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Total Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) and 2-Deoxy-β-KDO

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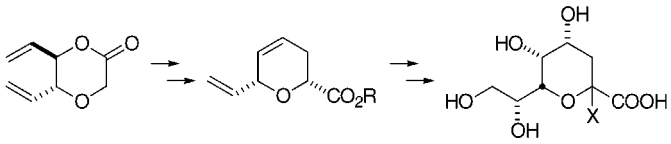
ABSTRACT



Total syntheses of KDO and 2-deoxy-β-KDO are reported. The C_2-symmetric dienediol 4 was desymmetrized by conversion to its corresponding 1,4-dioxanone 5. Ireland–Claisen rearrangement of 5 provided the 6-vinyldihydropyran-2-carboxylate template 6. Double-Sharpless asymmetric dihydroxylation gave the tetraol 7a, which was converted to KDO and 2-deoxy-β-KDO using methods similar to those previously reported. This synthetic scheme provides a flexible route to KDO and KDO analogues.

KDO (3-deoxy-D-*manno*-2-octulosonic acid, **1**) is a key component of the cell wall lipopolysaccharide (LPS) of Gram-negative bacteria. KDO residues form the necessary linkage between the polysaccharide and lipid A regions of LPS.[1] The enzyme CMP-KDO synthetase catalyzes what is believed to be the rate-limiting step of KDO incorporation into LPS,[2] and inhibitors of this enzyme have attracted interest as potential antibiotics. The most potent of these to date is 2-deoxy-β-KDO (**2**).[3] Most of the previous syntheses of **1**[1,4,5,6] and **2**[4b,7,8] are chemical or enzymatic semisyntheses starting from advanced carbohydrate precursors, and thus are not easily applicable to the synthesis of structurally diverse analogues. We report flexible *de novo* syntheses of **1** and **2**,

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(3) (a) Hammond, S. M.; Claesson, A.; Jansson, A. M.; Larsson, L.-G.; Pring, B. G.; Town, C. M.; Ekström, B. *Nature* **1987**, *327*, 730. (b) Goldman, R.; Kohlbrenner, W.; Lartey, P.; Pernet, A. *Nature* **1987**, *329*, 162.
(4) For chemical syntheses of KDO and related compounds starting from advanced carbohydrate precursors, see: (a) Jiang, S.; Rycroft, A. D.; Singh, G.; Wang, X.-Z.; Wu, Y.-L. *Tetrahedron Lett.* **1998**, *39*, 3809. (b) López-Herrera, F. J.; Sarabia-García, F. *Tetrahedron* **1997**, *53*, 3325. (c) Tsukamoto, H.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 6415. (d) Barton, D. H. R.; Jaszberenyi, J. Cs.; Liu, W.; Shinada, T. *Tetrahedron* **1996**, *52*, 2717. (e) Du, S.; Plat, D.; Baasov, T. *Tetrahedron Lett.* **1996**, *37*, 3545. (f) Gao, J.; Härter, R.; Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 3714. (g) Coutrot, Ph.; Grison, C.; Tabyaoui, M. *Tetrahedron Lett.* **1993**, *34*, 5089. (h) Haudrechy, A.; Sinaÿ, P. *J. Org. Chem.* **1992**, *57*, 4142. (i) Giese, B.; Linker, T. *Synthesis* **1992**, 46. (j) Frick, W.; Krülle, T.; Schmidt, R. R. *Liebigs Ann. Chem.* **1991**, 435. (k) Dondoni, A.; Merino, P. *J. Org. Chem.* **1991**, *56*, 5294. (l) Ramage, R.; MacLeod, A. M.; Rose, G. W. *Tetrahedron* **1991**, *47*, 5625. (m) Boons, G. J. P. H.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 273. (n) Horito, S.; Amano, M.; Hashimoto, H. *J. Carbohydr. Chem.* **1989**, *8*, 681. (o) Esswein, A.; Betz, R.; Schmidt, R. R. *Helv. Chim. Acta* **1989**, *72*, 213. (p) Branchaud, B. P.; Meier, M. S. *J. Org. Chem.* **1989**, *54*, 1320. (q) Shirai, R.; Ogura, H. *Tetrahedron Lett.* **1989**, *30*, 2263. (r) Itoh, H.; Kaneko, T.; Tanami, K.; Yoda, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3356. (s) Imoto, M.; Kusumoto, S.; Shiba, T. *Tetrahedron Lett.* **1987**, *28*, 6235. (t) Collins, P. M.; Overend, W. G.; Shing, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1139.
(5) For enzymatic syntheses of KDO and related compounds, see: (a) Kragl, U.; Gödde, A.; Wandrey, C.; Lubin, N.; Augé, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 119. (b) Sugai, T.; Shen, G.-J.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 413.
(6) For *de novo* syntheses of KDO and related compounds, see: (a) Schlessinger, R. H.; Pettus, L. H. *J. Org. Chem.* **1998**, *63*, 9089. (b) Hu, Y.-J.; Huang, X.-D.; Yao, Z.-J.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 2456. (c) Lubineau, A.; Augé, J.; Lubin, N. *Tetrahedron* **1993**, *49*, 4639. (d) Martin, S. F.; Zinke, P. W. *J. Org. Chem.* **1991**, *56*, 6600. (e) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793. (f) Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929.

