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The Synthesis of Glycoglycerolipids

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Abstract: A convenient synthetic route was developed for the synthesis of the novel glycolipids: 1, 2-di-O-acyl-3-O-(2′-acylamide-2′-deoxy-α-D-glucopyranosyl)-*sn*-glycerols. 10 new compounds of glycolipids with different acyl groups were obtained.

Key words: 2-N-Acetamide-glucose, glycolipids, glycoglycerolipids.

Glycolipids are important components of cell membranes and play an important role as signal transduction in celluar biology. The design and synthesis of glycolipids and their derivatives have highlighted potential therapeutic uses in the treatment of cancer, infection and other diseases.

Recently tumor inhibition activity of glycoglycerolipids has been demonstrated on the basis of their in vitro and in vivo antitumor promoting effect on Epstein-Barr virus early antigen (EBV-EA) activation induced by the TPA[2-5]. This promoted us to synthesize some glycoglycerolipids and their analogues for biological research in future.

The synthesis of 1, 2-di-O-acyl-3-O-(2′-acylamide-2′-deoxy-α-D-glucopyranosyl)-*sn*-glycerols with different acyl groups was achieved by an efficient method. The reaction of 2-N-acetamide-glucose with allyl alcohol provided allyl D-glycoside as mixtures of α and β anomers; subsequent recrystallization gave pure α anomer **1**. Protection of hydroxy group with benzyl was followed by oxidation[6, 7]of 1-O-allyl using OsO_4/NMO to obtain the diastereomeric diols **3** in the ratio of 1(**2*R***):1(**2*S***) determined by the ^{1}H NMR data. The chemical shifts of anomeric hydron of the two diastereoisomers are 4.65ppm and 4.63ppm respectively, and their integrals are almost same. And in this step the mixtures can not be isolated by general method. The esterification of **3** with various acyl chlorides afforded a series of triacylated derivatives **4-1f-j(2*S*)**, **4-2f-j(2*R*)**.

After acylation, it became easy to isolate the diastereoisomers of 1, 2-di-*O*-acyl-3-O-(2′-acylamide-2′-deoxy-3′,4′,6′-tri-benzyl-α-D-glucopyranosyl)-*sn*-glycerols by chromatography. Comparing the ^{1}H NMR data of the **4-1f-j**, **4-2f-j**, it was found that, except for the $C\underline{H}_2$-1 of the glycerol moiety, the other 1H NMR data of the diastereomeric compounds **4-1** and **4-2** are almost the same. For example, the chemical

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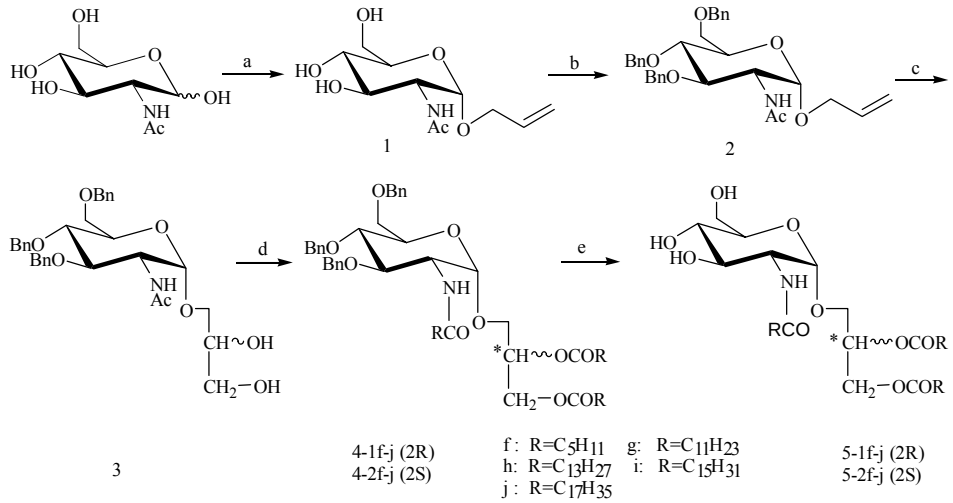
shifts of $C\underline{H_2}$-1 of compound **4-1b** are 4.37 ppm(CH_2-1a) and 4.05 ppm(CH_2-1b). And for the **4-2b,** they are 4.23 ppm (CH_2-1a) and 4.17 ppm(CH_2-1b). For **4-1** series, the difference of the chemical shifts of the CH_2-1a and CH_2-1b is more than 0.22 ppm. However for **4-2** series the value is smaller than 0.08 ppm. Then the **C**-2 stereochemistry of **4-1** series and **4-2** series was **2*S*** and **2*R*** respectively, determined by comparison of the NMR data[8]. Finally hydrogenolytic deprotection of the benzyl groups provided a series of designed new compounds **5-1f-j(2*S*)**, **5-2f-j(2*R*)** in good yield through five steps (**Schem 1**).

The structures of all compounds were confirmed by MS, ^{1}H-NMR, ^{13}C-NMR, and IR. The related data of **5-1b(2*S*)**, one of the title compounds, were followed: ^{1}H-NMR (600MHz, DMSO) δ: 7.45(d, 1H, *J*=7.7 Hz, NH), 5.08-5.05(m, 1H, CH-2), 4.92(d, 1H, *J*=5.2 Hz, OH-4′), 4.68(d, 1H, *J*=3.6 Hz, H-1′), 4.59(d, 1H, *J*=5.8 Hz, OH-3′), 4.38(t, 1H, *J*=6.1 Hz, OH-6′), 4.31(dd, 1H, *J*=3.3, 12.1 Hz, CH_2-1a), 4.14(dd, 1H, *J*=6.6, 12.1 Hz, CH_2-1b), 3.67(dd, 1H, *J*=5.2, 11.0 Hz, CH_2-3a), 3.64-3.60(m, 2H, H-2′, CH_2-6′a), 3.51-3.44(m, 3H, CH_2-6′b, H-3′, CH_2-3b), 3.35(ddd, 1H, J=2.2, 5.2, 10.9 Hz, H-5′), 3.16(ddd, 1H, *J*=5.2, 8.8, 14.0 Hz, H-4′), 2.30-2.21(m, 4H, 2C=OC$\underline{H_2}$), 2.13-2.04(m, 2H, NHCOC$\underline{H_2}$), 1.51-1.45(m, 6H, 3C=OCC$\underline{H_2}$), 1.30-1.24(m, 48H, 24CH_2), 0.85(t, 9H, *J*=7.1Hz, 3CH_3). Calculated Mass for $C_{45}H_{85}NO_{10}$ 799.62, MS: *m/z* $[M+H]^+$ 800.8, $[M-H]^-$ 798.6.

Scheme 1



Conditions and reagents: a. CH_2=CH-OH, BF_3-ether, reflux, 2h, 77%; b. DMF, BnBr, NaH, 0°C-r.t., Bu4N$^+$I$^-$, 5h, 75.4%; c. acetone-H_2O, OsO_4 / NMO, r. t, 1 h, 95%; d. pyridine, RCOOCl, DMAP, reflux; e. EtOAc-EtOH, Pd-C / H_2, r. t.

Through this simple route (Schem1), 10 title compounds of tri-acylated glycosylglycerols---**(2*R*)** and **(2*S*)** 1,2-di-O-acyl-3-O-(2′-acylamide-2′-deoxy-α-D- glucopyranosyl)-*sn*-glycerols with different acyl groups were synthesized. The acyl groups were hexanoyl, lauroyl, myristoyl, palmitoyl, stearoyl respectively.

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