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# A convenient synthesis of *C*-galactofuranosylic compounds (*C*-galactofuranosides)

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

**Abstract**

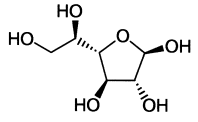
Galactofuranose sugar units are essential for the production of the cell coat of many pathogenic microorganisms. This sugar is not found in mammals, and so compounds that may interfere with the biosynthetic processing of this sugar unit provide interesting targets for drug design. This paper describes the use of a cyanation reaction for the production of a one-carbon extension of a galactofuranosylic unit at C-1, giving 2,5-anhydro-3,4,6,7-tetra-*O*-benzoyl-D-*glycero*-L-*manno*-heptononitrile. A procedure for the efficient hydrolysis of the introduced nitrile group to produce the methyl ester is reported, along with procedures for the synthesis of both the corresponding α,β-unsaturated, and 3-deoxy ester derivatives. 

*Keywords:* Galactofuranose; *C*-Glycosylic compounds; *C*-Glycosides; Cyanation

## 1. Introduction

Poor socioeconomic conditions in many third-world countries have led to the reoccurrence of many microbacterial diseases that were once thought to be on the decline. One such disease, tuberculosis, is responsible for an estimated three million deaths worldwide every year.[1] Furthermore, incomplete drug treatment of many sufferers has resulted in the emergence of drug-resistant strains of the microorganism, *Mycobacterium tuberculosis*, that causes this disease.[2,3] The significant mortality associated with tuberculosis, as well as appearance of new drug-resistant strains, has resulted in the urgent need for new, cost-effective treatments to combat this disease.

Galactofuranose **1** (Gal*f*) is one of the sugar units which is essential for the production of the peptidoglycan found in the cell coat of many pathogenic microorganisms, including *Mycobacterium tuberculosis*.[4–6] This peptidoglycan layer is essential for viability of the microorganism and provides a tough wall that is responsible, not only for preventing access of many antibacterial compounds, but is also thought to be responsible for the virulence of the organism. Since Gal*f* is not found in mammals, compounds that mimic Gal*f* and interfere with the biosynthetic enzymes that produce and utilise Gal*f* may provide interesting targets for the development of new drug treatments.




**1**

*C*-Glycosylic compounds (*C*-glycosides) form one class of compounds that have often shown interesting biological properties.[7,8] With regard to *C*-glycosides of Gal*f*, Kovensky et al. reported methods to gain access to α- and β-phosphonic acid derivatives of Gal*f*,

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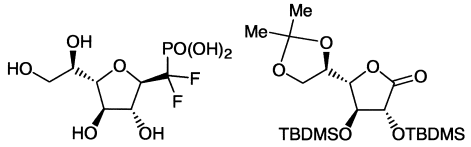
*C*-glycoside analogues of Gal*f* 1-phosphate.[9] For the synthesis of the β-difluoromethylenephosphonate derivative **2**, introduction of the carbon substituent at C-1 was achieved through olefination of protected galactono-1,4-lactone **3**.[9] Wheatley et al. have described the synthesis of the 1-α-ester derivative of Gal*f* **4**, from a rearrangement of the 2-*O*-trifluoromethanesulfonyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**5**) in the presence of acidic methanol.[10] Rearrangement of sugar γ- and δ-lactone 2-triflates in acidic[10] or basic[11] methanol has been applied to the synthesis of a range of C-1 methyl ester derivatives.

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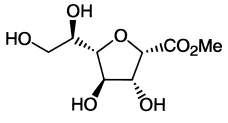


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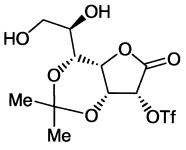
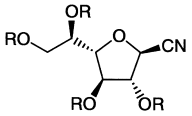
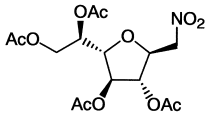



**5**

The introduction of a nitrile at C-1, however, offers a useful handle, which can subsequently be manipulated to arrive at a number of interesting *C*-glycosidic analogues.[12–16] Köll et al. have previously accessed the 1-β-cyano derivative **6** of peracetylated Gal*f* by reduction, with phosphorus trichloride, of the corresponding 1-β-nitromethyl Gal*f* derivative **7**.[17] The yield of **6** over three steps from galactose was, however, only 5%, principally due to a low (13%) yield in the preparation of **7** from galactose. Herein we report the use of the cyanation reaction to make the versatile, one-carbon homologated Gal*f* derivative, 2,5-anhydro-3,4,6,7-tetra-*O*-benzoyl-D-*glycero*-L-*manno*-heptononitrile (**9**). In this work, we were initially interested in forming a methyl ester at the C-1 position in order to arrive at a sialic acid–Gal*f*-type hybrid molecule. Thus, we have developed a method that efficiently converts the protected nitrile **9** into the desired, deprotected Gal*f* methyl ester **12**. Further elaboration from nitrile **9** led into the α,β-unsaturated ester **18** and the 3-deoxy derivative **20**.