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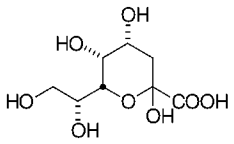
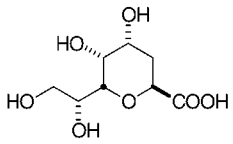
via a dihydropyran template **6** that may be applied toward the synthesis of a variety of analogues.



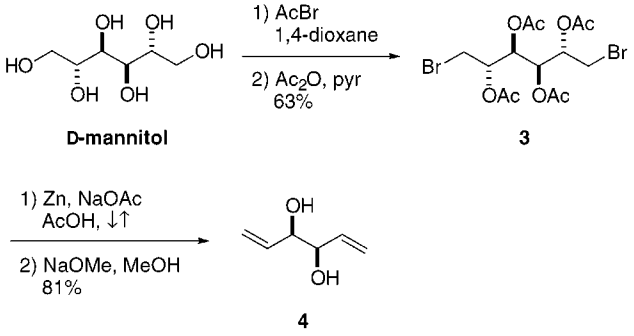
1
KDO



2
2-deoxy-β-KDO

The starting material for our synthesis, the C_2-symmetric dienediol **4**, initially was obtained using the method of Yadav et al.[9] However, the length of the synthesis (six steps from D-mannitol), inconvenience of scale-up, and overall poor yield (~20%) prompted us to design a shorter synthesis. By using a literature procedure, the dibromide **3** (Scheme 1) can

Scheme 1



easily be prepared from D-mannitol in one pot and 63% yield.[10] Double-reductive elimination using zinc, followed by methanolysis of the crude material, gave **4** in 81% yield.

The key sequence in the synthesis is the conversion of the C_2-symmetric dienediol **4** to the highly functionalized tetraol **7a** in four steps (Scheme 2). Alkylation of the stannylene acetal of **4** with *tert*-butyl bromoacetate proceeded with concomitant cyclization, providing the desymmetrized dioxanone **5**.[11] Addition of TFA after the alkylation step ensured complete lactonization. Conversion of **5** to the silyl ketene acetal using a modification of Angle's method,[12] followed by Ireland−Claisen rearrangement[13] and hydrolysis of the intermediate silyl ester,[14] gave **6a** in a one-pot procedure. Because of its acid sensitivity,[15] **6a** was converted immediately to its *tert*-butyl ester **6b** by a modification of Jackson's procedure.[16] Although boron trifluoride proved too harsh a catalyst for the esterification, excellent yields were obtained by relying on adventitious acid catalysis (although small amounts of **6a** persisted). The methyl ester of **6a** was also prepared, but suffered saponification under the subsequent Sharpless asymmetric dihydroxylation (SAD) conditions.

