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Formal Synthesis of (+)-3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (KDN) via Desymmetrization by Ring-Closing Metathesis

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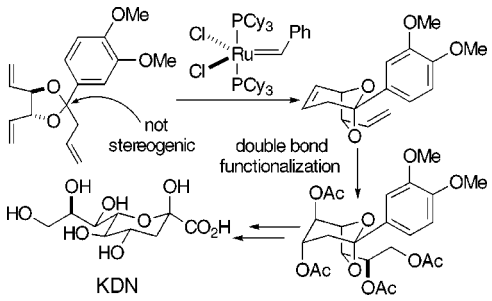
ABSTRACT



Formal synthesis of the naturally occurring deaminated sialic acid KDN, a potential oncofetal antigen, has been accomplished in 45% overall yield via a novel ketalization/ring-closing metathesis sequence. The rapid introduction of all oxygen functionality in a completely stereocontrolled manner exploited a rigid 6,8-dioxabicyclo[3.2.1]oct-2-ene ring system. This general synthetic strategy should provide access to a number of KDN and sialic acid analogues.

We recently reported short syntheses of (+)-*exo*-, *rac*-*endo*-, and enantiomerically enriched (+)-*endo*-brevicomin employing catalytic ring-closing olefin metathesis as a novel method for substrate desymmetrization in constructing the 6,8-dioxabicyclo[3.2.1]octane ring system.[1] To expand the utility of our intermolecular ketalization/intramolecular C−C bond formation strategy (Figure 1), the synthesis of more complex natural products has been pursued. These efforts have culminated in a short and efficient formal synthesis of (+)-3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, **1**, Figure 2), a deaminated sialic acid first isolated by Inoue in 1986 from the membrane polysialoglycoproteins of rainbow trout eggs.[2a] While KDN is thought to protect the egg membrane from attack by bacterial sialidases in the rainbow trout,[2b] the more recent discovery of elevated levels of free KDN in human fetal cord red blood cells and ovarian cancer cells indicates oncofetal antigen properties that could be important in the early detection of disease and as a marker for detecting disease recurrence.[2c]

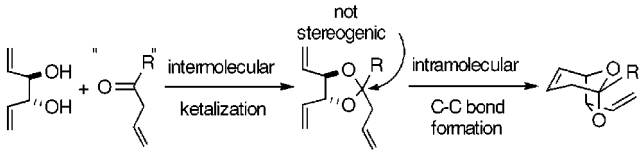


Figure 1. General strategy.

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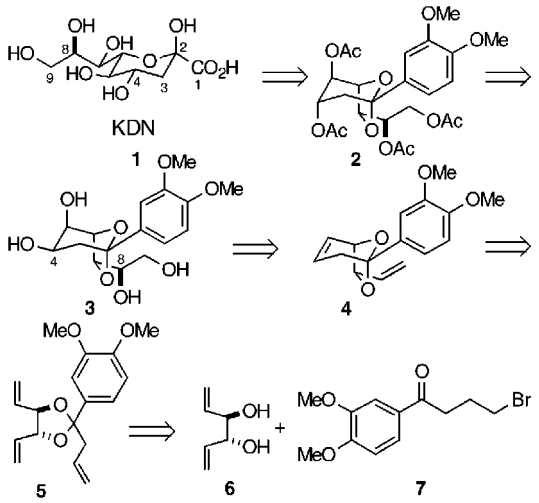


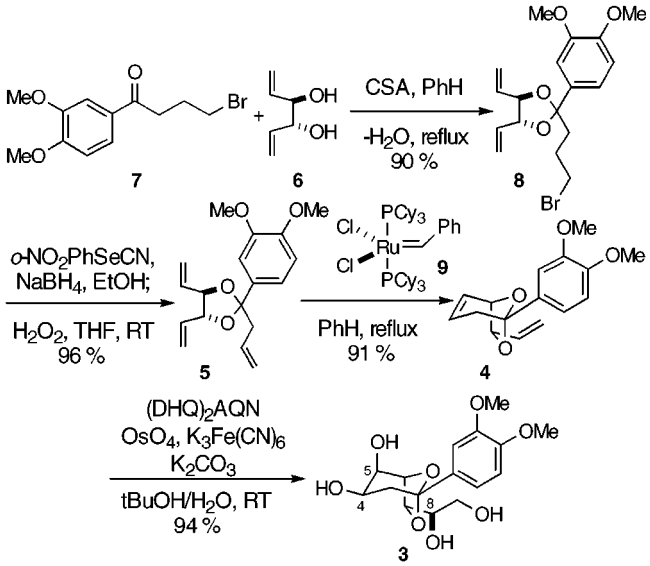
Figure 2. Retrosynthetic analysis.

