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Utility of Glycosyl Phosphites as Glycosyl Donors - Fructofuranosyl and 2-Deoxyhexopyranosyl Phosphites in Glycoside Bond Formation[1]

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Abstract: **The discussion of the ease of generating glycosyl donor properties in the important sugar categories (aldoses, ketoses, deoxy sugars, sugar uronates, and 3-deoxy-2-glyculosonates) implies that phosphites of ketoses and deoxy sugars, respectively, should be valuable donors. This is exhibited for fructofuranosyl phosphite 2 and for 2-deoxyhexopyranosyl phosphites 14a,b which are readily available and generally provide disaccharides in high yields.**

The glycosyl donor properties of sugars differ quite extensively with the functional groups present at the pyranosyl or furanosyl moiety[2,3]. For instance, for the most frequently occurring sugars, having identical leaving groups at the anomeric center and the same promoter system, the ease of generating glycosyl donor properties increases generally in the following order:

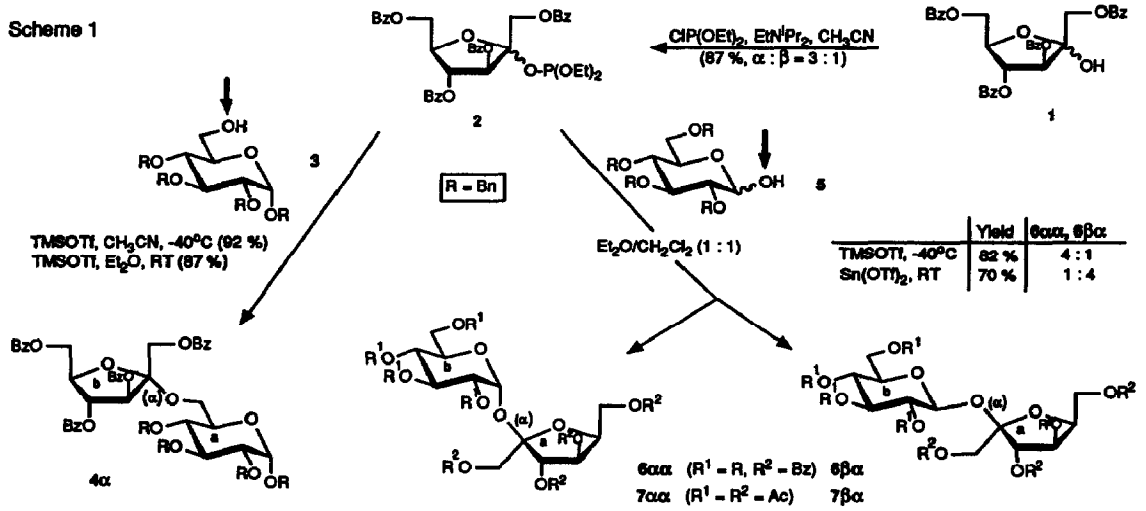
Sugar uronates (I) < aldoses (II) < deoxy sugars (III) ≤ ketoses (IV) ≤ 3-deoxy-2-glyculosonates (V)

Obviously, depending on relative configurations of functional groups, deoxy positions, and type of functional groups quite dramatic variations in the glycosyl donor properties are observed which lead to an overlap in these reactivity categories.

