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NEW RESULTS IN THE ISOPROPYLIDENATION OF GALACTOPYRANOSIDES. USEFUL INTERMEDIATES FOR THE SYNTHESIS OF GALACTOSE DERIVATIVES.

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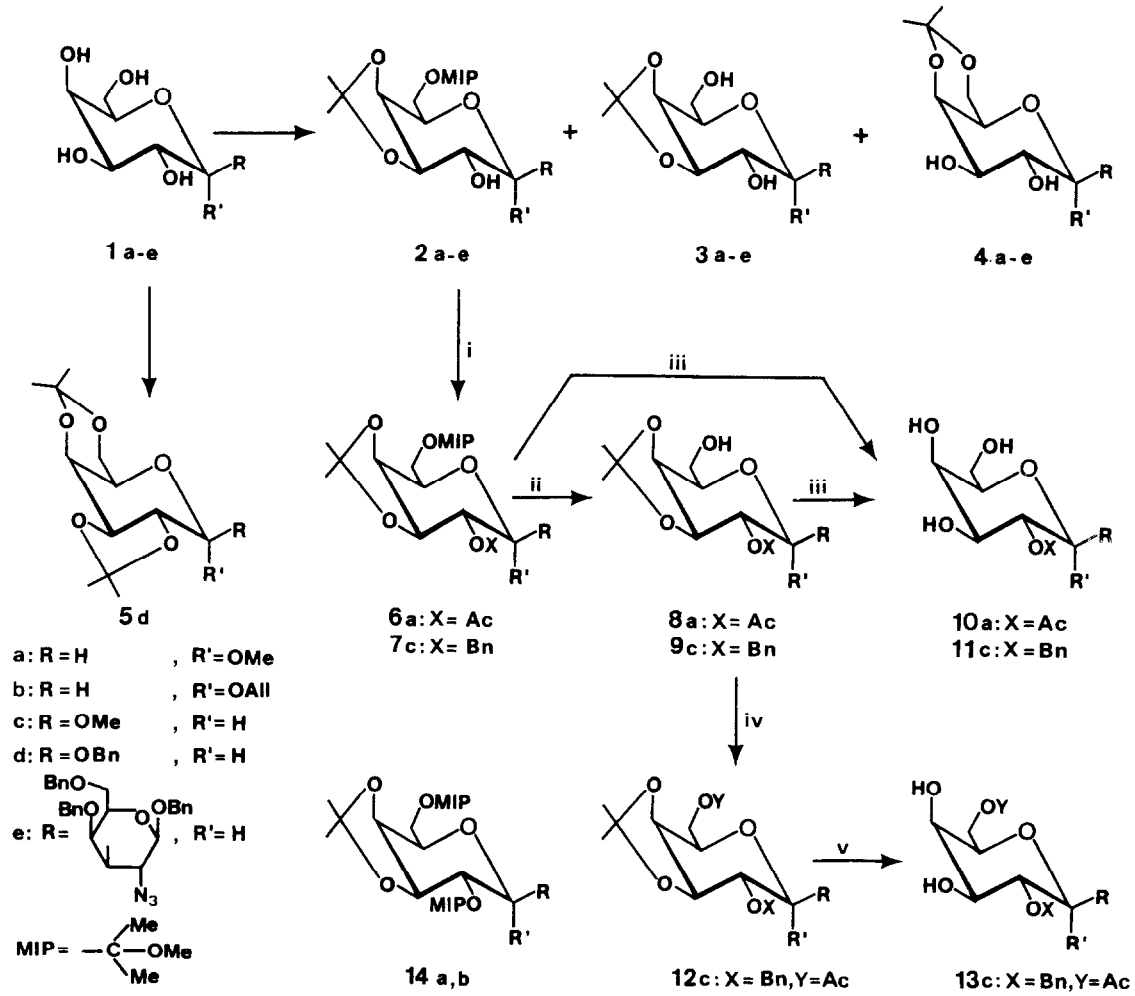
Abstract. *Reaction of several α- and β-galactopyranosides with 2,2-dimethoxypropane produced up to five types of mono-, bis-, and tris(isopropylidene)acetals, among which the 3,4-O-isopropylidene-6-O-(2-methoxyisopropyl) derivatives can be obtained in high yield and be useful intermediates for selective syntheses of 2-, 6-, and 2,6-O-substituted galactose derivatives.*

