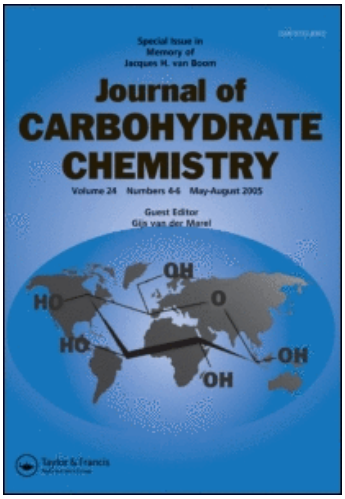

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COMMUNICATION

NOVEL DISACCHARIDES CONTAINING 3-DEOXY-D-MANNO-2-OCTULOSONIC ACID (KDO) AND LIPID A SUBUNIT ANALOGS

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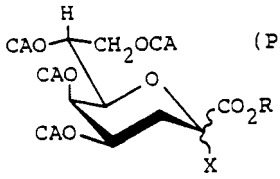
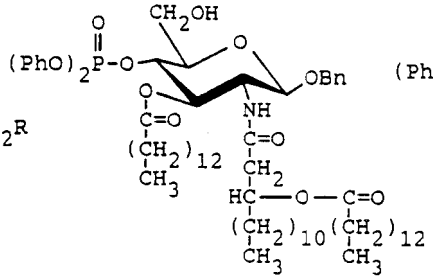
3-Deoxy-D-manno-2-octulosonic acid (KDO)[1] is a prominent constituent of bacterial lipopolysaccharides (LPS),[2] and recently it has been demonstrated[3,4] that the KDO part in the core region of LPS is α-ketosidically linked to O-6' of the D-glucosamine-disaccharide backbone of lipid A. Although the polysaccharide portion, including KDO, has been suggested[5,6] to be necessary for expression of antitumor and interleukin 1 (IL 1)-induction activities of LPS, the distinct biological roles of KDO in LPS are still obscure.

In a series of investigations[7-9] on the relationship of the molecular structure and the biological activity of the nonreducing-sugar subunit of bacterial lipid A, it has been found[10,11] that several kinds of the beneficial biological activities of endotoxin can be clearly elicited by some 4'-O-phosphono-D-glucosamine derivatives, such as GLA-27,[7] GLA-40,[8] GLA-59,[9a] and GLA-60.[9a] GLA-27 and GLA-47[9a] have also potent activity to stimulate the human complement cascade,[12a] and GLA-60 showed marked anti-infection



	R	X
1	Me	OH
2	Me	F
3	Me	Br
4	Bn	OH
5	Bn	F
6	Bn	Br



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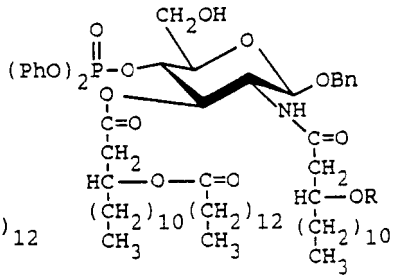
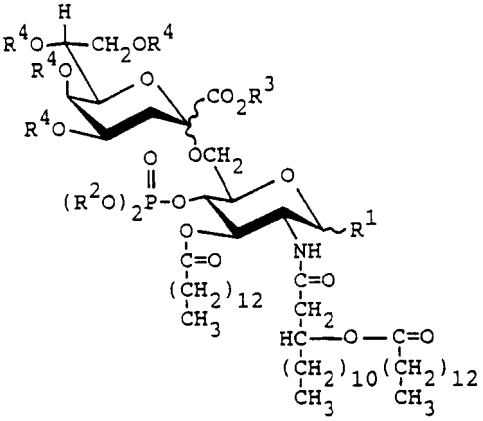
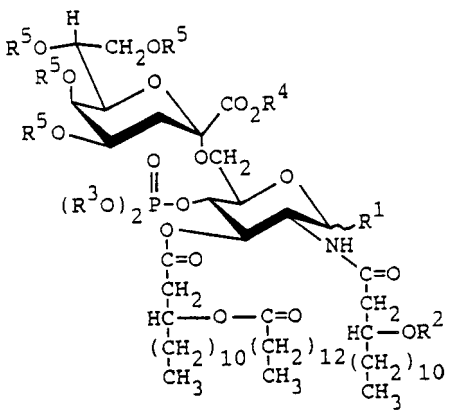


