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# Synthesis and NMR spectroscopic analysis of 3-nitro-pyranoside, 3-nitro-septanoside and 4-nitro-septanoside derivatives by condensation of the anion of nitromethane with glycoside dialdehydes

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ABSTRACT

The utility of the nitroaldol reaction for accessing 3-nitro-pyranoside, 3-nitro-septanoside or 4-nitro-septanoside derivatives, by reaction of the anion of nitromethane with glycoside dialdehydes is demonstrated. Initially, the feasibility of using unprotected glucoside dialdehydes was probed for the synthesis of the septanoside products, but this afforded pyranoside rather than septanoside targets. Subsequent studies utilised protected glycoside dialdehydes within the methodology, which allowed entry into a range of 3-nitro or 4-nitro-septanosides in good yield. NMR spectroscopic analysis allowed determination of the stereochemistry of each of the products thus afforded.



## 1. Introduction

In recent years, the development of carbohydrate analogues as potential drug targets has received intense interest due to the increasing knowledge of the roles of carbohydrates in biological and disease processes.[1] Whilst the synthesis of pyranoside and furanoside derivatives has been widely reported in the literature,[2] the synthesis of septanoside derivatives has been less commonly reported. However, since some seven-membered carbohydrate analogues have received interest for their therapeutic potential,[3,4] and septanoses may be able to adopt distorted conformations in glyco-enzyme binding sites,[5] their synthesis is gaining increased attention.[6] Of direct relevance to this study is the preparation of 3-nitroseptanosides via the nitroaldol reaction of the anion of nitromethane with glycoside dialdehydes; this a reaction we have reinvestigated and extended in this programme of work.[7]

A number of researchers[8] including ourselves have developed methods that allow selective cleavage of specific diol pairs within the carbohydrate framework. In previous work from our laboratory, we exploited this methodology to allow selective entry to morpholines or oxazepanes, after reductive amination of the dialdehydes thus formed. Herein we extend this study to potentially allow access to 4-nitro-septanosides, via nitroaldol reactions with the dialdehydes thus formed, without the need for extensive protecting group strategies.

## 2. Results and discussion

At the outset of this study, benzyl-β-D-glucopyranoside **1** was used as the substrate for the oxidative cleavage reactions, to afford the unprotected dialdehydes required for the nitro aldol reaction. Given the potential for the formation of complex mixtures of regio- and stereoisomeric products from the nitroaldol reaction, the use of the UV active substrate benzyl-β-D-glucopyranoside **1** was considered prudent, in order to allow facile monitoring of mixtures through TLC analysis. As shown in Scheme 1, the glucopyranoside was treated with 1.2 equiv of sodium periodate at low temperature for short reaction times, in order to access dialdehyde **2** resulting from selective cleavage of the C-3,4 diol pair.[8b] This was then reacted with 5 equiv of the anion of nitromethane, to potentially furnish 4-nitroseptanoside **4**. The analogous methyl-α-D-glucopyranoside substrate was also used within the investigation as it had previously been utilised within nitroaldol reactions.[9]

Despite much experimentation, it was not possible to access 4-nitroseptanoside **4** using the unprotected substrates; instead in all cases a complex mixture of products resulted, which could not be separated. Analysis of the $^1$H NMR spectra of the crude mixtures resulting from the study indicated that 3-nitro-pyranoside **5** was always formed as one component of the reaction mixture. It was not possible to ascertain whether nitroseptanosides had also been prepared due to the complexity of the product distribution. Moreover, despite extensive experimentation, it did not prove possible to optimise the methodology to bias formation of 4-nitroseptanoside **4** using the unprotected glycoside substrate **1**.

