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Highly α-Selective Synthesis of Sialyl Spirohydantoins by Regiospecific Domino Condensation/O→N Acyl Migration/N-Sialylation of Carbodiimides with Peracetylated Sialic Acid

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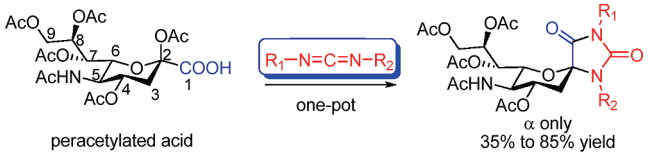

A novel and efficient process for the synthesis of α-sialyl spirohydantoin analogues via one-pot sequential reaction involving various carbodiimides and peracetylated Neu5Ac is reported. $BF_3 \cdot Et_2O$ mediating intramolecular *N*-sialylation with excellent α-selectivity is first demonstrated.

Introduction

Hydantoins (**1**, Figure 1) are an important class of heterocyclic compounds with numerous pharmaceutical applications that have been widely used in biological screenings. These compounds have been used as anticonvulsants,[1] antimuscarinics,[2] anticancers,[3] antivirals,[4] antidiabetics,[5] antiulcers, and antiarrythmics.[6]

The spirohydantoin nucleus incorporated at the anomeric position of the carbohydrates has been reported to show important biological activities. (+)-Hydantocidin (**2**, Figure 1), which includes 1-deoxy-L-ribofuranose with hydantoin scaffold, has potent herbicidal activity and is nontoxic in microorganisms and animals.[7] Glucopyranosylidene-spiro-hydantoin (**3**, Figure 1) was found to be one of the most potent inhibitors of glycogen phosphorylase known to date.[8]

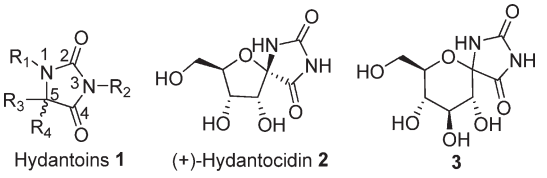

FIGURE 1. The structures of hydantoins and spirohydantoins.

Sialic acids are a family of 9-carbon carboxylated saccharides often found at the nonreducing terminus of glycans and play significant roles in a number of biological processes, including cell−cell recognition, cell-adhesion, and tumor metastasis.[9] *N*-Acetylneuraminic acid (Neu5Ac), a predominant sialic acid, is typically linked α-(2,3) or α-(2,6) to galactoside residues, or polymerized in the form of α-(2,8) or α-(2,9) linkages. Over the years, considerable attention has been paid to the development of methodologies and strategies for the synthesis of sialyl analogues, including *O*-sialosides,[10] *C*-sialosides,[11] and *N*-sialosides.[12] Furthermore, some studies have shown that sialyl nucleotides serve as inhibitors of sialyltransferase.[13] To our knowledge, synthesis

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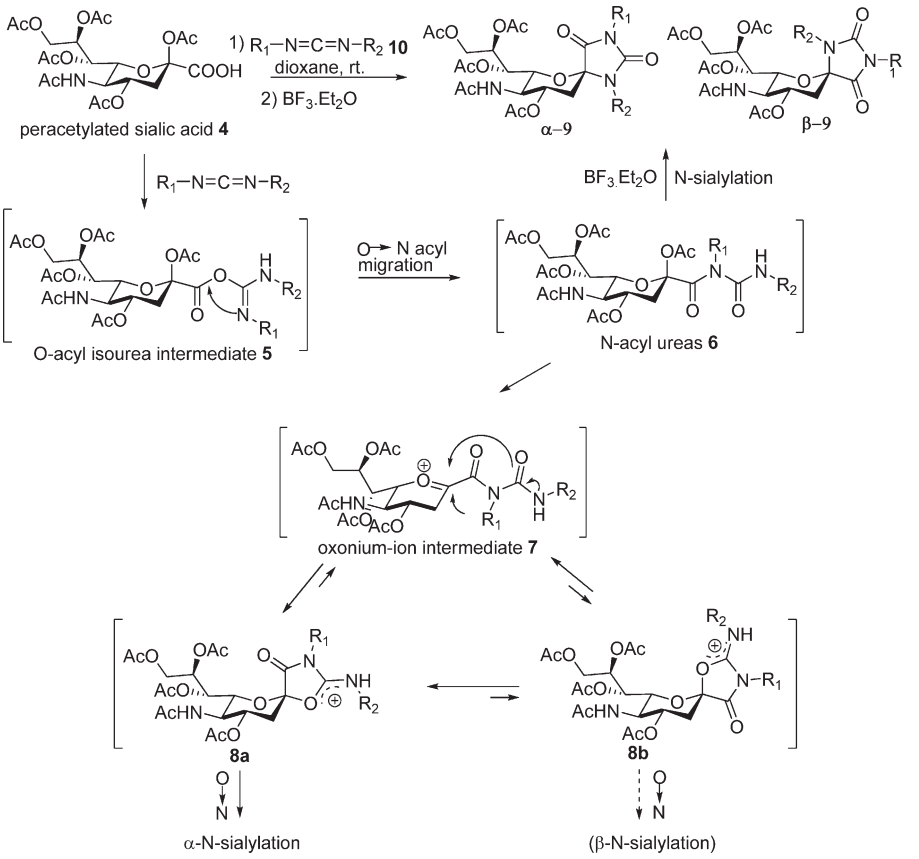
SCHEME 1. Proposed One-Pot Sequential Synthesis of Sialyl Hydantoins



