A Convenient Selective Synthesis of Monosaccharide Derivatives having only One Free Hydroxy Group

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Reactions of acetonide derivatives of glucose, allose, galactose and fructose with MeMgI in benzene under reflux afford the corresponding monosaccharide derivatives having only one free hydroxy group in moderate to good yield.

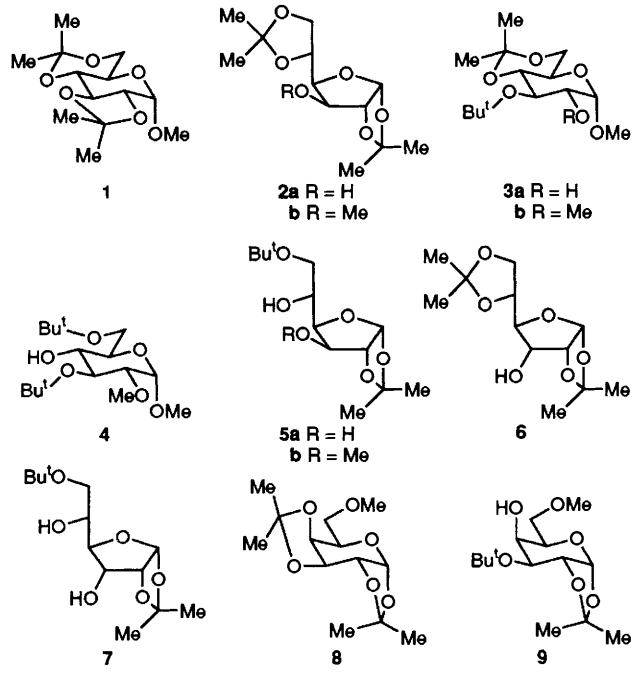
Selective protection of monosaccharides is extremely important in carbohydrate chemistry as well as in organic synthesis.[1] Multistep protection and deprotection are occasionally required to furnish monosaccharide derivatives having only one free hydroxy group. Carbohydrates having acetal protective groups are readily accessible.[2] Selective cleavage of one of the two C–O bonds in the acetal-protected monosaccharides will offer a useful entry for this purpose. Reductive cleavage of benzylidene acetals or the like has been used for the regioselective synthesis of certain monosaccharide derivatives.[3] However, a mixture of regioisomers is occasionally obtained. Recently, we found that acetonides can be cleaved regioselectively with the Grignard reagent when a neighbouring hydroxy or alkoxy group is present.[4] A possible chelation complex between the oxygen moieties and the Grignard reagent has been postulated to rationalize the selectivity of this reaction. We felt that this strategy could be extended to carbohydrate derivatives and now report our preliminary findings on the selective synthesis of various monosaccharide derivatives having one *one* free hydroxy group.

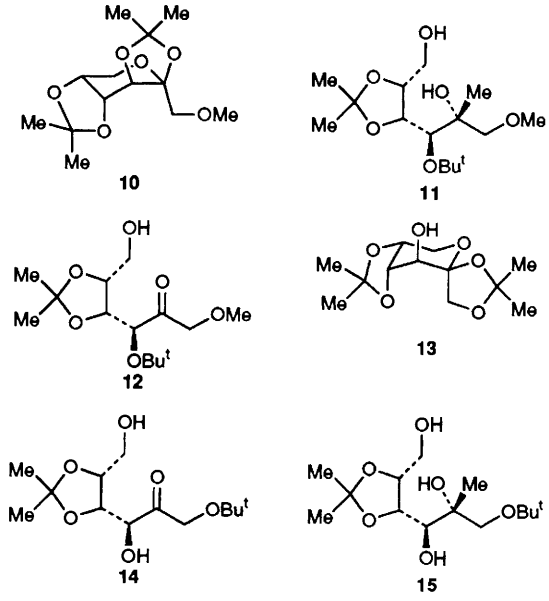
The two glucose acetonides **1** and **2** which are readily accessible by literature procedure,[2] were used to test the generality of the reaction. Thus, the reaction of **1** with 4 equiv. of MeMgI in benzene at 60 °C for 1 h afforded, after usual work-up, the corresponding 2-OH derivative **3a**† in 95% yield. An excess of the Grignard reagent was required to drive the reaction to completion. The structure of **3a** was proved by 2D-COSY and by X-ray diffraction methods.‡ Methylation of **3a** with MeI–NaH yielded **3b** which, when treated with MeMgI in benzene–ether solvent under reflux for 48 h gave, after work-up and chromatographic separation, the corresponding 4-OH derivative **4** in 58% yield.