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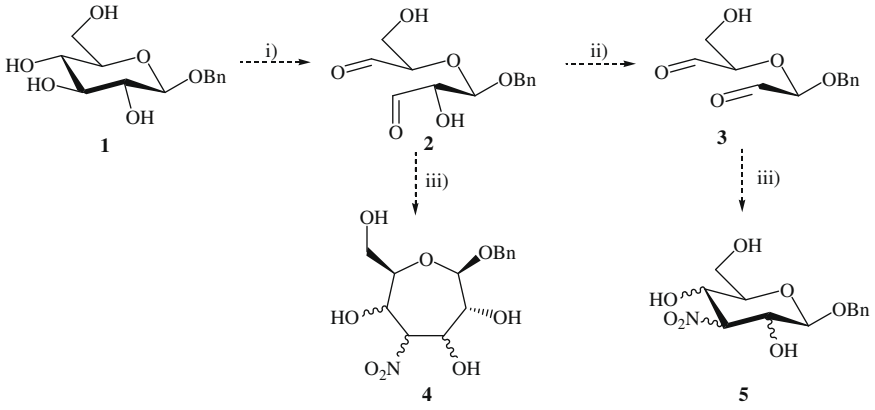



**Scheme 1.** Reagents and conditions: (i) $NaIO_4$, 1.2 equiv; (ii) $NaIO_4$, further 3.8 equiv; (iii) nitromethane, NaOMe, 5 equiv.

As 3-nitropyranoside **5** is of interest in its own right as a precursor to an aminoglycoside, attempts were made to improve the yield of its formation from the unprotected glycoside substrate **1**. Thus, tetraol **1** was treated with 5 equiv of $NaIO_4$ for an extended reaction time of 18 h to afford dialdehyde **3**. This was then utilised within the nitroaldol methodology under a range of conditions; the best results were obtained upon treatment of the dialdehyde with an excess of the anion of nitromethane, initially at −78 °C and then at 5 °C, for 18 h. This allowed the synthesis of nitroaldol **5** in 31% yield. This compares well with the yield of formation of **6**, previously reported as a result of using methyl-α-D-glucopyranoside within the oxidative cleavage methodology.[9] NMR spectroscopic analysis of **5** was utilised to determine the stereochemical features of **5** and this illustrated that H-1 (d, *J* 8.0 Hz), H-2 (dd, *J* 8.0, 10.5 Hz) and H-3 (app. t, *J* 10.0 Hz) were of an axial–axial–axial orientation, which suggests that the nitroaldol reaction has resulted in the formation of the *gluco*-pyranoside (Fig. 1).

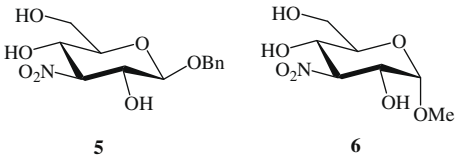



**Figure 1.**

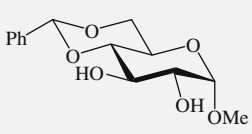
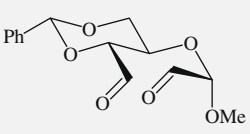
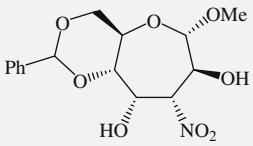
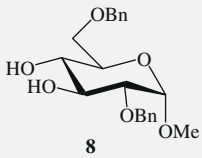
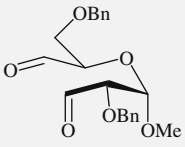
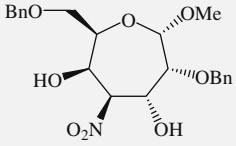
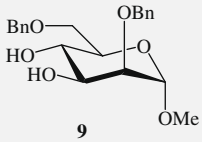
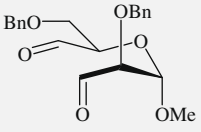
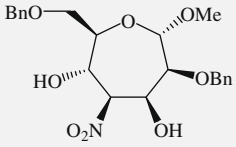
These results are in agreement with previous literature reports for pyranoside products, where the preferred trajectory of the nitronate is that which will lead to the resulting nitro group being equatorial to the ring, giving the most chair-like conformation and minimising $A^{(1,3)}$ non-bonding interactions between the oxygen atoms of the nitro group and the adjacent hydroxyl groups.[9]

