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

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

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

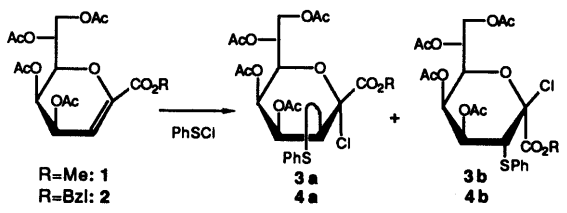
3-Deoxy-D-manno-2-octulosonic acid (KDO) is an important constituent of bacterial lipopolysaccharides (LPS).[1] KDO is an α-ketosidic component of LPS linked at O-6' of the D-glucosamine disaccharide of lipid A.[2] Synthesis of 2α-glycosides of KDO has been developed mainly using glycosyl halides of 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 2α-glycosides of KDO by using 2α-chloro-3β-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 2α-chloro-3β-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 CH_2Cl_2 (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 CH_2Cl_2 (10 ml), washed with aq. saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on a silica gel column in $CHCl_3$-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.

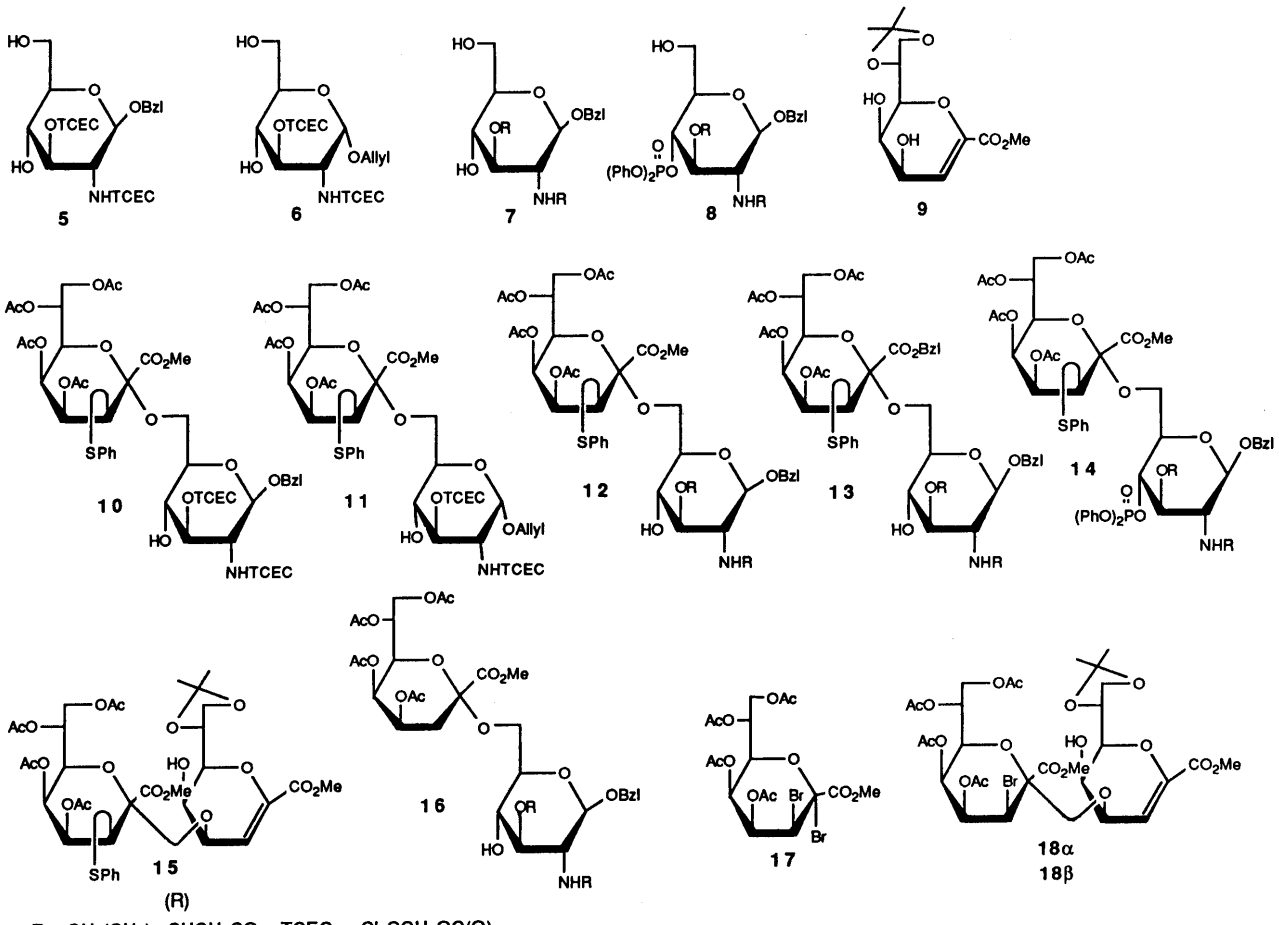
Table I. Solvent Effects on the Yield of the Adducts

