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Note

Anomeric O-acylation of Kdo using alkyl and aryl isocyanates

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Abstract—To develop a convenient method for the preparation of an α-Kdo derivative carrying a functional spacer at the reducing end, we examined anomeric O-acylation using Kdo and halogenated alkyl/aryl isocyanates as nucleophile and electrophiles, respectively. Reaction of a Kdo derivative with 2-chloroethyl isocyanate in the presence of DMAP gave an α-spiro product (82%) and an α-Kdo derivative of a dimeric isocyanate adduct (10%). Similar reaction with 4-(chloromethyl)phenyl isocyanate gave only the corresponding α-spiro product (81%). The NMR data show that the pyranose rings of both the alkyl and aryl spiro products adopt the $^5C_2$ conformation. Thus, we accomplished α-selective anomeric O-acylation by coupling the Kdo derivative with alkyl and aryl isocyanates.

Keywords: Kdo; Glycosylation; Lipooligosaccharide; Lipopolysaccharide

Lipooligosaccharides (LOS) produced by gram-negative bacteria consist of an oligosaccharide (OS) and lipid A, and the reducing end of an intact OS, 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO), is α-linked to lipid A. Several groups have examined the α-selective glycosidation of Kdo to introduce a functional spacer, which can be potentially utilized for further coupling to other macromolecules.[1–6] Up to date, two groups have accomplished the synthesis of an α-Kdo derivative carrying a spacer-arm in high yields.[5–7] However, these methods have not yet been fully developed as a general conjugation method for chemically synthesized OS containing Kdo at the reducing end.

To develop a convenient method for the preparation of an α-Kdo derivative carrying a functional spacer, we examined anomeric O-acylation using Kdo and a halogenated isocyanate as a nucleophile and an electrophile, respectively. Although O-acylation of α-hydroxyesters with alkyl and aryl isocyanates was reported by several investigators, this approach had not yet been applied to carbohydrates containing an α-hydroxyester.[8–11]

We chose a known Kdo derivative, methyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-α-D-*manno*-oct-2-ulosonate **1** for this study, and this starting material was synthesized as follows: acetylation of Kdo ammonium salt, esterification with diazomethane, bromination of the anomeric acetoxy group with titanium bromide,[12] and hydrolysis of the resulting bromide.[13] First, 2-chloroethyl isocyanate was chosen as a model (Scheme 1) and the coupling results in toluene at 50 °C are summarized in Table 1.

No reactions occurred when compound **1** was treated with 2-chloroethyl isocyanate in the presence of pyridine or DMAP as a base at room temperature. However, similar treatments of **1** with the isocyanate using DMAP (0.1–3.0 equiv) at 50 °C gave two products; the major and minor products were determined to be an α-spiro product **3** and an α-KDO derivative of the dimeric isocyanate adduct **4**, respectively, as will be described later. No O-acylation took place in pyridine under the same reaction conditions. The combined yields of **3** and **4** were 92% when **1** was treated with the isocyanate using either 1.0 or 3.0 equiv DMAP, and the reaction using 1.0 equiv of the base yielded the spiro compound **3** in optimal yield (82%). The results demonstrated that anomeric O-acylation using the isocyanate as an electrophile is α-stereospecific.

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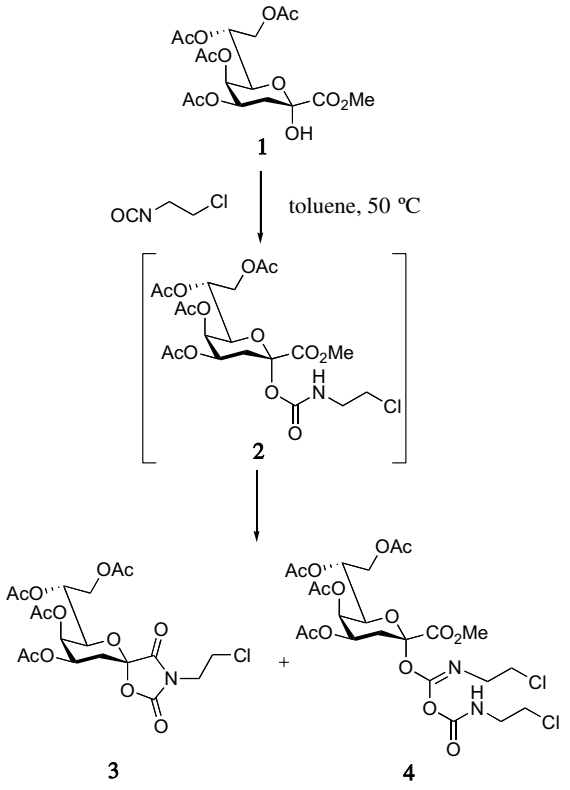


Scheme 1.