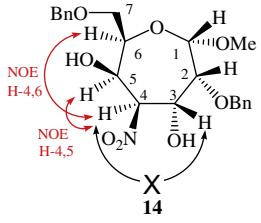
As it did not prove possible in the above approach to bias the reaction of unprotected glycosides, to form septanoside products, our attention was next turned to using protected glycopyranosides within the methodology. Diols **7**, **8** and **9** were selected for study, as these could allow access to 3-nitroseptanosides or 4-nitroseptanosides, extending the scope of the nitro aldol reaction that had previously only been reported for the synthesis of 3-nitroseptanosides.[7] In all cases the diols were formed by the literature methods[10–12] and were then treated with sodium periodate (5 equiv) at 0 °C for 5 h. Dialdehydes **10**, **11** and **12** thus formed were used without purification and were treated with the nitromethane anion in 1 M NaOMe solution at low temperature and then allowed to warm temperature overnight. Following neutralisation with acetic acid, the mixtures were purified by flash column chromatography to afford the products **13**, **14** and **15** in good yields over two steps, as indicated below in Table 1.

In all cases, NMR spectroscopic analysis was utilised to determine the stereochemistry of the targets formed. For 3-nitro-septanoside **13**, H-2 and H-3 shared a large coupling constant (10.5 Hz), whilst H-3 and H-4 displayed only a very small coupling constant (2.5 Hz). Moreover, the NOE difference spectrum showed that irradiation of H-3 enhanced the signals for H-4 and 5; likewise, the irradiation of H-5 enhanced the signals of H-3 and 4, suggesting that these protons are on the same side of the ring. As a result of these NMR spectroscopic studies, the product was assigned as methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-*glycero*-D-*altro*-septanoside **13**. It is likely from the observed coupling constants which were large for H-2 coupling to H-3, and H-5 coupling to H-6, and the conformational restraints imparted by the benzylidene ring, that the septanoside favours a chair conformation rather than a twist-chair, boat or twist-boat conformation.[13] Interestingly, previous reports have detailed the nitroaldol reaction of dialdehyde **10**[14] for the synthesis of 3-nitroseptanosides, but contrary to our results, product **13** did not feature as the major product of the reaction. Comparing analytical data (mp and specific rotation) obtained for **13** with those reported for minor products in the literature reports[14] provided further weight for our proposal that the major product of our reaction was the 3-deoxy-3-nitro-α-D-*glycero*-D-*altro*-septanoside **13**.

The formation of 4-nitro-septanoside **14** illustrated that the nitroaldol reaction was also effective when the position of the dialdehyde within the sugar framework was altered, hence allowing entry to 4-nitroseptanosides which can be considered as precursors to 4-aminoseptanosides. Since 4-amino-glycosides, and their analogues have received far less attention in the literature than 3-amino-glycosides and their analogues,[15] this represents a useful advance in synthetic methodology. The deduction of the stereochemistry of **14** was again possible by using NMR spectroscopy. However, the relative stereochemistry of the substituents at C-3, 4 and 5 could now no longer be confidently assigned on the basis of the multiplicities observed, or the coupling constants, for H-2 (dd, *J* 3.5, 2.0 Hz), H-3 (m), H-4 (dd, *J* 9.5, 3.5) or H-5 (m). The NOE spectrum proved more informative and showed that irradiation of H-4 enhanced the signals of H-5 and 6 but not of the adjacent H-3. This would indicate that H-4, 5 and 6 are on the same side of the ring and H-3 is on the opposite side of the ring, affording 4-deoxy-4-nitro-α-D-*glycero*-L-*manno*-septanoside **14** as shown in Figure 2. In light of these stereochemical assignments, the large coupling constant of 9.5 Hz for H-4 can be assigned to the coupling of H-4 with H-3, whilst the smaller coupling constant of 3.5 Hz reflects coupling between H-4 and H-5. With many resonances appearing as multiplets, it is not possible to comment further from

