SYNTHESIS OF BIOLOGICALLY ACTIVE GALACTOSYL AND GLUCOSYL-GLYCEROL DERIVATIVES

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Galactosyl and glucosyl-glycerol derivatives which mimic the structure of the lipoteichoic acid of Staphylococcus aureus were synthesized by using a chiral glycerol derivative. Glucosyl-glycerol derivatives (14 and 22) had stronger anti-inflammatory activity than galactosyl-glycerol derivatives (13 and 21).

KEYWORDS lipoteichoic acid; galactosyl-glycerol derivative; glucosyl-glycerol derivative; anti-inflammatory activity; (S)-1-O-acetyl-2-O-benzyl-glycerol

Membrane teichoic acids or lipoteichoic acids are important components of the cell wall of most Gram-positive bacteria. They are located in the inner region of the cell membrane and the wall. The structure of a lipoteichoic acid of Staphylococcus aureus has been elucidated by Baddiley.[1] It consists of a glycolipid unit joined by a phosphodiester linkage to a glyceryl phosphate polymer (Chart 1).

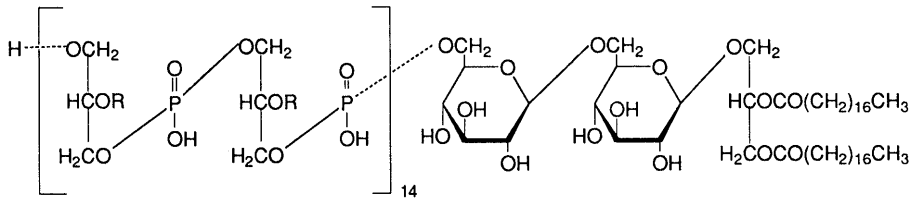

Chart 1

Recently, these glycerolipids (1 and 2) were isolated from the Okinawan marine sponge Phyllospongia foliacens by Kitagawa and coworkers.[2] A galactolipid (1) exhibits anti-inflammatory activity, and a sulfonoglycolipid (2) resists complement fixation reactions (Chart 2).

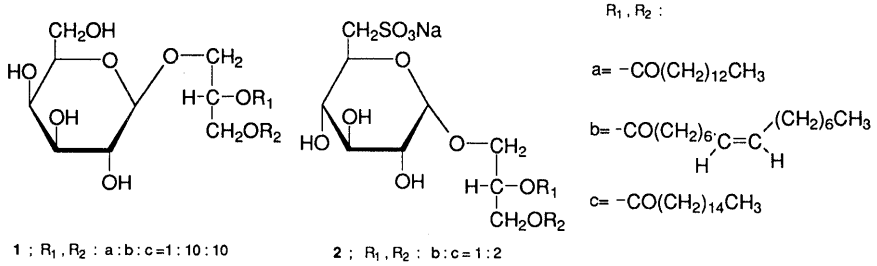

Chart 2

As a part of our synthesis studies of biologically active new compounds by modifying the cell wall structures of bacteria,[3] we report the stereoselective synthesis of (R)- and (S)-2,3-di-O-palmitoyl-1-O-galactopyranosyl-glycerol (13 and 21), (R)- and (S)-2,3-di-O-palmitoyl-1-O-glucopyranosyl-glycerol (14 and 22) in order to clarify the influence of such structural changes on anti-inflammatory activity.

