A palladium(0)-mediated approach to some novel C-4-substituted Neu5Ac2en derivatives

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The preparation of a range of novel C-4-modified 2,3-unsaturated *N*-acetylneuraminic acid analogues is reported. These compounds have been prepared from the 4-chloro-4-deoxy-*N*-acetylneuraminic acid derivatives 10 and 12 by using a palladium(0)-mediated coupling with organostannanes.

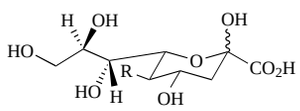
Introduction

There is an increasing interest in the chemistry and biology of the ulosonic acids. The saturated ulosonic acids, the most representative being *N*-acetylneuraminic acid (Neu5Ac, **1**), usually occupy terminal, non-reducing positions of glycoproteins, glycolipids and oligosaccharides.[1,2] *N*-Acetylneuraminic acid has been implicated in a number of biological processes such as cell adhesion and differentiation, and in molecular recognition.[1,2] The 2,3-unsaturated analogues of these sugars are known metabolites of the parent compounds and have been found in body fluids and secretions.[2] Over the past decade we have been interested in ulosonic acid analogues as inhibitors of sialidases and as biological probes for other ulosonic acid-recognising proteins.[3]

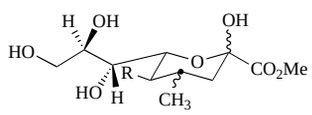
In efforts to elucidate structure–activity relationships of the ulosonic acids further at the molecular level, one of the most challenging and important areas in the chemistry of these sugars is with the development of efficient methods of introducing novel functional groups into these systems. To this end and perhaps not surprisingly a significant amount of sialic acid chemistry has been reported over the past decade.[4,5] As part of our ongoing programme to develop novel synthetic strategies towards the synthesis of Neu5Ac analogues and derivatives, we have recently focused our attention on C-4 *C*-branched ulosonic acids.

The C-4 position is of particular interest because the naturally occuring ulosonic acid 4-deoxy-4-methyl-*N*-glycolylneuraminic acid (4-deoxy-4-methyl-Neu5Gc, **2**) was initially reported in the early 1970s by Hotta and co-workers.[6] Two decades later, the first chemical synthesis of a 4-*C*-methyl derivative of Neu5Ac, compound **3**, and its corresponding 4-epimer **4** starting from the readily available 4-oxo-Neu5Ac derivative **5** was achieved by Hartmann *et al.*[7] Thus, methylenation of the keto sugar **5** with zirconium reagent CH_2I_2–Zn–Cp_2ZrCl_2 afforded the 4-*C*-methylene compound **6**.[7] Subsequent hydrogenation of ene **6** under standard conditions provided a 3:2 mixture of epimers **3** and **4**.[7] It should be noted that the keto sugar **5** was not reactive under Wittig and Peterson olefination conditions as the carbonyl group at C-4 was found to be prone to enolisation.[7] The more common organometallic carbon-based nucleophiles such as Grignard and lithio reagents are not expected to be suitable for carbon–carbon bond-forming reactions in the highly functionalised Neu5Ac system. Interestingly the milder and more selective cerium variants of some of these reagents, which are known to suppress enolisation, were found[7] to be unreactive towards the keto sugar **5**.

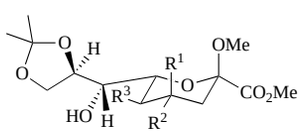
By employing the above mentioned organozirconium methodology, Hartmann *et al.* also prepared a series of 4-*C*-branched-chain Neu5Ac derivatives **7** and **8**.[7] We have recently demonstrated[8] that the methylene compound **6** can be stereoselectively epoxidised and the resulting epoxide opened by nucleophiles thereby providing an entry into more complex C-4 branched-chain derivatives such as **9**. These saturated Neu5Ac derivatives can be readily transformed into their corresponding 2,3-unsaturated analogues *via* acetolysis conditions.[9]