of spirohydantoins based on the sialic acid scaffold has not been reported yet.

We had previously reported an efficient approach for the dehydrative sialylation of various substrates with C-4-aminated sialyl-hemiketal donors based on the reaction of simultaneous stereoselective 2-*O*-deacetylation and 4-amination of peracetylated Neu5Ac.[14] In this study, we report the synthesis of spirohydantoins based on the sialic acid scaffold (sialyl spirohydantoins) by regiospecific one-pot domino condensation/O→N acyl migration/N-sialylation of carbodiimides with peracetylated sialic acid **4**. An attractive feature of this protocol is that high α-selectivity can be achieved via intramolecular *N*-sialylation of the urea group mediated by $BF_3 \cdot Et_2O$. To the best of our knowledge, this is the first report on the synthesis of sialyl spirohydantoins using readily available **4** and carbodiimides as starting materials.

We hypothesized that peracetylated sialic acid **4**, which can be easily synthesized from Neu5Ac, may undergo the following process (Scheme 1), leading to the formation of a wide range of sialyl spirohydantoins. Initially, carbodiimides **10**[15] rapidly react with the peracetylated sialic acid **4** to form *O*-acyl isourea intermediate **5**, which may undergo O→N acyl migration[16] to give *N*-acyl urea **6** in the absence of a nucleophile. Subsequently, the *N*-acyl urea **6** activated by an appropriate Lewis acid in situ would undergo intramolecular N-sialylation to afford the sialyl spirohydantoin. Under Lewis acid mediation, the *N*-acyl urea **6** may generate intermediate **7**, which is likely to be stabilized by the carbonyl group of the urea,[17] followed by the generation of intermediates **8a** and **8b**. In comparison with **8b**, **8a** may proceed smoothly from O- to N- acyl migration[16] due to less steric hindrance of the α face, which would furnish the desired α-sialyl spirohydantoins.

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(12) (a) Llinares, M.; Roy, R. *Chem. Commun.* **1997**, *21*, 2119–2120. (b) Sabesan, S. *Tetrahedron Lett.* **1997**, *38*, 3127–3130. (c) Ogura, H.; Fujita, H.; Furuhata, K.; Itoh, M.; Shitori, Y. *Chem. Pharm. Bull.* **1986**, *34*, 1479–1484.

(13) Kleineidam, R. G.; Schmelter, T.; Schwarz, R. T.; Schauer, R. *Glycoconjugate J.* **1997**, *14*, 57–66.

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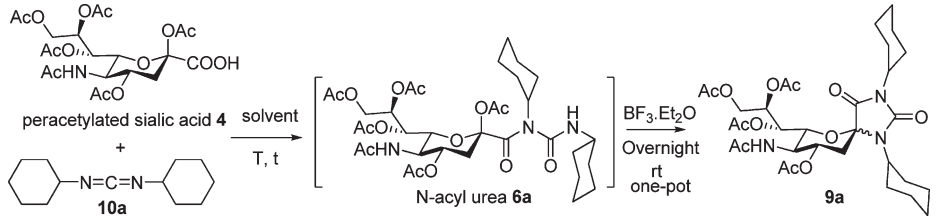
TABLE 1. Optimization of One-Pot Reaction Conditions



