Phenylboronic acid as a labile protective agent: the selective derivatisation of 1,2,3-triols

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The ability of phenylboronic acid to act as a labile protective agent for open-chain 1,2,3-triols is demonstrated in the highly selective terminal derivatisation of D-mannitol and an antiviral sialic acid derivative. Protection, derivatisation and deprotection are carried out in a single pot, yielding analytically pure products in moderate yield, without the need for chromatography or formal recrystallisation steps. In both classes of compound, the selectivity of protection is found to be complementary to existing methods, providing access to relatively uncommon 1,6-diesters and the 1,6-bis(benzyl ether) of D-mannitol, and 9-*o*-acylsialic acid derivatives.

Introduction

The ability of boronic acids to form esters with diols in a rapid and reversible manner has led to their incorporation into saccharide sensors[1] and sugar-permeable membranes[2–5] for purification[4] and drug-delivery applications.[5] The use of boronic acids as protective agents in organic synthesis was pioneered by Ferrier and others in the 1960s and 70s,[6] but the intervening years have seen little activity in the area. The ease of formation and cleavage of boronate esters, as well as the high level of selectivity of ester formation with particular diol arrangements,[2] and the potential for simple recovery of the boronic acid after use, make the further investigation of boronic acids as labile protective reagents highly desirable. Accordingly, there has been a resurgence of interest in the synthetic applications of boronic acids, with Aoyama's descriptions of the use of activating agents in conjunction with boronic acids,[7] as well as reports of a number of solid-phase reactions involving boronate ester formation.[8–10]

Our attention was drawn to the use of boronic acids as selective, labile protective agents during an examination of the selective functionalisation of the C7–C9 hydroxy groups of sialic acid derivatives. These reactions are of particular interest due to the importance of sialic acid derivatives as antivirals,[11] and the fact that the boronic acid methodology had not been widely applied to open-chain polyols.[6] Consequently, a study was undertaken to examine this type of reaction further, beginning with model reactions on D-mannitol.

Results and discussion

The aim of this study was to develop a practical and simple procedure which involved minimal purification and allowed for the recovery of the boronic acid after use. As D-mannitol is effectively a dimer of the triol region of sialic acid, complete with stereochemistry, this readily available alditol was used as a model for sialic acid derivatives. As will be seen, a simple, one-pot procedure has been developed that involves three chemical steps, and leads to the highly selective production of analytically pure esters or ethers, without the need for chromatography or formal recrystallisation.

Solutions of the bis(phenylboronate esters) of D-mannitol[12] were prepared by azeotropic removal of water from a mixture of D-mannitol, phenylboronic acid (PBA), benzene and a co-solvent; pyridine in the case of acylations, and *N*,*N*-dimethylformamide (DMF) in the case of alkylations. For the acylation reactions, the benzene was removed before the addition of the acid chloride. For the alkylations, NaH was used to deprotonate the boronate esters prior to treatment with an alkyl bromide. Once the reactions were complete, an aqueous work-up, including an NaOH wash, was, in all but the benzoylation case, sufficient to hydrolyse the intermediate derivatised mannitol bis(phenylboronates), to yield, after trituration, pure D-mannitol esters or ethers. The results are summarised in Scheme 1. The bis(phenylboronate ester) of D-mannitol 1,6-dibenzoate was found to be exceptionally stable, and required more elaborate deprotection methods.[13,14] The octanoylation of D-mannitol was repeated in the absence of PBA, and resulted in a crude reaction mixture containing multiple products from which a 16% yield of **1** was obtained after purification. This compares with a 48% yield of **1** when PBA was used.

The diboronate esters formed between mannitol and PBA[12] appear to react like 1,6-diols, yielding predominantly 1,6-diesters **1** and **2** and the 1,6-bis(benzyl ether) **3**. The high symmetry seen in the NMR spectra of the products of the esterification and benzylation reactions, as well as the observation that the protons and carbons adjacent to the primary hydroxy groups of D-mannitol show the largest downfield shift when acylated or benzylated, support the assignment of their structures as 1,6-mannitol derivatives. These compounds result from three individual reactions, so the yields obtained range from moderate to excellent, with the dioctanoate **1** and the previously undescribed bis(benzyl ether) **3** averaging 78–83% per step.

