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The Stereospecific Synthesis of KDN α-*C*-glycosides by Samarium Mediated Reductive Desulfonylation of Glycosyl Phenylsulfone

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Abstract: Samarium-mediated KDN *C*-glycoside formation under Barbier conditions is described. The α-selectivity at C-2' and the *S*-configuration of C-3'' in the *C*-disaccharide **15** are confirmed by empirical rules, molecular modeling and IRMA calculation based on NMR data (2D ROESY and ^{13}C NMR).

KDN, 3-deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosylonic acid, is a novel type of sialic acid in which the acetamido group at C-5 of *N*-acetylneuraminic acid is replaced by a hydroxyl group. This ulosonic acid was first isolated from rainbow trout eggs.[1] In the last 10 years, a number of KDN-glycoconjugates, exhibiting structural determinants related to human tumor-associated antigens, have been reported in mammals.[2] In addition, oligo/poly-KDN and KDN-glycoprotein play an important role in the binding of calcium ions.[3] KDN-containing gangliosides, KDN-GM_3 and KDN-GM_4, have been synthesized by Hasegawa's group and show potent inhibitor activity of cellular immune respones.[4]

A major problem encountered when adding the natural gangliosides to cells in culture is that they are readily metabolized complicating the results of these studies.[5] The application of glycosides containing nonhydrolyzable ulosonic acid (KDN, Neu5Ac, *etc.*) analog is an attractive approach to control events of crucial importance to glycobiology and immunology at the molecular level. Here we report the first stereocontrolled synthesis of KDN containing α-*C*-glycosides *via* glycosyl samarium (III) intermediates.[6]

KDN was prepared according to a previously described method,[7] and the KDN phenylsulfone (**1**) was synthesized using a similar procedure to that for preparing Neu5Ac phenylsulfone.[8] Treatment of a neat mixture of KDN phenylsulfone **1** and ketone **2** (1.2 equiv) in an inert atmosphere with 4 equiv of freshly prepared 0.1 M SmI_2 solution in THF at room temperature, gave a nearly instantaneous conversion to the KDN-*C*-glycoside **3** in excellent yield (Scheme 1). Unambiguously establishing the anomeric configuration of ulosonic acid glycosides is very difficult since there is no anomeric proton whose coupling can be correlated with a Karplus curve. Thus, the stereochemistry of the new glycosidic linkage in **3** was determined to be α based on empirical rules:[9] (1) The chemical shift of H-4 is at 4.84 ppm and the $J_{7,8}$ = 8.9 Hz.[10] (in the β-anomer H-4 should resonate at >5.0 ppm and $J_{7,8}$ should be 2-4 Hz); (2) The chemical shift difference between the two hydrogen atoms at position 9 of KDN [$\Delta(\delta H_{9a}-\delta H_{9b})$] is $\Delta\delta$ = 0.14 ppm (the β anomer should show a $\Delta\delta$ =

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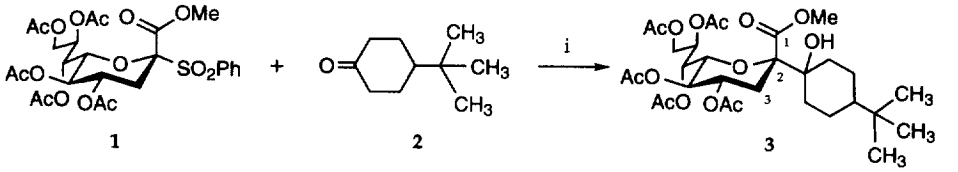
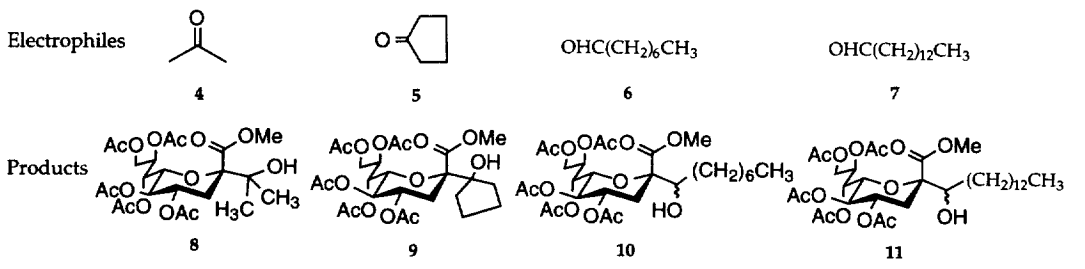
0.6-0.8 ppm). The α-selectivity was further confirmed by the ^3J coupling constants[11] of $J_{C1\text{-}H3ax}$ = 6.0 Hz and $J_{C1\text{-}3eq}$ < 1.0 Hz using selective ^{13}C NMR decoupling.

