Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8795-8796, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01953-3

Regioselective Sulfation of Galactose Derivatives through the Stannylene Procedure. New Synthesis of the 3'-O-Sulfated Lewis^a Trisaccharide.

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Abstract: Free or 6-protected β-D-galactopyranosides afforded, in excellent yields, the 3'-O-sulfate as the only product through the stannylene procedure. This methodology was successfully applied to the synthesis of the 3'-O- sulfated Lewis^a trisaccharide, an oligosaccharide reported as ligand of E- and L-selectins.

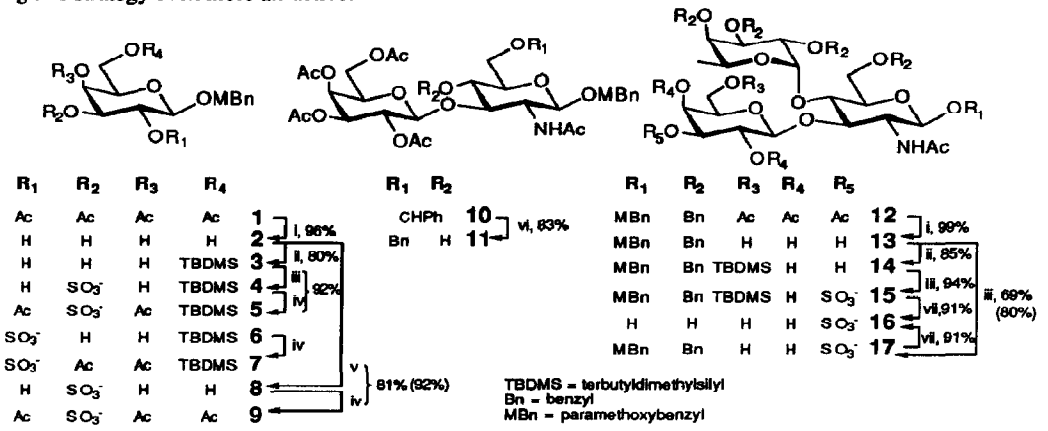
Sulfated carbohydrates are widely distributed in plants (algae) and animals where they occur principally as building blocks of glycosaminoglycans, the sugar chains of proteoglycans found in the extracellular matrix. Apart from the modification of the physical properties of the parent sugar chain, they now appear to influence many biological functions and become synthetic targets for possible therapeutic uses.[1] For example, the 3'-O-sulfated derivatives of the blood groups Lewis^a and Lewis^x series were recently shown to be good ligands for E- and L-selectins, two calcium-dependent mammalian lectins associated with early steps in the inflammatory response and lymphocyte extravasation into peripheral lymph nodes which makes them good candidates for anti-inflammatory drugs.[2]

Sulfation of simple sugars have already been performed using sulfuric acid, chlorosulfuric acid or sulfuryl chloride which generally gave complex mixtures. On the other hand, the use of sulfur trioxide complexes with pyridine or tertiary amine in solvents such as pyridine or N,N-dimethylformamide, generally gave good yields of sulfation, provided that only the hydroxyl groups to be sulfated are unprotected in the starting material. The regioselectivity is generally poor, except in favor of a primary alcohol.[3]

On the other hand, regioselectivity in sugar chemistry is often solved using the well-known stannylene methodology which is widely used with electrophiles such as acyl- or activated alkyl halides.[4] We now report in this paper, that stannylenes derived from β-D-galactopyranosides (mono- or oligosaccharides) react with SO_3-NMe_3 complexe to give high yields of the 3-O-sulfate in a one pot reaction, with a complete regioselectivity. We started first with paramethoxybenzyl 6-O-*ter*butyldimethylsilyl β-D-galactopyranoside **3**[5] having three secondary unprotected hydroxyl groups at C-2, C-3 and C-4. Direct reaction with SO_3-NMe_3 (1.5 equiv.) in pyridine afforded a mixture of monosulfates **4** (68%) and **6** (21%) while the reaction with the corresponding 2,3-di-O-butyl stannylene made *in situ* with dibutyltin oxide[6] afforded the 3-O-sulfate **4** in 92% yield as the only product isolated in the peracetylated form **5** after silica gel chromatography. The regioselectivity of sulfation was deduced from a downfield shift of the NMR signal for H-3 or H-2 of 0.7 ppm. Next we tried the reaction with the paramethoxybenzyl β-D-galactopyranoside **2** having four unprotected hydroxyl groups including a primary alcohol. The reaction, as above, first with dibutyltin oxide (1.1 equiv.) in toluene in the usual conditions for the formation of the 2,3-di-O-butyl stannylene followed by evaporation and addition of SO_3-NMe_3 (1.2 equiv.) in DMF at 0°C afforded **8** (81% ; 92% based on starting material recovery) as the only product isolated in the peracetylated form **9**.