*Selective temporary protection of diol functionalities via formation of dioxolane and 1,3-dioxane rings with acetone or its derivatives is a well established procedure in organic synthesis, particularly in the carbohydrate field.[1] One limitation (but in some case an advantage) is in the fact that several different acetals may be formed from a single polyol substrate in relative amounts greatly depending on reagent and reaction conditions. When applied to α- and β-galactopyranosides, the more stable 3,4-O-isopropylidene derivatives are the main products of the classical reaction with acetone and an acidic catalyst (thermodynamic control),[2] whereas the less stable 4,6-O-isopropylidene derivatives are obtained with 2,2-dimethoxypropane (DMP) and TsOH in DMF[3] (kinetic control). Reaction of allyl α-D-galactopyranoside (**1b**) with a 1:1 mixture of acetone and DMP (TsOH as catalyst) under reflux was reported to give a 68% yield of the 3,4-O-isopropylidene derivative.[4] In connection with a synthesis of a trisaccharide[5] we subjected the disaccharide **1e** to these conditions, but in a more dilute solution (0.05 instead of 0.57 M), and found that only minor amounts (24 and 5%) of the expected isopropylidene derivatives **3e** and **4e** were formed, the main product (65%) being the bis-isopropylidene derivative **2e**,[6] having a non-cyclic 2-methoxyisopropyl (MIP) acetal function in position 6, as proven by n.m.r.[7] and by the easy selective removal of the MIP group to give **3e**. Repetition of the reaction of **1b** under the reported[4] conditions showed that a substantial amount (at least 30%) of **2b** was formed.*

*In view of a possible interest of compounds of type **2** in oligosaccharide synthesis we applied the reaction to the galactosides **1a**, **1c** and **1d** (50 mM in 1:1 DMP/Me_2CO, TsOH, 5 h, reflux) and obtained compounds **2a**, **2c** and **2d** in isolated yields of 50-70%.[8] These products are easily separated from the complex reaction mixtures if these are quenched with Et_3N and subjected, after evaporation <u>in vacuo</u>, to a rapid chromatographic separation (preparative h.p.l.c. or flash chromatography on silica, elution with hexane/ethyl acetate 1:1 + 0.1% Et_3N). Evolution of the reaction was followed on **1d**, samples being withdrawn at intervals and analyzed by h.p.l.c. (conditions: LiChrosorb 10RP18, u.v. detector 200 nm, H_2O/CH_3CN gradient from 70:30 to 35:65). As shown in Table 1 **1d** has completely disappeared after 5 min. at 0°C giving rise to **2d**, **3d**, **4d** and to a fourth product identified as the diacetonide **5d** {m.p. 128-30°C (hexane), $[\alpha]_D^{20}$ -51.9° (c 1.0, $CHCl_3$)} with a <u>trans</u> fused dioxolane ring. The reaction slowly evolved to an equilibrium mixture composed essentially of **2d** and **3d**. The stucture of **5d***

was proven by n.m.r. [^{13}C n.m.r.: δ 110.6, 28.8, 18.9 (1,3-dioxanic Me_2C); 98.3, 26.4, 26.2 (dioxolanic Me_2C)] and by independent synthesis from ***1d*** *with 2-methoxypropene in DMF and TsOH, according to the method used for analogous compounds in the glucose series.*[9] *Compounds of type* ***5*** *were also obtained from* ***1a***, ***1b*** *and* ***1c***.

Cleaner reaction products and higher yields in compounds of type ***2*** *were achieved by carrying out the reaction in a dilute (50 mM) solution of* ***1*** *in neat DMP (catalytic amount of TsOH) at room temperature. Table 2 shows the evolution of the reaction of* ***1d*** *to give at equilibrium almost complete conversion into* ***2d*** *under these conditions. Isolated yields of* ***2c*** *and* ***2d*** *were at least 85%, those for the α-galactosides* ***1a*** *and* ***1b*** *were lower (around 50%) since a fifth component was present in the reaction mixture (ca. 25%). It was identified as the tris-acetal of type* ***14*** *by n.m.r.*[10] *and selective cleavage to* ***3a*** *and* ***3b***. *The reaction of* ***1d*** *with DMP/TsOH at a much higher concentration (ca. 0.8M, 1 h at room temperature) has been previously described and reported to give compounds* ***2d***, ***3d*** *and* ***4d*** *in a ratio of 4:5:1 and total isolated yield of 90%.*[11]



Reagents: ***i:*** *Ac_2O/Py for* ***6a***; *NaH,BnBr/DMF for* ***7c***. ***ii:*** *MeOH, traces of TsOH, room temp., 5 min.* ***iii:*** *80% AcOH, 90°C, 15 min.* ***iv:*** *Ac_2O/Py.* ***v:*** *90% CF_3COOH, room temp., 15 min.*

Table 1. Reaction of **1d** with 1:1 acetone/DMP

Time and temp.	Product composition %			
	2d	**3d**	**4d**	**5d**
5 min 0°C[a]	35	6	42	17
30 min 0°C	41	7	25	28
3 h 0°C	52	9	18	21
3h 0°C+2 h 20°C	68	15	6	11
3h 0°C+27 h 20°C	75	20	3	2

[a] **1d** completely dissolved after 5 min at 0°C

Table 2. Reaction of **1d** with neat DMP at 20 °C

Time	Product composition %			
	2d	**3d**	**4d**	**5d**
5 min[a]	69	<1	23	8
15 min	74	1	9	16
2 h	78	2	8	12
24 h	94	1	1	4
36 h	96	1	<1	2

