Synthesis of Spirolactonic *C*-Sialosides Induced by Samarium Diiodide

Justine Pezzotta,[a] Dominique Urban,[a] Régis Guillot,[b] Gilles Doisneau,*[a] Jean-Marie Beau*[a,c]

[a] Laboratoire de Synthèse de Biomolécules, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), Université Paris-Sud and CNRS, 91405 Orsay, France
Fax +33(1)69853715; E-mail: gilles.doisneau@u-psud.fr; E-mail: jean-marie.beau@u-psud.fr

[b] Service de Cristallographie, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), Université Paris-Sud and CNRS, 91405 Orsay, France

[c] Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles du CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France
E-mail: jean-marie.beau@cnrs.fr

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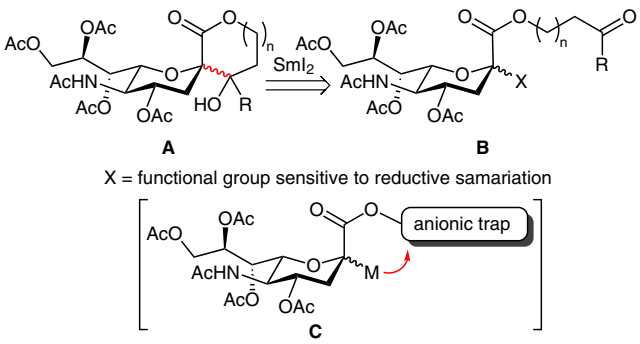
Abstract: A method for the synthesis of spiro-δ-lactonic α-*C*-sialosides by samarium diiodide mediated cyclization reactions of glycosyl 2-pyridylsulfides or acetates with appropriate carbonyl side chains has been developed.

Key words: carbohydrates, chemoselectivity, coupling, cyclization, samarium

N-Acetylneuraminic acid (Neu5Ac) is the most important and widespread member of the sialic acid series, which is part of the large ulosonic acid family. This nine-carbon sugar is mainly found at the terminal position of oligosaccharides and glycoconjugates. As a result of this external position, Neu5Ac is involved in many biological phenomena.[1–3] The α-glycosidic linkage of naturally occurring sialosides is, however, not stable to chemical and enzymatic hydrolytic conditions, making them poor tools for biological research. As a consequence, their C-glycosidic analogues,[4] in which the interglycosidic oxygen is replaced by a carbon atom, are of particular interest as biological tools, and their α-selective preparations have been extensively studied.[4a,b,d,5] High-yielding α-selective nucleophilic C-sialylations are achieved from enolate equivalents, which are conveniently obtained by reductive samariation of thioglycosides,[6,7] or, in a less direct approach, by deprotonation.[8] The simplest reductive procedure in the sialic acid series relies on samarium-mediated Reformatsky coupling reactions using anomeric acetates or 2-thiopyridyl sulfides.[9] Selective electrophilic α-C-sialylations of simple nucleophiles are also now available.[10]

While preparing potential ligands for the influenza surface glycoprotein hemagglutinin, we became interested in the preparation of α-C-glycosyl derivatives of Neu5Ac with spiro structures engaging the carboxylic acid function of the sugar.[11] Although the spirolactonic motif is widespread in many natural products, the stereoselective formation of the quaternary spirocenter remains a challenge.[12] The synthesis of spirolactones derived from carbohydrates has not been extensively reported.[13] They have been prepared as useful intermediates in the synthesis of analogues of C-gangliosides[8] or CMP-Kdo synthetase inhibitors.[14]

We report here an intramolecular Refortmatsky reaction[15,16] that provides spirolactonic α-C-sialosides with complete control of configuration at the quaternary stereogenic center. Intramolecular C-glycosylations promoted by SmI_2 have previously been demonstrated on hexoses glycosyl sulfones by trapping the initial anomeric radical with temporary silicon-tethered alkenes/alkynes, in a 5-*exo* cyclization fashion.[17]