8 R = C_{14}
9 R = Bom



	R^1	R^2	R^3	R^4
10α,β	OBn(β)	Ph	Me	CA
11α,β	OBn(β)	Ph	Me	H
12α,β	OH	H	Me	H
13	OBn(β)	Ph	Bn	CA
14	OBn(β)	Ph	Bn	H
15	OH	H	H	H



	R^1	R^2	R^3	R^4	R^5
16	OBn(β)	C_{14}	Ph	Bn	CA
17	OBn(β)	C_{14}	Ph	Bn	H
18	OBn(β)	Bom	Ph	Bn	CA
19	OBn(β)	Bom	Ph	Bn	H
20	OH	C_{14}	H	H	H
21	OH	H	H	H	H

Bn = $PhCH_2$; C_{14} = $CH_3(CH_2)_{12}CO$; Bom = $PhCH_2OCH_2$; CA = $ClCH_2CO$

activity.[12b] These compounds, however, do not exhibit toxic activity such as pyrogenicity, in contrast to the parent lipid A.

In a preceding paper,[13] the coupling of GLA-27 with methyl 4,5,7,8-tetra-O-acetyl-2-bromo-2,3-dideoxy-D-manno-2-octulopyranosonate has been described, but the KDO moiety of the resulting disaccharides are permanently protected by the acetyl groups and the methyl ester. We now describe an efficient synthesis of the novel disaccharides (12α, 12β, 15, 20, and 21) combining KDO or its methyl ester with GLA-27, GLA-47, and GLA-60, respectively.

Methyl 4,5,7,8-tetra-O-chloroacetyl-2,3-dideoxy-2-fluoro-D-manno-2-octulopyranosonate[14] (2), one of the glycosyl donors, has been synthesized by treatment of 1[15] with diethylaminosulfur trifluoride (DAST) in a good yield. The bromide 3 was prepared in a stepwise manner from 1 via the corresponding 2-O-acetyl derivative. In the similar manner, benzyl 4,5,7,8-tetra-O-chloroacetyl-2,3-dideoxy-2-fluoro-D-manno-2-octulopyranosonate[14] (5) and the bromide derivative 6 were synthesized starting from benzyl 4,5,7,8-tetra-O-chloroacetyl-3-deoxy-D-manno-2-octulosonate[15] (4).

As acceptors, we employed benzyl 2-deoxy-4-O-diphenylphosphono-3-O-tetradecanoyl-2-[(3R)-3-tetradecanoyloxytetradecanamido]-β-D-glucopyranoside[7b] (7), benzyl 2-deoxy-4-O-diphenylphosphono-2-[(3R)-3-tetradecanoyloxytetradecanamido]-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside[9a] (8), and benzyl 2-[(3R)-3-(benzyloxymethoxy)tetradecanamido]-2-deoxy-4-O-diphenylphosphono-3-O-[(3R)-3-tetradecanoyloxytetradecanoyl]-β-D-glucopyranoside[9a] (9).

