Tetrahedron Letters,Vol.24,No.4,pp 361-364,1983 0040-4039/83/040361-04$03.00/0
Printed in Great Britain

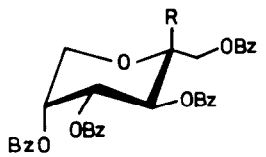
DISTRIBUTION OF TAUTOMERS IN ACYLATED KETOSES AN IMPORTANT FACTOR IN KETOSIDE SYNTHESIS[1)]

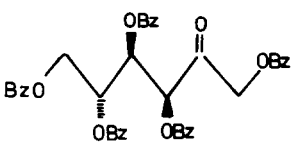
B. Kraska* and R. Lichtel

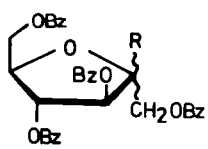
Institut für Organische Chemie u. Biochemie, TH Darmstadt
Petersenstr. 22, D-6100 Darmstadt, FRG

Summary: Formation of tautomers upon acylation of D-fructose and several 1-O-substituted derivatives thereof is studied and appropriate intermediates are used in stereoselective glycoside synthesis.

The inherent tendency of D-fructose to form open-chain derivatives[2)] is of considerable preparative significance. Both the synthetic potential in the construction of the chiral skeleton of eminent natural products[3)] and the use in ketoside synthesis[4)] strongly depend on the assistance of functional groups in stabilizing the required tautomer. To this end, we have studied the effect of C-1-OH group substituents on the distribution of tautomers formed during acylation of fructose. This investigation necessitated the reevaluation by spectroscopic means (^{1}H-, ^{13}C-nmr) of early reports[5)] concerning the spectrum of products obtained during benzoylation of D-fructose itself. In the presence of benzoylchloride/pyridine/chloroform at low to ambient temperatures (-15° - +20°C), a mixture of partially or fully acylated derivatives has been obtained.



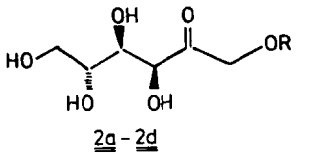




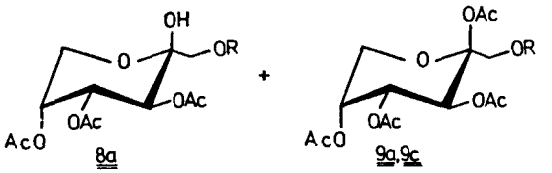
1a R=OH 1b R=OBz 1c R=Br 1d Bz=C_6H_5CO- 1e R=OH 1f R=OBz

In addition to the known[5)] benzoates 1a, 1d and 1e, separated by LC (CCl_4/EtOAc 5:1, silicagel) a crystalline pentabenzoate 1b ($[\alpha]_D$ = -212°, $CHCl_3$, m.p. 152-153° C) and a furanose perbenzoate 1f ($[\alpha]_D$ = +9°, $CHCl_3$) have been isolated. Both products are independently obtained either by selective benzoylation of 1a or 1e, respectively using DMAP/Bz_2O[6)] in CH_2Cl_2 or, in the case of 1b, by reacting glycosyl-bromide[7)] 1c with silverbenzoate in benzene (82%) or p-dioxane (70%)[8)].

Quite different, preponderant formation of even more versatile keto-derivatives together with a high proportion of conveniently blocked pyranose tautomers is observed when submitting 1-O-allyl[9)]- or -benzylethers[10)] 2a, 2b of D-fructose to the aforementioned benzoylation conditions. Conventional work-up and flash-chromatography yielded mainly spontaneously crystallizing fractions of the new 1-O-X-3,4,5-tri-O-benzoylpyranoses (X = allyl-, benzyl-) 4a, 4b and



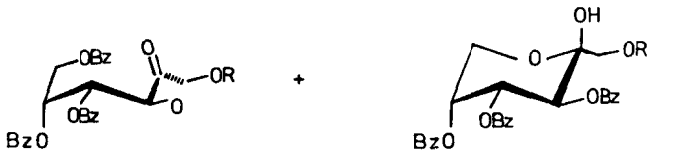
2a - 2d



8a 9a, 9c

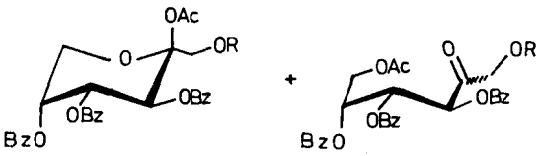
2a R = allyl
b R = benzyl
c R = tosyl
d R = methyl

BzCl
pyridine
CH_2Cl_2
-15° → +20°C



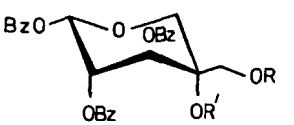
3a, 3b 4a - (4d)

