Tetrahedron Letters Vol. 21, pp 381 - 382 0040-4039/80/0122-0381$02.00/0

SYNTHESIS OF OLIGOSACCHARIDES BY USING LEVULINIC ESTER AS AN HYDROXYL PROTECTING GROUP

H.J. Koeners, J. Verhoeven and J.H. van Boom*

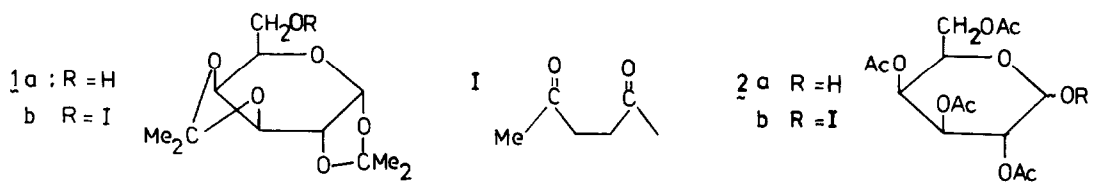
Gorlaeus Laboratories, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Summary: The fast, selective and mild removal of levulinyl groups with hydrazine from galactose, which also carries hydroxyl functions protected with acetyl groups, enables, under Koenigs-Knorr conditions, the synthesis of a trimer containing β-linked galactoses.

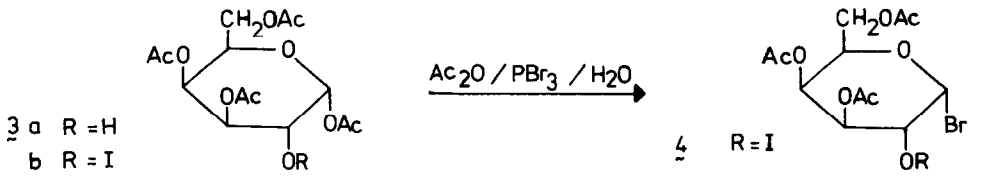
One of the problems which *inter alia* hampers the synthesis of oligosaccharides with a defined sequence and length is the lack of suitable and versatile protecting groups for alcoholic hydroxy functions.

We now wish to report that a combination of two base-labile groups *i.e.*, acetyl and levulinyl can be applied in the synthesis of oligosaccharides. In this approach the acetyl groups perform a persistent and the levulinyl a temporary blocking function.

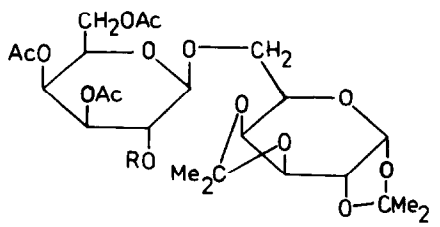
The introduction of the levulinyl group was performed by esterifying[1] levulinic acid with the hydroxy function of a suitably protected sugar derivative in the presence of 2-chloro-1-methyl pyridinium iodide (CMPI) and triethylamine (TEA) as the tertiary base. Thus,

