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Solvent Effect in the Synthesis of Sialosyl α(2–6) Galactosides: Is Acetonitrile the only Choice?

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In spite of notable achievements for the synthesis of α-sialosides that have been made in the past decades, sialylation reactions often require low temperatures (–40 to –78 °C) and the use of acetonitrile as a solvent. Herein we report that a C-5 oxazolidinone sialosyl donor gives high yields and stereoselectivities in the presence of dichloromethane and/or tetrahydrofuran at 0 °C. Surprisingly, high stereoselectivities and yields are obtained even at ambient temperature in tetrahydrofuran.

Introduction

N-Acetylneuraminic acid is the most common member of the sialic acid family, and it is expressed at the terminal position of glycoconjugates, linked to galactose and galactosamine through α(2–3) and α(2–6) glycosidic linkages, as well as α(2–8) and α(2–9) linked dimers. The exposed position of sialic acid in glycoconjugates enables them to a wide variety of biological phenomena, ranging from cell–cell adhesion and mobility, to viral and bacterial infection, and oncogenesis.[1,2] Therefore, sialosides have been important synthetic targets for the design of drugs and vaccines.

In spite of notable achievements in the chemistry of sialic acid that have been made in the past decades, the completely stereoselective synthesis of α-sialosides in high yields with a broad variety of differently functionalized acceptors is still a challenge. This type of glycosylation reactions are often plagued with low yield of the desired α-anomer. Hence, recent strategies have been focusing on minimizing side reactions (hydrolysis and elimination) and emphasizing the α-stereoselectivity. These recent developments include structural modifications at C-1, C-3 and C-5, as well as variation of the leaving group and solvent.[3–5] For the latter, acetonitrile is the most common solvent due to its active participation in the glycosylation reaction.[6,7] These reactions are usually performed at low temperatures (from –40 to –30 °C).

Whereas high stereoselectivity can be often obtained for the synthesis of α(2–3) linkages, glycosylation with primary galactoside acceptors (6-OH) is usually more difficult to stereocontrol. As a result, anomeric mixtures are often obtained in direct sialylations of primary hydroxy groups. Hence, the studies described herein have been focusing on the synthesis of the α(2–6) glycosidic bond with primary galactosyl acceptors. For this purpose we investigated sialylation of the novel sialosyl donor **1a**[8] with simple primary alcohols (**3** and **4**) and differently protected galactosyl C-6 acceptors (**2**, **5** and **6**, Figure 1). These reactions were performed in different solvent systems, and the results obtained were compared with those obtained in acetonitrile-controlled glycosylations[9] and with sialidations of the more traditional sialosyl donors **1b**–**d**.[10–12]

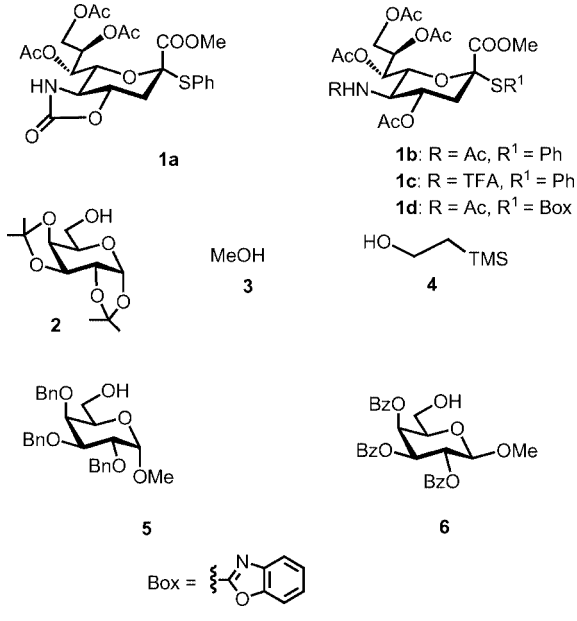

Figure 1. Sialosyl donors **1a**–**d** and glycosyl acceptors **2**–**6**.