Scheme 1 Target structures **A** and the proposed approach for the SmI_2-induced intramolecular coupling process

We believed that a chemoselective, one-electron reductive transfer from the reagent would operate, with the anomeric substituent X in **B** (OAc, SPy) being reduced first, instead of the carbonyl group. It would eventually lead, through a second electron transfer, to a samarium enolate or its organometallic equivalent **C**, triggering an *exo*-cyclization onto a suitably positioned carbonyl group. As noted earlier,[9] the reducing conditions used should not affect the many other reducible functional groups (ester, N- and O-Ac) present in the substrates.

To study this methodology, a series of Neu5Ac derivatives was prepared with a side chain equipped with an internal anionic trap. We took advantage of the anomeric carboxylic moiety in **1** and **2** to attach several chains with a carbonyl group by standard esterification reactions (Scheme 2). Acetylated carboxylic acid **1** was provided in quantitative yield as the β-anomer almost exclusively

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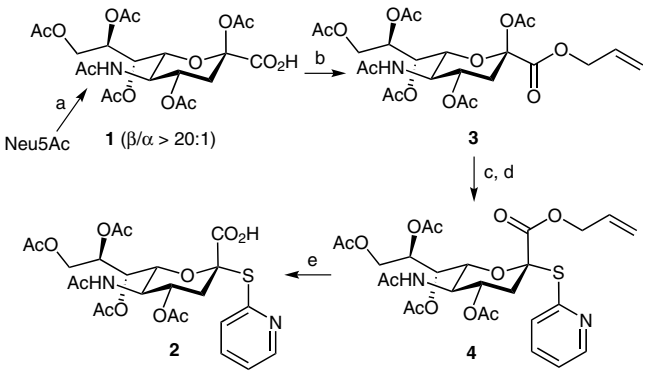
(β/α > 20:1) from commercially available Neu5Ac by using standard acetic anhydride/pyridine conditions.[18] Because we were unable to introduce directly the 2-thiopyridyl group at the anomeric position of carboxylic acid **1**, carboxylic acid **2**[19] was prepared by a four-step protection/deprotection sequence (Scheme 2). Thus, allyl ester formation by treatment of **1** with cesium carbonate and allylbromide in DMF furnished **3**,[20] and anomeric chlorination (AcCl in MeOH–CH_2Cl_2)[21] followed by a nucleophilic substitution with 2-mercaptopyridine[22] provided thioglycoside **4** (66% yield from **3**). Palladium-catalyzed deallylation conducted at room temperature in THF gave the corresponding carboxylic acid **2** in a 90% isolated yield.[23]



Scheme 2 Synthesis of carboxylic acids **1** and **2**. *Reagents and conditions*: (a) Ac_2O in pyridine, quantitative; (b) allylbromide (1.5 equiv), Cs_2CO_3 (1.5 equiv) in DMF, r.t., 5 h, 85%; (c) AcCl, MeOH–CH_2Cl_2 (1:1), r.t., 16 h; (d) 2-PyrSH (3 equiv), NBu_4HSO_3 (1 equiv), EtOAc–$NaHCO_3$ (aq) (1 M), r.t., 4 h, 66%, two steps; (e) morpholine (30 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF, r.t., 1 h; Dowex H^+, CH_2Cl_2, 0.5 h, 90%.

Esterification of the two sialic acid derivatives **1** and **2** with the appropriate keto-alcohols and 1,3-propanediol was best achieved under two different reaction conditions depending on the substrate. The application of either Yamaguchi's conditions[24] (trichlorobenzoylchloride, Et_3N and DMAP in CH_2Cl_2) starting from acid **1**, or conditions involving phosphorylazide activation [diphenylphosphorylazide (DPPA), Et_3N in DMF][25] for acid **2**, were applied with 3–6 equivalents of alcohols **5**–**11** (Table 1). All alcohols were commercially available, except for keto-alcohols **8**–**10**, which were prepared by following a standard synthetic sequence from 1,3-propanediol (monosilylation and PCC oxidation gave the 3-O-silylated propanal, which was treated with the appropriate Grignard reagent). The secondary alcohol thus obtained was oxidized with TEMPO and NaOCl and finally fluoride-mediated deprotection easily furnished the desired functionalized primary alcohols.