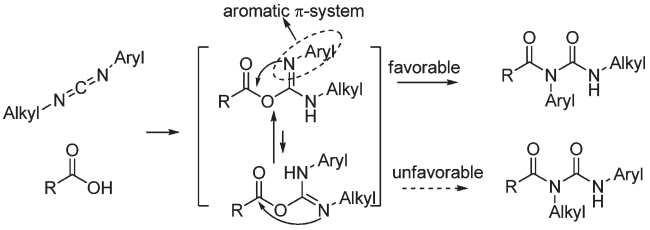
entry	solvent	T (°C)	t (h)	**10a** (equiv)	$BF_3 \cdot Et_2O$ (equiv)	**9a**: % yield[a] (α)[b]
1	dioxane	rt	12	1.1	3	53
2	dioxane	rt	24	1.1	3	66
3	dioxane	rt	48	1.1	3	66
4	CH_3CN	rt	24	1.1	3	16
5	DMF	rt	24	1.1	3	trace
6	CH_2Cl_2	rt	24	1.1	3	29
7	dioxane	rt	24	1.5	3	46
8	dioxane	40	24	1.1	3	60
9	dioxane	rt	24	1.1	2	55

[a]Isolated yields. [b]Determined by LC-MS on the crude reaction mixture and ^{1}H NMR analysis.

Results and Discussion

Initially, we chose *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a model carbodiimide to test the reaction conditions. The critical point in this reaction is the effective formation of intermediate, *N*-acyl urea **6**, as well as the Lewis acid-mediated intramolecular cyclization. As discussed in Scheme 1, direct reaction of **4** with DCC produced *N*-acyl urea **6a**, which was isolated in 85% yield and confirmed by LC-MS and NMR analysis. We observed that the $BF_3 \cdot Et_2O$, an inexpensive and easily available Lewis acid, could effectively catalyze the intramolecular *N*-sialylation of **6a** to afford the desired product **9a** in 78% yield. To avoid isolation of **6a**, we performed the reaction in a one-pot sequential fashion. We started by treating **4** (0.1 mmol) with DCC (0.11 mmol) in dioxane (2 mL) at room temperature for 12 h, followed by the addition of $BF_3 \cdot Et_2O$ (0.3 mmol). After overnight incubation, 53% yield of the desired product **9a** was obtained (entry 1, Table 1). When the reaction time of **4** with DCC was prolonged to 24 h, the yield increased to 66% (entry 2, Table 1). However, the yield did not increase when the reaction time of **4** with DCC was prolonged to 48 h (entry 3, Table 1). It did not work very well when performing the reaction in other solvents, such as CH_2Cl_2, DMF, and CH_3CN, due to inefficient formation of *N*-acyl urea **6a** monitored by thin-layer chromatography (TLC) analysis (entries 4−6, Table 1). The yields were also reduced when the amount of DCC was increased (entry 7, Table 1), or when the reaction temperature of **4** with DCC was increased to 40 °C (entry 8, Table 1). Finally, we found that reducing the amount of $BF_3 \cdot Et_2O$ reduced the yield slightly (55%, entry 9). The anomeric configuration of the α-sialyl hydantoin **9a** was determined by the long-range $J_{C\text{-}5,H\text{-}9ax}$ coupling constant of its hydrolyzed product **11** (see the Supporting Information).[18] By selective gated proton-decoupled ^{13}C NMR experiment, the coupling pattern of C-1 of the α anomer revealed a doublet C-1 signal with a coupling constant of 5.24 Hz, indicative of a (5*R*)-configuration.

SCHEME 2. Proposed Mechanism for the Reaction of Asymmetric *N*-Alkyl-*N*′-arylcarbodiimides with Acid



After determining the optimal conditions, we proceeded to examine the generality of the process. As illustrated in Table 2, we first demonstrated that a wide range of symmetric *N*,*N*′-dialkyl- and *N*,*N*′-diarylcarbodiimides can provide the corresponding sialyl spirohydantoins **9b**−**f** in moderate to good yields and with excellent α-selectivity (entries 1−5, Table 2). The reaction with *N*,*N*′-diisopropylcarbodiimide (DIC) was slower than that with DCC, furnishing the corresponding product **9b** in 35% yield. It is worth noting that a good yield was obtained when the reaction temperature of **4** with DIC was increased to 40 °C (entry 1, Table 2). Compared to symmetric *N*,*N*′-dialkylcarbodiimides, the symmetric *N*,*N*′-diarylcarbodiimides **10c**−**e** with electron-rich and electron-neutral groups (entries 2−4, Table 2) proceeded smoothly (84−85%), presumably due to the efficient O→N acyl migration of electron-rich and electron-neutral *N*,*N*′-diarylcarbodiimides. However, the reaction of *N*,*N*′-diarylcarbodiimide **10f** incorporating an electron-withdrawing group (entry 5, Table 2) was not very satisfactory and the yield was only 40%. It is well-known that the reaction of asymmetric *N*-alkyl-*N*′-arylcarbodiimides with acid will exclusively form the regioisomer of C=N bond migration conjugated with the aromatic π-system (Scheme 2).[16b] Finally, we investigated the sterically congested strongly asymmetric *N*-cyclohexyl-*N*′-arylcarbodiimide **10g**−**i** (entries 6−8, Table 2). As anticipated, compound **4** reacted smoothly with