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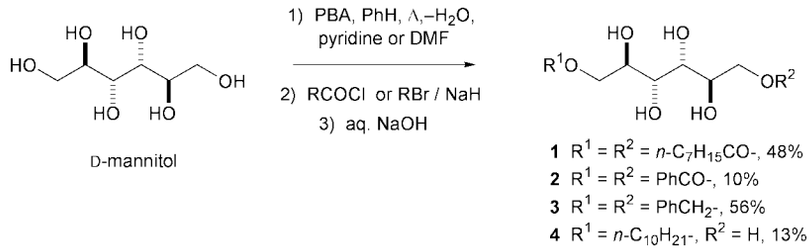
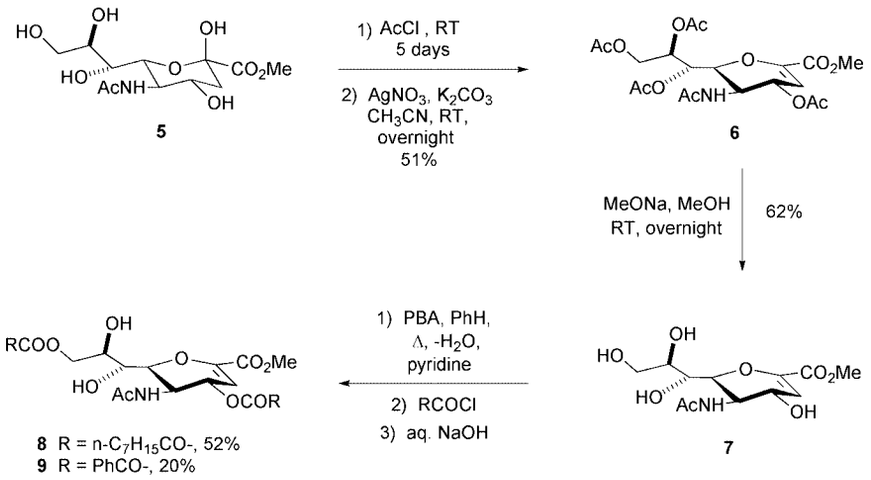


Scheme 1



Scheme 2

Phenylboronate esters have already been shown to be less nucleophilic than underivatised alcohols,[6] so it is not surprising that with the less reactive reagents, *i.e.* benzoyl chloride and decyl bromide, lower yields were obtained, and that only monoalkylation was observed with decyl bromide. LC-MS analysis of the crude product from the benzoylation reaction showed it to consist of predominantly PBA, **2**, and the bis-(phenylboronate ester) of **2**, indicating that the lower yield obtained from this reaction did not result from the production of multiple side products.

The PBA-assisted preparation of **1** was also repeated on a large scale using 36.5 g of D-mannitol and the PBA recovered from the basic washings by neutralisation and filtration. Although the procedure is unoptimised, 60% of the original PBA was reclaimed, demonstrating the utility of boronic acids to serve as recoverable protective agents.

To try to gain an insight into the reasons for the high stability of the bis(PBA ester) of **2**, a pure sample was prepared from pure dibenzoate **2** and PBA in a solventless reaction, and characterised. Unfortunately, the data obtained were not particularly useful in determining if the diboronate prefer to exist with five- or six-membered rings, but previous experimental findings with trigonal PBA esters[2] indicate that the 2,4 : 3,5-bis(phenylboronic ester), in which the boron atoms form part of six-membered rings, is likely to be the preferred form.

In order to investigate the application of the boronic acid approach to antiviral compounds, the sialic acid derivative **7** was prepared in three steps as shown in Scheme 2. The tetraol **7** was then acylated under similar conditions to those described for D-mannitol, yielding the 4,9-diacylated products **8** and **9** with an average yield of 80 and 59% for each of the three chemical steps. NMR and mass spectra of the major products of these reactions are consistent with the assigned structures, chemical-shift correlation (COSY) ^{1}H NMR spectroscopy being used to confirm the sites of acylation. In analogy with the results with D-mannitol, the PBA method results in a preference for acylation of the terminal hydroxy group of the triol region. The octanoylation of **7** was repeated in the absence of PBA, and resulted in a crude reaction mixture containing multiple products from which a 5% yield of **8** was obtained after purification. This compares with a 52% yield of **8** when PBA was used.