Anomeric esters **12**–**19** were provided in moderate to good yields (50–78%) under either Yamagushi's conditions (conditions A; Table 1, entries 1–4) or DPPA (conditions B; Table 1, entries 5 and 6). The DPPA procedure with peracetylated acid **1** was not effective, leading to the anomeric acylazido derivative as the unique product. The mono-ester obtained with 1,3-propanediol (Table 1, entry 6) was directly oxidized, using two equivalents of Dess Martin's periodinane reagent in dichloromethane,[26] to aldehyde **20** in 76% yield.

The reductive samariation of the sialyl esters was conducted at room temperature by using 3.0 equivalents of SmI_2 as a freshly prepared 0.1 M THF solution. We started our study with 2-thiopyridyl glycosides **18** and **19**, which were the most promising substrates for the desired regioselective reductive samariation of the anomeric substituent. Thioglycoside **18**[19] was very reactive and furnished the six-membered ring lactone **21**[19] in an excellent 90% yield (Table 2, entry 1). Lactone **21** was isolated as a 1:1 mixture of isomers, which were difficult to separate by using silica gel column chromatography.[27] The cyclization products showed a standard $_5C^2$-chair conformation, as determined by ^1H NMR analysis [$J_{H3ax–H4}$, $J_{H4–H5}$, and $J_{H5–H6}$ values of 10.7, 10.0, and 10.0 Hz for one isomer (**21R**; first eluted isomer) and 11.4, 10.8 and 10.8 for the other (**21S**; second eluted isomer)]. The equatorial orientation of the newly formed carbon–carbon bond at the anomeric center in both products was determined by the large values of $^3J_{C1–H3ax}$ of 9.5 Hz in **21R** and 10.5 Hz in **21S**.[6b,9a,b] Confirmation of the configuration at the quaternary center in **21S** was provided by a single-crystal X-ray analysis (Figure 1).[28] This also unambiguously established the stereochemistry at C1′ relative to the other asymmetric centers, showing an *S* configuration at this center in **21S**.

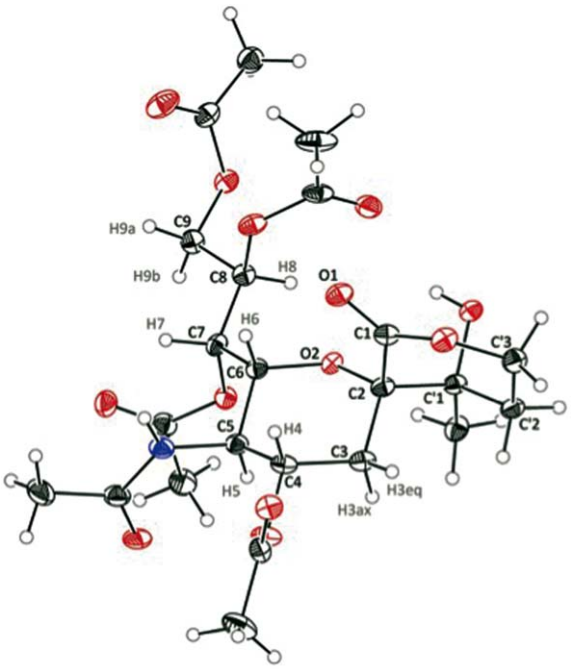
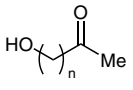
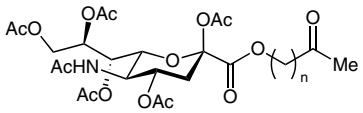
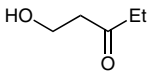
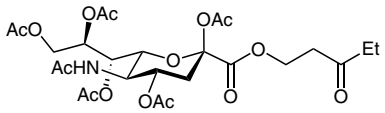
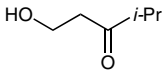
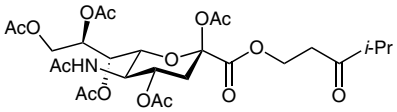
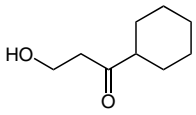
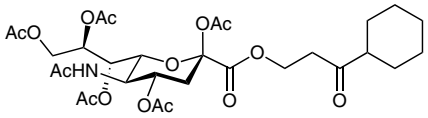
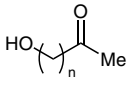
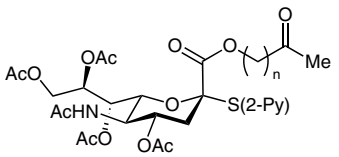
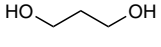
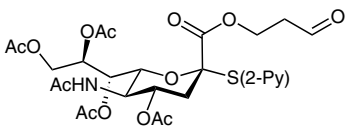