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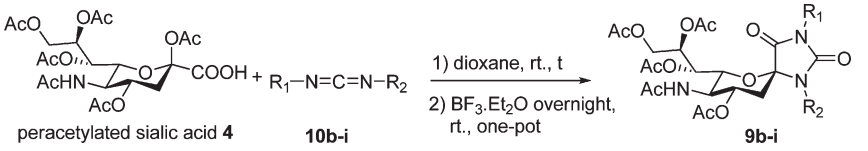
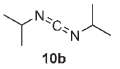
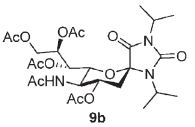
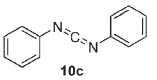
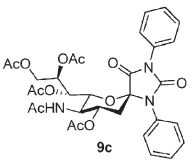
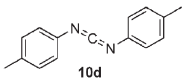
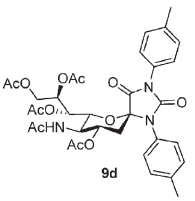
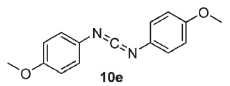
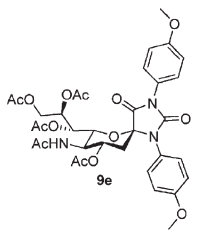
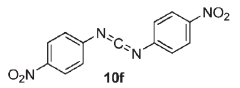
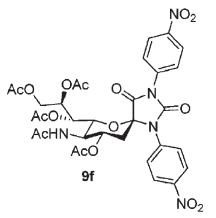
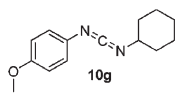
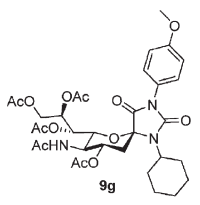
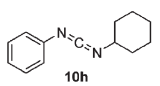
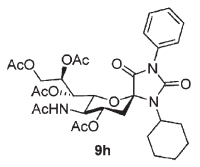
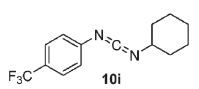
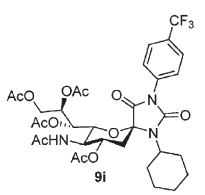
TABLE 2. Synthesis of Various Sialyl Spirohydantoin Analogues



peracetylated sialic acid **4** **10b-i** **9b-i**

Entry	Carbodiimide **10**	t (h)	Product	Product: yield[a] (α) [b]
1	 **10b**	48 30 [c]	 **9b**	35% 59%[c]
2	 **10c**	24	 **9c**	84%
3	 **10d**	24	 **9d**	84%
4	 **10e**	24	 **9e**	85%
5	 **10f**	48	 **9f**	40%
6	 **10g**	8	 **9g**	73%
7	 **10h**	16	 **9h**	70%
8	 **10i**	21	 **9i**	78%

[a]Isolated yields. [b]Determined by LC-MS on the crude reaction mixture and ^{1}H NMR analysis. [c]Reaction at 40 °C.

10g−i affording sialyl spirohydantoins **9g−i** as the single products with good yields (70−78%). It was found that the *N*-acyl urea intermediates while undergoing intramolecular cyclization via $BF_3 \cdot Et_2O$ mediation decomposed to other byproducts.[19]

Conclusion

In conclusion, we have developed a novel and efficient process for the synthesis of sialyl spirohydantoin analogues via one-pot sequential reaction involving carbodiimides and peracetylated Neu5Ac. We have demonstrated that $BF_3 \cdot Et_2O$ mediates intramolecular N-sialylation with excellent α-selectivity. This new synthetic strategy would be a useful tool for the preparation of a variety of biologically important modified Neu5Ac derivatives.

