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A study of the donor properties of sialyl phosphites having an auxiliary 3-(*S*)-phenylseleno group

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Dedicated to the memory of Professor Göran Magnusson

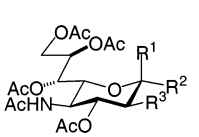
Abstract

Two phosphite sialyl donors, each having an auxiliary 3-(*S*)-phenylseleno group, were prepared and evaluated. The phenylseleno group was introduced via a new mode of generating phenylselenenic acid ('PhSeOH'). Although the sialyl donors provided fair yields (32–76%) of the desired sialosides in glycosylations of the reactive acceptor 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose, no sialylated products could be obtained with less reactive acceptors. The presence of a 5-*N*-acetylacetamido group on the phosphite sialyl donor did not appear to improve its sialylating capability. The weak C–Se bond, possibly in combination with a steric hindrance, which disfavors α-nitrilium ion formation, seem to explain the unsuccessful sialylations of the less reactive acceptors.

Keywords: Sialic acid phosphites; Auxiliary phenylseleno group; Phenylselenenic acid; Long-range coupling

1. Introduction

Gangliosides are glycosphingolipids characterized by the presence of sialic acid (*N*-acetylneuraminic acid, Neu5Ac), which terminates the saccharide chain via an α-glycosidic bond, e.g., to a galactose or sialic acid residue.[1] No β-glycosides of sialic acid have been found in nature. Due to the observed biological importance of gangliosides inter alia as tumor-associated antigens and receptors for various bacterial and viral pathogens, there is an ongoing demand for powerful methods of performing α-sialylations.[2] Since it is rather difficult to accomplish an α-sialylation in high yield, many researchers have addressed this problem over the years. In short, donors for α-sialylation seem to have evolved through four main stages. The first was the optimiza-



1 $R^1 = OP(OEt)_2$, $R^2 = CO_2Me$, $R^3 = H$

2 $R^1 = CO_2Me$, $R^2 = SMe$ (α/β 1:1), $R^3 = H$

3 $R^1 = Cl$, $R^2 = CO_2Me$, $R^3 = SPh$

4 $R^1 = CO_2Me$, $R^2 = SEt$, $R^3 = SPh$

5 $R^1 = OP(OEt)_2$, $R^2 = CO_2Me$, $R^3 = OC(S)PhO$

Fig. 1. Some typical available sialyl donors.

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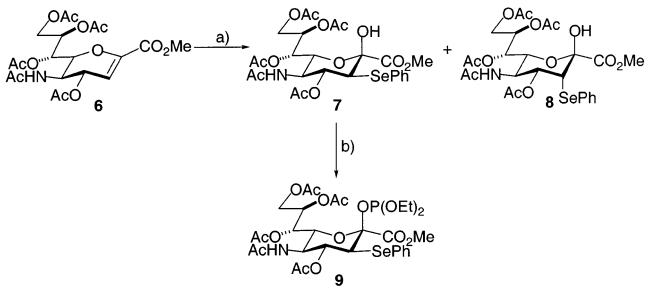


Scheme 1. Synthesis of the sialyl donor **9**. Reagents: (a) PhSeCl, H_2O, AgOTf, THF, 0 °C (51% **7** and 35% **8**, respectively). (b) $ClP(OEt)_2$, $EtN(i\text{-}Pr)_2$, CH_3CN, 0 °C (88%).

tion of the anomeric leaving group, where β-phosphites and α/β-thioglycosides (**1** and **2**, respectively; Fig. 1) gave the most useful results.[3] However, such sialyl donors are prone to eliminate and form a glycal (**6**) when unreactive acceptors are to be sialylated. They also yield α/β product mixtures.[4]

The second stage was the introduction of an auxiliary 3-(*S*)-substituent to suppress glycal formation and improve the α/β selectivity.[5] In this respect, the phenylseleno, phenylthio and thiobenzoyloxy groups gave the best results.[6]

Although giving fair to good α-sialylation yields, only halosugars such as **3** were at first equipped with such auxiliary substituents, thereby providing some room for continued development. The logical third stage was then to combine the best anomeric leaving group with the best auxiliary substituent, thereby providing for example the further improved sialyl donors **4** and **5**.[7] The fourth stage was the recent discovery that transformation of the 5-acetamido group of sialyl donors to a 5-*N*-acetylacetamido group improves sialylation yields in general.[8]

We now report a study of the phosphite sialyl donors **9** and **17** (Schemes 1 and 3, respectively) each having an auxiliary 3-(*S*)-phenylseleno group. These sialyl donors were anticipated to have the following properties: (i) convenient activation by use of a catalytic amount of an acidic promoter;[3a,b] (ii) stereospecific and high-yielding sialylation also of unreactive acceptors; (iii) easy removal of the phenylseleno group due to the weak C–Se bond (243 kJ/mol) as compared with the C–S and C–O bonds (272 and 336 kJ/mol, respectively). Aspect (iii) was deemed to be of considerable importance, particularly because the removal of an auxiliary phenylthio group can be rather difficult.[9]

2. Results and discussion

Preparation of the sialyl donor **9** *(Scheme 1).*—As starting material the readily available glycal **6**[10] was used, to which phenylselenenic acid ('PhSeOH') was added via in situ generation by mixing phenylselenenyl chloride, water and silver trifluoromethanesulfonate in tetrahydrofuran and keeping the reaction mixture at 0 °C for 7 days. The desired exo adduct **7** was provided in 51% yield and easily separated from its diastereomeric endo adduct **8** obtained in 35% yield. The original Sharpless method of generating phenylselenenic acid in a neutral equilibrium system by reacting diphenyl diselenide with hydrogen peroxide[11] gave a similar result, although here the addition reaction was very slow (weeks required at room temperature). Our method of generating phenylselenenic acid thus provides a higher reaction rate than the original method, and it may serve as an attractive alternative in other systems. The method generates trifluoromethanesulfonic acid, so an obvious proviso is that a potential substrate should not be too acid sensitive (but vide infra).