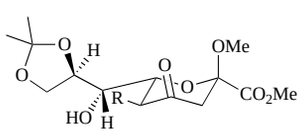
1 R = NHAc



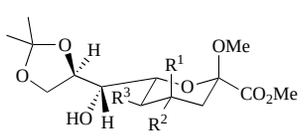
2 R = $NHCOCH_2OH$
C-4 undefined stereochemistry



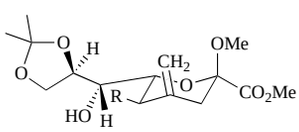
3 R^1 = H, R^2 = Me, R^3 = NHAc
4 R^1 = Me, R^2 = H, R^3 = NHAc
7 R^1 = OH, R^2 = Me, R^3 = NHAc
8 R^1 = Me, R^2 = OH, R^3 = NHAc



5 R = NHAc



9 R^1 = OH, R^2 = CH_2X (X = OMe, N_3, Cl), R^3 = NHAc



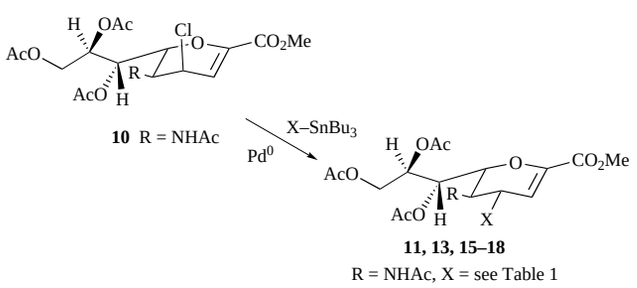
6 R = NHAc

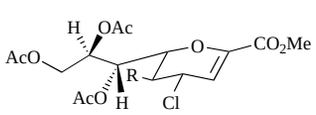
To the best of our knowledge, these examples represent the only syntheses of Neu5Ac derivatives and analogues having *C*-branching at the C-4 position. Thus we were prompted to investigate alternative methodology that would provide ready access to a wider range of C-4 *C*-branched 2,3-unsaturated Neu5Ac derivatives.

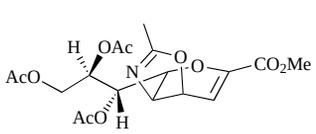
We have previously described[10] the synthesis of some C-4-halogenated derivatives of the per-acetylated methyl esters of the 2,3-unsaturated ulosonic acids, 5-acetamido-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonic acid (Neu5Ac2en) and 2,6-anhydro-3-deoxy-D-*glycero*-D-*galacto*-non-2-enonic acid (KDN2en). It was reasoned that these C-4-halogenated glycals, being functionalised allyl halides, would be useful synthetic intermediates in our attempt to prepare *C*-branched derivatives. For example, like carbonyl compounds, allyl halides react with organometallics to afford cross-coupled products. This reaction is widely used as a synthetic strategy to more highly functionalised organic molecules.[11] Indeed, one of the most useful carbon–carbon bond-forming reactions in this respect is the palladium(0)-catalysed coupling of an allyl halide with an organostannane.[11,12] This is due in part to the scope of this reaction along with its stereospecificity and functional group compatibility being often complementary to those of more conventional methods.

Results and discussion

We report here the exploitation of the palladium(0)-catalysed coupling of methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-chloro-3,4,5-trideoxy-D-*glycero*-D-*talo*-non-2-enonate[10] **10**