Since its isolation, KDN has been the subject of considerable synthetic interest.[2b,3] Total syntheses by Dondoni,[3a] Takahashi,[3b] and Banwell[3c] have appeared, but most work in this area has focused on the enzymatic[3d−i] or chemical[3j−q] elongation of D-mannose or its derivatives. Each previous total synthesis has involved extensive protection/deprotection and/or nonselective reactions. Each mannose elongation strategy has utilized four starting material stereocenters and native functionality, which, while expeditious for KDN, limits possibilities for derivative synthesis. Many derivatives of KDN,[2b,3a,j,4] such as *C*-glycosides,[4a−c] amino derivatives,[4d−j] deoxy sugars,[2b,4k,l] unsaturated analogues,[4f,j,m−p] and epimers,[3a,j] have been identified and pursued as important synthetic building blocks, biological probes, and drug candidates, suggesting the need for an efficient and versatile synthesis route.

Our retrosynthetic analysis of KDN revealed the protected 2,7-anhydro sugar derivative **2** as a suitable precursor (Figure 2). The hydropyran ring in bicyclic acetal **2** is constrained to be in the opposite chair conformation from that in KDN, forcing four of five substituent groups into axial orientations. This feature was expected to assist both stereoselective functionalization and ultimate hydrolysis of the bicyclic acetal template. The electron rich 3,4-dimethoxy-benzene carboxyl surrogate[5] was chosen to facilitate acetal hydrolysis prior to oxidative unmasking of the acid, avoiding potential difficulties in the ring opening.[3a] Tetraol **3** appeared readily accessible from diene **4** via a double Sharpless asymmetric dihydroxylation[6,7] using the recently developed $(DHQ)_2AQN$ ligand[6b] to properly set the C-8 stereocenter. To access tetraacetate **2** from **3** would require an inversion to secure the natural C-4 configuration of KDN. The diene **4** was envisioned as the product of a ring-closing metathesis reaction of pseudo-C_2-symmetric triene **5**, which could be obtained via an intermolecular ketalization/elimination sequence[1] between enantiomerically pure diene diol **6**[7] and ketone **7**.[8]

The formal synthesis of KDN began with an acid catalyzed ketalization between **6** and **7**, both of which were readily prepared on a large scale by modified literature procedures (Scheme 1).[7,8] Careful optimization was needed

Scheme 1. Synthesis of Tetraol **3**



due to inhibition of the reaction by the electron rich aromatic ring and the known instability of γ-haloketones.[9] Refluxing a benzene solution of diene diol **6** (1 equiv, 0.5 M), CSA (0.1 equiv), and ketone **7** (2 equiv) with azeotropic removal of water gave ketal **8** (90%) on a 10 g scale. Selenide displacement, oxidation, and eliminination following Sharpless' procedure[10] produced triene **5** in 96% yield. All attempts to prepare **5** by ketalization between diene diol **6** and the appropriate β,γ-unsaturated ketone gave only the product resulting from double bond migration.

With triene substrate **5** in hand, ring-closing metathesis proceeded readily using the Grubbs ruthenium benzylidene catalyst **9** (0.02 equiv, Scheme 1).[11] This reaction was best performed by adding the catalyst in benzene slowly over 1.5 h to a refluxing solution of **5** in benzene (0.01 M), giving 5-aryl-7-vinyl-6,8-dioxabicyclo-[3.2.1]oct-2-ene **4** (91%). A double dihydroxylation using the conditions previously

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reported[7] provided tetraol **3** (94%) as white pellets after chromatography to remove iron salt impurities and recrystallization from EtOAc to remove coeluting anthraquinone ligand. No other stereoisomers were detected in the ^{1}H NMR of **3** before or after recrystallization. Use of the $(DHQ)_2AQN$ ligand,[6b] which has been shown to increase the rate and stereoselectivity of reactions with terminal alkenes, was needed for dihydroxylation of the terminal olefin to occur. When commercially available AD-mix-α was used, only the internal olefin experienced dihydroxylation.

