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Preliminary communication

A new and stereospecific approach to Kdo-containing disaccharides using phenylselenyl triflate

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3-Deoxy-D-*manno*-2-octulosonic acid (Kdo) as a ketosidic component in the core region of Gram-negative bacterial lipopolysaccharide (LPS)[1] seems to play a biologically important role in being mitogenic and in amplifying the antitumor activity of lipid A, the active center of endotoxin. The Kdo region of LPS is bound to the glucosamine disaccharide backbone of lipid A through an α-(2→6) linkage[2].

Glycosylation of Kdo is one of the most important steps in the synthesis of bacterial LPS. Thus far, the synthesis of Kdo-containing oligosaccharides has only been approached by conventional glycosylation procedures[3] involving glycosyl halides of Kdo as glycosyl donors, and most of them do not lead exclusively to α glycosides.

We now report a new and stereoselective glycosylation of Kdo employing the phenylselenyl group as a stereocontrolling auxiliary, generated from the highly electrophilic phenylselenyl triflate[4].

In a typical example, to a stirred mixture of phenylselenyl chloride (0.24 mmol) and 4Å molecular sieves (0.5 g) in $ClCH_2CH_2Cl$ (2.0 mL) was added silver triflate (0.20 mmol) and trimethylsilyl triflate (0.012 mmol) at 0° under argon. After stirring for 30 min, a solution of **1** (0.12 mmol) and **6** (0.10 mmol) in $ClCH_2CH_2Cl$ (4.0 mL) was added dropwise. The mixture was stirred for 1 h at 0°, filtered, and the filtrate was washed with aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel in 10:1 $CHCl_3$–Me_2CO to give the desired α-(2→6)-linked disaccharide **10** [40% yield, m.p. 90–93°, $[\alpha]_D^{23}$ +7.2° (*c* 0.28, $CHCl_3$)]. The configuration of the 3-substituents of **10** was determined from the $J_{3e,4a}$ value (5.2 Hz). No β-linked product was detected by t.l.c. The results are summarized in Table I.

In contrast, in a similar attempted glycosylation[5] using phenylselenyl chloride and 2,4,6-trimethylpyridine, coupling of **1** and **6** did not proceed.

The reaction of phenylselenyl triflate with a glycal-like double bond evidently occurs by stereospecific anti-addition (*A*), with diaxial opening of a cyclic

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TABLE I

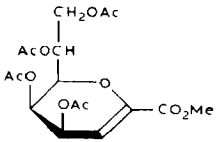
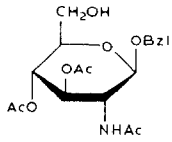
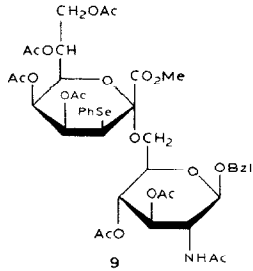
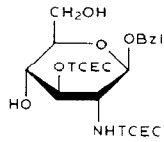
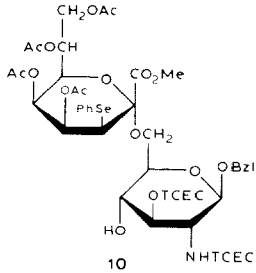
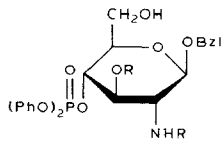
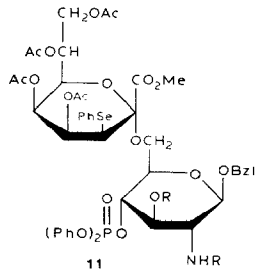
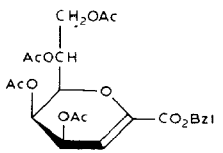
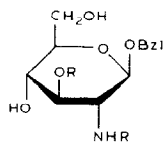
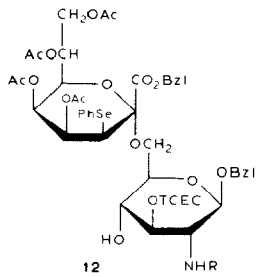
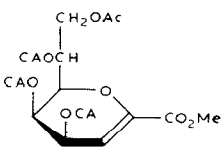
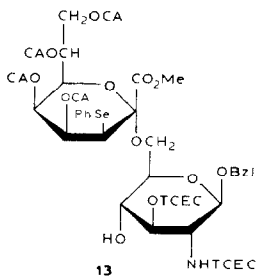
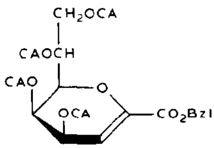
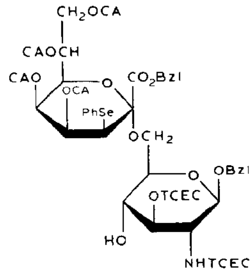
Entry	*Glycal*	*Alcohol*[a]	*Product*	*Yield (%)*
1	 1	 5	 9	35
2	1	 6	 10	40
3	1	 7	 11	74
4	 2	 8	 12	59
5	 3	6	 13	56

