A NEW SYNTHESIS OF α -GLYCOSIDICALLY-LINKED DISACCHARIDES USING 2 α -CHLORO-3 β -PHENYLTHIO KDO DERIVATIVES

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Stereoselective α -glycosidation was achieved using 2 α -chloro-3 β -phenylthio KDO having an axial neighbouring group at C-3 which was easily removed later.

KEYWORDS stereoselective α -glycosidation; 2 α -chloro-3 β -phenylthio KDO; lipid A; D-glucosamine; silver triflate

3-Deoxy-D-manno-2-octulosonic acid (KDO) is an important constituent of bacterial lipopolysaccharides (LPS).¹⁾ KDO is an α -ketosidic component of LPS linked at O-6' of the D-glucosamine disaccharide of lipid A.²⁾ Synthesis of 2 α -glycosides of KDO has been developed mainly using glycosyl halides of KDO as the glycosyl donors.³⁾ However, these glycosidations do not lead to α -glycosides exclusively, due to the lack of the neighbouring group participation and the poor electrophilic properties of C-2 of KDO. Therefore, reactions are always accompanied by a considerable amount of 2-deoxy-2,3-dehydro KDO which is formed through elimination of HX. In a previous paper,⁴⁾ we reported a stereoselective glycosidation of KDO using the phenylselenenyl group as a stereocontrolling substituent generated from phenylselenenyl triflate. We now describe the highly stereoselective synthesis of 2 α -glycosides of KDO by using 2 α -chloro-3 β -phenylthio KDO derivatives (**3a** and **4a**) prepared from phenylsulfenyl chloride and 2-deoxy-2,3-dehydro-KDO derivatives (**1** and **2**). The axially oriented phenylthio group of 2 α -chloro-3 β -phenylthio KDO prevents the elimination and assists the α -selective glycosidation through neighbouring-group participation of the sulfide group.⁵⁾ The phenylthio groups of the products were easily removed by tin hydride reduction.^{5c)}

Phenylsulfenyl chloride was added to 2-deoxy-2,3-dehydro KDO as follows. To a solution of **1** (0.12 mmol, 48 mg) in CH₂Cl₂ (1.0 ml) was added freshly prepared phenylsulfenyl chloride (0.36 mmol, 52 mg) and the mixture was allowed to stand for 1 day at 30-35°C in the dark. The mixture was then diluted with CH₂Cl₂ (10 ml), washed with aq. saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column in CHCl₃-IPE (10:3) to give two phenylthio adducts: **3a**⁶⁾ in 49% yield (32 mg) and **3b**⁶⁾ in 37% yield (24 mg). The axial orientation of the substituent at C-3 of **3a** is evident from the J_{3e,4a} value (1.1 Hz). As shown in Table I, adding phenylsulfenyl chloride to the glycal esters in the absence of solvent gave the 2,3-diaxial adducts almost exclusively.

Table I. Solvent Effects on the Yield of the Adducts

Glycal Ester	Solvent	Product Yield (%)	3a/3b ^{a)}
1	CH ₂ Cl ₂	86	57/43
1	CH ₃ CN	83	84/16
1	CH ₃ NO ₂	90	66/34
1	neat	82	100/0
4a/4b^{a)}			
2	CH ₂ Cl ₂	75	59/41
2	neat	96	100/0

a) Determined by individual isomer separation.

In a typical example, silver triflate (0.43 mmol, 110 mg) in toluene (1.0 ml) was added to a stirred mixture of **3a** (0.26 mmol, 142 mg), **7** (0.17 mmol, 190 mg), Na_2HPO_4 (0.51 mmol, 72 mg) and molecular sieves 4A (1.5 g) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (10 ml) at room temperature in the dark under argon. The mixture was stirred for 20 h at 40–50°C. After filtration through Celite, the filtrate was evaporated *in vacuo*. The residue was purified by preparative TLC on a silica gel in $\text{CHCl}_3\text{--Me}_2\text{CO}$ (10:1) to give the desired $\alpha(2'\text{--}6)$ linked disaccharide (**12**)⁶⁾ in 70% yield (196 mg) and unchanged (**7**) (24 mg). The configuration at C-3' of **12** was determined from the $J_{3e,4a}$ value (5.5 Hz). The corresponding β -isomer could not be detected. Other results obtained with various alcohols are listed in Chart 1.

Entry ^{a)}	Donor ^{b)}	Acceptor ^{b)}	Product	Yield (%) ^{c)}
1	3a	5	10	67
2	3a	6	11	45
3	3a	7	12	70
4	4a	7	13	33
5	3a	8	14	58
6	3a	9	15	31

a) All reactions were carried out under argon in the presence of MS 4A,

Solvent: $\text{ClCH}_2\text{CH}_2\text{Cl}$; b) Molar ratio of halide : acceptor was 1.5 : 1 ;

c) Isolated yield based on the acceptor.

