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Synthesis of Tigogenyl 2-Deoxy–2-phthalimido-D-glucopyranoside Derivatives and Study of their ^{1}H-NMR Spectrum

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Abstract: Two protected tigogenyl glycosides were synthesized *via* parallel synthesis of oligosaccharide. Using chemical synthesis and conformational analysis the reason of the proton signal of 2″ acetyl group shifted up field in ^{1}H-NMR was discussed.

Keywords: Phthalimido group, tigogenyl glycoside, anisotropic effect.

Tigogenyl glycoside is a structurally diverse class of plant glycosides, which have attracted much attention in recent years because of the host of biological activities they exhibit[1-5]. In order to study the structure-activity relationships of tigogenyl glycosides with N-acetylglucosamine, glucosamine and tigogenin used as starting materials, *via* parallel synthesis of oligosaccharides, tigogenin glycosides with different sugar chains were got in an efficient way.

Compound **2**[7] (**Scheme 1**) was used as a donor, conjugation with tigogenin in the presence of $CdCO_3$ as a promoter in CH_3CN under reflux to give **3** ($J_{1',2'}$=8.7 Hz) in a yield of 87%[8]. Deacetylation of **3** and then reacted with *p*-methoxybenzaldehyde dimethyl acetal in the presence of *p*-toluene-sulphonic acid monohydrate in DMF offered **4**. Regioselective reductive ring-opening of **5** gave **6**.

Using $BF_3{\cdot}Et_2O$ (**Scheme 2**) as a promoter **4** could couple with the two different donors **7** and **8** [9]. $1''\rightarrow3'$ glycosidic linkage compounds **9** (H-1″ at δ 4.54, $J_{1'',2''}$=8.1 Hz) and **10** (H-1″ at δ 4.58, $J_{1'',2''}$=7.8 Hz)were gotten respectively.

It was found that the ^{1}H-NMR signals of H-1′ and H-2′ in **9** and **10** were changed compared to those of **4**, and the proton signal of one acetyl group was shifted up field (δ 1.50 for **9** and δ 1.52 for **10**). However when compound **6** was used as an acceptor to couple with the same donor **7** or **8**, the same phenomena did not take place, but to give compounds **15** (H-1″at δ 4.50, $J_{1'',2''}$=8.4 Hz) and **16** (H-1″at δ 4.52, $J_{1'',2''}$=8.1 Hz), the $1''\rightarrow4'$ glycosidic linkage products.

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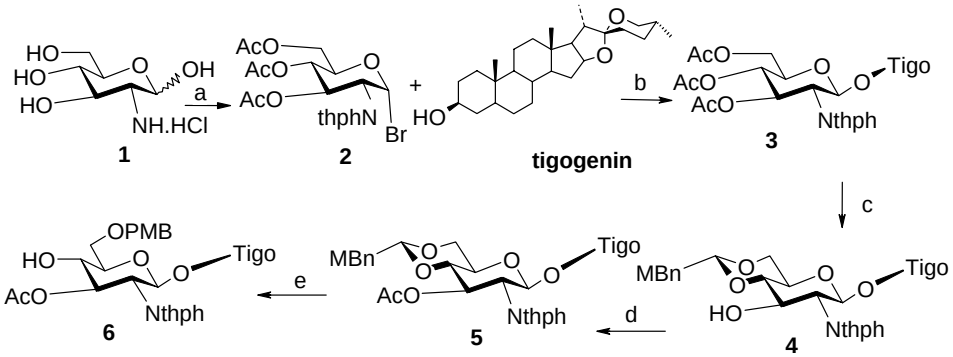
Scheme 1



Reagents and conditions: (a) (i) NaOMe, MeOH (ii) $Phth_2O$, Et_3N (iii) Ac_2O, pyridine (iv) HBr/HOAc (36% yield over four steps). (b) $CdCO_3$, CH_3CN 80°C reflux (87%). (c) (i)1mol/l MeONa/MeOH, 1:1 MeOH-CH_2Cl_2 (ii) *p*-methoxybenzaldehyde dimethyl acetal, *p*-toluene-sulphonic acid monohydrate, DMF 50°C under aspirator pressure (65% yield over two steps). (d) Ac_2O, pyridine (90%). (e) sodium cyanoborohydride, trifluoroacetic acid, DMF (73%).

