25 g) in 1 M H_2SO_4 (500 mL)). Column chromatography was performed on silica gel (70-230 mesh). Solvent systems used for TLC and column chromatography are as follows: System A = 3:2 (Petroleum Ether: Ethyl Acetate); System B = 7:3 (Petroleum Ether: Ethyl Acetate); System C = 1:1 (Petroleum Ether: Ethyl Acetate); System D = 2:3 (Petroleum Ether: Ethyl Acetate).

General Procedure A, For Esterification Using 0.1 Mol Eq. CAN:

The partially protected derivative (1.0 mmol) was dissolved in Ac_2O (1-2 mL) and stirred at 50 °C. Ceric ammonium nitrate (0.1 mmol) was added and stirring maintained. After completion of the reaction, saturated $NaHCO_3$ (20 mL) was added and the reaction stirred at rt for 10 minutes. The mixture was then diluted with CH_2Cl_2 (50 mL), washed with

water (3 x 100 mL), and the organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum and the residue was then subjected to column chromatography.

General Procedure B, For Esterification Using 3.0 Mol Eq. CAN Per Free OH:

Ceric ammonium nitrate (1.5 mmol per free non-anomeric hydroxyl) was suspended in Ac_2O (2-4 mL) and stirred at 50 °C until all of the CAN had dissolved. The partially protected derivative (0.5 mmol) was then added and stirring maintained. After completion of the reaction, saturated $NaHCO_3$ (20 mL) was added and the reaction stirred at rt for 10 minutes. The mixture was then diluted with CH_2Cl_2 (50 mL), washed with water (3 x 100 mL), and the organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum and the residue was then subjected to column chromatography.

Characterization Data:

6-*O*-Acetate-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside, (**1a)**. White solid; m.p. = 109.0 – 110.0 °C; R_f (System A) = 0.42; $[\alpha]_D$ = - 53.6 (*c*, 1.2, $CHCl_3$); NMR data:[48] ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.340 (3H, s, C*H*$_3$(CH$_3$)C-), 1.341 (3H, s, CH$_3$(C*H*$_3$)C-), 1.45 (3H, s, C*H*$_3$(CH$_3$)C-), 1.52 (3H, s, CH$_3$(C*H*$_3$)C-), 2.09 (3H, CH$_3$CO-), 4.03 (1H, m, H-5), 4.18 (1H, dd, $J_{5,6}$ = 7.7 Hz, $J_{6,6'}$ = 11.5 Hz, H-6), 4.24 (1H, bd, $J_{3,4}$ = 7.9 Hz, H-4), 4.29 (1H, dd, $J_{5,6'}$ = 4.7 Hz, $J_{6,6'}$ = 11.5 Hz, H-6'), 4.33 (1H, dd, $J_{1,2}$ = 4.9 Hz, $J_{2,3}$ = 2.1 Hz, H-2), 4.62 (1H, $J_{2,3}$ = 2.1 Hz, $J_{3,4}$ = 7.9 Hz, H-3), 5.54 (1H, d, $J_{1,2}$ = 4.9 Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 20.9 (1C, *C*H$_3$CO-), 24.5 (1C, *C*H$_3$(CH$_3$)C-), 24.9 (1C, CH$_3$(*C*H$_3$)C-), 25.9 (1C, *C*H$_3$(CH$_3$)C-), 26.0 (1C, CH$_3$(*C*H$_3$)C-), 63.4 (1C, C-6), 65.9 (1C, C-5), 70.4 (1C, C-2), 70.7 (1C, C-3), 71.0 (1C, C-4), 96.3 (1C, $J_{C1\text{-}H1}$ = 177.1