Glycal Ester	Solvent	Product Yield (%)	3a/3b[a]
1	CH_2Cl_2	86	57/43
1	CH_3CN	83	84/16
1	CH_3NO_2	90	66/34
1	neat	82	100/0
			4a/4b[a]
2	CH_2Cl_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 $ClCH_2CH_2Cl$ (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 $CHCl_3$-Me_2CO (10:1) to give the desired α(2'-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 : $ClCH_2CH_2Cl$; 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 α(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 α(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 2α-bromo-3β-bromo KDO (**17**), [δ4.88(d,$J_{3e,4a}$=4.1Hz, 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 α(2'-4)-linked disaccharide derivative (**18α**; 58% yield) and its β-isomer (**18β**; 8% yield).

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6) **3a**: syrup, $[\alpha]_D^{22}$+66.0° (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, $J_{3e,4a}$=1.1Hz, H-3), 3.82(3H, s, CO_2Me), 4.12(1H, dd, $J_{8a,7}$=4.3 and $J_{8a,8b}$=9.2Hz, H-8a), 4.38(1H, dd, $J_{6,5}$=1.8 and $J_{6,7}$=9.2Hz,H-6), 4.57(1H, dd, $J_{8b,7}$=1.8Hz, H-8b), 5.20(1H, ddd, H-7), 5.28(1H,dd, $J_{5,4}$=3.0Hz, H-5), 5.46(1H, dd, H-4), and 7.28-7.48(5H, m, Ph). FABMASS (NBA) m/z 547 $(M+H)^+$. **3b**: syrup, $[\alpha]_D^{22}$+10.4° (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, $J_{3a,4a}$=11.9Hz, H-3), 3.93 (3H, s, CO_2Me), 4.00(1H, dd, $J_{6,5}$=1.1 and $J_{6,7}$=9.5Hz, H-6), 4.15(1H, d, $J_{8a,7}$=3.8 and $J_{8a,8b}$=12.4Hz, H-8a), 4.49(1H, dd, $J_{8b,7}$=2.7Hz, H-8b), 5.14(1H, ddd, H-7), 5.42(1H, dd, $J_{4,5}$=3.2Hz, H-5), 5.48(1H, dd, H-4), and 7.27-7.56(5H, m, Ph); FABMASS (NBA) m/z 547 $(M+H)^+$. **12**: syrup, $[\alpha]_D^{22}$+7.38° (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=6.2Hz, 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, $J_{3e,4a}$=5.5Hz, H-3), 4.51(1H, d, $J_{1,2}$=8.5Hz, H-1), 4.58, 4.89(each 1H, d, J_{gem}=12Hz, CH_2-Benzyl), 5.82(1H, br d, $J_{NH,2}$=9.0Hz, NH), and 7.02-7.35(10H, m, Ph); FABMASS(NBA) m/z 1675 $(M+Na)^+$, 1653 $(M+H)^+$.

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(Received November 14, 1989)