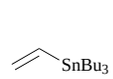
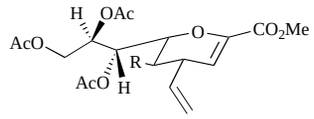
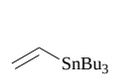
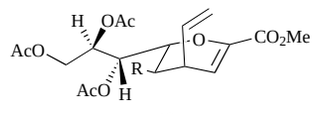
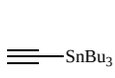
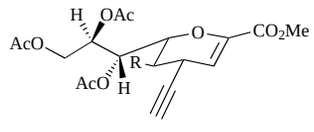
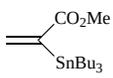
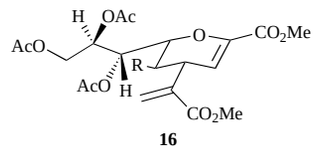
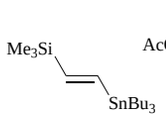
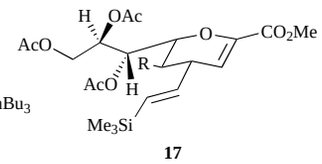
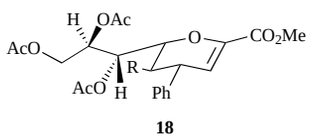



12 R = NHAc


14

with various organotin reagents towards the synthesis of some novel Neu5Ac2en derivatives. For example, we found that compound **10** reacted readily with tributyl(vinyl)tin in the presence of a catalytic amount of bis(dibenzylideneacetone)palladium(0) and triphenylphosphine to provide the cross-coupled product **11**. The reaction proceeded, not unexpectedly,[12] with complete inversion of stereochemistry about C-4. In an effort to ascertain the stereochemical course of this reaction in this system unambiguously, the reaction was repeated using the 4-chloro-4-deoxy epimer, methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-chloro-3,4,5-trideoxy-D-*glycero*-D-*galacto*-non-2-enonate[10] **12**. Predictably, only the corresponding 4-deoxy-4-*epi*-*C*-vinyl-substituted Neu5Ac2en derivative **13** was formed, although in poorer yield. Furthermore, these reactions also occurred regioselectively α to the carbon bearing the leaving

Table 1

Entry	Substrate	Organostannane	Product [a]	% Isolated yield [b]
1	**10**		 **11**	35
2	**12**		 **13**	18
3	**10**		 **15**	49
4	**10**		 **16**	33
5	**10**		 **17**	35
6	**10**	Ph—SnBu3	 **18**	36

[a] R = NHAc.
[b] Isolated after flash chromatography.

group, with no evidence of any γ-coupled product. The two C-4 epimers, **11** and **13**, can readily be distinguished on the basis of the coupling constants of the 3-H resonances from the respective ^{1}H NMR spectra (**11**: $J_{3,4}$ 2.6 Hz; **13**: $J_{3,4}$ 4.6 Hz). Typically, a smaller coupling is associated with an axial proton at C-4 (D-*glycero*-D-*galacto* configuration), while a larger coupling is more characteristic of 4-*epi*-glycals (D-*glycero*-D-*talo* configuration) of Neu5Ac.[13]

The mechanism of this coupling reaction has been widely studied and reviewed by Stille and co-workers.[12] It is thought that the reaction proceeds *via* a sequence of catalytic events which initially involves the oxidative addition of the palladium(0) catalyst to the allyl halide, generating an allylpalladium(II) halide.[14] This species then undergoes transmetallation with the organotin reagent to give a diorganopalladium(II) complex which reductively eliminates[15] to yield the coupled product.

Initial results obtained with compound **10** and tributyl(vinyl)tin encouraged us to examine the generality of this reaction using a variety of organotin reagents (Table 1). The results illustrate the efficacy of the reaction not only with vinyl- and ethynyl-stannanes but also with an aryltin reagent. With the exception of the reaction of compound **12** with tributyl(vinyl)tin, all products were formed in modest yields (33–49%). Treatment of compound **10** with (*E*)-1-(tributylstannyl)-2-(trimethylsilyl)ethylene afforded a reaction product that led us to conclude that the vinyltin reagent coupled stereospecifically