Hz, C-1), 108.7 (1C, $CH_3(CH_3)C$-), 109.6 (1C, $CH_3(CH_3)C$-), 170.9 (1C, CH_3CO-). HRMS calculated for $C_{14}H_{22}O_7Na$: 325.1258; found: 325.1242 $(M + Na)^+$.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-nitro-α-D-galactopyranoside, (**1b)**. Colourless oil; R_f (System A) = 0.22; $[\alpha]_D$ = - 75.0 (*c*, 0.32, $CHCl_3$); NMR data:[23] ^1H NMR (400 MHz, $CDCl_3$): δ: 1.34 (3H, s, $CH_3(CH_3)C$-), 1.35 (3H, s, $CH_3(CH_3)C$-), 1.46 (3H, s, $CH_3(CH_3)C$-), 1.51 (3H, s, $CH_3(CH_3)C$-), 4.08 (1H, td, $J_{4,5}$ = 1.9 Hz, $J_{5,6}$ = 6.1 Hz, $J_{5,6'}$ = 6.0 Hz, H-5), 4.25 (1H, dd, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 1.9 Hz, H-4), 4.35 (1H, dd, $J_{1,2}$ = 5.0 Hz, $J_{2,3}$ = 2.6 Hz, H-2), 4.60 – 4.62 (2H, m, H-6, H-6'), 4.65 (1H, $J_{2,3}$ = 2.6 Hz, $J_{3,4}$ = 7.9 Hz, H-3), 5.53 (1H, d, $J_{1,2}$ = 5.0 Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 24.4 (1C, $CH_3(CH_3)C$-), 24.9 (1C, $CH_3(CH_3)C$-), 25.9 (1C, $CH_3(CH_3)C$-), 26.0 (1C, $CH_3(CH_3)C$-), 64.6 (1C, C-5), 70.3 (1C, C-2), 70.7, 70.9 (2C, C-3 and C-4), 71.6 (1C, C-6), 96.2 (1C, $J_{C1\text{-}H1}$ = 184.1 Hz, C-1), 109.0 (1C, $CH_3(CH_3)C$-), 109.9 (1C, $CH_3(CH_3)C$-). HRMS calculated for $C_{12}H_{19}O_8NNa$: 328.1003; found: 328.0991 $(M + Na)^+$.

