A General Method for the Stereospecific Synthesis of C-Glycosides of Ulosonic acids by Samarium-Mediated Reductive Dechlorination

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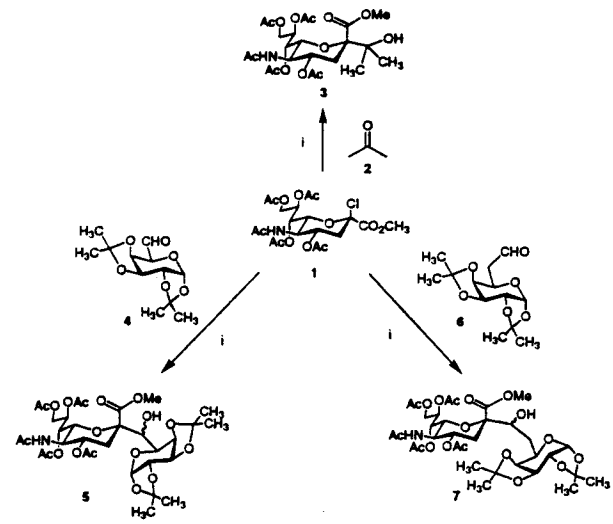
Abstract: C-glycosylation reactions were performed with the 2-chloro derivatives of NANA, KDN and KDO. C-glycosides were obtained when carbonyl compounds (ketone or sugar aldehyde) were coupled to the 2-chloro-derivatives of these ulosonic acids under Barbier conditions.

Ulosonic acids are a diverse family of complex monosaccharides that serve important biological functions. The most common ulosonic acids are *N*-acetylneuraminic acid (NANA), 3-deoxy-D-glycero-D-galactonulosonic acid (KDN) and 3-deoxy-D-manno-2-octulosonic acid (KDO), important constituents of many glycoconjugates, often occupying the non-reducing ends of oligosaccharide chains. Glycoproteins containing NANA, for example, are involved in a number of biological processes including cell interactions with other cells, microorganisms, toxins and antibodies.[1] The biological functions of ulosonic acids are derived from their size, negative charge and their natural position as the terminal residue on cell surface glycoconjugates. *C*-glycosides of ulosonic acids are of particular interest for their potential pharmaceutical applications. These are expected to have both improved enzymatic hydrolytic stability and an exoanomeric conformation similar to the corresponding *O*-glycosides.[2]

The synthesis of *C*-glycosides is a well established area of carbohydrate chemistry.[3] The utility of glycosyl chlorides in the formation of *C*-glycosides has been appreciated for some time. Until recently the aglycone portion of this radical pathway was limited to allylsilane, 1,3-dimethoxy benzene.[3a] Sinaÿ[4] and Wong[5] examined the possibility of coupling chloride and ketone (or aldehyde) under SmI_2 mediated radical reactions. In the presence of a protecting group at *C*-2, glycal was produced, in place of the desired *C*-glycoside. NANA-*C*-glycoside was reported by Bednarski[6] through NANA-glycosyl chloride with $(nBu)_3SnCH_2CH{=}CH_2$ and a catalytic amount of $[(nBu)_3Sn]_2$, affording a 1:1 mixture of NANA-*C*-glycoside. By using glycosyl aryl sulfones, Beau and co-workers prepared the corresponding 1,2-trans-*C*-glycosides under Barbier conditions.[7] A similar approach was used in the first examples of the NANA[8] and KDN[9] *C*-disaccharide synthesis in our laboratory, using pyridyl and phenyl sulfones as nucleophiles. There are two disadvantages of using sulfones as nucleophiles: 1) additional steps are required for their preparation and 2) they often produce a very unpleasant odor. In this paper we describe a new finding, that the ulosonic acid containing *C*-glycosylation method developed in our laboratory can be performed with the 2-chloro-derivatives of NANA, KDN and KDO.

KDN and KDO were prepared according to previously described methods.[10] Glycosyl chloride derivatives of KDN and KDO were synthesized using a similar procedure to that used for preparing NANA-glycosyl chloride. NANA-glycosyl chloride (**1**) and ketone (**2**) (1.2 equiv.) were reacted in an inert atmosphere with 4 equiv. of freshly prepared 0.1 M SmI_2 solution in THF at room temperature. We found that 2.5 equiv. of SmI_2 is the minimum amount for this reaction while 4 or more equiv. gave the best yields. This reaction results in a nearly instantaneous conversion to the desired *C*-glycoside of NANA (**3**) in 95 % yield (Scheme1).