Experiment Section

General Methods. The reagents (chemicals) were purchased from commercial sources, and used without further purification. Carbodiimides (**10c**, **10e**, **10g**, **10h**, **10i**) were prepared according to ref 15. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15−0.2 mm thickness). Compound spots were visualized by UV light (254 nm) and/or by staining with iodine. Column chromatography was performed on silica gel FCP 200−300. Optical rotations were measured on a polarimeter. NMR spectra were run on 300 or 400 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on a spectrometer.

General Experimental Procedure for the Carbodiimides Reacted with Peracetylated Sialic Acid 4. To a stirred solution of peracetylated sialic acid **4** (0.19 mmol) in dioxane (3 mL) was added carbodiimide (1.1 equiv), then the mixture was stirred at room temperature, followed by the addition of $BF_3 \cdot Et_2O$ (3.0 equiv). The resulting solution was stirred overnight and then the saturated sodium bicarbonate solution or water (1 mL) was added. The mixture was extracted with ethyl acetate (EA); the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by silica gel column chromatography (chloroform/acetone, from 15/1 to 10/1) to afford the product.

Typical Procedure for Deprotection of Sialyl Spirohydantoin 9a. To a solution of **9a** (100 mg, 0.15 mmol) in methanol (2 mL) was added a catalytic amount of sodium methoxide. The solution was stirred for 0.5 h at room temperature and then quenched with Dowex 50WX2, 100−200 mesh, ion-exchange resin. The mixture was filtered through Celite and concentrated under reduced pressure to give **11**.