Direct treatment of the endo adduct **8** with trifluoromethanesulfonic acid in tetrahydrofuran led to partial epimerisation into the exo adduct **7** (~ 25% yield) and formation of numerous by-products, including the glycal **6**. Studies by others have shown that highly reactive electrophilic species, such as bromine and $(PhS)_3SbCl_6$, prefer endo addition to sialic acid glycals.[5,7b] In summary, these observations support our assumption that the obtained **7**/**8** ratio is the result of a direct addition of phenylselenenic acid and not of any significant epimerisation. A weak buffering effect may thus be present in our system. In contrast to the results reported for the tetra-O-benzylated analogues **21** and **22**,[6b] no epimerization was observed under basic conditions (DBU).

Treatment of the hemiketal **7** with diethyl phosphorochloridite in the presence of *N*-ethyldiisopropylamine in acetonitrile afforded

the α-phosphite sialyl donor **9** in 88% yield. Unexpectedly, compound **9** was found to be stable over several months if stored as an amorphous powder under argon at −30 °C.

Acceptors used in the present study.—The study of the sialyl donors **9** and **17** was performed with the acceptors **10**,[12] **11**[13] and **12**,[7d] each chosen for a particular reason (Fig. 2). The diisopropylidenyl galactoside **10** was chosen due to its high reactivity, which should easily provide a sialylated product. The hexabenzyl lactoside **11** and the 9-O-benzylated sialic acid glycal **12** were chosen due to their low reactivity and consequent importance in establishing the full potential of sialyl donors. Indeed, the usefulness of any sialyl donor is mainly governed by its ability to α-sialylate unreactive acceptors. As a general rule, sialyl donors having an auxiliary group should be reserved only for cases where low yields of an α-sialylated product are expected. Sialyl donors such as **1** and **2** are acceptable in the α-sialylation of reactive acceptors, such as **10**, whereas their α-sialylation yields are expected to be impractically low (if any) for the acceptors **11** and **12**.

Evaluation of the sialyl donor **9**.—The optimum conditions for activating sialyl phosphites are well established, and they normally involve treatment with a catalytic amount of either trimethylsilyl trifluoromethanesulfonate or trifluoromethanesulfonic acid in acetonitrile or dichloromethane at a temperature between −40 and −78 °C.[3b] Hence, our first trial was to treat the sialyl donor **9** with the galactoside **10** in acetonitrile at −40 °C in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate, which afforded the desired β-sialoside **13** in 76% yield (Scheme 2). The only by-product observed was the glycal **6**. This result was promising, particularly in view of the fact that a tetra-O-benzylated 2-fluoro analogue of **9** afforded β-sialylated product in 46% yield with the galactoside **10**.[6b] However, when the sialyl donor **9** was treated with the more demanding acceptors **11** and **12** under *exactly* the same conditions, not even a trace of β-sialylated product could be obtained. The only products obtained were the glycal **6**, recovered pure acceptor and trace amounts of trimethylsilyl-*O*-protected acceptor. In contrast to the expected result and despite several modifications in line with the optimum conditions referred to above, the sialyl donor **9** was consistently unable to provide any glycoside with the acceptors **11** and **12**. As a comparison, the available sialyl donor **4** having an auxiliary 3-(*S*)-phenylthio group provided the β-sialylated product in 67% yield with the acceptor **11**.[7a] In summary, we therefore had to conclude that the sialyl donor **9** lacks the ability to sialylate unreactive acceptors.

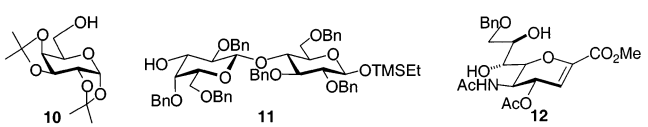
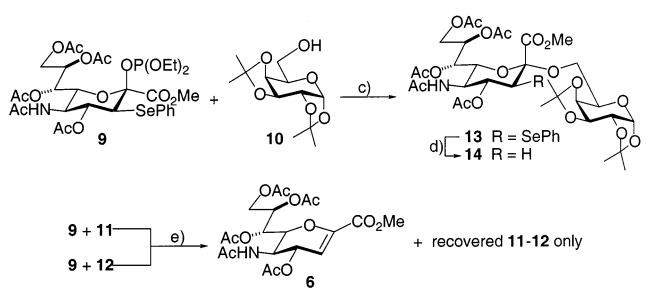


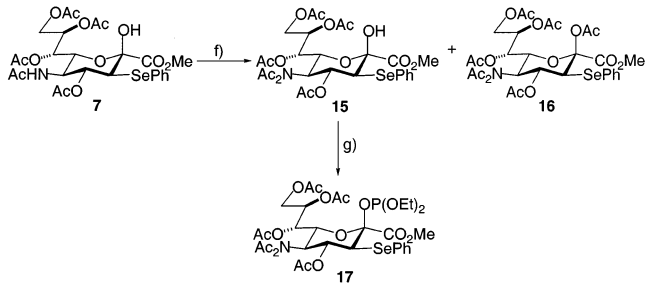
Fig. 2. Acceptors used in the evaluation of the sialyl donors **9** and **17**.



