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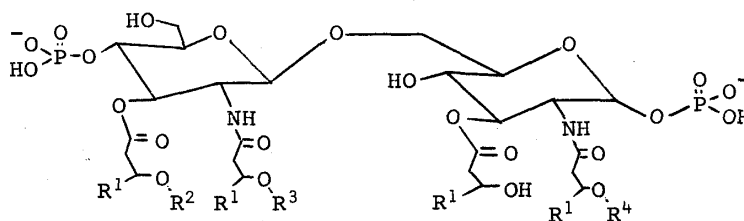
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New development of a general key-intermediate for synthesis of lipid A and related compounds and its conversion into lipid X are described.

KEYWORDS — lipid A; lipid X; glucosamine derivative; chemo-selection; 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⁾

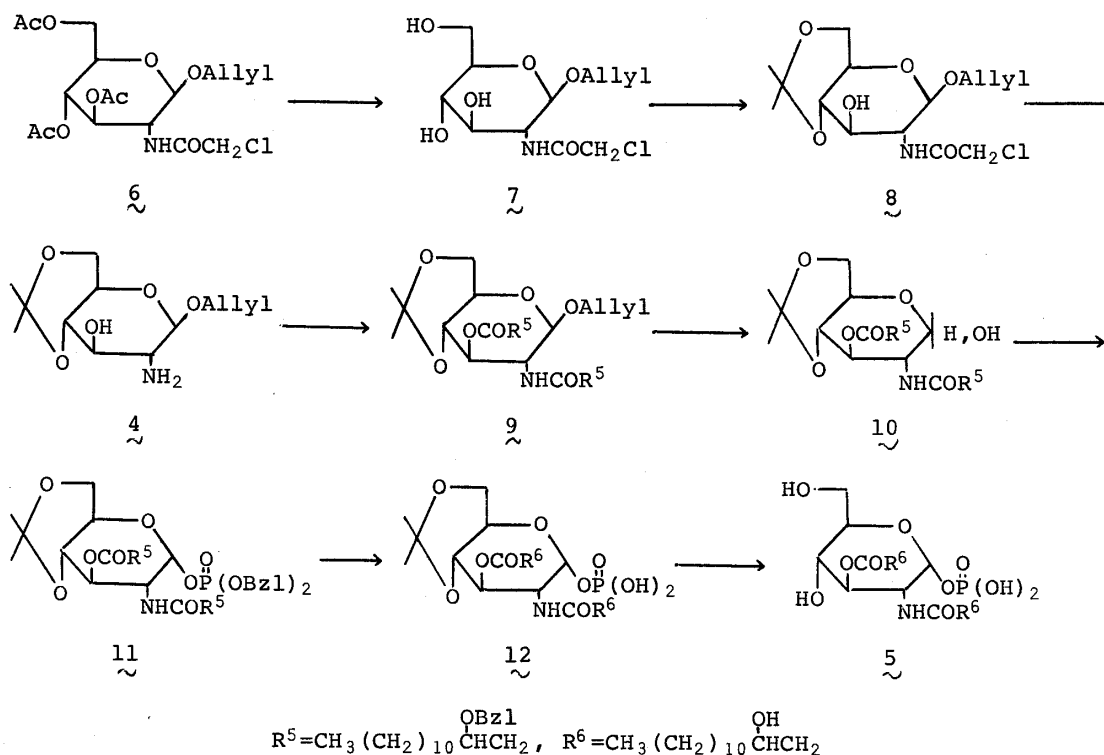
Very recently, the structures of bacterial lipids A such as Escherichia coli, Salmonella minnesota and Proteus mirabilis have been proposed as 1,⁴⁾ 2,^{4c)} and 3,^{4c)} as indicated below.



- 1; R¹=CH₃(CH₂)₁₀-, R²=CH₃(CH₂)₁₂CO-, R³=CH₃(CH₂)₁₀CO-, R⁴=H
 2; R¹=CH₃(CH₂)₁₀-, R²=CH₃(CH₂)₁₂CO-, R³=CH₃(CH₂)₁₀CO-, R⁴=CH₃(CH₂)₁₄CO-
 3; R¹=CH₃(CH₂)₁₀-, R²=CH₃(CH₂)₁₂CO-, R³=CH₃(CH₂)₁₂CO-, R⁴=H or CH₃(CH₂)₁₄CO-

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-acetyl 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 $\text{NH}_3\text{-CH}_3\text{OH}$ (1:10) at room temperature for 12 h gave allyl 2-chloroacetamido-2-deoxy- β -D-glucopyranoside (**7**)⁹⁾ [94%, mp 155-157°C, $[\alpha]_{\text{D}}^{22} -33.3^\circ$ (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, $[\alpha]_{\text{D}}^{22} -54.2^\circ$ (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-phenylenediamine¹⁰⁾, thiourea¹¹⁾, and N,N-pentamethylenethiourea¹²⁾, successful removal of the N-chloroacetyl group was effected with pyridine¹³⁾ 90-100°C for 2 h and then 5% aqueous $\text{NaOH-CH}_3\text{OH}$ ¹³⁾ (1:1) at room temperature for 1.5 h to afford **4**⁹⁾ [90% from **8**, mp 80-81°C, $[\alpha]_{\text{D}}^{27} -72.0^\circ$ (c=1.04, CHCl_3)] after purification with a silica gel column ($\text{CHCl}_3\text{-CH}_3\text{OH}$, 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-benzoyloxyltetradecanoyl chloride-dimethylaminopyridine in CH_2Cl_2 -pyridine at room temperature for 15 h to afford **9**⁹⁾ [84%, mp 69-71°C, $[\alpha]_{\text{D}}^{25} -14.0^\circ$ (c=1.00, CHCl_3)]. The glycosidic allyl group of **9** was removed by isomerization with an iridium complex $[\text{Ir}(\text{COD})(\text{PCH}_3(\text{C}_6\text{H}_5)_2)\text{PF}_6]$ (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, $[\alpha]_{\text{D}}^{22} +10.1^\circ$

($c=1.76$, CHCl_3]. Phosphorylation of the α -glycosidic hydroxyl group was effected with $n\text{-BuLi}$ 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 $101\text{--}103^\circ\text{C}$, $[\alpha]_D^{17} +49.4^\circ$ ($c=0.17$, CHCl_3)] after purification with a silica gel column ($\text{CHCl}_3\text{--CH}_3\text{OH}$ 5:1). The isopropylidene group was removed by 90% acetic acid at 80°C for 10 min to afford $5^{9)}$ [quant., mp $94\text{--}96^\circ\text{C}$, $[\alpha]_D^{22} +14.6^\circ$ ($c=0.14$, $\text{CHCl}_3\text{--CH}_3\text{OH}$, 1:1)].¹⁵⁾

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

REFERENCES AND NOTES

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