While the rigid bicyclic framework of **3** clearly set the stereochemistry of the C-4, C-5 vicinal diol on the six-membered ring as evidenced by ^{1}H NMR coupling constants (H-3_{ax}:H-4 = 11 Hz; H-3_{eq}:H-4 = 6.5 Hz; H-4:H-5 = 4 Hz), the C-8 stereochemistry could not be determined by NMR. To confirm that this stereocenter had been correctly set, **3** was converted to dithionocarbonate derivative **10** (Figure 3).

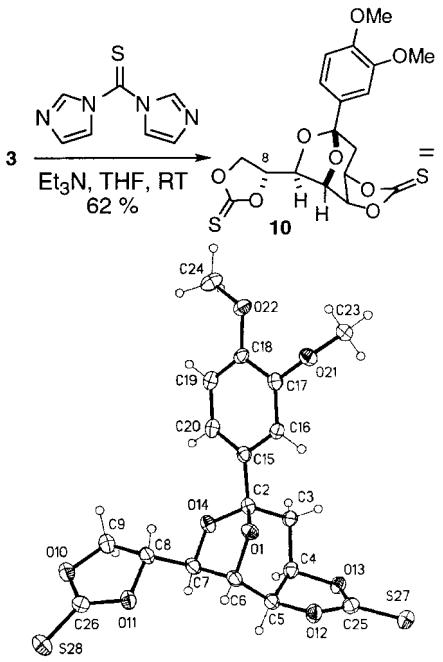
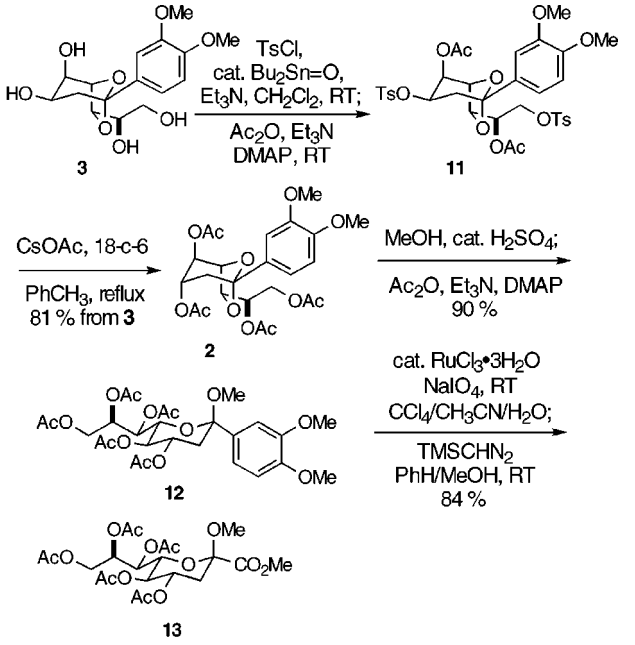


Figure 3. Determination of C-8 stereochemistry.

This material was recrystallized (acetone/MeOH), and its structure was confirmed by X-ray crystallography.[12]

Inversion of the C-4 stereocenter to reveal the natural configuration of KDN required differentiation of the four hydroxyls in **3**. This was cleanly accomplished by a tin-catalyzed tosylation reaction (Scheme 2).[13] While this recently reported reaction had only been used for the rapid monotosylation of the primary hydroxyl of an acyclic 2°, 1° vicinal diol, both the equatorial and primary hydroxyls of tetraol **3** were selectively sulfonylated without detection of any other disulfonylation products. Stirring a suspension of **3** in methylene chloride (0.05 M) with *p*-toluenesulfonyl chloride (2.1 equiv), triethylamine (2.1 equiv), and dibutyltin oxide (0.05 equiv) for 12 h gave an unstable ditosylate that