SUPPORTING INFORMATION

Supporting Information: Full experimental detail, ^1H, ^{13}C and selected 2D NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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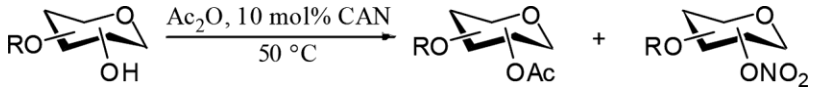
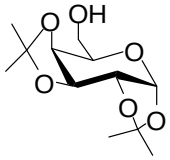
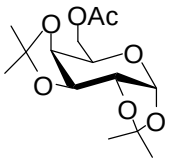
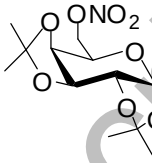
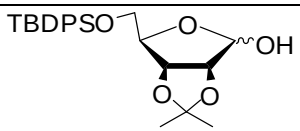
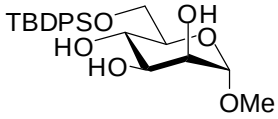
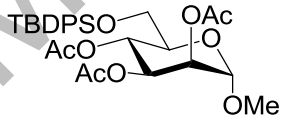
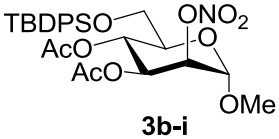
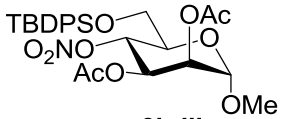
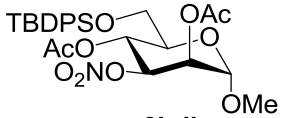
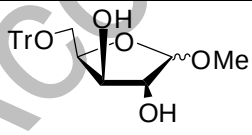
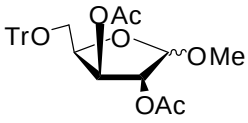
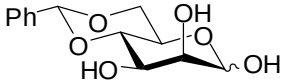
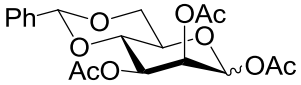
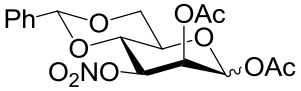
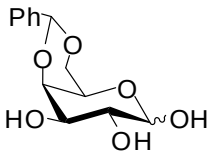
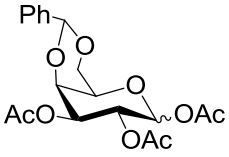
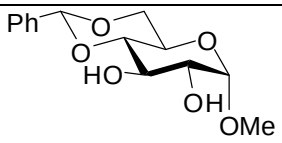
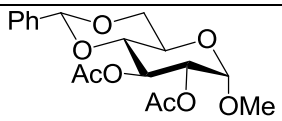
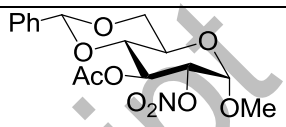
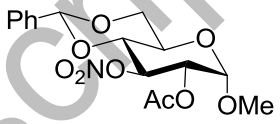
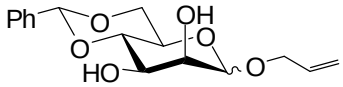
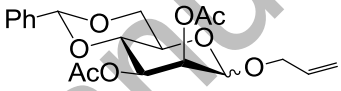
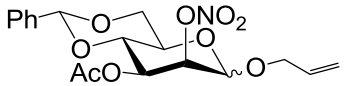
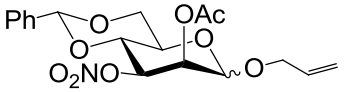
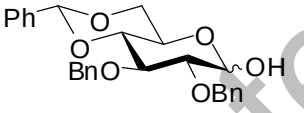
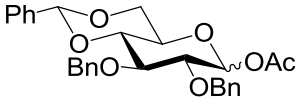
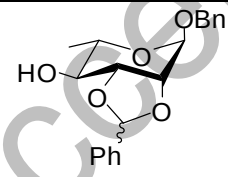
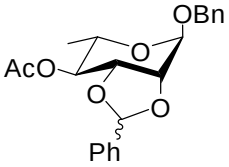
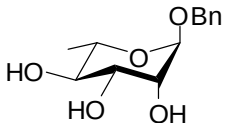
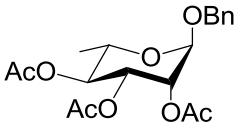
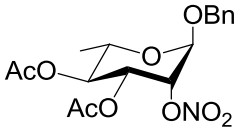
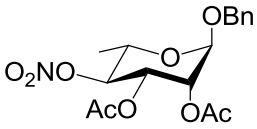
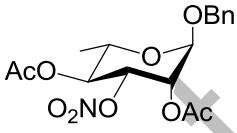
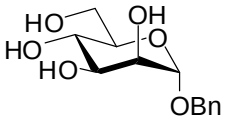
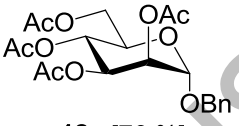
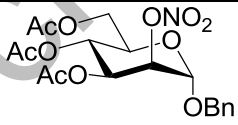
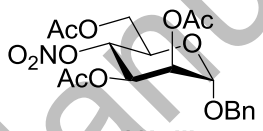
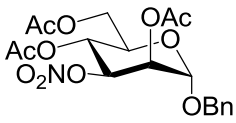
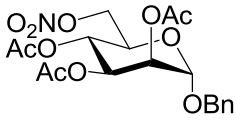
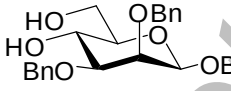
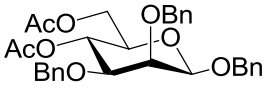
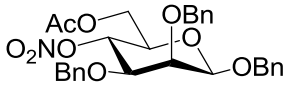
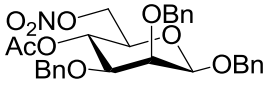
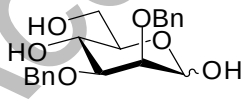
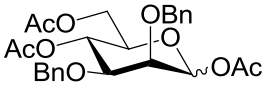
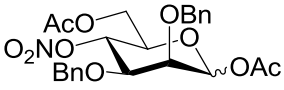
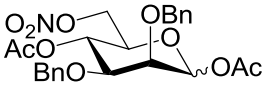
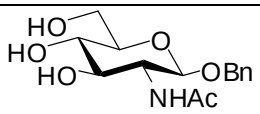
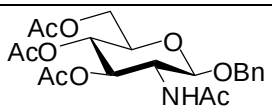
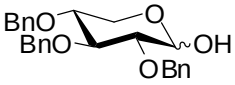
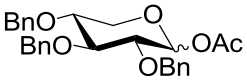
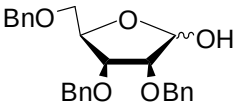
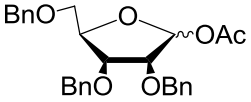
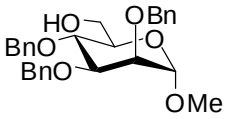
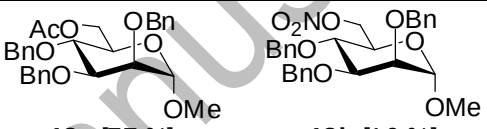
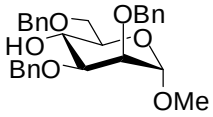
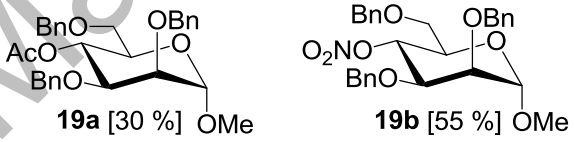
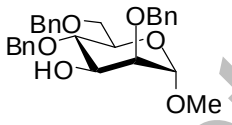
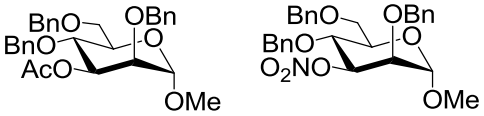
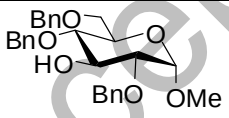
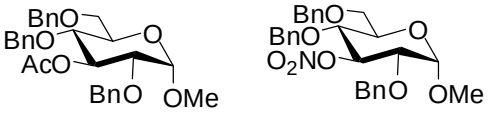
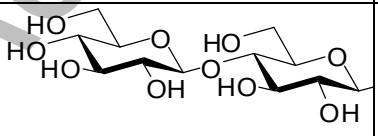
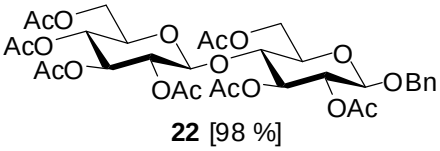
Table 1. Esterification of diversely protected carbohydrates