**Table 1**

| Diol | Dialdehyde | Septanoside product | Yield over 2 steps (%) |
|---|---|---|---|
|  **7** |  **10** |  **13** | 43 |
|  **8** |  **11** |  **14** | 35 |
|  **9** |  **12** |  **15** | 42 |

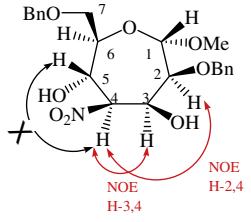


**14**

**Figure 2.**

this study as to whether septanoside **14** prefers the chair-twist, chair, boat or twist-boat conformation.

For entry to the final target **15**, mannose-derived diol **9** was utilised. A successful reaction was again seen here allowing entry to 4-nitro-septanoside **15** which was isomeric with **14**. 4-Nitroseptanoside **15** was again characterised by $^{1}H$, $^{13}C$ and NOE NMR spectroscopy in a similar manner to the previous derivatives **13** and **14**. NOE studies for **15** illustrated that irradiation of H-2 led to an enhancement of the signals for H-3 and 4; irradiation of H-4 enhanced the signals of H-2 and 3. Furthermore, irradiation of H-4 showed no NOE enhancement of H-5. As the stereochemistry of H-2 and H-1 are predefined from the mannopyranoside framework, and for an enhancement of H-2 and 3 to be achieved by H-4, product **15** would have to be 4-deoxy-4-nitro-α-D-*glycero*-D-*talo*-septanoside, as illustrated in Figure 3.



**15**

**Figure 3.**

The $^{1}H$ NMR data for **15** were fully consistent with this stereochemical assignment, with H-2 presented as a dd with *J* values of 6.5 (coupling to H-1) and 1.0 Hz (coupling to H-3). The H-3 and H-5 presented as multiplets whilst H-4 was presented as a dd with *J* values of 10 Hz (coupling to H-5) and 6.5 Hz (coupling to H-3). H-6 coupled to H-5 with a *J* value of 10.0 Hz.

## 3. Conclusions

Oxidative cleavage and nitroaldol protocols successfully allowed the synthesis of nitro-pyranoside **6** in a good yield that was comparable with those previously reported for related substrates.[9] Although unprotected glucopyranosides were not effective as precursors to 4-nitro-septanosides, the nitroaldol reaction of regioselectively protected pyranosides **7**, **8** and **9** did prove useful for entry to either 3- or 4-nitroseptanosides **13**, **14** and **15**. Thus targets **13**, **14** and **15** were accessed in good yields of 43%, 35% and 42%, respectively. The NMR and NOE spectroscopic studies were used to determine the stereochemical features of the targets. Since a number of carbohydrate mimetics containing the amine functional group have found interest as new antibacterial agents,[17] the derivatives prepared herein are now being further modified chemically, to afford 3-amino-pyranoside and 3-amino- and 4-amino-septanosides. The results of these studies will be reported in due course.

## 4. Experimental

Melting points were obtained using an Electrothermal digital melting point apparatus. Specific rotation measurements were measured using a Perkin–Elmer 341 polarimeter. Solutions were made using $CHCl_3$ or MeOH and measurements were taken at a wavelength of 589 nm and are quoted in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. Infrared spectra were recorded on a Perkin–Elmer Paragon 1720-X FT-IR spectrometer. Liquid samples were placed as thin films between sodium chloride plates. Absorption maxima frequencies

are measured in wavenumbers ($cm^{-1}$). The following abbreviations are used to report the degree of absorption: s (strong), m (medium), w (weak) and br (broad).