Figure 1 Single-crystal X-ray structure of the peracetylated spiro *C*-sialoside **21S** (ORTEP drawing); ellipsoids are drawn at the 30% probability level

Surprisingly, thiopyridyl glycoside **19**, with an additional methylene group, only provided a complex reaction mixture from which the seven-membered-ring lactone could not be identified. Although the reduction rate (first electron transfer) of an anomeric axial β-acetate was slow compared to that of the 2- thiopyridyl group (2 h versus less than 1 min),[9a,b] regioselective reduction of the β-acetate anomeric substituent **13** also occurred, giving the same spirolactones **21** in 70% yield, also as a 1:1 mixture of isomers (Table 2, entry 3). Treatment of β-acetate **12** or **14** under identical SmI_2 in THF conditions did not give the expected five- or seven-membered lactones **22** or **23** (Table 2, entries 2 or 4). Again, complex mixtures were produced from which no cyclized product could be identified. The reductive cyclization of aldehyde **20**, equipped with the easily reduced thio-pyridyl group, was inefficient for cyclization.[29] In this case, the chemoselectivity of the reduction was lost. Pinacol derivatives were obtained as the only identified products from the crude reaction mixture, arising from electron transfer in the aldehyde first.

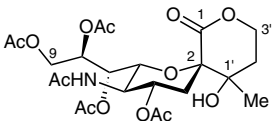
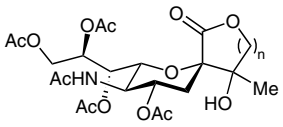
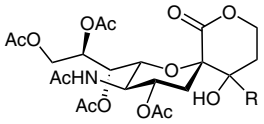
This intramolecular Sm(II) reductive coupling process thus appeared to be selective for the formation of δ-lactones. This was confirmed by treating, under our reductive samariation conditions, anomeric acetates **15**–**17**, which provided the corresponding δ-lactones **24**–**26** in 77–84%

Table 1 Esterification of Acids **1** and **2** with Keto-Alcohols and 1,3-Propanediol

Entry	Alcohol	Ester	Conditions[a]	Yield (%)[b]
				
1	**5** (n = 1) **6** (n = 2) **7** (n = 3)	**12** (n = 1) **13** (n = 2) **14** (n = 3)	A	61 (n = 1) 60 (n = 2) 68 (n = 3)
				
2	**8**	**15**	A	77
				
3	**9**	**16**	A	60
				
4	**10**	**17**	A	50
				
5	**6** (n = 2) **7** (n = 3)	**18** (n = 2) **19** (n = 3)	B	53 (n = 2) 78 (n = 3)
				
6	**11**	**20**[c]	B	72[d]

[a] Conditions A: trichlorobenzoylchloride (1.5 equiv), Et_3N (1.5 equiv), DMAP (0.5 equiv), CH_2Cl_2. Conditions B: diphenylphosphorylazide (DPPA; 1.2 equiv), Et_3N (1.2 equiv), DMF.
[b] Isolated yields after silica gel chromatography.
[c] Compound **20** (76%) was obtained after Dess–Martin oxidation of the mono-ester of 1,3-propanediol (see text).
[d] Isolated yield of the mono-ester of **11**.

