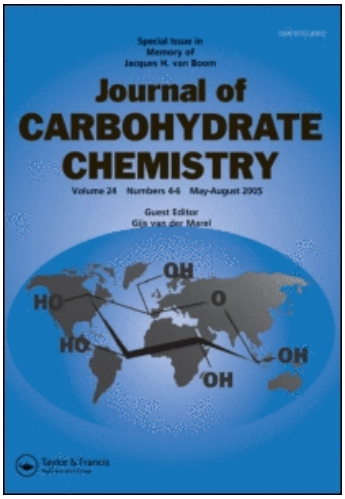

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COMMUNICATION

A NEW TWO-STEP STEREOSPECIFIC SYNTHESIS OF GLYCIDIC SPIROACETALS.

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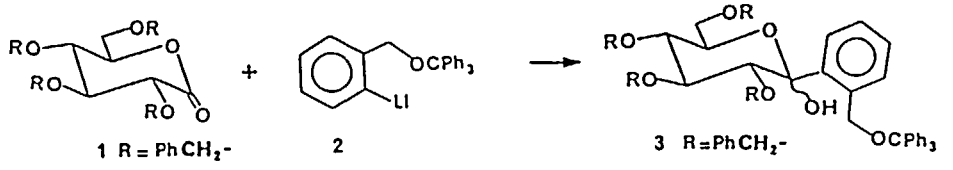
The spiroacetal moiety has received much attention in recent years owing to its occurence in several biologically important natural products.[1] In that field, the antibiotics avermectins,[2] milbemycins[3] and papulacandins[4] are of particular interest to us because a carbohydrate precursor could be employed for their syntheses.[5-7] Other glycidic spiroacetals were obtained by photocarbocyclization of 2-carbophenyl-β-D-glucopyranosides.[8]

As a part of a continuing programme[9] of C-C bond-formation at the anomeric center of a sugar moiety we have initiated some studies in that area. We report herein a new straightforward synthesis of a spiroacetal of the papulacandin type.

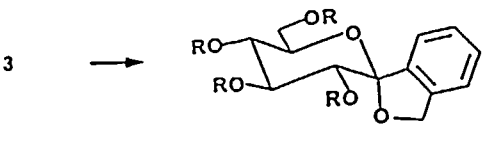
In a previous work[10] we demonstrated that aryl-β-D-C-glucosides could be prepared in a stereospecific manner by condensation of an aryllithium derivative with 2,3,4,6-tetra-O-benzyl-D-gluconolactone[11] (1) followed by reduction by triethylsilane in the presence of $BF_3.Et_2O$. We also observed that an O-trityl ether function was cleaved under the reduction conditions. Thus, we anticipated that the product resulting from condensation of 1 with an

organolithium derivative bearing a suitably placed O-trityl ether could directly cyclize during the reduction step (Scheme).

The required suitably protected organolithium compound 2 was efficiently prepared by exchange between triphenylmethyl 2-bromobenzyl ether[12] and *sec*-BuLi in toluene at low temperature (-78°C). Transfer of 2 (1.4 eq) to a cooled solution (-78°C) of 1 (350mg, 0.65 mmol) in toluene followed by hydrolysis after completion of the reaction (30 min) and classical work-up afforded a mixture of hemiacetals 3 together with triphenymethyl benzyl ether. Reduction of the crude mixture ($BF_3.Et_2O$, $HSiEt_3$, CH_3CN, -40→20°C, 1h) yielded the protected spiroacetal[13] 4 after purification by preparative TLC or flash chromatography (61% overall yield). Actually, the reducing agent ($HSiEt_3$) is not necessary and the cyclization could be achieved with $BF_3.Et_2O$ alone but the reaction is cleaner and the isolated yield higher when triethylsilane is added.



1 R = $PhCH_2$- 2 3 R = $PhCH_2$-



4 R = $PhCH_2$-

5 R = H

6 R = Ac

Debenzylation of 4 (Pd/C, methanol-ethyl acetate, 1:1) afforded 5 (mp 62°C, $[\alpha]_D^{20}$ +38.8°, *c* 1, chloroform) in quantitative yield. Under these conditions none of the other three O-benzylic bonds present in the spiroacetal rings was cleaved.

Peracetylated derivative 6 was obtained under classical conditions (Ac_2O, DMAP, pyridine) in 90% yield (mp 112°C, $[\alpha]_D^{20}$ +23.5°, *c* 1.1, chloroform). Additional structural proof was obtained from 6. The presence of only four acetoxy groups in 6, as determined by ^1H NMR (4s, δ 1.72, 2.0, 2.05, 2.07), confirmed that the integrity of the spiroacetal function was respected during the debenzylation step. Furthermore the large values of the coupling constants between $H_{2'}$, $H_{3'}$,$H_{4'}$, and $H_{5'}$ (10 Hz) were in agreement with previous reports [7,14] and clearly indicated a $^4C_1$ (D) conformation for the pyranoic ring. This observation is a good indication for an equatorial (β) position of the aromatic ring because in the α-anomer of phenyl-D-C-glucopyranoside the coupling constants are smaller due to conformational changes.[15]

This reductive cyclization of strategically functionalized hemiketals constitutes a very straightforward synthesis of spiroacetals. The extension of this methodology to other spiroacetals is currently under study.

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Doctor Jean-Marc Valéry is acknowledged for recording the ^{13}C and ^1H NMR spectra. We also acknowledge the financial support of the Centre National de la Recherche Scientifique.

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