With the two classes of compound studied here, the protective properties of PBA are complementary to existing protection strategies. PBA essentially protects the four internal hydroxy groups of D-mannitol, leaving the terminal ones available for functionalisation, in contrast to the existing ketal and acetal approaches, which protect the 1,2-,[15] 1,3-[16] or 3,4-[17] hydroxy groups. The potentially synthetically useful 1,6-dialkanoates and the 1,6-bis(benzyl ether) **3** of D-mannitol are now readily available *via* this boronate method.[18] While bulky substituents such as the trityl group can be selectively introduced at the 9-OH of sialic acid derivatives,[19] other derivatisations, such as tosylation,[20] tend to react at both the 8- and 9-OH groups. Ketal protection of the 8,9-OH groups allows selective reaction at the 7-OH,[21] whilst the tin-based methods lead to selective reaction at the 8-OH.[22] The approach described here now gives simple access to 9-substituted sialic acid derivatives.

In summary, the utility of PBA to serve as a highly selective and recoverable protective agent for open-chain 1,2,3-triols has been demonstrated. With PBA, the sequence of protection, derivatisation, then deprotection can be carried out in one pot, giving analytically pure, terminally substituted products in moderate yield after a simple trituration or precipitation. The use of PBA is also attractive because it can be readily recovered and re-used. The use of boronic acids for selective derivatisation reactions of open-chain polyols will be the subject of further investigations. These results will be reported in due course.

Experimental

General methods

All non-specialised starting materials were commercially available research-grade chemicals and were used without further purification. TLC was performed on aluminium-backed silica

sheets (25 DC-Alufolien Kieselgel 60 F_{254}). For sialic acid derivatives, plates were thermally developed with cerium(IV) sulfate–ammonium molybdate, while potassium permanganate in sodium hydroxide was used for the mannitol derivatives. Mps of solid compounds were measured on a Reichert hot-stage melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, and $[a]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. Microanalyses were performed by Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. IR spectra were recorded on a Perkin-Elmer 1600 Series Fourier Transform Spectrophotometer. Samples were mounted as either KBr discs or Nujol (paraffin) mulls on sodium chloride plates. Both ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer, while two-dimensional correlated spectra were recorded on a Bruker DPX 300 MHz spectrometer. Tetramethylsilane (TMS) was employed as the internal standard (δ 0.00), when spectra were recorded in deuteriochloroform ($CDCl_3$) or D_6-dimethyl sulfoxide (D_6-DMSO) solvents. For spectra recorded in deuterium oxide (D_2O) or D_4-methanol (CD_3OD), *tert*-butyl alcohol was used as the internal reference (δ 1.24). High-resolution mass spectra were recorded on a Bruker BioApex 47e Fourier Transform mass spectrometer. Samples were dissolved in methanol and ionised using an electrospray ionisation (ESI) source. Liquid chromatography mass spectra (LCMS) were recorded with a Waters 2690 separations module liquid chromatography system, a Waters Symmetry C18 column, CH_3CN–water gradient elution and a Micromass Platform II API QMS electrospray mass spectrometer.

D-Mannitol 1,6-dioctanoate 1

D-Mannitol (546 mg, 3.0 mmol) and phenylboronic acid (732 mg, 6.0 mmol) were dissolved in pyridine (10 mL), then benzene (50 mL) was added. The resulting solution was refluxed under argon for 2 h, with azeotropic removal of water. The benzene was then removed under vacuum and the solution was cooled to 0 °C. *n*-Octanoyl chloride (1.1 mL, 6.0 mmol) was then added with stirring and the reaction mixture was stirred under argon overnight at room temperature. The resulting mixture was quenched with ice and extracted with ethyl acetate (100 mL). The organics were washed successively with 1 M HCl, water, 1 M NaOH, water (2×) and brine. The organic layer was dried over Na_2SO_4 and filtered. Removal of the organic solvent at 60 °C under reduced pressure afforded a white solid, which was triturated with hexane to give the pure 1,6-dioctanoate (620 mg, 48%) as a very fine white powder.