Diene **6b** was immediately carried into the attempted double SAD,[17] and after 3 days at 0 °C the diene was cleanly converted to a mixture of **7a**[18] and its C(7) epimer **7b** in 81% and 4% yields, respectively.[19] It was hoped that the endocyclic olefin could be dihydroxylated from the desired α-face under SAD conditions. However, in all cases surveyed—$(DHQ)_2$−AQN, $(DHQD)_2$−AQN, $(DHQ)_2$−PHAL, $(DHQD)_2$−PHAL—dihydroxylation occurred from the undesired β-face.[17] The same facial selectivity was observed in the dihydroxylation of **6b** with OsO_4/NMO, suggesting that the facial bias imparted by the C(6) substituent overrides any influence the SAD ligands may have. Qualitatively, use of the new ligand $(DHQ)_2$−AQN[20] gave better diastereoselectivity than $(DHQ)_2$−PHAL at C(7).

Comparing the dihydroxylation of **6b** using $(DHQ)_2$−AQN, $(DHQD)_2$−AQN, and standard OsO_4/NMO conditions,[21] we believe that the desired dihydroxylation at the terminal olefin is a mismatched case, as evidenced by $(DHQD)_2$−AQN being more selective for the formation of **7b** than $(DHQ)_2$−AQN is for the formation of **7a**, and OsO_4/NMO favoring **7b**.

Transesterification of **7a** to the methyl ester was followed by differentiation of the two vicinal diols by selective formation of the C(7), C(8) acetonide, providing **8**. The unprotected hydroxyls were inverted using a modification of Augé's protocol.[6c] After treatment of the ditriflate with *n*-Bu_4NOBz, the major products were monobenzoate alcohols, with inversion having occurred at both C(4) and C(5).

(7) For chemical syntheses of 2-deoxy-β-KDO starting from advanced carbohydrate precursors, see: (a) Ohrui, H.; Morita, M.; Meguro, H. *Carbohydr. Res.* **1992**, *224*, 319. (b) Boons, G. J. P. H.; van Delft, F. L.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1992**, *48*, 885. (c) Claesson, A. *J. Org. Chem.* **1987**, *52*, 4414.

(8) For a *de novo* synthesis of 2-deoxy-β-KDO, see: Craig, D.; Pennington, M. W.; Warner, P. *Tetrahedron Lett.* **1995**, *36*, 5815.

(9) Yadav, J. S.; Mysorekar, S. V.; Pawar, S. M.; Gurjar, M. K. *J. Carbohydr. Chem.* **1990**, *9*, 307.

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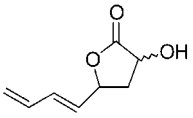
(12) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947.

(13) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787. (b) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.

(14) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102.

(15) Trace amounts of acid cause rearrangement to the lactone **12**, presumably via ring opening to the pentadienyl cation.



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(16) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.

