SYNTHESSES OF BIOLOGICALLY ACTIVE SIALOSYLGLYCEROL DERIVATIVES

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New sialosylglycerol derivatives were synthesized and found to inhibit the phospholipase A₂ and C activities.

KEYWORDS  sialosylglycerol derivative; phospholipase A₂ inhibitor; phospholipase C inhibitor; polysaccharide; hexadecanoic acid

A constituent of bacterial cell wall has various biological activities such as immunological response, phage receptor, endotoxin etc.. In 1981, the capsular polysaccharide of Neisseria meningitidis, which plays the main antigen role, was structurally defined (Fig 1). The polysaccharide consists of a polymer of (α2-9) sialic acid, which has many important functions as constituents of glycoconjugate, and phosphoglycerolipid. Recently we have synthesized a series of biologically active compounds designed on the basis of the chemical structure of bacterial cell wall. Here, we describe the synthesis of the sialosylglycerolipids (1α₂α₂, 1β₂α₂, 2α₂, and 2β₂) which imitate the partial structure of the capsular polysaccharide. The synthetic design of these compounds was determined as follows. The absolute configuration of the glycerol C-2 (S) was the same as that of the natural product and the 2-hydroxyl glycerolipid (lyso type) was expected to inhibit phospholipase A₂ by feedback regulation. Four kinds of fatty acid (a-d) were studied to determine the differences among their biological activities due to the fatty acid type. Similarly, sialosyl-(R)-glycerol derivatives were studied with regard to their palmitoyl type.

![Fig 1](image)

Chart 1 shows the synthetic route of the sialosyl-(S)-glycerol derivatives. (S)-1-O-Acetyl-2-O-benzylglycerol (3), the chiral starting material was treated with trityl chloride and pyridine to give the 3-tritylated compound (4; 72.5%, oil, [α]₀ +11.3°). Alkaline hydrolysis of the acetate (4) led to the (R)-1-O-trityl-2-Ο-benzylglycerol derivatives (5; 77.4%, mp 59-62 °C, [α]₀ +22.5°). The 3-hydroxyl compound (5) was acylated with acyl chlorides and triethylamine to yield 6α₂α₂ (6α; 85.0%, oil, [α]₀ +22.5°).
Chart 1
[\delta]_D +12.6^\circ, 6_c; 93.7\%, oil, [\alpha]_D +11.6^\circ, 6_c; 86.0\%, oil, [\beta]_D +4.7^\circ, 6_o; 88.8\%, oil, [\gamma]_D +9.3^\circ). The trityl group of 6a-a was removed by hydrolysis with 80\% aqueous acetic acid at 80^\circ C to afford (S)-1-0-acetyl-2-0-benzyglycerols (S-7a-a, S-7b; 74.6\%, oil, [\alpha]_D -4.8^\circ, S-7a; 80.3\%, oil, [\alpha]_D -5.7^\circ, S-7b; 73.9\%, oil, [\alpha]_D -6.4^\circ, S-7a; 85.8\%, oil, [\alpha]_D -8.0^\circ). These were used as the glycosyl acceptor. (R)-Glycerol derivative (R-7a) was synthesized in the following way. The 1-0-hydroxyl compound (5) was chloroacetylated to give 8 (91.5\%, oil, [\alpha]_D +10.7^\circ). Destritylation of the chloroacetyl compound (8) gave the 3-hydroxy compound (9, 69.0\%, oil, [\alpha]_D -3.1^\circ). The compound (10, 70.1\%, oil, [\alpha]_D +2.8^\circ) was obtained by treating 9 with palmityl chloride and triethylamine. Dechloroacetylation of 10 was achieved with diisopropylethylamine and thiourea to yield the (R)-glycosyl acceptor (R-7a, 92.7\%, oil, [\alpha]_D +4.7^\circ). S-7a-a was glycosylated with the glycosyl donor (11) in the presence of Hg(CN)_2, HgBr, and molecular sieves 4A to give 12a-a and 12b-a, respectively. The resulting anemic mixture was separated by preparative TLC (CHCl_3-MeOH = 20:1) and their structures were confirmed on the basis of the chemical shift of the H-3eq atom of 12a-a and 12b-a in the H-NMR spectrum: the H-3eq chemical shift of a glycoside was lower than that of \beta glycoside (12a-a; 26.9\%, amorphous, [\alpha]_D -8.5^\circ, 12b-a; 32.4\%, amorphous, [\alpha]_D -5.5^\circ, 12a; 10.8\%, amorphous, [\alpha]_D -3.7^\circ, 12b-a; 11.5\%, amorphous, [\alpha]_D -6.6^\circ, 12c-a; 15.6\%, amorphous, [\alpha]_D -18.2^\circ, 12c-b; 27.0\%, amorphous, [\alpha]_D -10.7^\circ, 12d-a; 17.1\%, amorphous, [\alpha]_D -16.7^\circ, 12d-b; 23.5\%, amorphous, [\alpha]_D -8.2^\circ). 12a-a and 12b-a were hydrogenolysed with Pd(OH)_2/C in methanol to give the sialosyl-(S)-glycerol derivatives (14a-a and 14b-a, 14a-a; 71.2\%, amorphous, [\alpha]_D -11.3^\circ, 14b-a; 74.1\%, amorphous, [\alpha]_D -12.6^\circ, 14b-a; 95\%, amorphous, [\alpha]_D -8.0^\circ, 14b-a; 87\%, amorphous, [\alpha]_D -10.0^\circ, 15c-a; 95\%, amorphous, [\alpha]_D -7.8^\circ, 15b-a; 96\%, amorphous, [\alpha]_D -5.1^\circ, 15c-a; 82\%, amorphous, [\alpha]_D -4.9^\circ, 15b-a; 85\%, amorphous, [\alpha]_D -6.0^\circ).^4,5 Sialosyl-(R)-glycerol derivatives (2a and 2b) were synthesized in the same manner. The (R)-1-0-hexadecanoyl-2-0-benzyglycerol (R-7a) was glycosylated with 11 in the presence of Hg(CN)_2, HgBr, and molecular sieves 4A to give an anemic mixture of sialosylglycerol compounds (13a and 13b, 13a; 24.6\%, amorphous, [\alpha]_D -10.8^\circ, 13b; 20.9\%, amorphous, [\alpha]_D -7.0^\circ). 13a and 13b were each hydrogenolysed with Pd(OH)_2/C to yield the sialosyl-(R)-glycerol derivatives (2a and 2b, 2a; 86.2\%, amorphous, [\alpha]_D -3.6^\circ, 2b; 84.8\%, amorphous, [\alpha]_D -4.8^\circ). Preliminary examination of the biological activities revealed that the lyso-sialosylpalmitylglycerol derivatives (14a-a, 14b-a, 2a-a, and 2b-a) have the most powerful phospholipase A, and phospholipase C inhibitory activities among the investigated sialosyl derivatives.\(^6,7\)

REFERENCES AND NOTES

4. \(^1\)H-NMR of H-3eq (ppm, J-Hz): 12a-a; 2.59 (1H, dd, J=4.9, 12.9), 12b-a; 2.61 (1H, dd, J=4.4, 12.4), 12c-a; 2.61 (1H, dd, J=4.9, 12.4), 12d-a; 2.61 (1H, dd, J=4.6, 12.4), 13a-a; 2.61 (1H, dd, J=4.6, 12.7). Because H-3eq signals of 12b-a and 13b were overlapped by the methylene protons of fatty acid, the evidence of \(\beta\) linkage was the fact that H-3eq signals were not found at downfield less than 2.49 ppm.

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