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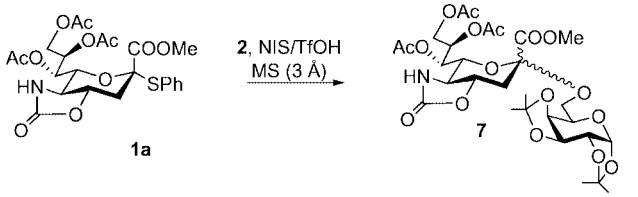
Results and Discussion

To start our investigation, the protected oxazolidinone thioglycoside donor **1a** was coupled with galactosyl acceptor **2** in the presence of NIS/TfOH promotion system using a range of solvents to afford the disaccharide **7** (Table 1). For all experiments, the various solvent systems were taken to the lowest (above freezing) temperature possible, which was maintained unless no reaction occurred, at which point the temperature was increased incrementally. On the basis of previous results reported by Takahashi et al. for the synthesis of α(2–8) and α(2–9) dimers,[13] by our group for the synthesis of α(2–3) and α(2–6) galactosides,[8] and by Crich et al. using its *N*-acetylated version,[14,15] we already know that oxazolidinone-fused rings produce high stereoselectivities and yields in the presence of nitrile solvents and dichloromethane at low temperatures (–40 to –78 °C). After glycosylation, it is possible to open the oxazolidinone ring in basic medium to afford the corresponding free amine[8] or the acetamido functionality from the *N*-acetylated oxazolidinone precursor.[14]

Table 1. Glycosylations of donor **1a** with acceptor **2** in different solvents.



Entry	Solvent system	Temperature	Reaction time	Yield	Ratio (α/β)
1	MeCN	–40 °C	5 min	90%	13:1
2	DCM	–78 °C	5 min	98%	9:1
3	DCM	–40 °C	5 min	99%	7:1
4	DCM/MeCN[a]	–40 °C	5 min	97%	9:1
5	Tol	–60 °C	5 h	87%	3:1
6	Tol/MeCN[a]	–40 °C	5 min	99%	11:1
7	Tol/DCM[a]	–60 °C	1 h	99%	9:1
8	THF	–20→0 °C	16 h	60%	>20:1[b]
9	THF	0 °C	16 h	70%	14:1
10	THF	r.t.	16 h	98%	7:1

[a] 1:1 (v/v) ratio of each solvent. [b] Conservative estimate.

Thus, as expected, we obtained high stereoselectivities and yields when acetonitrile at –40 °C and dichloromethane at –78 °C were used as solvent (α/β = 13:1 and 9:1, Entries 1 and 2, respectively, Table 1). As to reactions in dichloromethane, an increase in the temperature to –40 °C led to a decreased anomeric ratio (7:1, Entry 3). Conversely, no decrease in stereoselectivity was observed when a dichloromethane/acetonitrile (1:1, v/v) mixture was used (α/β = 9:1, Entry 4).

The use of toluene as the reaction solvent resulted in a substantial increase of the reaction time and decrease in the stereoselectivity. As a result, the requisite disaccharide **7** was obtained at –60 °C in 5 h (α/β = 3:1, Entry 5). A toluene/acetonitrile or toluene/dichloromethane (1:1, v/v) mixture resulted in shortening of the reaction time and increasing of the stereoselectivity (Entries 6 and 7). As compared to the result obtained in toluene (Entry 5), it is possible that the improvement observed herein is due to the influence of acetonitrile and dichloromethane (Entries 6 and 7, respectively). Surprisingly, when neat tetrahydrofuran was used as a solvent, the disaccharide **7** was obtained in a remarkable stereoselectivity of (α/β > 20:1, Entry 8).

The lack of elimination side product and the presence of unreacted sialosyl donor **1a** led us to belief that the reaction conditions could be improved to address the relatively modest yield (60%). In fact, THF also proved to be an excellent solvent when the reaction was performed at 0 °C giving rise to disaccharide **7** in an improved yield of 70% and excellent stereoselectivity (α/β = 14:1, Entry 9). When the reaction was performed at room temperature, the disaccharide **7** was obtained in even higher yield (98%), but the anomeric ratio was reduced to α/β = 7:1. Nevertheless, this is still a remarkable result. In fact, to the best of our knowledge, no direct sialidation of thiosialosyl donors has yet been reported to provide α-linked product as the main diastereomer in high yield at room temperature.

