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Convenient Syntheses of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) and 3-Deoxy-D-*glycero*-D-*galacto*-2-nonulosonic Acid (KDN) Derivatives from D-Mannose

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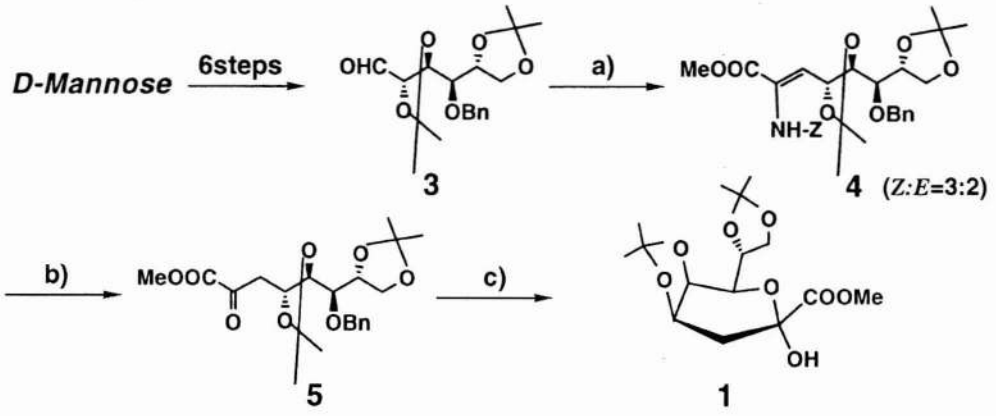
Horner -Wittig reactions of 4-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-D-mannose and 2,3,4,5,6,7-hexa-*O*-benzyl-6-D-*glycero*-2,3,4,5-D-*galacto*-heptose with methyl 2-benzyloxycarbonylamino-2-(diethoxyphosphoryl)acetate gave the corresponding α-dehydroamino acid derivatives in good yields, respectively. They were converted to methyl 3-deoxy-4,5:7,8-di-*O*-isopropylidene-α-D-*manno*-2-octulopyranosonate and methyl (methyl 3-deoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate via methyl α-oxoalkanoate derivatives

3-Deoxy-D-*manno*-2-octulosonic acid (KDO) is an eight-carbon sugar found in Gram-negative bacteria. This unusual sugar KDO is an integral component of lipopolysaccharides (LPS) from cell walls of Gram-negative bacteria and connects the lipophilic part of LPS (i.e., Lipid A) to the inner-core saccharide region via a ketosidic bond.[1] Recently, the synthesis of KDO analogues has become important for studies aimed at the development of an entirely new class of Gram-negative antibacterials targeting the KDO biosynthetic pathway.[1-3] On the other hand, the deaminated sialic acid, 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN), has been first isolated by Inoue and co-workers[4] from the membrane polysialoglycoproteins of *Salmo gairdneri* (rainbow trout) eggs. It is reported that its function as terminal unit is obviously the protection of the membrane against bacterial sialidases.[4-6] Therefore, it can be expected that this sialic acid analogue can be introduced into biologically interesting glycoproteins in order to protect them against sialidase activations of some bacteria. Such background gave an impetus to induce many chemical[1, 7-11] and enzymatic[3] syntheses of 3-deoxy-2-ulosonic acid derivatives.

We now report a facile and effective simple method for the synthesis of 3-deoxy-2-ulosonic acid derivatives

