Formal Synthesis of 3-Deoxy-D-*manno*-Octulosonic Acid (KDO) and 3-Deoxy-D-*arabino*-2-heptulosonic Acid (DAH)

Tapan Kumar Pradhan,[a] Chun Cheng Lin,[b] Kwok Kong Tony Mong*[a]

[a] Applied Chemistry Department, National Chiao Tung University (NCTU), Hsinchu, Taiwan, R.O.C.
Fax +886(3)5723764; E-mail: tmong@mail.nctu.edu.tw

[b] Chemistry Department, National Tsing Hua University (NTHU), Hsinchu, Taiwan, R.O.C

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Abstract: Practical synthetic routes to 3-deoxy-D-*manno*-octulosonic acid (KDO) and 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) from common sugar substrates are reported. Chain homologation of the sugar substrates was accomplished by Wittig olefination and Corey–Fuchs alkynylation. A new cyclization strategy was investigated to access the desired pyranosyl isomer of the KDO target.

Key words: carbohydrates, Wittig, Corey–Fuchs, cyclization

3-Deoxy-2-ulosonic acids constitute a specific class of acidic monosaccharides that are present in a wide range of complex oligosaccharides and glycoconjugates. These compounds have been found to play important roles in many biological systems.[1] For example, 3-deoxy-D-*manno*-octulosonic acid (KDO) is the key component of the core structure of a number of lipopolysaccharides (LPSs), which are found in nearly all members of Enterobacteriaceae bacteria (Figure 1).[2] *N*-Acetyl-neuraminic acid (Neu5Ac) is the non-reducing-end saccharide residue of most mammalian oligosaccharides.[3] 3-Deoxy-D-*arabino*-2-heptulosonic acid (DAH) is an intermediate generated in the biosynthesis of aromatic amino acids.[4] The potential use of 3-deoxy-2-ulosonic acids and their analogues as enzyme inhibitors or starting materials for complex oligosaccharide synthesis justifies the interest in developing practical schemes to prepare these carbohydrate targets.[5,6]

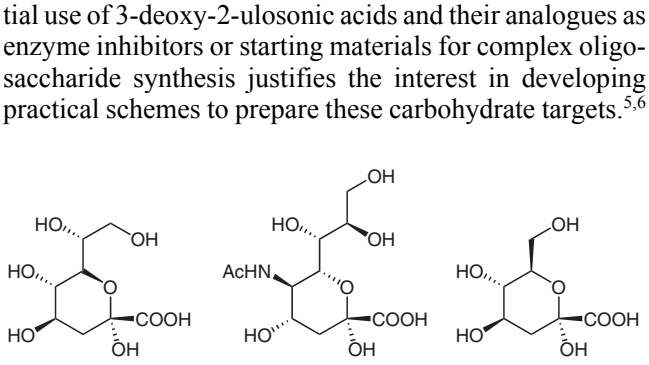
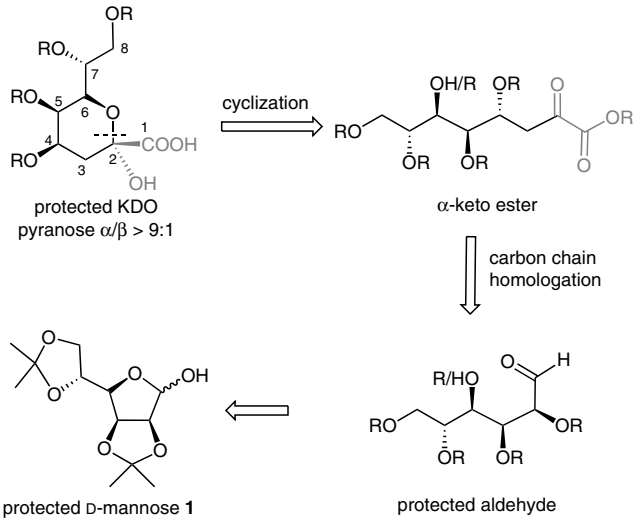


Figure 1 Structures of KDO, Neu5Ac, and DAH

In a project relating to the synthesis of complex lipooligosaccharides, gram quantities of KDO monosaccharide building blocks were required. Literature reports revealed that the KDO building blocks can be prepared from carbohydrate substrates with a shorter carbon chain or non-carbohydrate small molecules.[5] Particularly attractive is the use of the sugar substrates because the chirality of the substrates is incorporated into the desired KDO target. For practical reasons, the proposed scheme used D-mannose as a starting material. The typical procedure for KDO synthesis from carbohydrate substrates involves: (i) elongation of the sugar carbon chain, (ii) installation of an α-keto ester function, followed by (iii) cyclization of the α-keto ester to yield the desired pyranose isomer.

