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Concise synthesis of 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO) as a protected form based on a new transformation of α,β-unsaturated ester to α-oxocarboxylic acid ester via diol cyclic sulfite

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Abstract—A concise synthesis of KDO (**1**) as the suitably protected form (**2**) from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**3**) was achieved in five steps (overall 65% yield). The key step is the efficient transformation of readily available α,β-unsaturated ester to α-oxocarboxylic acid ester. The newly β-elimination of the corresponding diol cyclic sulfite and the in situ trap (DBU/TMSCl) into enol silyl ether was developed to give the tautomeric equivalent of α-oxocarboxylic acid ester. The deprotection of acid labile TMS ether provided the desired product.

3-Deoxy-D-*manno*-oct-2-ulosonic acid (KDO, **1**) is a component in the outer membrane lipopolysaccharide (LPS) of Gram-negative bacteria and connected with the lipophilic part (lipid A) via α-ketoside linkage.[1] (Fig. 1).

Its biological as well as medicinal importance invoked chemical[2,3] and enzymatic[4] syntheses. Among them, carbohydrate-based chemical synthesis, starting from D-mannose (six carbons) via two-carbon elongation is the most reliable. All of them put special emphasis on the elaboration of the two-carbon unit, which is later converted to α-oxocarboxylic acid moiety. Inspired by the result that a cyclic sulfate of a terminal diol had been converted to a methyl ketone,[5] we proposed the base treatment of cyclic sulfite **B** (Fig. 2). The β-elimination

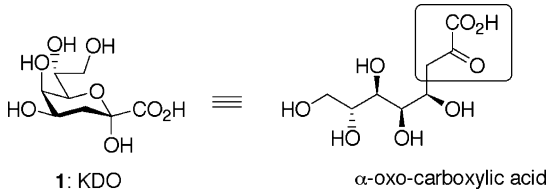

Figure 1.

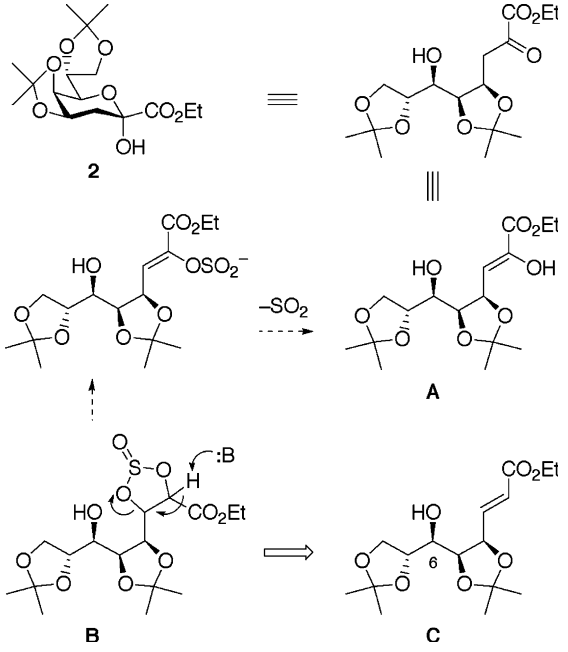

Figure 2.

Keywords: KDO; Cyclic sulfite; β-elimination.
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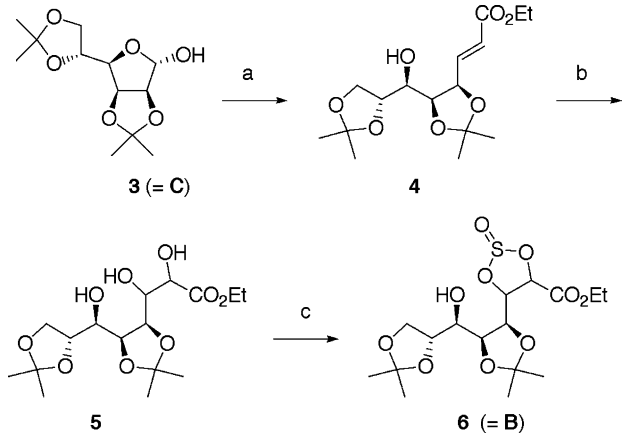
and the subsequent release of SO_2 from the unstable sulfite intermediate would provide the enol **A**. This transformation might have an advantage that the starting material **C** is applied without any protection on C-6 hydroxyl group.