(17) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

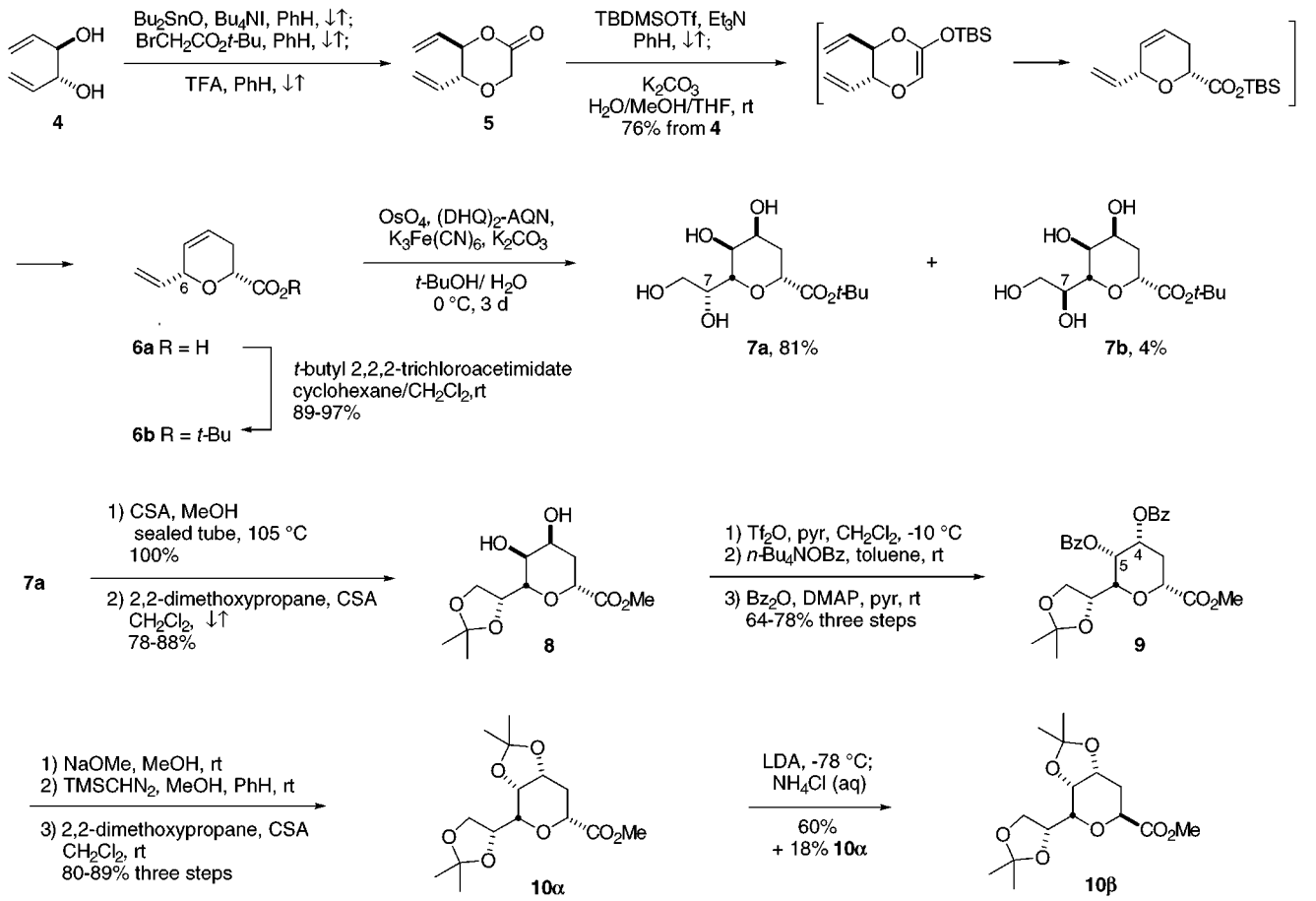
(18) The structure was confirmed by X-ray crystallography.

(19) Removal of the bright yellow $(DHQ)_2$−AQN ligand during workup, by extraction with 3% H_2SO_4 saturated with K_2SO_4,[17] was unsuccessful. Copious amounts of yellow precipitate interfered with product isolation. Although traces of the ligand did not interfere with subsequent steps, pure **7a** could be obtained, if desired, after several chromatography/recrystallization cycles.

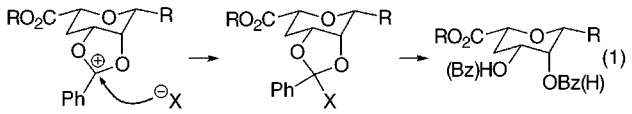
(20) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

(21) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

Scheme 2



Presumably, after one substitution the intermediate monobenzoate displaces the second triflate to form a bridged acyloxonium species, as shown in eq 1. Hydrolysis of this species would produce the mixture of monobenzoate alcohols.



Treatment of the mixture with benzoic anhydride (DMAP, pyr) gave good yields of dibenzoate **9** after recrystallization.[18] Immediate methanolysis of the mixture of monobenzoate alcohols with NaOMe was examined, but gave complex reaction mixtures. Methanolysis of the benzoates, treatment with $TMSCHN_2$[22] and acetonide formation gave **10**α,[23] an intermediate in Augé's synthesis of KDO. Since adventitious saponification occurred to a slight extent during the methanolysis step, $TMSCHN_2$ was used to re-esterify any carboxylic acid.

Claesson and co-workers report that **10**α could be epimerized with sodium methoxide, which gave within 2 min a 1:4 thermodynamic ratio of **10**α**:10**β according to GC.[24] Using these conditions, we observed only a trace of epimerization by TLC, with more forcing conditions leading only to saponification. However, quenching the lithium enolate of **10**α with ammonium chloride gave a 60% yield of **10**β[23] along with 18% of recovered **10**α.