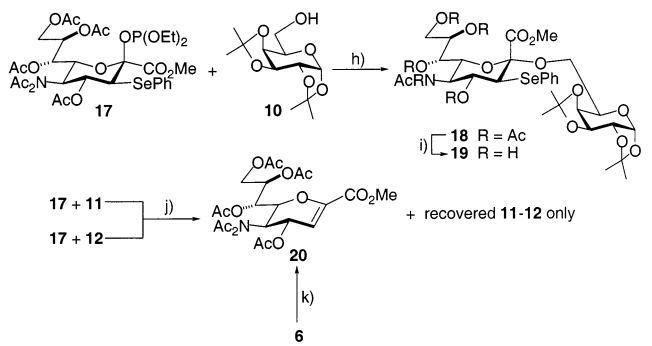
Scheme 2. Evaluation of sialyl donor **9** with the acceptors **10**–**12**. Reagents: (c) Me_3SiOTf (cat.), MeCN, AW 300, −40 °C (76%). (d) Ph_3SnH, AlBN, $C_6H_5CH_3$, reflux (92%). (e) Me_3SiOTf (cat.) or TfOH (cat.), MeCN or CH_2Cl_2 or MeCN–CH_2Cl_2, AW 300 (if any), −78 → −40 °C.

The auxiliary phenylseleno group of **13** was conveniently removed by treatment with triphenyltin hydride–azoisobutyronitrile in refluxing toluene for 1 h, thereby providing the known α-sialoside **14**[14] in 92% yield (Scheme 2). Removal of phenylthio groups under these conditions normally requires refluxing at least overnight, and a significant amount of starting material is nevertheless often recovered.[9a,b] At least the problem of easy removal could thereby be well met by the sialyl donor **9**.

Preparation of the sialyl donor **17** *(Scheme 3)*.—In our attempts to synthesize an improved analogue of **9**, we observed that the 5-acetamido group of the hemiketal **7** could be selectively acetylated before its anomeric hydroxyl group. Treating the hemiketal **7** with



Scheme 3. Synthesis of the 5-*N*-acetylacetamido sialyl donor **17**. Reagents: (f) $CH_3(CH_2{=})COAc$, $TsOH{\cdot}H_2O$, 65 °C (66% **15** and 19% **16**, respectively). (g) $ClP(OEt)_2$, $EtN(i\text{-}Pr)_2$, CH_3CN, 22 °C then work-up in the presence of Et_3N (85%).



Scheme 4. Evaluation of the 5-*N*-acetylacetamido sialyl donor **17** with the acceptors **10**–**12**. Reagents: (h) Me_3SiOTf (cat.), MeCN, −40 °C (~50% crude **18**). (i) NaOMe, 1:1 MeOH–CH_2Cl_2, 22 °C (32% from **17**). (j) Me_3SiOTf (cat.), MeCN, AW 300 (if any), −40 °C. (k) $CH_3(CH_2{=})COAc$, $TsOH{\cdot}H_2O$, 65 °C (90%).

isopropenyl acetate in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate at 65 °C overnight thus gave the desired 5-*N*-acetylacetamido hemiketal **15** in 66% yield, together with the peracetylated analogue **16** in 19% yield. ^1H NMR analysis of an aliquot of the reaction mixture confirmed that the **15**/**16** ratio formed was 3:1. We also noticed that it was necessary to keep the concentrations of both the hemiketal **7** and the catalyst at a fairly low level (below 0.08 and 0.016 M, respectively) in order to avoid uncontrollable formation of **16**. Careful attempts to selectively remove the anomeric *O*-acetyl group of **16** under acidic conditions (heating in 500:200:1 toluene–acetic acid–water) were unsuccessful and primarily led to N-deacetylation. We therefore concluded that the anomeric (tertiary) hydroxyl group of **7** is indeed very sterically hindered and quite unreactive under the acetylating conditions set forth above. This type of selective acetylation may perhaps be observed in other 3-(*S*)-substituted Neu5Ac derivatives, but this remains to be tested.

Treatment of the 5-*N*-acetylacetamido hemiketal **15** with diethyl phosphorochloridite in the presence of *N*-ethyldiisopropylamine in acetonitrile then gave the corresponding α-phosphite sialyl donor **17** in 85% yield. This compound was very acid-sensitive and required the presence of a base, such as triethylamine, during work-up in order not to hydrolyze into the hemiketal **15**.

Evaluation of the 5-N-*acetylacetamido sialyl donor* **17**.—When the sialyl donor **17** was treated with the galactoside **10** under the same conditions as those used for the sialyl donor **9**, the desired β-sialoside **18** was obtained in about 50% yield. However, ^1H NMR analysis revealed that the product **18** was no more than 80% pure and contaminated inter alia by the corresponding 5-*N*-acetylacetamido glycal **20** (Scheme 4). Since we failed to obtain even a trace of pure **18** by conventional chromatography, the crude product **18** was subjected to deacetylation by treatment with sodium methoxide in dichloromethane–methanol, whereby the deacetylated β-sialoside **19** could be obtained pure in a total yield of 32% (calculated from **17**). In view of this result, it was not surprising that compound **17** was incapable of sialylating the acceptors **11** and **12** in the presence of trimethylsilyl trifluoromethanesulfonate in acetonitrile at −40 °C, but instead provided only the glycal **20** and recovered acceptor as main products. Clearly, the 5-*N*-acetylacetamido group of **17** did not confer any improved sialylating power as compared with donor **9**.

We also prepared the 5-*N*-acetylacetamido glycal **20** in 90% yield directly from the glycal **6** by treating the latter with isopropenyl acetate under standard conditions (Scheme 4).