First, (R)-glycerols, (R)-galactosyl-glycerol (13) and (R)-glucosyl-glycerol derivatives (14) were synthesized as shown in Chart 3. (S)-1-O-Acetyl-2-O-benzyl-glycerol (3)[4] was treated with 3,4-dihydro-2H-pyran and pyridinium p-toluenesulfonate (PPTS) in dichloromethane at 0℃, followed by deacetylation with NH_4OH-MeOH (1:10) at room temperature to give the tetrahydropyranylated compound (4) (83%, syrup, $[\alpha]_D$ +26.5°). The glycosylation of (R)-2-O-benzyl-1-O-tetrahydropyranyl-glycerol (4) with monosaccharide donors (5) and (6) was performed with Ag_2O, I_2, and powdered Molecular Sieves 4A (MS4A), followed by detetrahydropyranylation with PPTS in EtOH at 55℃ to give the glycosides (7) and (8) (7: 39%, syrup, $[\alpha]_D$ -17.8°, 8: 36%, syrup, $[\alpha]_D$ -16.6°). The configuration of the glycosidic linkage of 7 and 8 was assigned as β from the ^{1}H-NMR spectrum of their anomeric protons at δ 4.53 as a doublet with $J_{1',2}$=8.0Hz and δ 4.57 as a doublet with $J_{1',2}$=8.5 Hz, respectively. The benzyl groups in 7 and 8 were removed by hydrogenolysis with palladium-on-carbon (Pd-C) to give the 2,3-dihydroxyl compounds (9) and (10) in 94% and 99% yields, respectively. The acylation of 9 and 10 with palmitoyl chloride, trietylamine, and 4-dimethylaminopyridine (DMAP) gave the diacylated compounds (11) and (12) in 85% and 72% yields, respectively. Selective removal of the acetyl groups of 11 and 12 with hydrazine monohydrate[5] at reflux for 15 min in 85% EtOH gave the (R)-galactoglycerolipid (13) and (R)-glucoglycerolipid (14) (13; 18%, mp 83-84℃, $[\alpha]_D$ -6.8°, 14; 30%, mp 77-79℃, $[\alpha]_D$ -11.0°).

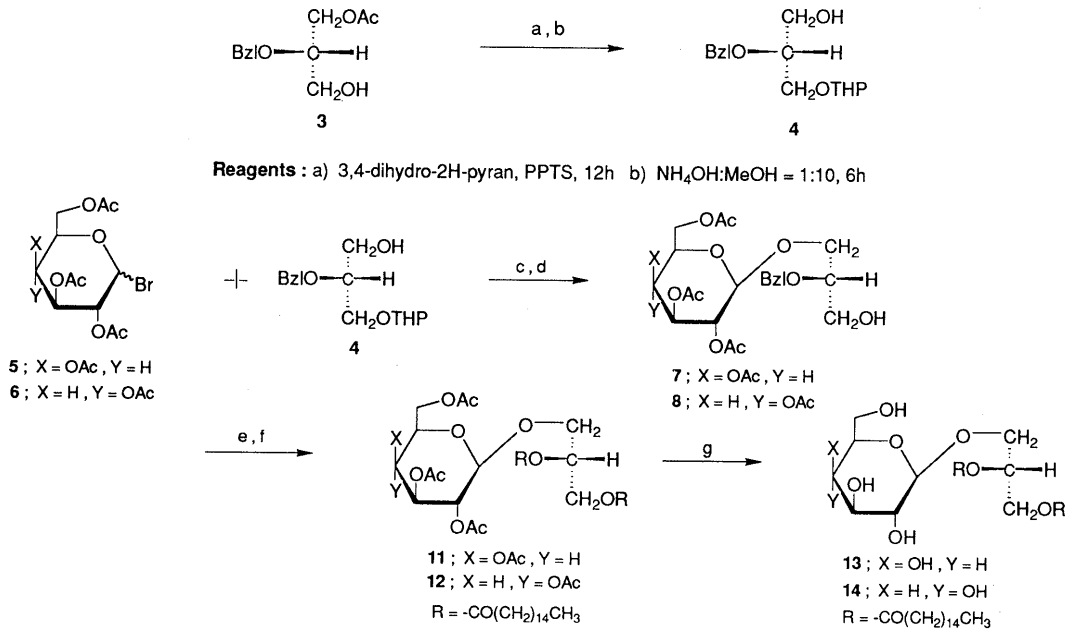

Chart 3

Next, (S)-glycerols, (S)-galactosyl-glycerol (21), and (S)-glucosyl-glycerol derivatives (22) were also synthesized as shown in Chart 4. The 3-hydroxyl group of 4 was protected with benzyl bromide, NaH, and n-Bu_4NI to afford 15 in 96% yield. The removal of the tetrahydropyranyl group of 15 with PPTS in EtOH at 55℃ gave the glycosyl acceptor of (S)-1,2-di-O-benzyl-glycerol (16) (80%, syrup,

$[\alpha]_D$ -18.2°). Similarly, the glycosylation of 16 with monosaccharide donors (5) and (6) followed by debenzylation gave the 2,3-dihydroxyl compounds (17) and (18) in 67% and 65% yields, respectively. The β-configuration of the anomeric protons of 17 and 18 was confirmed by ^{1}H-NMR spectrum data, which revealed a signal for H-1 at δ 4.53 (J=7.5 Hz) and at δ 4.56 (J=8.1 Hz), respectively. The acylation of 17 and 18 gave the diacylated compounds (19) and (20) in 66% and 58% yields, respectively. Finally, the selective deacetylation gave the (S)-galactoglycerolipid (21) and (S)-glucoglycerolipid (22) (21; 52%, mp 79-81℃, $[\alpha]_D$ -11.5°, 22; 22%, mp 82-84℃, $[\alpha]_D$ -11.7°). The structures of all compounds were characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy, as well as infrared (IR) spectroscopy and elemental analyses. The ^{1}H-NMR spectrum of 21 was identical with that of 1c.