The conversions of **10**α/β to **1** and **2** are shown in Scheme 3. With **10**β as the starting material, hydrolysis of the acetonides with aqueous acetic acid, saponification of the methyl ester with aqueous sodium hydroxide, and ion exchange with Sephadex SP-25 (NH_4^+ form) provided 2-deoxy-β-KDO **2** as its ammonium salt. The conversion of **10**α to KDO requires oxidation at C-2. Oxidation of the lithium enolate of **10**α with MoO_5·Py·HMPA (MoOPH)[25] proved to be superior to the method previously employed by Augé.[6c] With the use of the same deprotection sequence as that employed for **10**β, hemiacetal **11**[23,26] was converted to KDO[23,27] and isolated as the ammonium salt. Conveniently,

(22) Shioiri, T.; Aoyama, T.; Hashimoto, N. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

(23) Spectral data agree with those previously reported.

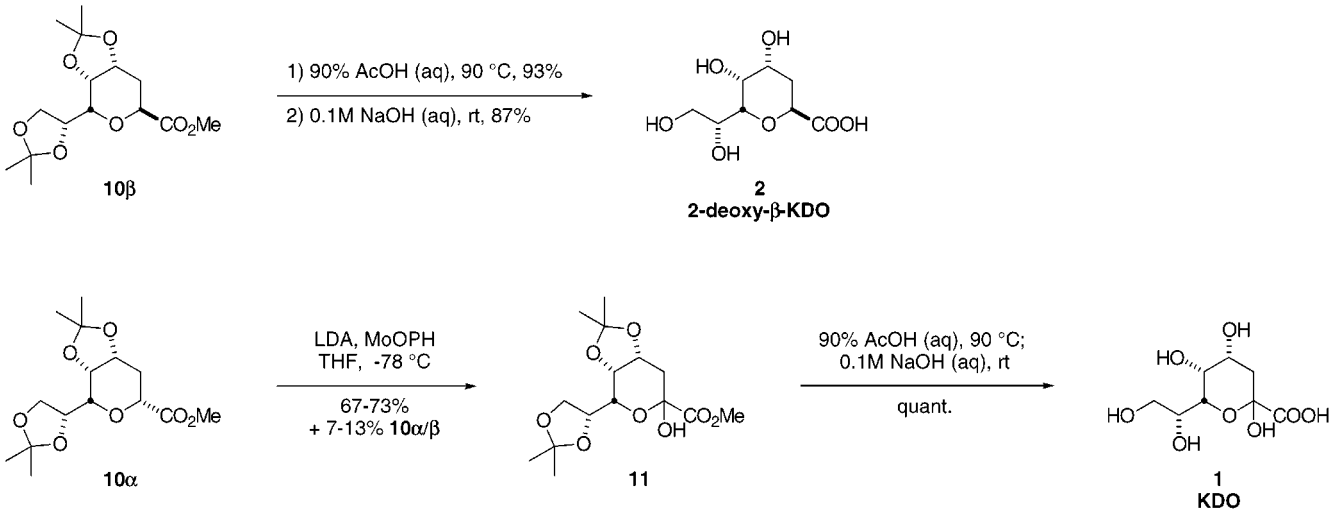
(24) Luthman, K.; Orbe, M.; Wåglund, T.; Claesson, A. *J. Org. Chem.* **1987**, *52*, 3777.

(25) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (b) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127.

(26) Hemiacetal **11** was obtained and used as an undetermined mixture of anomers. However, the pure α-anomer could be obtained by recrystallization as described in ref 4s.

(27) Physical and spectral data also agreed with those of an authentic sample purchased from Sigma.

Scheme 3



the ester **10***β* recovered from the KDO synthesis could be diverted to the synthesis of 2-deoxy-*β*-KDO.

In summary, we have demonstrated the rapid elaboration of dienediol **4** to a highly functionalized tetrahydropyran suitable for the syntheses of (+)-KDO and 2-deoxy-*β*-KDO**.** In addition, the diene **6** could serve as a versatile template for the construction of analogues. Further refinements and extensions of this synthetic route are being investigated and will be reported as events merit.

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