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AN EFFICIENT ROUTE TO 3-DEOXY-D-*MANNO*-2-OCTULOSONIC ACID (KDO) DERIVATIVES *VIA* A 1,4-CYCLIC SULFATE APPROACH

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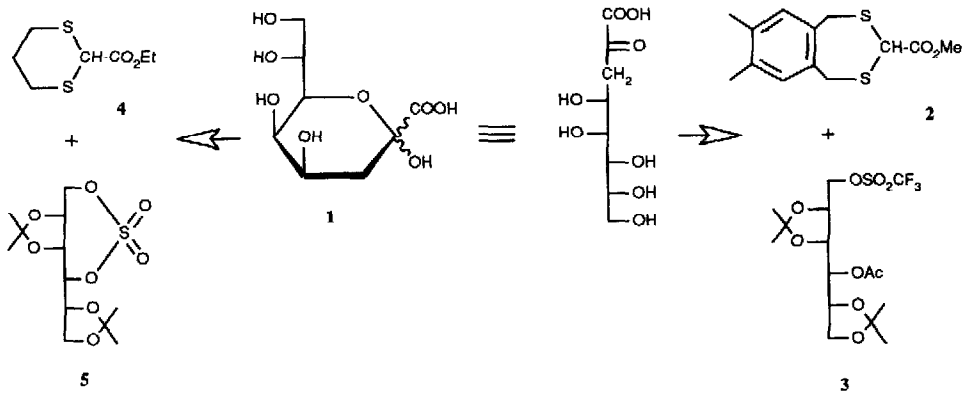
ABSTRACT: Treatment of 2,3:5,6-di-O-isopropylidene-D-mannitol with thionyl chloride followed by oxidation gave the corresponding 1,4-cyclic sulfate. Ring opening of the cyclic sulfate with the anion of ethyl 1,3-dithiane-2-carboxylate, and subsequent acidolysis and unmasking of the thioketal, afforded ethyl 4,5:7,8-di-O-isopropylidene-3-deoxy-α(ß)-D-*manno*-2-octulosonate in an excellent yield.

It is well established[1] now that the eight-carbon sugar 3-deoxy-D-manno-2-octulosonic acid (KDO) is an integral component of lipopolysaccharides isolated from cell walls of Gram-negative bacteria. In order to facilitate a detailed study of the biological function of oligosaccharides containing KDO units, an easy access to KDO derivatives suitable for *oligosaccharide synthesis* is imperative.

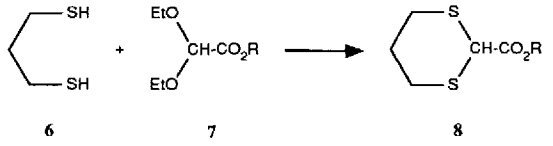
Thus far, several routes to the synthesis of KDO (**1**) have been published. In most of the approaches, the eight-carbon skeleton was assembled by extending a five or six-carbon chiral sugar synthon (*i.e.*, D-arabinose or D-mannose, respectively) at the potential C-1 aldehyde function with a three-carbon[2] or two-carbon unit[3], respectively, *via* aldol or Wittig-reactions. On the other hand, in the well-known Cornforth procedure[4] to **1**, D-arabinose is condensed with a four-carbon unit followed by decarboxylation. Furthermore, enzymatic[5] and *de novo*[6] synthetic routes to KDO have also been reported.



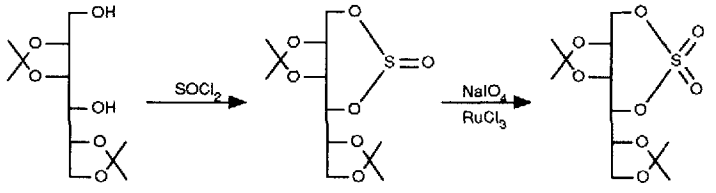
As part of a programme[7] to prepare KDO containing fragments of the inner-core region of *Neisseria meningitidis*, we here report a practical and efficient method to the KDO-synthon **13** which can also be easily deblocked to give KDO (**1**).

Recently, Shiba *et al.*[8] reported a new route to KDO, the crucial step of which consisted of nucleophilic replacement of a triflate group at C-1 of the D-mannitol derivative **3** with the anion of the methyl glyoxylate dithioacetal **2**. Further processing of the thus obtained condensation product afforded the protected KDO derivative **13** (R=Me) in an overall yield of 42% (based on **2**). The main advantage of this nucleophilic substitution approach is the exclusive formation of the required D-*manno* configuration and not, as observed in most routes to KDO *via* an aldol- or Wittig-type elongation, the concomitant formation of the unwanted D-*gluco* configuration. The latter attractive feature urged us to examine whether the Shiba approach could be improved substantially by using the easily accessible[9] dithioacetal of ethyl glyoxylate **8** and the 1,4-cyclic sulfate of D-mannitol **5**.