The experiment was repeated with the omission of phenylboronic acid, giving a 16% yield of the 1,6-dioctanoate. Compound **1** had mp 131–132 °C (lit.,[23] 132–136 °C); $[a]_D^{28}$ −7.7 (c 0.065 in $CHCl_3$) (Found: C, 60.80; H, 9.67. $C_{22}H_{42}O_8$ requires C, 60.81; H, 9.74%); ν_{max}(KBr)/cm^{-1} 1603, 1444, 1347, 1179; δ_H(300 MHz; D_6-DMSO + D_2O) 0.79 (6 H, t, *J* 6.9, 2 × CH_3), 1.18 [16 H, br s, 2 × $(CH_2)_4CH_3$], 1.47 (4 H, m, 2 × CO_2CH_2-CH_2), 2.25 (4 H, t, *J* 7.3, 2 × $CO_2CH_2CH_2$), 3.52 [2 H, d, *J* 8.9, 2 × C*H*(OH)CH(OH)CH_2], 3.63 [2 H, ddd, *J* 2.4, 6.4 and 8.9, 2 × CH_2C*H*(OH)], 3.93 [2 H, dd, *J* 6.0 and 11.9, 2 × CH^{a}H^b-CH(OH)], 4.21 [2 H, dd, *J* 2.1 and 11.4, 2 × CH^a*H*^{b}CH(OH)]; δ_C(75 MHz; D_6-DMSO) 15.0, 23.1, 25.5, 29.4, 29.5, 32.1, 34.6, 67.8, 69.2, 69.9, 173.9; *m*/*z* (ESI) 457.2782 (M + Na$^+$. $C_{22}H_{42}O_8$·Na$^+$ requires *m*/*z*, 457.2777).

D-Mannitol 1,6-dibenzoate 2

Treatment of D-mannitol (2.18 g, 12.0 mmol) with phenylboronic acid (2.96 g, 24.0 mmol), pyridine (40 mL), benzene (50 mL) and benzoyl chloride (2.78 mL, 12.0 mmol) in an identical manner as that described for the preparation of D-mannitol 1,6-dioctanoate **1**, followed by the same aqueous work-up, yielded a crude oil (1.96 g) which did not crystallise on treatment with hexane. LC-MS and ^{1}H NMR analysis of this oil indicated that it consisted of a mixture of PBA, the title dibenzoate **2** and a large amount of the bis(phenylboronate ester) of **2**. A sample of the crude oil was re-dissolved in an organic solvent and further washed with 1 M NaOH but this failed to produce the desired dibenzoate **2**. Another sample of the crude oil (100 mg) was stirred at room temperature with neopentyl glycol (52 mg, 0.51 mmol) in dry acetone (5 mL) for 2 h.[13] The acetone was then removed under reduced pressure and the resulting solid was washed successively with hexane, hot ethyl acetate–hexane (1 : 1) and water, then recrystallised from ethanol to yield pure 1,6-dibenzoate **2** (24 mg, 10%) as a very fine white powder. Replacement of neopentyl glycol with propane-1,3-glycol, or the use of H_2O_2 to cleave the phenylboronate esters,[14] gave similar yields of the dibenzoate; mp 177–178 °C (lit.,[18] 182 °C); $[a]_D^{28}$ +12.0 (*c* 0.050 in THF) (Found: C, 61.68; H, 5.48. $C_{20}H_{22}O_8$ requires C, 61.53; H, 5.68%); ν_{max}(KBr)/cm^{-1} 3510, 3426, 3063, 2901, 1701, 1603, 1453, 1402, 1289, 1138, 1087, 1027, 710; δ_H(300 MHz; D_6-DMSO + D_2O) 3.72 [2 H, d, *J* 9.2, 2 × C*H*(OH)CH(OH)CH_2], 3.82 [2 H, m, 2 × CH_2C*H*(OH)], 4.26 [2 H, dd, *J* 5.8 and 11.4, 2 × CH^{a}H^b-CH(OH)], 4.47 [2 H, dd, *J* 1.4 and 11.4, 2 × CH^a*H*^{b}CH(OH)], 7.49 (4 H, br t, *J* 7.8, ArH), 7.62 (2 H, m, ArH), 7.98 (4 H, dd, *J* 1.4 and 8.4, ArH), δ_C(75 MHz; D_6-DMSO) 67.7, 68.2, 69.0, 128.4, 129.0 (br), 129.2 (br), 129.2, 130.0, 133.0, 165.8; *m*/*z* (ESI) 413.1222 (M + Na$^+$. $C_{20}H_{22}O_8$·Na$^+$ requires *m*/*z*, 413.1212).