Previously, different approaches have been developed and the chemistry employed included: (i) ring-closing metathesis[5h] or Diels–Alder cycloaddition for formation of the pyranose scaffold,[7] and (ii) Horner–Emmons–Wittig reaction,[8] thiane anion addition,[5a] allylation,[9] or propargylation for elongation of the sugar chain.[10] Despite this progress, the possibility of adapting these methods for large-scale preparation remains a concern. A point in case is the cyclization step in KDO synthesis, in which formation of undesired furanose isomer occurs frequently;[5h,10] this creates difficulties in product purification and decreases the reaction yield. We herein report a new synthetic scheme for a fully protected KDO hemiacetal. The reported scheme is highly selective for the formation of the desired pyranose isomer. In addition, we applied the same strategy for the preparation of protected 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH).



Scheme 1 Retrosynthetic analysis

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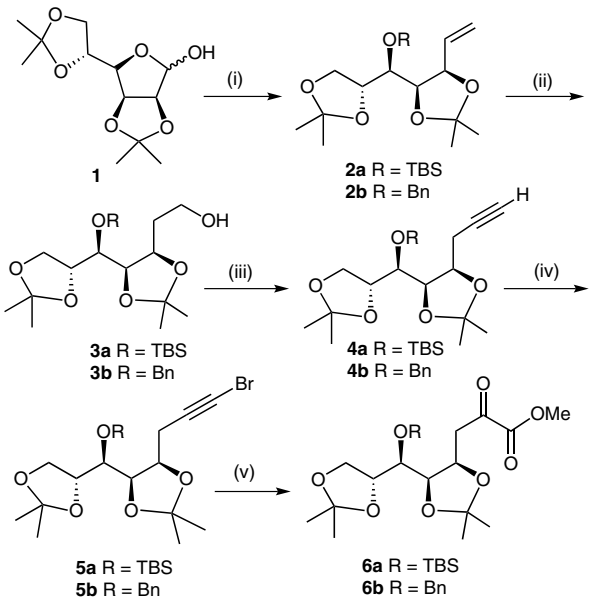
Scheme 1 lays out the retrosynthetic analysis of the KDO target. Disconnection at the C_2–O_{ring} bond gives a linear α-keto ester, which is derived from oxidative cleavage of an alkyne intermediate. The alkyne intemediate is made available from an acetonide-protected mannose precursor through olefination, hydroboration-oxidation, and Corey–Fuchs alkynylation. It should be noted that the proposed aldehyde precursor is derived from commercially available acetonide-protected D-mannose.

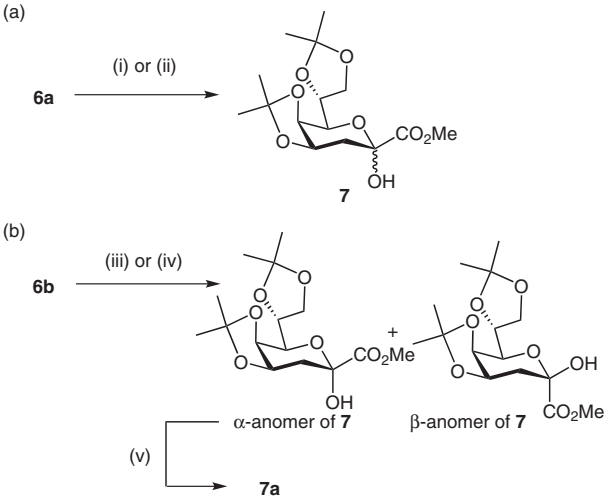
Synthesis of the target KDO commenced with diacetonide-protected D-*manno*-furanose, which was obtained from D-mannose by standard procedures.[11] The D-*manno*-furanose was submitted to Wittig olefination and subsequent protection of the C5 hydroxyl as the *tert*-butyldimethylsilyl ether function (TBS) furnished the expected alkene **2a** in 69% yield (Scheme 2). Regioselective reduction of **2a** by 9-BBN afforded alcohol derivative **3a** in high yield (75%) as a single regioisomer. Alcohol **3a** was oxidized to yield an aldehyde that underwent Corey–Fuchs reaction to afford the desired alkyne **4a**.[12] Conversion of **4a** into the desired α-keto ester **6a** was achieved by sequential bromination[13] and alkyne oxidative cleavage by $KMnO_4$.[10] At this stage, the desired KDO should be obtained after TBS ether deprotection and cyclization (Scheme 3). In practice, the silyl ether deprotection was non-trivial. Treatment of **6a** with either HF-pyridine[14] or TBAF/acetic acid[15] resulted in a complex reaction mixture, and the desired KDO pyranose isomer **7** was obtained in disappointing yield (20% at best). We reasoned that migration of the acetal function might occur during the deprotection, leading to the complex mixture of KDO diastereomers.[10,16]

Taking lessons from the aforementioned observations, we then employed neutral conditions in pyranose cyclization.