*General observations regarding the 3-(*S*)-phenylseleno group*.—The main reason for the results above is probably the weak C–Se bond, but we also believe that steric hindrance was of some importance. The latter consideration is supported by the unexpected long-range *J* couplings of 1.0–1.9 Hz observed in the ^1H NMR analysis of the 3-(*S*)-phenylseleno com-

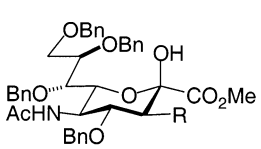
pounds **7**, **9**, **15** and **17** (Table 1). Such long-range *J* couplings have been observed in other carbohydrates,[15] where they are considered indicative of a so-called 'W-conformation', in this case for the atom sequence H-3–C-3–C-2–O–R (R = H or $P(OEt)_2$). We have found no reports in the literature of such long-range *J* couplings in other Neu5Ac hemiketals or phosphites carrying a 3-(*S*)-bromine, iodine, phenylthio (compound **22**) or thiobenzoyloxy (compound **5**) substituent.[5,6b,7d] However, a long-range *J* coupling of 1.5 Hz was reported for the tetra-O-benzylated hemiketal **21**, which carries a 3-(*S*)-phenylseleno substituent.[6b]

These NMR results show that a 3-(*S*)-phenylseleno group confers a fairly rigid 'W-conformation' in Neu5Ac derivatives. The rotation around the C-2–OR bond thus appears to be restricted, probably due to steric interference from the phenylseleno group. For compound **15**, this steric effect may explain the selective N-acetylation of the 5-acetamido group over the anomeric hydroxyl group. It appears likely that the phenylseleno group also sterically disfavors the formation of an α-nitrilium ion in a nitrile solvent,[17] and this would in turn reduce the β-sialylating capability beyond what is expected purely on the basis of the weak C–Se bond.

Table 1
NMR analysis of long-range *J* couplings in 3-(*S*)-SePh substituted Neu5Ac derivatives

Compound	$J_{C\text{-}1,H\text{-}3}$ (Hz) [a]	$J_{H\text{-}3,OH}$ (Hz)	$J_{H\text{-}3,P}$ (Hz)	Configuration [b]
7	2.3 [c]	1.6 [d]	–	α
9	<1.0 [e]	–	1.1 [e]	α
15	1.5 [c]	1.9 [d]	–	α
17	1.5 [e]	–	1.0 [e]	α
21	–	1.5 [d]	–	α

[a] Measured according to Ref. 16.
[b] Anomeric (non-carboxyl) substituent.
[c] In CD_3OD.
[d] In $CDCl_3$.
[e] In C_6D_6.
–: Inaccessible or not measured.



21 R = SePh
22 R = SPh

3. Concluding remarks

In general, reactive acceptors tend to give lower α/β ratios than less reactive acceptors when sialylated with a donor lacking an auxiliary 3-(*S*) group.[18] Hence, in the not too uncommon situation where a reactive acceptor yields an undesired α/β mixture, our donor **9** might provide an alternative due to its convenient preparation, high β-stereoselectivity and easy phenylseleno group removal.

4. Experimental

General methods.—NMR spectra were recorded at 400 or 500 MHz. Assignment of ^{1}H NMR spectra was achieved using 2D methods (COSY, HETCOR). Optical rotations were measured at 22 °C. Chemical shifts are expressed in ppm using residual $CHCl_3$, C_6HD_5 or CHD_2OD as reference. Reactions were monitored by thin-layer chromatography (TLC) using alumina plates coated with Silica Gel 60 F254 (E. Merck) and visualized using either UV light or by charring with H_3PO_4 (aq 5% dip solution). Preparative chromatography was performed with Amicon silica gel (35–70 μm, 60 Å). Tetrahydrofuran (THF) was sonicated and filtered through a column of Al_2O_3 (activity I, E. Merck) immediately before use. Dichloromethane, toluene and $EtN(i\text{-}Pr)_2$ were stored over 4 Å molecular sieves (3 Å for MeCN) and filtered through a column of Al_2O_3 as above. Compounds obtained as white powders were precipitated with *n*-hexane from a ~1:2 chloroform–diethyl ether solution. All reactions were carried out under an Ar atmosphere. Anomeric configurations of Neu5Ac residues were determined in accordance with Ref. 16.

Methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-3,5-dideoxy-3-phenylseleno*-D-erythro-α-L-gluco-*2-nonulopyranosonate* (**7**) *and methyl 5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy-3-phenylseleno*-D-erythro-α-L-manno-*2-nonulopyranosonate* (**8**).—To a stirred, ice-cooled solution of methyl 5-acetamido-

4,7,8,9-tetra-*O*-acetyl-2,3,5-trideoxy-D-*glycero*-D-*galacto*-non-2-enopyranosonate (**6**, 264 mg, 0.558 mmol) in THF (1.40 mL) was added PhSeCl (192 mg, 1.11 mmol) immediately followed by water (22 mg, 1.22 mmol) and AgOTf (257 mg, 1.12 mmol). The reaction mixture was stirred vigorously for an additional 5 min, and then kept dark at 2 °C. After 7 days, Et_3N (0.30 mL) was added under ice-cooling, after which the reaction mixture was filtered (Celite), washed with 1:1 toluene–acetone (4×10 mL) and concentrated. The residue was chromatographed (4:1 → 3:1 toluene–acetone, gradient) to give **7** (185 mg, 51%, pure α) and **8** (127 mg, 35%, α/β ~ 12:1), both as white powders. Data for compound **7**: $[\alpha]_D$ +28° (*c* 0.99, $CHCl_3$). ^1H NMR (CD_3OD): δ 7.56–7.27 (m, 5 H, SePh), 5.41 (dd, 1 H, $J_{4,5}$ 10.2, $J_{3,4}$ 11.1 Hz, H-4), 5.37 (dd, 1 H, $J_{6,7}$ 2.4, $J_{7,8}$ 6.0 Hz, H-7), 5.12 (ddd, 1 H, $J_{8,9A}$ 2.6, $J_{8,9B}$ 6.6 Hz, H-8), 4.41 (dd, 1 H, $J_{9A,9B}$ 12.4 Hz, H-9A), 4.38 (dd, 1 H, $J_{5,6}$ 10.5 Hz, H-6), 4.03 (dd, 1 H, H-9B), 4.01 (bt, 1 H, H-5), 3.79 (s, 3 H, CO_2Me), 3.58 (d, 1 H, H-3), 2.07, 2.05, 1.99, 1.80, 1.75 (s, 3 H each, Ac); ^{13}C NMR (CD_3OD): δ 172.2, 171.4, 170.8, 170.7, 170.6, 168.6 ($J_{C\text{-}1,H\text{-}3}$ 2.3 Hz, C-1), 133.5, 130.5, 129.2, 127.7, 97.8, 74.7, 70.9, 70.3, 68.3, 62.4, 52.6, 50.8, 50.3, 21.6, 19.8, 19.7, 19.6, 19.5. HR FAB-MS for $C_{26}H_{33}NNaO_{13}Se$ [M + Na]: Calcd 670.1017. Found 670.1031.