[a] **1d** not completely dissolved after 5 min at 20°C

A detailed interpretation of the complicated interplay of reactions and equilibria is certainly very difficult, but it is very likely, as previously proposed,[11,12] that the primary 6-OH group is the site of first attack, either by acetone, if present, to give the **hemiacetal**, or by DMP to give the 6-O-MIP acetal by transacetalation. Both intermediates can rapidly cyclize to compounds of type **4**, but the 6-O-MIP derivative can alternatively react with acetone or DMP to give **2**. A slower process giving **2** would be a rearrangement of **4** to the more stable **3**, followed by a fast attack by DMP on 6-OH. A parallel acetalation of **4** gives **5** that only very slowly evolves to **2**. The fast conversion of **3d** and the very slow one of **5d** into **2d** were checked by subjecting the pure compounds to the reaction conditions. The further transformation of **2a** and **2b** into **14a** and **14b** may be related to the higher reactivity of equatorial 2-OH groups of α-glycosides with electrophiles.[13]

The high yield preparation of compounds of type **2** could offer a simple access to galactosides functionalized at position 2 or 6, or at both. The formation of MIP derivatives has been occasionally mentioned and also used in a few instances for protection purposes,[14] but may often have escaped attention owing to the ease with which the 2-methoxyisopropyl group is lost, even under weakly acidic conditions. Protracted contact with silica (as in a slow chromatography), or the use of solvents containing traces of acid and water (n.m.r. or $[\alpha]$ measurements), for instance, may lead to partial or total conversion into **3**. On the other hand, if properly treated, compounds **2** can be easily isolated, purified and stored, or even used as crude products in one-pot procedures, and the lability of the MIP group is very useful since it allows its complete removal under conditions that do not affect dioxolane rings. Some preliminary applications are given in the Scheme. Acetylation of **2a** gave compound **6a**, converted into methyl 2-O-acetyl-α-D-galactopyranoside **10a** {m.p. 98-9°C (AcOEt/hexane), $[\alpha]_{578}$ +219.2° (c 1.0, H_2O), lit.[15,16] 82-2.5°C, $[\alpha]_{578}$ +206° (c 1.0, H_2O)} in overall yield of 60% from **2a**. Benzylation of **2c** produced **7c** that was completely deprotected to methyl 2-O-benzyl-β-galactopyranoside **11c** {m.p. 147-8°C (Me_2CO/hexane); $[\alpha]_D$ +7.9° (c 0.92, MeOH); 83% yield from **2c**; lit.[17] m.p. 148-9°C, $[\alpha]_D$ +9.24° (c 0.73, MeOH)}, or selectively cleaved to **9c** {m.p. 90-2°C (AcOEt/hexane), $[\alpha]_D$ +46.1°(c 2.8, $CHCl_3$); lit.[18] syrup, $[\alpha]_D$ +4°($CHCl_3$)}, acetylated to **12c**, then converted into methyl 6-O-acetyl-2-O-benzyl-β-galactopyranoside (**13c**) {m.p. 66-70°C (AcOEt/hexane); $[\alpha]_D$ +28.1°(c 1.1, $CHCl_3$)} in 71% overall yield from **2c**. These

approaches are definitely simpler and more direct than previously reported ones. Scopes and limitations are under further investigation with particular attention to the use of compounds of type **2** *in the synthesis of oligosaccharides containing galactose units.*

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6. *All new compounds gave satisfactory elemental analytical and spectral data.*
7. *^{1}H n.m.r. ($CDCl_3$, 80 MHz): δ 3.14 (s, OMe); 1.53 and 1.29 (2 s, dioxolanic Me_2); 1.26 (s, 6H, MIP Me_2). ^{13}C n.m.r. ($CDCl_3$, 20 MHz): δ 110.1 (dioxolane acetalic C); 104.5 (C-1'); 100.7 (C-1); 100.1 (MIP acetalic C); 48.6 (MeO); 28.2 and 26.3 (dioxolanic Me_2); 24.5 and 24.3 (MIP Me_2).*
8. *Compounds **2a-e** are syrups. $[\alpha]_D^{20}$ values (c ca. 1, $CHCl_3$): **2a** +91.4°; **2b** +92.4°; **2c** +1.6°; **2d** -17.5° (lit.[11] -20°); **2e** -5.2°. In all these compounds diagnostic ^{1}H and ^{13}C signals for the cyclic and non-cyclic acetal functions closely corresponded to those given above (ref. 7) for **2e** and to those previously reported for **2d** (ref. 11).*
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10. *^{1}H n.m.r. of **14a**: δ 4.55 (d, 1H, J 3.5 Hz, H-1); 3.30 (s, MeO-1); 3.17 and 3.12 (2 s, MeO of MIP); 1.43 (s, 3H), 1.30 (s, 6H) and 1.27 (s, 9H) (6 isopropylidene Me groups). **14b** ^{1}H n.m.r. had closely analogous signals, except for the 1-OR signals.*
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