Table 1. Reaction of **1** with 2-chloroethyl isocyanate

Entry	Base (equiv)	Yield of **3**[a]	Yield of **4**[a]
1	Pyridine (3.0)	No reaction	
2	DMAP (0.1)	49%	6%
3	DMAP (1.0)	82%	10%
4	DMAP (3.0)	69%	23%

[a] Isolated yield.

The structures of compounds **3** and **4** described as above were determined by 2D NMR spectroscopy (DQF-COSY, HMQC, HMBC). In addition, the assignments of the exocyclic ^{1}H and ^{13}C chemical shifts of both **3** and **4** were confirmed by comparing their NMR data to those of methyl 2,4,5,7,8-penta-*O*-acetyl-α(**5**)- and β(**6**)-D-*manno*-octulosonate (Chart 1). ^{1}H and ^{13}C NMR data of compounds **3**–**6** are shown in Tables 2 and 3, respectively.

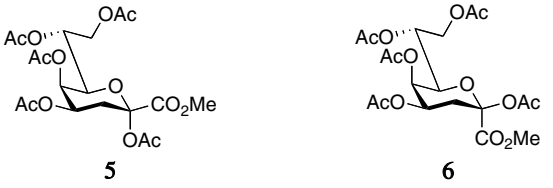


Chart 1. Structures of methyl 2,4,5,7,8-penta-*O*-acetyl-α(**5**)- and β(**6**)-D-*manno*-octulosonates.

Table 2. ^{1}H NMR (500 MHz) data for compounds **1** and **3**–**7**

Compound[a,b]	**1**	**3**	**4**	**5**	**6**	**7**
H-3a	1.91	2.59	2.29	2.22	2.20	2.66
H-3e	2.43	2.01	2.37	2.25	2.40	2.11
H-4	5.35	5.37	5.34	5.32	5.17	5.42
H-5	5.37	5.46	5.43	5.39	5.35	5.49
H-6	4.34	4.37	4.31	4.17	4.62	4.41
H-7	5.15	5.18	5.22	5.22	5.14	5.20
H-8a	4.14	4.28	4.47	4.47	4.20	4.40
H-8b	4.39	4.22	4.16	4.11	4.43	4.24
$^{2}J_{3a,3e}$	12.0	12.0	13.0	12.0	13.0	13.0
$^{3}J_{3a,4}$	12.0	13.0	12.5	13.0	13.0	13.0
$^{3}J_{3e,4}$	4.5	5.0	5.0	5.5	4.5	5.0
$^{4}J_{3e,5}$	0.5	0.5	0.5	0.5	0.5	0.5
$^{3}J_{4,5}$	n.d.[c]	3.0	3.0	3.0	n.d.	3.0
$^{3}J_{5,6}$	n.d.	1.5	1.5	1.5	1.5	n.d.
$^{3}J_{6,7}$	9.5	10.0	9.5	9.5	9.5	8.5
$^{3}J_{7,8a}$	2.0	3.5	3.0	2.0	2.0	3.5
$^{3}J_{7,8b}$	4.5	2.0	2.0	4.0	5.0	2.0
$^{2}J_{8a,8b}$	12.5	12.5	12.5	12.5	12.5	12.5

[a] ^{1}H-Chemical shifts (ppm) in $CDCl_3$ at 25 °C were determined by comparatively analyzing the 2D NMR spectroscopic data (DQF-COSY and HMQC), and the *J* couplings (Hz) were obtained by analyzing either the DQF-cosy or 1D NMR spectra.

[b] The ^{1}H chemical shifts of other protons are listed in the experimental section.

[c] n.d.: not determined.