at the double bond (retention, *E*-isomer) of the tin coupling partner. This finding is in agreement with a previous report on other systems.[16] Typically,[12] palladium(0)-catalysed cross-coupling reactions of allyl halides and organotins employ equimolar amounts of the coupling partners. However, in our present work we found it necessary to use an excess of the organostannane to limit competing internal nucleophilic displacement by the acetamide functionality at C-5. When the 4-*epi*-chloro-4-deoxy compound **10** was used as the substrate (Table 1, entries 1, 3–6), the oxazoline **14** represented about 25% of the isolated reaction product and was isolated as the main product (41%) following reaction of the 4-chloro-4-deoxy compound **12** with tributyl(vinyl)tin (Table 1, entry 2). The latter result could well be related to the chloride **12** being inherently unstable[10] with respect to decomposition to the oxazoline **14** upon storage at room temp. Chloroform was the solvent of choice for this transformation. When tetrahydrofuran (THF) was employed as solvent, little or no cross-coupled product was observed (data not shown). Rather, the oxazoline **14** was obtained as the major product of the reaction.

In conclusion, the Pd^0-mediated cross-coupling between the easily accessed chloride **10** and organostannanes offers a convenient entry into some novel C-4 *C*-branched Neu5Ac2en derivatives which would otherwise be difficult to achieve. The reaction proceeds, in the Neu5Ac2en system, with complete regio- and stereo-selectivity. Thus, only α-coupled products are observed, displaying inversion of configuration at the carbon (C-4) bearing the allylic chloride.

Experimental

General

The ^{1}H NMR (300 MHz; unless otherwise stated) and the ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AMX300 spectrometer at 303 K. ^{1}H NMR spectra were referenced to $SiMe_4$ (δ 0); ^{13}C NMR spectra were referenced to $CDCl_3$ (δ_C 77.0). *J*-Values are in Hz. Both low-resolution (LR) and high-resolution (HR) fast-atom bombardment (FAB) mass spectra were obtained on a JEOL JMS-DX 300 spectrometer. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Reactions were monitored by TLC on Kieselgel 60 F_{254} plates (Merck 5554) and the plates were developed by spraying with 95% aq. ethanol containing 5% H_2SO_4 and charring for several minutes. Triphenylphosphine (Aldrich) and bis(dibenzylideneacetone)palladium(0) (Lancaster Synthesis) were used as received. Chloroform was put through a short plug of basic alumina just prior to use. All reactions were performed under anhydrous conditions in flame-dried glassware under argon.

Preparation of the organotin reagents

The organotin reagents were either obtained commercially: tributyl(phenyl)tin (Fluka), tributyl(vinyl)tin and tributyl(ethynyl)tin (Aldrich); or were prepared according to known methods: methyl 1-(tributylstannyl)propenoate from methyl propynoate.[17] However, rather than obtaining this product exclusively as reported,[17] some (*E*)-methyl 1-(tributylstannyl)-propenoate (~8%, by ^{1}H NMR spectroscopy) was also obtained. These isomers were separated, in a combined isolated yield of 94%, on a silica gel column eluted with 2–5% diethyl ether in hexanes: R_f of methyl 1-(tributylstannyl)propenoate in Et_2O–hexanes (1:19) 0.48; R_f of the other isomer in the same solvent system 0.33. The ^{1}H NMR spectroscopic data for methyl 1-(tributylstannyl)propenoate were in good agreement with those reported in the literature;[17] selected ^{1}H NMR (90 MHz) for (*E*)-methyl 1-(tributylstannyl)propenoate: δ_H 3.75 (3 H, s, CO_2Me), 6.30 (1 H, d, *J* 19.3) and (1 H, d, *J* 19.3). (*E*)-1-(Trimethylsilyl)-2-(tributylstannyl)ethylene was prepared, in 62% yield after distillation, by treating trimethylsilylacetylene with tributyltin hydride as previously[18] described.

