Communications to the Editor

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A NEW METHODOLOGY FOR CHEMOSELECTION OF ONE AMINO AND FOUR HYDROXYL GROUPS OF GLUCOSAMINE DERIVATIVES AND ITS USE FOR SYNTHESIS OF LIPID X[1,2]

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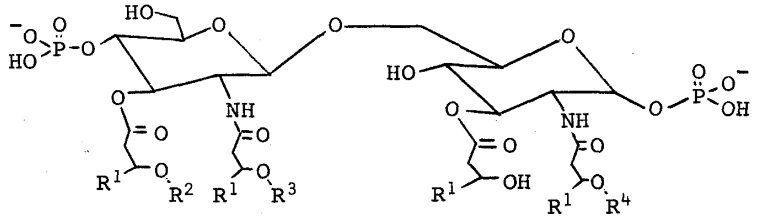
New development of a general key-intermediate for synthesis of lipid A and related compounds and its conversion into lipid X are described.

KEYWORDS —— lipid A; lipid X; glucosamine derivative; chemoselection; lipid X synthesis

Bacterial lipopolysaccharides (LPS) possess a variety of biological activities, e.g., endotoxicity, adjuvanticity, antitumor activity, and so on, and lipids A, fragments from LPS, have been shown to have many of these activities.[3]

Very recently, the structures of bacterial lipids A such as Escherichia coli, Salmonella minnesota and Proteus mirabilis have been proposed as 1,[4] 2,[4c] and 3[4c] as indicated below.



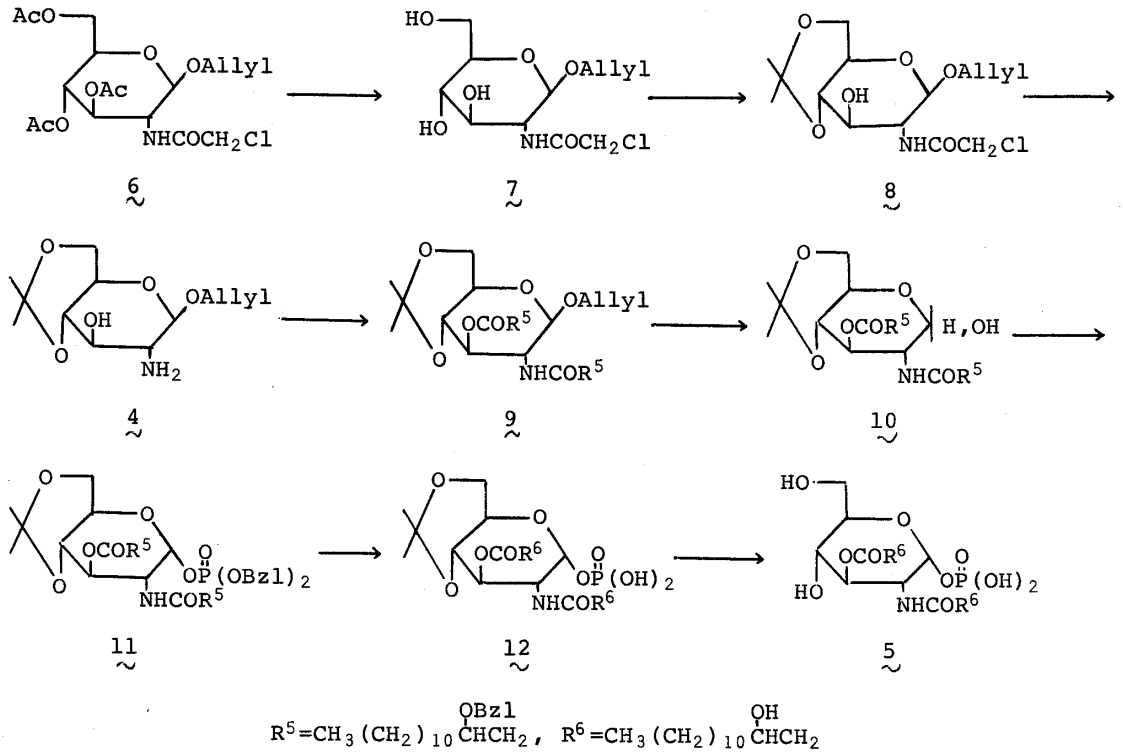
1; R^1=$CH_3(CH_2)_{10}$-, R^2=$CH_3(CH_2)_{12}CO$-, R^3=$CH_3(CH_2)_{10}CO$-, R^4=H