Chart 1

The phenylthio group at C-3' of **12** was removed by treatment with Ph_3SnH and AIBN in the absence of solvent at 120–130°C to afford the corresponding $\alpha(2'-6)$ disaccharide (**16**) in 82% yield.

Recent structural investigations on the inner-core region of a number of rough-mutant LPS have revealed an $\alpha(2'-4)$ -linked KDO disaccharide as a common constituent,⁷⁾ the glycal derivative (**15**) of which we also obtained stereoselectively as shown in Chart 1 (Entry 6). By contrast, the neighbouring-group participating glycosidation of 2 α -bromo-3 β -bromo KDO (**17**), [$\delta 4.88(\text{d}, J_{3e,4a}=4.1\text{Hz}, \text{H}-3)$] prepared from **1** and bromine in quantitative yield, with **9** in the presence of silver triflate and N,N,N',N' -tetramethylurea in CH_2Cl_2 gave a mixture of the $\alpha(2'-4)$ -linked disaccharide derivative (**18a**; 58% yield) and its β -isomer (**18b**; 8% yield).

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- 6) **3a**: syrup, $[\alpha]_D^{22} +66.0^\circ$ ($c=1.59$, CHCl_3); IR (film): 1750(C=O), 743, and 691 cm^{-1} (Ph); ^1H NMR (CDCl_3) δ : 1.88, 2.00, 2.07, 2.08(3H each, s, AcO), 3.70(1H, d, $J_{3e,4a}=1.1\text{Hz}$, H-3), 3.82(3H, s, CO_2Me), 4.12(1H, dd, $J_{8a,7}=4.3$ and $J_{8a,8b}=9.2\text{Hz}$, H-8a), 4.38(1H, dd, $J_{6,5}=1.8$ and $J_{6,7}=9.2\text{Hz}$, H-6), 4.57(1H, dd, $J_{8b,7}=1.8\text{Hz}$, H-8b), 5.20(1H, ddd, H-7), 5.28(1H, dd, $J_{5,4}=3.0\text{Hz}$, H-5), 5.46(1H, dd, H-4), and 7.28–7.48(5H, m, Ph). FABMASS (NBA) m/z 547 ($\text{M}+\text{H}$)⁺. **3b**: syrup, $[\alpha]_D^{22} +10.4^\circ$ ($c=1.39$, CHCl_3); IR (film): 1753(C=O), 747, and 692 cm^{-1} (Ph); ^1H NMR (CDCl_3) δ : 2.00, 2.05, 2.07, 2.08(3H each, s, AcO), 3.63(1H, d, $J_{3a,4a}=11.9\text{Hz}$, H-3), 3.93(3H, s, CO_2Me), 4.00(1H, dd, $J_{6,5}=1.1$ and $J_{6,7}=9.5\text{Hz}$, H-6), 4.15(1H, d, $J_{8a,7}=3.8$ and $J_{8a,8b}=12.4\text{Hz}$, H-8a), 4.49(1H, dd, $J_{8b,7}=2.7\text{Hz}$, H-8b), 5.14(1H, ddd, H-7), 5.42(1H, dd, $J_{4,5}=3.2\text{Hz}$, H-5), 5.48(1H, dd, H-4), and 7.27–7.56(5H, m, Ph); FABMASS (NBA) m/z 547 ($\text{M}+\text{H}$)⁺. **12**: syrup, $[\alpha]_D^{22} +7.38^\circ$ ($c=1.95$, CHCl_3); IR (film): 3459(NH), 3356(OH), 1744(ester), 1660, 1545(amide), 733 and 692 cm^{-1} (Ph); ^1H NMR(CDCl_3) δ : 0.88(12H, t, $J=6.2\text{Hz}$, CH_3 -Myristoyl), 1.25(88H, br s, CH_2 -Myristoyl), 1.88, 2.06, 2.09, 2.14(3H each, s, AcO), 3.40(3H, s, CO_2Me), 3.93(1H, d, $J_{3e,4a}=5.5\text{Hz}$, H-3), 4.51(1H, d, $J_{1,2}=8.5\text{Hz}$, H-1), 4.58, 4.89(each 1H, d, $J_{\text{gem}}=12\text{Hz}$, CH_2 -Benzyl), 5.82(1H, br d, $J_{\text{NH},2}=9.0\text{Hz}$, NH), and 7.02–7.35(10H, m, Ph); FABMASS(NBA) m/z 1675 ($\text{M}+\text{Na}$)⁺, 1653 ($\text{M}+\text{H}$)⁺.
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