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Practical Synthesis of 2-Keto-3-deoxy-D-glycero-D-galactononulosonic Acid (KDN)

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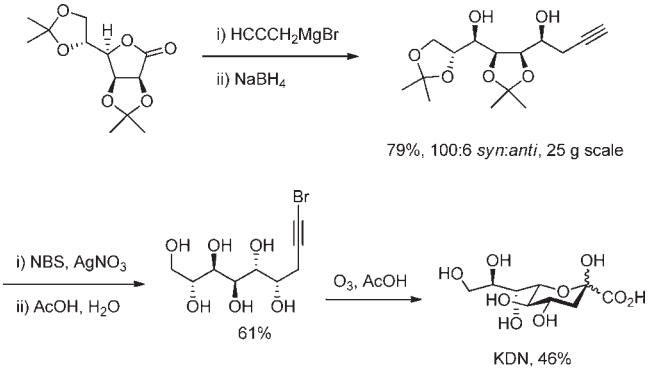
ABSTRACT



Reaction of propargylmagnesium bromide with 2,3;5,6-di-*O*-isopropylidene-D-mannonolactone followed by highly stereoselective reduction of the so-formed lactol with sodium borohydride gives a *syn*-diol from which practical syntheses of 2-keto-3-deoxy-D-glycero-D-galactononulosonic acid (KDN) and various partially protected derivatives have been achieved all of which feature the oxidative unmasking of the α-keto acid moiety from the alkyne.

2-Keto-3-deoxy-D-glycero-D-galactononulosonic acid (KDN, **1**) is a close analog of *N*-acetylneuraminic acid (NeuAc) arising from replacement of the *N*-acetyl moiety by a hydroxyl group,[1,2] whose increased occurrence relative to NeuAc in a variety of human cancers is currently attracting considerable attention.[3] These observations coupled with poor availability from natural sources have combined, in recent years, to make KDN an important target for organic synthesis. Ongoing projects in our laboratory related to the development of stereocontrolled methods for the synthesis of KDN glycosides[4] and their application in synthesis necessitated a facile, scalable route to KDN. Besides the original synthesis from NeuAc,[5] elegant de novo syntheses of KDN have been accomplished by the Burke and Banwell groups,[6,7] and an indium-mediated protecting group-free synthesis has been described by Ogura[8] and Chan,[9] while biomimetic enzyme-mediated condensations of phosphoenol pyruvate with mannose have been deployed by the Wong,[10] Paulson,[11] and Seeberger groups.[12] These methods, however, did not meet criteria of ease of operation and scalability. Accordingly, we sought to develop a new route, which we report here.

Consideration of the biosynthetic pathway to KDN[2] directed us to a route based on the condensation of a derivative of mannose with a pyruvate equivalent

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(11) Blixt, O.; Paulson, J. C. *Adv. Synth. Catal.* **2006**, *345*, 687–690.
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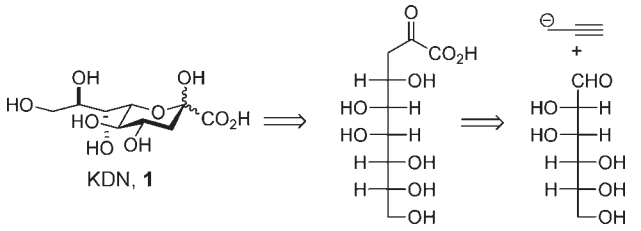
(Scheme 1). Precedent from our own laboratory[13] and others prompted us to investigate the propargyl anion as a pyruvate equivalent to be revealed in due course by oxidation of the alkyne moiety.