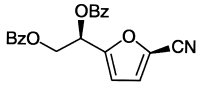

**6** R = Ac
**9** R = Bz




**7**

## 2. Results and discussion

Previous workers have shown that access to one-carbon extensions of sugars is best achieved by a cyanation reaction whereby 1-*O*-acyl sugars react with TMSCN under Lewis acidic conditions to introduce a cyano group into the anomeric position of the sugar.[12,18,19] This reaction when applied to perbenzoylated Gal*f* **8**[20,21] resulted in the production of the desired nitrile **9** in a satisfying 80% yield (Scheme 1). This reaction not unexpectedly furnished the β-isomer exclusively. As our initial goal was to make a methyl ester at the C-1 position, we required a method to hydrolyse the nitrile to the acid, which we could subsequently methylate to produce the desired methyl ester. Unfortunately, under standard acidic or basic hydrolysis conditions, elimination occurred to produce a furan derivative, for example, the benzoylated furan nitrile **13** from attempted acidic hydrolysis. A similar result has previously been reported by Albrecht et al. who had attempted to perform reductive hydrolysis of a C-1 cyano function in ribose.[22] A report by Poonian and Nowoswiat,[23] who had formed the methyl imidate **14** from benzoylated ribosyl cyanide that was then utilised in a heterocyclisation, prompted us to examine the formation of the corresponding methyl imidate of Gal*f* under anhydrous conditions. The methyl imidate should be easily hydrolysed to the desired methyl ester under relatively mild conditions. Reaction of the nitrile **9** with anhydrous sodium methoxide overnight[†] furnished the fully deprotected methyl imidate **10**. This compound could be easily isolated from the reaction by neutralisation, followed by removal of the solvent, or alternatively, it could be hydrolysed *in situ* with a small amount of Dowex 50 ($H^+$) resin and water to give the crude methyl ester **12**. The deprotected ester **12** was most readily purified and characterised as the corresponding peracetylated derivative. Accordingly, peracetylation of the crude ester yielded the acetylated C-1 ester **11** in a respectable 68% yield (after flash chromatography) from **9** over three steps. O-Deacetylation of **11** gave the desired Gal*f* ester **12**.

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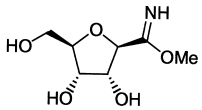
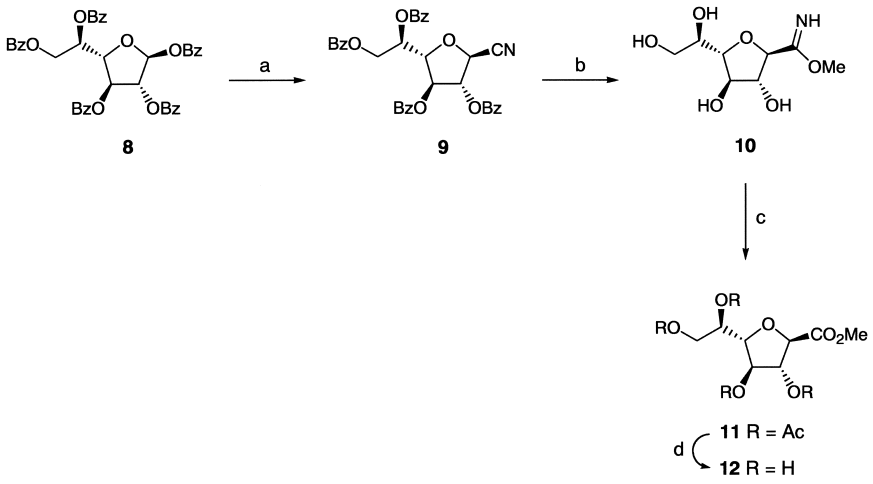



**14**

Having established an efficient route to one of our target compounds, we set about making two further derivatives, namely the corresponding α,β-unsaturated ester derivative **18** and the 3-deoxy derivative **20**. Elimination of the C-3 benzoyl group in **9**, to produce the α,β-unsaturated derivatives, was easily achieved via a simple two-step procedure (Scheme 2). Firstly, reaction of the nitrile **9** with DBU[24] at room temperature for three days, furnished the desired intermediate **15** in virtually

[†] If the reaction was left for only 4 h compared with 20 h, a 1:1 mixture of the desired methyl ester **11** as well as the peracetylated Gal*f* nitrile **6**[17] was subsequently isolated. This result shows that the methyl imidate **10** was slow to form.