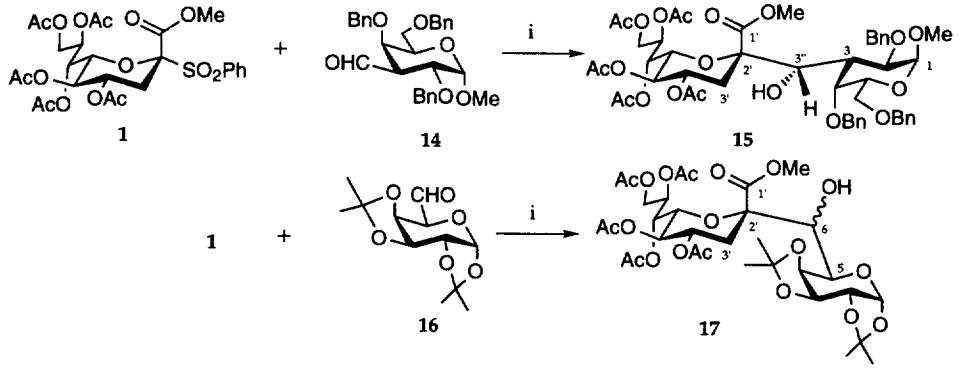




Scheme 1. i. 4 equiv of SmI_2 (0.1 M in THF)

The reactions of sulfone **1** with ketones (**4** and **5**) or aldehydes (**6** and **7**) under Barbier conditions give the corresponding *C*-glycosides **8-11** in excellent overall yields (85-96%).[10] *C*-glycosides **10** and **11** are formed as *R/S* (about 1:1) diastereomers at newly formed bridge-carbon. Conjugated carbonyl compounds like crotonaldehyde (**12**) and methyl pyruvate (**13**) were not reactive with **1** under the conditions used.

KDN(α2-3)Gal and KDN(α2-6)GalNAc are core structures in the naturally occurring KDN oligosaccharides. Thus, our *C*-glycosylation methodology was applied to the synthesis of *C*-linked KDN(α2-3)Gal and KDN(α2-6)Gal derivatives. Coupling of phenylsulfone **1** with sugar electrophile **14**[12] under Barbier conditions diastereoselectively generated (2-3) linked *C*-disaccharide **15**, while a similar reaction with **16**[13] gave 2.3 : 1 ratio of diasteromers at newly formed chiral center (C-6).



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

The structural determination of KDN *C*-disaccharide **15** was based on 1D-NMR (^1H and ^{13}C) and 2D-ROESY.[10] Again, empirical rules were used for the elucidation of the anomeric configuration of **15**: The chemical shift of H-4' (4.47 ppm), the $J_{7',8'}$ value (8.6 Hz) and the $\Delta\delta$ ($H_{9'a}$-$H_{9'b}$) value (0.22 ppm)

demonstrated the α-configuration of the KDN residue in **15**. Three-bond coupling constants (^3J) of C-1'/H-3'ax and C-1'/H-3'eq are 5.1 Hz and <1 Hz, respectively, supporting the α-assignment. Furthermore, the ^{1}H-^{1}H ROESY showed negative NOEs for H-6'/methyl ester and H-3'eq/H-3, confirming the α-configuration on C-2'. The negative cross-peaks between the proton at the bridging carbon atom (H-3'') and both the C-6 protons of the *galacto* moiety showed that they are spatially close, indicating *S*-configuration of the newly formed chiral center (C-3''). To confirm this diastereoselectivity, ROESY experiments were performed under mixing times of 250, 375, 500, and 625 ms to define NOE build-up curves and used in an iterative relaxation matrix approach (IRMA) simulation.[14] The spatial distances of protons were quantified from peak intensities based on a distance of 1.77 Å for H-6a to H-6b of the *galacto* moiety (see Table 1). The *S* and *R* *C*-disaccharides of **15** were modeled on Silicon Graphics using SYBYL version 6.3. After energy minimization under Tripos forcefield (parameters used in the molecular modeling: T = 298 K, dielectric constant = 1.0 for organic solvent), key distances for each configuration were determined (see Table 1). The modeled *S*-configuration (**15**) most closely matched the results calculated from NOE peak intensities, fully supporting the assignment of *C*-disaccharide **15**.

Table 1. Comparison of Selected Distances (Å) from Modeling to those Calculated from NOEs

	H-3"/H-3ax	H-3"/H-3eq	H-3"/H-3	H-3"/H-6a	H-3"/H-6b
S-(**15**)	3.34	2.76	3.07	4.22	4.46
R-(**15**)	2.38	3.01	2.45	6.22	6.57
Calculated	3.4 ± 0.1	2.9 ± 0.1	2.9 ± 0.1	3.7 ± 0.1	n.d.