On a different note, we observed that all the glycosylations performed in THF appear much slower than those performed in acetonitrile. More importantly, on some occasions, reactions in THF did not go to completion even after 16 h as compared to a typical sialylation in MeCN (Entry 1, Table 1). With the intent of shortening the reaction time, while still maintaining a good control over the stereoselectivity and yield, we investigated a series of sialylations using a mixture of tetrahydrofuran and dichloromethane with the temperature and the solvent ratio being the major variables. These experiments are listed in Table 2.

Table 2. Glycosylations of donor **1a** with acceptor **2** in DCM/THF.

Entry	Solvent system	Temperature	Reaction time	Yield	Ratio (α/β)
1	DCM/THF (1:1)	–40 °C	16 h	89%	>20:1
2	DCM/THF (1:1)	0 °C	3 h	98%	>20:1
3	DCM/THF (3:1)	0 °C	3 h	97%	>20:1
4	DCM/THF (5:1)	0 °C	3 h	98%	>20:1

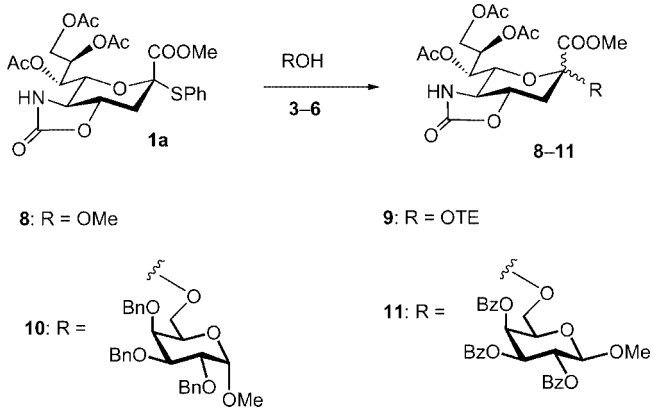
Thus, when the sialylation between sialosyl donor **1a** and galactosyl acceptor **2** was performed in a dichloromethane/tetrahydrofuran (1:1, v/v) mixture at –40 °C, the disaccharide **7** was obtained in high yield (89%) with an α/β anomeric ratio >20:1 (Entry 1, Table 2). In spite of this overall excellent result, the reaction rate was still on the slow side (16 h). When a similar reaction was set at 0 °C, this led to an increase of the yield to 98%, while still allowing for excellent stereoselectivity (α/β > 20:1, Entry 2). As evident from the data presented, this reaction was notably faster (3 h).

No significant changes in yield, stereoselectivity and reaction time were observed with increasing the DCM/THF ratio to 3:1 and 5:1 (Entries 3 and 4, respectively).

To investigate the applicability of this method to other primary glycosyl acceptors, the sialosyl donor **1a** was coupled with the simple alcohols **3** and **4** as well as with differently protected galactoside C-6 acceptors **5** and **6**. In order to generate comprehensive comparison data, these reac-

tions were performed under both traditional reaction conditions (acetonitrile at –40 °C) and the optimized conditions using tetrahydrofuran (neat or as a mixture with dichloromethane) at 0 °C. The results of these experiments are presented in Table 3.

Table 3. Glycosylation of sialosyl donor **1a** with glycosyl acceptors **3**–**6**.



Entry[a]	Solvent system	Temperature	Product	Yield	Ratio (α/β)
1[8]	MeCN	–40 °C	**8**	95%	1.7:1
2	DCM/THF (5:1)	0 °C	**8**	99%	1:1.5
3	THF	0 °C	**8**	83%	3.5:1
4	THF	r.t.	**8**	53%	3:1
5[8]	MeCN	–40 °C	**9**	82%	>20:1
6	DCM/THF (5:1)	0 °C	**9**	85%	>20:1
7[8]	MeCN	–40 °C	**10**	91%	8:1
8	DCM/THF (5:1)	0 °C	**10**	77%	10:1
9	DCM/THF (1:1)	0 °C	**10**	62%	7:1
10	MeCN	–40 °C	**11**	85%	7:1
11	DCM/THF (5:1)	0 °C	**11**	86%	8:1

[a] All reactions were completed within 1–3 h.

