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Synthesis of KDO and analogues from a novel mannose-derived precursor

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Abstract—The application of the readily available 1-thio-1,2-*O*-isopropylidene acetal (TIA) **6** (four steps from D-mannose) to the synthesis of analogues of KDO is illustrated by the preparation of KDO **1**, 1-deoxy-β-KDO **2** and the β-C-KDO glycoside **3**.

The incorporation of 3-deoxy-D-manno-octulosonic acid (KDO) **1** in the lipopolysaccharide (LPS) is a vital step in the assembly of the protective outer membrane of Gram-negative bacteria.[1] Since this mechanism is peculiar to these organisms, inhibitors of KDO metabolism are attractive as potential antibacterial agents.[2] Investigations have been primarily directed at two enzymic targets: KDO8P synthase, which catalyses the reaction of arabinose-5-phosphate (A5P) and phosphoenol pyruvate (PEP) to KDO-8-phosphate (KDO8P), and CMP-KDO synthetase, which mediates the condensation of KDO8P and cytidine pyrophosphate to cytidine-5′-monosphophate-KDO (CMP-KDO).[2] Accordingly the synthesis of analogues of intermediates associated with these processes have attracted attention (Fig. 1).[3] Herein, we illustrate the versatility of a novel precursor for KDO analog synthesis, 1-thio-1,2-*O*-isopropylidene acetal (TIA) **6**. The chemistry is applied to the syntheses of KDO **1**, 2-deoxy-β-KDO **2**,[4] a potent inhibitor of CMP-KDO synthetase, and the novel, 'exact', β-*C*-glycoside **3**.[5] The strategy for *C*-glycoside **3** lays the groundwork for the synthesis of complex, hydrolytically stable inhibitors of CMP-KDO synthetase and the subsequent lipid A transferase.[3h]

Our synthetic plan is based on the success of TIA's in oxocarbenium ion cyclizations.[6] Thus **6** and the appropriate acid partner **7** may be converted to C1-substituted glycals **4** or **5**. Hydration or reduction of **4** and synthetic manipulation of the furan residue would provide KDO **1** or 2-deoxy-β-KDO **2**. α-*C*-Alkylation on **5** would be a key step in the synthesis of **3** (Scheme 1).

TIA **6** was obtained in four straightforward steps from D-mannose. First, the known 1-*O*-acetate-1,2-*O*-isopropylidene **9**[7] was prepared in 92% yield by the Suarez procedure on 2,3,5,6-di-*O*-isopropylidene-mannofuranose **8**.[8] Treatment of **9** under controlled conditions with thiophenol and $BF_3{\cdot}OEt_2$, and hydrolysis of the product, then provided **6** in 45% yield from **9** (Scheme 2).

Conversion of **6** to enol ether **11** proceeded in 63% overall yield, and entailed DCC mediated esterification[9] with 2-furoic acid, followed by Tebbe methylenation[10] of the ester **10**. The key oxocarbenium cyclization on **11** was promoted by methyl triflate in dichloromethane in

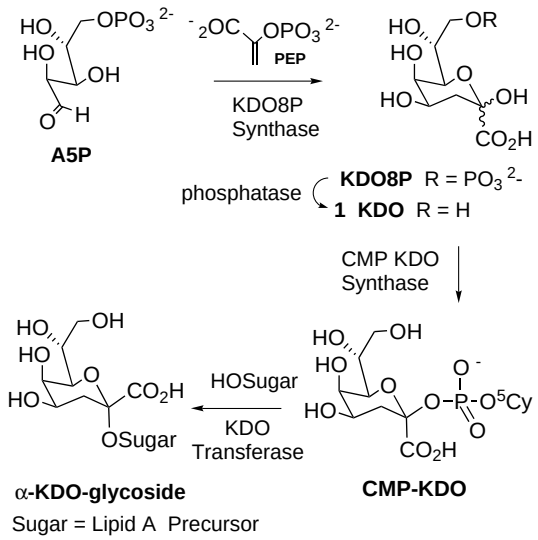

Figure 1. Biosynthesis of KDO α-glycosides.