(2*R*,3*S*)-3-(Acetyloxy)-3-[(3*R*,4*R*,6*R*)-4,6-bis(acetyloxy)-6-{[1-cyclohexyl(cyclohexylcarbamoyl)amino]carbonyl}-3-acetamidooxan-2-yl]-2-(prop-1-en-2-yloxy)propyl Acetate, 6a. To a stirred solution of peracetylated sialic acid **4** (100 mg, 0.19 mmol) in dioxane (3 mL) was added *N*,*N*′-dicyclohexylcarbodiimide (43.7 mg, 0.21 mmol). The solution was stirred for 24 h at room temperature, then concentrated under vacuum. The crude was extracted with EA; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by silica gel column chromatography (chloroform/acetone, from 8/1 to 6/1) to afford **6a** in yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 6 Hz 1H), 5.42 (dd, *J* = 2.0, 4.8 Hz, 1H), 5.55−5.31 (m, 1H), 5.26 (dt, *J* = 5.2, 10.8 Hz, 1H), 4.92−4.89 (m, 1H), 4.74 (dd, *J* = 2.0, 12.0 Hz, 1H), 4.19−4.06 (m, 2H), 4.00 (dd, *J* = 2.0, 10.8 Hz, 1H), 3.90 (dd, *J* = 7.2, 12.0 Hz, 1H), 3.72−3.66 (m, 1H), 2.72 (dd, *J* = 10.8, 13.2 Hz, 1H), 2.36 (dd, *J* = 5.2, 13.2 Hz, 1H), 2.24−2.20 (m, 1H), 2.17−2.16 (m, 4H), 2.13 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H), 1.82−1.75 (m, 6H), 1.65−1.49 (m, 4H), 1.33−1.10 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.1, 170.8, 170.2, 170.0, 168.3, 167.3, 153.5, 100.5, 73.4, 71.9, 69.0, 67.4, 63.0, 57.2, 50.6, 48.8, 36.39, 32.2, 31.8, 31.6, 29.6, 26.2, 26.1, 25.5, 25.4, 24.9, 24.5, 23.1, 21.0, 20.8, 20.7, 20.6. MS (ESI, *m*/*z*) 747.9 [M + Na]$^+$. HRMS (ESI) calcd for $C_{34}H_{51}N_3O_{14}Na$ ([M + Na]$^+$) 748.3269, found 748.3267.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1,3-dicyclohexyl-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9a. Method A: To a stirred solution of **6a** (100 mg, 0.14 mmol) in dioxane (3 mL) was added $BF_3{\cdot}Et_2O$ (53 μL, 0.42 mmol). The solution was stirred overnight, and then water (1 mL) was added. The crude was extracted with EA; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by silica gel column chromatography (chloroform/acetone, from 12/1 to10/1) to afford **9a** in 77% yield . **Method B: 9a** was prepared according to the general experimental procedure. $[\alpha]^{18}_D$ +9 (*c* 0.055, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (m, 1H), 5.48 (dt, *J* = 5.2, 11.6 Hz, 1H), 5.28 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.26−5.24 (m, 1H), 4.51 (dd, *J* = 2.0, 10.8 Hz, 1H), 4.24−4.14 (m, 2H), 4.03 (dd, *J* = 6.0, 12.8 Hz, 1H), 3.85 (m, 1H), 3.59 (m, 1H), 2.30 (dd, *J* = 5.2, 13.2 Hz, 1H), 2.18−2.10 (m, 6H), 2.02 (m, 6H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81−1.55 (m, 10H), 1.34−1.10 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 170.3, 170.0, 169.3, 168.9, 141.6, 97.1, 72.3, 68.7, 68.6, 66.9, 62.3, 53.7, 52.9, 48.9, 35.5, 34.0, 33.8, 28.5, 28.2, 25.8, 25.7, 25.1, 24.4, 24.3, 23.1, 20.8, 20.8, 20.7. LC/MS (75% MeOH/25% H_2O), t_R = 10.787 min, MS (ESI, *m*/*z*) 666.3 [M + H]$^+$. HRMS (ESI) calcd for $C_{32}H_{47}N_3O_{12}Na$ ([M + Na]$^+$) 688.3057, found 688.3063.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1,3-diisopropyl-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9b. $[\alpha]^{18}_D$ +7 (*c* 0.18, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52−5.45 (m, 2H), 5.30−5.25 (m, 2H), 4.52 (dd, *J* = 2.0, 10.8 Hz, 1H), 4.30 (quint, *J* = 6.8 Hz, 1H), 4.24−4.17 (m, 2H), 4.04 (dd, *J* = 5.2, 12.8 Hz, 1H), 3.94 (quint, *J* = 6.0 Hz, 1H), 2.32 (dd, *J* = 5.2, 13.2 Hz, 1H), 2.18−2.12 (m, 4H), 2.04−2.03 (m, 6H), 2.01 (s, 3H), 1.91 (s, 3H), 1.42−1.38 (m, 6H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 170.3, 170.0, 169.3, 168.9, 141.9, 97.2, 72.3, 68.6, 68.5, 67.0, 66.9, 62.3, 48.9, 46.3, 45.3, 35.5, 24.1, 23.8, 23.2, 20.8, 20.8, 20.7, 18.9, 18.7. LC/MS (65% MeOH/35% H_2O), t_R = 5.787 min, MS (ESI, *m*/*z*) 586.2 [M + H]$^+$. HRMS (ESI) calcd for $C_{26}H_{39}N_3O_{12}Na$ ([M + Na]$^+$) 608.2431, found 608.2416.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1,3-diphenyl-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9c. $[\alpha]^{18}_D$ −5 (*c* 0.12, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.42 (m, 5H), 7.34−7.30 (m, 2H), 7.13−7.09 (m, 3H), 5.57−5.51 (m, 2H), 5.40−5.35 (m, 1H), 5.29 (dd, *J* = 2.0, 8.8 Hz, 1H), 4.49 (dd, *J* = 2.0, 10.4 Hz, 1H), 4.29−4.21 (m, 2H), 4.03 (dd, *J* = 6.0, 12.4 Hz, 1H), 2.57 (dd, *J* = 5.2, 13.2 Hz, 1H), 2.30 (dd, *J* = 11.6, 13.2 Hz, 1H), 2.15 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.90 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 170.3, 170.0, 169.4, 167.8, 143.8, 143.1, 131.0, 129.1, 128.7, 127.0, 124.5, 123.3, 98.6, 72.4, 68.4, 68.1, 66.6, 62.4, 48.7, 35.1, 23.1, 20.8, 20.7, 20.6. LC/MS (61% MeOH/39% H_2O), t_R = 8.151 min, MS (ESI, *m*/*z*) 654.2 [M + H]$^+$. HRMS (ESI) calcd for $C_{32}H_{35}N_3O_{12}Na$ ([M + Na]$^+$) 676.2118, found 676.2117.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1,3-di-*p*-tolyl-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9d. $[\alpha]^{18}_D$ −14 (*c* 0.11, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H),

(19) See analysis of the crude spectrum section in the Supporting Information.

