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Alkylidenecarbene insertion at anomeric C–H bonds. Synthesis of 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) and 3-deoxy-D-*manno*-2-octulosonic acid (KDO)

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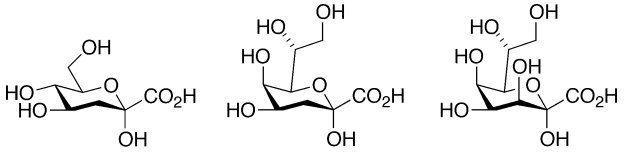
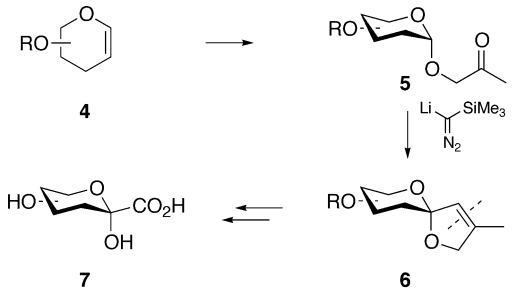
Abstract—A novel method for the homologation of glycals to the corresponding 3-deoxy-2-ulosonic acids, based on the [1,5]-C–H bond insertion of alkylidenecarbenes, is presented. The application of this approach is illustrated through the synthesis of 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) and 3-deoxy-D-*manno*-2-octulosonic acid (KDO). © 2002 Published by Elsevier Science Ltd.

The ulosonic acids are a family of complex monosaccharides that participate in a wide range of biological processes. 3-Deoxy-D-*arabino*-2-heptulosonic acid (DAH, **1**), for example, is a key intermediate in the biosynthesis of aromatic amino acids in plants and bacteria via the shikimic acid pathway,[1] while 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **2**)[2] and D-*glycero*-D-*talo*-octulosonic acid (KO, **3**)[3] are key components of the lipopolysaccharides (LPS) present on the surface of Gram-negative bacteria. The increasing occurrence of bacterial pathogens resistant to antibiotics, has stimulated much interest in the biosynthesis of shikimic acid and LPS, which are essential for normal bacterial cell growth yet absent in humans.[4] It is not surprising then, given the pivotal role which ulosonic acids play in these pathways, that there is much interest in the development of synthetic routes to DAH (**1**),[5] KDO (**2**),[6] KO (**3**),[7] and analogs of these natural products.[8]



We recently reported a novel method for the preparation of [4.5]spiroketal glycosides **6** based on the [1,5]-C–H insertion reaction of alkylidenecarbenes generated from 2-oxopropyl glycosides **5**.[9] As part of a study to examine the use of these insertion products as synthetic building blocks, we now report the preparation of DAH (**1**) and KDO (**2**) using the strategy outlined in Scheme 1. We envisioned that a range of ulosonic acids **7** could be readily accessed via homologation of glycals **4** through a sequence of glycosylation, alkylidenecarbene C–H insertion, to form **6**,[10] and oxidative cleavage of the dihydrofuran ring to unmask the C-2 carboxylate group. In addition to being applicable to a variety of glycal precursors, we anticipated that this approach would also offer an entry point to 3-substituted ulosonic acids, including KO (**3**) as well as provide conformationally restricted scaffolds, i.e. **6**, with which to construct analogs of **1** and **2**.



Scheme 1. A general approach to the synthesis of ulosonic acids from glycals based on the [1,5]-C–H insertion reaction of alkylidenecarbenes.