Scheme 1. Reagents and conditions: (a) TMSCN, $BF_3{\cdot}OEt_2$, $CH_3NO_2$, rt, (80%); (b) 1 M NaOMe–MeOH, rt; (c) i. Dowex 50 ($H^+$) resin, $H_2O$, rt; ii. $Ac_2O$, pyridine, rt (68% over 3 steps, b and c); (d) 1 M NaOMe–MeOH, rt (95%).

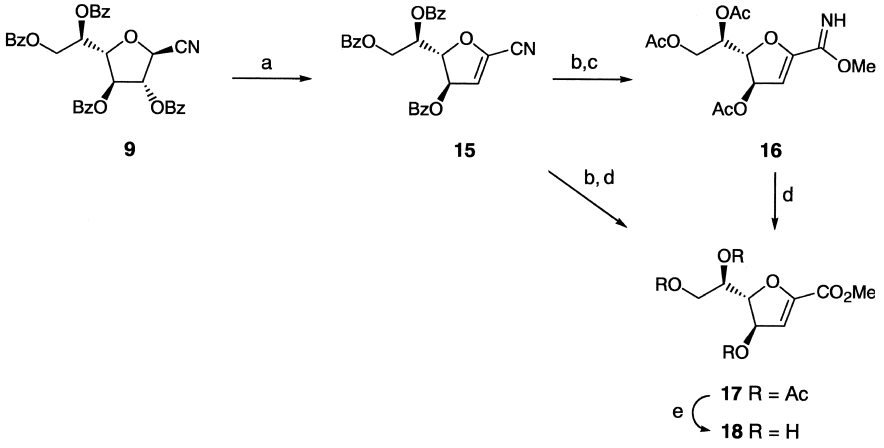
quantitative yield. In the second step, it was assumed that addition of methanol to the nitrile, followed by hydrolysis with Dowex 50 ($H^+$) using the conditions described above, and finally acetylation, should furnish the protected α,β-unsaturated methyl ester **17**. Unfortunately, using the standard conditions, only the methyl imidate **16** was isolated from the reaction in 61% yield, even after prolonged exposure to the Dowex 50 ($H^+$)–water mixture. This result was rather surprising; however, it was subsequently found that the α,β-unsaturated imidate **16** could be relatively easily hydrolysed in situ by treatment with a slight excess of 20% aqueous acetic acid. Acetylation of the crude product from this reaction furnished the peracetylated α,β-unsaturated ester **17** in an overall yield of 89% over three steps. Standard O-deacetylation gave the target Gal*f* α,β-unsaturated ester **18**.

The protected glycal **17** provides a potential entry point into a range of other Gal*f* derivatives, including the saturated 3-deoxy derivative **20**. Standard hydrogenation[25] of the α,β-unsaturated ester derivative **17** in ethyl acetate with palladium-on-carbon provided the 3-deoxy derivative **19** in quantitative yield (Scheme 3). Standard O-deacetylation gave the target 3-deoxy-Gal*f* derivative **20**.

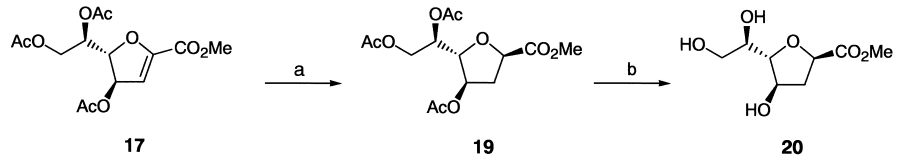
The work outlined here illustrates an expedient entry into a number of interesting galactofuranosyl *C*- glycosides. These compounds are of interest as potential drug candidates in the fight against *Mycobacterium tuberculosis*, the biological pathogen responsible for the disease tuberculosis. Biological testing of these compounds is presently being undertaken and will be reported elsewhere.