Preparation of the starting materials[10]

Compound **10** was prepared by treating methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*talo*-non-2-enonate with chlorotrimethylsilane and $BF_3{\cdot}Et_2O$, as previously[10] described. This reaction gave compound **12** (~9% yield) which can be isolated from substrate **10** by column chromatography on silica gel. For the reaction shown in Table 1, entry 2, the 4-deoxy-4-chloro compound **12** was prepared by treating the alcohol, methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*talo*-non-2-enonate, sequentially with 2-dimethylamino-*N*,*N*′-diphenyl-1,3,2-diazaphospholidine and sulfuryl dichloride in dichloromethane, as reported earlier.[10] Except for the coupling reactions of the chlorides **10** and **12** with tributyl(vinyl)tin (Table 1, entries 1 and 2), where purified samples of the starting materials were used, all the other reactions (Table 1, entries 3–6) were performed on crude samples of compound **10**. In these cases, no attempts were made to isolate small amounts of the corresponding 4-*epi*-substituted products.

Representative procedure for the reaction of compound 10 with the organostannanes

To a solution of methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-chloro-3,4,5-trideoxy-D-*glycero*-D-*talo*-non-2-enonate **10** (56 mg, 0.124 mmol) in chloroform (3 cm^3) were added triphenylphosphine (2.0 mg, ~6 mol%) and bis(dibenzylideneacetone)palladium(0) (2.2 mg, ~3 mol%), resulting in a deep red solution. An excess of the tin reagent (0.500 mmol) was then added and after a few minutes a clear yellow solution was obtained. This was heated at 50 °C until TLC indicated that all starting material had been consumed (24–48 h). The reaction mixture was cooled, saturated aq. potassium fluoride (5 cm^3) was added, and the mixture was stirred vigorously for 2 h. The precipitate was filtered off, and washed with chloroform (2 × 5 cm^3). The organic layer was separated, washed with brine and dried (Na_2SO_4). The residue obtained after removal of solvent was purified by chromatography on a silica gel column. The product was eluted using a combination of ethyl acetate and hexanes (1:1–2:1).

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,4,5-trideoxy-4-*C*-ethenyl-D-*glycero*-D-*galacto*-non-2-enonate 11. R_f 0.53 (EtOAc); δ_H($CDCl_3$) 1.94, 2.06, 2.07 and 2.12 (12 H, s, NH*Ac*, OAc), 3.04 (1 H, ddd, *J* 2.6, 10.1 and 10.1, H-4), 3.79 (3 H, s, CO_2Me), 3.97 (1 H, pseudo q, *J* 9.8, H-5), 4.18 (1 H, dd, *J* 2.3 and 9.8, H-6), 4.20 (1 H, dd, *J* 7.3 and 12.4, H^a-9), 4.73 (1 H, dd, *J* 2.7 and 12.4, H^b-9), 5.18 (1 H, dd, *J* 2.0 and 17.1, C-CH=CH_{trans}), 5.19 (1 H, d, *J* 9.8, NH), 5.31 (1 H, m, C-CH=CH_{cis}), 5.32 (1 H, ddd, *J* 2.7, 4.8 and 7.3, H-8), 5.50 (1 H, dd, *J* 2.3 and 4.8, H-7), 5.68 (1 H, ddd, *J* 8.0, 10.1 and 17.1, C-C*H*=CH_2) and 5.96 (1 H, d, *J* 2.6, H-3); δ_C($CDCl_3$) 20.7 and 23.1 (NHCO*C*H_3, OCO*C*H_3), 44.2 (C-4), 47.1 (C-5), 52.2 (CO_2*Me*), 62.3 (C-9), 68.0 (C-6), 71.7 (C-8), 76.9 (C-7), 112.4 (C-3), 117.9 (CH=*C*H_2), 136.3 (*C*H=CH_2), 143.3 (C-2) and 162.2, 170.1, 170.3 and 170.7 (carbonyls); LRMS (FAB) 442 (M^+ + H, 49%), 414 (29) and 382 (31); HRMS (FAB) Calc. for $C_{20}H_{28}NO_{10}$ [M^+ + H]: 442.1713. Found: *m*/*z* 442.1693.