The reaction of **2a**[2a] under the same conditions gave (in 65% yield) **5a** having hydroxy groups at C(3) and C(5) positions which has also been proved by X-ray diffraction methods.‡ In a similar manner, treatment of **2b**[2b] with MeMgI afforded **5b** exclusively in 68% yield. The presence of a β-hydroxy or β-methoxy group at C(3) appears not to be essential for the selectivity of this ring-opening process. Thus, the reaction of allose derivative **6** also afforded 54% yield of the corresponding 5-OH product **7**. These results indicate that the chelation with the oxygen atom on the five-membered heterocycle may play a predominant role in these reactions.

The reaction with galactose derivative **8**[2c] furnished the 4-hydroxy derivative **9** in 52% yield. Presumably, the chelation with the methoxy group at C(6) controls the regioselectivity.

The transformations involving fructose derivatives were interesting. Thus, treatment of **10**[2d] with MeMgI under usual conditions gave **11** selectively in 75% yield. Apparently, the





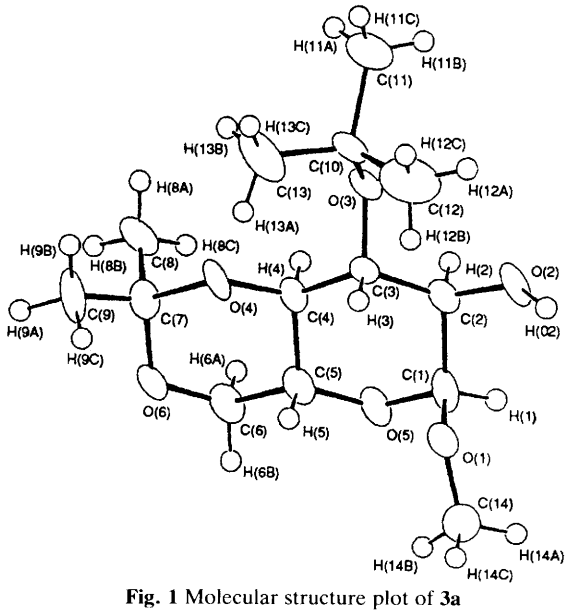


Fig. 1 Molecular structure plot of **3a**

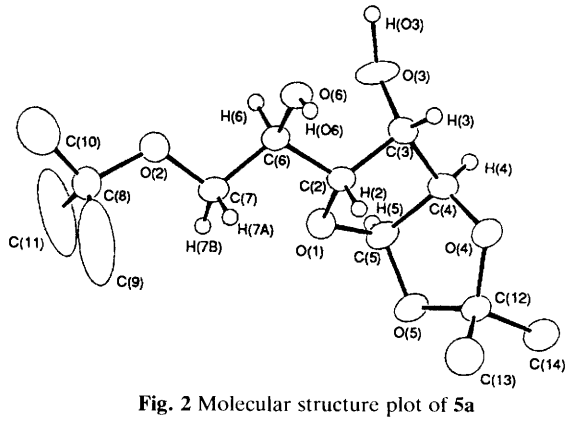


Fig. 2 Molecular structure plot of **5a**

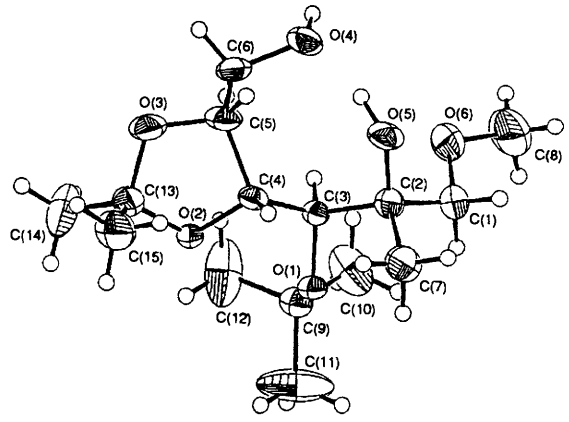


Fig. 3 Molecular structure plot of **11**

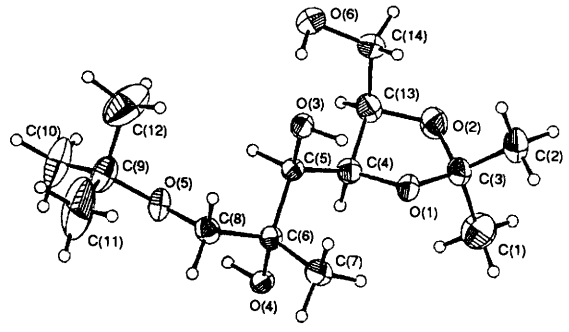


Fig. 4 Molecular structure plot of **15**

methoxy group at C(1) would assist the cleavage reaction to occur at C(2) presumably giving intermediate **12** which will further react with MeMgI stereoselectively to yield **11**. In a similar manner, the hydroxy group at C(3) also aids the regioselective ring opening of the acetonide at C(2) in the reaction of **13**[2d] to afford intermediate **14** which also reacted with MeMgI to give **15** (55%). The structures of both **11** and **15** were unambiguously proved by X-ray diffraction methods.‡ The stereoselectivity can readily be rationalized by means of chelation with the neighbouring oxygen function.