## 3. Experimental

*General methods.*—Perbenzoylated galactofuranose **8** was prepared as per known literature methods using




Scheme 2. Reagents and conditions: (a) DBU, $CH_2Cl_2$, rt (97%); (b) 1 M NaOMe–MeOH, rt; (c) i. Dowex 50 ($H^+$) resin, $H_2O$, rt; ii. $Ac_2O$, pyridine, rt; (d) i. 20% HOAc, rt; ii $Ac_2O$, pyridine, rt; (e) 1 M NaOMe–MeOH, rt (95%).




Scheme 3. Reagents and conditions: (a) $H_2$, 60 psi, 10% Pd/C (quant); (b) 1 M NaOMe–MeOH, rt (95%).

either the one-step procedure reported by D'Accorso et al.,[20] or the three-step procedure of Kohn et al.[21] via reduction of galactonolactone using disiamyl borane.[26] The latter method[21] proved to give better overall yields of **8** in our hands. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ using a Bruker AM 300 spectrometer. Chemical shifts are given in ppm relative to the solvent used [$CDCl_3$: 7.26 for $^1$H; 77.0 for $^{13}$C]. ESI mass spectra (ESIMS) were obtained using a Micromass Platform II electrospray-ionization spectrometer, and HRMS were obtained using a Bruker BioApex II FTMS. Reactions were monitored by TLC on aluminium plates coated with Silica Gel 60 $F_{254}$ (E. Merck) and visualised with either 10% $H_2SO_4$ in EtOH, $I_2$, or ninhydrin. All compounds were purified by flash chromatography using E. Merck Silica Gel 60 (0.040–0.063 mm). All new compounds gave the expected spectroscopic data.

*2,5-Anhydro-3,4,6,7-tetra*-O-*benzoyl*-D-glycero-L-manno-*heptononitrile* (**9**).—To a solution of perbenzoylated galactofuranose **8**[20,21] (9.6 g, 13.7 mmol) in dry $CH_3NO_2$ (50 mL) stirring at room temperature under an atmosphere of $N_2$ was added TMS-CN (8.2 mL, 4.5 equiv) followed by boron trifluoride diethyl etherate (350 μL, 0.2 equiv). After 30 min TLC showed the reaction was complete. The solvent was removed *in vacuo*, and the resulting black oil was purified by flash chromatography to yield 6.6 g (80% yield) of the compound **9** as a white crystalline solid: $R_f$ 0.66 (2:1 hexane–EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 7.30–8.10 (m, 20 H, 4 × $OCOC_6H_5$), 6.03 (m, 1 H, H-6), 5.86 (br.s, 1 H, H-4), 5.79 (br.s, 1 H, H-3), 5.12 (br.s, 1 H, H-2), 4.85 (dd, 1 H, $J_{7,6}$ 3.9, $J_{7,7'}$ 12.0 Hz, H-7), 4.80 (m, 1 H, H-5), 4.70 (dd, 1 H, $J_{7',6}$ 6.6 Hz, H-7′); $^{13}$C NMR ($CDCl_3$): $\delta$ 165.9, 165.6, 165.2, 165.1 (4 × $OCOC_6H_5$), 133.9, 133.3, 133.1, 130.0, 129.9, 129.6, 129.3, 129.1, 128.6, 128.5, 128.5, 128.4, 128.3, 127.8, (aromatic C), 115.2 (C-1), 84.5 (C-5), 80.7 (C-3), 77.4 (C-4), 71.5 (C-2), 70.2 (C-6), 63.3 (C-7); ESIMS: *m*/*z* (relative intensity, %) 623 [$(M + NH_4)^+$, 100], 606 [$(M + H)^+$, 5], 484 ($M^+$-$C_6H_5CO_2$, 20); HRMS: Calcd for $C_{35}H_{31}N_2O_9$ $(M + NH_4)^+$ 623.20295; found 623.2022.