7.12 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 5.54 (dt, J = 5.1, 11.4 Hz, 1H), 5.39−5.27 (m, 2H), 5.29 (dd, J = 1.8, 8.7 Hz, 1H), 4.49 (dd, J = 1.8, 10.5 Hz, 1H), 4.29−4.18 (m, 2H), 4.03 (dd, J = 6.1, 12.8 Hz, 1H), 2.55 (dd, J = 4.8, 13.2 Hz, 1H), 2.40 (s, 3H), 2.33−2.25 (m, 4H), 2.14 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.3, 170.0, 169.4, 167.9, 143.7, 140.5, 139.1, 134.0, 129.7, 129.2, 128.4, 126.7, 123.2, 98.6, 72.4, 68.5, 68.2, 66.6, 62.4, 48.7, 35.1, 23.1, 21.2, 20.9, 20.8, 20.7, 20.6. LC/MS (60% MeOH/40% H_2O), t_R = 15.706 min, MS (ESI, m/z) 682.2 $[M + H]^+$. HRMS (ESI) calcd for $C_{34}H_{39}N_3O_{12}Na$ ($[M + Na]^+$) 704.2431, found 704.2430.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1,3-bis(4-methoxyphenyl)-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9e. $[\alpha]^{18}_D$ −15 (c 0.15, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.55−5.52 (m, 2H), 5.39−5.35 (m, 1H), 5.28 (dd, J = 2.0, 9.6 Hz, 1H), 4.49 (dd, J = 2.0, 10.4 Hz, 1H), 4.29−4.20 (m, 2H), 4.02 (dd, J = 6.0, 12.4 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.56 (dd, J = 5.2, 13.2 Hz, 1H), 2.31 (t, J = 12.4 Hz, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.3, 170.0, 169.4, 167.9, 159.7, 156.6, 143.4, 136.0, 128.3, 124.8, 123.6, 114.3, 113.8, 98.6, 72.4, 68.6, 68.0, 66.6, 62.4, 55.4, 48.7, 35.2, 23.1, 20.9, 20.8, 20.7, 20.6. LC/MS (65% MeOH/35% H_2O), t_R = 14.219 min, MS (ESI, m/z) 714.1 $[M + H]^+$. HRMS (ESI) calcd for $C_{34}H_{39}N_3O_{14}Na$ ($[M + Na]^+$) 736.2330, found 736.2328.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1,3-bis(4-nitrophenyl)-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9f. $[\alpha]^{18}_D$ −32 (c 0.14, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 9.2 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 9.2 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 5.51 (dt, J = 5.2, 11.2 Hz, 1H), 5.41−5.37 (m, 1H), 5.33−5.26 (m, 2H), 4.43 (dd, J = 2.0, 10.4 Hz, 1H), 4.31−4.21 (m, 2H), 4.00 (dd, J = 6.4, 12.4 Hz, 1H), 2.63 (dd, J = 5.2, 13.2 Hz, 1H), 2.33 (dd, J = 11.6, 13.2 Hz, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.94 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.7, 170.6, 170.0, 169.7, 167.0, 149.0, 147.5, 144.6, 144.5, 136.1, 127.8, 124.7, 124.4, 123.8, 99.1, 72.7, 68.4, 68.0, 66.6, 62.5, 48.7, 34.8, 23.0, 20.7. LC/MS (65% MeOH/35% H_2O), t_R = 7.397 min, MS (ESI, m/z) 684.0 $[M + H]^+$. HRMS (ESI) calcd for $C_{32}H_{33}N_5O_{16}$-Na ($[M + Na]^+$) 766.1820, found 766.1805.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1-cyclohexyl-3-(4-methoxyphenyl)-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9g. $[\alpha]^{18}_D$ +7 (c 0.12, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 5.55−5.52 (m, 2H), 5.38−5.28 (m, 2H), 4.51 (dd, J = 1.8, 10.5 Hz, 1H), 4.33−4.18 (m, 2H), 4.03 (dd, J = 5.4, 12.6 Hz, 1H), 3.82 (s, 3H), 3.68 (br, 1H), 2.50 (dd, J = 4.8, 13.2 Hz, 1H), 2.28 (dd, J = 11.4, 13.2 Hz, 1H), 2.17 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H), 1.78−1.56 (m, 8H), 1.37−1.14 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.3, 170.0, 169.2, 168.1, 159.2, 127.9, 124.0, 114.0, 97.8, 72.3, 68.8, 68.0, 66.6, 62.4, 55.4, 54.2, 48.7, 35.4, 33.9, 33.6, 25.6, 24.7, 24.6, 23.1, 20.8, 20.7, 20.5. LC/MS (65% MeOH/35% H_2O), t_R = 11.381 min, MS (ESI, m/z) 690.0 $[M + H]^+$. HRMS (ESI) calcd for $C_{33}H_{43}N_3O_{13}Na$ ($[M + Na]^+$) 712.2694, found 712.2692.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1-cyclohexyl-3-phenyl-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9h. $[\alpha]^{18}_D$ +14 (c 0.085, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 4H), 7.38−7.34 (m, 1H), 5.59−5.52 (m, 2H), 5.36−5.29 (m, 2H), 4.50 (dd, J = 2.0, 10.4 Hz, 1H), 4.29 (q, J = 10.0, 1H), 4.20 (dd, J = 2.0, 12.4 Hz, 1H), 4.02 (dd, J = 5.2, 12.4 Hz, 1H), 3.69 (m, 1H), 2.52 (dd, J = 5.2, 13.2 Hz, 1H), 2.28 (dd, J = 11.6, 13.2 Hz, 1H), 2.17 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.89 (s, 3H), 1.83−1.57 (m, 8H), 1.37−1.15 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.3, 170.0, 169.2, 167.9, 142.1, 131.4, 128.7, 128.4, 126.5, 97.7, 72.3, 68.7, 68.0, 66.6, 62.4, 54.2, 48.8, 35.4, 33.9, 33.6, 25.6, 24.6, 24.5, 23.1, 20.8, 20.7, 20.4. LC/MS (65% MeOH/35% H_2O), t_R = 11.158 min, MS (ESI, m/z) 660.3 $[M + H]^+$. HRMS (ESI) calcd for $C_{32}H_{41}N_3O_{12}Na$ ($[M + Na]^+$) 682.2588, found 682.2600.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-acetoxy-7-[((1*S*,2*R*)-1,2,3-triacetoxy)propyl]-1-cyclohexyl-3-(4-(trifluoromethyl)phenyl)-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 9i. $[\alpha]^{18}_D$ +30 (c 0.08, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 4H), 5.53 (dt, J = 5.2, 10.4 Hz, 1H), 5.39−5.34 (m, 2H), 5.29 (dd, J = 2.0, 9.2 Hz, 1H), 4.45 (dd, J = 2.0, 10.4 Hz, 1H), 4.30 (q, J = 10.4 Hz, 1H), 4.19 (dd, J = 2.4, 12.4 Hz, 1H), 4.02 (dd, J = 6.0, 12.4 Hz, 1H), 3.71 (m, 1H), 2.53 (dd, J = 5.2, 13.2 Hz, 1H), 2.31 (dd, J = 11.6, 13.2 Hz, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.93 (s, 3H), 1.85−1.58 (m, 8H), 1.41−1.17 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 170.3, 170.0, 169.2, 167.6, 141.5, 134.6, 130.3, 130.0, 126.7, 125.8, 125.0, 122.2, 97.8, 72.4, 68.6, 68.0, 66.6, 62.4, 54.3, 48.7, 35.2, 33.8, 33.5, 25.5, 24.5, 23.1, 20.8, 20.7, 20.4. LC/MS (70% MeOH/30% H_2O), t_R = 17.959 min, MS (ESI, m/z) 728.2 $[M + H]^+$. HRMS (ESI) calcd for $C_{33}H_{40}N_3O_{12}NaF_3$-($[M + Na]^+$) 750.2462, found 750.2469.