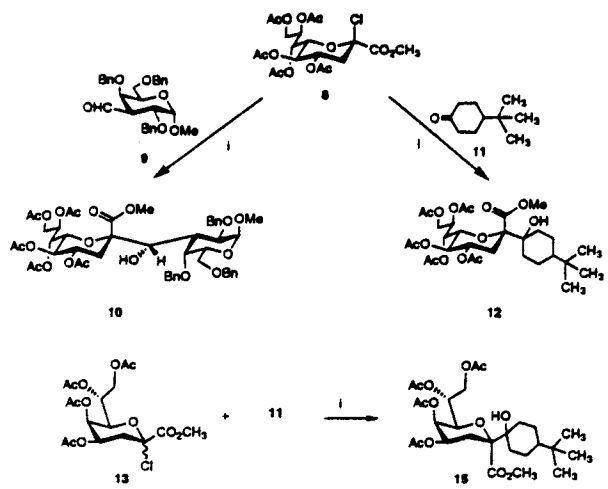


Scheme 1 - i. 4 equiv of SmI_2 (0.1 M in THF)

Next, a very efficient synthesis of *C*-disaccharides (**5**) and (**7**) was performed using the above stratagem. Coupling of the glycosyl chloride (**1**) and sugar aldehydes (**4**) or (**6**) again instantaneously generated the desired α-*C*-disaccharides (**5**) and (**7**) in an 88% and >95% yield respectively, based on NANA. Empirical rules[11] and ^1H-^{13}C decoupling experiments[8b] were used to deduce the α-configuration of these products. The H-4 signals in both (**5**) (4.57-4.62 ppm) and (**7**) (4.74-4.84 ppm) are observed at <5.00 ppm (in the β-anomer H-4 should be observed at >5.00 ppm). Little or no stereocontrol was observed at the newly formed stereocenter on the hydroxymethylene bridge. *C*-disaccharide (**5**) was formed in a 3:1 diastereomeric mixture while *C*-disaccharide (**7**) was obtained as a 1:1 diastereometric mixture (Scheme 1).

The reaction leading to NANA α-*C*-glycosides were next examined using KDN and KDO glycosyl chlorides. As we expected, KDN α-*C*-glycosides and KDO β-*C*-glycosides were afforded in excellent yield respectively (Scheme 2). The α-selectivity in the anomeric configuration and the *S*-configuration[8a] of alcohol in *C*-disaccharide (**10**) are confirmed by empirical rules, molecular modeling and IRMA calculation based on NMR data (2D ROESY and ^{13}C NMR).[9]

KDO-*C*-glycosides have been previously synthesized through the alkylation of the ester enolate giving β-stereoselectivity.[12] The *C*-glycosylation of (**13**) is stereospecific forming a single *C*-glycoside (**15**). ^1H-^{13}C decoupling experiments[13] were done to assign the anomeric configuration of KDO-*C*-glycoside. Some empirical ^1H-NMR rules have been used for deducing the anomeric configurations of KDO derivatives. However, these rules often lead to ambiguous assignment. This is due to the fact that the substituents can greatly influence the chemical shifts of the neighboring protons.[14] A definitive determination of the anomeric configurations of KDO derivatives can be achieved by comparison of the proton-coupled ^{13}C-NMR signals of the C-1 in α- and β-anomers.[15] In the typical $^5C_2$ chair conformation of KDO



Scheme 2- i. 4 equiv of SmI_2 (0.1 M in THF)

derivatives, the dihedral angles of (C-1)-(C-2)-(C-3)-(H-3ax) in α- and β-anomers are nearly 60° and 180°, respectively. Therefore α-anomeric configuration would give a small value for the coupling constant between C-1 and H-3ax ($J_{C\text{-}1,\ H\text{-}3ax}$ < 1 Hz) and the β-anomer would give a relatively large coupling constant ($J_{C\text{-}1,\ H\text{-}3ax}$ = 5-6 Hz) according to Karplus relationship.[16] The $J_{3ax,4}$ = 12.5 Hz and $J_{3eq,4}$ = 4.9 Hz confirmed that KDO-*C*-glycoside is in the $^5C_2$ conformation and also the ^3J coupling constant of $J_{C\text{-}1,\ H\text{-}3ax}$ = 6.0 Hz confirmed that KDO-*C*-glycoside is in the β configuration.

This study demonstrates a new simple procedure for the *C*-glycosylation of ulosonic acids through their chloro-derivatives under Barbier conditions.