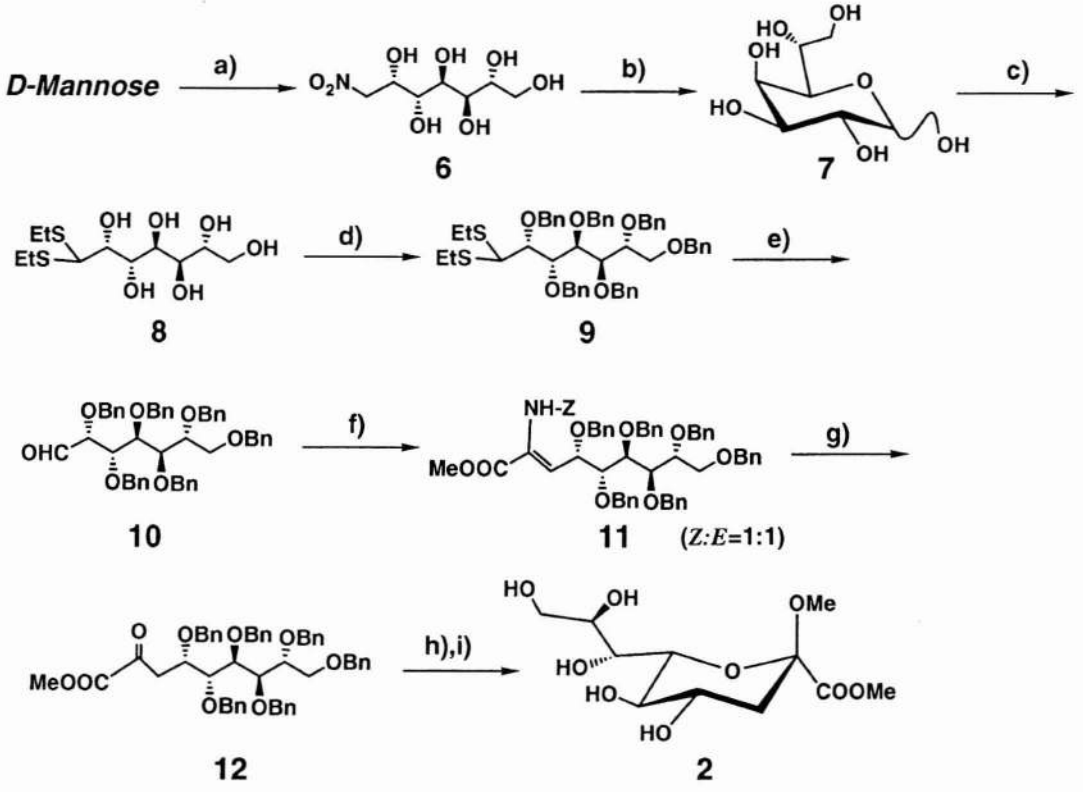
in this communication. The synthesis of KDO began with the preparation of 4-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-D-mannose (**3**),[12] which was derived from D-mannose in six steps (See scheme 1). The reaction of **3** with methyl 2-benzyloxycarbonylamino-2-(diethoxyphosphoryl)acetate[13,14] in the presence of sodium hydride in dichloromethane gave the Horner-Wittig adduct (**4**, Z:E=3:2) in 80% yield. A selective debenzyloxycarbonylation of **4** under the condition of catalytic reduction in benzene (5% Pd/C, H_2) gave the corresponding methyl α-oxoalkanoate derivative [**5**: ^{1}H NMR δ=7.35-7.34 (m, 5H, Ph), 4.79 (ABq, 2H, -CH_2Ph), 4.73 (m, 1H, H-4), 4.26 (dd, 1H, $J_{5,6}$=5.8Hz, H-5), 4.15 (m, 1H, H-7), 4.11 (m, 1H, H-8), 3.88 (dd, 1H, $J_{8,8'}$=6.7Hz, $J_{7,8'}$=0.9Hz, H-8'), 3.83 (s, 3H, -COOMe), 3.61 (dd, 1H, $J_{6,7}$=5.8Hz, H-6), 3.25 (dd, 1H, $J_{3,4}$=8.5Hz, $J_{3,3'}$=16.4Hz, H-3), 3.16 (dd, 1H, $J_{3',4}$=4.9Hz, H-3')] in 65% yield. Debenzylation of **5** in the presence of 10% $Pd(OH)_2$ in ethanol gave the desired KDO derivative of methyl 3-deoxy-4,5,7,8-di-*O*-isopropylidene-α-D-*manno*-2-octulopyranosonate (**1**) in 60% yield, of which NMR data were identical with those reported.[15] Previously, syntheses of α-oxoalkanoates from α-dehydroamino esters[16] and α-oxoalkanoic acids from α-dehydroamino acids[17] were reported, but general syntheses of 3-deoxy-2-ulosonic acid derivatives via α-dehydroamino acid derivatives were not studied yet.