Coupling of the acceptor 7 with 2 was performed by the procedure of Nicolaou et al.[16] to give the α-glycoside 10α {$[\alpha]_D$ +9.4° (c 0.4, chloroform)} in 27% yield, and the β-glycoside 10β {$[\alpha]_D$ +4° (c 0.6, chloroform)} in 41% yield, respectively. The α-disaccharide 10α was also obtained in 67% yield by treatment of 7 (1 mol. equiv.) with the bromide 3 (1.3 mol. equiv.) in the presence of mercury(II) cyanide, mercury(II) bromide and molecular sieves 4 Å in dichloromethane by a slight modification of the procedure reported by Paulsen et al.[17] The chloroacetyl groups of 10α and 10β were cleaved by treatment with hydrazinedithiocarbonate (HDTC)[18] in 2:1

2,6-lutidine-acetic acid solution at 0 °C to afford 11α {mp 54-56 °C, $[\alpha]_D$ -1.7° (c 0.24, chloroform)}, and 11β {mp 62-65 °C, $[\alpha]_D$ -4.3° (c 0.35, chloroform)} in about 90% yields, respectively. Hydrogenolytic removal of the benzyl and the phenyl groups was carried out with palladium and Adams' platinum catalysts, respectively, to give 12α {mp 143-145 °C, $[\alpha]_D$ +29° (c 0.4, 3:1 ethanol-chloroform)}, and 12β {mp 138-139 °C, $[\alpha]_D$ +26° (c 0.3, 3:1 ethanol-chloroform)} in high yield.

When compound 5 was employed for the coupling with 7, in contrast to the result from 2, the reaction was too slow to obtain disaccharide products in a desirable yield. Accordingly, the synthesis of the disaccharides (15, 20, and 21) containing the carboxyl free KDO was accomplished with the bromide 6 as previously described for the preparation of 10α with 3. Three of the glycosyl acceptors (7, 8, and 9) were each coupled with 6 to give the corresponding α-disaccharide products 13 {65%, mp 32-33 °C, $[\alpha]_D$ +10° (c 1.3, dichloromethane)}, 16 {59%, mp 30 °C, $[\alpha]_D$ +14° (c 1.4, dichloromethane)}, and 18 {61%, $[\alpha]_D$ +12° (c 1.8, dichloromethane)}, respectively.

Selective removal of the chloroacetyl groups from 13, 16, and 18 was respectively performed with HDTC as described for 10α and 10β, to afford 14 {mp 56-58 °C, $[\alpha]_D$ +2° (c 1.6, dichloromethane)}, 17 {mp 51-53 °C, $[\alpha]_D$ +8° (c 0.8, dichloromethane)}, and 19 {$[\alpha]_D$ +8° (c 1, dichloromethane)}. The benzyl, benzyloxymethyl and phenyl groups were finally cleaved by successive hydrogenolyses with palladium and platinum catalysts to give 15 {mp 168-169 °C, $[\alpha]_D$ +22° (c 1, 1:1 dichloromethane-methanol)}, 20 {mp 172-174 °C, $[\alpha]_D$ +11° (c 0.5, 1:1 dichloromethane-methanol)}, and 21 {mp 162-164 °C, $[\alpha]_D$ +26° (c 0.5, 1:1 dichloroethane-ethanol)} in good yields.

In conclusion, five novel disaccharides containing KDO and the biologically active, lipid A subunit analogs, have been synthesized from the suitably protected KDO-halides and the 4-O-phosphono-D-glucosamine acceptors. All new compounds were characterized by IR and NMR spectra (270 or 500 MHz), and gave elemental analyses in satisfactory accord with theory.

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14. Approximately 1:1 mixture of α- and β-fluoride; compound 2 had $[\alpha]_D$ +57° (c 0.5, chloroform), and compound 5 had $[\alpha]_D$ +50° (c 0.5, dichloromethane).

15. Compound 1 had $[\alpha]_D$ +41° (c 1, chloroform): ^{1}H NMR δ 2.20 (dd, J = 12.5 and 4.8 Hz, H-3e) and 2.47 (near t, J = 12 Hz, H-3a), and compound 4 had $[\alpha]_D$ +30° (c 0.7, dichloromethane): ^{1}H NMR δ 2.01 (dd, J = 12-13 and 5 Hz, H-3e) and 2.52 (near t, J = 12-13 Hz, H-3a).

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