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Preliminary communication

Synthesis of two analogues of *Rhodomicrobium vannielii* Lipid A

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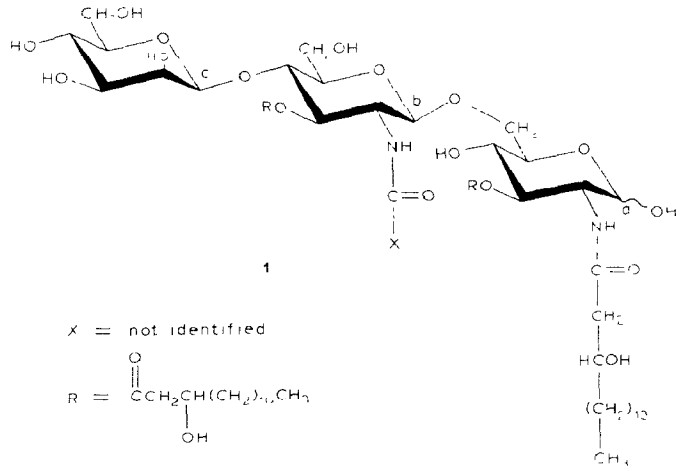
In 1983, Holst and co-workers[1] reported the structure (**1**) of a Lipid A fragment of *Rhodomicrobium vannielii*, which lacked covalently linked phosphate groups, but contained instead β-D-mannopyranose (1 → 4)-linked at the non-reducing-end 2-amino-2-deoxy-D-glucose. As part of a project[2] to synthesise Lipid A derivatives, we have prepared the analogues **14** and **15** of *Rm. vannielii* Lipid A.



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The synthesis of the trisaccharide part of **14** and **15** was accomplished starting from monosaccharide derivatives **2**–**4**. Coupling of **2**[3] with **3**[4] in CH_2Cl_2, in the presence of silver zeolite[5], afforded, together with 9% of the α-coupled product (removed by column chromatography), 71% of the disaccharide derivative **5**[6], $[\alpha]_D^{20}$ 32° (*c* 1, chloroform). N.m.r. data: ^{1}H, δ 5.41 (s, H-1a), 4.32 (s, H-1b); ^{13}C, δ 100.52 ($J_{C,H}$ 173.0 Hz, C-1a), 98.8 ($J_{C,H}$ 154.1 Hz, C-1b). Treatment of **5** with 17:1 $(Ac)_2O$–CF_3COOH for 4 h at 20° gave a quantitative yield of αβ-**6**. ^{1}H-N.m.r. data: δ 6.26 (d, $J_{1,2}$ 3.7 Hz, H-1aα), 4.43 (s, H-1bα), 5.42 (d, $J_{1,2}$ 6.4 Hz, H-1aβ), 4.38 (s, H-1bβ). Hydrolysis[7] of **6** with

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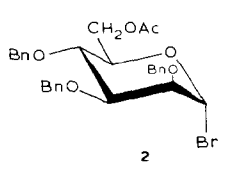
$NH_2NH_2 \cdot HOAc$ in *N,N*-dimethylformamide for 1 h at 20° gave 85% of **7**. ^{1}H-N.m.r. data: δ 5.25 (d, $J_{1,2}$ 3.5 Hz, H-1a), 4.43 (s, H-1b). Treatment[8] of **7** with oxalyl bromide in chloroform–*N,N*-dimethylformamide afforded a quantitative yield of **8**, R_F 0.51 (acetone–CH_2Cl_2, 3:97). ^{1}H-N.m.r. data: δ 6.34 (d, 4.5 Hz, H-1a), 4.42 (s, H-1b).

6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl bromide[9], methanol, Ag_2CO_3, and powdered molecular sieves (3 Å) were stirred for 2 h at 20° in CH_2Cl_2. Zemplén deacetylation of the product gave 85% of **4**, m.p. 122°, $[\alpha]_D^{20}$ −39° (*c* 1, methanol). N.m.r. data: ^{1}H, δ 4.21 (d, $J_{1,2}$ 7.8 Hz, H-1), 3.56 (s, OMe); ^{13}C, δ 103.0 (C-1), 61.6 (C-6).



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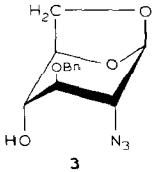

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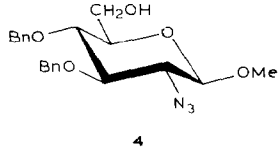

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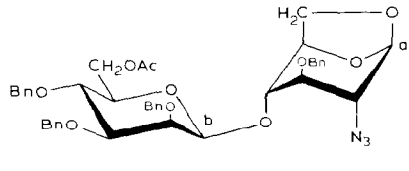

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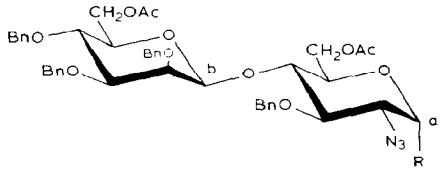
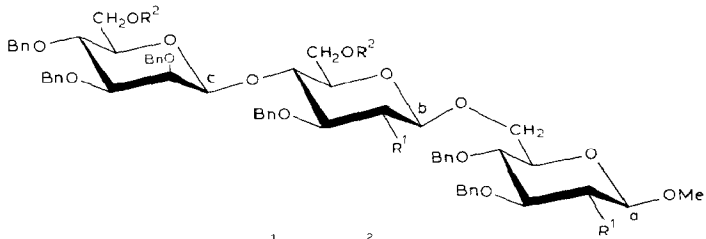