Table 3. ^{13}C NMR (125 MHz) data for compounds **1** and **3**–**7**

Compound[a,b]	**1**	**3**	**4**	**5**	**6**	**7**
C-1[c]	169.2	166.9	166.0	170.4	168.1	165.8
C-2	95.2	101.9	99.8	97.3	96.5	101.5
C-3	30.6	29.1	31.0	31.0	31.4	29.1
C-4	66.5	66.4	65.7	65.8	66.2	65.4
C-5	64.7	63.8	63.8	63.8	63.9	63.8
C-6	68.4	71.6	70.4	69.6	75.6	71.5
C-7	67.6	67.1	67.2	67.2	67.7	67.3
C-8	62.3	61.7	61.9	62.1	61.8	61.6

[a] ^{13}C-Chemical shifts (ppm) in $CDCl_3$ at 25 °C were determined by comparatively analyzing the 2D NMR data (DQF-COSY, HMQC, and HMBC).

[b] Only the data for the skeletal carbon atoms are presented, and those for other carbon atoms are listed in the experimental section.

[c] The $^{3}J_{C\text{-}1,H\text{-}3a}$ and $^{3}J_{C\text{-}1,H\text{-}3e}$ values of compounds **3**, **4**, and **7** were determined to be <1 Hz by the proton-coupled QUAT experiments.

The spiro-ring system of **3** was determined by confirming that C-1 and the nitrogen atom of the imide are connected (Fig. 1) and that **3** retains the pyranose ring. The presence of two sets of $^{3}J_{C,H}$ cross-relay peaks ascribed to each carbonyl carbon of C-1 (166.9 ppm) and C-imide (152.1 ppm) and the methylene protons of the C$\underline{H_2}$CH$_2$Cl in the HMBC spectrum (Fig. 1), and the absence of a methyl signal due to COOMe in the ^{1}H NMR spectrum confirmed that anomeric O-acylation and subsequent intramolecular nucleophilic cyclization took place to form an oxazolidine-2,4-dione structure.

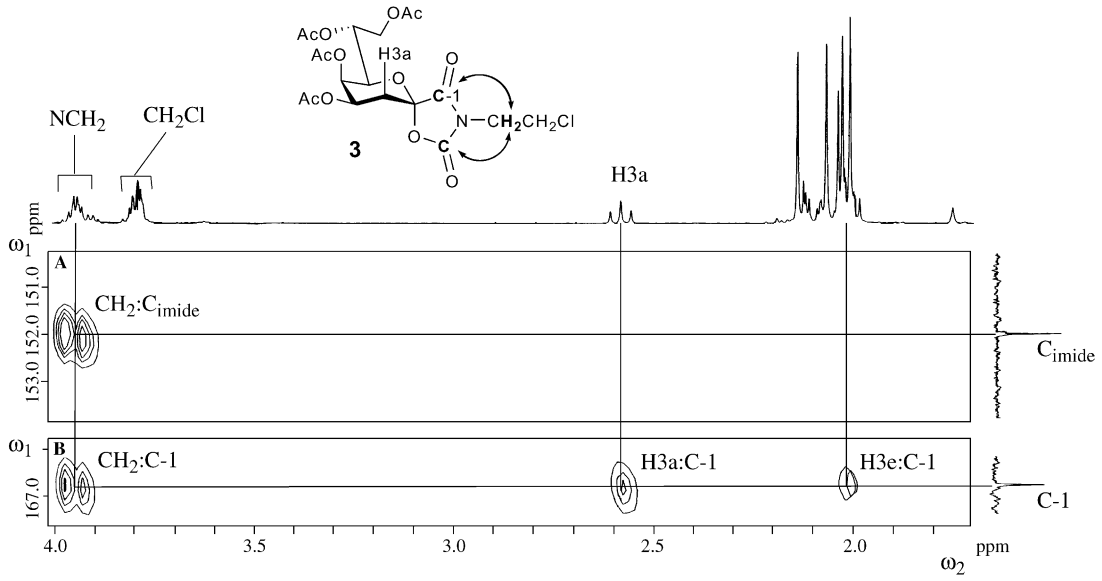


Figure 1. Partial HMBC spectrum of compound **3** in $CDCl_3$ at 25 °C. Only partial $^{13}C/^{1}H$ cross-peaks are labeled.