Scheme 1. Strategic Disconnections in the Synthesis of KDN



We first investigated the reaction of propargylmagnesium bromide with 2,3;5,6-diisopropylidene-D-mannofuranose **2** (Scheme 2, path a) but were deterred by the unfavorable 1:2 *syn*:*anti* selectivity of the resulting adduct **3**.[14] We turned instead to reaction of the Grignard reagent with the corresponding lactone **4** which led to the isolation of a single isomer of a cyclic hemiacetal **5** arising from attack on the *endo*-face of the bicyclic electrophile (Scheme 1, path b). This selectivity, which has precedent,[15] is presumably the result of chelation between the multiple ether groups in the lactone and the organometallic reagent.[16] Whatever the reason for the selectivity, this addition reaction could be reliably run on a 25 g scale and the adduct **5** taken forward to the next step without purification. Reduction with sodium borohydride in methanol on a 5 g scale at −15 °C gave a high yield of a 100:3 *syn*/*anti* mixture of the desired diol **3**, which could be recrystallized from ether/pentane,[17] and which compares favorably with a previous indium-mediated *syn*-selective condensation of α-bromomethacrylate with mannose.[9] On the 25 g scale, the selectivity fell slightly to a still acceptable 100:6 ratio (Scheme 2, path b). The efficiency of the reduction reaction was dependent on the dryness of the sodium borohydride, with dry, free-flowing samples providing the results illustrated and moist samples resulting in contamination with up to 10% of the allene **6** (Scheme 2). The use of sodium cyanoborohydride as a reductant in this process was not satisfactory and led to the formation of complex reaction mixtures. The use of lithium borohydride gave 61% of **3** but with the much reduced selectivity of 100:68 in favor of the *syn*-isomer, while application of lithium aluminum hydride in THF gave 68% of **3** but with reversal of selectivity (*syn*/*anti* = 1:9).

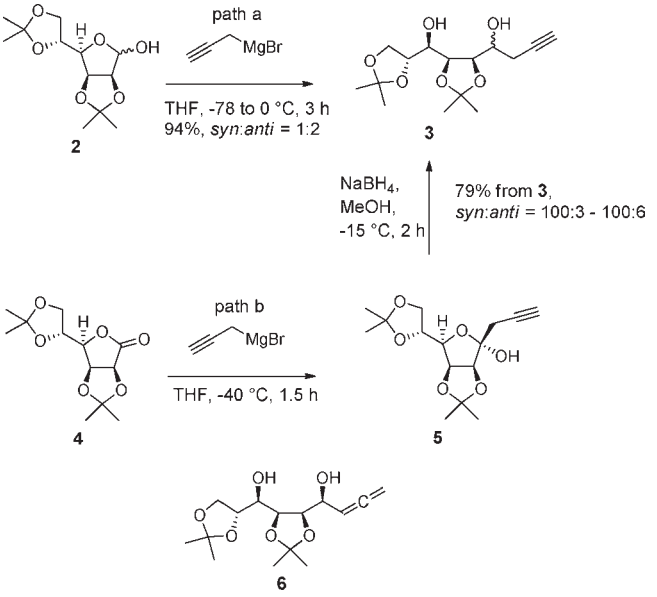
(14) According to the literature this reaction affords a mixture of isomers favoring the *anti*-isomer when conducted in diethyl ether: Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 2760–2762.

(15) van Hooft, P. A. V.; El Oualid, F.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H.; Leeuwenburgh, M. A. *Org. Biomol. Chem.* **2004**, *2*, 1395–1403.

(16) The stereochemical assignment of **5** rests on the NOE correlation between the propargyl hydrogens and a methyl group of an acetonide moiety. Accordingly there is no NOE correlation between the propargyl hydrogens and H's 6 and 7 (KDN numbering).

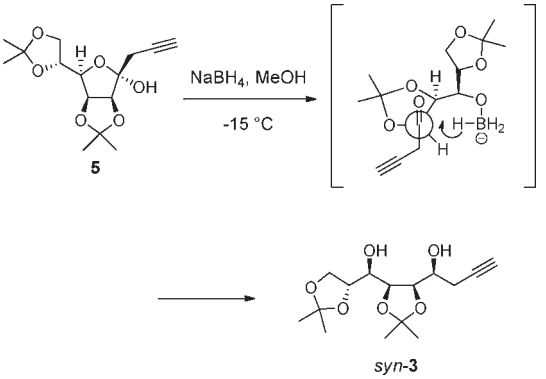
(17) The stereochemical assignment in the *syn* and *anti* pair **3** ultimately rests on the conversion of the *syn*-isomer to KDN.