Table 2 Synthesis of Spirolactone *C*-Sialosides by Reductive Cyclization[a]

Entry	Substrate	Spiro-*C*-sialoside	Yield (%)[b]
			
1	**18**	**21**[c]	90
	19	–	–
			
2	**12** (n = 1)	**22** (n = 1)	–
3	**13** (n = 2)	**21** (n = 2)	70
4	**14** (n = 3)	**23** (n = 3)	–
			
5	**15**	**24** (R = Et)	77
6	**16**	**25** (R = *i*-Pr)	84
7	**17**	**26** (R = *c*-Hex)	80

[a] Reaction conditions: SmI_2 (3.0 equiv), THF, r.t., 0.5–2 h.
[b] Isolated yield as a 1:1 mixture of diastereomers.
[c] The two diastereomers **21R** (first eluted isomer) and **21S** (second eluted isomer) were separated by silica gel column chromatography.

yields as 1:1 mixtures of stereoisomers (Table 2, entries 5–7).

As previously demonstrated in the intermolecular process, this intramolecular version provides the equatorial ('α' orientation) carbon–carbon bond at the anomeric center with high selectivity with either an α-precursor (2-thiopyridyl glycoside **18**) or a β-substrate (β-anomeric acetates), pointing to a common intermediate. There is, however, no control of the facial attack on the carbonyl, giving rise to δ-lactones **21** and **24**–**26** as 1:1 mixtures of diastereomers. The unsuccessful formation of five- and seven-membered-ring spirolactones might be due to the severe steric constraints in the pre-cyclizing structures of the samarium enolate intermediate. Excellent results were obtained for the formation of six-membered-ring products even starting from the anomeric acetates, which were easily accessible in two steps from commercial Neu5Ac.

In conclusion, the reductive samariation for the intramolecular coupling reaction in the sialic acid series was successfully developed for the α-selective preparation of anomeric δ-spirolactones. Work is in progress to provide more details on this transformation and to extend this procedure to the preparation of more complex cyclic *C*-sialosides, which should be useful for exploring molecular interactions with relevant binding proteins.