As Figure 1 also shows, the cross-relay peaks due to C-1 and the C-3 methylene protons (H-3a and H-3e) confirmed that the ^{13}C satellite signal at 166.9 ppm is C-1. In addition to the above HMBC experiment, the assignments of H-3a (2.59 ppm) and H-3e (2.01 ppm) were confirmed by their $^{3}J_{H,H}$ and $^{4}J_{H,H}$ coupling data: $^{3}J_{3a,4}$ (13.0 Hz), $^{3}J_{3e,4}$ (5.0 Hz) and $^{4}J_{3e,5}$ (0.5 Hz) (Table 2). Finally, cross-relay peaks due to $^{3}J_{H\text{-}6,C\text{-}2}$ confirmed the identities of both C-2 and the 2,6-pyranosonate structure of **3**. The quaternary ^{13}C-2 satellite signal at 101.9 ppm was easily distinguished from the two quaternary carbonyl carbons (C-1 and C-imide), and the assignment of H-6 was also confirmed by both DQF-COSY and HMQC experiments. Thus, we determined that **3** has a spiro structure.

The anomeric configuration of **3** was determined to be α from the $^{3}J_{C\text{-}1,H\text{-}3a}$ and $^{3}J_{C\text{-}1,H\text{-}3e}$ values (both <1 Hz) obtained by the proton-coupled QUAT experiment. The $^{3}J_{C\text{-}1,H\text{-}3a}$ value showed that the spatial orientations of the C-3 methylene protons and C-1 are *gauche* but not *anti*,[14] which does not support that **3** is in a β-chair form where the H-3a–C-3–C-2–C-1 torsion angle is ~180° (Chart 2). Neither α- nor β-boat forms are supported by $^{3}J_{C\text{-}1,H\text{-}3e}$, $^{3}J_{3a,4}$, and $^{3}J_{3e,4}$ values obtained

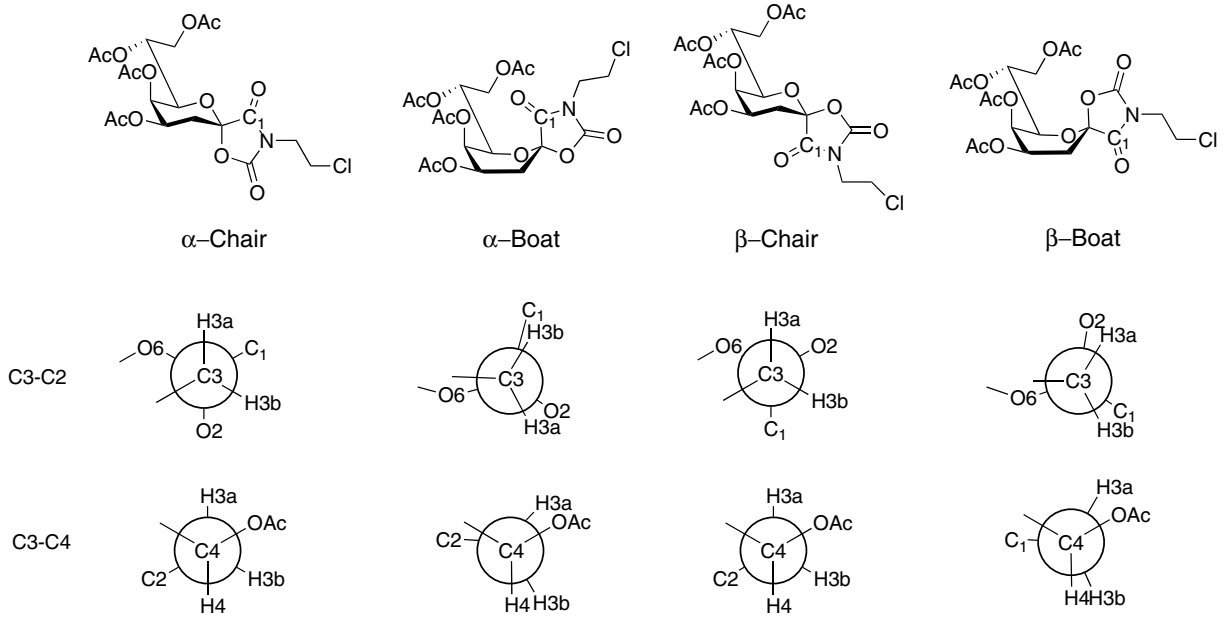


Chart 2. Chair and boat conformations of α- and β-Kdo spiro compounds and Newman projections of each conformer along the C-3–C-2 and C-3–C-4 bonds.