DMAP/Ac_2O
CH_2Cl_2



5a - 5d 6a, 6b

1. $TiBr_4/CH_2Cl_2$
2 R'OH/$CdCO_3$/
Drierite



7a - 7d R'= - CH_3
7e R'= - $CH(CH_3)_2$; R= benzyl

PHYSICAL DATA OF NEW COMPOUNDS

	3a	3b	4a	4b	4c	4d	5a	5b	5c	5d
$[\alpha]_D^*$	+55°	+68°	-251°	-220°	-174°	-278°	-242°	-283°	-210°	-236°
m.p. (°C)	86-87	142-143	96-97	79-80	85-87	125-126	118-119	111-112	124-125	95-96

	6a**	6b	7a	7b	7c	7d	7e	8a	9a	9c
$[\alpha]_D^*$	+10°	+70°	-75°	-76°	-21°	-65°	-48°	-103°	-19°	-74°
m.p. (°C)	syrup	86-88	syrup	syrup	85-86	syrup	syrup	91	75	108-109

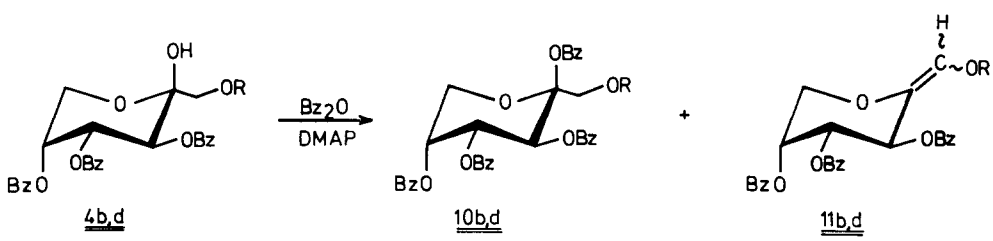
* in $CHCl_3$, c = 1; ** unstable

the corresponding 2-keto-3,4,5,6-tetrabenzoates 3a, 3b. Increasing amounts of fully characterized furanose-forms have been isolated with rising reaction temperature. - Interestingly, when benzoylating 1-O-methyl-fructose[11], all attempts to isolate the open-chain derivative 4d failed. It was obtained instead by subsequent hydrogenolysis (Pd/C/EtOH) and etherification (CH_3I/Ag_2O) of 4b. Thus, contrary to the observed effect of other electron-donating substituents, introduction of the methyl group at C-1-OH favours formation of cyclic tautomers as effectively as do electron-withdrawing groups at this position. We could show 1-O-mesyl- and -tosyl-groups to stabilize preferentially furanose- and pyranose-forms.

Nearly exclusive formation of cyclic (pyranose) tautomers is observed, when the acylation is performed in strongly acidic media (Ac_2O/H_2SO_4)[12] e.g. conversion of 2a, 2c ⟶ 8a, 9a,c
These conditions, however, are not generally feasible for temporary blocking-groups.

Competition between open-chain (6a, 6b) and pyranose tautomers (5a, 5b) also occurs during acetylation of pyranoid 2-OH-benzoates such as 4a, 4b required for subsequent transformation of the latter into glycosyl-halides and further into ketosides. Short exposure(4a,b) to DMAP/Ac_2O/Et_3N at 20° C in CH_2Cl_2 afforded mainly (70 - 80 %) highly crystalline 2-keto-6-O-acetyl-derivatives 6a, 6b, whereas heating with NaOAc/Ac_2O mixtures[13] gave nearly 1:1 ratios of these compounds and the desired 2-O-acetyl-3,4,5-tri-O-benzoyl-pyranoses 5a, 5b. Prolonged reaction of 4a or 4b with DMAP under the same conditions surprisingly leads in high yield (80 - 85 %) to the pyranoid tautomers preferentially. Accordingly, a longer reaction in the presence of NaOAc/Ac_2O likewise favours the pyranose form, though with concurrent degradation of the saccharides. The overall reaction may be interpreted in terms of an equilibrium between open-chain and pyranose-form and the preferential formation of the latter under thermodynamically controlled conditions. The apparent ease of equilibration possibly allows to exchange the C-6-substituent of acyclic derivatives like 6a or 6b against other nucleophiles. We are currently investigating the scope of this valuable method for grafting additional functional groups onto the sugar backbone.

Unlike acetylation, benzoylation of e.g. 4b,d (DMAP/Bz_2O/CH_2Cl_2) mainly affords the cyclic tetrabenzoates 10b (65 %) and 10d (62 %), which tend to eliminate benzoic acid with formation of exocyclic enol-ethers (11b, 11d) as E/Z mixtures.



4b,d 10b,d 11b,d

Attempts to purify the perbenzoates by column-chromatography (silicagel, CH_2Cl_2/EtOAc 20:1) only increases the yield of olefins. The reduced stability of these molecules compared with the acetates is clearly a consequence of a better leaving group at the anomeric center and not without precedent in ketose chemistry[14].