As a starting comparison point, methyl sialoside **8** was obtained with an α/β anomeric ratio of 1.7:1 in acetonitrile (Entry 1, Table 3). Whereas a loss of stereoselectivity in a DCM/THF (5:1) mixture was observed, a similar reaction performed in neat THF led to an improved stereoselectivity (compare Entries 2 and 3). In the latter case, the use of THF as the reaction solvent allowed to sufficiently slow down the reaction to achieve a better stereoselectivity control. A similar stereoselectivity, yet reduced yield were observed in reactions at ambient temperature (Entry 4).

For the sialylation of 2-(trimethylsilyl)ethanol (**4**), we observed complete stereoselectivity and nearly identical yields both in acetonitrile at –40 °C and DCM/THF (5:1) at 0 °C (Entries 5 and 6). Encouraged by these results, we performed a series of glycosylations between the sialosyl donor **1a** and the galactosyl acceptors **5** and **6** in tetrahydrofuran/dichloromethane. Results of these couplings were compared with those reported for MeCN.[8] Encouragingly, for both glycosyl acceptors, the sialylation in dichloromethane/tetrahydrofuran (5:1) at 0 °C gave comparable or even superior stereoselectivities than those achieved in acetonitrile at –40 °C. For example, the elaborated reaction conditions allowed to achieve the desired disaccharides **10** and **11** in good yields and stereoselectivities (α/β = 10:1 and 8:1, Entries 8 and 11, respectively).

In order to investigate whether the effect of tetrahydrofuran could be extended to sialidation of common 5-acetamido and 5-(trifluoroacetamido) derivatives, we set out to investigating sialosyl donors **1b–d**. The derivatives **2** and **5** were selected as glycosyl acceptors for these studies, and the reactions were performed in solvent systems involving acetonitrile, dichloromethane, and tetrahydrofuran or mixtures thereof. The results of these extended experiments are summarized in Table 4.

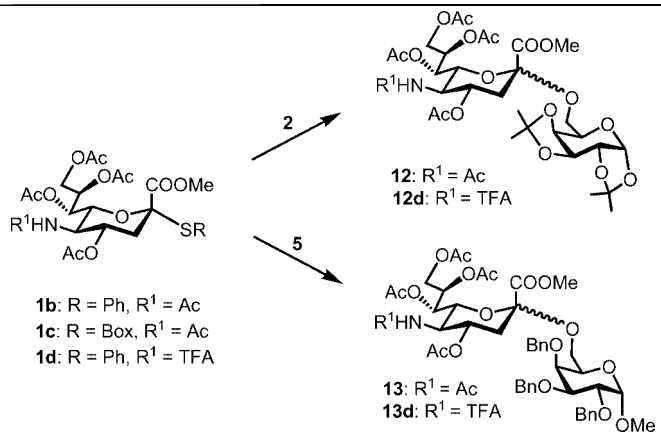
Coupling of **1b**[10] with the isopropylidene acceptor **2** in acetonitrile at –40 °C gave the disaccharide **12** in 65% yield (α/β = 6:1, Entry 1, Table 4). The use of dichloromethane resulted in a significant increase of the yield but a loss of the stereoselectivity. Thus, the disaccharide **12** was isolated in 90% yield as an α/β = 1:1.5 mixture (Entry 2). A similar reaction performed in tetrahydrofuran at ambient temperature did not offer any advantage (Entry 3), yet maintained a good stereocontrol. Shorter reaction time and higher stereoselectivity, however, were observed in the presence of DCM/THF (1:1) at 0 °C. As a result, the disaccharide **12** was obtained in 58% yield as α/β = 5:1 anomeric mixture (Entry 4).