In conclusion, the first synthesis of KDN *C*-glycosides is reported. In this synthesis, KDN phenylsulfone was used to prepare the organosamarium intermediate that reacted quantitatively with ketones or aldehydes. This approach provides for the easy formation of tertiary C-C bonds and has advantages compared to the lithium species,[15] since it can tolerate acetyl groups and use milder reaction conditions. The *C*-disaccharides obtained are being used to synthesize more complex KDN-glycoconjugates for biological evaluation.

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References and Notes:

1. Nadano, D.; Jwasaki, M.; Endo, S.; Kitajima, K.; Inoue, S.; Inoue, Y. *J. Biol. Chem.* **1986**, *261*, 11550-7.
2. (a) Plancke, Y.; Wieruszeski, J.-M.; Alonso, C.; Boilly, B.; and Strecker, G. *Eur. J. Biochem.* **1995**, *231*, 434-439. (b) Maes, E.; Plancke, Y.; Delplace, F.; Strecker, G. *Eur. J. Biochem.* **1995**, *230*, 146-156. (c) Moolenaar, C. E.; Muller, E. J.; Schol, D. J.; Figdor, C. G.; Bock, E.; Bitter-Suermann, D.; Michalidas, R. J. *Cancer Res.* **1990**, *50*, 1102-1106.
3. Shimoda, Y.; Kitajima, K.; Inoue, S.; Inoue, Y. *Biochemistry* **1994**, *33*, 1202-1208.
4. (a) Hasegawa, A.; Suzuki, N.; Kozawa, F.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1996**, *15*, 639-648. (b) Terada, T.; Toyoda, T.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1995**, *14*, 769-790.
5. Private communication with Dr. E. G. Bremer, Children's Memorial Institue, Chicago, Illinois, USA.
6. (a) Vlahov, I. R.; Vlahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480-1481; (b) Mazeas, D.; Skrydstrup, T.; Beau, J.-M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 909-912. (c) Namy, J.; Collin J.,

Bied, C.; Kagan, H. *Synlett* **1992**, 733-734. (d) Curran, D.; Fevig, T.; Jasperse, C.; Totleben, M.; *ibid* **1992**, 943-961. (e) Molander, G.; McKie, J. *J. Org. Chem.* **1991**, *56*, 4112-4120.