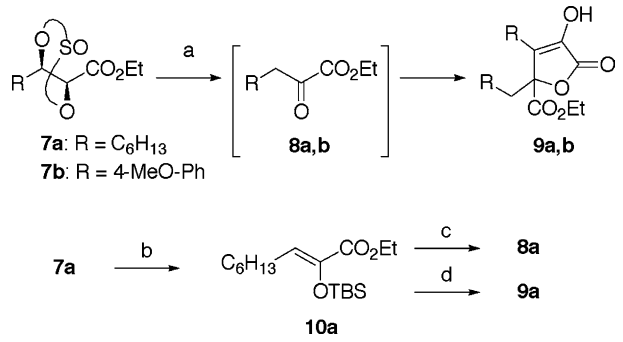
Toward this end, Wittig olefination[6] of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **3** afforded **4** as the mixture of geometrical isomers (E/Z = 18/1). The crude material was passed through a short column of silica gel to remove triphenylphosphine oxide and the products were dihydroxylated to give a stereoisomeric mixture of **5** (dr = 38:16:2:1) in 90% yield from **3**. As expected, the C-6 hydroxyl group was well distinguished by the five-membered cyclic sulfite formation to give the key intermediate **6** (= **B**) (Scheme 1).

The initial attempt of the base treatment achieved miserable results of a very complex mixture. At this stage, the aldol reaction of the resulting enol form **A** onto the tautomeric keto form was suspected, and we made simple model studies. Indeed, when cyclic sulfite **7** was treated with DBU, the major product was the self-condensed butyrolactone **9**.[7] The possible intermediate, enolate was effectively trapped with the silylating reagent, TBSCl to give an enol ether **10a** with pure (Z)-configuration (87% from **7a**). The deprotection under fluoride-mediated acidic conditions (TBAF-AcOH) provided the desired α-oxocarboxylic acid ester **8a** in 90% yield. The basic conditions (TBAF) again forced the deprotection reaction to the self-condensed product **9** (91%) (Scheme 2).

Encouraged by these results, we treated the cyclic sulfite **6** with DBU (4.0 equiv) in the presence of TMSCl (3.8 equiv). The enol product was trapped as a bis-TMS ether **11**, but the labile nature enabled the simultaneous deprotection of hydroxyl group on C-6 to give **2**[8] in 75% yield. The advantage of the TMS group is shown as below. When the similar reaction was attempted using TBSCl, even with a low equivalent (1.5 equiv), the formation of bis-TBS ether **12b** could not be avoided (10%,



Scheme 1. (a) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 6 h (E/Z = 18/1); (b) OsO_4, NMO, acetone–H_2O (2/1), rt, 10 h (90% in two steps); (c) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min.



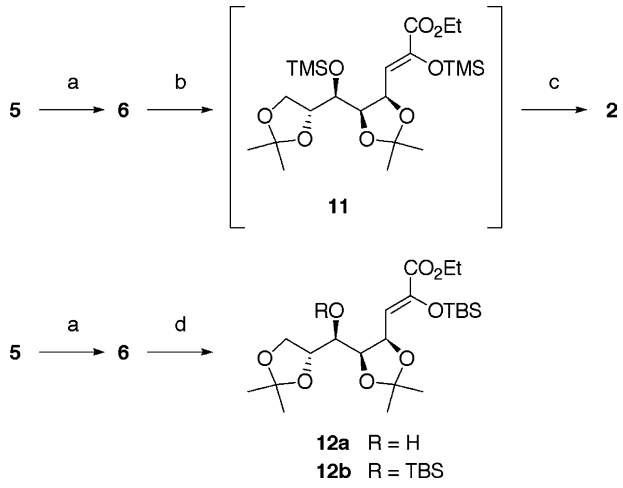
Scheme 2. (a) DBU, CH_2Cl_2, rt, 2 h (**9a**: 89%), 0 °C, 38 h (**9b**: 75%); (b) DBU, TBSCl, THF, 0 °C to rt, 4 h (87%); (c) TBAF, AcOH, THF, rt, 12 h (90%); (d) TBAF, THF, 0 °C, 30 min (91%).