(5*R*,7*R*,8*R*,9*S*)-8-Acetamido-9-hydroxy-7-((1*S*,2*R*)-1,2,3-hydroxypropyl)-1,3-dicyclohexyl-6-oxa-1,3-diazaspiro[4.5]decane-2,4-dione, 11. $[\alpha]^{22}_D$ −29.2 (c 0.13, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 4.37 (dt, J = 5.2, 11.2 Hz, 1H), 4.27 (dd, J = 1.6, 10.4 Hz, 1H), 3.92−3.84 (m, 2H), 3.76−3.70 (m, 1H), 3.64−3.56 (m, 3H), 3.47 (d, J = 9.2 Hz, 1H), 2.34 (dd, J = 5.2, 13.2 Hz, 1H), 2.12−2.13 (m, 2H), 2.02 (s, 3H), 1.92 (dd, J = 11.6, 13.2 Hz, 1H), 1.84−1.60 (m, 10H), 1.33−1.16 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 171.1 (C-1, $J_{C\text{-}1,H\text{-}3ax}$ = 5.24 Hz), 146.4, 99.8, 75.2, 71.7, 70.3, 67.8, 65.6, 55.8, 54.7, 54.2, 50.1, 39.7, 35.8, 35.7, 30.1, 29.9, 27.4, 26.8, 26.3, 23.1. MS (ESI, m/z) 496.0 $[M + H]^+$. HRMS (ESI) calcd for $C_{24}H_{39}N_3O_8Na$ ($[M + Na]^+$) 520.2635, found 520.2646.

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Supporting Information Available: Detailed experimental procedures, general method for LC/MS, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra and LC/MS spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.