2; R^1=$CH_3(CH_2)_{10}$-, R^2=$CH_3(CH_2)_{12}CO$-, R^3=$CH_3(CH_2)_{10}CO$-, R^4=$CH_3(CH_2)_{14}CO$-

3; R^1=$CH_3(CH_2)_{10}$-, R^2=$CH_3(CH_2)_{12}CO$-, R^3=$CH_3(CH_2)_{12}CO$-, R^4=H or $CH_3(CH_2)_{14}CO$-

Although there are many attempts to synthesize lipids A, no generally applicable route for synthesis of lipids A and the related compounds has been developed.[5]

We wish to describe here new development of 4 as a general key-intermediate for synthesis of lipids A and the related compounds, and its conversion into lipid X (5),[6] the Salmonella lipid A precursor, as follows.



Our methodology includes new development of selective removal of the N-acyl group from the acid-unstable 4,6-isopropylidene compound 8 leading to the novel key-compound 4, whose one amino and four hydroxyl groups can be chemically distinguishable from each other and easily convertible into the required substituents for lipids A and the related compounds.[7]

Synthesis of the key compound 4 was carried out as below. Treatment of allyl 3,4,6-tri-O-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranoside (6)[8] with 28% aqueous NH_3-CH_3OH (1:10) at room temperature for 12 h gave allyl 2-chloroacetamido-2-deoxy-β-D-glucopyranoside (7)[9] [94%, mp 155-157°C, $[\alpha]_D^{22}$ -33.3° (c=1.00, CH_3OH)]. The compound (7) was then converted into an isopropylidene derivative (8)[9] with 2,2-dimethoxypropane-TsOH in DMF at room temperature for 2 h [87%, mp 154-155°C, $[\alpha]_D^{22}$ -54.2° (c=1.00, $CHCl_3$)]. Although several attempts failed to remove the N-chloroacetyl group of 8 using usual de-N-chloroacetylating reagents such as ortho-phenylenediamine[10], thiourea[11], and N,N-pentamethylenethiourea[12], successful removal of the N-chloroacetyl group was effected with pyridine[13] 90-100°C for 2 h and then 5% aqueous NaOH-CH_3OH[13] (1:1) at room temperature for 1.5 h to afford 4[9] [90% from 8, mp 80-81°C, $[\alpha]_D^{27}$ -72.0° (c=1.04, $CHCl_3$)] after purification with a silica gel column ($CHCl_3$-CH_3OH, 15:1). For further conversion of 4 into lipid X, the free amino and hydroxyl groups of 4 were acylated with optically pure (R)-3-benzyloxytetradecanoyl chloride-dimethylaminopyridine in CH_2Cl_2-pyridine at room temperature for 15 h to afford 9[9] [84%, mp 69-71°C, $[\alpha]_D^{25}$ -14.0° (c=1.00, $CHCl_3$)]. The glycosidic allyl group of 9 was removed by isomerization with an iridium complex $[Ir(COD)(PCH_3(C_6H_5)_2]PF_6$ (5 mol%) in THF at 50°C for 2 h[14a] followed by cleavage with I_2 in aqueous THF[14b] to afford 10[9] [62% from 9, syrup, $[\alpha]_D^{22}$ +10.1°

(c=1.76, $CHCl_3$)]. Phosphorylation of the α-glycosidic hydroxyl group was effected with n-BuLi in THF at -70°C and then with dibenzylphosphorochloridate at the same temperature.[14c] After stirring for 5 min at -70°C and then for 5 min at -50°C, the whole mixture was immediately subjected to hydrogenolysis with 10% Pd-on-carbon to afford 12[9] [27% from 10, mp 101-103°C, $[\alpha]_D^{17}$ +49.4° (c=0.17, $CHCl_3$)] after purification with a silica gel column ($CHCl_3$-CH_3OH 5:1). The isopropylidene group was removed by 90% acetic acid at 80°C for 10 min to afford 5[9] [quant., mp 94-96°C, $[\alpha]_D^{22}$ +14.6° (c=0.14, $CHCl_3$-CH_3OH, 1:1)].[15]

Further application of this methodology to synthesis of lipids A will be discussed elsewhere.

REFERENCES AND NOTES

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