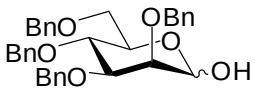
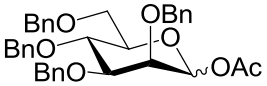


Entry	Substrate	Time (h)	Product (s) [Yield (%)][a]
1		0.3	 **1a** [74 %]  **1b** [18 %]
2		0.7	 **2** [95 %] α:β = 1:1
3		2	 **3a** [88 %]  **3b-i**  **3b-iii**  **3b-ii** **3b** [10 %] i:ii:ii = 1:1.6:1
4		0.5	 **4** [83 %]
5		3	 **5a** [86 %] α:β = 1:1.9  **5b** [8 %] α:β < 1:10

6		1.25	 **6** [92 %] α:β = 1:0.3
7		0.6	 **7a** [70 %]  **7b-i** **7b** [26 %] i:ii = 1:0.4  **7b-ii**
8		2	 **8a** [79 %]  **8b-i** **8b** [16 %] i:ii = 1:4.5  **8b-ii**
9		0.2	 **9** [96 %] α:β = 1:0.2
10		0.75	 **10** [97 %]

11		2	 **11a** [74 %]  **11b-i**  **11b-iii**  **11b-ii** **11b** [18 %] i:ii:iii = 1:1.1:0.7
12		3	 **12a** [76 %]  **12b-i**  **12b-iii**  **12b-ii** **12b** [22 %] i:ii:iii:iv = 1:1:1.3:1.6  **12b-iv**
13		0.5	 **13a** [65 %]  **13b-i** **13b** [26 %] i:ii = 1:0.3  **13b-ii**
14		0.5	 **14a** [85 %]  **14b-i** **14b** [10%] iα:iiα:iβ:iiβ = 1:0.7:0.2:0.2  **14b-ii**

15		1	 **15** [90 %]
16		0.3	 **16** [98 %] α:β = 1:0.3
17		0.3	 **17** [98 %] α:β = 1:0.5
18		0.3	 **18a** [77 %] **18b** [16 %]
19		0.4	 **19a** [30 %] **19b** [55 %]
20		0.4	 **20a** [29 %] **20b** [58 %]
21		0.4	 **21a** [58 %] **21b** [31 %]
22		2	 **22** [98 %]

23		0.2	 **23** [47 %] α:β = 1:0.5 **Unassigned di-*O*-acetylated products** [32 %]

[a]Yields of chromatographically pure compounds. Ratios of nitrated isomers determined by ^{1}H NMR; not separable by silica gel chromatography.

