Carbohydrate Research, 111 (1983) C13–C15
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Preliminary communication

Synthesis of *O*-{2-deoxy-2-[(*3R*)-3-hydroxytetradecanamido]-β-D-glucopyranosyl 4-phosphate}-(1→6)-2-deoxy-2-[(*3R*)-3-hydroxytetradecanamido]-D-glucose. The disaccharide route

DANIEL CHARON and LADISLAS SZABÓ

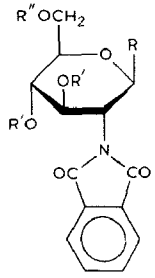
Équipe de Recherche No. 55 du Centre National de la Recherche Scientifique, Centre d'Études Pharmaceutiques, Université de Paris-Sud, F-92290 Châtenay-Malabry (France)

(Received August 3rd, 1982; accepted for publication, September 4th, 1982)

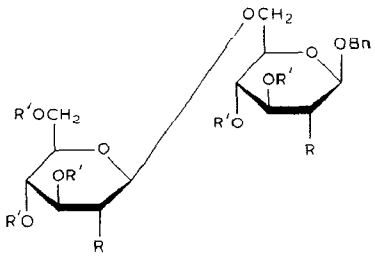
The synthesis of *O*-{2-deoxy-2-[(*3R*)-3-hydroxytetradecanamido]-β-D-glucopyranosyl 4-phosphate}-(1→6)-2-deoxy-2-[(*3R*)-3-hydroxytetradecanamido]-D-glucose (**16**) by coupling two monosaccharide units bearing the required substituents is described in the accompanying communication[1]; in the present work, the benzyl glycoside of the unsubstituted disaccharide **8** was prepared first, and the substituents were introduced subsequently. The main advantage of the second method is that the amide-bound fatty acids are introduced at a relatively late stage of the synthesis, and the number of chromatographic purifications required is thus considerably reduced.

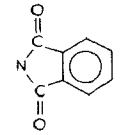
The starting material for the synthesis was 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride[2] (**1**), which was condensed with benzyl alcohol in 1:1 (v/v) nitromethane–toluene in the presence of mercury dicyanide for 24 h at 20° to give **3** in 79% yield, m.p. 109°, (4:1 ether–hexane); $[\alpha]_D^{20}$ −12° (*c* 1, chloroform). Deacetylation by Zemplén's method at 0° gave the triol **4** in 97% yield, m.p. 177° (ethyl acetate–hexane), $[\alpha]_D^{20}$ −34°, (*c* 1, methanol). Treatment of **4** with chlorotriphenylmethane (1.1 mol.equiv.) in pyridine for 16 h at 20°, and then with acetic anhydride (excess) led to the acetylated 6-triphenylmethyl ether **5** in 92% yield, m.p. 194–195° (1:1 tetrachloromethane–methanol), $[\alpha]_D^{20}$ +12°, (*c* 2, chloroform), which was condensed according to Bredereck *et al.*[3] with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide[4] (**2**) in nitromethane in the presence of silver perchlorate and molecular sieve 4A for 16 h at 20° to yield the fully protected disaccharide **6** in 65–70% yield, m.p. 135° (methanol), $[\alpha]_D^{20}$ +6.6° (*c* 1.5 chloroform); ^{1}H-n.m.r. (400 MHz, $CDCl_3$): δ 5.19 ($J_{1,2}$ 9 Hz, H-1) and 5.51 ($J_{1',2'}$ 9 Hz, H-1'). Zemplén deacetylation at 0° gave the phthalimido benzyl glycoside **7** (92% yield), precipitated from ether, amorphous (dec. 150°), $[\alpha]_D^{20}$ −46° (*c* 1, methanol). Simultaneous removal of both phthalimido groups with hydrazine[5] gave the benzyl glycoside of disaccharide **8** in 87% yield, m.p. 227–230° (methanol), $[\alpha]_D^{20}$ −65.4° (*c* 1, water); ^{1}H-n.m.r. (400 MHz, D_2O): δ 4.24 ($J_{1,2}$ 8 Hz, H-1) and 4.30 ($J_{1',2'}$ 8 Hz, H-1'). Treatment of **8** in methanol for 16 h at 20° with 3-acetoxy-D-tetradecanoic anhydride (2.6 mol/mol) gave **9** in 82% yield, m.p. 218–220° (ethanol), $[\alpha]_D^{20}$ −23° (*c* 0.4, 3:1 oxolane–1-propanol). Disaccharide **9** was further characterized by preparing the heptaacetyl derivative **10**, which crystallized readily in 80% yield from ethyl acetate–hexane, m.p. 194–196°, $[\alpha]_D^{20}$ −13° (*c*