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,4,5-trideoxy-4-*C*-ethenyl-D-*glycero*-D-*talo*-non-2-enonate 13. R_f 0.53 (EtOAc); δ_H($CDCl_3$) 1.93, 2.06 and 2.10 (12 H, s, NH*Ac*, OAc), 3.30 (1 H, ddd, *J* 4.6, 6.0 and 11.0, H-4), 3.81 (3 H, s, CO_2Me), 4.13 (1 H, dd, *J* 4.3 and 7.9, H-6), 4.22 (1 H, dd, *J* 7.4 and 12.2, H^a-9), 4.51 (m, 1 H, H-5), 4.68 (1 H, dd, *J* 3.3 and 12.2, H^b-9), 5.35–5.17 (4 H, m, H-8, NH, C-CH=CH_{trans}, C–CH=CH_{cis}), 5.43 (1 H, pseudo t, *J* 4.3 and 4.3, H-7), 5.74 (1 H, ddd, *J* 7.1, 10.1 and 17.2, C-C*H*=CH_2) and 6.03 (1 H, d, *J* 4.6, H-3).

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,4,5-trideoxy-4-*C*-ethynyl-D-*glycero*-D-*galacto*-non-2-enonate 15. R_f 0.55 (EtOAc); δ_H($CDCl_3$) 1.99, 2.04, 2.05 and 2.13 (12 H, s, NH*Ac*, OAc), 2.11 (1 H, d, *J* 2.7, C≡CH), 3.71 (1 H, ddd, *J* 2.7, 2.7 and 9.5, H-4), 3.78 (3 H, s, CO_2Me), 3.92 (1 H, ddd, *J* 8.7, 9.5

and 9.5, H-5), 4.20 (1 H, dd, *J* 6.6 and 12.4, H^a-9), 4.37 (1 H, dd, *J* 2.4 and 9.2, H-6), 4.62 (1 H, dd, *J* 2.8 and 12.4, H^b-9), 5.35 (1 H, ddd, *J* 2.8, 5.4 and 6.6, H-8), 5.48 (1 H, dd, *J* 2.4 and 5.4, H-7), 5.70 (1 H, d, *J* 9.5, NH) and 5.98 (1 H, d, *J* 2.7, H-3); $\delta_C(CDCl_3)$ 20.8 and 23.3 (NHCO*C*H$_3$, OCO*C*H$_3$), 30.9 (C-4), 48.4 (C-5), 52.3 (CO_2*Me*), 62.1 (C-9), 70.5 (C≡*C*H), 68.0, 71.7 and 76.1 (C-6, -7, -8), 81.2 (*C*≡CH), 109.3 (C-3), 143.2 (C-2) and 170.2 and 170.4 (carbonyls); LRMS (FAB): 440 (M^+ + H, 65%), 414 (31), 380 (30); HRMS (FAB): Calc. for $C_{20}H_{26}NO_{10}$ [M^+ + H]: 440.155 67. Found: *m*/*z* 440.155 02.

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,4,5-trideoxy-4-*C*-[1-(methoxycarbonyl)ethenyl]-D-*glycero*-D-*galacto*-non-2-enonate 16. R_f 0.48 (EtOAc); $\delta_H(CDCl_3)$ 1.85, 2.05, 2.06 and 2.10 (12 H, s, NH*Ac*, OAc), 3.72 (1 H, dd, *J* 2.5 and 10.5, H-4), 3.76 and 3.79 (6 H, s, 2 × CO_2Me), 4.18 (3 H, m, H-5, -6, H^a-9), 4.72 (1 H, dd, *J* 2.6 and 12.4, H^b-9), 5.30 (1 H, ddd, *J* 2.6, 4.7 and 7.3, H-8), 5.36 (1 H, d, *J* 8.3, NH), 5.47 (1 H, br d, *J* 4.7, H-7), 5.85 [1 H, s, C(CO_2Me)=C*H*^{a}], 5.90 (1 H, d, *J* 2.5, H-3) and 6.34 [s, 1 H, C(CO_2Me)=C*H*^{b}]; $\delta_C(CDCl_3)$ 20.7 and 23.0 (NHCO*C*H$_3$, OCO*C*H$_3$), 407 (C-4), 47.5 (C-5), 52.2 (CO_2Me), 62.3 (C-9), 67.9 (C-7), 71.8 (C-8), 77.8 (C-6), 112.3 (C-3), 127.9 [C(CO_2Me)=*C*H$_2$], 138.7 [*C*(CO_2Me)=CH$_2$] and 143.9 (C-2), 162.1, 167.2, 170.0 and 170.4 (carbonyls); LRMS (FAB): 500 (M^+ + H, 100%), 458 (21), 440 (34) and 414 (37); HRMS (FAB): Calc. for $C_{22}H_{30}NO_{12}$ [M^+ + H]: 500.1768. Found: *m*/*z* 500.1789.