For the coupling of the sialosyl donor **1b** with the acceptor **5** in MeCN, the disaccharide **13** was obtained in 48% yield (α/β = 3:1, Entry 5). The use of DCM/THF system led to an improved yield (76%) of disaccharide **13**, yet slightly decreased stereoselectivity (α/β = 1.5:1, Entry 6). It is noteworthy to mention that both glycosylations went to completion in only 30 min, suggesting that the nature of the glycosyl acceptor is also significant for the glycosylation outcome. Our attempts to increase the stereoselectivity for the synthesis of **13** by slowing the reaction rate by using lower temperatures and/or using neat THF, resulted in sluggish reactions.

The coupling of the *S*-benzoxazolyl (SBox) sialosyl donor **1c**[12] with the glycosyl acceptor **2** in the presence of DCM/THF afforded the disaccharide **12**. The latter was obtained in an excellent yield of 94% and high anomeric ratio (α/β = 4.5:1, Entry 7). This results can serve as an illustrative example of how the approach developed herein can improve previously reported results achieved in MeCN (70%, α/β = 1.6:1).[12]

In addition, we wanted to investigate if the tetrahydrofuran solvent systems could lead to high stereoselectivities of sialylations with the 5-(trifluoroacetamido) sialosyl donor **1d**.[16] Thus, coupling of the sialosyl donor **1d** with the isopropylidene acceptor **2** in tetrahydrofuran at room temperature gave the requisite disaccharide **12d** in 61% yield as an α/β = 6:1 anomeric mixture, (Entry 9, Table 4). A similar coupling in acetonitrile gave the same stereoselectivity but in higher yield (88%, α/β = 6:1).[17] On the other side, coupling of the sialosyl donor **1d** with the glycosyl acceptor **5** gave high yield and stereoselectivity when a DCM/THF (1:1) mixture was used. This allowed us to obtain the disaccharide **13d** in 72% (α/β = 10:1, Entry 12). In this case, a similar glycosylation in acetonitrile gave the disaccharide **13d** in a higher yield (96%), but significantly lower stereoselectivity (α/β = 3:1).[17] From the data sur-

Table 4. Glycosylation of sialosyl donors **1b–d** with acceptors **2** and **5**.



Entry	Donor/Product	Solvent system	Temperature	Yield	Reaction time	Ratio (α/β)
1	**1b**/**12**	MeCN	–40 °C	65%	16 h	6:1
2	**1b**/**12**	DCM	–40 °C	90%	16 h	1:1.5
3	**1b**/**12**	THF	r.t.	52%	24 h	2:1
4	**1b**/**12**	DCM/THF	0 °C	58%	16 h	5:1
5	**1b**/**13**	MeCN	–40 °C	48%	30 min	3:1
6	**1b**/**13**	DCM/THF	0 °C	76%	30 min	1.5:1
7	**1c**/**12**	DCM/THF	0 °C	94%	16 h	4.5:1
8	**1c**/**12**	THF	r.t.	50%	1 h	1.5:1
9	**1d**/**12d**	THF	r.t.	61%	20 h	7:1
10	**1d**/**12d**	DCM	–40 °C	98%	5 min	1:1
11	**1d**/**12d**	DCM/THF	0 °C	65%	16 h	6:1
12	**1d**/**13d**	DCM/THF	0 °C	72%	30 min	10:1

veyed it is evident that also in this case a THF-based solvent systems proved extremely competitive to conventionally used acetonitrile.

Conclusions

We discovered that tetrahydrofuran can be used as advantageous solvent for the chemical sialylation at 0 °C. Used either neat or in a mixture with dichloromethane, it offers in some cases a higher stereoselectivity control in comparison to that of conventionally used acetonitrile at –40 °C. This effect is especially pronounced with 4,5-oxazolidinone or 5-(trifluroracetamido)-protected sialosyl donors. For both classes of glycosyl donors, successful coupling reactions could be performed at ambient temperature, a useful trait that is not common for chemical sialylations. To this end, this observation is the most valuable result that opens new exciting venues for further studies. The beneficial effect of tetrahydrofuran is pronounced for the common 5-acetamido donors; however, a similar outcome to that achieved under conventional reaction conditions could be easily achieved. At this point it is not yet clear whether the effect of tetrahydrofuran is due to its formal participation. As previously proposed for the glycosyl donors of the D-*gluco* series,[18] THF might be actively involved to form an intermediate similar to that obtained with diethyl ether. Additionally, because the longer reaction time required for reactions in THF in comparison to similar reactions in MeCN, the effect of the solvent polarity might have to be brought into consideration. Lower reactivity is also related to the presence of unreacted donors observed in THF reactions en lieu of the elimination product that is often obtained as the major side product in MeCN reactions. Similar glycosylations using diethyl ether as solvent gave high yields, shorter reaction times but decreased stereoselectivities than THF-mediated sialylations, yet maintaining a good stereocontrol towards the α-anomer. Further investigation of the solvent effects, including those of diethyl ether and 1,4-dioxane, and application of the developed methodology to other classes of natural sialosides [e.g. α(2–3)Gal and α(2–6)GalNAc] are currently under investigation.