7. Nakamura, M.; Furuhata, F.; Yamasaki, T.; and Ogura, H. *Chem. Pharm. Bull.* **1991**, *39*, 3140-3144.
8. Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *187*, 35-42.
9. Kanie, O.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1988**, *7*, 501-506.
10. Selected NMR and HR(FAB)MS data: **1**. 2.27 (t, 1 H, H-3ax), 3.07 (dd, 1 H, H-3eq), 3.86 (s, 3 H, COOCH_3), 3.94 (dd, 1 H, H-6), 4.03 (dd, 1 H, H-9a), 4.20 (dd, 1 H, H-9b), 4.69 (t, 1 H, H-5), 4.88 (ddd, 1 H, H-8), 4.94 (ddd, 1 H, H-4), 5.22 (dd, 1 H, H-7), 7.60-7.88 (m, 5 H, Ph). **3**. 95%, $[\alpha]_D$ -38 ° (*c* 0.1, $CHCl_3$); ^{13}C NMR: 169.8 (C-1), 85.8 (C-2), 74.7 (C-6), 71.8 (C-4), 70.6 (C-8), 68.1 (C-5), 67.9 (C-7), 67.0 (bridge-C), 62.4 (C-9), 52.4 (OCH_3), 47.6 (C-3); ^1H NMR: 0.92 (s, 9 H, C(CH_3)$_3$), 0.95 -1.86 (m, 10 H, cyclohexyl and O*H*), 1.97 (t, 1 H, $J_{3ax,3eq} = J_{3ax,4}$ = 13.4 Hz, H-3ax), 2.00 (s, 6 H, 2 CH_3CO), 2.05, 2.09, 2.19 (3 s, 9 H, 3 CH_3CO), 2.55 (dd, 1 H, $J_{3eq,4}$ = 1.8 Hz, H-3eq), 3.81 (s, 3 H, COOCH_3), 4.09 (dd, 1 H, $J_{5,6}$ = 9.6, $J_{6,7}$ < 1 Hz, H-6), 4.13 (dd, 1 H, $J_{9a,9b}$ = 12.1, $J_{8,9a}$ = 5.1 Hz, H-9a), 4.27 (d, 1 H, $J_{8,9b}$ < 1 Hz, H-9b), 4.79 (t, 1 H, $J_{4,5} = J_{5,6}$ = 9.6 Hz, H-5), 4.84 (ddd, 1 H, H-4), 5.33 (d, 1 H, $J_{7,8}$ = 8.9 Hz, H-7), 5.41-5.47 (m, 1 H, H-8). HR(FAB)MS: calcd for $C_{30}H_{46}O_{14}Na$ 653.2785. Found: m/z 653.2809 $(M+Na)^+$. **8**. 96%, $[\alpha]_D$ -70 ° (*c* 0.1, $CHCl_3$); 1.21, 1.26 (2 s, 6 H, 2 CH_3), 1.93 (t, 1 H, $J_{3ax,3eq} = J_{3ax,4}$ = 12.5 Hz, H-3ax), 2.01, 2.02, 2.11, 2.20, 2.40 (5 s, 15 H, 5 CH_3CO), 2.60 (dd, 1 H, $J_{3eq,4}$ = 4.5 Hz, H-3eq), 2.85 (s, 1 H, O*H*), 3.85 (s, 3 H, COOCH_3), 4.10 (dd, 1 H, $J_{5,6}$ = 9.8, $J_{6,7}$ = 2.2 Hz, H-6), 4.11 (dd, 1 H, $J_{9a,9b}$ = 12.5, $J_{8,9a}$ = 5.9 Hz, H-9a), 4.30 (dd, 1 H, $J_{8,9b}$ = 2.6 Hz, H-9b), 4.82 (t, 1 H, $J_{4,5} = J_{5,6}$ = 9.8 Hz, H-5), 4.85 (ddd, 1 H, H-4), 5.34 (dd, 1 H, $J_{7,8}$ = 8.6 Hz, H-7), 5.45 (ddd, 1 H, H-8). HR(FAB)MS: calcd for $C_{23}H_{34}O_{14}Na$ 557.1846. Found: m/z 557.1858 $(M+Na)^+$. **15**. 92%, $[\alpha]_D$ -48 ° (*c* 0.1, $CHCl_3$); 1.977, 2.008, 2.011, 2.030, 2.158 (5 s, 15 H, 5 COCH_3), 2.05 (dd, 1 H, $J_{3'ax,3'eq}$ = 13.1, $J_{3'ax,4'}$ = 11.0 Hz, H-3'ax), 2.57 (dd, 1 H, $J_{3'eq,4'}$ = 4.8 Hz, H-3'eq), 2.74 (bd, 1 H, $J_{2,3}$ = 6.4, $J_{3,4}$ and $J_{3,3''}$ < 0.5 Hz, H-3), 3.45 (s, 3 H, OCH_3), 3.56-3.60 (m, 2 H, 2 H-6), 3.76 (s, 3 H, COOCH_3), 3.88 (bs, 1 H, H-3''), 3.97 (dd, 1 H, $J_{1,2}$ = 3.2 Hz, H-2), 4.00 (dd, 1 H, $J_{5',6'}$ = 10.3, $J_{6',7'}$ = 1.8 Hz, H-6'), 4.05 (dd, 1 H, $J_{9'a,9'b}$ = 12.5, $J_{8',9'a}$ = 5.4 Hz, H-9'a), 4.27 (dd, 1 H, $J_{8',9'b}$ = 2.3 Hz, H-9'b), 4.37-4.40 (m, 2 H, H-5 and O*H* at C-3''), 4.41, 4.61 (2 d, 2 H, *J* 12.6 Hz, PhCH_2), 4.45, 4.64 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 4.47 (bs, 1 H, $J_{4,5}$ < 0.5 Hz, H-4), 4.51, 4.58 (2 d, 2 H, *J* 12.4 Hz, PhCH_2), 4.73 (d, 1 H, H-1), 4.82 (t, 1 H, $J_{4',5'} = J_{5',6'}$ = 10.3 Hz, H-5'), 4.95 (ddd, 1 H, H-4'), 5.31 (dd, 1 H, $J_{7',8'}$ = 8.6 Hz, H-7'), 5.42 (ddd, 1 H, H-8'), 7.20-7.40 (m, 15 H, 3 Ph). HR(FAB)MS: calcd for $C_{49}H_{60}O_{19}Na$ 975.3627. Found: m/z 975.3635 $(M+Na)^+$.
11. Kononov, L. O. and Magnusson, G. *Acta Chem Scandinavica* **1998**, *52*, 141-144.
12. Schmidt, R. and Beyerbach, A. *Liebigs Ann. Chem.* **1992**, 983-986.
13. Dess, D. B. and Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.
14. Borgias, B. A. and James, T. L. *Methods in Enzymology*, Eds: Oppenheimer, N. J.; James, T. L., Academic Press Inc., San Diego, **1989**, *176*, 169-183.
15. Crich, D. and Lim, L. B. L. *J. Chem. Soc. Perkin Trans. I* **1991**, 2209-2214.