Scheme 2. Formation of the *syn*-Diol **3**



The operation of a chelation controlled model for the sodium borohydride reduction of **5** is unlikely under the reaction conditions employed, and we favor instead a model based on internal delivery such as has been suggested for other isopropylidene-protected lactols.[18] Thus, it appears reasonable that an alkoxyborohydride generated in the course of lactol ring opening delivers the hydride intramolecularly along a Felkin−Anh-type trajectory to the ketone leading predominantly to the *syn*-product (Scheme 3). The ability to obtain the *syn*-alcohol **3** in high yield and selectivity in just two steps from commercially available lactone **4** is an important aspect of this synthesis, as inversion of the corresponding *anti*-product[19] was anticipated to be difficult in both the KDN and closely related NeuAc series.[20,21]

Scheme 3. Model for *syn*-Selective Reduction of Lactol **5**



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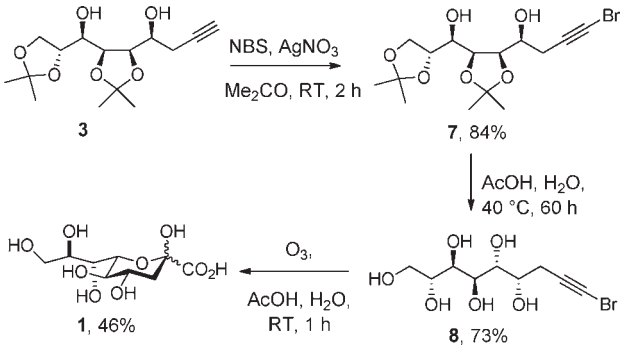
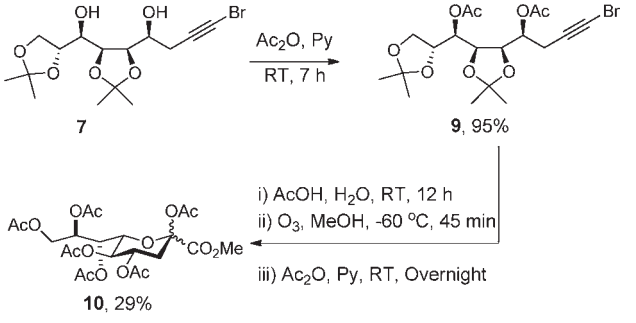
syn-Diol **3** was converted to the bromoalkyne **7** in 84% yield by treatment with NBS and silver nitrate. Removal of the two acetonide groups with aqueous acetic acid then gave the bromoalkynyl pentaol **8** in 73% yield and set the stage for the final revealing of the α-keto acid moiety, which was achieved by ozonolysis and which yielded the target **1** in 46% yield (Scheme 4). In this manner KDN was accessed in gram scale quantities in a highly stereocontrolled manner from the readily available diacetone mannofuranose and propargyl bromide in five steps and 22% overall yield.

Scheme 4. Oxidative Conversion of *syn*-Diol **3** to KDN



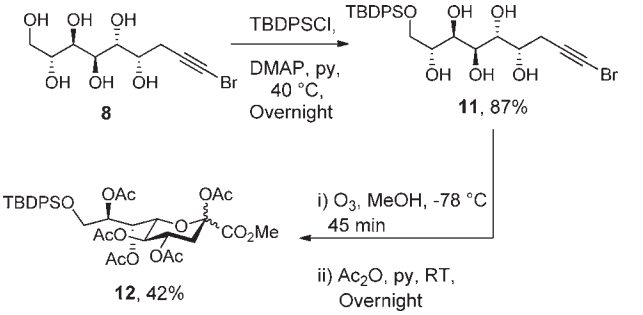
The highly crystalline nature and low solubility of the bromoalkynyl pentaol **8**, however, rendered further scale-up of this protocol difficult. Therefore, we resorted to the use of protecting groups with a view to increasing solubility and facilitating scale-up. Acetylation of diol **7** gave a diacetate **9** that, following cleavage of the acetonide groups in the standard manner, was subject to ozonolysis in methanol resulting in the formation of a relatively complex reaction mixture. Nevertheless, following peracetylation, the KDN derivative **10** was isolated in 29% yield (Scheme 5).

