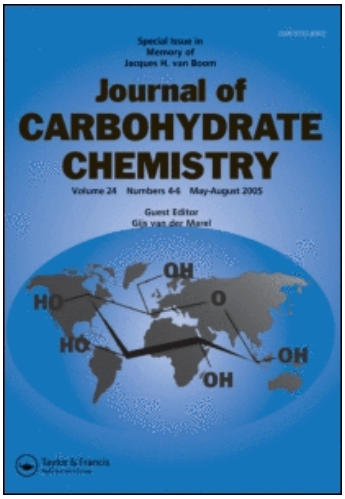

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A New Synthesis of 3-Deoxy-D-Manno-Octulosonic Acid (KDO) From D-Mannose Via Condensation of Dioxene

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COMMUNICATION

A NEW SYNTHESIS OF 3-DEOXY-D-MANNO-OCTULOSONIC ACID (KDO) FROM D-MANNOSE VIA CONDENSATION OF DIOXENE

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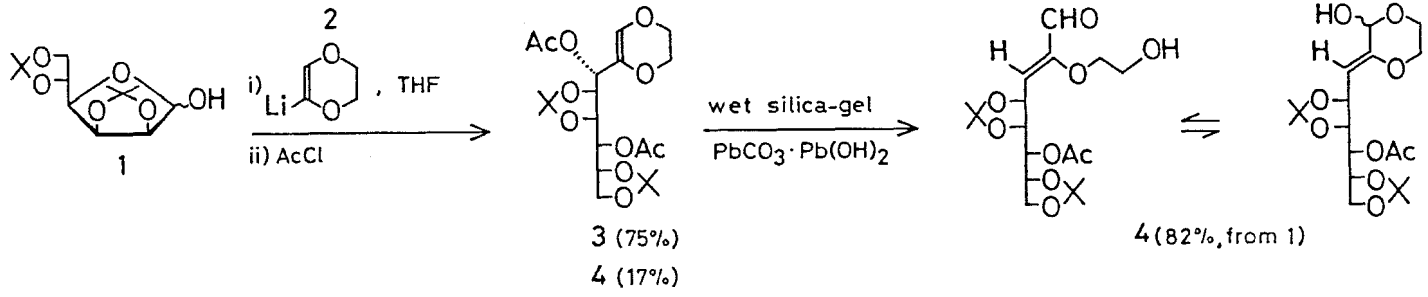
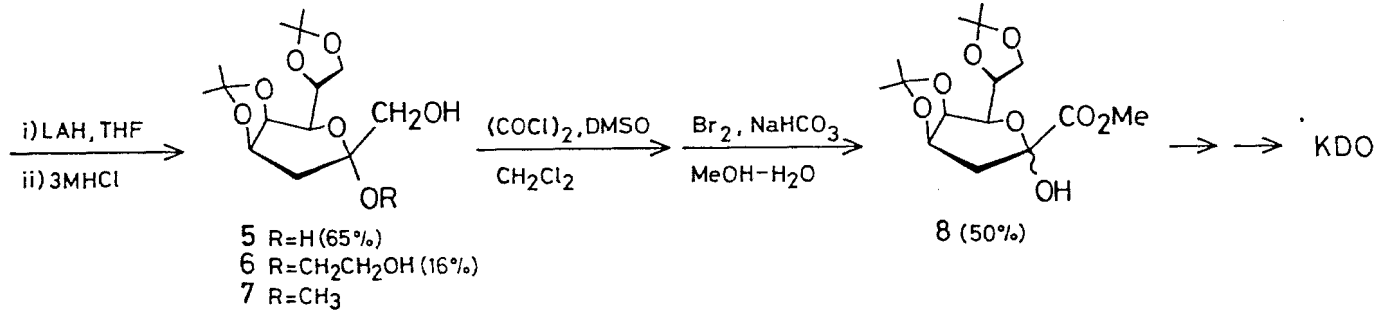
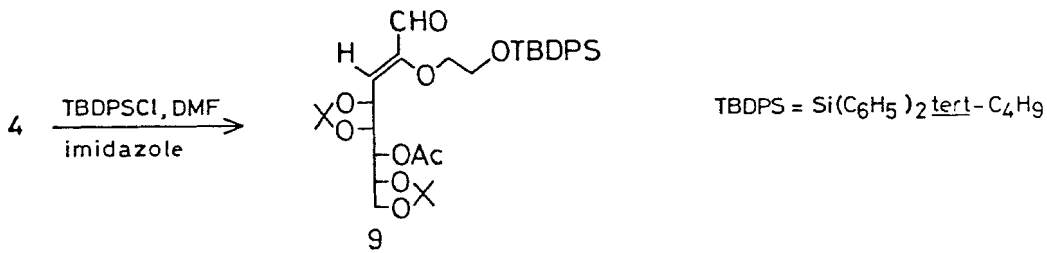
The title compound has long been known as an essential component of lipopolysaccharides (LPS) and capsular polysaccharides which exist in the outer membrane of Gram-negative bacteria. KDO has attracted additional attention as a consequence of some remarkable discoveries; i) mutants unable to produce KDO are non-viable,[1] ii) KDO is not present in mammalian cells,[2] iii) the 2-deoxy analog of β-KDO represents a new class of synthetic antimicrobial agent.[3,4] Although syntheses of KDO have been reported by many groups,[5-8] a more efficient synthetic method endowed with the potential for synthesis of not only complex glycoconjugates but also biologically significant analogs is required.