TABLE I *(continued)*

Entry	*Glycal*	*Alcohol*[a]	*Product*	*Yield (%)*
6	 **4**	**6**	 **14**	61

[a]Ac = CH_3CO–; CA = $ClCH_2CO$–; R= $CH_3(CH_2)_{10}\overset{(R)}{C}HCH_2CO$– with $CH_3(CH_2)_{12}C(=O)O$ on the CH; TCEC = Cl_3CCH_2OCO–.

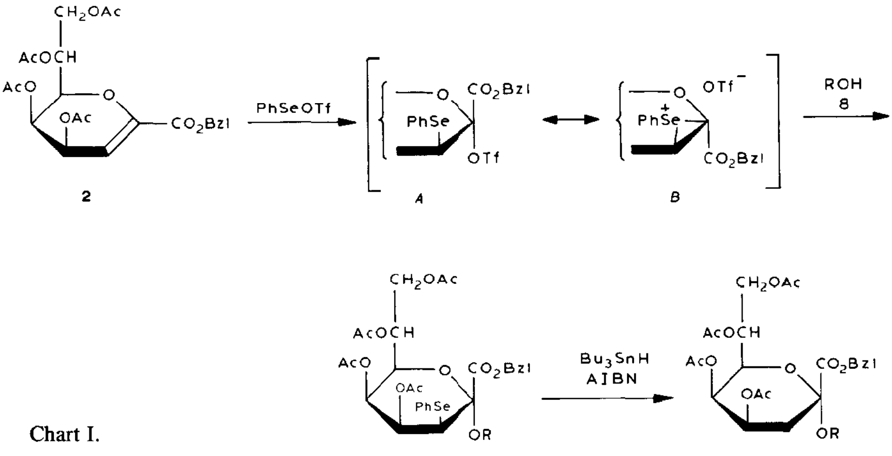


Chart I.

episelenonium ion (*B*) in the transition state, and giving only the α-ketosidic glycoside. (Chart I.)

To confirm the anomeric configuration of **12**, the 3-phenylselenyl group was removed by tributylstannane[6] and azoisobutanonitrile (AIBN) in toluene at 110° to afford the corresponding α-(2→6) disaccharide **15** [65% yield, syrup, $[\alpha]_D^{23}$ +10.9° (*c* 0.42, $CHCl_3$)] [lit.[7] $[\alpha]_D^{24}$ +11.5° (*c* 1.46, $CHCl_3$)].

The glycoside **15** may be used for preparation of the tetra-*O*-acetyl-α-Kdo-(2→6)-2-amino-2-deoxy-D-glucose 4-phosphate analog[7] of lipid A, which possesses mitogenic activity comparable with that[8] of lipid A.

In entries *5* and *6*, we protected the hydroxyl group of Kdo by the monochloroacetyl group. The latter group may be removed selectively in the presence of other functions[9].

This new method thus affords Kdo conjugates by use of glycosyloxyselenation followed by reductive removal of the phenylselenyl group.

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