Scheme 5. Synthesis of the Protected KDN Ester **10**



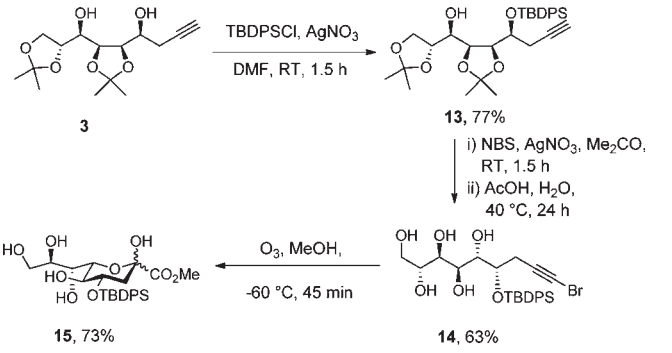
Alternatively, silylation of the pentaol **8** with *tert*-butyldiphenylsilyl chloride gave the monosilyl derivative **11** of which ozonolysis in methanol followed by peracetylation gave the differentially protected KDN ester **12** in an improved yield of 42% for the oxidative step (Scheme 6).

Scheme 6. Synthesis of the Protected KDN Ester **12**



In a further example, silylation of diol **3** with *tert*-butyldiphenylsilyl chloride was found to occur selectively at the homopropargylic position to give a silyl ether **13** in 77% yield that was converted to bromoalkynyl tetraol **14** in the standard manner in 62% yield for the two steps. Ozonolysis of **14** in methanol then resulted in the isolation of the selectively protected KDN ester **15** in 73% isolated yield (Scheme 7).

Scheme 7. Synthesis of the Protected KDN Ester **14**



Finally, and most conveniently for larger scale work, silylation of diol **3** with *tert*-butyldimethylsilyl chloride under forcing conditions gave 91% of the bissilyl ether **16** which was converted to the corresponding alkynyl bromide **17** in 80% yield in the usual way. Oxidation of this alkyne was best achieved with potassium permanganate which enabled isolation of the α-ketoester **18** in excellent yield. When oxidation of the bromoalkyne **17** was conducted by ozonolysis, in the usual manner, ketoester **18** was isolated in 42% yield along with 33% of a decarbonylated methyl ester **19**. Methanolysis of the crude α-ketoester acquired from the permanganate oxidation followed by peracetylation resulted in the isolation of the KDN derivative **10** in 61% overall yield from the

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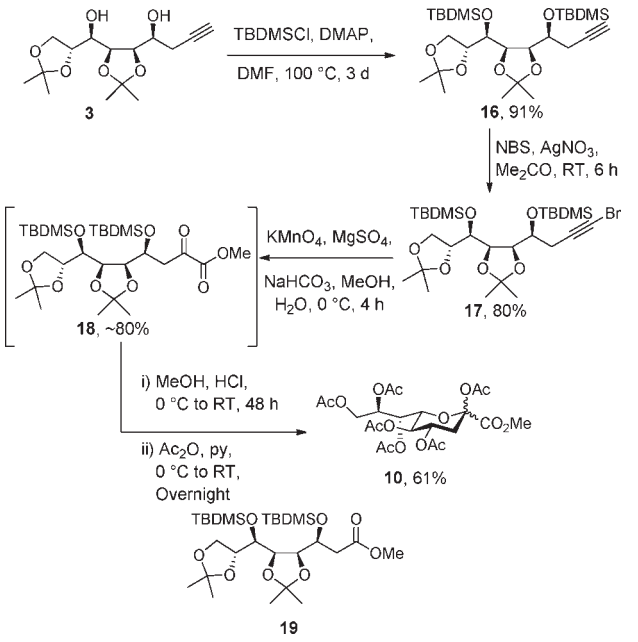
(21) Sheng, L.; Wu, Y.-L. *Tetrahedron* **2002**, *58*, 9049–9054.

Scheme 8. Second Synthesis of the Protected KDN Ester **10**



bromoalkyne **17** (Scheme 8). In this manner >6 g of ester **10** could be obtained in a reliable manner by a simple three-step protocol requiring only a single purification from 12 g of the bromoalkyne **17**. The overall yield of **10** obtained in this manner from the lactone **4** is 35%.

Overall, we describe a practical convenient and scalable route to KDN and some of its partially protected derivatives by a pathway that compares well with previous literature approaches. A particular feature of the chemistry described is the direct *syn*-selective entry into the diol **3** that avoids the need to conduct the difficult inversion of the *anti*-isomer whose analogs were previously more readily available. The ability to introduce a variety of different protecting groups at different locations prior to the final oxidative cyclization is a particular feature and one that will be of use when selectively protected KDN derivatives are needed for subsequent purposes.

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Supporting Information Available. Full experimental details and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.