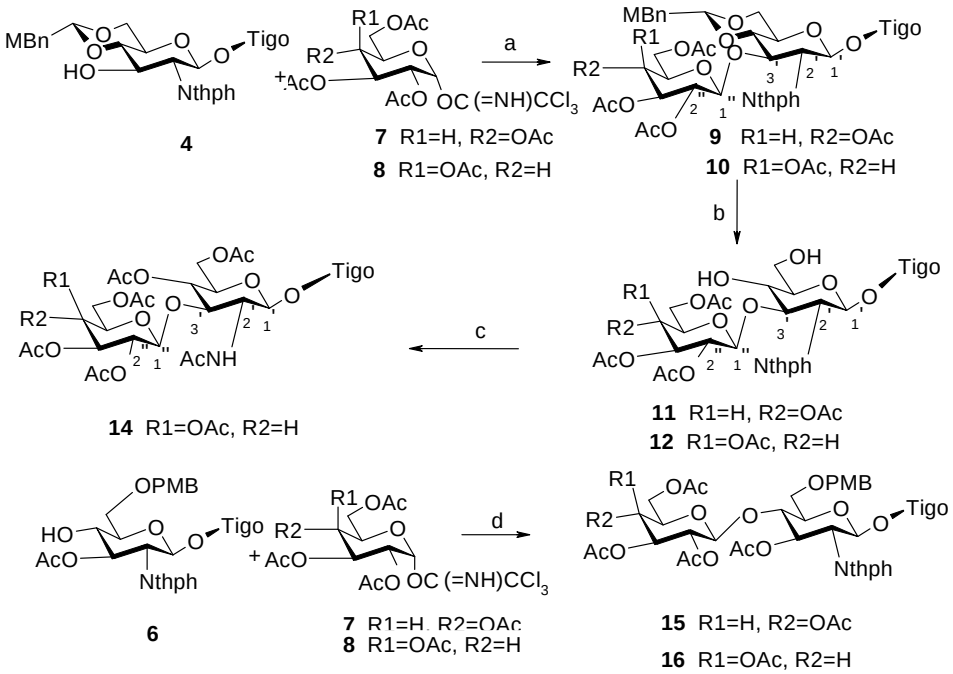
Removed off (**Scheme 2**) the *p*-methoxybenzylidene of **9** and **10**, **11** and **12** were obtained in a yield of 96% and 94% respectively. The data of ^{1}H-NMR spectrum of **11** and **12** revealed that the proton signal of acetyl groups at 2″ were at δ 1.45 and 1.50 respectively. Deprotection of phthalimido and then acetylation, phthalimido protected **11** and **12** were changed into acetylimido **13** and **14**. ^{1}H-NMR spectrum of **13** and **14** showed that all the proton signals of the acetyl groups of **13 a**nd **14** were appeared at δ 1.95-2.07. All these data proved that the shielding effect of phthalimido group of **9** and **10** caused the proton signal of the acetyl group to be shifted up field.

It was well established[10] that an equatorial phthalimido group has a strong deshielding effect on neighboring axial hydrogen atoms. Therefore, a slight variation in the time-averaged orientation of the phthalimido group could cause a change of the chemical shifts of the neighboring axial hydrogen atoms. In fact a change in the orientation of the phthalimido group is to be expected when the substituted group on 3′-OH position. In the case of **4**, the substituent was a hydroxyl group; in the case of **9** and **10**, the substituents were much bulker acetylated β-D-glucospyranosyl group and acetylated β-D-galactopyranosyl group respectively, thus H-1′ gave its signal at δ 5.24 for **9** and 5.23 for **10** but at δ 5.37 for **4**. A change in the orientation of the phthalimido group should also affect the chemical shift of H-2′.

Because of the anisotropic effect of phthalimido group, it was thought that the 2″acetyl group located just at the shielding region, so the proton signal of this acetyl group was shifted to up field in ^{1}H-NMR spectrum.