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,4,5-trideoxy-4-*C*-[(*E*)-2-(trimethylsilyl)ethenyl]-D-*glycero*-D-*galacto*-non-2-enonate 17. R_f 0.80 (EtOAc); $\delta_H(CDCl_3)$ 0.03 (9 H, s, $SiMe_3$), 1.85, 2.04, 2.05 and 2.10 (12 H, s, NH*Ac*, OAc), 2.99 (1 H, ddd, *J* 2.6, 5.6 and 8.7, H-4), 3.77 (3 H, s, CO_2Me), 3.98 (1 H, ddd, *J* 8.7, 9.8 and 9.8, H-5), 4.15 (1 H, dd, *J* 2.2 and 9.8, H-6), 4.18 (1 H, dd, *J* 7.3 and 12.6, H^a-9), 4.73 (1 H, dd, *J* 2.6 and 12.6, H^b-9), 5.28 (1 H, d, *J* 9.8, NH), 5.30 (1 H, ddd, *J* 2.6, 4.7 and 7.3, H-8), 5.49 (1 H, dd, *J* 2.2 and 4.7, H-7), 5.73 (1 H, d, *J* 18.4, C*H*$SiMe_3$), 5.80 (1 H, dd, *J* 5.6 and 18.4, C*H*=C$SiMe_3$) and 5.95 (1 H, d, *J* 2.6, H-3); $\delta_C(CDCl_3)$ −1.6 ($SiMe_3$), 20.7, 20.8 and 23.1 (NHCO*C*H$_3$, OCO*C*H$_3$), 46.9 and 47.2 (C-4, -5), 52.2 (CO_2Me), 62.3 (C-9), 68.1, 71.8 and 77.0 (C-6, -7, -8), 112.3 (C-3), 134.6 (CSi), 143.1 (C-2), 143.2 (*C*H=CSi) and 162.2, 169.7, 170.3 and 170.6 (carbonyls); LRMS (FAB): 514 (M^+ + H, 100%), 498 (10), 472 (29) and 454 (52); HRMS (FAB): Calc. for $C_{23}H_{36}NO_{10}Si$ [M^+ + H]: 514.2109. Found: *m*/*z* 514.2102.

Methyl 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-3,4,5-trideoxy-4-*C*-phenyl-D-*glycero*-D-*galacto*-non-2-enonate 18. R_f 0.58 (EtOAc); $\delta_H(CDCl_3)$ 1.83, 2.04, 2.06 and 2.07 (12 H, s, NH*Ac*, OAc), 3.81 (3 H, s, CO_2Me), 3.81 (1 H, m, H-5), 3.92 (1 H, dd, *J* 2.3 and 9.9, H-4), 4.21 (1 H, dd, *J* 6.8 and 12.5, H^a-9), 4.56 (1 H, dd, *J* 1.7 and 9.5, H-6), 4.67 (1 H, dd, *J* 2.6 and 12.5, H^b-9), 5.33 (1 H, m, H-8), 5.48 (1 H, dd, *J* 2.0 and 5.3, H-7), 5.60 (1 H, br d, NH) and 6.09 (1 H, d, *J* 2.3, H-3); $\delta_C(CDCl_3)$ 20.8 and 22.9 (NHCO*C*H$_3$, OCO*C*H$_3$), 44.9 and 50.0 (C-4, -5), 52.2 (CO_2*Me*), 62.3 (C-9), 68.2, 71.4 and 77.0 (C-6, -7, -8), 113.9 (C-3), 127.5, 127.9, 128.6 and 139.8 (C_{arom}), 143.6 (C-2) and 162.3, 170.0, 170.1, 170.3 and 170.6 (carbonyls); LRMS (FAB): 492 (M^+ + H, 100%), 450 (39), 432 (63) and 414 (18); HRMS (FAB): Calc. for $C_{24}H_{30}NO_{10}$ [M^+ + H]: 492.1870. Found: *m*/*z* 492.1880.