Data for compound **8**: $[\alpha]_D$ −3.6° (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.87–7.22 (m, 5 H, SePh), 6.19 (d, 1 H, $J_{5,NH}$ 9.3 Hz, NH), 5.57 (dd, 1 H, $J_{3,4}$ 4.1, $J_{4,5}$ 10.3 Hz, H-4), 5.35 (dd, 1 H, $J_{6,7}$ 1.8, $J_{7,8}$ 3.0 Hz, H-7), 5.28 (ddd, 1 H, $J_{8,9A}$ 2.4, $J_{8,9B}$ 8.6 Hz, H-8), 4.95 (dd, 1 H, $J_{9A,9B}$ 12.4 Hz, H-9A), 4.44 (q, 1 H, H-5), 4.35 (dd, 1 H, $J_{5,6}$ 10.7 Hz, H-6), 4.17 (dd, 1 H, H-9B), 3.94 (d, 1 H, H-3), 3.82 (s, 3 H, CO_2Me), 2.24, 2.09, 2.03, 1.93, 1.69 (s, 3 H each, Ac); ^{13}C NMR ($CDCl_3$): δ 172.8, 171.8, 171.0, 170.9, 170.8, 168.8, 134.4, 130.3, 129.5, 128.3, 98.1, 73.8, 72.3, 70.5, 69.5, 63.4, 53.1, 52.1, 47.4, 23.6, 21.6, 21.3, 21.2, 20.7. HR FAB-MS for $C_{26}H_{33}NNaO_{13}Se$ [M + Na]: Calcd 670.1017. Found 670.1034.

Methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-3,5-dideoxy-2*-O-*(diethylphosphite)-3-phenylseleno*-D-erythro-α-L-gluco-*2-nonulopyranosonate* (**9**).—To a stirred, ice-cooled solution of compound **7** (145 mg, 0.224 mmol) in MeCN (0.50 mL) was added $EtN(i\text{-}Pr)_2$ (0.12 mL, 0.70 mmol) followed by dropwise addition of $ClP(OEt)_2$ (0.070 mL, 0.49 mmol). After 4 h, *t*-BuOH (0.035 mL) was added dropwise under ice-cooling, after which the reaction mixture was concentrated.

The residue was chromatographed (6:1 toluene–acetone) on a short column (< 15 cm) to give **9** (152 mg, 88%) as a white powder. $[\alpha]_D$ +22° (*c* 0.98, C_6H_6). ^1H NMR (C_6D_6): δ 7.44–6.83 (m, 5 H, SePh), 5.81 (dd, 1 H, $J_{6,7}$ 2.4, $J_{7,8}$ 3.7 Hz, H-7), 5.75 (t, 1 H, *J* 10.5 Hz, H-4), 5.59 (m, 1 H, H-8), 5.04 (dd, 1 H, $J_{8,9A}$ 2.2, $J_{9A,9B}$ 12.4 Hz, H-9A), 4.84 (dd, 1 H, $J_{5,6}$ 10.7 Hz, H-6), 4.75 (q, 1 H, *J* 10.3 Hz, H-5), 4.60 (d, 1 H, $J_{5,NH}$ 10.2 Hz, NH), 4.38 (dd, 1 H, $J_{8,9B}$ 6.9 Hz, H-9B), 4.31–4.07 (m, 4 H, $2OCH_2CH_3$), 4.00 (dd, 1 H, $J_{3,4}$ 10.9, $J_{3,P}$ 1.1 Hz, H-3), 3.32 (s, 3 H, CO_2Me), 1.92, 1.88, 1.72, 1.55, 1.44 (s, 3 H each, Ac), 1.33 (t, 3 H, *J* 7.1 Hz, OCH_2CH_3), 1.26 (t, 3 H, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (C_6D_6): δ 170.8, 170.4, 170.3, 170.2, 169.6, 167.2 ($J_{C\text{-}1,H\text{-}3} < 1.0$ Hz, C-1), 133.8, 129.5, 128.7, 127.8, 101.6, 74.2, 73.7, 73.5, 68.6, 63.0, 59.9, 59.8, 58.8, 58.7, 53.1, 51.6, 51.0, 22.8, 21.2, 20.8, 20.6, 20.4, 17.4, 17.4, 17.2, 17.2. HR FAB-MS for $C_{30}H_{42}NNaO_{15}PSe$ [M + Na]: Calcd 790.1354. Found 790.1362.