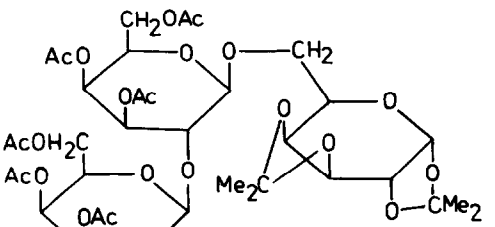


reacting together the galactose derivative 1a (R=H, 2 mmole) with levulinic acid (2.2 mmole), CMPI (2.4 mmole) and TEA (4.8 mmole) in dry dioxane (4 ml) gave, after work-up and purification by column chromatography, 1b (1.82 mmole) as a homogeneous oil[2b]. In the same way, the galactose unit 2a could be converted into the derivative 2b (R=I), which was isolated as a crystalline solid[2a] (m.p. 119°C, ethanol) and was the pure β-isomer[2b]. However, levulination of 3a (R=H), using TEA as the base, afforded solely 2b (R=I) instead of the required compound 3b (R=I). Fortunately, however, the formation of 2b (R=I) could be virtually avoided by using 1,4-diazabicyclo [2,2,2] octane (DABCO) as tertiary base. Thus, by adding in portions a solution of DABCO (60 mmole) in dry dioxane (40 ml) to a stirred solution of 3a (R=H, 20 mmole) containing CMPI (24.0 mmole) and levulinic acid (22.0 mmole) in dry dioxane (40 ml), 3b (R=I, 18 mmole) was obtained as a homogeneous oil[3]. Analysis of 3b (R=I) by ^{1}H-NMR revealed the presence (5-10%) of isomeric 2b (R=I). Deblocking of the levulinyl group from either 1b or 2b (R=I) could be performed by treating[4] these compounds with hydrazine hydrate (1.0 M) in pyridine/acetic acid for 10 min at 20°C. Work-up of the reaction mixture afforded solely - t.l.c. analysis and ^{1}H-NMR spectroscopy - 1a or 2a (R=H). Treatment of 3b (R=I) with phosphorus tribromide in a mixture of acetic anhydride and water[5] gave exclusively, as followed by ^{1}H-NMR and t.l.c. analysis, the required bromo derivative 4 (R=I) as a colourless oil[6]. For the



introduction of the interglycosidic bonds we used the method of Koenigs-Knorr[7]. Thus, condensation of 4 (R=I, 8.8 mmole) with 1a (R=H, 7 mmole) in dry acetonitrile (40 ml) in the presence of $HgBr_2$ (4.4 mmole) and $Hg(CN)_2$ (4.4 mmole) afforded, after work-up and purification by column chromatography, dissaccharide 5a (R=I, 4.9 mmole) as a homogeneous glass[2b].Removal





5 a R=I, b R=H 6 a R=I, b R=H

of the levulinyl group was performed by treating 5a (R=I, 4.2 mmole) in pyridine (40 ml) with a solution of hydrazine hydrate (1.0 M) in pyridine/acetic acid (3:2,v/v, 40 ml). After 10 min, the cooled reaction mixture was quenched by the addition of pentane-2,4-dione, and 5b (R=H, 4.2 mmole) was obtained, after work-up and precipitation with pet. ether (40-60°C, 200 ml), as a homogeneous solid[2a,b,c]. Condensation of 5b (4.6 mmole) with 4 (7.5 mmole), under the same conditions as before, afforded 6a (R=I) as a homogeneous glass which, after delevulination with hydrazine, gave 6b (R=H, 2.3 mmole) as a homogeneous solid[2a,b,c].

In conclusion, the data presented in this paper demonstrate that the mild and fast deprotection of levulinic ester functions with hydrazine[8] can be applied successfully in the synthesis of oligosaccharides.

REFERENCES AND NOTES

1. K. Saigo, M. Usui, K. Kikuchi, E. Shimada and T. Mukaiyama, Bull. Chem. Soc. Japan, 50 1863 (1977).
2. a) Satisfactory C/H analytical data were obtained. b) The identity of the compound was established by 1-H NMR spectroscopy. c) The compound contained, as evidenced by 1-H NMR spectroscopy (360 MHz), solely β-linkages.
3. The corresponding glucose derivative could easily be levulinated at the 2-position by using levulinic acid anhydride (1.1 eq.) in the presence of pyridine (1.5 eq.) and 4-dimethylaminopyridine (0.1 eq.).
4. J.H. van Boom and P.M.J. Burgers, Recl. Trav. Chim. Pays-Bas, 97, 73 (1978).
5. M. Bárczai-Martos and F. Körosy, Nature, 165, 369 (1950).
6. Treatment of the corresponding glucose derivative with *bromine free* hydrogen bromide afforded the bromo derivative in a quantitative yield.
7. B. Helferich and W. Ost, Chem. Ber. 95, 2612 (1962).
8. The conditions as developed by A. Hassner *et al.*, J. Amer. Chem. Soc. 97, 1614 (1975) or Tse-Lok Ho *et al.*, Synthetic Comm. 5, 91 (1975) for the removal of the levulinyl group proved to be unsuitable in this particular study.

(Received in UK 21 November 1979)