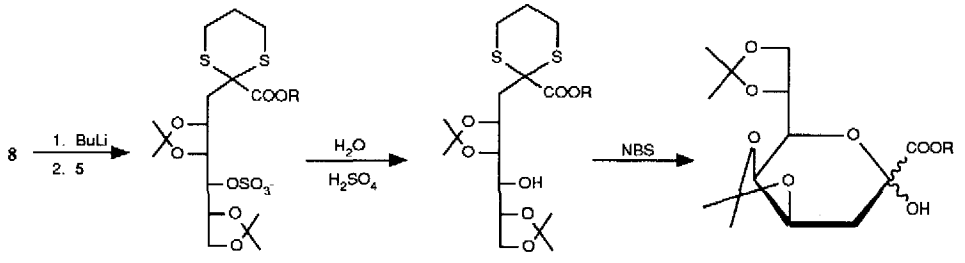
The synthesis of the crucial intermediate **5** is based on the recently by Sharpless *et al.*[10] reported synthetic route to vicinal cyclic sulfates which are very prone to nucleophilic attack. In a first attempt to prepare the 1,4-cyclic sulfate **5**, 2,3:5,6-di-0-isopropylidene-D-mannitol **9**, obtained[11] in high yield by reduction of 2,3:5,6-di-0-isopropylidene-D-mannose with $NaBH_4$, was treated with sulfuryl chloride. Unfortunately[12], instead of **5**, the corresponding tetrahydrofuran derivative, presumably resulting from an intramolecular cyclisation of C-4-OH on the rapidly formed C-1 chlorosulfate, was isolated. However, the 1,4-cyclic sulfate could be obtained in high yield by the two-step Sharpless procedure. Thus, dropwise



6 **7** **8**



9 **10** **5**



11 **12** **13**

addition of thionyl chloride (0.5 ml) to a cooled (-15°C) solution of **9** (4.6 mmol) in CH_2Cl_2 (14 ml) and in the presence of Et_3N (4 eq) gave, after workup (15 min) and purification of the slightly coloured product by passing it through a pad of silica gel, homogenous cyclic sulfite **10** as a mixture of diastereoisomers. Oxidation of **10** thus obtained in a mixture of CH_2Cl_2 (14 ml) and acetonitrile (14 ml) and H_2O (21 ml) was easily accomplished using the catalytic RuO_4 system[10a]. TLC-analysis[13], after 30 min at 20°C revealed complete conversion of **10** (Rf 0.68) into **5** (Rf 0.71). Workup and purification, as mentioned earlier for **10**, afforded **5** in an overall yield of 85% (based on **9**). Compound **5** (1 mmol) in THF (1 ml) was now added to a stirred solution of the anion of **8** (R=Et), which was prepared *in situ* by treating **8** (R=Et, 1.2 mmol) with BuLi (1.2 mmol) in the presence of HMPA (0.8 ml) in THF (2 ml) at -70°C. TLC analysis[13], after 1.5 h at 20°C, showed nearly complete conversion of **5** (Rf 0.71) into the charged product **11** (Rf O). Hydrolysis of the sulfate group was effected[10b] by neutralizing the mixture first with concd. H_2SO_4 followed by the addition of H_2O (1 eq.) and H_2SO_4 until pH 3. After heating the solution for 2 h at 50°C, TLC-analysis indicated complete conversion of **11** (Rf O) into product **12** (Rf 0.46). Workup and purification, in a similar fashion as mentioned for **10**, furnished homogeneous **12** in an overall yield of 82% (based on **5**). Finally, unmasking of the dithioacetal group in **12** with NBS (5 eq) in

acetone-water (97:3, v/v) for 1 min at 0°C, gave, after workup and purification (silica gel chromatography) the KDO derivative **13** (R=Et) as a mixture of anomers in an overall yield of 57% (based on **9**). Acidolysis ($HOAc/H_2O$) of the isopropylidene groups and subsequent basic hydrolysis (0.1 N NaOH) of the ethyl esther gave KDO (**1**) which was isolated as the crystalline ammonium salt; m.p. 120-122°C; $[\alpha]_D^{\circ}$ +38.7 (c 1, H_2O); Lit[4]. m.p. 121-124°C, $[a]_D^{\circ}$ + 40.3 (c=1.9, H_2O). Further, ^1H- and ^{13}C-n.m.r. data of 13 (R=Et) and the NH_4^+-salt of KDO were in full accord with the proposed structures and in good agreement with reported data[14,8].