1,2,3,4-Di-O-*isopropylidene-6*-O-*[methyl [5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy-3-phenylseleno*-D-erythro-β-L-gluco-*2-nonulopyranosyl]onate]*-α-D-*galactopyranose* (**13**).—To a mixture of compound **9** (51.8 mg, 0.068 mmol), 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (74.3 mg, 0.285 mmol) and activated AW300 molecular sieves (0.30 g) was added MeCN (0.50 mL), and the mixture was vigorously stirred at rt for 10 min. The temperature was then lowered to −40 °C, and Me_3SiOTf (5.0 μL, 0.027 mmol) was added. After 80 min Et_3N (0.060 mL) was added, after which time the reaction mixture was filtered (Celite), washed with 1:1 $CHCl_3$–acetone (2×10 mL) and concentrated. The residue was chromatographed (4:1 toluene–acetone) to give **13** (46 mg, 76%) as a white powder. $[\alpha]_D$ −16° (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.68–7.24 (m, 5 H, SePh), 5.54 (d,

1 H, $J_{1,2}$ 5.0 Hz, H-1), 5.38 (d, 1 H, $J_{5',NH}$ 9.5 Hz, NH), 5.37–5.31 (m, 2 H, H-4′, H-8), 5.28 (dd, 1 H, $J_{6,7}$ 1.8, $J_{7,8}$ 7.6 Hz, H-7), 4.60 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 7.9 Hz, H-3), 4.31 (dd, 1 H, H-2), 4.27 (dd, 1 H, $J_{8,9A}$ 2.7, $J_{9A,9B}$ 12.5 Hz, H-9A), 4.23 (dd, 1 H, $J_{4,5}$ 1.7 Hz, H-4), 4.20–4.09 (m, 3 H, H-5′, H-6′, H-9B), 4.02 (dd, 1 H, $J_{5,6A}$ 6.2, $J_{6A,6B}$ 9.0 Hz, H-6A), 3.96 (dt, 1 H, H-5), 3.88 (dd, 1 H, $J_{5,6B}$ 5.6 Hz, H-6B), 3.85 (s, 3 H, CO_2Me), 3.25 (d, 1 H, $J_{3',4'}$ 11.4 Hz, H-3′), 2.09, 2.09, 2.04, 2.02, 1.88, 1.51, 1.44, 1.36, 1.33 (s, 3 H each, Ac, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 171.2, 170.7, 170.4, 170.2, 169.8, 168.3 ($J_{C\text{-}1',H\text{-}3'}$ 6.1 Hz, C-1), 134.9, 130.7, 129.2, 128.1, 109.4, 108.7, 101.3, 96.5, 73.5, 72.5, 71.1, 70.9, 70.8, 69.4, 67.5, 67.2, 63.8, 62.3, 52.7, 52.6, 50.3, 26.4, 26.2, 25.2, 24.9, 23.4, 21.1, 21.0, 20.9. HR FAB-MS for $C_{38}H_{51}NNaO_{18}Se$ [M + Na]: Calcd 912.2169. Found 912.2157.

*1,2;3,4-Di-*O*-isopropylidene-6-*O*-[methyl-[5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero-α-*D*-galacto-2-nonulopyranosyl]onate]-α-*D*-galactopyranose* (**14**).—To a stirred solution of compound **13** (45.1 mg, 0.051 mmol) in toluene (1.0 mL) was added AlBN (12.5 mg, 0.076 mmol) and Ph_3SnH (0.13 mL, 0.51 mmol). After refluxing for 1 h, the reaction mixture was allowed to reach rt and then applied directly to a silica gel column and chromatographed (30:1 → 10:1 $CHCl_3$–acetone, gradient) to give **14** (34.0 mg, 92%) as a white powder. The ^1H NMR data were in agreement with those reported.[14]

*Methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-3-phenylseleno-*D*-erythro-α-*L*-gluco-2-nonulopyranosonate* (**15**) *and methyl 2,4,7,8,9-penta-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-3-phenylseleno-*D*-erythro-α-*L*-gluco-2-nonulopyranosonate* (**16**).—To a stirred solution of compound **7** (50.5 mg, 0.078 mmol) in isopropenyl acetate (1.0 mL) was added *p*-TsOH·H_2O (3.0 mg, 0.016 mmol) and the reaction mixture was then stirred at 65 °C. After 14 h Et_3N (0.060 mL) was added and the reaction mixture was concentrated in the presence of toluene. The residue was chromatographed repeatedly (15:1 toluene–acetone) to give **15** (35.5 mg, 66%) and **16** (10.9 mg, 19%), both as white powders. Data for compound **15**: $[\alpha]_D$ + 64° (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.54–7.24 (m, 5 H, SePh), 5.92 (dd, 1 H, $J_{3,4}$ 10.7, $J_{4,5}$ 10.2 Hz, H-4), 5.31–5.26 (m, 2 H, H-6, H-8), 5.11 (dd, 1 H, $J_{6,7}$ 1.7, $J_{7,8}$ 8.1 Hz, H-7), 4.44 (d, 1 H, $J_{OH,3}$ 1.9 Hz, OH-2), 4.33 (t, 1 H, $J_{5,6}$ 10.2 Hz, H-5), 4.18 (dd, 1 H, $J_{8,9A}$ 2.5, $J_{9A,9B}$ 12.5 Hz, H-9A), 4.06 (dd, 1 H, $J_{8,9B}$ 6.0 Hz, H-9B), 3.83 (5, 3 H, CO_2Me), 3.69 (dd, 1 H, H-3), 2.38, 2.28, 2.12, 2.09, 2.02, 1.76 (s, 3 H each, Ac); ^{13}C NMR ($CDCl_3$): δ 174.4, 173.7, 170.9, 170.4, 170.3, 169.9 ($J_{C\text{-}1,H\text{-}3}$ 1.5 Hz, C-1), 168.6, 133.8, 130.1, 129.3, 127.9, 97.2, 72.0, 69.0, 68.1, 67.4, 62.4, 57.7, 53.9, 50.2, 28.3, 26.6, 21.1, 21.1, 21.0, 20.6. HR FAB-MS for $C_{28}H_{35}NNaO_{14}Se$ [M + Na]: Calcd 712.1120. Found 712.1136.