On the other hand, the synthesis of KDN began with the preparation of 6-D-*glycero*-2,3,4,5-D-*galacto*-heptose (**7**)[18] which was derived from D-mannose by nitromethane condensation (86% yield) and Nef oxidation (80% yield) (See scheme 2). Nitromethane condensation of D-mannose was carried out in a mixed solvent (methanol:water=50:1) by the use of 50 equiv. of nitromethane and 2 equiv. of DBU as a base. Under these conditions, pure crystalline product (**6**) was isolated only by filtration of the resulting mixture. A treatment of **7** with ethanethiol in the presence of hydrochloric acid gave the corresponding dithioacetal derivative (**8**) in good yield. Benzylation of **8** with sodium hydride and benzyl bromide in DMF gave the perbenzylated derivative (**9**) (2 steps,70% yield). 2,3,4,5,6,7-Hexa-*O*-benzyl-6-D-*glycero*-2,3,4,5-D-*galacto*-heptose (**10**) was obtained by a treatment of **9** with methyl iodide and sodium carbonate in a mixed solvent (acetonitrile : water=3 : 1) in good yield. In a manner similar to that mentioned above, the reaction of **10** with methyl 2-benzyloxycarbonylamino-2-(diethoxyphosphoryl)acetate in the presence of sodium hydride in dichloromethane gave the Horner-Wittig adduct (**11**, Z:E=1:1) in good yield (2 steps, 80% yield). A selective debenzyloxycarbonylation of **11** under the conditions of catalytic reduction in benzene (5% Pd/C, H_2) gave the corresponding methyl α-oxoalkanoate derivative [**12**: ^{1}H NMR δ=7.32-7.20 (m, 5H x 6, Ph x 6), 4.74-4.41 (m, 2H x 6, -CH_2Ph x 6), 4.23 (ddd, 1H, $J_{3,4}$=8.1Hz, H-4), 3.97 (dd, 1H, $J_{5,6}$=3.0Hz, $J_{4,5}$=4.3Hz, H-5), 3.83 (dd, 1H, $J_{6,7}$=10.2Hz, H-6), 3.79 (m, 2H, H-8 and H-9), 3.69 (m, 2H, H-7 and H-9'), 3.65 (s, 3H, -COOMe), 3.30 (dd, 1H, $J_{3,3'}$=17.2Hz, H-3), 3.03 (dd, 1H, $J_{3',4}$=3.9Hz, H-3')] in 40% yield. Such a low yield of **12** was caused by an inevitable



a) $(EtO)_2P(=O)CHCOOMe$,NaH/CH_2Cl_2, 80%. b) 5%Pd-C,H_2/Benzene, 65%. c) 10%$Pd(OH)_2$,H_2/EtOH, 60%.

Scheme 1.



a) CH_3NO_2,DBU/MeOH,H_2O, 86%. b) Nef oxidation, 80%. c) EtSH/HClaq.. d) NaH,BnBr/DMF.(2steps,70%). e) MeI,Na_2CO_3/75%CH_3CNaq.. f) $(EtO)_2P(=O)CHCOOMe$,NaH/CH_2Cl_2.(2steps,80%). g)5%Pd-C,H_2/Benzene, 40%. h)10%$Pd(OH)_2$,H_2/EtOH. i)Dowex $50H^+$/MeOH.(2steps,30%).

Scheme 2.

reduction of the C=C double bond as a side reaction. Reductive debenzylation of **12** in the presence of 10% $Pd(OH)_2$ and H_2 in ethanol followed by glycosidation with methanol in the presence of Dowex 50 H^+ gave the desired KDN derivative of methyl (methyl 3-deoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate (**2**) (2 steps, 30% overall yield), of which NMR data were identical with those reported.[4] The above methods by the use of stable Horner-Wittig reagent will provide a route to large scale synthesis of 3-deoxy-2-ulosonic acid derivatives. Synthesis of **10** starting from D-mannose involving DBU catalyzed nitromethane condensation in aqueous methanol could be a practical and useful method for a large scale synthesis.

Incidentally, we also synthesized sialic acid derivative, methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate, from D-mannosamine in 9 steps (16% overall yield) and methyl (methyl 4,5,7-tri-*O*-acetyl-3-deoxy-α-D-*arabino*-2-heptulopyranosid)onate from D-arabinose in 9 steps (30% overall yield) by the use of 2-*t*-butoxycarbonylamino-2-(diethoxyphosphoryl)acetate through a similar strategy.

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