The successful synthesis of the KDO-derivative **13** indicates that the cyclic sulfate methodology is also applicable to a 1,4-diol system present in an open-chain sugar configuration. The latter finding opened the way to prepare the key intermediate **5** on a large scale (*i.e.*, 30 g) without encountering any difficulties. Further, the easy conversion of **8** (R=Et) into **8** (R=Me, Benzyl) enabled us to prepare the corresponding KDO-derivatives **13** (R=Me, Bn) in excellent yields. In conclusion we firmly believe that the cyclic sulfate methodology will be of great value for the synthesis of important natural products[15].

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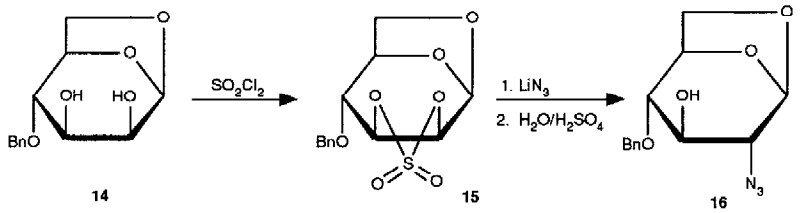
12. In this respect it is of interest to note that conversion of a vicinal diol system, which is part of a rigid skeleton (*e.g.*, closed sugars), to a cyclic sulfate can be readily accomplished using sulfuryl chloride. Thus, by using SO_2Cl_2 Tewson [J. Org. Chem. **48,** 3507 (1983)] obtained methyl 4,6-0-benzylidene-ß-D-mannopyranoside-2,3-cyclic sulfate in a yield of 60%. We also showed that the vicinal cyclic sulfate **15** could be isolated in a yield of 85% by treating 1,6-anhydro-4-0-benzyl-ß-D-mannopyranoside **14** with SO_2Cl_2. Ring opening of the cyclic sulfate with LiN_3 in DMF (80°C, 3 h) proceeded with high regio- and stereoselectivity at C-2 to furnish, after mild acidic hydrolysis of the sulfate group, the valuable 2-azido-D-glucose synthon **16** in 82% yield. A similar high degree of regio- and

stereoselectivity was reported by Tewson and Soderlind [Carbohydr. Chem. **4,** 529 (1985)] in a fluoride ion-assisted ring opening of the 2,3-cyclic sulfate of 1-propenyl 4,6-0-benzylidene-ß-D-mannopyranoside.



14 15 16

13. Silica gel. Eluant; Acetone : CH_2Cl_2 (3:97, v/v).

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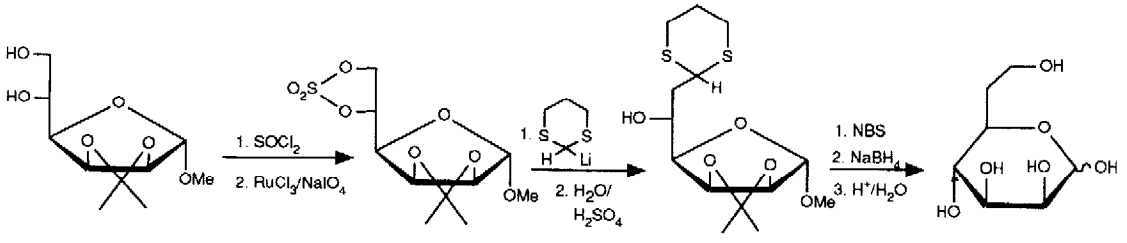
15. For example the naturally occurring 6-deoxy-D-manno-heptose sugar **20** was prepared as follows. In the first step **17** was converted in the cyclic sulfate **18.** Ring opening of **18** with the anion of 1,3-dithiane, and subsequent acidic hydrolysis, gave **19** in an overall yield of 85%. Unmasking of the dithiane function followed by reduction, and finally acidolysis, gave **20** in an excellent yield. The same compound was prepared earlier by Borén *et al.* [Acta Chem. Scand. **26,** 4143 (1972)] *via* a multi-step procedure, the crucial step of which (Wittig reaction) proceeded in a very low yield.



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