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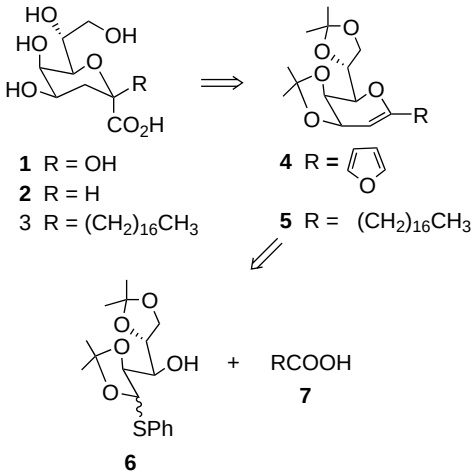
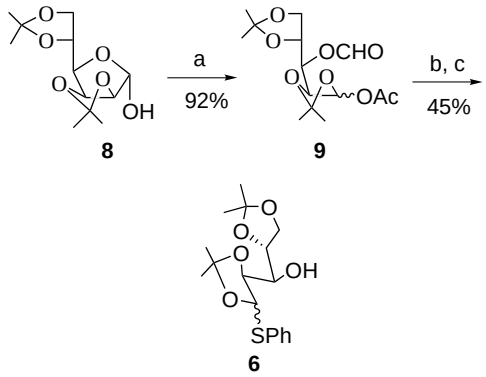


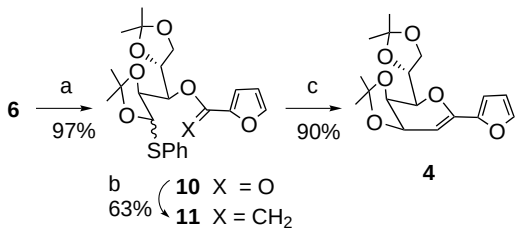
Scheme 1.



Scheme 2. (a) Iodosobenzene diacetate, I_2, cyclohexane; (b) PhSH, CH_2Cl_2, $BF_3{\cdot}OEt_2$, –40°C; (c) NaOMe, MeOH.

the presence of 2,6-di-*tert*-butyl-4-methylpyridine. The desired glycal **4** was obtained in 92% yield (Scheme 3).

Methanolysis of **4**, followed by oxidative degradation of the furan,[11] proceeded smoothly providing a single ketal acid **12**. Hydrogenation of glycal **4**, followed by processing of the furan as before and methylation of the resulting acid, gave a single methyl ester **13**. The structures of **12** and **13** were confirmed by comparison with NMR data for the known compounds.[5b,12] The preparation of **12** and **13** constitutes formal syntheses of KDO **1** and 2-deoxy-β-KDO **2**. It is known that acid hydrolysis of **12** leads to **1**,[12] and base mediated isomerization of **13**, followed by acetal hydrolysis, has been shown to give **2**[4] (Scheme 4).



Scheme 3. (a) 2-Furoic acid, DCC, DMAP, PhH; (b) Tebbe reagent, THF–toluene (3:1), pyridine, –78 to 0°C; (c) MeOTf, DTBMP, CH_2Cl_2, MS.

Alkylation of the enolate derived from methyl ester **13** with simple electrophiles is known to give predominantly β-*C*-glycosides of KDO.[5b] The use of complex electrophiles in this reaction has not been reported. As a model study for the synthesis of β-*C*-glycosides containing more complex aglycone segments, we examined the reaction of glycal **5** with different nucleophiles. Thus, application of the two-step esterification-Tebbe protocol on TIA **6** and stearic acid provided the enol ether **14** in 82% yield from **6**. Methyl triflate-promoted cyclization of **14** afforded glycal **5** in 60% yield, together with 10% of the hydrated derivative. Attempts at alkylation of the oxocarbenium intermediate presumed to be generated in the cyclization reaction, or in the acid treatment of glycal **5**, led to low yields of alkylated product. The alkylation of the thioacetal **15** derived by addition of thiphenol to **5** was more successful. Treatment of **15** with propargyltrimethylsilane[13] and $SnCl_4$ gave a single allenyl adduct **16** in 65% yield. The configuration of **16** was confirmed by observation of a NOE between one of the allenyl protons and the axial proton at C6 (KDO numbering). Ozonolysis of the allenyl residue in **16**, oxidation of the derived aldehyde, and acetal hydrolysis provided β-*C*-glycoside **3** (Scheme 5).

