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SYNTHESIS OF TIGOGENYL β-O-CELLOBIOSIDE HEPTAACETATE AND GLYCOSIDE TETRAACETATE VIA SCHMIDT'S TRICHLOROACETIMIDATE METHOD; SOME NEW OBSERVATONS.

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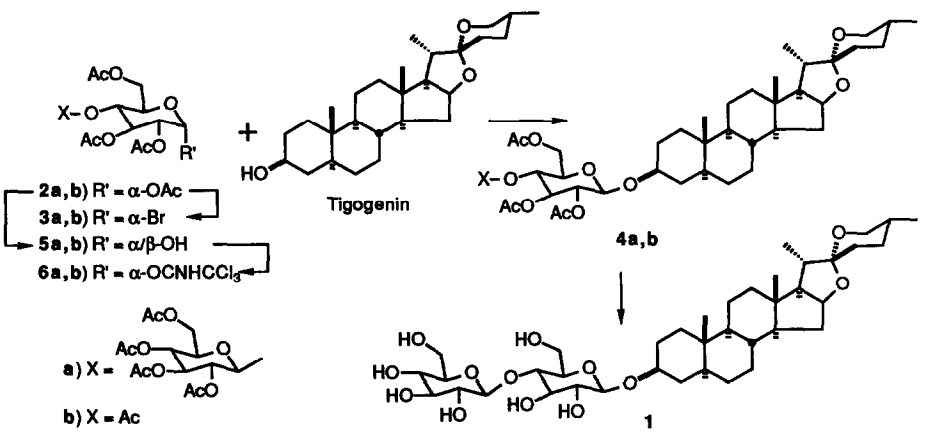
Summary: In studying the synthesis of tigogenyl β-O-cellobioside **1** via the trichloroacetimidate method of Schmidt, cesium carbonate was found to be an efficient reagent for the synthesis of peracetylated disaccharide α-trichloroacetimidates. Zinc bromide was superior to $BF_3 \cdot Et_2O$ for coupling these disaccharide α-trichloroacetimidates with the steroid tigogenin.

Rene Malinow et al.[1] have described the effect of tigogenyl β-O-cellobioside **1** for lowering serum cholesterol in monkeys and proposed a mechanism of action which involves the blocking of intestinal absorption of cholesterol by **1**. Since the synthesis described by Malinow used titanium tetrabromide (**2a** to **3a**) and mercuric cyanide (**3a** to **4a**) and was not suitable for bulk preparation, we examined the trichloroacetimidate method of Schmidt[2] as an alternative.



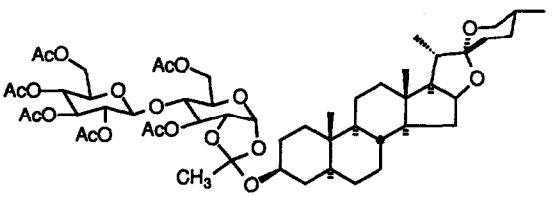
While our work was in progress, α-O-cellobiosyl trichloroacetimidate heptaacetate **6a** was mentioned in a publication by Ganem where it was prepared using standard Schmidt conditions (NaH, CCl_3CN, CH_2Cl_2; then $BF_3 \cdot Et_2O$).[3] When NaH or DBU[4] was used as the catalyst in the formation of **6a**, the reaction mixtures became quite dark and purification of **6a** required filtration of the crude product through silica gel. This was unsuitable for large scale

preparations. However, treatment of 1-hydroxy-cellobiose heptaacetate **5a**[5] with cesium carbonate (5-10 mol%) in methylene chloride was very effective for the preparation of O-α-cellobiosyl trichloroacetimidate heptaacetate **6a** which was isolated as a light yellow to white solid in >90% yield.[6] The formation of the thermodynamic α-anomer **6a** is both fast and very clean with none of the color formation which we observed with the stronger basic catalysts. Indeed, **6a** has been generated in situ and reacted with tigogenin after filtering off the cesium carbonate. Both 1-hydroxy-lactose and 1-hydroxy-maltose heptaacetates formed α-trichloroacetimides in >90% yield with cesium carbonate and trichloroacetonitrile in methylene chloride solution,[7] while 1-hydroxy-pyranoglucose tetraacetate **5b** gave a 3.3 : 1 mixture of α/β-anomers **6b**. These results are consistent with the rationale that cesium carbonate increases the nucleophilicity of the α-anomeric hydroxyl group to give the thermodynamic α-trichloroacetimidate directly rather than by equilibration of the kinetic β-imidate which is formed first with NaH or K_2CO_3 as catalyst.[8]