Additionally, our conjecture was supported by conformational analysis. In the present paper the technique of random conformational searching[11] was applied to locate energy minima of a molecule. The conformation of backbone atoms of compound **9** was constructed with reference to the fragment of SYBYL. The conformation of sugar chain was determined by random conformation search program in SYBYL, the detailed algorithms and methods of which are described in SYBYL manual. The maximum

Scheme 2

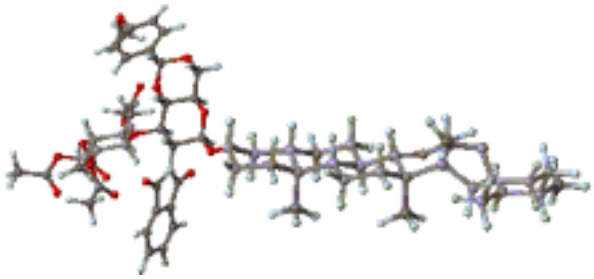


Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, under argon protection, -78°C to rt, (**9** yield 65% and **10** yield 63%); (b) 80% HOAc, rt, 24hr, (**11** yield 96% and **12** yield 94%); (c) (i)hydrazine hydrate, EtOH, rt, 48hr. (ii) Ac_2O, pyridine (45% to 48% yield over two steps); (d)$BF_3.Et_2O$, CH_2Cl_2, under argon protection, -78°C to rt. (**15** yield 55% and **16** yield 60%).

search cycles were set to 200 and the torsion changes were defined in 20 rotatable bonds. Tripos force field and Gast-Hück charges were selected for minimization and other parameters were defined as default.

The results from random search indicated that the conformation of compound **9** listed in **Figure 1** was preferred, since it was most frequently found in the process of the search and simultaneously presented the lowest energy. It showed that the protons of 2″acetyl group located just at the shielding region of phthalimido group and the distance from the protons of 2″acetyl group to the center of phthalimido group is 3.97Å.

Figure 1 Global energy minimum conformation of **9**



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11. Selected ^{1}H-NMR data of **4**, **9**, **13**.
12. Spectral data of **4**: (300MHz, $CDCl_3$), (δ*ppm*, J Hz): 7.88-7.42(m, 4H, Nthph), 7.43-6.88(m, 4H, MBn), 5.52(s, 1H, $MeOC_6H_4CHO_2$), 5.37(d, 1H, J=8.7, H-1′), 4.61(dd, 1H, J=7.8, 8.1, H-3′), 4.34(m, 2H, H-16 and H-2′), 4.22(dd, 1H, J=7.8, 9.3, H-4′), 3.8-3.3(m, 9H, H-3, CH_3O, H-26, H-5′, H-6′), 0.94(d, 3H, J=7.2, H-27), 0.76(s, 3H, H-18).
13. Spectral data of **9**: (300MHz, $CDCl_3$), (δ*ppm*, J Hz): 7.89-7.46(m, 4H, Nthph), 7.44-6.87(m, 4H, MBn), 5.52(s, 1H, $MeOC_6H_4CHO_2$), 5.24(d, 1H, J=8.4, H-1′), 5.00-4.86(m, 2H, H-3″and H-4″), 4.82-4.68(m, 2H, H-2″and H-2′), 4.54(d, 1H, J=8.1, H-1″), 4.37-4.23(m, 3H, H-3′, H-4′and H-16), 4.00-3.73(m, 7H, CH_3O, H-6′ and H-6″), 3.64-3.20(m, 5H, H-3, H-26, H-5′ and H-5″), 1.98(s, 3H, CH_3CO), 1.91(s, 3H, CH_3CO), 1.85(s, 3H, CH_3CO), 1.50(s, 3H, CH_3CO), 0.94(d, 3H, J=6.9 H-27), 0.76 (s, 3H, H-18).
14. Spectral data of **13**: (500MHz, $CDCl_3$), (δ *ppm* J Hz): 5.80(d, 1H, J=8.0, NH), 5.14(m, 2H,H-3″and H-4″), 5.04(dd, 1H, J=9.5, 9.5, H-4′), 4.89(dd, 1H, J=9.5, 9.5, H-3′), 484(m, 1H, H-2″), 4.60 (m, 2H, H-1′ and H-1″), 4.36 (dd, 1H, J=7.0, 15, H-16), 4.32-4.20 (m, 2H, H-6″), 4.10(m, 2H, H-6′), 3.66 (m, 2H, H-5′ and H-5″), 3.55-3.33(m, 3H, H-3 and H-26), 2.96 (m, 1H, H-2′), 2.07(s, 3H, CH_3CO), 2.05(s, 3H, CH_3CO), 2.04(s, 3H, CH_3CO), 2.02(s, 3H, CH_3CO), 2.00(s, 3H, CH_3CO), 1.99(s, 3H, CH_3CO), 1.97(s, 3H, CH_3CO).

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