Acknowledgment

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(19) **Selected Spectroscopic Data; Acid 2:** ^{1}H NMR ($CDCl_3$, 360 MHz): δ = 8.78 (d, *J* = 5.2 Hz, 1 H, ArH), 7.81 (t, *J* = 7.7 Hz, 1 H, ArH), 7.40 (d, *J* = 7.7 Hz, 1 H, ArH), 7.31 (dd, *J* = 7.7, 5.2 Hz, 1 H, ArH), 6.59 (d, $J_{NH–H5}$ = 10.1 Hz, 1 H, NH), 5.37 (ddd, $J_{H4–H3ax}$ = 10.8 Hz, $J_{H4–H5}$ = 10.1 Hz, $J_{H4–H3eq}$ = 5.4 Hz, 1 H, H-4), 5.34 (dd, $J_{H7–H8}$ = 8.1 Hz, $J_{H7–H6}$ = 1.8 Hz, 1 H, H-7), 5.08 (ddd, $J_{H8–H7}$ = 8.1 Hz, $J_{H8–H9b}$ = 5.5 Hz, $J_{H8–H9a}$ = 2.8 Hz, 1 H, H-8), 4.19 (q, $J_{H5–H6} = J_{H5–H4} = J_{H5–NH}$ = 10.1 Hz, 1 H, H-5), 4.09 (dd, $J_{H9a–H9b}$ = 12.2 Hz, $J_{H9a–H8}$ = 2.8 Hz, 1 H, H-9a), 4.04 (dd, $J_{H6–H5}$ = 10.1 Hz, $J_{H6–H7}$ = 1.8 Hz, 1 H, H-6), 3.89 (dd, $J_{H9b–H9a}$ = 12.2 Hz, $J_{H9b–H8}$ = 5.5 Hz, 1 H, H-9b), 2.88 (dd, $J_{H3eq–H3ax}$ = 12.3 Hz, $J_{H3eq–H4}$ = 5.4 Hz, 1 H, H-3_{eq}), 2.17, 2.10, 2.07 (s, 3 × 3 H, 3OAc), 2.05 (m, 1 H, H-3_{ax}), 2.04 (s, 3 H, OAc), 1.94 (s, 3 H, NHAc). ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 170.9, 170.6, 170.5, 170.4, 169.9, 169.7 (6C, 6CO), 153.7, 147.3, 139.3, 124.6, 121.8 (5C, 5C-Ar), 85.7 (C-2), 74.8 (C-6), 69.9 (C-4), 68.8 (C-8), 66.8 (C-7), 61.6 (C-9), 49.3 (C-5), 37.8 (C-3), 23.1 (NHAc), 20.7–21.0 (4C, 4OAc). HRMS: *m*/*z* calcd for $C_{24}H_{30}N_2NaO_{12}S$: 593.1417; found: 593.1405.
Pyridylsulfide 18: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.46 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1 H, ArH), 7.67 (dt, *J* = 7.8, 1.8 Hz, 1 H, ArH), 7.58 (dt, *J* = 7.8, 0.9 Hz, 1 H, ArH), 7.19 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1 H, ArH), 5.56 (d, $J_{NH–H5}$ = 9.2 Hz, 1 H, NH), 5.32 (dd, $J_{H7–H8}$ = 8.0 Hz, $J_{H7–H6}$ = 1.2 Hz, 1 H, H-7), 5.21 (ddd, $J_{H8–H7}$ = 8.0 Hz, $J_{H8–H9b}$ = 5.2 Hz, $J_{H8–H9a}$ = 2.7 Hz, 1 H, H-8), 4.85 (ddd, $J_{H4–H3ax\ or\ H5}$ = 11.4 Hz, $J_{H4–H5\ or\ H3ax}$ = 10.1 Hz, $J_{H4–H3eq}$ = 4.7 Hz, 1 H, H-4), 4.56–4.50 (m, 1 H, CH_2-O), 4.29 (dd, $J_{H9a–H9b}$ = 12.4 Hz, $J_{H9a–H8}$ = 2.7 Hz, 1 H, H-9a), 4.20–4.05 (m, 4 H, H-9b, H-6, H-5, CH_2-O), 2.90-2.80 (m, 2 H, H-3_{eq}, CH_2), 2.74–2.64 (m, 1 H, CH_2), 2.17, 2.12 (s, 2 × 3 H, 2OAc) 2.07 (m, 1 H, H-3_{ax}), 2.05, 2.02 (s, 2 × 3 H, 2OAc), 2.01 (s, 3 H, Me), 1.98 (s, 3 H, NHAc). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 206.1 (ketone), 170.6, 170.2, 170.0, 167.3 (6C, 6CO), 153.1, 149.7, 137.2, 129.1, 122.8 (5C, 5C-Ar), 86.0 (C-2), 74.6 (C-6), 69.5 (C-4), 69.4 (C-8), 67.5 (C-7), 62.0 (C-9), 60.5 (CH_2), 48.8 (C-5), 41.8 (CH_2), 38.3 (C-3), 30.1 (Me), 23.2 (NHAc), 20.8–21.0 (4C, 4OAc). HRMS: *m*/*z* calcd for $C_{28}H_{36}N_2NaO_{13}S$: 663.1836; found: 663.1857.