12a[9]: 62%), which in turn made the deprotection of TBS group (especially at C-6) very difficult (Scheme 3).

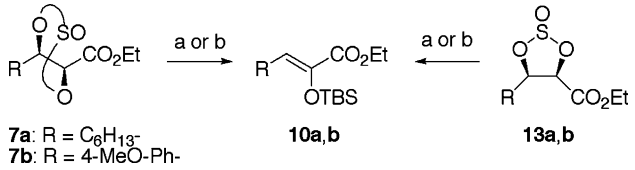
In this way, a very short-step synthesis of the protected form of KDO (**2**), which is compatible with the chemical glycosylation was achieved; in only five steps from D-mannose derivative **3** of high availability.

In our elimination-based synthesis, the intermediate **6** consisted of four stereoisomers and the major *trans* isomers and the minor *cis* isomers equally transformed to products as the single isomer. We became interested in the reaction pathway of the β-elimination and independently submitted the *trans* (**7a**,**b**) and *cis* (**13a**,**b**) isomers. Surprisingly, both materials provided the (*Z*)-configured products (**10a**,**b**), and the stereocourse did not depend upon the solvents (THF/CH_3CN) (Scheme 4).

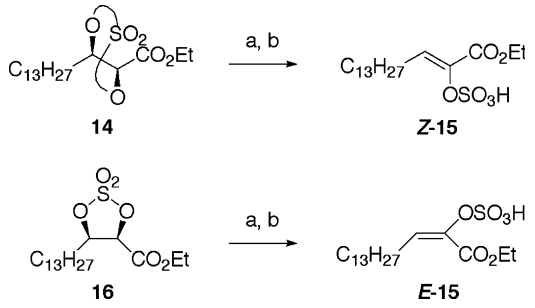
In contrast, when a *trans* cyclic sulfate **14** was submitted to a similar β-elimination reaction, the resulting enol sulfate [*Z*-15] had a *Z*-configuration with considerable stability and was isolated in 94% yield. From the isomeric *cis* cyclic sulfate **16**, *E*-**15** was obtained in quan-



Scheme 3. (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) DBU, TMSCl, THF, −60 °C to rt, 2 h; (c) 1 M HCl, 0 °C, 1 h (75% in three steps); (d) DBU, TBSCl, THF, −78 °C to −60 °C, 45 min (**12a**: 62%, **12b**: 10% in two steps).



Scheme 4. (a) DBU, TBSCl, THF, 0 °C to rt, 4 h (87% from **7a**), 1 h (77% from **13a**); (b) DBU, TBSCl, CH_3CN, rt, 1 h (99% from **7b**, 83% from **13b**).



Scheme 5. (a) DBU, CH_2Cl_2, 0 °C, 10 min; (b) aq NH_4Cl, 0 °C, 10 min (***Z*-15**: 97% from **14**, ***E*-15**: 99% from **16**).

titative yield and the results clearly show the reaction proceeded by *trans* anti-elimination. In turn, the lower stability of enol sulfite than that of enol sulfate might cause the isomerization of *E*-enol to stable *Z*-enol via α-oxocarboxylic acid ester before being trapped by TBSCl under the reaction conditions. However, there was no positive evidence by the TLC detection of α-oxocarboxylic acid ester during the reaction (Scheme 5).

In conclusion, a concise synthesis of KDO was achieved based on a new β-elimination reaction of cyclic sulfite as the key step.