D-Mannitol 1,6-dibenzoate bis(phenylboronate)

D-Mannitol 1,6-dibenzoate (50 mg, 0.13 mmol) and PBA (31 mg, 0.26 mmol) were ground together with an agate mortar and pestle and heated gently with a heat gun for 5 min, after which time the mixture became a colourless viscous liquid. On cooling, the diboronate ester crystallised as a white solid (73 mg, >99%), ν_{max}(KBr)/cm^{-1} 1711, 1600, 1288, 1144, 1027, 831, 705; δ_H(300 MHz; D_6-DMSO + D_2O) 4.78 [4 H, m, 2 × CH_2-CH(OBPh)], 4.85 [(2 H, m, 2 × CH_2C*H*(OBPh)], 4.95 [2 H, br s, 2 × C*H*(OBPh)CH(OBPh)CH_2], 8.19 (20 H, m, ArH), δ_C(75 MHz; D_6-DMSO) 64.2, 65.9, 72.1, 127.5, 128.4, 129.2, 129.5, 131.2, 133.2, 134.0, 165.9; *m*/*z* (LCMS-ESI) 598.9 (M + H$^+$ + 2H_2O), 580.9 (M + H$^+$ + H_2O), 477.0 (85%), 459.0 (80), 355.1 (40).

D-Mannitol 1,6-bis(benzyl ether) 3

D-Mannitol (546 mg, 3.0 mmol) and phenylboronic acid (723 mg, 6.0 mmol) were dissolved in dimethylformamide (30 mL), then benzene (30 mL) was added. The resulting solution was refluxed under argon for 2 h, with azeotropic removal of water, then cooled to 0 °C and 60% NaH (160 mg, 4 mmol) was added. The mixture was stirred at room temperature under argon for 30 min, then cooled to 0 °C. Benzyl bromide (0.71 mL, 6.0 mmol) was added with stirring and the reaction mixture was stirred overnight at 70 °C under argon. The resulting mixture was then poured into ice-cold 1 M NaOH, and extracted with ethyl acetate. The organics were washed with water (2×), and then with brine, and the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a viscous liquid. This residue was triturated with hexane to afford the pure 1,6-bis(benzyl ether) (611 mg, 56%) as a fine white powder, mp 146–148 °C; $[a]_D^{27}$ +6.1 (*c* 0.003 in DMSO) (Found: C, 66.38; H, 7.14. $C_{20}H_{26}O_6$ requires C, 66.28; H, 7.23%); ν_{max}(KBr)/cm^{-1} 1454, 1128, 1094; δ_H(300 MHz; D_6-DMSO + D_2O) 3.42 (2 H, dd, *J* 9.8 and 6.3, 2 × C*H*^{a}H^{b}OCH_2Ph), 3.54 [2 H, d, *J* 8.7, 2 × C*H*-(OH)CH(OH)CH_2], 3.62 [4 H, m, 2 × C*H*(OH)CH^a*H*^{b}-OCH_2Ph], 4.47 (4 H, s, 2 × OCH_2Ph), 7.25 (10 H, m, 10 × ArH); δ_C(75 MHz; D_6-DMSO) 69.1, 69.7, 72.2, 73.1, 127.2, 128.0, 128.0, 138.7; *m*/*z* (ESI) 385.1630 (M + Na$^+$. $C_{20}H_{26}O_6$·Na$^+$ requires *m*/*z*, 385.1627).