Experimental Section

General Glycosylation Procedure: A mixture of the sialosyl donor **1** (0.012–0.022 mmol), acceptor **2**/**5**/**6** (0.006–0.011 mmol) or **3**/**4** (0.024–0.044) and activated molecular sieves (3 Å, 30.0–57.0 mg) in the solvent of choice (0.4–0.6 mL) was stirred under argon at –40 °C for 16 h. Then the temperature was adjusted to the desired setting. After stirring for additional 30 min, NIS (0.024–0.044 mmol) and TfOH (0.002–0.004 mmol) were added. The reaction mixture was stirred until TLC indicated that the reaction had gone to completion or no further progress was observed. Then, the reaction mixture was diluted with DCM (5 mL), filtered through Celite, washed with 20% aqueous $Na_2S_2O_3$ (2 mL) and brine (2 mL×2). The organic phase was separated, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by size exclusion column chromatography (Sephadex LH-20; MeOH/CH_2Cl_2, 1:1, v/v elution) to allow the target sialoside.

Methyl (7,8,9-Tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate-(2→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (7): $[\alpha]_D^{26}$ = –19.4 (*c* = 1.1, $CHCl_3$). ^{1}H NMR for **7α**: δ = 1.24, 1.35, 1.44, 1.56 (4 s, 12 H, CCH_3), 2.07, 2.19, 2.21 (3 s, 9 H, $OCOCH_3$), 2.11 (t, 1 H, 3-H′$_{ax}$), 2.91 (dd, $J_{3'eq,3'ax}$ = 12.2, $J_{3'eq,4'}$ = 3.7 Hz, 1 H, 3-H′$_{eq}$), 3.06 (t, $J_{5',6'}$ = 11.2 Hz, 1 H, 5′-H), 3.54 (m, 1 H, 6-H$_b$), 3.79 (s, 3 H, CO_2CH_3), 3.81–4.04 (m, 3 H, 4′,5,6-H$_a$), 4.22–4.40 (m, $J_{6',7'}$ = 2.0 Hz, 5 H, 2,4,6′,9′-H), 4.61 (dd, 1 H, 3-H), 5.13 (dd, $J_{7',8'}$ = 9.5 Hz, 1 H, 7′-H), 5.33 (s, 1 H, NH), 5.50 (dt, $J_{8',9a'}$ = 2.9, $J_{8',9b'}$ = 7.3 Hz, 1 H, 8′-H), 5.53 (d, $J_{1,2}$ = 5.1 Hz, 1 H, 1-H) ppm. ^{13}C NMR: δ = 20.7, 20.8, 20.9, 24.7, 24.9, 26.0, 26.1, 29.7, 37.3, 52.8, 57.9, 61.6, 63.7, 66.4, 67.2, 68.8, 70.6, 73.6, 76.8, 77.2, 96.3, 100.0, 108.5, 109.2, 159.3, 168.3, 169.5, 170.5, 171.5 ppm. HR-FAB MS: calcd. for $C_{29}H_{41}NO_{17}Na$ [M + Na]$^+$ 698.2272, found 698.2253.