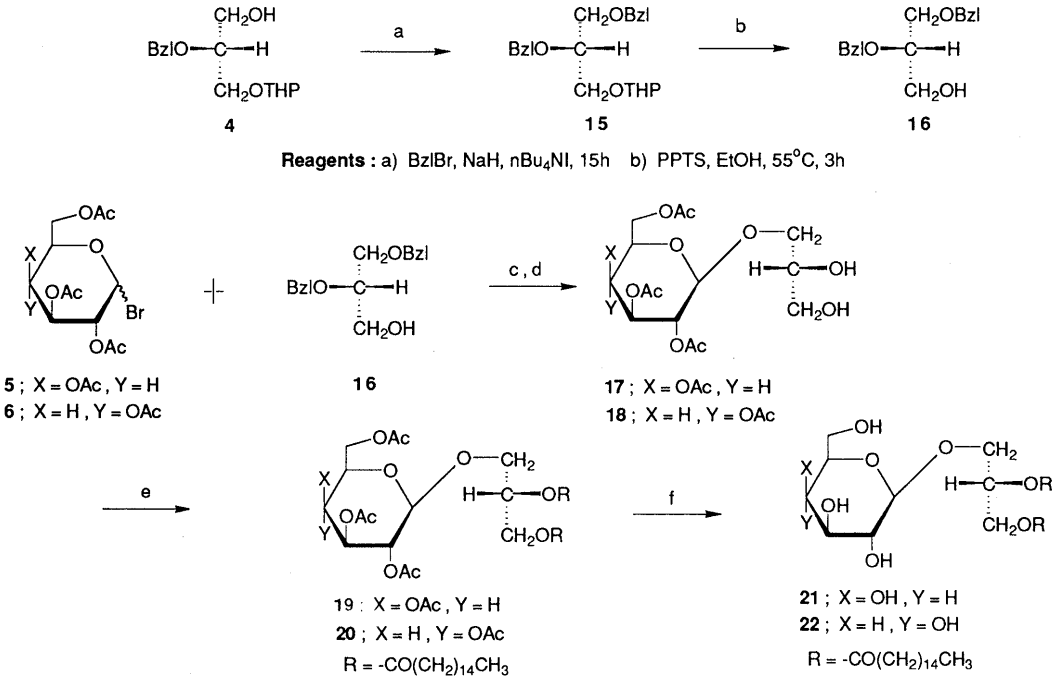

Chart 4

Preliminary biological examination revealed that glucosyl glycerolipids (14 and 22) had stronger anti-inflammatory activity than galactosyl glycerolipids (13 and 21).

ACKNOWLEDGEMENT We are grateful to Professor I. Kitagawa for providing the ^{1}H-NMR spectrum of 1c.

REFERENCES

1) a) P. A. Lambeat, I. C. Hancock, and J. Baddiley, Biochem. Biophys. Acta, 472, 1 (1977); b) J. J. Oltvoort, M. Kloosterman, and C. A. A. Van Boeckel, and J. H. Van Boom, Carbohydr. Res., 130, 147 (1984).
2) H. Kikuchi, Y. Tsukitani, T. Manada, T. Fujii, M. Kobayashi, and I. Kitagawa, Chem. Pharm. Bull., 30, 3544 (1982).
3) Part XXV : S. Akamatsu, K. Ikeda, and K. Achiwa, Chem. Pharm. Bull., 39, 518 (1991).
4) Y. Terao, M. Murata, K. Achiwa, T. Nisino, M. Akamatu, and M.Kamimura, Tetrahedron Lett., 29, 5173 (1988).
5) H. P. Wehrli and Y. Pomeranz, Chem. Phys. Lipids, 3, 357 (1969).

(Received March 8, 1991)