D-Mannitol 1-(decyl ether) 4

Treatment of D-mannitol (182 mg, 1.0 mmol) with phenylboronic acid (244 mg, 2.0 mmol), 60% NaH (160 mg, 4 mmol) and decyl bromide (0.42 mL, 2.0 mmol) in dimethylformamide (10 mL) and benzene (10 mL) in an identical manner to that described for the preparation of D-mannitol 1,6-bis(benzyl ether) **3** afforded a yellow oil, which was purified *via* flash column chromatography (ethyl acetate–hexane, 1 : 2) to yield the pure decyl ether[24] (46 mg, 13%) as an off-white powder, δ_H(300 MHz; D_6-DMSO + D_2O) 0.83 (3 H, t, *J* 6.6, CH_3), 1.22 [14 H, br s, $(CH_2)_7CH_3$], 1.46 [2 H, m, $CH_2(CH_2)_7CH_3$], 3.53–3.36 (10 H, m); δ_C(75 MHz; D_6-DMSO) 14.5, 22.7, 25.2, 26.7, 28.3, 28.7, 30.6, 31.2, 32.1, 63.8, 69.7, 70.3, 70.7, 71.4, 72.6, 73.4; *m*/*z* (ESI) 345.2241 (M + Na^+. $C_{16}H_{34}O_6{\cdot}Na^+$ requires *m*/*z*, 345.2253).

N-Acetyl-4,7,8,9-tetra-*O*-acetyl-2-chloro-2-deoxyneuraminic acid methyl ester

N-Acetylneuraminic acid methyl ester[25] **5** (6.5 g, 20 mmol) was dissolved in acetyl chloride (100 mL, 1.4 mol) and the solution was stirred at room temperature for 5 days under a calcium chloride drying tube. ^{1}H NMR showed the reaction to be complete after this time, and remaining acetyl chloride was removed at 40 °C under reduced pressure to afford the title chloride[26] as a viscous orange oil (10.0 g), δ_H(300 MHz; $CDCl_3$) 1.92 (3 H, s, NAc), 2.05, 2.06, 2.07, 2.12 (12 H, 4 × s, 4 × OAc), 2.25 (1 H, dd, *J* 2.7 and 13.9, 3-H^{ax}), 2.78 (1 H, dd, *J* 4.8 and 13.8, 3H^{eq}), 3.87 (3 H, s, OCH_3), 4.06 (1 H, dd, *J* 5.8 and 12.5, 9-H), 4.20 (1 H, dd, *J* 10.4 and 20.9, 5-H), 4.35 (1 H, dd, *J* 2.4 and 10.8, 6-H), 4.42 (1 H, dd, *J* 2.8 and 12.5, 9-H′), 5.17 (1 H, m, 8-H), 5.39 (1 H, ddd, *J* 4.7, 10.8 and 21.5, 4-H), 5.47 (1 H, dd, *J* 2.4 and 7.0, 7-H), 5.58 (1 H, d, *J* 10.4, N*H*Ac); δ_C(75 MHz; $CDCl_3$) 20.6, 20.7, 20.8, 21.0, 23.0, 40.6, 48.7, 53.8, 62.1, 66.9, 68.7, 70.0, 73.8, 96.5, 165.4, 169.6, 169.8, 170.5, 170.7, 170.8.

N-Acetyl-4,7,8,9-tetra-*O*-acetyl-2,3-didehydro-2-deoxyneuraminic acid methyl ester[27] 6

The title compound was prepared according to the procedure of Wu and co-workers.[28] To crude *N*-acetyl-4,7,8,9-tetra-*O*-acetyl-2-chloro-2-deoxyneuraminic acid methyl ester (10.0 g, ≈19.6 mmol) were added K_2CO_3 (1.6 g, 11.6 mmol) and $AgNO_3$ (10.2 g, 60 mmol). Acetonitrile (250 mL) was then added with rapid stirring, and the mixture was stirred overnight in the dark, under argon at room temperature. The resulting silver chloride (white precipitate) was filtered off through a Celite pad and washed with ethyl acetate. The combined filtrate and washings were cooled to 0 °C to precipitate any remaining silver chloride, after which the ethyl acetate was removed at 40 °C under reduced pressure. The reaction mixture was then purified by flash column chromatography (ethyl acetate–hexane, 3 : 2) to afford the protected glycal (4.8 g, 51% over two steps) as a cream foam; δ_H(300 MHz; $CDCl_3$) 1.92 (3 H, s, NAc), 2.03, 2.04, 2.06, 2.10 (12 H, 4 × s, 4 × OAc), 3.78 (3 H, s, OCH_3), 4.17 (1 H, dd, *J* 6.9 and 12.3, 9-H), 4.37 (2 H, m, 5-H and 6-H), 4.57 (1 H, dd, *J* 3.3 and 12.7, 9-H′), 5.34 (1 H, m, 8-H), 5.47 (2 H, m, 7-H and 4-H), 5.53 (1 H, d, *J* 9.0, N*H*Ac), 5.99 (1 H, d, *J* 3.2, 3-H); δ_C(75 MHz; $CDCl_3$) 20.7 (br), 20.9, 23.1, 46.5, 52.6, 61.9, 67.6, 67.9 (br), 76.6, 107.8, 144.9, 161.4, 169.9, 170.0 (br), 170.3, 170.5.