6 R = OAc
7 R = OH
8 R = Br

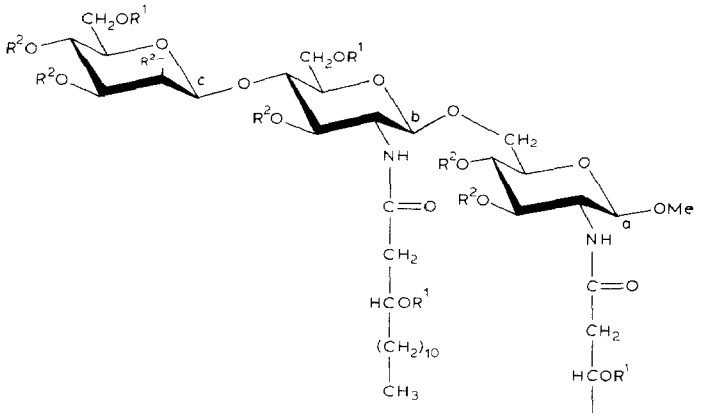


9 R^1 = N_3, R^2 = Ac
10 R^1 = N_3, R^2 = H
11 R^1 = NH_2, R^2 = H

Glycosidation of **8** with **4** in the presence of silver zeolite and powdered molecular sieves (4 Å) in CH_2Cl_2 afforded, after stirring for 2 days at 20°, 60% of the trisaccharide derivative **9**, $[\alpha]_D^{20}$ −25° (*c* 1, chloroform), R_F 0.46 (acetone–CH_2Cl_2, 5:95). N.m.r. data: ^{1}H, δ 4.19 (d, $J_{1,2}$ 7.9 Hz, H-1a), 4.32 (d, $J_{1',2'}$ 7.9 Hz, H-1b), 4.43 (s, H-1c); ^{13}C, δ 103.0 (C-1a), 102.5 (C-1b), 101.0 (C-1c). Zemplen deacetylation of **9** gave a quantitative yield of **10**, $[\alpha]_D^{20}$ −9° (*c* 1, chloroform), R_F 0.37 (acetone–CH_2Cl_2, 1:10). Selective reduction[10] of the azide groups of **10**, using H_2S in 3.5:1 pyridine–water for 19 h at 20°, gave 92% of **11**, R_F 0.42 (MeOH–CH_2Cl_2, 1:9), with no i.r. absorption for

azide. *N*-Acylation of **11** with 3-(*R*)-hydroxytetradecanoic acid[11] in 1,4-dioxane in the presence of *N*-ethylmorpholine, 1-hydroxybenzotriazole, and dicyclohexylcarbodiimide for 2 h at 20° gave 88% of **12**, m.p. 134–135°, $[\alpha]_D^{20}$ −26° (*c* 1, chloroform). ^{13}C-N.m.r. data: δ 102.6 (C-1a), 101.4 (C-1b), 101.0 (C-1c). Hydrogenolysis of **12** (10% Pd/C) in 14:5:1 EtOH–*N*,*N*-dimethylformamide–AcOH for 16 h at 20°, with purification of the product on Sephadex LH-20, afforded 89% of the Lipid A derivative **14**, m.p. 218–221° (dec.) $[\alpha]_D^{20}$ −25° (*c* 1, *N*,*N*-dimethylformamide), R_F 0.15 ($CHCl_3$–acetone–MeOH–AcOH–H_2O, 50:20:10:10:5). ^{13}C-N.m.r. data: δ 172.8, 182.4 (C = O), 102.8 (C-1a), 102.7 (C-1b), 102.0 (C-1c).

Treatment of **12** with octanoic anhydride in pyridine in the presence of 4-dimethylaminopyridine at 20° for 16 h afforded 92% of **13**, $[\alpha]_D^{20}$ −6° (*c* 0.5, chloroform), R_F 0.8 (acetone–CH_2Cl_2, 1:9). ^{13}C-N.m.r. data: δ, 173.4, 173.3, 169.9, 169.7 (6 C = O), 101.4 (C-1a), 100.8 (C-1b), 99.8 (C-1c). Hydrogenolysis of **13** (10% Pd/C) in 14:2:1 2-propanol–*N*,*N*-dimethylformamide–AcOH for 16 h at 20° and purification by short-column chromatography gave 57% of the Lipid A derivative **15**, m.p. 190–192° (dec.), $[\alpha]_D^{20}$ −13° (*c* 1, MeOH–CH_2Cl_2, 1:1), R_F 0.51 (MeOH–CH_2Cl_2, 15:85). ^{13}C-N.m.r. data: δ 101.7 (C-1a), 100.9 (C-1b), 100.5 (C-1c).



12 $R^1 = H$, $R^2 = Bn$

13 $R^1 = C(=O)(CH_2)_6CH_3$, $R^2 = Bn$

14 $R^1 = H$, $R^2 = H$

15 $R^1 = C(=O)(CH_2)_6CH_3$, $R^2 = H$

The above synthesis of Lipid A derivatives **14** and **15** differs from previous syntheses [2,12] in that 2-azido-2-deoxy-D-glycopyranosyl units are used as synthons. Notwithstanding the presence of a non-participating azide group at the glycon **8**, the required β-(1 → 6) linkage could be introduced selectively between **8** and **4** by taking advantage of the insoluble silver zeolite catalyst[13].

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