Tetrahedron Letters No. 20, pp 1717 - 1720, 1978. 0040-4039/78/0508-1717. $02.00/0.

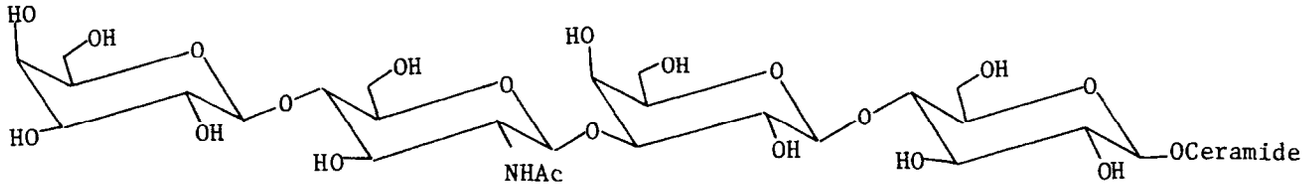
SYNTHESIS OF PARAGLOBOSIDE ANALOGS

Mitree M. Ponpipom*, Robert L. Bugianesi and T. Y. Shen

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065 (U.S.A.)

(Received in USA 14 December 1977; received in UK for publication 23 March 1978)

The tetrasaccharide paragloboside[1,2], βGal(1→4)βGlcNAc(1→3)βGal(1→4)Glc(1→1)ceramide, was first isolated from human erythrocytes. Recently, it was identified as a specific surface component of polyoma-transformed NIL# cells (NILpy)[3] and was considered to be a possible surface antigen associated with NILpy tumor[4].

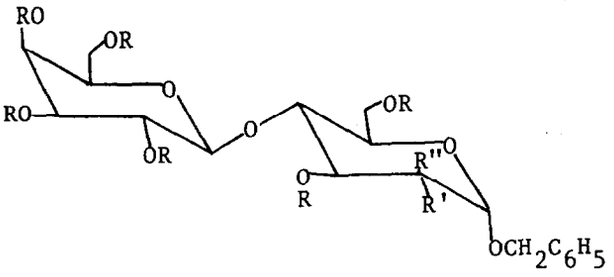


Paragloboside

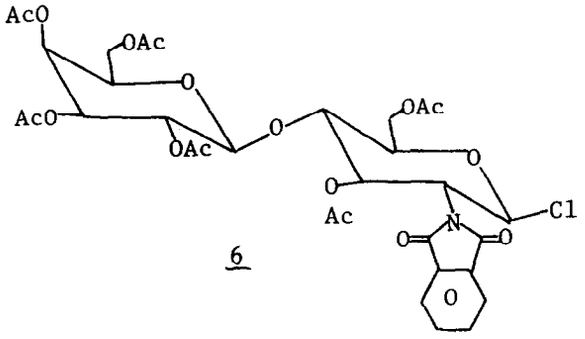
In this communication we report a chemical synthesis of 11, a benzyl analog of paragloboside. The key intermediates for the synthesis were 3,6-di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (6) and benzyl 2,3,6-tri-O-acetyl-4-O-(2,4,6-tri-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (8). Lemieux and coworkers[5] have already demonstrated the usefulness of 2-deoxy-2-phthalimidoglycosyl halides in the preparation of 2-amino-2-deoxy-β-glycopyranosides.

A mixture of 1 and 2 was prepared by diborane reduction of benzyl 2-acetoximino-3,6-di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyranosyl)-α-D-arabino-hexopyranoside, $[\alpha]_D^{25}$ + 12° (c 1.45, $CHCl_3$), which was obtained from dimeric 3,6-di-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyranosyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride[6], m.p. 122-123°, $[\alpha]_D^{25}$ + 68° (c 1.08, $CHCl_3$), by treatment with benzyl alcohol followed by acetic anhydride-pyridine. The mixture containing 1 and 2 was characterized by conversion into the peracetate 4, m.p. 102-104°; $[\alpha]_D^{25}$ + 56.4° (c 1.56, $CHCl_3$)[7]; n.m.r. (chloroform-d): δ5.68 (d, J 9.5 Hz, NH), 4.87 (d, $J_{1,2}$ 3.5 Hz, H-1), 4.26 (octet, $J_{2,3}$ 10.5 Hz, H-2), 5.27 (q, $J_{3,4}$ 8.0 Hz, H-3), 4.54 (d, $J_{1',2'}$ 8.5 Hz, H-1'), 5.16 (q, $J_{2',3'}$ 10.5 Hz, H-2'), 4.98 (q, $J_{3',4'}$ 3.5 Hz, H-3'), 5.37 (d, H-4'), and the peracetate 5, m.p. 136-138°; $[\alpha]_D^{25}$ -26° (c 1.16, $CHCl_3$); n.m.r. (chloroform-d): δ5.69 (d, J 8.0 Hz, NH), 4.60 (d, J≈2.5 Hz, H-1), 4.66 (octet, H-2), 4.57 (d, $J_{1',2'}$ 8.0 Hz, H-1'), 5.16 (q, $J_{2',3'}$ 10 Hz, H-2'), 5.34 (d, $J_{3',4'}$ 3.0 Hz, H-4'),

NIL, hamster embryo fibroblasts.