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Footnotes

† All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR data and elemental analyses. The structures were assigned with the help of 2D-COSY experiments and/or X-ray diffraction methods, whenever necessary. *Selected NMR data*: **3a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (s, 9 H, Bu^t), 1.35 (s, 3 H, Me), 1.42 (s, 3 H, Me), 2.18 (d, *J* 7.6 Hz, 1 H, OH), 3.36 [t, *J* 9.8 Hz, 1 H, C(4) H], 3.38 (s, 3 H, OMe), 3.44 [ddd, *J* 4.0, 7.6, 9.8 Hz, 1 H, C(2) H], 3.57 [dt, *J* 5.0, 9.8 Hz, 1 H, C(5) H], 3.64 [t, *J* 9.8 Hz, 1 H, C(3) H], 3.67 [t, *J* 9.8 Hz, 1 H, C(6) H], 3.81 [dd, *J* 5.0, 9.8 Hz, 1 H, C(6) H], 4.75 [d, *J* 4.0 Hz, 1 H, C(1) H]. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 29.0, 29.3, 55.1, 62.6, 64.1, 72.1, 72.4, 73.3, 74.5, 99.1, 100.2. **4**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 18 H, Bu^t), 1.79 (br s, 1 H, OH), 3.02 [dd, *J* 3.3, 9.4 Hz, 1 H, C(2) H], 3.26 [t, *J* 9.0 Hz, 1 H, C(4) H], 3.37 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.54–3.59 [m, 1 H, C(5) H], 3.71–3.76 [m, 2 H, C(3) H and C(6) H], 3.79 [dd, *J* 3.3, 11.4 Hz, 1 H, C(6) H], 4.80 [d, *J* 3.3 Hz, 1 H, C(1) H]. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.23, 29.30, 54.86, 59.54, 62.41, 71.47, 72.66, 72.73, 75.32, 77.20, 82.05, 97.64. **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 9 H, Bu^t), 1.24 (s, 3 H, Me), 1.44 (s, 3 H, Me), 2.86 (br s, 2 H, OH), 3.44 [dd, *J* 5.0, 9.6 Hz, 1 H, C(6) H], 3.65 [dd, *J* 3.3, 9.6 Hz, 1 H, C(6) H], 4.07–4.11 [m, 2 H, C(3) H and C(5) H], 4.33 [t, *J* 2.3 Hz, 1 H, C(4) H], 4.52 [d, *J* 3.7 Hz, 1 H, C(2) H], 5.95 [d, *J* 3.7 Hz, 1 H, C(1) H]. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.16, 26.77, 27.41, 62.74, 69.47, 73.72, 75.66, 80.21, 85.09, 104.86, 111.52. **5b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.12 (s, 9 H, Bu^t), 1.24 (s, 3 H, Me), 1.41 (s, 3 H, Me), 2.85 (d, *J* 5.2 Hz, 1 H, OH), 3.32–3.40 [m, 1 H, C(6) H], 3.40 (s, 3 H, OMe), 3.54 [dt, *J* 3.2, 8.0 Hz, 1 H, C(6) H], 3.79 [m, 1 H, C(3) H], 3.89–4.02 [m, 2 H, C(4) H and C(5) H], 4.48 [d, *J* 3.7 Hz, 1 H, C(2) H], 5.80 [d, *J* 3.7 Hz, 1 H, C(1) H]. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.13, 26.59, 27.41, 57.95, 63.34, 67.79, 73.15, 79.74, 81.59, 84.01, 104.89, 111.46. **7**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.21 (s, 9 H, Bu^t), 1.34 (s, 3 H, Me), 1.57 (s, 3 H, Me), 2.41 (d, *J* 4.2 Hz, 1 H, OH), 3.48 [dd, *J* 4.6, 9.8 Hz, 1 H, C(6) H], 3.64 [dd, *J* 3.2, 9.8 Hz, 1 H, C(6) H], 3.72 (d, *J* 4.7 Hz, 1 H, OH), 3.89 [dd, *J* 3.7, 8.7 Hz, 1 H, C(4) H], 3.97–4.01 [m, 1 H, C(5) H], 4.04–4.13 [m, 1 H, C(3) H], 4.64 [t, *J* 3.8 Hz, 1 H, C(2) H], 5.76 [d, *J* 3.8 Hz, 1 H, C(1) H]. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.35, 26.67, 27.34, 62.66, 70.11, 70.86, 74.33, 79.57, 80.88, 103.80, 112.85. **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (s, 9 H, Bu^t), 1.32 (s, 3 H, Me), 1.48 (s, 3 H, Me), 2.84 (d, *J* 2.9 Hz, 1 H, OH), 3.37 (s, 3 H, OMe), 3.56 [dd, *J* 6.0, 9.9 Hz, 1 H, C(6) H], 3.64 [dd, *J* 5.8, 9.9 Hz, 1 H C(6) H], 3.76 [t, *J* 4.5 Hz, 1 H, C(3) H], 3.74–3.83 [m, 1 H, C(4) H], 3.97–4.02 [m, 2 H, C(2) H and C(5) H], 5.54 [d, *J* 4.5 Hz, 1 H, C(1) H]. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.50, 27.62, 28.50, 59.28, 67.23, 70.34, 71.76, 75.36, 97.26, 107.96. **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3 H, Me), 1.21 (s, 9 H, Bu^t), 1.34 (s, 3 H, Me), 1.40 (s, 3 H, Me), 2.62 [br t, *J* 5.2 Hz, 1 H, C(6) OH], 3.08 [d, *J* 9.1 Hz, 1 H, C(1) H], 3.18 [s, 1 H, C(2) OH], 3.35 (s, 3 H, OMe), 3.52 [d, *J* 9.1 Hz, 1 H, C(1) H], 3.53–3.59 [m, 1 H, C(6) H], 3.70–3.78 [m, 1 H, C(6) H], 4.00 [d, *J* 9.3 Hz, 1 H, C(3) H], 4.21–4.30 [m, 2 H, C(4) H and C(5) H]. ^{13}C NMR (75 MHz) δ 25.35, 28.10, 29.31, 58.92, 62.05, 69.83, 73.82, 75.69, 77.85, 78.32. **15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 3 H, Me), 1.18 (s, 9 H, Bu^t), 1.37 (s, 3 H, Me), 1.49 (s, 3 H, Me), 2.97 (dd, *J* 5.1, 7.7 Hz, 1 H, OH), 3.07 (s, 1 H, OH), 3.22 (d, *J* 8.6 Hz, 1 H), 3.39 (d, *J* 8.6 Hz, 1 H), 3.57 (d, *J* 8.5 Hz, 1 H), 3.66–3.79 (m, 3 H), 4.22 (dt, *J* 9.0, 4.9 Hz, 1 H), 4.42 (dd, *J* 1.5, 6.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.22, 25.20, 27.17, 27.42, 61.59, 67.33, 72.08, 73.07, 73.57, 74.46, 78.11, 108.17. Compound **15** decomposed after several hours in $CDCl_3$ solution.

‡ Crystal data, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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