After olefination of **1**, the C5 hydroxyl function of the resulting alkene was protected with a benzyl ether function to give alkene **2b**. The latter was submitted to the same reaction sequence, affording the expected α-keto ester **6b** via intermediates **3b**, **4b**, and **5b**. The overall yield of **6b** was 29% from **2b**. Final deprotection of the benzyl ether in **6b** was conducted under mild hydrogenolysis conditions using Pd-C as the catalyst. To our delight, the resulting O-6 unprotected α-keto ester cyclized to furnish the KDO hemiacetal **7** in 90% yield without issue (Scheme 3). Unexpectedly, the α/β-anomeric ratio of **7** was found to be dependent on the solvent conditions. Hydrogenolysis in polar MeOH solution furnished **7** with ca. 1:1 α/β-anomeric ratio, but in less polar hexane–EtOAc (1:1) mixture, the α-anomer was formed predominantly (α/β, ≥9:1). For confirmation of the α-configuration, the α-anomer of **7** was converted into a known acetyl-protected α-KDO derivative **7a**, the NMR data of which were in good agreement with the literature data.[5h,17,18] For example, in the ^{1}H NMR spectra, the difference in chemical shift between the C3 axial and equatorial protons is 0.6 ppm; which is consistent with the literature value observed for the α-anomer of the KDO sugar (0.6–1.19 ppm) and, hence, confirms the α-configuration of **7a**.[18]



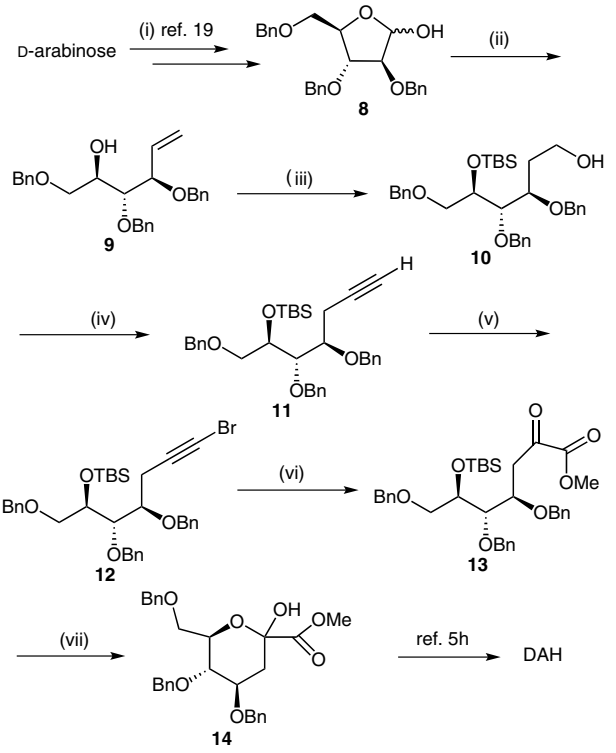
Scheme 2 *Reagents and conditions*: (i) $Ph_3P{=}CH_2$, THF, *t*-BuOK, –78 °C to r.t., 6 h (85%); For **2a**, TBSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C to r.t., 10 min (87%); For **2b**, BnBr, NaH, TBAI, THF, 0 °C to r.t., 6 h (93%); (ii) 9-BBN, THF, 0 °C to r.t., overnight, H_2O_2, 4% NaOH, 4–5 h; for **3a** 75% and for **3b** 70%; (iii) a. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 2 h; b. CBr_4, TPP, Et_3N, CH_2Cl_2, 0 °C, 2 h; c. or EtMgBr, THF, –78 to 0 °C, 1 h; for **4a** 65% over three steps and **4b** 70% over three steps; (iv) NBS, $AgNO_3$, acetone, 0 °C to r.t.; for **5a**, 30 min, 95% and for **6a**, 1 h, 85%; (v) $KMnO_4$, $NHCO_3$, $MgSO_4$, MeOH–H_2O (5:1), 0 °C; for **6a**, 4 h, 80% and for **6b**, 5 h, 75%.



Scheme 3 *Reagents and conditions*: (i) HF·Py, THF, 10 h, 20% (recovered yield); (ii) TBAF, acetic acid, THF, 0 °C, 10 min, product not isolable; (iii) 5% Pd/C, H_2, EtOAc–hexane (1:1 v/v), r.t., 10 h, 96%, α/β >9:1; (iv) 5% Pd/C, H_2, MeOH, r.t., 1–2 h, 90%, α/β ca. 1:1; (v) Ac_2O, pyridine, r.t., quantitative.