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(13) General procedure: Glycosyl chloride (50 mg) and 1.2-2.0 equiv. of electrophile (ketone or sugar aldehyde) were dried together under high vacuum for 4 h and SmI_2 (4 equiv. freshly prepared from Sm and ICH_2CH_2I, 0.1 M in THF) was added in one portion at room temperature. The reaction mixture was concentrated under reduced pressure after 5 min, then purified on silica gel column with EtOAc as eluent. All new compounds were confirmed by NMR and HR FABMS. Selected HRFABMS and ^{1}H-NMR data [values of δ_H at 500 MHz measured in $CDCl_3$: **3** 1.20, 1.30 (2s, 2 × 3 H, $C(CH_3)_2$), 1.95 (t, 1 H, $J_{3a,\ 3eq}$ = 12.5 Hz, $J_{3a,4}$ = 12.5 Hz, H-3_{ax}), 1.98, 2.02, 2.03, 2.11, 2.18 (5s, 5 × 3 H, 5Ac), 2.55 (dd, 1 H, $J_{3eq,\ 4}$ = 2.1 Hz, H-3_{eq}), 3.80 (s, 3 H, $COOCH_3$), 4.00 - 4.20 (m, 3 H, H-5, H-6, H-9a), 4.38 (dd,1 H, $J_{8,9b}$ = 1.2 Hz, $J_{9a,9b}$ = 11.6 Hz, H-9b), 4.80 (ddd, 1 H, $J_{3ax,4} = J_{4,5}$ = 12.5, $J_{4,NH}$ = 8.9 Hz, H-4), 5.30 (d, 1 H, NH), 5.40 - 5.45 (m, 1 H, H-7), 5.52 - 5.60 (m, 1 H, H-8). HRFABMS calcd for $C_{23}H_{35}NO_{13}$ (M + Na)$^+$: 556.2019. Found: *m/z* 556.2006 (M + Na)$^+$. **7** (R,S mixture), 1.31, 1.38, 1.40, 1.47, 1.50, 1.54, 1.56 (8s, 12 H), 1.75 (t, 1 H, H-3_{eq}), 1.88 (t, 1 H, H-3_{eq}), 2.01, 2.02, 2.03, 2.04, 2.05 (5s, 5x3 H, 5Ac), 2.13, 2.14, 2.15, 2.16, 2.18 (5s, 5x3 H, 5Ac), 2.38 (dd, 1 H, H-3_{ax}), 2.47 (dd, 1 H, H-3_{ax}), 3.77 (s, 3 H, $COOCH_3$), 3.79 (s, 3 H, $COOCH_3$), 3.87-4.40 (m, 22 H, H-2', H-3', H-4', H-5', H-6', H-6, H-9a, H-9b, H-5, H-7"), 4.62 (dd, 2 H, H-1'), 4.74-4.84 (m, 2 H, H-4), 5.07 (dd, 2 NHAc), 5.30-5.36 (m, 2 H, H-7), 5.42-5.85 (m, 2 H, H-8). HRFABMS calcd for $C_{33}H_{49}NO_{18}$ (M + Na)$^+$: 770.2853. Found: *m/z* 770.2847 (M + Na)$^+$. **15** 0.89 (s, 9 H, $C(CH_3)_3$), 0.97-1.90 (m, 10 H, cyclohexyl and OH), 1.98, 2.01, 2.07, 2.12 (4s, 12 H, 4 $COCH_3$), 2.26 (dd, 1 H, $J_{3eq,\ 4}$ = 4.94 Hz, H-3_{eq}), 2.31 (t, 1 H, $J_{3ax,\ 4}$ = 12.5 Hz, H-3_{ax}), 3.81 (s, 3 H, $COOCH_3$), 4.09 (dd, 1 H, $J_{6,7}$ = 5.12 Hz, H-6), 4.27 (dd, 1 H, $J_{8a,8b}$ = 13.1 Hz, $J_{8,7}$= 7.33 Hz, H-8a), 4.36 (d, 1 H, $J_{7,8b}$= 3.48 Hz, H-8b), 4.78-4.84 (m, 1 H, H-4), 5.09-5.14 (m, 1 H, H-7), 5.27 (bs, 1 H, H-5). HRFABMS calcd for $C_{27}H_{42}O_{12}$ (M + Na)$^+$ 558.6220. found: m/z 558.6217 (M + Na)$^+$. ^{13}C NMR: 171.3, 171.06, 171.61, 170.3, 170.09 (C-1 and 4 Ac), 86.5 (C-2), 71.2 (C-6), 70.6 (C-5), 68.72 (C-4), 66.7 (C-8), 52.7 (OCH_3).

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