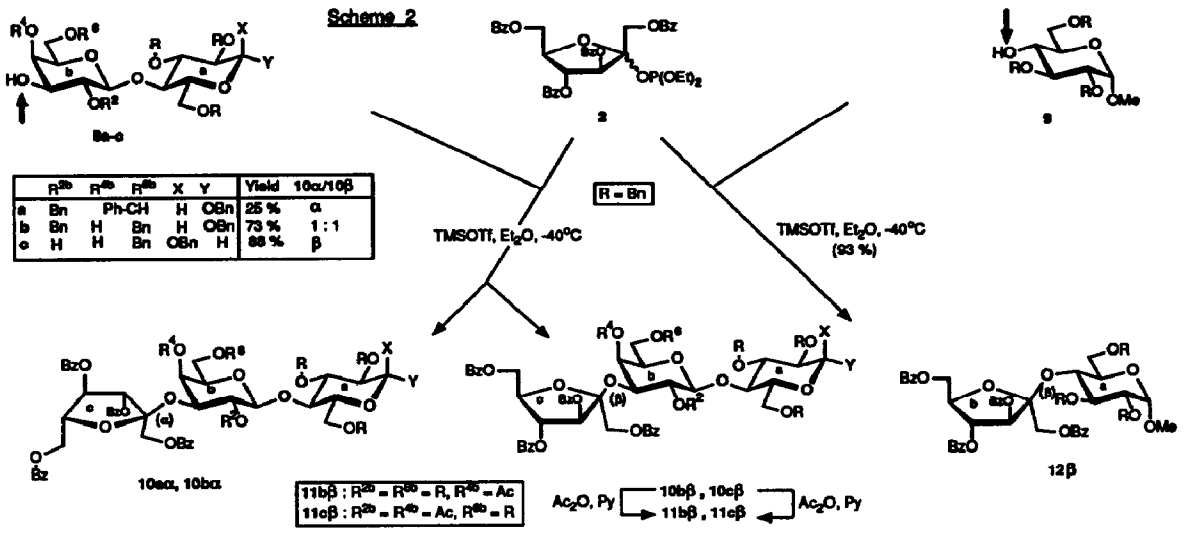
For the glycosyl donors requiring the highest activation (categories I, II, III) O-glycosyl trichloroacetimidates were shown by us and others to be very efficient[2,4]. However, for sugars of categories IV and V the generation of trichloroacetimidates was less successful[2,5] and some trichloroacetimidates of 2-deoxy sugars (category III) proved to be less stable[2,6]. Therefore, for these sugar types a simple leaving group providing the same advantageous properties as the trichloroacetimidate moiety was desired, i.e. (i) convenient synthesis, (ii) stability of the activated intermediate, and (iii) release of the glycosylating species with catalytic amounts of a promoter.

For N-acetylneuraminic acid (category V) we could demonstrate that phosphites exhibit the required sialyl donor properties[5]; the readily available sialyl phosphites can be activated by catalytic amounts of TMSOTf, thus furnishing ganglioside derivatives in good yields[5], as also confirmed by other researchers[7]. Therefore, phosphite moieties could also act as efficient leaving groups with other sugar categories, as for instance ketoses (IV) and deoxy sugars (III); but they are expectedly not as effective with aldoses (II) and especially O-acyl protected derivatives[5,8,9]. The lower reactivity of aldohexopyranosyl phosphites and of corresponding uronates has been recently demonstrated by independent studies[10,11], which exhibit the requirement of high acid concentrations for activation, thereby lowering yields and/or diastereomeric control, if neighboring group assistance by acyl groups is not available. Because O-benzyl protected fucosyl phosphites (category III) exhibited under inverse procedure[12] conditions excellent glycosyl donor properties[13], it was of interest to investigate 2-deoxy sugars and ketoses for further evaluating the scope of glycosyl phosphites as glycosyl donors.

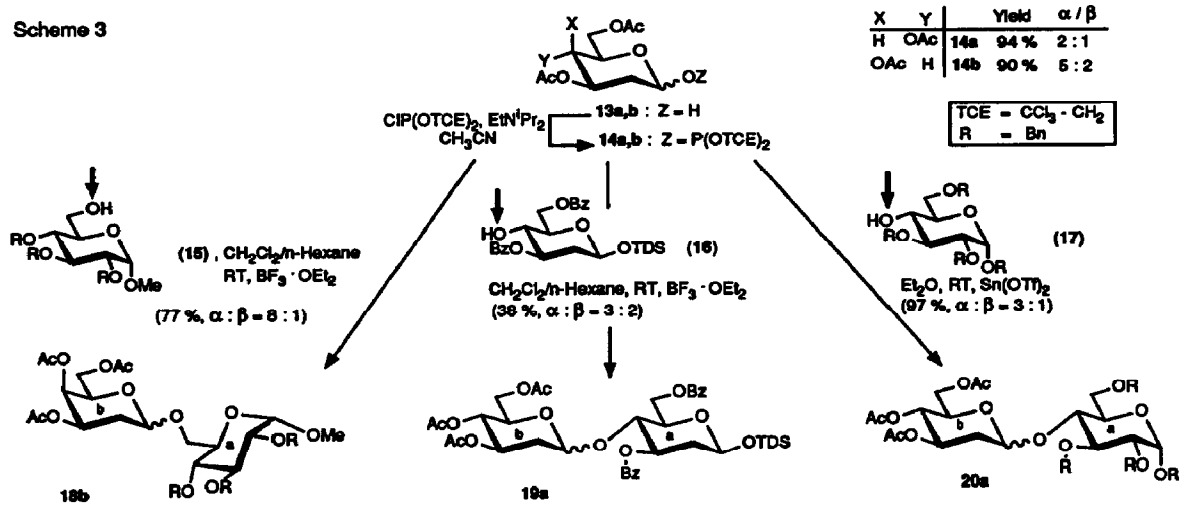
The widespread occurrence of fructofuranosides in nature is a great stimulus to arrive at highly stereoselective and high yielding glycoside bond formation, which still can be regarded as a difficult problem[14,15]. Only for not directly accessible thioorthoesters as glycosyl donors and reactive acceptors selective α-furanoside formation in good yields was reported[15]. For the investigation of fructofuranosyl phosphites as donors, readily available 1,3,4,6-tetra-O-benzoyl-fructose 1[16] (Scheme 1) was reacted with diethyl phosphorochloridite as phosphitylating agent in the presence of Hünig's base to afford phosphite 2 in high yield. The structural assignment of the α/β-anomers could be based on ^{1}H-NMR and ^{13}C-NMR data[17] and their comparison with related compounds[18]. Reaction of 2 with 6-O-unprotected glucose derivative 3[19] as acceptor afforded in acetonitrile as solvent and TMSOTf as catalyst at -40°C exclusively the α-disaccharide 4α[17] in practically quantitative yield. A similar result was obtained in ether as solvent at room temperature.