All $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX-250 spectrometer or a Bruker AMX-400 spectrometer using $CDCl_3$ or $CD_3OD$ as an internal standard. $^1H$ NMR spectra were recorded at 250 MHz or 400 MHz and chemical shifts ($\delta_H$ values) are quoted in units of parts per million (ppm). The following abbreviations are used: s (singlet), d (doublet), t (triplet), app. t (apparent triplet), dd (double doublet), dt (double triplet), ddd (double double doublet) and quin (quintet). Coupling constants ($J$ values) are measured in hertz to the nearest 0.5 Hz. $^{13}C$ NMR spectra were recorded at 63 MHz or 101 MHz using $CDCl_3$ as an internal standard and chemical shifts ($\delta_C$ values) are quoted in units of ppm.

High resolution mass spectrometric data were recorded on a Hewlett Packard Series 1050 spectrometer for chemical ionisation (CI) or electron impact ionisation (EI) or a Bruker MicroTof LC TOF MS for electrospray ionisation (ESI). Molecular ions and molecular ion fragments are reported as mass/charge ($m/z$) ratios.

Flash chromatography was performed on silica gel 60 (Merck or Fisher) using head pressure by means of compressed air or bellows. TLC analysis was performed using Merck silica 60 $F_{254}$ aluminium-backed plates of 0.2 mm depth. Compounds were visualised on TLC plates using UV light ($\lambda$ = 254 nm) or using an ethanol/sulfuric acid dip (25:1), phosphomolybdic acid (20% ethanol), vanillin or ninhydrin spray.

All chemicals and solvents were obtained from Aldrich, Fisher Scientific or Lancaster and used as required. Anhydrous solvents were used as bought and glassware oven-dried prior to use. Experimental procedures were carried out under an argon atmosphere when an inert atmosphere was required.

### 4.1. Benzyl 3-deoxy-3-nitro-β-D-glucopyranoside 5

*Part A*: Benzyl-β-D-glucopyranoside **1**[16] (1.23 g, 4.55 mmol) was dissolved in MeOH (20 mL) and cooled to 0 °C. Next, $NaIO_4$ (4.88 g, 22.75 mmol) was dissolved in distilled water (20 mL) and added dropwise to the methanol solution. The reaction mixture was stirred for 18 h before evaporation to dryness. The residue was diluted with EtOAc and filtered through a pad of silica and Celite®. The filtrate was concentrated in vacuo to yield crude dialdehyde **3** (630 mg).

*Part B*: At first, 1 M NaOMe (1 mL) was added to a flask containing anhydrous $CH_2Cl_2$ (2 mL). Nitromethane (0.64 mL, 11.7 mmol) was then added and the solution was cooled to −75 °C. The crude dialdehyde **3** (630 mg, 2.35 mmol) in anhydrous $CH_2Cl_2$ (4 mL) was added dropwise and the reaction mixture was stirred under argon for 18 h, warming to 5 °C. The reaction mixture was evaporated to dryness and passed through a DOWEX ion-exchange column eluting with water. The combined aqueous fractions were extracted with EtOAc (3 × 60 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (1:1 toluene/EtOAc) yielded **5** as a colourless solid (422 mg, 31%). Mp 174–176 °C; $[\alpha]_D^{20} = -29.1$ ($c$ 1.01, MeOH); $\nu_{max}$ (NaCl disc/$cm^{-1}$) 3424 (m, OH), 3247 (m, OH), 2915 (w, CH), 1553 (s, $NO_2$ (antisymmetric)), 1369 (m, $SO_2$ (symmetric)), 1082 (s, C–O), 1033 (s, C–O); $\delta_H$ (400 MHz, $CD_3OD$) 3.40 (1H, ddd, $J$ 12.0, 5.5, 2.5, C(5)H), 3.78 (1H, dd, $J$ 12.0, 5.5, C(6)H), 3.88 (1H, dd, $J$ 10.5, 8.0, C(2)H), 3.93 (1H, dd, $J$ 12.0, 2.5, C(6′)H), 4.02 (1H, app. t, $J$ 10.0, C(4)H), 4.49 (1H, d, $J$ 8.0, C(1)H), 4.54 (1H, app. t, $J$ 10.0, C(3)H), 4.73 (1H, d, $J$ 12.0, $OCH_2Ph$), 4.99 (1H, d, $J$ 12.0, $OCH_2Ph$); $\delta_C$ (101 MHz, $CD_3OD$) 62.1 (C6), 69.3 (C4), 71.9 ($OCH_2Ph$), 72.4 (C2), 78.2 (C5), 96.0 (C3), 102.8 (C1), 128.8–129.3 (ArC), 138.8 (ArC); $m/z$ (CI) 300 ($[M+H]^+$, 2%), 282 (26), 181 (100). Found $[M+H]^+$ 300.1093, $C_{13}H_{18}NO_7$ requires 300.1083.