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7. The self-condensation could be avoided by lowering concentration of the substrate (12 mM) and by trapping of enolate with the excessive base (3.3 equiv). The reverse addition of substrate to the base was also efficient. As a result, the yield of **8a** increased to 82%. However, **2** could not be obtained from **6** by the improved procedure.
8. Ethyl 4,5:7,8-di-*O*-isopropylidene-3-deoxy-β-D-*manno*-2-octulopyranosonate (**2**): To a solution of **5** (159 mg, 0.44 mmol) in 5 mL of CH_2Cl_2 was added Et_3N (0.18 mL, 1.3 mmol) and thionyl chloride (0.050 mL, 0.66 mmol) and the mixture was stirred for 1 h at 0 °C under N_2 atmosphere. The mixture was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with a saturated NH_4Cl solution and brine and dried over Na_2SO_4. The solvent was evaporated in vacuo to afford cyclic sulfite **6**. To a solution of crude **6** in 5 mL of THF was added TMSCl (0.17 mL, 1.3 mmol) and DBU (0.26 mL, 1.8 mmol) at −60 °C under N_2 atmosphere and then the mixture was warmed to room temperature. After stirring 2 h, the mixture was cooled to 0 °C and 1 mL of 1 M HCl was added and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The conventional workup and chromatography (*n*-hexane:ethyl acetate = 7:1) gave **2** (113 mg, 0.33 mmol) in 75% yield from **5**: $[\alpha]_D^{24}$+28.9 (*c* 0.950, $CHCl_3$) [lit.[3c] $[\alpha]_D^{24}$+29.1 (*c* 1.6, $CHCl_3$)]; IR (NaCl) 3403, 2937, 2986, 1742, 1455, 1372, 1218, 1151, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, $J = 6.9$ Hz, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 1.47 (s, 3H) 1.89 (dd, $J = 4.9$, 14.6 Hz, 1H), 2.50 (dd, $J = 6.3$, 14.6 Hz, 1H), 3.70 (s, 1H), 3.90 (dd, $J = 2.0$, 8.3 Hz, 1H), 4.00 (dd, $J = 4.4$, 8.8 Hz, 1H), 4.08 (dd, $J = 5.9$, 8.8 Hz, 1H), 4.24–4.30 (m, 3H), 4.35 (ddd, $J = 2.0$, 4.4, 5.9 Hz, 1H), 4.51 (ddd, $J = 4.8$, 6.3, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 25.4, 25.8, 27.0, 27.1, 32.3, 62.4, 66.8, 69.9, 70.5, 71.3, 73.9, 94.3, 109.1, 109.3, 169.5; HRMS (FAB) calcd for $C_{16}H_{28}O_8$: 347.1706 $(M+H)^+$. Found: 347.1682.
9. Ethyl 6-hydroxy-2-*t*-butyldimethylsilyloxy-4,5:7,8-bis-isopropylideneoxy-2-octenoate (**12a**): $[\alpha]_D^{24}$−42.5 (*c* 1.00, $CHCl_3$); IR (NaCl) 3558, 3027, 2989, 2932, 2858, 1721, 1649, 1471, 1463, 1383, 1373, 1320, 1252, 1160, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.21 (s, 3H), 0.96 (s, 9H), 1.31 (dd, $J = 6.8$, 7.3 Hz, 3H), 1.34 (3H, s), 1.38 (3H, s), 1.40 (3H, s), 1.53 (3H, s), 2.12 (d, $J = 8.3$ Hz, 1H), 3.40 (t, $J = 7.8$, 8.3 Hz, 1H), 3.96–4.04 (m, 2H), 4.08 (m, 1H), 4.18 (ddd, $J = 6.8$, 7.3, 14.2 Hz, 1H), 4.28 (ddd, $J = 6.8$, 7.3, 14.2 Hz, 1H), 4.45 (d, $J = 7.8$ Hz, 1H), 5.30

(dd, J = 7.8, 8.3 Hz, 1H), 6.21 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.29, −4.04, 14.2, 18.6, 24.3, 25.3, 25.9, 26.6, 26.8, 61.5, 66.9, 70.7, 72.0, 76.0, 76.4, 108.6, 109.2, 116.1, 143.4, 163.8; HRMS (FAB) calcd for $C_{22}H_{40}O_8NaSi$: 483.2390 $(M+Na)^+$. Found: 483.2400.