N-Acetyl-2,3-didehydro-2-deoxyneuraminic acid methyl ester 7

Sodium metal (0.4 g) was dissolved in freshly distilled dry methanol (30 mL) under argon with stirring to generate sodium methoxide. The pure protected glycal **6** (4.5 g, 9.5 mmol) was dissolved in methanol (100 mL) and 5 mL of the sodium methoxide solution was added. The reaction mixture was stirred overnight under argon at room temperature. Dowex H^+ resin was then added (until pH 7.0) and the resulting precipitate was re-dissolved with minimal water. The reaction mixture was then filtered through a Celite pad and the residue was washed with methanol in water (50%). Removal of solvent at 40 °C under reduced pressure resulted in a solid residue, which was recrystallised from boiling methanol. The pure deprotected glycal **7** was then collected as a white powder *via* filtration (1.8 g, 62%), and dried under high vacuum; mp 225–226 °C (lit.,[29] 225–227 °C); δ_H(300 MHz; CD_3OD) 2.07 (3 H, s, NAc), 3.60 (1 H, dd, *J* 1.2 and 9.3, 7-H), 3.69 (1 H, dd, *J* 5.3 and 11.3, 9-H), 3.81 (3 H, s, OCH_3), 3.85 (1 H, dd, *J* 3.0 and 11.4, 9-H′), 3.92 (1 H, m, 8-H), 4.02 (1 H, dd, *J* 8.6 and 10.8, 5-H), 4.19 (1 H, dd, *J* 1.2 and 10.8, 6-H), 4.45 (1 H, dd, *J* 2.6 and 8.7, 4-H), 5.97 (1 H, d, *J* 2.4, 3-H); δ_C(75 MHz; D_2O) 25.1, 55.8, 57.1, 66.0, 70.0, 70.8, 72.8, 79.0, 115.4, 145.6, 166.3, 177.1.