*Methyl 3,4,6,7-tetra*-O-*acetyl-2,5-anhydro*-D-glycero-L-manno-*heptanoate* (**11**).—To a solution of the nitrile **9** (300 mg, 0.5 mmol) in dry MeOH (25 mL) under an atmosphere of $N_2$ was added one equiv of NaOMe (0.5 mL of a 1 M solution in dry MeOH). The reaction was left to stir at room temperature overnight. The reaction was neutralised with Dowex 50W × 8 ($H^+$) resin, and water (100 μL was added). After stirring for 1 h the resin was filtered off and washed thoroughly with a 3:1 mixture of MeOH and water. Solvent was removed *in vacuo*, and the residue was dried under high vacuum overnight. Pyridine (10 mL), followed by acetic anhydride (5 mL), was added and the reaction was left to stir for 12 h. After this time the solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography to yield 131 mg (68% yield) of the desired methyl ester **11** as a colourless oil: $R_f$ 0.28 (3:2 hexane–EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 5.43 (dd, 1 H, $J_{3,2}$ 2.7, $J_{3,4}$ 2.1, Hz, H-3), 5.36 (m, 1 H, H-6), 5.12 (dd, 1 H, $J_{4,5}$ 4.0 Hz, H-4), 4.60 (d, 1 H, H-2), 4.39 (dd, 1 H, $J_{7,6}$ 4.3, $J_{7,7'}$ 11.8 Hz, H-7), 4.36 (br.d, 1 H, H-5), 4.18 (dd, 1 H, $J_{7',6}$ 6.9 Hz, H-7′), 3.80 (s, 3 H, $OCH_3$), 2.14, 2.13, 2.05 (3 × s, 12 H, 4 × $OCOCH_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.3, 169.9, 169.5, 169.4, 169.3 (4 × $OCOCH_3$ and C-1), 82.4 (C-5), 80.9 (C-3), 79.4 (C-2), 77.2 (C-4), 69.6 (C-6), 62.5 (C-7), 52.4 ($OCH_3$), 21.4, 20.8, 20.6 (4 × $OCOCH_3$); ESIMS: *m*/*z* (relative intensity, %) 413 [$(M + Na)^+$, 10], 408 [$(M + NH_4)^+$, 40], 391 [$(M+H)^+$, 5], 331 ($M^+$-$OCOCH_3$, 100); HRMS: Calcd for $C_{16}H_{26}NO_{11}$ $(M + NH_4)^+$ 408.15058; found 408.15001.

*3,4,6,7-Tetra*-O-*acetyl-2,5-anhydro*-D-glycero-L-manno-*heptononitrile* (**6**).—To a solution of the nitrile **9** (300 mg, 0.5 mmol) in dry MeOH (20 mL) under an atmosphere of $N_2$ was added one equiv of NaOMe (0.5 mL of a 1 M solution in dry MeOH). The reaction was left to stir for 4 h at room temperature. After this time the reaction was neutralised with Dowex 50W × 8 ($H^+$) resin, and water (100 μL) was added. After stirring for 1 h the resin was filtered off and washed thoroughly with a 3:1 mixture of MeOH and water. Solvent was removed *in vacuo*, and the residue dried under high vacuum overnight. Pyridine (10 mL), followed by acetic anhydride (5 mL), was added, and the reaction was left to stir for 12 h. After this time the solvent was removed *in vacuo*, and two compounds were separated by silica gel chromatography, giving 86.5 mg of methyl 3,4,6,7-tetra-*O*-acetyl-2,5-anhydro-D-*glycero*-L-*manno*-heptanoate (**11**) (44% yield) and 89 mg of 3,4,6,7-tetra-*O*-acetyl-2,5-anhydro-D-*glycero*-L-*manno*-heptononitrile (**6**)[17] (46% yield). The acetylated nitrile **6** was obtained as a colourless oil: $R_f$ 0.44 (3:2 hexane-EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 5.36 (m, 2 H, H-3 and

H-6), 5.16 (dd, 1 H, *J* 1.0, 2.7 Hz, H-4), 4.78 (br.s, 1 H, H-2), 4.33 (m, 2 H, H-5 and H-7), 4.17 (dd, 1 H, $J_{7',6}$ 6.6, $J_{7',7}$ 12.0 Hz, H-7′), 2.15, 2.14, 2.12, 2.06 (4 × s, 12 H, 4 × $OCOCH_3$); ESIMS: *m*/*z* (relative intensity, %) 380 [$(M + Na)^+$, 25], 375 [$(M + NH_4)^+$, 60], 331 ($M^+$-CN, 35), 298 ($M^+$-$CH_3CO_2H$, 100); HRMS: Calcd for $C_{15}H_{23}N_2O_9$ $(M + NH_4)^+$ 375.14035; found 375.13981.