Table 2 ^{1}H and ^{13}C NMR comparisons of acetylated derivatives to their nitrated counterparts

^{1}H NMR (δ ppm)			^{13}C NMR (δ ppm)		
Acetylated product	Mono-nitrated equivalent	Δ	Acetylated product	Mono-nitrated equivalent	Δ
1a	**1b**	0.38	**1a**	**1b**	8.2
H-6: 4.18	H-6: 4.60		C-6: 63.4	C-6: 71.6	
H-6': 4.29	H-6': 4.62				
5a	**5b**	0.11	**5a**	**5b**	7.8
H-3: 5.22	H-3: 5.33		C-3: 69.9	C-3: 77.7	
7a	**7b-i**	0.19	**7a**	**7b-i**	7.3
H-2: 4.91	H-2: 5.10		C-2: 71.6	C-2: 78.9	
7a	**7b-ii**	0.15	**7a**	**7b-ii**	9.5
H-3: 5.58	H-3: 5.73		C-3: 68.9	C-3: 78.4	
8a	**8b-ii**	0.12	**8a**	**8b-ii**	8.9
H-3: 5.44	H-3: 5.56		C-3: 68.4	C-3: 77.3	
11a	**11b-i**	0.13	**11a**	**11b-i**	8.3

H-2: 5.30	H-2: 5.43		C-2: 69.5	C-2: 77.8	
11a	**11b-ii**	0.09	**11a**	**11b-ii**	8.3
H-3: 5.36	H-3: 5.45		C-3: 69.5	C-3: 77.8	
11a	**11b-iii**	0.13	**11a**	**11b-iii**	8.5
H-4: 5.09	H-4: 5.22		C-4: 71.1	C-4: 79.6	
13a	**13b-i**	0.23	**13a**	**13b-i**	9.0
H-4: 5.38	H-4: 5.61		C-4: 68.3	C-4: 77.3	
13a	**13b-ii**	0.40	**13a**	**13b-ii**	8.6
H-6: 4.20	H-6: 4.59		C-6: 63.3	C-6: 71.9	
H-6': 4.28	H-6': 4.68				
14a	**14b-i**	0.21	**14a**	**14b-i**	8.9
H-4: 5.47	H-4: 5.68		C-4: 67.4	C-4: 76.3	
14a	**14b-ii**	-	**14a**	**14b-ii**	5.5
H-6: 4.12	H-6: 3.70	0.40	C-6: 62.7	C-6: 68.2	
H-6': 4.21	H-6': 3.83				
18a	**18b**	-	**18a**	**18b**	10.6
H-6: 4.32	H-6: 3.84	0.49	C-6: 63.6	C-6: 74.2	
H-6': 4.34	H-6': 3.84				
19a	**19b**	0.34	**19a**	**19b**	8.5

H-4: 5.35	H-4: 5.69		C-4: 69.1	C-4: 77.6	
20a	**20b**	0.17	**20a**	**20b**	8.6
H-3: 5.21	H-3: 5.38		C-3: 74.6	C-3: 83.2	
21a	**21b**	0.13	**21a**	**21b**	9.9
H-3: 5.51	H-3: 5.64		C-3: 73.5	C-3: 83.4	

Table 3. Optimization Protocol with 1,2;3,4 di-*O*-isopropylidene-α-D-galactopyranoside

Entry	mol. eq. CAN	T (°C)	Conditions	Time (h)	Yield[d] [%]		Ratio (1**a**:1**b**)
					1a	**1b**	
1	0.001	rt	A[a]	18	98	-	1**a** only
2	0.01	rt	A	6	88	7	12:1
3	0.1	rt	A	3	86	10	9:1
4	1.0	rt	A	0.5	74	20	3.6:1
5	3.0	rt	A	0.25	69	21	3.3:1
6	3.0	50	A	< 0.1	63	28	2.3:1
7	3.0	60	A	< 0.1	67	23	2.9:1
8	1.0	80	A	< 0.1	54	31	1.7:1
9	1.5	80	A	< 0.1	55	29	1.9:1
10	3.0	rt	B[b]	< 0.1	54	39	1.4:1
11	3.0	50	B	< 0.1	32	63	0.5:1
12	3.0	60	B	< 0.1	39	56	0.7:1
13	3.0	105	C[c]	< 0.1	83	8	11:1
14	0.5	60	B	< 0.1	66	26	2.5:1
15	1.1	60	B	< 0.1	62	30	2.1:1
16	1.5	60	B	< 0.1	53	38	1.4:1
17	1.5	80	B	< 0.1	27	53	0.5:1