N-Acetyl-2,3-didehydro-2-deoxy-4,9-di-*O*-octanoylneuraminic acid methyl ester 8

The methyl ester **7** (305 mg, 1.0 mmol) and phenylboronic acid (122 mg, 1.0 mmol) were dissolved in a mixture of dimethylformamide (1.5 mL) and pyridine (6 mL), then benzene (30 mL) was added. The resulting solution was refluxed under argon for 2 h, with the azeotropic removal of water. The benzene was then removed under vacuum and the solution residue was cooled to 0 °C. *n*-Octanoyl chloride (0.34 mL, 2.0 mmol) was then added with stirring and the reaction mixture was stirred overnight at room temperature under argon. The resulting mixture was quenched with ice and extracted with ethyl acetate (100 mL). The organics were washed successively with 1 M HCl, water, 1 M NaOH, water (2×) and brine. The organic layer was then dried over Na_2SO_4 and filtered. Removal of the organic solvent under reduced pressure at 40 °C resulted in a white solid. This solid was as taken up in ethyl acetate (4 mL), and hexane (30 mL) was added to yield, after centrifugation, the 4,9-dioctanoate product (370 mg, 52%) as a white powder. The experiment was repeated with the omission of phenylboronic acid, to give only a 5% yield of the 4,9-dioctanoate. Compound **8** had mp 134–135 °C (Found: C, 60.02; H, 8.50; N, 2.71. $C_{28}H_{47}NO_{10}$ requires C, 60.34; H, 8.50; N, 2.71%); ν_{max}(Nujol mull)/cm^{-1} 3506, 3257, 3075, 2932, 1729, 1644, 1567, 1461, 1377, 1317, 1264, 1195, 1158, 1104, 1076, 986, 760; δ_H(300 MHz; CD_3OD) 0.94 (6 H, t, *J* 6.7, 2 × CH_3), 1.35 [16 H, m, 2 × $(CH_2)_4CH_3$], 1.65 (4 H, m, 2 × OCH_2CH_2), 2.00 (3 H, s, NAc), 2.28, 2.29 (4 H, 2 × t, *J* 7.5, 7.3, 2 × OCH_2CH_2), 3.61 (1 H, dd, *J* 1.1 and 9.2, 7-H), 3.82 (3 H, s, OCH_3), 4.13 (1 H, m, 8-H), 4.18 (1 H, dd, *J* 6.1 and 17.2, 9-H), 4.30 (1 H, dd, *J* 8.6 and 11.1, 5-H), 4.39 (1 H, dd, *J* 11.6 and 11.6, 6-H), 4.43 (1 H, dd, *J* 2.1 and 11.1, 9-H′), 5.70 (1 H, dd, *J* 2.6 and 8.8, 4-H), 5.90 (1 H, d, *J* 2.6, 3-H); δ_C(75 MHz; CD_3OD) 14.4 (br), 14.6 (br), 22.8, 23.7, 26.1, 30.1 (br), 32.9, 35.0, 35.1, 52.8, 52.9, 67.6 (br), 68.8, 69.8, 70.2, 77.8 (br), 109.0, 146.6, 163.6, 174.0, 174.8, 175.4, *m*/*z* (ESI) 580.3109 (M + Na^+. $C_{28}H_{47}NO_{10}{\cdot}Na^+$ requires *m*/*z*, 580.3098).

N-Acetyl-4,9-di-*O*-benzoyl-2,3-didehydro-2-deoxyneuraminic acid methyl ester 9

The methyl ester **7** (305 mg, 1.0 mmol) was treated with phenylboronic acid (122 mg, 1.0 mmol), benzoyl chloride (0.23 mL, 2.0 mmol) and benzene (30 mL) in a mixture of dimethylformamide (1.5 mL) and pyridine (6 mL), in an identical manner to that used for the preparation of the dioctanoate **8**. After work-up, the crude product was purified *via* flash column chromatography (ethyl acetate–hexane, 1 : 1) to afford the pure 4,9-dibenzoate (120 mg, 20%) as a white powder, mp 198–200 °C; ν_{max}(Nujol)/cm^{-1} 3354, 2924, 2854, 1719, 1655, 1602, 1560, 1457, 1377, 1316, 1265, 1178, 1111, 1071, 1026, 980, 713; δ_H(300 MHz; CD_3OD) 1.93 (3 H, s, NAc), 3.76 (1 H, dd, *J* 1.0 and 9.3, 7-H), 3.80 (3 H, s, OCH_3), 4.26 (1 H, m, 8-H), 4.44 (1 H, dd, *J* 6.1 and 11.5, 9-H), 4.53 (2 H, m, 5-H and 6-H), 4.68 (1 H, dd, *J* 2.4 and 11.5, 9-H′), 5.89 (1 H, dd, *J* 2.6 and 9.2,

4-H), 6.04 (1 H, d, *J* 2.6, 3-H), 7.49 (4 H, br t, *J* 8.2, ArH), 7.62 (2 H, m, ArH), 8.06 (4 H, ddd, *J* 1.4, 8.4 and 16.4, ArH); δ_C(75 MHz; CD_3OD) 22.7, 52.9, 53.0, 68.2, 69.1, 69.8, 71.3, 77.8 (br), 108.8, 108.9, 129.4, 129.5, 130.5, 130.7, 131.4, 134.1, 134.5, 146.8, 163.7, 167.5, 174.0, 178.0; *m*/*z* (ESI) 536.1522 (M + Na^+. $C_{26}H_{27}NO_{10}{\cdot}Na^+$ requires *m*/*z*, 536.1533).

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