*Methyl 2,5-anhydro*-D-glycero-L-manno-*heptanoate* (**12**).—To a solution of the acetylated ester **11** (411 mg, 1.05 mmol) in dry MeOH (10 mL) under an atmosphere of $N_2$ was added NaOMe (0.26 mL of a 1 M solution in dry MeOH, 0.25 equiv). The reaction was left to stir at room temperature for 2 h. After this time the reaction was neutralised with aqueous acetic acid (20% solution), all volatile compounds were removed *in vacuo*, and the residue was dried under high vacuum overnight to yield 222 mg (95% yield) of the desired deprotected methyl ester **12** as a slightly yellow oil: $^1$H NMR ($D_2O$): $\delta$ 4.48 (d, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.32 (t, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 4.17 (dd, 1 H, $J_{4,5}$ 5.4 Hz, H-4), 3.98 (dd, 1 H, $J_{5,6}$ 4.0 Hz, H-5), 3.81 (m, 1 H, H-6), 3.77 (s, 3 H, $OCH_3$), 3.69 (dd, 1 H, $J_{7,6}$ 4.5, $J_{7,7'}$ 11.7 Hz, H-7), 3.62 (dd, 1 H, $J_{7',6}$ 7.3 Hz, H-7′); $^{13}$C NMR ($D_2O$): $\delta$ 173.1 (C-1), 84.0 (C-5), 81.3 (C-3), 79.2 (C-2), 76.6 (C-4), 70.7 (C-6), 62.6 (C-7), 52.8 ($OCH_3$).

*2,5-Anhydro-4,6,7-tri*-O-*benzoyl-3-deoxy*-D-glycero-L-manno-*hept-2-enonitrile* (**15**).—To a solution of 2,5-anhydro-3,4,6,7-tetra-*O*-benzoyl-D-*glycero*-L-*manno*-hepto nonitrile (**9**) (1.024 g, 1.7 mmol) in dry $CH_2Cl_2$ (30 mL) stirring at room temperature under an atmosphere of $N_2$ was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 506 μL, 2 equiv). After 72 h TLC showed reaction was complete. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield 794 mg (97% yield) of **15** as a slightly off-white foam: $R_f$ 0.63 (3:1 hexane–EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 7.38–8.10 (m, 20 H, 4 × $OCOC_6H_5$), 6.11 (m, 2 H, H-3 and H-4), 5.95 (m, 1 H, H-6), 5.10 (br.t, 1 H, *J* 3.3 Hz, H-5), 4.76 (dd, 1 H, $J_{7,6}$ 5.1, $J_{7,7'}$ 11.7 Hz, H-7), 4.70 (dd, 1 H, $J_{7',6}$ 6.4 Hz, H-7′); $^{13}$C NMR ($CDCl_3$): $\delta$ 165.8, 165.7, 165.3 (4 × $OCOC_6H_5$), 135.4 (C-2), 133.7, 133.2, 129.8, 129.7, 129.6, 129.2, 128.8, 128.6, 128.5, 128.4, (aromatic C), 113.3 (C-3), 110.3 (C-1), 85.7 (C-5), 78.0 (C-4), 70.8 (C-6), 62.4 (C-7); ESIMS: *m*/*z* (relative intensity, %) 506 [$(M + Na)^+$, 5], 501 [$(M + NH_4)^+$, 100]; HRMS: Calcd for $C_{28}H_{25}N_2O_7$ $(M + NH_4)^+$ 501.16617; found 501.16567.