Methyl (7,8,9-Tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-2-methoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate (8): $[\alpha]_D^{26}$ = –5.7 (*c* = 0.64, $CHCl_3$). ^{1}H NMR for **8α**: δ = 1.99 (t, 1 H, 3-H$_{ax}$), 2.03–2.19 (m, 9 H, $OCOCH_3$), 2.87 (dd, $J_{3eq,3ax}$ = 12.0, $J_{3eq,4}$ = 3.6 Hz, 1 H, 3-H$_{eq}$), 3.15 (t, $J_{5,6}$ = 10.0 Hz, 1 H, 5-H), 3.34 (s, 3 H, CO_2CH_3), 3.81 (s, 3 H, OCH_3), 3.94 (dt, 1 H, 4-H), 4.27 (dd, $J_{6,7}$ = 1.5 Hz, 1 H, 6-H), 4.30 (s, 2 H, 9-H), 5.14 (dd, $J_{7,8}$ = 9.6 Hz, 1 H, 7-H), 5.38 (s, 1 H, NH), 5.52 (dt, $J_{8,9a}$ = 2.6, $J_{8,9b}$ = 5.3 Hz, 1 H, 8-H) ppm; selected ^{1}H NMR spectroscopic data for **8β**: δ = 1.99 (t, 1 H, 3-H$_{ax}$) 2.03–2.19 (m, 9 H, $OCOCH_3$), 2.63 (dd, 1 H, 3-H$_{eq}$), 3.08 (t, 1 H, 5-H), 3.23 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, OCH_3), 4.27–4.41 (m, 3 H, 6,9-H), 4.61 (dd, 1 H, 4-H), 5.18 (dd, 1 H, 7-H), 5.31–5.43 (m, 2 H, NH, 8-H) ppm. ^{13}C NMR for **8**: δ = 20.6, 20.7, 21.0, 29.6, 52.8, 52.9, 57.9, 61.7, 69.9, 68.8, 73.4, 76.5, 100.3, 159.2, 168.2, 169.8, 170.5, 171.5 ppm. HR-FAB MS: calcd. for $C_{18}H_{25}NO_{12}Na$ [M + Na]$^+$ 470.1274, found 470.1283.

Methyl {7,8,9-Tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-2-[2-(trimethylsilyl)ethoxy]-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside}onate (9): Analytical data for **9α**: $[\alpha]_D^{26}$ = +1.8 (*c* = 0.80, $CHCl_3$). ^{1}H NMR: δ = 0.04 [s, 9 H, $Si(CH_3)_3$], 0.86 (m, 2 H, CH_2TMS), 2.03–2.18 (m, 9 H, $OCOCH_3$), 1.99 (t, 1 H, 3-H$_{ax}$), 2.86 (dd, $J_{3eq,3ax}$ = 13.2, $J_{3eq,4}$ = 3.5 Hz, 1 H, 3-H$_{eq}$), 3.02 (t, $J_{5,6}$ = 10.1 Hz, 1 H, 5-H), 3.30 (m, 1 H, OCH_{2b}), 3.76 (s, 3 H, CO_2CH_3), 3.79–3.96 (m, 2 H, 4-H, OCH_{2a}), 4.22 (dd, $J_{6,7}$ = 1.8 Hz, 1 H, 6-H), 4.27 (m, 2 H, 9-H), 5.09 (dd, $J_{7,8}$ = 7.8 Hz, 1 H, 7-H), 5.31 (s, 1 H, NH), 5.44 (dt, $J_{8,9a}$ = 2.7, $J_{8,9b}$ = 7.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR: δ = –1.5, 17.9, 20.6, 20.8, 21.0, 29.2, 37.7, 52.7, 57.9, 61.7, 63.1, 66.9, 68.8, 73.2, 76.8, 99.9, 159.3, 168.5, 169.6, 170.5, 171.5 ppm. HR-FAB MS: calcd. for $C_{22}H_{35}NO_{12}SiNa$ [M + Na]$^+$ 556.1826, found 556.1809.

