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The Synthesis of 3,4-Di-*O*-methyl-D-galactose

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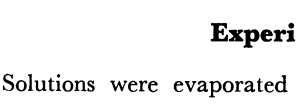
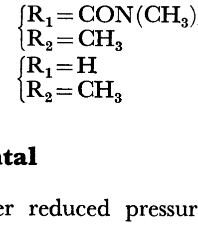
Partially methylated sugars are important for the structural investigation of polysaccharides. In the course of our studies on the polysaccharide from certain species of red seaweeds, 3,4-di-*O*-methyl-D-galactose has been needed as a reference compound. This partially methylated sugar was synthesized by Bacon and Bell.[1] But their method of synthesis has the disadvantages that the starting compound (methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside) was obtained in a low yield,[2] and that the succeeding step involves the use of nitrogen pentoxide, which is inconvenient to handle. We have carried out the synthesis through the different route reported below.

1,6-Anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose(I), prepared by the method of Hann and Hudson,[3] has been used as a starting compound. Its free hydroxyl group at C_2 was first blocked with a phenylcarbamoyl group (I→II). The *O*-isopropylidene group was then removed by methanolysis (II→III). The newly fromed hydroxyl groups at C_3 and C_4 were methylated (III→IV), and the blocking substituent was removed reductively with lithium aluminum hydride (IV→V).[4] Finally, the 1,6-anhydro-ring was opened. The product was identical in the physical constants with 3,4-di-*O*-methyl-β-D-galactose, which had been reported by Bacon and Bell. The intermediates (II—V) are the new compounds. Since these compounds crystallize well except IV, and the yield was considerably high in each step, the synthesis has been performed very easily.



(I) R=H
(II) R=$CONHC_6H_5$



(III) $\begin{cases} R_1=CONHC_6H_5 \\ R_2=H \end{cases}$
(IV) $\begin{cases} R_1=CON(CH_3)C_6H_5 \\ R_2=CH_3 \end{cases}$
(V) $\begin{cases} R_1=H \\ R_2=CH_3 \end{cases}$

Experimental

Solutions were evaporated under reduced pressure in a rotary evaporator. Melting points were measured on a micro hot stage with Yanagimoto apparatus Model MP-S2.

*1,6-Anhydro-3,4-*O*-isopropylidene-2-*O*-phenylcarbamoyl-β-D-galactopyranose(II).* To a solution of I[3] (5.0 g) in dry pyridine (50 m*l*), phenylisocyanate (3.5 g) was added, and the mixture was heated at 100°C for 2 hr. Evaporation of the solution gave the crystalline II, which was triturated with ethanol and filtered; yield 7.9 g (100%), mp 226—228°C. It was recrystallized twice from ethanol (600 m*l*); needles, mp 229.5—230.5°C, $[\alpha]^{25}_{D}-30.0°$ (*c* 1.0 in chloroform).

Found: C, 59.87; H, 6.02; N, 4.38%. Calcd for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; N, 4.36%.

*1,6-Anhydro-2-*O*-phenylcarbamoyl-β-D-galactopyranose(III).* A solution of II (7.0 g) in 1% methanolic hydrogen chloride (200 m*l*) was refluxed for 3 hr, neutralized with silver carbonate, and filtered. Evaporation of the filtrate gave crystalline III; yield 5.8 g (95%), mp 158—161°C. It was recrystallized twice from water; needles, mp 162—163°C, $[\alpha]^{25}_{D}+24.7°$ (*c* 0.85 in methanol).

Found: C, 55.55; H, 5.41; N, 5.05%. Calcd for $C_{13}H_{15}O_6N$: C, 55.51; H, 5.38; N, 4.98%.

*1,6-Anhydro-3,4-di-*O*-methyl-2-*O*-(*N*-methyl-phenylcarbamoyl)-β-D-galactopyranose (IV).* The compound III (3.0 g) was methylated twice with iodomethane (20 m*l*) and silver oxide (20 g) in *N*,*N*-dimethylformamide (30 m*l*) by the method of Kuhn and his coworkers.[5] The product was obtained as a slightly colored syrup; yield 2.8 g (82%), $[\alpha]^{25}_{D}+14.9°$ (*c* 0.75 in chloroform). (Found: OCH_3, 19.0%).

*1,6-Anhydro-3,4-di-*O*-methyl-β-D-galactopyranose (V).* According to the procedure of Bouveng,[4] IV (2.7 g) was treated with excess lithium aluminum hydride (0.7 g) in boiling tetrahydrofuran for 3 hr. The syrupy crude product obtained was purified by dissolution in water and extraction with hexane to remove an oily material. Evaporation of the aqueous solution gave crystalline V; yield 1.5 g (94%), mp 76—79°C. It was further purified by recrystallization twice from a mixture of ethyl acetate and hexane (3: 5 v/v); tetragonals, mp 81°C, $[\alpha]^{25}_{D}-41.1°$ (*c* 0.90 in water).

Found: C, 50.52; H, 7.41%. Calcd for $C_8H_{14}O_5$: C, 50.56; H, 7.61%.

*3,4-Di-*O*-methyl-β-D-galactose.* The compound V (1.2 g) was hydrolysed with 4% hydrochloric acid (40 m*l*) at 100°C for 4 hr, at which time the optical rotation of the solution reached the constant value ($[\alpha]_D-41\rightarrow+113°$). The hydrochloric acid was removed by neutralization with silver carbonate and filtration. Evaporation of the filtrate afforded crystalline 3,4-di-*O*-methyl-β-D-galactose; yield 1.2 g (92%), mp 164—166°C. It was recrystallized from a small volume of methanol; mp 170—171°C, $[\alpha]^{20}_{D}+90.2\rightarrow+117.3°$ (*c* 0.92 in water). Literature values are mp 164—166°C and $[\alpha]^{20}_{D}+95.7\rightarrow+117.1°$ in water.[1] (Found: C, 46.10; H, 7.79; OCH_3, 22.0%).

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4) H. O. Bouveng, *Acta Chem. Scand.*, **15**, 87 (1961).

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