Data for compound **16**: $[\alpha]_D$ + 19° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.56–7.27 (m, 5 H, SePh), 5.94 (dd, 1 H, $J_{4,5}$ 9.8, $J_{3,4}$ 10.7 Hz, H-4), 5.18 (dd, 1 H, $J_{6,7}$ 1.9, $J_{7,8}$ 5.5 Hz, H-7), 5.00 (m, 2 H, H-6, H-8), 4.43 (dd, 1 H, $J_{8,9A}$ 2.6, $J_{9A,9B}$ 12.4 Hz, H-9A), 4.40 (t, 1 H, $J_{5,6}$ 10.0 Hz, H-5), 4.19 (dd, 1 H, $J_{8,9B}$ 6.1 Hz, H-9B), 3.71 (s, 3 H, CO_2Me), 3.35 (d, 1 H, H-3), 2.38, 2.32, 2.21, 2.13, 2.02, 2.01, 1.89 (s, 3 H each, Ac); ^{13}C NMR ($CDCl_3$): δ 174.5, 174.1, 171.0, 170.8, 170.4, 170.3, 168.1, 165.2 ($J_{C\text{-}1,H\text{-}3}$ 1.5 Hz, C-1), 134.6, 129.6, 129.4, 128.5, 100.6, 71.7, 70.7, 70.1, 68.0, 61.9, 57.5, 53.5, 50.8, 28.5, 26.8, 21.4, 21.3, 21.3, 21.2, 20.9. HR FAB-MS for $C_{30}H_{37}NNaO_{15}Se$ [M + Na]: Calcd 754.1225. Found 754.1230.

*Methyl 4,7,8,9-tetra-*O*-acetyl-5-(*N*-acetylacetamido)-3,5-dideoxy-2-*O*-(diethyl phosphite)-3-phenylseleno-*D*-erythro-α-*L*-gluco-2-nonulopyranosonate* (**17**).—To a stirred, ice-cooled solution of compound **15** (38.7 mg, 0.056 mmol) in MeCN (0.80 mL) was added $EtN(i\text{-}Pr)_2$ (0.040 mL, 0.23 mmol) and then $ClP(OEt)_2$ (0.023 mL, 0.16 mmol) dropwise. After 30 min the reaction mixture was allowed to reach rt. After 2.5 h, *t*-BuOH (0.040 mL) was added under ice-cooling, and the reaction mixture was concentrated. The residue was chromatographed (15:1:0.075 toluene–acetone–Et_3N) on a silica gel column, which had been preconditioned with 200:1 toluene–Et_3N, to give **17** (38.6 mg, 85%) as a white powder. $[\alpha]_D$ + 46° (*c* 1.00, C_6H_6). ^1H NMR (C_6D_6): δ 7.47–6.82 (m, 5 H, SePh), 6.49 (t, 1 H, $J_{4,5}$ 10.5 Hz, H-4), 5.97 (dd, 1 H, $J_{6,7}$ 1.7, $J_{5,6}$ 10.2

Hz, H-6), 5.73 (dd, 1 H, $J_{7,8}$ 5.3 Hz, H-7), 5.65 (ddd, 1 H, $J_{8,9A}$ 2.5, $J_{8,9B}$ 6.0 Hz, H-8), 4.92 (t, 1 H, H-5), 4.84 (dd, 1 H, $J_{9A,9B}$ 12.5 Hz, H-9A), 4.57 (m, 1 H, OCH_2CH_3), 4.43 (dd, 1 H, H-9B), 4.43 (m, 1 H, OCH_2CH_3), 4.22 (m, 2 H, OCH_2CH_3), 4.06 (dd, 1 H, $J_{3,P}$ 1.0, $J_{3,4}$ 10.6 Hz, H-3), 3.29 (s, 3 H, CO_2Me), 2.07, 1.91, 1.89, 1.77, 1.68, 1.48 (s, 3 H each, Ac), 1.47 (t, 3 H, J 7.0 Hz, OCH_2CH_3), 1.26 (t, 3 H, J 7.0 Hz, OCH_2CH_3); ^{13}C NMR (C_6D_6): δ 174.2, 173.7, 170.8, 170.4, 170.4, 169.6, 167.7 ($J_{C\text{-}1,H\text{-}3}$ 1.5 Hz, C-1), 134.1, 130.9, 129.6, 128.9, 101.7, 72.6, 72.3, 71.1, 68.7, 62.5, 61.1, 60.9, 58.5, 58.3, 53.2, 53.0, 28.3, 26.7, 21.4, 20.9, 20.8, 20.4, 17.5, 17.5, 17.4, 17.4. HR FAB-MS for $C_{32}H_{44}NNaO_{16}PSe$ [M + Na]: Calcd 832.1461. Found 832.1441.