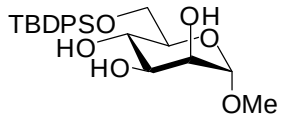
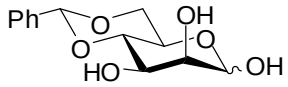
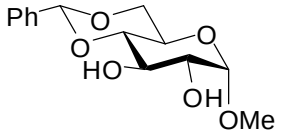
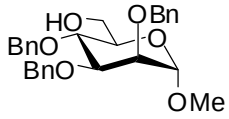
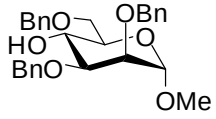
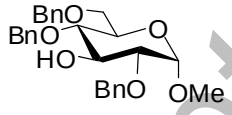
[a]Sugar dissolved in Ac_2O first, followed by addition of CAN.

[b]CAN and Ac_2O stirred until stated temperature was achieved, followed by addition of sugar.

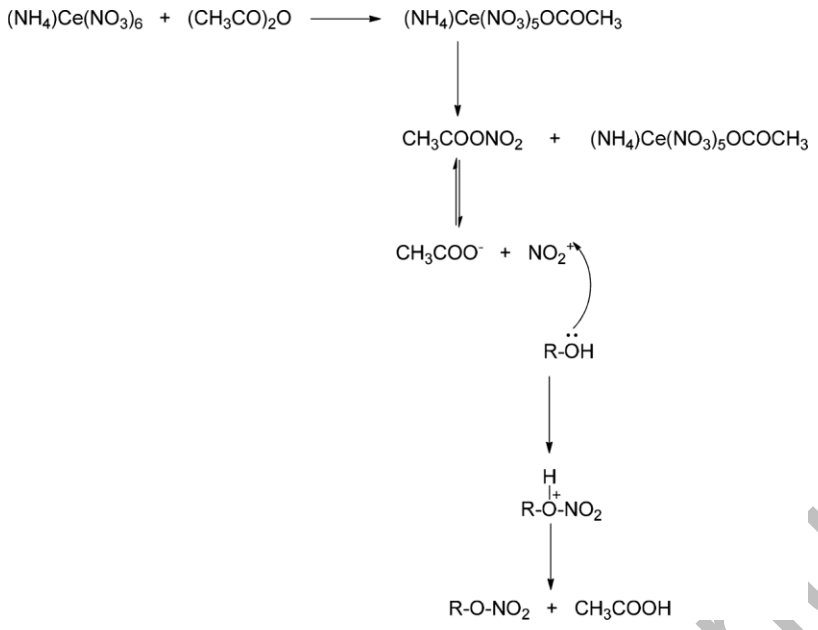
[c]Sugar added only after the visible evolution of NO_2 ceased.

[d]Isolated yield

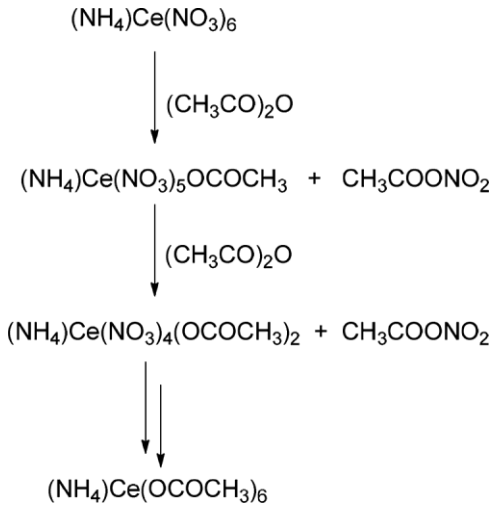
Table 4 Esterification results under pre-mixing conditions (3.0 mol eq. CAN per free OH / 50 °C)

Entry	Substrate	Time	Product (s) [Yield (%)]
1		0.3	**3a** [23%] **3b** [68%] i:ii:iii = 1:1.6:1
2		0.3	**5a** [28%] **5b** [33%]
3		0.2	**7a** [25%] **7b**[35%] i:ii = 1:0.4
4		< 0.1	**18a** [16%] **18b** [33%]
5		< 0.1	**19a** [25%] **19b** [20%]
6		< 0.1	**21a** [29%] **21b** [44%]

Scheme 1. Application of Tanemura's mechanism to account for nitrated derivatives



Scheme 2. Sequential replacement of the six nitrate groups of CAN by Ac_2O



Scheme 3. Acetyl nitrate as both the active acetylating and nitrating species