Glycosidation of tigogenin with **6a** and $BF_3{\cdot}Et_2O$ as the catalyst in methylene chloride solution at room temperature gave yields of **4a** in the range 35-40 % along with tigogenyl acetate as a major side product. In a related example, tigogenin reacted with α/β-O-pyranoglucosyl trichloroacetimidate tetraacetate **6b** and $BF_3{\cdot}Et_2O$ catalyst to yield O-β-tigogenyl glucoside tetraacetate **4b** in 10-15% yield with tigogenyl acetate now the major product.

Rather than replace the C_2 acetate with a bulky ester to prevent acyl transfer to the steroid as described by both Schmidt[9] and Ogawa,[10] we explored other Lewis acid catalysts which might allow us to improve the coupling yield.[11]

The most useful result was achieved with zinc bromide as catalyst where the reaction proceeded in two stages at room temperature. Initially, the steroid and **6a** were consumed and after two hours at room temperature, the intermediate orthoester **7** could be isolated as a pure crystalline compound and characterized by its NMR spectrum and easy hydrolysis to regenerate tigogenin and cellobiose hexaacetate.[12]



7

Continued exposure to zinc bromide (30 mol%) at room temperature overnight or at reflux for several hours, gave **4a** in 50 to 60% yield after treatment of the crude reaction mixture with

acetic anhydride.[13] The acetylation converted some tigogenyl O-β-cellobioside hexaacetate to **4a**.[14] Interestingly, little of this hexaacetate was observed in the BF_3•Et_2O catalyzed coupling.

The improvement in the glycosidation yield with zinc bromide was most striking for the glucosidation of tigogenin with O-α/β-pyranoglucosyl trichloroacetimidate tetraacetate **6b** where the desired product **4b** was isolated in 40% yield, most of it by direct crystallization from the crude reaction mixture. This can be compared with a ca. 10% yield with boron trifluoride etherate as the catalyst. Similar results were found with the lactose and maltose peracetylated α-trichloroacetimidates.

Among the other Lewis acids tested, magnesium bromide etherate formed orthoester **7** in 80% isolated yield.[15] Orthoester **7** was stable in the presence of this catalyst at room temperature and required refluxing to cause rearrangement; but the rearrangement step was less efficient than with zinc bromide with more tigogenyl acetate formation.

In conclusion, we have found that zinc bromide is an effective catalyst for the glycosidation of tigogenin with either O-α-cellobiosyl trichloroacetimidate heptaacetate **6a** or trichloroacetimidoyl O-α-pyranoglucosyl tetraacetate and that an orthoester intermediate **7** can be isolated in high yield in the former case. Also, the reagent of choice for the formation of the thermodynamic α-trichloroacetimidates of peracetylated glycosides is cesium carbonate in methylene chloride, which gives very clean products in high yields.

References and Footnotes

[1] Malinow, M.R.; Gardner, J.O.; Nelson, J.T.; McLaughlin, P.; Upson, B.; Aigner-Held, R. *Steroids*, **1986**, *48*, 197. Malinow, M.R. U.S. Patent 4,602,003, **1986**.

[2] Schmidt, R.R. *Pure and Appl. Chem.* **1989**, *61*, 1257

[3] Lietta, L.J.; Bernotas, R.C.; Wilson, D.B.; Ganem, B. *J. Amer. Chem. Soc.* **1989**, *111*, 783. Schmidt has reported a benzylated derivative of α-O-cellobiosyl trichloroacetimidate: Schmidt, R.R.; Michel, J. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 72.

[4] Numata, M.: Sugimoto, M.; Koike, K.; Ogawa, T. *Carbohydrate Res.* **1987**, *163*, 209.

[5] Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydrate Res.* **1975**, *39*, 368.