because higher values for both $^{3}J_{C\text{-}1,H\text{-}3e}$ and $^{3}J_{3e,4}$ and a lower value for $^{3}J_{3a,4}$ would be expected if **3** is in either form. Similar considerations preclude that **3** is in a twist- or skew boat conformation. Thus, we determined that the anomeric configuration of **3** is α. In addition to the $^{3}J_{C,H}$ values described above, the $^{3}J_{H,H}$ coupling data (Table 2) showed that the pyranose ring of **3** is in the $^{5}C_{2}$ conformation (Chart 2) as found in the α-Kdo derivative **5**.

In a similar manner, we determined that the minor product is an α Kdo derivative of the dimeric isocyanate adduct **4**. Two sets of $^{3}J_{C,H}$ cross-relay peaks (HMBC experiment), CH_2:C′ and CH_2:C″ (Chart 3), confirmed that O-acylation of the 2-*O*-carbamate **2** but not N-acylation took place to give the dimeric structure **4** (Chart 3 and Scheme 1). The anomeric configuration of **4** was determined to be α based on the $^{3}J_{C\text{-}1,H\text{-}3a}$ and $^{3}J_{C\text{-}1,H-3e}$ values (<1 Hz), and the $J_{H,H}$ data (Table 2) confirmed that **4** adopts the $^{5}C_{2}$ conformation.

We also examined the reaction of **1** with an aryl derivative to extend the utility of isocyanate as an electrophile (Scheme 2). The results using 4-(chloromethyl)phenyl isocyanate are summarized in Table 4, and the products obtained were identified in a similar manner as described earlier for **3** and **4**. Treatment of **1** with the electrophile

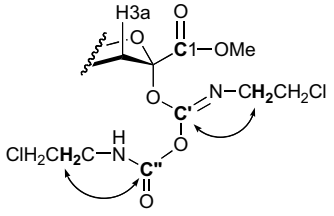
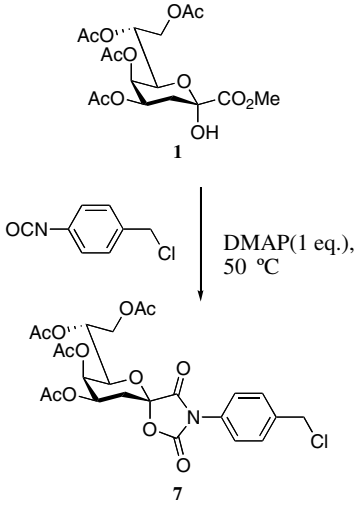


Chart 3. HMBC correlations for compound **4**.



Scheme 2.

Table 4. Reaction of **1** with 4-(chloromethyl)phenyl isocyanate

Solvent	Yield of **7**[a]
Toluene	31%
$ClCH_2CH_2Cl$	44%
THF	81%

[a] Isolated yield.

in toluene or dichloroethane in the presence of DMAP gave the corresponding α-spiro product (31–44%) together with other numerous products that could not be separated by flash chromatography. Speculating that the reaction of DMAP with the halogen function of the 2-*O*-acylated products may have resulted in the formation of by-products, we employed a more polar solvent, THF, instead of toluene or dichloroethane to avoid possible side reactions. Similar treatments of **1** in THF gave the α-spiro product **7** in 81% yield, and a dimeric isocyanate adduct was not detected in the reaction mixture.

The reaction of α-hydroxy esters such as methyl lactate or ethyl butyrate with alkyl isocyanates was studied by Kano et al., who obtained the corresponding oxazolidine-2,4-dione derivatives.[9] Similar oxazolidine derivatives were also synthesized by treating a benzo[α]quinilidine derivative with alkyl and aryl isocyanates in moderate yields.[8] However, the use of isocyanate as an electrophile was not extended to a carbohydrate derivative containing an α-hydroxy ester. This study is the first example of such reaction and showed that oxazolidine derivatives can be prepared in high yield under relatively mild conditions.