1 R = R'' = H, R'=NH_2
2 R = R' = H, R''=NH_2
3 R = R' = H, R''=$NHCH_2CH_3$
4 R = Ac, R'=NHAc, R''=H
5 R = Ac, R'=H, R''=NHAc



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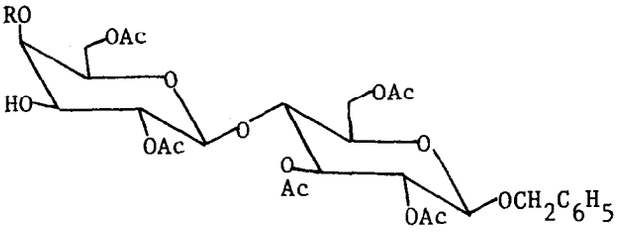
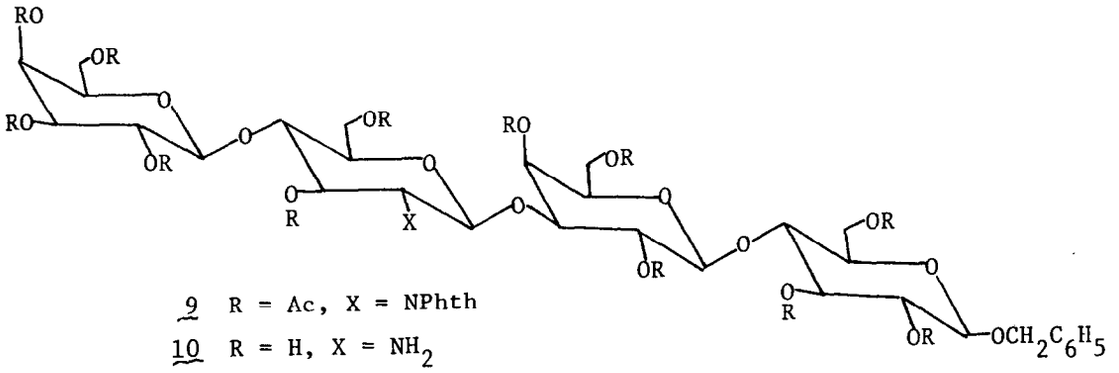
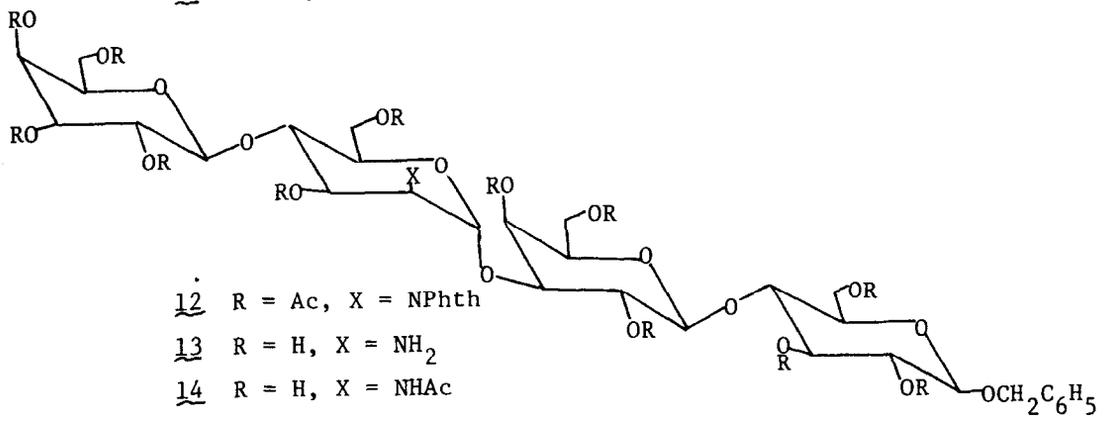


7 R = H
8 R = Ac



9 R = Ac, X = NPhth
10 R = H, X = NH_2
11 R = H, X = NHAc



12 R = Ac, X = NPhth
13 R = H, X = NH_2
14 R = H, X = NHAc

which were isolated in the ratio of 72:28. During the diborane reduction, a crystalline by-product 3 was also isolated, m.p. 108-110°; $[\alpha]_D^{25}$ -60° (c 1.0, MeOH). The formation of 3 is easily explained by O→N migration[8] of an acetyl group during the reduction, with further reduction in the medium.