0008-6215/83/0000–0000/$03.00

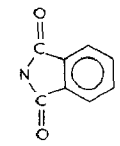


1 R = Cl, R′ = R″ = Ac
2 R = Br, R′ = R″ = Ac
3 R = OBn, R′ = R″ = Ac
4 R = OBn, R′ = R″ = H
5 R = OBn, R′ = Ac, R″ = Tr



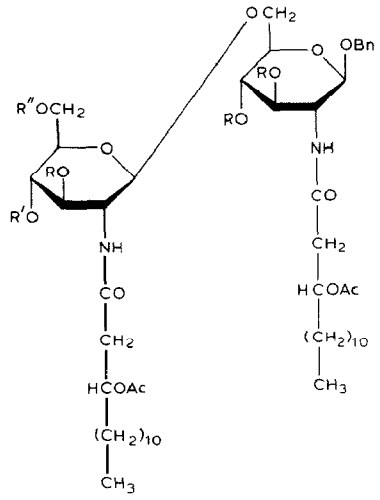


6 R = , R′ = Ac

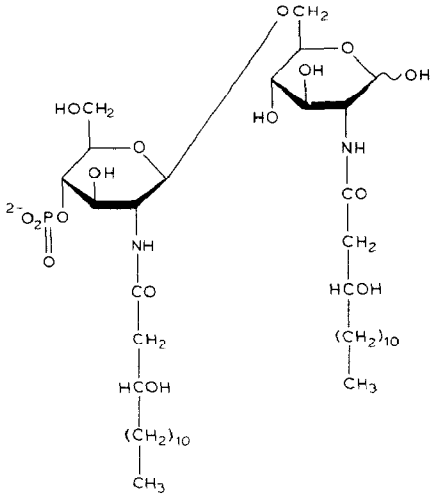


7 R = , R′ = H

8 R = NH_2, R′ = H



9 R = R′ = R″ = H
10 R = R′ = R″ = Ac
11 R = H, R′, R″ = CHPh
12 R = Ac, R′, R″ = CHPh
13 R = Ac, R′ = R″ = H
14 R = Ac, R′ = H, R″ = CH_2OBn
15 R = Ac, R′ = $OP(OPh)_2$, R″ = CH_2OBn



16

1, chloroform); the ^{1}H-n.m.r. (400 MHz) spectrum was of first order and all peaks could be readily assigned ($J_{1,2} = J_{1',2'} = 8$ Hz). The 3-acetoxy-D-tetradecanoic anhydride was prepared from 3-hydroxy-D-tetradecanoic acid[6] as follows: the benzyl ester was acetylated

with acetic anhydride–sodium acetate for 2 h at 100°, the benzyl group was removed by catalytic hydrogenation in the presence of palladium–carbon, and the resulting acetylated, free acid was treated with dicyclohexylcarbodiimide in ether to give a liquid at 20° and solid at 4° (overall yield 80%).

Disaccharide **9** was treated with α,α-dimethoxytoluene (1.5 mol.equiv.) in *N,N*-dimethylformamide with a catalytic amount of *p*-toluenesulfonic acid for 3 h at 60° to yield the 4′,6′-*O*-benzylidene derivative **11** in 95% yield (not recrystallized), m.p. 196–198°, $[\alpha]_D^{20}$ −31.6° (*c* 0.56, oxolane). The crude product was acetylated with acetic anhydride–pyridine at 80° to yield, after column chromatography (Silica gel Merck 60; 2:1, v/v, dichloromethane–ethyl acetate), the pentaacetyl derivative **12** in 70% yield, m.p. 212–215° (dichloromethane), $[\alpha]_D^{20}$ −34° (*c* 0.8, chloroform), from which the benzylidene group was removed, by treatment with 4:1 (v/v) acetic acid–water for 1.5 h at 100°, to yield the crude diol **13** in 90% yield (lyophilized powder). Without further purification, this was treated with (benzyloxy)methyl bromide[7] in dichloromethane in the presence of *N,N,N′,N′*-tetramethylurea (4 mol.equiv.) for 3–5 h at 0° (t.l.c. in 32:3:16, v/v, ethyl acetate–ethanol–hexane) to give 6′-(benzyloxy)methyl ether **14**, which was directly phosphorylated, in pyridine, with diphenylphosphoryl chloride (1.5 mol.equiv.) in the presence of 4-dimethylaminopyridine (1.5 mol.equiv.) for ~2 h at 20°. After the usual processing[8], phosphate **15** was purified by column chromatography (silica gel; 8:5, v/v, ethyl acetate–hexane) and recovered by lyophilization from its solution in benzene (yield 47% from **12**), m.p. 143°, $[\alpha]_D^{20}$ −85° (*c* 0.8, chloroform); The protecting groups were removed in the following order: benzyl groups by hydrogenolysis in the presence of palladium–carbon[9], phenyl groups by hydrogenolysis in the presence of Adams platinum catalyst, and *O*-acetyl groups with ammonia in methanol or magnesium methylate. The disaccharide phosphate **16** was isolated as the monoammonium salt (70% yield), browning at 150°; dec. 165°, $[\alpha]_D^{25}$ +19° (*c* 0.25; 1:1, v/v, pyridine–methanol).

Elementary analyses and ^{1}H-n.m.r. spectra of all compounds were in agreement with the proposed structures. Melting points of derivatives containing fatty acid residues refer to material purified by column chromatography and pure by t.l.c.; variations of the m.p. up to 10° were observed from one preparation to another when complete removal, *in vacuo*, of the last traces of adhering solvents was not accomplished.

REFERENCES

1 P. Szabó, S. A. Safarti, C. Diolez, and L. Szabó, *Carbohydr. Res.*, RJ-1079.
2 S. Akiya and T. Osawa, *Chem. Pharm. Bull.*, 8 (1960) 583–587.
3 H. Bredereck, A. Wagner, G. Faber, H. Ott, and J. Rauther, *Chem. Ber.*, 92 (1959) 1135–1139.
4 B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, 19 (1954) 1786–1792.
5 M. Fujinaga and Y. Matsushima, *Bull. Chem. Soc. Jpn.*, 37 (1964) 468–470.
6 M. Demary, G. Puzo, and J. Asselineau, *Nouv. J. Chim.*, 2 (1978) 373–378.
7 O. Hindsgaul, Doctoral Thesis, University of Alberta, Edmonton, 1980.
8 P. Szabó and L. Szabó, *J. Chem. Soc.*, (1961) 448–457.
9 D. B. Collum, J. H. McDonald III, and W.C. Still, *J. Am. Chem. Soc.*, 102 (1980) 2117–2118.