In summary, the easily accessible TIA **6** (35%, four steps from D-mannose) has been shown to be a versatile precursor for the synthesis of KDO and analogues. The syntheses of KDO **1** and 2-deoxy-β-KDO **2** proceeds through the central furanoglycal **4**, which may also be used as a precursor to 3-substituted analogues. The synthesis of *C*-glycoside **3** represents a potentially general strategy for the assembly of complex KDO-β-*C*-glycosides. These directions, as well as the evaluation of furanoglycal **4** and related glycals as KDO glycosyl donors, are being pursued.

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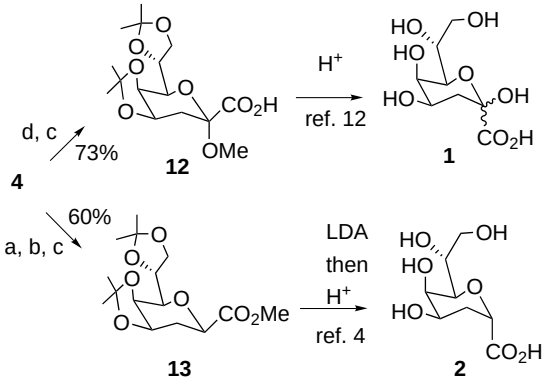
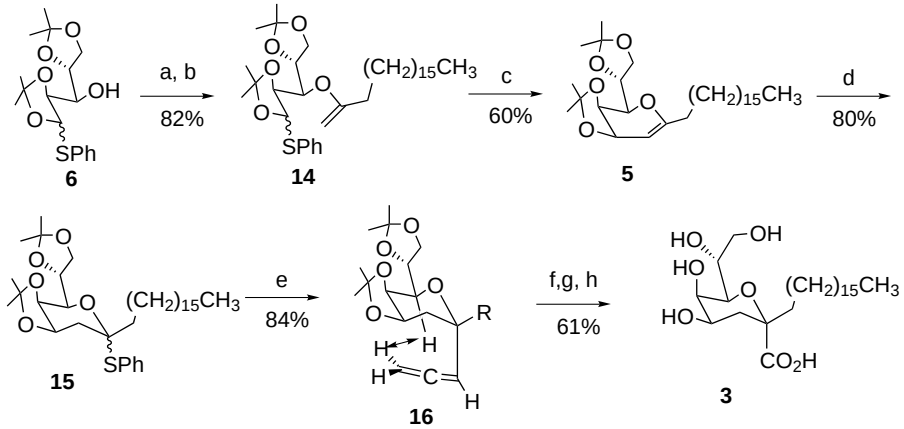


Scheme 4. (a) H_2, Pd/C, EtOAc; (b) RuO_2, $NaIO_4$, CH_3CN; (c) CH_2N_2; (d) MeOH, CSA.



Scheme 5. (a) Stearic acid, DCC, DMAP, PhH; (b) Tebbe reagent, THF–toluene (3:1), pyridine, −78 to 0°C; (c) MeOTf, DTBMP, CH_2Cl_2, MS; (d) PhSH, $Ph_3P{\cdot}HBr$; (e) $SnCl_4$; propargylTMS, CH_2Cl_2; (f) O3 then Ph_3P; (g) $NaClO_2$; (h) 2N HCl–THF.

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