Compound 6, m.p. 173-174°; $[\alpha]_D^{25}$ + 29.3° (c 1.5, $CHCl_3$); n.m.r. (chloroform-d): δ6.21 (d, $J_{1,2}$ 9.5 Hz, H-1), 4.42 (q, $J_{2,3}$ 10.5 Hz, H-2), 5.77 (q, $J_{3,4}$ 8.0 Hz, H-3), 4.55 (d, $J_{1',2'}$ 8.0 Hz, H-1'), 5.14 (q, $J_{2',3'}$ 10.5 Hz, H-2'), 4.97 (q, $J_{3',4'}$ 3.5 Hz, H-3'), 5.35 (d, H-4'), was prepared from a mixture of 1 and 2 via 1,3,6-tri-O-acetyl-4-O-(tetra-O-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranose, m.p. 265-266°; $[\alpha]_D^{25}$ + 32° (c 1.5, $CHCl_3$)[9] using aluminum chloride in chloroform as a chlorinating agent[10]. The other key intermediate 8, m.p. 120-122°; $[\alpha]_D^{25}$ -33° (c 1.53, $CHCl_3$); n.m.r. (chloroform-d): δ4.53 (d, $J_{1,2}$ 8.0 Hz, H-1), 5.02 (q, $J_{2,3}$ 9.5 Hz, H-2), 5.16 (t, $J_{3,4}$ 9.5 Hz, H-3), 4.43 (d, $J_{1',2'}$ 8.0 Hz, H-1'), 4.86 (q, $J_{2',3'}$ 10.5 Hz, H-2'), 3.80 (m, $J_{3',4'}$ 3.5 Hz, H-3'), 5.30 (q, $J_{4',5'}$ 1.0 Hz, H-4'), was prepared from 7, $[\alpha]_D^{25}$ -28° (c 1.53, $CHCl_3$)[11] by reaction with triethyl orthoacetate followed by controlled acid hydrolysis[12].

For the glycosylations, a solution of 6 (excess) was reacted with 8 in nitromethan containing 1:1 complex[5] of silver trifluoromethanesulfonate (silver triflate) and 2,4,6-trimethylpyridine (s-collidine) at -30° under strictly anhydrous conditions. The product 9 was isolated in 83% yield (based on the disappearance of 8), m.p. 126-127°; $[\alpha]_D^{25}$ -5.3° (c 1.5, $CHCl_3$). Deblocking of 9 with n-butylamine in refluxing methanol afforded 10, m.p. 200° (dec.); $[\alpha]_D^{25}$ -3.0° (c 1.33, H_2O); R_f 0.2 ($CHCl_3$-MeOH-H_2O, 70:30:3); n.m.r. (D_2O): δ4.62 (d, J 8.0 Hz, H-1"), 4.56 (d, J 8.0 Hz, H-1), 4.49 (d, J 8.0 Hz, H-1"'), 4.44 (d, J 8.0 Hz, H-1'), 3.35 (t, J 9.0 Hz, H-3"), 2.75 (t, J 9.0 Hz, H-2"), which was N-acetylated to give 11, m.p. 286-288°; $[\alpha]_D^{25}$ -11° (c 1.0, H_2O). If a mixture of 6 and its 2-epimer was used for the condensation with 8, it gave the tetrasaccharides 9 and 12 which could be separated by HPLC. Compound 12 had m.p. 121-123°; $[\alpha]_D^{25}$ -1.3° (c 1.5, $CHCl_3$). Deblocking of 12 afforded 13, $[\alpha]_D^{25}$ + 32.6° (c 1.5, H_2O); R_f 0.15 ($CHCl_3$-MeOH-H_2O, 70:30:3); n.m.r. (D_2O): δ5.08 (broad S, H-1"), 4.58 (d, J 8.0 Hz, H-1), 4.53 (d, J 8.0 Hz, H-1"'), 4.49 (d, J 8.0 Hz, H-1'), 3.40 (H-2"), which was again reacetylated to give 14, m.p. 175-177°; $[\alpha]_D^{25}$ + 28° (c 1.5, H_2O).

This communication showed that by using the phthalmido protecting group and silver triflate-s-collidine complex[5] as a catalyst, the synthesis of the paragloboside analogs 11 and 14 could be accomplished in high yields[13] with excellent stereoselectivity.

Acknowledgments

The authors thank Dr. B. H. Arison for performing n.m.r. and Mr. J. P. Gilbert and his associates for elementary microanalyses.

References and Notes

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13. All compounds gave correct microanalyses and exhibited n.m.r. spectral characteristics that were in agreement with their structures.