Reaction of 2 with less reactive acceptors having secondary hydroxy groups led to interesting results. 1-O-Unprotected 5[20] afforded in Et_2O/CH_2Cl_2 as solvents and TMSOTf as catalyst at -40°C preferentially the expected "α,α-sucrose" derivative 6αα[17] and some "β,α-sucrose" 6βα[17]; the α/β-ratio at the glucose moiety essentially displays the anomer ratio in acceptor 5. However, with $Sn(OTf)_2$ as catalyst at room temperature the 6αα/6βα ratio is due to fast anomerization essentially reversed, thus reflecting the higher reactivity of the equatorial hydroxy group[2,21]. Hydrogenolytic O-debenzylation of both compounds, subsequent debenzoylation ($MeOH/H_2O$, NEt_3) and O-acetylation (Ac_2O, pyridine) furnished known O-acetyl derivatives 7αα and 7βα, respectively[14,22]. An especially interesting case proved to be fructofuranosylation of lactose in 3b-O-position (Scheme 2): with 8a[23] as acceptor in ether at -40°C and TMSOTf as catalyst only the α-connected derivative 10aα[17] was obtained, though in low yield; with 3b,4b-O-unprotected 8b[24] the yield was increased and a 1:1 mixture of 10bα[17] and 10bβ was isolated; with 2b,3b,4b-O-unprotected 8c[8] only the β-connected derivative 10cβ was obtained in very high yield, thus reminding of ketosylation with sialyl donors where similar observations regarding protection and at least yield are made[5]. The attachment of the fructofuranosyl moiety at 3b-O was confirmed by the ^{1}H-NMR data of 11bβ[17] and 11cβ[17] obtained from 10bβ and 10cβ by O-acetylation. Reaction of 2 with 4-O-unprotected acceptor 9[25] gave under the same conditions again exclusively β-connected 12β. Similar observations were made for other acceptors with secondary hydroxy groups[9]. Thus, in general for less accessible secondary hydroxy groups a preference for β-selection and for more accessible hydroxy groups an α-preference, respectively, is observed which cannot be fully explained.



	R2b	R4b	R6b	X	Y	Yield	10α/10β
a	Bn	Ph-CH		H	OBn	25 %	α
b	Bn	H	Bn	H	OBn	73 %	1 : 1
c	H	H	Bn	OBn	H	88 %	β



X	Y		Yield	α / β
H	OAc	14a	94 %	2 : 1
OAc	H	14b	90 %	5 : 2

The presence of 2-deoxy-glycopyranoside moieties in various natural products has already led to different approaches for selective glycoside bond formations[26]. Reaction of O-acetyl protected glucose and galactose **13a,b**[27] with bis(trichloroethyl) phosphorochloridite in the presence of Hünig's base afforded the corresponding phosphites **14a,b**[17] in practically quantitative yield as α/β-mixtures. Reaction of **14b** with 6-O-unprotected acceptor **15**[19] in dichloromethane/n-hexane at room temperature in the presence of BF_3-OEt_2 as catalyst afforded preferentially known α-disaccharide **18bα**[28] (α:β-ratio, 8:1) in good yield. Similarly, **14a** gave with 4-O-unprotected silyl 2-deoxy-glucopyranoside **16**[17] as less reactive acceptor (presence of benzoyl groups in 3- and 6-position) disaccharides **19a** (α:β = 3:2)[17]; the lower yield is due to partial loss of the silyl group under the reaction conditions. Increase in yield was accomplished by applying the inverse

procedure[12] and changing the reaction conditions; thus from **14a** and **17**[25] as acceptor in the presence of $Sn(OTf)_2$ as catalyst disaccharide **20a** (α:β-ratio = 3:1)[17] was obtained in practically quantitative yield.