After preparation of the protected KDO **7**, we were interested in applying this method for the synthesis of other ulosonic acids. Thus, protected DAH was selected as the target, which was prepared from readily available D-arabinose. Scheme 4 outlines the synthetic route to our DAH target. The scheme commenced with per-*O*-benzyl D-ara-

binosyl hemiacetal **8**,[19] which underwent Wittig olefination, hydroxyl protection by TBS silyl ether, and hydroboration to give arabinotitol derivative **10** in 62% yield over three steps. The alditol was oxidized to furnish the desired aldehyde by Swern oxidation, and followed by conversion into alkyne **11** through Corey–Fuchs alkynylation. Subsequent bromination and $KMnO_4$-mediated oxidative cleavage of the alkyne produced the desired α-keto ester. Final deprotection of the TBS ether function at the C5 hydroxyl group furnished the protected α-anomer of DAH **14** in 67% yield (from **13**).[5h,20] Unlike the KDO synthesis, deprotection of the TBS function and cyclization took place under acidic conditions (HCl in $MeOH/CH_2Cl_2$ mixture), which favored α-anomer formation. In addition, because no acetal functions are present in **14**, complications arising from migration of the acetal groups were eliminated.



Scheme 4 *Reagents and conditions* (i) see Collam and Lowry;[19] (ii) $Ph_3P{=}CH_2$, THF, *t*-BuOK, –78 °C to r.t., 30 min, 80%; (iii) a. TBSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C to r.t., 10 min, 85%; b. 9-BBN, THF, 0 °C to r.t., overnight, H_2O_2, 4% aq NaOH, 5 h, 92%; (iv) a. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 2 h; b. CBr_4, TPP, Et_3N, CH_2Cl_2, 0 °C, 1 h; c. EtMgBr, THF, –78 to 0 °C, 1 h, 60% over three steps; (v) NBS, $AgNO_3$, acetone, 0 °C to r.t., 1 h, 93%; (vi) $KMnO_4$, $NaHCO_3$, $MgSO_4$, MeOH–H_2O (5:1), 0 °C, 2–3 h, 80%; (vii) 6% aq HCl, CH_2Cl_2–MeOH (2:3 v/v), 0 °C to r.t., 90%; (viii) see Hekking et al.[5h] TPP = triphenylphosphine; TBSOTf = *tert*-butyldimethylsilyl triflate.

In conclusion, we have developed a practical scheme for the preparation of protected 3-deoxy-D-*manno*-octulosonic acid (KDO) and 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) from small sugar substrates. The Wittig olefination and Corey–Fuchs alkylation were used to elongate the carbon chain. A new cyclization strategy was described that was used to obtain the desired KDO pyranose isomer in good yield.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) Analytical data of **7**: $[\alpha]_D^{33}$ +22.8 (*c* 0.326, $CHCl_3$) {Lit. 5h $[\alpha]_D^{22}$ +21.1 (*c* 0.25 in $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 5 H), 4.91 (d, *J* = 11.6 Hz, 1 H), 4.75 (d, *J* = 11.6 Hz, 1 H), 4.36 (dd, *J* = 12.9, 6.7 Hz, 1 H), 4.23–4.15 (m, 2 H), 4.09 (dd, *J* = 8.3, 6.4 Hz, 1 H), 3.96 (dd, *J* = 8.3, 7.7 Hz, 1 H), 3.91 (t, *J* = 4.5 Hz, 1 H), 2.60 (td, *J* = 2.9, 6.5 Hz, 1 H), 2.03 (t, *J* = 2.6 Hz, 1 H), 1.50 (s, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.3, 127.2, 108.8, 108.4, 80.5, 78.9, 77.7, 77.0, 75.4, 73.6, 70.1, 66.3, 26.9, 26.2, 25.6, 24.9, 20.3. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{24}O_8Na$: 355.1355; found: 355.1363
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(20) Analytical data of **14**: $[\alpha]_D^{33}$ +25.94 (*c* 0.175, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.12 (m, 15 H), 4.91 (d, *J* = 10.6 Hz, 1 H), 4.65 (dd, *J* = 17.3, 11.6 Hz, 2 H), 4.59 (d, *J* = 12.2 Hz, 1 H), 4.57 (d, *J* = 10.6 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 4.04 (m, 1 H), 3.83 (s, 3 H), 3.82–3.57 (m, 4 H), 2.30 (dd, *J* = 12.6, 5.0 Hz, 1 H), 2.09 (t, *J* = 12.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 138.4, 138.3, 138.2, 128.4, 128.3, 127.9, 127.8, 127.6, 127.6, 127.5, 94.9, 78.0, 77.5, 74.9, 73.3, 73.1, 71.8, 68.9, 53.3, 36.1; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{32}O_7Na$: 515.2030; found: 515.2040.