### 4.2. Methyl 5,7-*O*-benzylidene-3-deoxy-3-nitro-α-D-*glycero*-D-*altro*-septanoside 13

*Part A*: Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **7**[10] (2.48 g, 8.79 mmol) was dissolved in methanol (50 mL) and cooled to 0 °C. Next, $NaIO_4$ (9.39 g, 44.00 mmol) was dissolved in distilled water (150 mL) and added to the methanolic solution. The reaction mixture was stirred for 5 h before evaporation of the solvent. The white solid was partially dissolved with EtOAc and filtered through a pad of silica and Celite®. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the crude dialdehyde **10** as a white solid (1.36 g).

*Part B*: In an oven-dried three-necked round-bottomed flask, sodium (2.40 g) was added portionwise to anhydrous methanol (50 mL) under argon. Nitromethane (0.26 mL, 4.84 mmol) was added to the sodium methoxide solution and the contents were cooled to −40 °C. Crude dialdehyde **10** (1.36 g, 4.84 mmol) was solubilised in anhydrous acetonitrile (50 mL) and anhydrous DMF (10 mL) and added dropwise to the methanolic solution. The contents were cooled further to −64 °C and stirred under argon overnight, after which it was allowed to warm to 9 °C. The reaction mixture was re-cooled to −57 °C and then quenched with Amberlite® IR-120 ($H^+$) and acetic acid. The solution was then filtered and partitioned between water (60 mL) and $CH_2Cl_2$ (60 mL). The aqueous phase was further extracted with $CH_2Cl_2$ (2 × 60 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (4:1 toluene/EtOAc) yielded **13** as colourless crystals (1.29 g, 43%). Mp 189–190 °C; $[\alpha]_D^{20} = +23.7$ ($c$ 1.75, MeOH); $\nu_{max}$ (NaCl disc/$cm^{-1}$) 3356 (br s, OH), 1598 (m, $NO_2$ (asymmetric)), 1361 (s, $NO_2$ (symmetric)), 1056 (m, C–O), 1033 (m, C–O), 1016 (m, C–O), 754 (m, CH (arom)); $\delta_H$ (400 MHz, $CD_3OD$) 3.46 (3H, s, $OCH_3$), 3.69 (1H, app. t, $J$ 10.5, C(7)H), 3.80 (1H, t, $J$ 9.5, 3.0, C(5)H), 4.15 (1H, app. dt, $J$ 10.0, 6.0, C(6)H), 4.27 (1H, dd, $J$ 10.5, 6.0, C(7′)H), 4.50 (1H, br d, $J$ 2.5, C(4)H), 4.57 (1H, d, $J$ 5.5, C(1)H), 4.62 (1H, dd, $J$ 10.5, 5.5, C(2)H), 4.95 (1H, dd, $J$ 10.5, 2.5, C(3)H), 5.62 (1H, s, PhC*H*), 7.36–7.38 (3H, m, Ph), 7.52–7.54 (2H, m, Ph); $\delta_C$ (101 MHz, $CD_3OD$) 56.4 ($OCH_3$), 59.0 (C6), 69.7 (C2), 70.2 (C7), 71.1 (C4), 81.5 (C5), 90.0 (C3), 102.2 (PhCH), 107.3 (C1), 127.5–129.9 (ArC), 139.1 (ArC); $m/z$ (CI) 342 ($[M+H]^+$, 33%), 341 ($[M]^+$, 39%), 310 (56), 169 (47), 149 (100). Found $[M]^+$ 341.1119, $C_{15}H_{19}NO_8$ requires 341.1111.