Then we turned to the preparation of our target : the 3'-O-sulfated Lewis^a trisaccharide **16** we have recently[7] synthesized and which has been shown to be a good ligand for E- and L-selectins. This new methodology offers a more rapid route avoiding several protection-deprotection steps. Indeed, compound **13**, made from a common precursor **10** in three high yielding steps[8] and having the same four unprotected hydroxyl groups as in **2**, afforded the sulfate **17** in 69% yield (80% based on starting material recovery) as the only product isolated directly after silica gel chromatography.

Alternatively, protection of the primary alcohol by a *ter*butyldimethylsilyl protecting group gave **14** (85%) which led to the sulfate **15** in 94% isolated yield, making this two-step sulfation a higher yielding route. Both compounds **15** and **17** were separately transformed into **16** in one step by hydrogenation over 10% Pd/C in 91% isolated yields. It is noteworthy that both the *ter*butyldimethylsilyl and benzyl protecting groups were removed during the reduction step,[9] making this strategy even more attractive.



Reagents and Conditions[10]. i : NEt_3-MeOH-H_2O, 1-8-1, 20h, rt. ii : *ter*butyldimethylsilyl chloride (1.1 equiv), pyridine, 14h, rt. iii : a)Bu_2SnO (1.1 equiv), toluene, 16h at reflux with continuous removal of water b) after evaporation of toluene, SO_3-NMe_3 (1.2 equiv), DMF, 5h, rt. iv : Ac_2O-pyridine, 1-1, 16h, rt. v : as for iii but the sulfation step was performed at 0°C for 7.5h. vi : $NaBH_3CN$, HClgas, THF, 2h, O°C. vii : H_2 (1 atm), 10% Pd/C, 16h, rt.

Acknowledgements.

Université Paris-Sud and CNRS are gratefully acknowledged for financial support.

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5 Compound **3** was prepared as followed : peracetylated α-D-galactopyranoside trichloroacetimidate and paramethoxy benzyl alcohol (BF_3-Et_2O, CH_2Cl_2, 0.5h, 0°C) gave **1** (95%, mp 74°C, $[\alpha]_D^{20}$ -33 (c 2, CH_2Cl_2)) which was deacetylated (NEt_3-MeOH-H_2O, 1-8-1, 20h, rt) to **2** (96%, mp 108°C, $[\alpha]_D^{20}$ -41 (c 1.9, CH_3OH)). Then, silylation (*ter*butyldimethylsilyl chloride, pyridine, 14h, rt) afforded **3** (80%, $[\alpha]_D^{20}$ -37 (c 2.3, CH_2Cl_2)).

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8 Compound **13** was prepared as followed : reductive opening of the benzylidene acetal in **10** ($NaBH_3CN$, HClgas, THF, 2h, O°C) gave **11** (83%, mp 95°C, $[\alpha]_D^{20}$ -16 (c 1.4, CH_2Cl_2)). Fucosylation with perbenzyl α-L-fucopyranosyl bromide (Bu_4NBr, CH_2Cl_2-DMF, 4-1, 18h, rt) gave **12** (89%, mp 120°C, $[\alpha]_D^{20}$ -80 (c 1, CH_2Cl_2)) which was deacetylated as above to **13** (99%, mp 100°C, $[\alpha]_D^{20}$ -85 (c 0.4, CH_2Cl_2)).

9 Cormier J.F. ; Isaac M.B. ; Chen L.F. *Tetrahedron Lett.* **1993**, *34*, 243-246.

10 All new compounds were fully characterized by ^1H and ^{13}C NMR and gave satisfactory centesimal analysis. **5** : $[\alpha]_D^{20}$ -10 (c 1.5, CH_2Cl_2), ^1H NMR (250 MHz, $CDCl_3$-MeOD, 8-2) δ 4.48 (dd, 1H, J = 3.5, 10 Hz, H-3). **7** :$[\alpha]_D^{20}$ -32 (c 2, CH_2Cl_2), ^1H NMR (250 MHz, $CDCl_3$-MeOD, 8-2) δ 5.11 (dd, 1H, J = 3.5, 10 Hz, H-3), 4.55 (dd, 1H, J = 8, 10 Hz, H-2). **9** : mp 97°C, $[\alpha]_D^{20}$ 23 (c 1.6, CH_2Cl_2), ^1H NMR (250 MHz, $CDCl_3$-MeOD, 8-2) δ 4.51 (dd, 1H, J = 3.5, 10 Hz, H-3). **16** was found identical to the trisaccharide previously reported[7].

(*Received in France* 8 *September* 1994; *accepted* 28 *September* 1994)