Methyl (7,8,9-Tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside)onate-(2→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside) (10): $[\alpha]_D^{26}$ = –3.67 (*c* = 0.52, $CHCl_3$). ^{1}H NMR for **10α**: δ = 1.94 (t, 1 H, 3-H′$_{ax}$), 1.96, 2.08, 2.11 (3 s, 9 H, $OCOCH_3$), 2.78 (dd, $J_{3'eq,3'ax}$ = 12.0, $J_{3'eq,4'}$ = 3.7 Hz, 1 H, 3-H$_{eq}$), 2.95 (t, $J_{5',6'}$ = 10.0 Hz, 1 H, 5′-H), 3.27–3.37 (m, 4 H, 5-H, OCH_3), 3.57 (s, 3 H, CO_2CH_3), 3.68–3.99 (m, 6 H, 2,3,4,4′, 6-H), 4.14 (dd, $J_{6',7'}$ = 2.0 Hz, 1 H, 6′-H), 4.16–4.22 (m, 2 H, 9′-H), 4.60 (d, 1 H, 1-H), 4.57–4.94 (6d, 6 H, CH_2Ph), 5.03 (dd, $J_{7',8'}$ = 9.8 Hz, 1 H, 7′-H), 5.28 (s, 1 H, NH), 5.36 (dt, $J_{8',9'a}$ = 2.7, $J_{8',9'b}$ = 5.1 Hz, 1 H, 8′-H), 7.18–7.34 (m, 15 H, aromatic) ppm. ^{13}C NMR for **10**: δ = 20.6, 20.8, 21.0, 22.7, 29.4, 29.7, 31.9, 47.6, 52.9, 55.4, 57.8, 59.1, 61.6, 67.0, 68.8, 68.9, 73.3, 73.6, 74.4, 74.9, 76.4, 77.2, 78.9, 98.8, 127.4, 127.5, 127.7, 127.9, 128.2, 128.4, 138.5, 138.8, 142.0, 142.2, 142.5, 168.2, 169.5, 170.4, 171.5 ppm. HR-FAB MS: calcd. for $C_{45}H_{53}NO_{17}Na$ [M + Na]$^+$ 902.3211, found 902.3270.

Methyl [7,8,9-Tri-*O*-acetyl-5,4-*N*,*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranoside]onate-(2→6)-(methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside) (11): $[\alpha]_D^{26}$ = +1.9 (*c* = 0.57, $CHCl_3$). ^{1}H NMR for **11α**: δ = 2.01 (t, 1 H, 3′-H$_{ax}$), 2.22, 2.15, 2.07 (3 s, 9 H, $OCOCH_3$), 2.76 (dd, $J_{3'eq,3'ax}$ = 12.62, $J_{3'eq,4'}$ = 3.77 Hz, 1 H, 3-H$_{eq}$), 3.04 (t, $J_{5',6'}$ = 10.36 Hz, 1 H, 5′-H), 3.43 (s, 3 H, OCH_3), 3.60 (s, 3 H, CO_2CH_3), 3.88–3.85 (m, 2 H, 4′-H, 6$_a$), 4.20 (m, 1 H, 5-H), 4.26 (dd, 1 H, 6′-H), 4.35 (m, 2 H, 9′-H), 4.75 (d, *J* = 7.78 Hz, 1 H, 1-H), 5.13 (dd, $J_{7',8'}$ = 9.61 Hz, 1 H, 7′-H), 5.48 (dt, 1 H, 8′-H), 5.61 (dd, 1 H, 3-H), 5.69 (d, 1 H, 2-H), 5.99 (d, *J* = 2.83 Hz, 1 H, 4-H), 7.30–8.10 (m, 15 H, aromatic) ppm. ^{13}C NMR for 11: δ = 14.3, 20.8, 20.9, 21.1, 22.87, 29.5, 29.9, 32.1, 37.6, 53.0, 57.5, 57.9, 62.2, 67.0, 67.8, 68.9, 70.0, 71.9, 72.0, 74.1, 76.6, 76.9, 100.8, 102.5, 128.4, 128.5, 128.7, 129.1, 129.6, 129.7, 129.9, 130.0, 130.1, 133.3, 133.5, 142.1, 142.4, 142.6, 159.4, 165.4, 165.5, 165.7, 169.9, 170.7, 171.8 ppm. HR-FAB MS: calcd. for $C_{45}H_{48}NO_{20}$ [M + H]$^+$ 922.2770, found 922.2845.

Supporting Information (see footnote on the first page of this article): Selected NMR spectra and full characterization data of new compounds.

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