*Methyl 4,6,7-tri*-O-*acetyl-2,5-anhydro-3-deoxy*-D-glycero-L-manno-*hept-2-enoimidate* (**16**).—To a solution of 2,5-anhydro-4,6,7-tri-*O*-benzoyl-3-deoxy-D-*glycero*-L-*manno*-hept-2-enonitrile (**15**) (157 mg, 0.3 mmol) in dry MeOH (10 mL) under an atmosphere of $N_2$ was added NaOMe (0.24 mL of a 1 M solution in dry MeOH, 0.75 equiv). The reaction was left to sir at room temperature overnight. The reaction was neutralised with Dowex 50W × 8 ($H^+$) resin, and water (100 μL) was added. After stirring for 1 h the resin was filtered off and washed thoroughly with a 3:1 mixture of MeOH and water. Solvent was removed *in vacuo*, and the residue dried under high vacuum overnight. Pyridine (5 mL), followed by acetic anhydride (2.5 mL), was added, and the reaction was left to stir for 12 h. After this time the solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography to yield 65.1 mg (61% yield) of the imidate **16** as a colourless oil: $R_f$ 0.36 (1:1 hexane–EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 7.94 (br.s, 1 H, NH), 5.75 (br.apparent t, 1 H, *J* 3.0 Hz, H-4), 5.65 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 5.35 (m, 1 H, H-6), 4.69 (br.dd, 1 H, *J* 3.6, 3.9 Hz, H-5), 4.35 (dd, 1 H, $J_{7,6}$ 4.6, $J_{7,7'}$ 11.7 Hz, H-7), 4.21 (dd, 1 H, $J_{7',6}$ 6.6 Hz, H-7′), 3.84 (s, 3 H, $OCH_3$), 2.08, 2.07, 2.06 (3 × s, 9 H, 3 × $OCOCH_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.2, 169.9, (3 × $OCOCH_3$), 140.4 (C-1), 123.7 (C-2), 100.7 (C-3), 84.3 (C-5), 78.8 (C-4), 70.7 (C-6), 61.7 (C-7), 53.2 ($OCH_3$), 20.8, 20.6 (3 × $OCOCH_3$); ESIMS: *m*/*z* (relative intensity, %) 352 [$(M + Na)^+$, 10], 330 [$(M + H)^+$, 100], 270 ($M^+$-$CH_3CO_2H$, 30), 210 ($M^+$-2 × $CH_3CO_2H$, 80).

*Methyl 4,6,7-tri*-O-*acetyl-2,5-anhydro-3-deoxy*-D-glycero-L-manno-*hep-2-enoate* (**17**).—To a solution of the α,β-unsaturated nitrile derivative **15** (310 mg, 0.64 mmol) in dry MeOH (20 mL) under an atmosphere of $N_2$ was added NaOMe (0.48 mL of a 1 M solution in dry MeOH, 0.75 equiv). The reaction was left to stir at room temperature overnight before being neutralised with an aqueous acetic acid solution (20%). After stirring for 1 h the solvent was removed *in vacuo*, and the residue was dried under high vacuum overnight. Pyridine (10 mL), followed by acetic anhydride (5 mL), was added, and the reaction was left to stir for 12 h. After this time the solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography to yield 190 mg (89% yield) of the desired α,β-unsaturated methyl ester **17** as a colourless oil: $R_f$ 0.6 (1:1 hexane–EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 5.97 (d, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 5.73 (br.apparent t, 1 H, $J_{4,5}$ 3.3 Hz, H-4), 5.35 (m, 1 H, H-6), 4.73 (br.dd, 1 H, *J* 3.6, 4.2 Hz, H-5), 4.34 (dd, 1 H, $J_{7,6}$ 4.6, $J_{7,7'}$ 11.8 Hz, H-7), 4.24 (dd, 1 H, $J_{7',6}$ 6.4 Hz, H-7′), 3.84 (s, 3 H, $OCH_3$), 2.07, 2.05 (3 × s, 9 H, 3 × $OCOCH_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 170.3, 170.1, 169.9, (3 × $OCO_2CH_3$), 159.5 (C-1), 152.4 (C-2), 107.5 (C-3), 84.6 (C-5), 77.9 (C-4), 70.0 (C-6), 61.7 (C-7), 52.4 ($OCH_3$), 20.7, 20.6, 20.5 (3 × $OCOCH_3$); ESIMS: *m*/*z* (relative intensity, %) 331 [$(M + H)^+$, 5]; HRMS: Calcd for $C_{14}H_{22}NO_9$ $(M + NH_4)^+$ 348.12946; found 348.12894.

*Methyl 2,5-anhydro-3-deoxy*-D-glycero-L-manno-*hep-2-enoate* (**18**).—To a solution of the protected ester **17** (456 mg, 1.38 mmol) in dry MeOH (10 mL) under an atmosphere of $N_2$ was added NaOMe (0.34 mL of a 1 M solution in dry MeOH, 0.25 equiv). The reaction was left to stir at room temperature for 2 h. After this time the reaction was neutralised with aqueous acetic acid

(20% solution), all volatile compounds were removed *in vacuo*, and the residue was dried under high vacuum overnight to yield 267 mg (95% yield) of the desired deprotected α,β-unsaturated methyl ester **18** as a slightly yellow oil: $^1$H NMR ($D_2O$): $\delta$ 6.08 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 5.07 (dd, 1 H, $J_{4,5}$ 3.9 Hz, H-4), 4.46 (t, 1 H, $J$ 3.9 Hz, H-5), 3.82 (br.s, 4 H, H-6, $OCH_3$), 3.71 (dd, 1 H, $J_{7,6}$ 4.8, $J_{7,7'}$ 11.7 Hz, H-7), 3.64 (dd, 1 H, $J_{7',6}$ 7.2 Hz, H-7′); $^{13}$C NMR ($D_2O$): $\delta$ 162.0 (C-1), 149.7 (C-2), 112.2 (C-3), 88.9 (C-5), 75.2 (C-4), 72.0 (C-6), 61.8 (C-7), 52.8 ($OCH_3$).