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References

1 A. P. Corfield and R. Schauer, *Sialic Acids*: *Chemistry*, *Metabolism and Function* in *Cell Biology Monographs*, ed. R. Schauer, Springer-Verlag, Wien, 1982, vol. 10, p. 195.
2 R. Schauer, S. Kelm, G. Reuter, P. Roggentin and L. Shaw, *Biochemistry and Role of Sialic Acids*, ed. A. Rosenberg, Plenum Press, New York, 1995, p. 7.
3 M. von Itzstein, W.-Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. van Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D. M. Ryan, J. M. Woods, R. C. Bethell, V. G. Hotham, J. M. Cameron and C. R. Penn, *Nature*, 1993, **363**, 48; J. C. Wilson, D. C. M. Kong, Y.-T. Li and M. von Itzstein, *Glycoconjugate J.*, 1996, **13**, 927.
4 M. von Itzstein and R. J. Thomson, *The Synthesis of Novel Sialic Acids as Biological Probes* in *Top. Curr. Chem.*, 1997, **186**, 119.
5 M. von Itzstein and R. J. Thomson, *Curr. Med. Chem.*, 1997, **4**, 185.
6 K. Hotta, M. Kurokawa and S. Isaka, *J. Biol. Chem.*, 1970, **245**, 6307.
7 M. Hartmann, R. Christian and E. Zbiral, *Monatsh. Chem.*, 1991, **122**, 111.
8 D. R. Groves and M. von Itzstein, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2817.
9 G. B. Kok, D. R. Groves and M. von Itzstein, *Chem. Commun.*, 1996, 2017.
10 G. B. Kok, A. K. Norton and M. von Itzstein, *Synthesis*, 1997, 1185.
11 See for example: J. P. Collman and L. S. Hegedus in: *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, 1980, ch. 11; E. Negishi, *Acc. Chem. Res.*, 1982, **15**, 340; *Current Trends in Organic Syntheses*, ed. H. Nozaki, Pergamon Press, New York, 1983, p. 269.
12 F. K. Sheffy, J. P. Godschalx and J. K. Stille, *J. Am. Chem. Soc.*, 1984, **106**, 4833.
13 E. Schreiner, E. Zbiral, R. G. Kleineidam and R. Schauer, *Carbohydr. Res.*, 1991, **216**, 61.
14 J. K. Stille and K. S. Y. Lau, *Acc. Chem. Res.*, 1977, **10**, 434; J. K. Stille in: *The Chemistry of the Metal-Carbon Bond*, ed. F. R. Hartley and S. Patai, Wiley, New York, 1985, vol. 2, p. 625.
15 D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1979, **101**, 4981; 4992; A. Gillie and J. K. Stille, *J. Am. Chem. Soc.*, 1980, **102**, 4933; M. K. Loar and J. K. Stille, *J. Am. Chem. Soc.*, 1981, **103**, 4174; A. Moravskiy and J. K. Stille, *J. Am. Chem. Soc.*, 1981, **103**, 4182.
16 J. W. Labadie, D. Tueting and J. K. Stille, *J. Org. Chem.*, 1983, **48**, 4634.
17 H. X. Zhang, F. Guibé and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857.
18 R. F. Cunico and F. J. Clayton, *J. Org. Chem.*, 1976, **41**, 1480.

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