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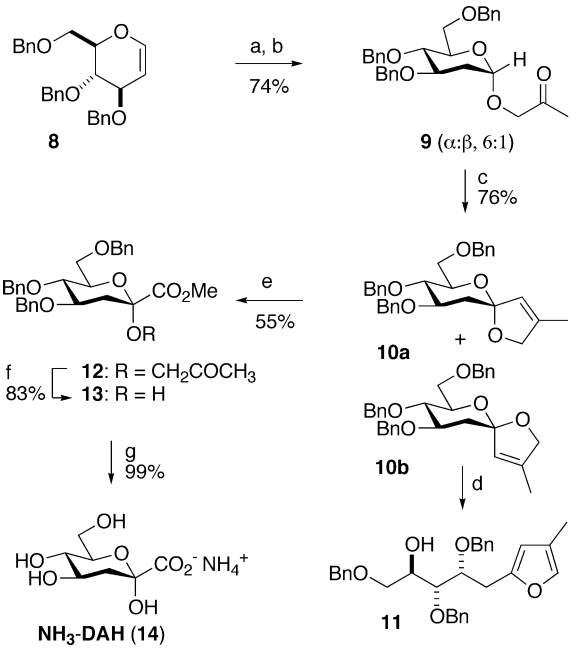
Our route to **1** commenced from tri-*O*-benzyl-D-glucal (**8**)[11] which underwent efficient glycosylation with methallyl alcohol, in the presence of triphenylphosphine hydrobromide (TPHB),[12] to provide a chromatographically inseparable mixture of 2-deoxy glycosides (Scheme 2). This mixture was then subjected to Lemieux–Johnson oxidation, which provided the corresponding 2-oxopropyl glycosides **9** (α:β, 6:1) in high yield. Upon addition of this mixture of ketones to a solution of [(trimethylsilyl)diazomethane]lithium in THF at −78°C,[13] insertion proceeded with retention of configuration to provide spiroketal glycosides **10a** and **10b** in 76% yield, again in a 6:1 ratio. While these compounds proved to be chromatographically inseparable, brief exposure to aqueous ammonium chloride triggered the selective rearrangement of the minor spiroketal diastereomer **10b** to furan **11**.[14] This alcohol could then be easily separated by flash chromatography to provide pure **10a** in 65% overall yield from **9**.

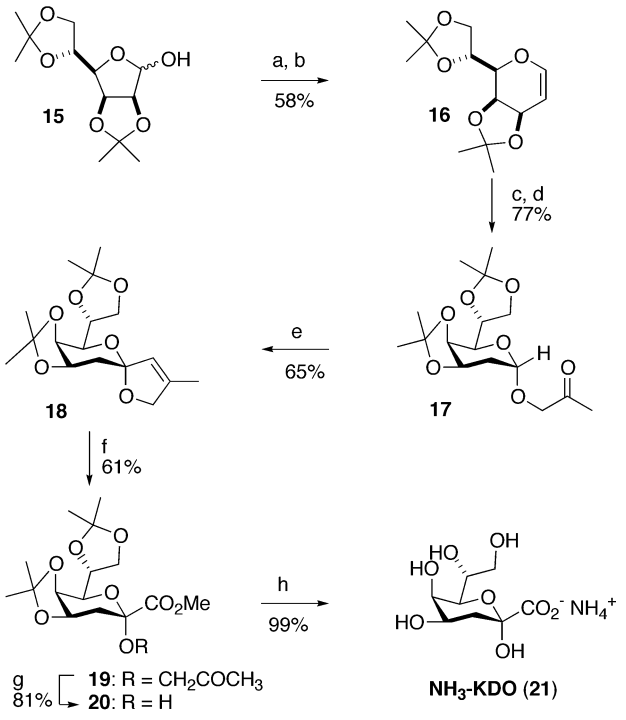
Ozonolysis of dihydrofuran **10a** now gave the expected keto aldehyde which, because of its instability, was immediately subjected to a sequence of Pinnick oxidation ($NaClO_2$)[15] and methylation (CH_2N_2) to provide DAH glycoside **12** in an overall yield of 55% from **10a**. The relative stereochemistry of the anomeric center of **12** was determined using a gated proton decoupled ^{13}C NMR experiment which revealed a $J_{C\text{-}1,H\text{-}3ax}$ value of 1.0 Hz that is consistent with the expected α-anomer.[16]



Scheme 2. Synthesis of DAH (**1**). *Reagents and conditions*: (a) methallyl alcohol, TPHB (3 mol%), CH_2Cl_2, rt, 15 min, 80%; (b) OsO_4 (2 mol%), $NaIO_4$, THF, H_2O, rt, 2.5 h, 95%; (c) $Me_3SiCLiN_2$, THF, −78→0°C, 90 min, then $NaHCO_3$, H_2O, 76%; (d) NH_4Cl, H_2O, rt, 10 min; (e) (i) O_3/O_2, CH_2Cl_2, −78°C, 5 min, then Zn, AcOH, 3 h, (ii) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, 2-methyl-2-butene, 6 h, (iii) CH_2N_2, Et_2O, 0°C, 2 min, 55% from **10a**; (f) SmI_2, THF, MeOH, −78°C, 5 min, 83%; (g) (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 3 h, (ii) NaOH, MeOH, H_2O, rt, 2 h, then Dowex 50W, 99%.