[6] Cellobiose heptaacetate **5a** (10 g, 0.157 mol); prepared from the octaacetate according to the method of Excoffier et. al.,[5] was dissolved in methylene chloride (100 ml) and treated with trichloroacetonitrile (4 ml) and cesium carbonate (0.52 g, 1.6 mmol). After stirring at room temperature for 5 h, the reaction was washed with water, with brine and dried over $MgSO_4$. Filtration and evaporation of the organic solution afforded **6a** (95%) which was recrystallized from ethyl acetate / hexanes; 8.5 g, 70% yield; mp 192-94°C; $[\alpha]_D$ +53.7° (c=0.932, acetone); NMR ($CDCl_3$, 300 MHz) δ 8.63 (s, 1), 6.45 (d, 1), 5.50 (t, 1), 5.1 (m, 3), 4.9 (t, 1), 4.52 (m, 2), 4.37 (dd, 1), 4.07 (m, 3), 3.82 (t, 1), 3.65 (m, 1), 2.10 (s, 3), 2.07 (s, 3), 1.97 (m, 15). Anal. Calcd. for $C_{28}H_{36}O_{18}NCl_3$: C, 43.06; H, 4.65; N, 1.79. Found: C, 43.02; H, 4.49; N, 1.81.

[7] O-α-Lactosyl trichloroacetimidate heptaacetate was isolated as an amorphous solid from hexanes in 91% yield: NMR ($CDCl_3$, 300 MHz) δ 8.66 (s,1), 6.48 (d, 1), 5.56 (t, 1), 5.33 (d,1), 5.15-5.02 (m, 2), 4.95 (dd,1), 4.50 (m, 2), 4.20 (m, 4), 3.87 (m, 2), 2.15-1.95 (6s, 21). O-α-maltosyl trichloroacetimidate heptaacetate was isolated as an amorphous solid from hexanes in 95% yield: NMR ($CDCl_3$, 300 MHz) δ 8.65 (s,1), 6.46 (d,1),5.59 (dd,1), 5.39(m, 2), 5.05 (t,1), 5.00 (dd, 1), 4.87 (dd,1), 4.49 (d,1), 4.20 (m, 3), 4.06 (m, 2), 3.92 (m,1), 2.15-1.95 (6s, 21). Both of these were one spot by tlc in several solvent systems.

[8] Schmidt, R.R.; Michel, J.; Roos, M. *Liebigs. Ann. Chem.* **1984**, 1343.

[9] Schmidt, R.R.; Zimmermann, P. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 725.

[10] Sato, S.; Nunomura, S.; Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 4079.

[11] Wulff, G.; Röhle, G.; Krüger, W. *Chem. Ber.*, **1972**, *105*, 1097. These authors studied the reaction of tigogenin and α-bromo glucosyl tetraacetate under the influence of a variety of silver carboxylate salts.

[12] Schmidt also has described the isolation of an orthoester from a BF_3 catalyzed reaction when very low levels of catalyst were used; however, it was accompanied by the desired glycosidation product. Zimmermann, P.; Bommer, R.; Bär, T.; Schmidt, R.R. *J. Carbohydrate Chem.* **1988**, *7*, 435.

[13] O-α-Cellobiosyl trichloroacetimidate heptaacetate **6a** (1.15g, 1.47 mmol) and tigogenin (0.54g, 1.3 mmol) were stirred in dry methylene chloride (20 ml) at room temperature with 3A molecular sieves (0.2g) for 4h. Anhydrous zinc bromide (0.2g, 0.89 mmol, Aldrich Chemical Company) was added in one portion. After 2h, tlc (silica gel; 3:1, chloroform : ethyl acetate) showed formation of the orthoester and the reaction was heated to reflux overnight. Acetic anhydride (1 ml, 10.6 mmol) was added at RT and the reaction stirred for 3h. The reaction was filtered, washed with water and brine and dried over $MgSO_4$. The product was isolated by flash chromatography over silica gel with chloroform / ethyl acetate (4:1) as eluant. The yield was 0.8g (59%) and the material was identical to that prepared by Malinow's procedure.[1]

[14] Banoub, J.; Bundle, D.R. *Can. J. Chem.* **1979**,*57*, 2091.

[15] Data for **7**: mp 187.5-188.5 °C; $[\alpha]_D$ -17.8° (c = 1.023, $CHCl_3$); NMR ($CDCl_3$, 300 MHz) δ 5.60(d, 1, J = 6), 5.52(d, 1, J =3), 5.20-5.03(m, 2), 4.98(t, 1, J =9), 4.67(d, 1, J =8), 4.41-4.02 (m, 6), 3.79(m,2), 3.63-3.30 (m, 4), 2.10-1.98 (6s, 18), 1.70 (s over m). Anal. Calcd. for $C_{53}H_{78}O_{20}$: C, 61.49; H, 7.60. Found: C, 61.14; H, 7.54.

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