### 4.3. Methyl 2-*O*-benzyl-4-deoxy-4-nitro-7-benzyloxymethyl-α-D-*glycero*-L-*manno*-septanoside 14

*Part A*: Methyl 2,6-di-*O*-benzyl-α-D-glucopyranoside **8**[11] (496 mg, 1.33 mmol) was dissolved in methanol (20 mL) and cooled to 0 °C. Next, $NaIO_4$ (1.42 g, 6.63 mmol) was dissolved in distilled water (20 mL) and added to the methanolic solution. The reaction mixture was stirred for 5 h before evaporation of the solvent. The white residue was diluted with EtOAc and filtered through a pad of silica and Celite®. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the crude dialdehyde **11** as a colourless syrup (320 mg).

*Part B*: At first, 1 M NaOMe (1 mL) was added to a flask containing anhydrous $CH_2Cl_2$ (10 mL) and powdered 4 Å MS (242 mg), after which the solution was cooled to −60 °C. Nitromethane (0.23 mL, 4.29 mmol) was then added dropwise followed by dialdehyde (**11**) (320 mg, 0.859 mmol) in anhydrous $CH_2Cl_2$ (3 mL). The reaction mixture was stirred under argon overnight, warming to room temperature. The reaction was quenched by the dropwise addition of 1 M HCl, before the contents were partitioned between water (40 mL) and $CH_2Cl_2$ (40 mL). The aqueous phase was further extracted with EtOAc (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (3:2 $Et_2O$/petroleum ether (bp 30–40))

yielded **14** as a colourless syrup (202 mg, 35%). $[\alpha]_D^{20} = +96.9$ (*c* 1.0, $CHCl_3$); $\nu_{max}$ (NaCl disc/$cm^{-1}$) 3460 (br s, OH), 2913 (s, CH), 1557 (s, $NO_2$ (antisymmetric)), 1497 (m C=C (arom)), 1454 (s, C=C (arom)), 1366 (s, $NO_2$ (symmetric)), 1096 (s, C–O), 1045 (s, C–O), 739 (s, CH (arom)), 698 (s, CH, arom)); $\delta_H$ (400 MHz, $CDCl_3$) 2.94 (1H, br s, C(3)O*H*), 3.12 (1H, br s, C(5)O*H*), 3.45 (3H, s, $OCH_3$), 3.59 (1H, d, *J* 1.5, C(7)H), 3.60 (1H, d, *J* 1.0, C(7′)H), 4.11 (1H, dd, *J* 3.5, 2.0, C(2)H), 4.43–4.44 (2H, m, C(5,6)H), 4.49–4.58 (3H, m, C(3)H, $OCH_2Ph$), 4.64 (1H, d, *J* 11.5, $OCH_2Ph$), 4.73 (1H, d, *J* 3.5, C(1)H), 4.88 (1H, d, *J* 11.5, $OCH_2Ph$), 4.97 (1H, dd, *J* 9.5, 3.5, C(4)H), 7.24–7.36 (10H, m, Ph); $\delta_C$ (101 MHz, $CDCl_3$) 56.0 ($OCH_3$), 66.9 (C3), 69.2 (C5 or C6), 70.3 (C7), 70.5 (C5 or C6), 73.4 ($OCH_2Ph$), 75.7 ($OCH_2Ph$), 81.4 (C2), 91.7 (C4), 100.2 (C1), 127.7–128.6 (ArC), 137.3–137.9 (ArC); *m/z* (CI) 434 ([M+H]$^+$, 3%), 361 (30), 342 (14), 310 (41), 181 (100). Found [M+H]$^+$ 434.1804, $C_{22}H_{28}NO_8$ requires 434.1815.