1,2;3,4-Di-O-*isopropylidene*-*6*-O-*[methyl (4,7,8,9-tetra*-O-*acetyl*-*5*-N-*acetylacetamido*-*3,5-dideoxy*-*3*-*phenylseleno*-D-erythro-*β*-L-gluco-*2*-*nonulopyranosyl)onate]*-α-D-*galacto*-*pyranose* (**18**) *and 1,2;3,4-di*-O-*isopropylidene*-*6*-O-*[methyl (5-acetamido*-*3,5-dideoxy*-*3*-*phenylseleno*-D-erythro-*β*-L-gluco-*2*-*nonulo*-*pyranosyl)onate]*-α-D-*galactopyranose* (**19**).—To a stirred solution of compound **17** (34.9 mg, 0.043 mmol) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (21.5 mg, 0.083 mmol) in MeCN (0.40 mL) at −40 °C was added Me_3SiOTf (3.0 μL, 0.017 mmol). After 40 min *t*-BuOH (0.040 mL) and Et_3N (0.060 mL) were added, and the reaction mixture was concentrated. The residue was chromatographed (15:1 → 8:1 toluene–acetone, gradient) to give crude **18** (22 mg, 50%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 7.73–7.24 (m, 5 H, SePh), 5.92 (t, 1 H, $J_{3',4'} = J_{4',5'}$ 9.6 Hz, H-4′), 5.55 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 5.31 (m, 1 H, H-8), 5.10 (dd, 1 H, $J_{6',7}$ 1.7, $J_{7,8}$ 7.4 Hz, H-7), 5.02 (dd, 1 H, $J_{5',6'}$ 10.2 Hz, H-6′), 4.60 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 7.8 Hz, H-3), 4.32 (dd, 1 H, H-2), 4.15 (dd, 1 H, $J_{8,9B}$ 5.3, $J_{9A,9B}$ 12.5 Hz, H-9B), 3.88 (s, 3 H, CO_2Me), 3.25 (d, 1 H, H-3′), 2.38, 2.27 (s, 3 H each, Ac_2N), 2.11, 2.08, 2.03, 1.96 (s, 3 H each, 4OAc), 1.49, 1.45, 1.35, 1.33 (s, 3 H each, $2C(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 174.6, 173.8, 170.7, 170.2, 170.1, 170.0, 167.4 ($J_{C\text{-}1',H\text{-}3'}$ 5.9 Hz, C-1), 135.0, 131.3, 129.3, 128.1, 109.5, 108.8, 101.2, 96.6, 71.9, 71.4, 70.9, 70.8, 70.0, 69.3, 67.6, 67.4, 64.3, 61.9, 57.5, 53.8, 52.7, 28.2, 26.4, 26.3, 26.2, 25.3, 24.7, 21.2, 21.1, 20.9, 20.8. To crude compound **18** (22 mg) dissolved in 1:1 CH_2Cl_2–MeOH (1.0 mL) was then added 1 M NaOMe in MeOH (0.025 mL, 0.025 mmol) at rt. After 1.5 h AcOH (0.040 mL) was added, and the reaction mixture was concentrated. The residue was chromatographed (10:1 → 5:1 $CHCl_3$–EtOH, gradient) to give **19** (9.9 mg, 32% from **17**) as a white powder. $[\alpha]_D$ −75° (*c* 0.50, CH_3OH). ^{1}H NMR (CD_3OD): δ 7.77–7.23 (m, 5 H, SePh), 5.46 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.58 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 7.9 Hz, H-3), 4.32 (dd, 1 H, H-2), 4.22 (dd, 1 H, $J_{4,5}$ 1.6 Hz, H-4), 4.05 (dd, 1 H, $J_{3',4'}$ 10.5, $J_{4',5'}$ 9.8 Hz, H-4′), 3.99–3.94 (m, 2 H, H-5, H-6A), 3.94 (dd, 1 H, $J_{5',6'}$ 10.7 Hz, H-5′), 3.81 (s, 3 H, CO_2Me), 3.79 (dd, 1 H, $J_{6',7}$ 1.4 Hz, H-6′), 3.79–3.71 (m, 3 H, H-6B, H-8, H-9A), 3.62 (dd, 1 H, $J_{8,9B}$ 5.1, $J_{9A,9B}$ 11.0 Hz, H-9B), 3.45 (dd, 1 H, $J_{7,8}$ 9.1 Hz, H-7), 3.08 (d, 1 H, H-3′), 1.99 (s, 3 H, NAc), 1.46, 1.37, 1.32 (3 s, 12 H, $2C(CH_3)_2$); ^{13}C NMR (CD_3OD): δ 174.9, 169.9, 135.9, 133.1, 130.1, 128.7, 110.5, 110.1, 102.7, 97.9, 74.1, 73.5, 72.6, 72.2, 72.1, 71.8, 70.4, 68.9, 65.2, 64.4, 57.9, 54.2, 52.9, 29.7, 26.7, 26.5, 25.4, 24.9, 22.8. HR FAB-MS for $C_{30}H_{43}NNaO_{14}Se$ [M + Na]: Calcd 744.1746. Found 744.1734.

Methyl 4,7,8,9-tetra-O-*acetyl*-*5*-*(*N-*acetyl*-*acetamido) - 2,3,5 - trideoxy* - D - glycero - D-galacto-*non*-*2*-*enopyranosonate* (**20**).—To a stirred solution of methyl 5-acetamido-4,7,8,9-tetra - *O* - acetyl - 2,3,5 - trideoxy - D - *glycero* - D-*galacto*-non-2-enopyranosonate (**6**, 89.7 mg, 0.189 mmol) in isopropenyl acetate (2.0 mL) was added *p*-$TsOH \cdot H_2O$ (1.8 mg, 0.010 mmol), and the reaction mixture was then stirred at 65 °C. After 16 h, Et_3N (0.10 mL) was added and the reaction mixture was concentrated in the presence of toluene. The residue was chromatographed (15:1 toluene–acetone) to give **20** (88.1 mg, 90%) as a white powder. $[\alpha]_D$ +51° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.08 (dd, 1 H, $J_{3,4}$ 2.8, $J_{4,5}$ 9.3 Hz, H-4), 5.94 (d, 1 H, H-3), 5.35 (ddd, 1 H, $J_{7,8}$ 6.1, $J_{8,9A}$ 2.9, $J_{8,9B}$ 6.3 Hz, H-8), 5.23 (dd, 1 H, $J_{6,7}$ 1.7 Hz, H-7), 5.16 (dd, 1 H, $J_{6,7}$ 1.7, $J_{5,6}$ 10.1 Hz, H-6), 4.56 (t, 1 H, H-5), 4.53 (dd, 1 H, $J_{9A,9B}$ 12.5 Hz, H-9A), 4.18 (dd, 1 H, H-9B), 3.81 (s, 3 H, CO_2Me), 2.39 (bs, 6 H,

Ac_2N), 2.11, 2.07, 2.05, 2.03 (s, 3 H each, 4OAc); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.6, 170.2, 170.0, 161.8, 146.6, 109.2, 76.5, 70.4, 68.0, 67.5, 62.1, 55.3, 52.8, 21.0, 21.0, 21.0, 20.9. HR FAB-MS for $C_{22}H_{29}NNaO_{13}$ [M + Na]: Calcd 538.1537. Found 538.1528.

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