*Methyl 4,6,7-tri-*O*-acetyl-2,5-anhydro-3-deoxy-*D*-glycero-*L*-manno-heptanoate* (**19**).—To a solution of the α,β-unsaturated ester **17** (257 mg, 0.78 mmol) in EtOAc (20 mL) was added palladium-on-activated carbon (66 mg of 10% wt.). The reaction was subjected to 60 psi pressure of $H_2$ on a Parr hydrogenator and left shaking overnight. The palladium was filtered off, and the solvent was removed *in vacuo* to furnish 257 mg (100% yield) of the desired 3-deoxy derivative **19** as a colourless oil: $R_f$ 0.5 (1:1 hexane–EtOAc); $^1$H NMR ($CDCl_3$): $\delta$ 5.24 (m, 1 H, H-6), 5.17 (apparent pent, 1 H, $J$ 2.4 Hz, H-4), 4.66 (t, 1 H, $J_{2,3}$ 8.1 Hz, H-2), 4.38 (dd, 1 H, $J_{7,6}$ 4.5, $J_{7,7'}$ 11.7 Hz, H-7), 4.23 (br.dd, 1 H, $J$ 2.4, 3.9 Hz, H-5), 4.22 (dd, 1 H, $J_{7',6}$ 6.6 Hz, H-7′), 3.78 (s, 3 H, $OCH_3$), 2.32 (m, 2 H, H-3 and H-3′), 2.08, 2.07, 2.05 ($3\times$ s, 9 H, $3\times OCOCH_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 171.3 (C-1), 170.4, 170.0, 169.8 ($3\times OCOCH_3$), 83.5 (C-2), 77.0, 75.4 (C-4 and C-5), 70.5 (C-6), 62.2 (C-7), 52.2 ($OCH_3$), 35.9 (C-3), 20.9, 20.7, 20.6 ($3\times OCOCH_3$); ESIMS: $m/z$ (relative intensity, %) 355 [$(M+Na)^+$, 20], 350 [$(M+NH_4)^+$, 100]; 333 [$(M+H)^+$, 40]; 273 ($M^+$-$CH_3CO_2H$, 70); HRMS: Calcd for $C_{14}H_{24}NO_9$ $(M+NH_4)^+$ 350.14511; found 350.14442.

*Methyl 2,5-anhydro-3-deoxy-*D*-glycero-*L*-manno-heptanoate* (**20**).—To a solution of the protected 3-deoxy ester **19** (490 mg, 1.47 mmol) in dry MeOH (25 mL) under an atmosphere of $N_2$ was added NaOMe (0.5 mL of a 1 M solution in dry MeOH, 0.3 equiv). The reaction was left to stir at room temperature for 2 h. After this time the reaction was neutralised with aqueous acetic acid (20% solution), all volatile compounds were removed *in vacuo*, and the residue was dried under high vacuum overnight to yield 304 mg (100% yield) of the desired deprotected 3-deoxy methyl ester **20** as a slightly yellow oil: $^1$H NMR ($D_2O$): $\delta$ 4.38 (br.s, 1 H, H-6), 3.90 (br.s, 1 H, H-4), 3.75 (s, 3 H, $OCH_3$), 3.50–3.70 (m, 3 H, H-5, H-7 and H-7′), 2.25 (br.s, 2 H, H-3 and H-3′), H-2 not observed (probably hidden under HOD peak at 4.74 ppm); $^{13}$C NMR ($D_2O$): $\delta$ 174.7 (C-1), 87.1 (C-5), 76.1 (C-2), 72.1 (C-4), 71.3 (C-6), 62.6 (C-7), 52.7 ($OCH_3$), 38.1 (C-3); ESIMS: $m/z$ (relative intensity, %) 229 [$(M+Na)^+$, 35], 207 [$(M+H)^+$, 100]; HRMS: Calcd for $C_8H_{15}O_6$ $(M+H)^+$ 207.08686; found 207.08634.

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