Similar to the α-hydroxy esters as described above, the alkyl and aryl oxazolidine-2,4-diones **3** and **7** are presumably produced after the formation of a 2-*O*-carbamate product **2**. In the case of the reaction with the alkyl isocyanate, subsequent intra-nucleophilic cyclization or O-acylation of **2** yields **3** and **4**. Isolation of **3** as a major product suggests that the nucleophilic cyclization reaction is much faster than the O-acylation. This may become more pronounced in the case of reaction with the aryl isocyanate. The aryl spiro product **7** is thermodynamically more stable than the alkyl spiro compound **3** because of its structure in resonance, which could facilitate faster cyclization reaction.

In conclusion, we achieved an α-selective anomeric O-acylation in high yield using Kdo as a nucleophile and halogenated isocyanate derivatives as an electrophile. Treatment of the Kdo derivative **1** with 2-chloroethyl isocyanate in the presence of DMAP gave the α-spiro product **3** (82%) and an α-ketal of the dimeric isocyanate adduct **4** (10%). Only the corresponding α-spiro product **7** was obtained (81%) with 4-(chloromethyl)phenyl isocyanate. The NMR data show that the pyranose rings of both the alkyl and aryl spiro products adopt the $^{5}C_{2}$ conformation.

1. Experimental

1.1. General methods

Optical rotations and melting points (uncorrected) were measured with a HORIBA SEPA-200 polarimeter and a YANAGIMOTO micro melting point apparatus, respectively. All NMR spectra were recorded at 25 °C in $CDCl_3$ using a JEOL JNM-ECP 500 MHz NMR spectrometer equipped with a Silicon Graphics O_2 computer. Chemical shifts are reported in ppm relative to internal Me_4Si (δ_H 0.00) for ^1H NMR and $CDCl_3$ (δ_C 77.00) for ^{13}C NMR. 2D NMR data (DQF-COSY, HMQC and HMBC) were processed using a Delta program (JEOL USA. Inc.) in a similar manner as described previously.[15–17] High resolution electrospray ionization mass spectrometry (HRESIMS) was carried out in the positive ion mode using a JEOL JMS-T100LC.[16,17] Silica Gel 60 F_{254} (E. Merck) was used for thin-layer chromatography (TLC), and compounds were detected under UV light (254 nm) or by spraying with 10% conc. H_2SO_4 in MeOH and then heating the plates at 120 °C for 5 min. All the reactions were carried out under argon using dry solvents. We prepared starting compound **1** from the Kdo ammonium salt by using the methods of Paulsen et al.[12] and Kiso et al.[13]

1.2. (1*S*)-3,4,6,7-Tetra-*O*-acetyl-3′-(2-chloroethyl)spiro-[1,5-anhydro-2-deoxy-D-*manno*-heptitol-1,5′-[1,3]oxazolidine-2′,4′-dione] (3) and methyl 4,5,7,8-tetra-*O*-acetyl-2-[2′-aza-4′-chloro-1′-[N-(2″-chloroethyl)carbamoyloxy]-but-1′-enyloxy]-3-deoxy-α-D-*manno*-octulosonate (4)