Scheme 2. Completion of the Total Synthesis



was peracetylated to give ditosylate diacetate **11**. The use of stoichiometric amounts of tin for stannylene acetal formation to achieve selective equatorial protection of a sugar-derived cis vicinal diol is well-known,[14] but this is the first example using a catalytic amount of tin.[15]

Because of its limited stability, **11** was routinely taken on to the next reaction by addition of toluene to the combined pure fractions of **11** after column chromatography. Following evaporation of the chromatography solvent (ether), cesium acetate (10 equiv) and 18-crown-6 (2 equiv) were added. Heating at reflux for 18 h gave inverted tetraacetate **2**[16] (81% overall from **3** after one recycling of recovered monotosylate triacetate). This sluggish S_N2 reaction failed when other solvents or oxygen nucleophiles were utilized.

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After some experimentation, it was found that simply adding a drop of sulfuric acid to **2** in methanol at 0 °C cleanly gave methyl glycoside **12** after 3 h (90%, 100% based on recovered **2**), following acetylation of the initially formed methanolysis product. Longer reaction time or increased temperature gave several polar acetate cleavage products which could all be converted to **12** and **2** after peracetylation, but this lowered the yield slightly and did not significantly improve the overall conversion.

Final unmasking of the carboxylic acid function was best achieved using RuO_4, formed in situ by adding a catalytic amount of $RuCl_3 \cdot 3H_2O$ (0.05 equiv) to a 2:2:3 $CCl_4/CH_3CN/H_2O$ mixture containing **12** and $NaIO_4$ (12 equiv).[5b−e,17] After 3 h at ambient temperature, clean conversion to KDN pentaacetate methyl glycoside was achieved, isolated as methyl ester **13** (84%), for which all data (^{1}H NMR; melting point; IR; HRMS; and optical rotation) were in agreement with the literature.[18,19] The formal synthesis of KDN has thus been achieved in 45% overall yield from diene diol **6**, employing our convergent ketalization/ring-closing metathesis strategy. Global deprotection of **13** has been achieved previously by moist methanol/sodium methoxide ester cleavage[19a] and methyl glycoside hydrolysis (refluxing $AcOH/H_2O$).[3a] This efficient and unique entry to KDN synthesis should make possible the stereocontrolled construction of various KDN derivatives due to the conformationally defined bicyclic acetal template and readily differentiated hydroxyls in the 2,7-anhydro sugar analogue **3**. The synthesis of other sialic acids via this route is presently being pursued and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **2**−**5**, **7**, **8**, and **10**−**13**; comparison of full characterization for **13** with literature data; X-ray crystallographic data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Data for **13**: ^{1}H NMR ($CDCl_3$) δ 5.42 (dd, J = 5.5, 2.5 Hz, 1H), 5.32 (ddd, J = 11.5, 10, 5 Hz, 1H), 5.31 (ddd, J = 6.5, 5.5, 2 Hz, 1H), 4.90 (t, J = 10 Hz, 1H), 4.71 (dd, J = 12.5, 2.5 Hz, 1H), 4.15 (dd, J = 12.5, 6.5 Hz, 1H), 4.06 (dd, J = 10, 2 Hz, 1H), 3.82 (s, 3H), 3.26 (s, 3H), 2.52 (dd, J = 13, 5 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.84 (dd, J = 13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6 (C), 170.2 (C), 170.00 (C), 169.92 (C), 169.8 (C), 167.1 (C), 98.7 (C), 70.8 (CH), 69.9 (CH), 69.1 (CH), 67.8 (CH), 67.4 (CH), 62.0 (CH_2), 52.7 (CH_3), 51.3 (CH_3), 36.9 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 20.72 (CH_3), 20.67 (CH_3), 20.6 (CH_3); IR (thin film) 2956, 1748, 1373, 1220, 1050 cm^{-1}; $[\alpha]^{24}_D$ −6.8° (c = 0.28, $CHCl_3$); mp 115−116 °C; HRMS (FAB) calcd. for $C_{21}H_{30}O_{14}Na$ ($M+Na^+$) 529.1533, found 529.1555.