### 4.4. Methyl 2-*O*-benzyl-4-deoxy-4-nitro-7-benzyloxymethyl-α-D-*glycero*-D-*talo*-septanoside 15

*Part A*: Methyl 2,6-di-*O*-benzyl-α-D-mannopyranoside **9**[12] (317 mg, 0.846 mmol) was dissolved in methanol (20 mL) and cooled to 0 °C. Next, $NaIO_4$ (904 mg, 4.23 mmol) was dissolved in distilled water (20 mL) and added to the methanolic solution. The reaction mixture was stirred until completion of the reaction as determined by TLC analysis. The solvent was removed in vacuo and the white residue was diluted with EtOAc and filtered through a pad of silica and Celite®. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the crude dialdehyde **12** as a colourless syrup (305 mg).

*Part B*: At first, 1 M NaOMe (1 mL) was added to a flask containing anhydrous $CH_2Cl_2$ (10 mL) and powdered 4 Å MS (308 mg), and the solution was cooled to −65 °C. Nitromethane (0.22 mL, 4.09 mmol) was then added dropwise followed by dialdehyde **12** (305 mg, 0.818 mmol) in anhydrous $CH_2Cl_2$ (7 mL). The reaction mixture was stirred under argon for 19.5 h, and then warmed to room temperature. The reaction was quenched by the dropwise addition of 1 M HCl, before the contents were partitioned between water (40 mL) and $CH_2Cl_2$ (40 mL). The aqueous phase was further extracted with EtOAc (2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (2:1 toluene/$Et_2O$)) yielded **15** as a golden colour syrup (153 mg, 42%). $[\alpha]_D^{20} = +49.4$ (*c* 1.06, $CHCl_3$); $\nu_{max}$ (NaCl disc/$cm^{-1}$) 3437 (m, OH), 2918 (m, CH), 1555 (s, $NO_2$ (antisymmetric)), 1453 (m, C=C (arom)), 1368 (m, $NO_2$ (symmetric)), 1102 (s, C–O), 1060 (s, C–O), 739 (m, CH (arom)), 698 (m, CH (arom)); $\delta_H$ (400 MHz, $CDCl_3$) 3.42 (3H, s, $OCH_3$), 3.54 (1H, dd, *J* 6.5, 1.0, C(2)H), 3.69 (1H, dd, *J* 10.0, 3.5, C(7)H), 3.76 (1H, dd, *J* 10.0, 4.0, C(7′)H), 3.81 (1H, app. dt, *J* 10.0, 4.0, C(6)H), 4.33 (1H, dd, *J* 10, 6.5, C(4)H), 4.53 (1H, d, *J* 12.0, $OCH_2Ph$), 4.55–4.57 (1H, m, C(3)H), 4.61–4.67 (4H, m, C(5)H, $OCH_2Ph$), 4.74 (1H, d, *J* 6.5, C(1)H), 7.29–7.38 (10H, m, Ph); $\delta_C$ (101 MHz, $CDCl_3$) 56.2 ($OCH_3$), 67.9 (C5), 69.0 (C6), 70.6 (C7), 72.9 ($OCH_2Ph$), 73.3 (C3), 73.7 ($OCH_2Ph$), 80.7 (C2), 93.9 (C4), 102.9 (C1), 127.8–128.7 (ArC), 137.2–137.4 (ArC); *m/z* (ESI) 456 ([M+Na]$^+$, 100%). Found [M+Na]$^+$ 456.1623, $C_{22}H_{27}NO_8Na$ requires 456.1629.

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