Typical procedure: To a soln of methyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-D-*manno*-2-octulosonate **1** (105 mg, 0.25 mmol) and *N*,*N*-dimethylaminopyridine (DMAP) (30 mg, 0.25 mmol) in toluene (2.6 mL) was added a soln of 2-chloroethyl isocyanate (64 μL, 0.75 mmol) in toluene (1.0 mL) at room temperature. After stirring for 15 h at 50 °C, the mixture was diluted with EtOAc (10 mL) and satd $NaHCO_3$ (10 mL). The aq layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated under diminished pressure. The residue was purified by flash column chromatography (5:1 CH_2Cl_2–Et_2O) to give **3** (108 mg, 82%) as a colorless syrup and **4** as a pale yellow syrup (16 mg, 10%). Compound **3**: $[\alpha]_D^{20}$ +34 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$; data for the ring and the exocyclic protons are shown in Table 2) δ: 3.94–3.97 (m, 2H, –C*H*$_2$CH$_2$Cl), 3.77–3.83 (m, 2H, –CH$_2$C*H*$_2$Cl), 2.14 (s, 3H, COC*H*$_3$), 2.07 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$). ^{13}C NMR ($CDCl_3$; data for the skeletal carbon atoms are shown in Table 3) δ: 170.8, 170.2, 169.66, 169.65, (4 × *C*OCH$_3$), 152.1 (O*C*ON), 41.7 (–*C*H$_2$CH$_2$Cl), 39.5 (–CH$_2$*C*H$_2$Cl), 20.5 (CO*C*H$_3$). HRESIMS: [M+Na$^+$] calcd for $C_{19}H_{24}ClNNaO_{12}$: 516.0885, found 516.0908. Compound **4**: $[\alpha]_D^{20}$ +38 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$; data for the ring and the exocyclic protons are shown in Table 2) δ: 4.18–4.22 (m, 2H, –NHC*H*$_2$CH$_2$Cl), 3.85 (s, 3H, COOCH$_3$), 3.73–3.85 (m, 4H, =NC*H*$_2$C*H*$_2$Cl), 3.60–3.65 (m, 2H, –NHCH$_2$C*H*$_2$Cl), 2.11 (s, 3H, COC*H*$_3$), 2.02 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$), 2.00 (s, 3H, COC*H*$_3$). ^{13}C NMR ($CDCl_3$; data for the skeletal carbon atoms are shown in Table 3) δ: 170.3, 170.2, 169.7, 169.6, (4 × *C*OCH$_3$), 153.3 (O*C*ON), 153.0 (O*C*ON), 46.0 (–*C*H$_2$CH$_2$Cl), 42.6 (–*C*H$_2$CH$_2$Cl), 42.8 (–CH$_2$*C*H$_2$Cl), 42.1 (–CH$_2$*C*H$_2$Cl), 31.0 (COO*C*H$_3$), 20.6 (4 × CO*C*H$_3$). HRESIMS: [M+Na$^+$] calcd for $C_{23}H_{32}Cl_2N_2NaO_{14}$: 653.1128, found 653.1132.

1.3. (1*S*)-3,4,6,7-Tetra-*O*-acetyl-3′-[(4-chloromethyl)-phenyl]spiro-[1,5-anhydro-2-deoxy-D-*manno*-heptitol-1,5′-[1,3]oxazolidine-2′,4′-dione] (7)

Typical procedure: To a soln of methyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-D-*manno*-2-octulosonate **1** (41 mg, 0.098 mmol) and *N*,*N*-dimethylaminopyridine (24 mg, 0.20 mmol) in THF (2.0 mL) was added a soln of 4-(chloromethyl)phenyl isocyanate (51 mg, 0.31 mmol) in THF (1.0 mL) at room temperature. After stirring for 6 h at 50 °C, the mixture was diluted with EtOAc (10 mL) and satd $NaHCO_3$ (5 mL). The aq layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated under diminished pressure. The residue was purified by thin-layer chromatography (1:1 hexane–EtOAc) to give a colorless syrup. (44 mg, 81%); $[\alpha]_D^{20}$ +48 (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$; data for the ring and the exocyclic protons are shown in Table 2): δ: 7.54 (d, 2H, *J* 7.0, Ar*H*), 7.48 (d, 2H, *J* 7.0, Ar*H*), 4.62 (s, 2H, C*H*$_2$Cl), 2.16 (s, 3H, COC*H*$_3$), 2.09 (s, 3H, COC*H*$_3$), 2.05 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$); ^{13}C NMR ($CDCl_3$; data for the skeletal carbon atoms are shown in Table 3): δ 170.5, 170.2, 167.7, 169.7, (4 × *C*OCH$_3$) 151.2 (O*C*ON), 138.7 (Ar), 130.1 (Ar), 129.6 (Ar), 125.8 (Ar), 45.1 (*C*H$_2$), 20.6 (CO*C*H$_3$); HRESIMS: [M+Na$^+$] Calcd for $C_{24}H_{26}ClNNaO_{12}$ 578.1041, found 578.1020.

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