In conclusion, not only phosphites of 3-deoxy-2-glyculosonates but also phosphites of normal ketoses and of 2-deoxy glycoses exhibit very good glycosyl donor properties. Thus the phosphite method ideally complements the trichloroacetimidate method[2] in the higher reactivity range.

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17. Selected NMR data of new compounds [^{1}H-NMR (250 MHz, $CDCl_3$); ^{13}C-NMR (62.9 MHz, $CDCl_3$); ^{31}P-NMR (161.7 MHz, $CDCl_3$)]. **2**: δ_H = 5.59 (dd, $J_{3,4}$ = 0.9 Hz, $J_{4,5}$ = 4.2 Hz, 1 H, 4-Hα), 6.01 (d, $J_{3,4}$ = 0.9 Hz, 1 H, 3-Hα), 6.05 (m, 2 H, 3-Hβ, 4-Hβ), δ_C = 103.76 (d, $J_{2,P}$ = 4.9 Hz, 1 C, 2-Cα), 107.15 (d, $J_{2,P}$ = 5.5 Hz, 1 C, 2-Cβ), δ_P = 133.62 (s, Pβ), 134.37 (s, Pα). **4α**: δ_H = 5.46 (dd, $J_{3,4}$ = 1.3 Hz, $J_{4,5}$ = 5.3 Hz, 1 H, 4b-H), 5.90 (d, $J_{3,4}$ = 1.3 Hz, 1 H, 3b-H). **6$\alpha\alpha$**: δ_H = 5.39 (dd, $J_{3,4}$ = 0.5 Hz, $J_{4,5}$ = 4.6 Hz, 1 H, 4a-H), 5.94 (d, $J_{3,4}$ = 0.5 Hz, 1 H, 3a-H). **6$\beta\alpha$**: δ_H = 5.58 (dd, $J_{3,4}$ = 1.8 Hz, $J_{4,5}$ = 4.7 Hz, 1 H, 4a-H), 6.06 (d, $J_{3,4}$ = 1.8 Hz, 1 H, 3a-H). **10$\alpha\alpha$**: δ_H = 5.54 (m, 1 H, 4c-H), 5.91 (d, $J_{3,4}$ = 0.9 Hz, 1 H, 3c-H). **10bα**: δ_H = 5.52 (dd, $J_{3,4}$ = 1.8 Hz, $J_{4,5}$ = 5.9 Hz, 1 H, 4c-H), 5.99 (d, $J_{3,4}$ = 1.8 Hz, 1 H, 3c-H). **11bβ**: δ_H = 5.51 (d, $J_{3,4}$ = 4.1 Hz, $J_{4,5}$ = 6.0 Hz, 1 H, 4c-H), 6.10 (d, $J_{3,4}$ = 1.4 Hz, 1 H, 3c-H). **11cβ**: δ_H = 5.69 (dd, $J_{3,4}$ = 4.5 Hz, $J_{4,5}$ = 6.5 Hz, 1 H, 4c-H), 5.98 (d, $J_{3,4}$ = 4.5 Hz, 1 H, 3c-H). **12β**: δ_H = 5.70 (dd, $J_{3,4}$ = 5.3 Hz, $J_{4,5}$ = 5.8 Hz, 1 H, 4b-H), 6.01 (d, $J_{3,4}$ = 5.3 Hz, 1 H, 3b-H). **14a**: δ_H = 5.84 (dd, $J_{1,P}$ = 5.4 Hz, $J_{1,2}$ = 2.2 Hz, 1 H, 1-Hα), δ_P = 137.49 (s, Pβ), 138.45 (s, Pα). **14b**: δ_H = 5.89 (dd, $J_{1,P}$ = 7.2 Hz, $J_{1,2}$ = 2.0 Hz, 1 H, 1-Hα), δ_P = 136.04 (s, Pα). **16**: δ_H = 2.32 (br, 1 H, 4-OH), 4.94 (dd, $J_{1,2}$ = 2.0 Hz, $J_{1,2'}$ = 9.3 Hz, 1 H, 1-H). **19a**: δ_H = 5.03 (d, J = 3.2 Hz, 1 H, 1b-Hβ), 5.33 (d, $J_{1,2}$ = 2.6 Hz, 1 H, 1b-Hα). **20a**: δ_H = 5.22 (m, 1 H, 1b-Hβ), 5.44 (d, $J_{1,2}$ = 2.8 Hz, 1 H, 1b-Hα).
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