Lactones 21: *First eluted isomer* **21R**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.75 (d, $J_{NH–H5}$ = 10.0 Hz, 1 H, NH), 5.62 (ddd, $J_{H4–H3ax}$ = 10.7 Hz, $J_{H4–H5}$ = 10.0 Hz, $J_{H4–H3eq}$ = 5.7 Hz, 1 H, H-4), 5.32 (dd, $J_{H7–H8}$ = 9.6 Hz, $J_{H7–H6}$ = 2.4 Hz, 1 H, H-7), 5.23 (ddd, $J_{H8–H7}$ = 9.6 Hz, $J_{H8–H9b}$ = 5.5 Hz, $J_{H8–H9a}$ = 2.7 Hz, 1 H, H-8), 4.48 (ddd, *J* = 11.2, 10.7, 4.7 Hz, 1 H, CH_2-O), 4.26 (ddd, *J* = 11.2, 6.2, 2.7 Hz, 1 H, CH_2-O), 4.26 (dd, $J_{H9a–H9b}$ = 12.8 Hz, $J_{H9a–H8}$ = 2.7 Hz, 1 H, H-9a), 4.07 (q, $J_{H5–H6} = J_{H5–H4} = J_{H5–NH}$ = 10.0 Hz, 1 H, H-5), 3.97 (dd, $J_{H9b–H9a}$ = 12.8 Hz, $J_{H9b–H8}$ = 5.5 Hz, 1 H, H-9b), 3.95 (dd, $J_{H6–H5}$ = 10.0 Hz, $J_{H6–H7}$ = 2.4 Hz, 1 H, H-6), 2.52 (s, 1 H, OH), 2.44 (ddd, *J* = 14.3, 10.7, 6.2 Hz, 1 H, CH_2), 2.32 (dd, $J_{H3eq–H3ax}$ = 13.6 Hz, $J_{H3eq–H4}$ = 5.7 Hz, 1 H, H-3_{eq}), 2.11, 2.08, 2.03, 2.01 (s, 4 × 3 H, 4OAc), 1.95 (dd, $J_{H3ax–H3eq}$ = 13.6 Hz, $J_{H3ax–H4}$ = 10.7 Hz, 1 H, H-3ax), 1.89 (s, 3 H, NHAc), 1.68 (ddd, *J* = 14.3, 4.7, 2.7 Hz, 1 H, CH_2), 1.42 (s, 3 H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.0, 170.7, 170.6, 170.0, 169.8 (6C, 6CO), 79.7 (C-2), 73.2 (C-OH), 72.7 (C-6), 70.8 (C-4), 68.0 (C-8), 67.0 (C-7), 66.2 (CH_2), 62.3 (C-9), 49.2 (C-5), 32.0 (CH_2), 30.5 (C-3), 23.5 (CH_3), 23.1 (NHAc), 20.7, 20.8, 21.0 (4C, 4OAc). HRMS: *m*/*z* calcd for $C_{23}H_{33}NNaO_{13}$: 554.1850; found: 554.1831.
Second eluted isomer **21S**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.87 (d, $J_{NH–H5}$ = 10.8 Hz, 1 H, NH), 5.40 (ddd, $J_{H8–H7}$ = 9.6 Hz, $J_{H8–H9b}$ = 5.6 Hz, $J_{H8–H9a}$ = 2.4 Hz, 1 H, H-8), 5.34 (dd, $J_{H7–H8}$ = 9.6 Hz, $J_{H7–H6}$ = 2.5 Hz, 1 H, H-7), 5.21 (ddd, $J_{H4–H3ax}$ = 11.6 Hz, $J_{H4–H5}$ = 10.8 Hz, $J_{H4–H3eq}$ = 4.8 Hz, 1 H, H-4), 4.73 (dd, $J_{H6–H5}$ = 10.8 Hz, $J_{H6–H7}$ = 2.5 Hz, 1 H, H-6), 4.56 (ddd, *J* = 11.3, 8.7, 6.0 Hz, 1 H, CH_2-O), 4.27 (ddd, *J* = 11.3, 6.6, 4.5 Hz, 1 H, CH_2-O), 4.23 (dd, $J_{H9a–H9b}$ = 12.4 Hz, $J_{H9a,H8}$ = 2.4 Hz, 1 H, H-9a), 4.12 (q, $J_{H5–H4} = J_{H5,H6} = J_{H5,NHAc}$ = 10.8 Hz, 1 H, H-5), 4.02 (dd, $J_{H9b–H9a}$ = 12.4 Hz, $J_{H9b–H8}$ = 5.6 Hz, 1 H, H-9b), 3.39 (s, 1 H, OH), 2.29 (dd, $J_{H3eq–H3ax}$ = 13.2 Hz, $J_{H3eq–H4}$ = 4.8 Hz, 1 H, H-3_{eq}),