Conversion of the acetates 5a - 5d into the bromides (1,5 eq $TiBr_4$/anhydr. CH_2Cl_2, 20° C, 3h) and subsequent solvolyses (MeOH, IprOH/$CdCO_3$/drierite) afforded a series of hitherto unknown alkyl-α-D-fructosides in ca. 85 % yield and remarkably high stereoselectivity (α:β = 20:1).

In the case of glycosides 7a,b,d, problems associated with reactions at the anomeric center have been successfully circumvented by direct glycosidation using methanol/triflate mixtures as additional method[15]. Due to the non-participating blocking groups at C-1-OH, concurrent orthoester formation characteristic of earlier syntheses of α-D-fructopyranosides[16] is avoided. All new glycosides have been fully characterized and, by ^{1}H-nmr (300 MHz), are shown to adopt a near to $^5C_2$ chair-conformation with a quasi axial anomeric substituent and equatorially oriented primary hydroxylgroup. - We are currently extending our efforts to the synthesis of ketose-derived di- and oligosaccharides.

Acknowledgement: Miss B. Schifferdecker is thanked for skilled experimental assistance. Generous financial support by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Footnotes and References

1. Presented in part XI[e] Journeês des Glucides, Paris 5.-7.7.1982.

2. S. Angyal, G.S. Bethell, D.E. Cowley, and V.A. Pickles, Austr. J. Chem. 29, 1239 (1976).

3. L. Banfi, M.G. Beretta, L. Colombo, C. Gennari, and C. Scolastico, J. Chem. Soc., Chem. Commun. 1982, 488.

4. L.M.J. Verstraeten, Adv. Carbohydr. Chem. 22, 229 (1967).

5. P. Brigl and W. Schinle, Ber. Dtsch. Chem. Ges. 66, 325 (1933); ibid 67, 127 (1934).

Though the reliability of the author's data is high, additional structural proof for the "2-keto-pentabenzoate" 1d is provided by ^{1}H-nmr (300 MHz; $CDCl_3$): δ = 4.55 and 4.96 (2x dd, H-6,6'); 5.17 (m, H-1,1'); 5.98 (ddd, H-5); 6.04 (d, H-3); 6.42 (dd, H-4). The new pyranose pentabenzoate 1b has: δ = *4.26 and 4.32 (2x dd, H-6,6'); 4.81 and 5.56 (2x d, H-1,1'); 5.87 (m, H-5); 6.04 (dd, H-4); 6.51 (d, H-3).*

6. G. Höfle, W. Steglich, and H. Vorbrüggen, Angew. Chem. Int. Ed. Engl. 17, 569 (1978).

7. R.K. Ness and H.G. Fletcher, jr., J. Am. Chem. Soc. 75, 2619 (1953).

8. *Under these conditions, no change of configuration at the anomeric center (β-D ⟶ α-D) is observed; such an inversion occurs, however, with AgOAc/Ac_2O at 60°C:* R. Lichtel, Diplomarbeit, TH Darmstadt 1978; cf. ref. 13.

9. *2a (syrup,* $[\alpha]_D$ = *-23°, p-dioxane) has been obtained via etherification (NaH, allylbromide toluene, 80°C, 24 h) of known* [H. Ohle and G. Berend, Ber. Dtsch. Chem. Ges. 60, 1159 (1927)] *2,3-4,5-di-O-isopropylidene-β-D-fructopyranose and subsequent hydrolysis (0.1 N H_2SO_4/100°C/ 2 h) of the resulting oil (*$[\alpha]_D$ = *-32°, $CHCl_3$).*

10. *2b has been prepared similarly from the known di-acetone-derivative* [A. Klemer, G. Rodemeyer, and F. Linnenbaum, Chem. Ber. 109, 2849 (1976)] *as a syrup, (*$[\alpha]_D$ = *-25° in EtOH).*

11. H. Ohle, Ber. Dtsch. Chem. Ges. 58, 2577 (1925).

12. F. Micheel and L. Tork, Chem. Ber. 93, 1013 (1960).

13. H. Paulsen, K. Heyns, and H. Köster, Chem. Ber. 100, 2669 (1967).

14. K. Tokuyama, E. Tsujino, and M. Kiyokawa, Bull. Chem. Soc. Jpn. 33, 1344 (1965); R.K. Ness and H.G. Fletcher, jr., J. Org. Chem. 33, 181 (1968); P. Köll, E. Steinweg, J. Metzger, and B. Meyer, Liebigs Ann. Chem. 1982, 1052.

15. A.A. Pavia, J.-M. Rocheville, and S.N. Ung, Carbohydr. Res. 79, 79 (1980).

16. E. Pacsu, J. Am. Chem. Soc. 57, 745 (1935); H. Steinlin, L. Camarda, and A. Vasella, Helv. Chim. Acta 62, 378 (1979).

(Received in Germany 29 October 1982)