We now wish to describe a new facile synthesis of KDO from D-mannose which has all asymmetric carbons of KDO. The two-carbon unit was effectively elongated by condensation of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose (1) with lithiated dioxene (2)[9] as a key step. The easily available starting material 1 was condensed with 2 in tetrahydrofuran (THF), where after mixing of the reactants at -30°C, the temperature was allowed to rise to 0°C for about 5 h, and kept at 0°C for 7 h. Successive acetylation by addition of acetyl chloride (3







equivalents) to the reaction mixture improved the efficiency of isolation. A single diastereomer **3**[10] was obtained and purified by flash column chromatography (hexane-acetone, 10:1) to give crystals of **3** (mp 97-100℃) in 75 % yield together with a considerable amount (17 %) of 2-eno-aldehyde **4**,[11] which was deduced to be formed due to the acidity of silica-gel. Thus, **3** was partially hydrolyzed on wet silica-gel (containing 5 equivalents of water) in the presence of basic lead carbonate[12] at 50℃ for 2 h to give **4** in 81 % yield from **1**. In the ^{1}H NMR spectrum of **4** three characteristic signals due to aldehyde and two acetal protons resonated at δ 9.23 (s), 5.24 (s) and 5.22 (s) in chloroform-d, respectively. These signals indicate clearly that **4** exists as a tautomeric mixture of aldehyde and the two corresponding hemiacetals.

The aldehyde **4** was reduced with lithium aluminum hydride in THF at room temperature for 15 min and then the enol ether was hydrolyzed by acidification with 3 M HCl to afford a diol derivative **5** (65%). Additionally, α-ketoside **6** produced via competitive intramolecular cyclization with the acid was obtained in 16% yield. Finally, **5** was successively oxidized with oxalyl chloride and dimethyl sulfoxide in dichloromethane at -60℃ and with bromine in methanol-H$_2$O (9:1) in the presence of excess sodium hydrogencarbonate to give the desired KDO derivative **8** in 50% yield. Two non-oxidized compounds **5** and **7** were recovered in 15% and 7% yields, respectively. The structure of **8** was ascertained from ^{1}H and ^{13}C NMR spectral data.[13] Quantitative conversion of the compound **8** into KDO has been already reported by other group.[7] Consequently, we established the synthetic route of KDO from D-mannose in 8 steps. This synthesis provides some advantages in synthesizing biologically significant KDO derivatives.

ACKNOWLEDGEMENT

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REFERENCES AND FOOTNOTES

1. D. Rick and M. Osborn, J. Proc. Natn. Acad. Sci. U.S.A., **69**, 3756 (1972).

2. S. M. Hammond, in The Bacterial Cell Surface, S. M. Hammond, P. A. Lambert and A. N. Rycroft, Eds. ; Croom Helm : London, 1984, p.57.

3. S. M. Hammond, A. Claesson, A. M. Jansson, L. G. Larsson, B. G. Pring, C. M. Town and B. Ekstrom, Nature, **327**, 730 (1987).

4. R. Goldman, W. Kohlbrenner, P. Lartey and A. Pernet, Nature, **329**, 162 (1987).

5. F. M. Unger, Adv. Carbohydr. Chem. Biochem., **38**, 323 (1981).

6. S. J. Danishefsky, W. H. Pearson and B. E. Segmuller, J. Am. Chem. Soc., **107**, 1280 (1985).

7. M. Imoto, S. Kusumoto and T. Shiba, Tetrahedron Lett., **28**, 6235 (1987).

8. M. D. Bednarski, D. C. Crans, R. DiCosimo, E. S. Simon, P. D. Stein, G. M. Whitesides and M. J. Schneider, Tetrahedron Lett., **29**, 427 (1988).

9. M. Fetizon, I. Hanna and J. Rens, Tetrahedron Lett., **26**, 3453 (1985).

10. Compound **3** had $[\alpha]_D$ +19° (c 1.4, $CHCl_3$) : ^1H NMR (100 MHz, $CDCl_3$) δ 5.26 (d, $J_{3,4}$=10.0 Hz, H-3), 4.59 (dd, $J_{4,5}$=6.0 Hz, H-4). The large value of $J_{3,4}$ in contrast to the small coupling constant (2.4 Hz) between the corresponding protons of a similar carbon-nucleophile adduct i.e., 2,5-di-O-acetyl-3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptose trimethylenedithioacetal, may indicate that the configuration at C-3 position is (S).
H. Paulsen, M. Schuller, A. Heitmann, A. M. Nashed and H. Redlich, Liebigs Ann. Chem., **1986**, 675.

11. The Z-form of **4** could be first confirmed by the NOE study of **9** derived by chemoselective silylation of tautomeric mixture **4** with tert-butylchlorodiphenylsilane and imidazole (95%, syrup). The silyl ether **9** had $[\alpha]_D$ -26° (c 3.5, $CHCl_3$) : ^1H NMR (100 MHz, $CDCl_3$) δ 9.11 (s, H-1), 5.77 (d, $J_{3,4}$=6.7 Hz, H-3). NOE was observed between these protons.

12. By use of a large excess of basic lead carbonate, acetic acid formed from **3** was neutralized in order to prevent the hydrolysis of isopropylidene groups.

13. Compound **8** had $[\alpha]_D$ +38° (c 0.73, $CHCl_3$) and mp 121-123°C (lit. mp 122-124°C)[7] : ^1H NMR (100 MHz, $CDCl_3$), δ 3.64 (s, OH, exchangeable), 2.52 (dd, $J_{2e,3}$=6.3 Hz, $J_{2e,2a}$=15.0 Hz, H-2e), 1.91 (dd, $J_{2a,3}$=4.9 Hz, H-2a). ^{13}C NMR (22.5 MHz, $CDCl_3$), δ 170.1 (C-1), 94.4 (C-2), 66.9 (C-8), 32.5 (C-2).