2.15, 2.14 (s, 2 × 3 H, 2OAc), 2.09 (m, 1 H, CH_2), 2.06, 2.01 (s, 2 × 3 H, 2 × OAc), 1.97 (m, 1 H, CH_2), 1.94 (dd, $J_{H3ax–H3eq}$ = 13.2 Hz, $J_{H3ax–H4}$ = 11.6 Hz, 1 H, H-3_{ax}), 1.90 (s, 3 H, NHAc), 1.36 (s, 3 H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.7, 170.8, 170.7, 170.5, 170.4, 170.0 (6C, 6CO), 80.7 (C-2), 73.6 (C-6 or C-OH), 73.4 (C-6 or C-OH), 69.6 (C-4), 67.7 (C-8), 67.2 (C-7), 66.6 (CH_2), 62.8 (C-9), 49.1 (C-5), 32.9 (C-3), 32.7 (CH_2), 23.1 (NHAc), 21.7 (CH_3), 20.7, 20.8, 20.9, 21.0 (4C, 4OAc). HRMS: *m*/*z* calcd for $C_{23}H_{33}NNaO_{13}$: 554.1850; found: 554.1831.

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(27) **Reductive Cyclization of 18; Typical Procedure:** A freshly prepared solution of samarium diiodide (0.1 M in THF, 4.7 mL, 3.0 equiv) was added to sialyl derivative **18** (100 mg, 0.16 mmol) previously dissolved in THF (0.5 mL) under an argon atmosphere. The solution was stirred at r.t. for 2 h. The initial blue color of the mixture then became yellow. The reaction was quenched by the addition of a few drops of a sat. aq NH_4Cl. The aqueous layer was extracted four times with CH_2Cl_2 and the organics layers were combined and washed with sat. aq $NaHCO_3$. The aqueous layers were extracted three times with CH_2Cl_2 and the organic layers were combined, dried under Na_2SO_4, filtered and concentrated under vacuum. The obtained residue was purified by silica gel chromatography (toluene–acetone, 3:1 to 2:1), furnishing the separated two stereoisomers of spirolactones **21** (75 mg total, 0.14 mmol, 90%). Spirolactone **21S** was recrystallized in CH_2Cl_2–Et_2O (mp 207 °C).

(28) The X-ray diffraction data were collected with a Kappa X8 APPEX II Bruker diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). CCDC 959507 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

(29) For the formation of similar spirocyclic six-membered lactones by using a SmI_2-mediated aldol reaction with aldehydes, see: (a) Helm, M. D.; Sucunza, D.; Da Silva, M.; Helliwell, M.; Procter, D. J. *Tetrahedron Lett.* **2009**, *50*, 3224. (b) Helm, M. D.; Da Silva, M.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron* **2009**, *65*, 10816.