Removal of the 2-oxopropyl group was then accomplished by treatment of **12** with 2 equiv. of samarium diiodide in methanol,[17] which selectively cleaved the C–O bond of the α-alkoxy ketone to furnish hemiacetal **13** as a single α-anomer. No further reduction was observed; α-alkoxy esters are known to be inert under these conditions.[17] Finally, hydrogenolytic removal of the *O*-benzyl groups, saponification of the ester moiety and ion exchange with DOWEX 50W resin afforded DAH (**1**), which was then converted to the ammonium salt **14** by treatment with ammonia in methanol. The spectral and physical properties of this material were in accordance with those previously reported.[18]

Our synthesis of KDO (**2**) began from 2,3,5,6-di-*O*-isopropylidene-D-*manno*-furanose (**15**),[19] which underwent olefination with the Wittig reagent derived from (methoxymethyl)triphenylphosphonium chloride to provide a chromatographically inseparable mixture of enol ethers (*E*:*Z*, 7:3) in excellent yield (Scheme 3).[20] Pyrolysis of this material, under reduced pressure in the presence of catalytic $Hg(OAc)_2$, now gave **16** through intramolecular vinyl transetherification.[21]



Scheme 3. Synthesis of KDO (**2**). *Reagents and conditions*: (a) $Ph_3PCH_2(OMe)Cl$, *t*-BuOK, THF, reflux, 4 h, 96%; (b) $Hg(OAc)_2$ (30 mol%), 110°C, 20 mmHg, 3 h, 60%; (c) methallyl alcohol, TPHB (3 mol%), CH_2Cl_2, rt, 15 min, 81%; (d) OsO_4 (2 mol%), $NaIO_4$, THF, H_2O, rt, 2.5 h, 95%; (e) $Me_3SiCLiN_2$, THF, −78→0°C, 90 min, 65%; (f) (i) O_3/O_2, CH_2Cl_2, −78°C, 5 min, then Zn, AcOH, −78°C→rt, 3 h, (ii) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, 2-methyl-2-butene, rt, 6 h, (iii) CH_2N_2, Et_2O, 0°C, 2 min, 61% from **18**; (g) SmI_2, THF, MeOH, −78°C, 5 min, 81%; (h) (i) AcOH, H_2O, 90°C, 50 min, (ii) NaOH, H_2O, rt, 2 h, then Dowex 50W, (iii) NH_3, MeOH, 99%.

Acid-catalyzed (TPHB) addition of methallyl alcohol to this glycal proceeded with complete diastereoselectivity to yield the α-glycoside which, upon oxidative cleavage, was converted to 2-oxopropyl glycoside **17** in good overall yield. Exposure of this ketone to [(trimethylsilyl)diazomethane]lithium, as before, now furnished spiroketal glycoside **18** as a single diastereomer in 65% yield. Ozonolysis of **18** gave the keto aldehyde, which was converted to KDO α-glycoside **19** through oxidation ($NaClO_2$) and methylation (CH_2N_2). Treatment of this glycoside with SmI_2 then furnished hemiacetal **20** as a 5:1 mixture of α and β anomers respectively.[22]

Removal of the isopropylidene groups and saponification of the methyl ester now furnished KDO (**1**), which was isolated and characterized as the crystalline ammonium salt **21**. A comparison of the spectral and physical properties of this material with those previously reported indicated a close match.[23]

In summary, we report a novel method for the preparation of ulosonic acids involving the homologation of glycals through a sequence of glycosylation, alkylidenecarbene C–H insertion and oxidative cleavage. This strategy was successfully applied to the synthesis of the natural products DAH (**1**) and KDO (**2**). Furthermore, compounds **12** and **19** are potential masked DAH and KDO glycosyl donors; 2-oxopropyl glycosides are readily converted, via Baeyer–Villiger oxidation, to the corresponding *O*-acetoxymethyl glycosides, which Mereyala has recently developed as a novel class of glycosyl donors.[24] Further studies aimed at establishing this possibility and expanding our synthetic approach to other ulosonic acids are currently underway.

Acknowledgements

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