Alkyloxytris(dimethylamino)phosphonium Salts. Part 21.[1] Anomeric Hydroxy-group Activation of 2,3:4,6-Di-*O*-isopropylidene-α-D-manno-pyranose, Thioglycosylation and Glycosylation

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The action of carbon tetrachloride and tris(dimethylamino)phosphine at low temperature on 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranose affords the α anomeric form of the corresponding alkoxytris(dimethylamino)-phosphonium chloride. The condensation of aromatic thiols with this salt leads to β-thiomannosides by an S_N2 process and the condensation of alcohols, preceded by the action of silver salts in order to avoid the formation of the glycosyl chlorides, yields a mixture of α- and β-mannosides.

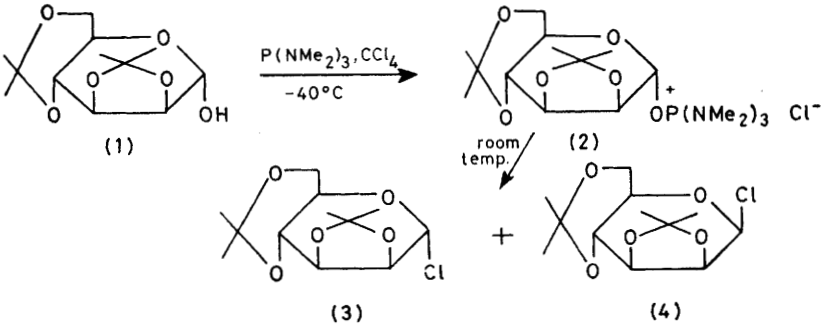
OUR interest in applications of the activation of anomeric hydroxy-groups of carbohydrates, *via* alkoxytris(dimethylamino)phosphonium (ATDP) salts,[2] has led us to investigate the reaction of a substrate related to mannopyranose. The preparation of mannosides is less well documented than that of glucosides. The great difference in reactivity of glycosyl halides in the *gluco* and *manno* series, due to the difference in the relative stereochemistry of the halogen atom and the substituent at C-2, has been demonstrated by Isbell and Frush.[3] Oligosaccharides, including mannose, are of considerable interest owing to their presence in glycoprotein branchings.[4] Thiomannosides are also of interest as substrates or inhibitors of glycosidases. Their preparation is poorly documented.

In this paper we describe a study of the activation of the anomeric hydroxy-group of the 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranose (1), chosen because it is a derivative bearing non-participating and easily removable protecting groups and because of the simplicity of its preparation.[5] The corresponding ATDP salt reacted with thiols and alcohols including carbohydrates.

RESULTS AND DISCUSSION

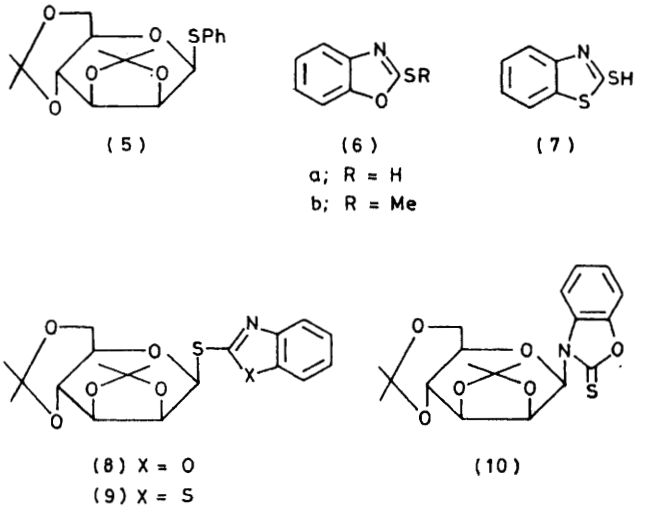
The formation and stability of the ATDP salt (2) was studied by ^{31}P n.m.r. spectroscopy (Bruker 90 spectrometer at 36.4 MHz) at −40 °C. A single peak at +34.6 p.p.m. (downfield from phosphoric acid in hexadeuterioacetone as external reference) was observed. In the ^1H n.m.r. spectrum only one doublet at δ 2.80 p.p.m. ($^3J_{H-P}$ 10 Hz) was present for the dimethylaminophosphonium groups. The 1-H signal was masked by other ring protons and thus the anomeric configuration could not be determined by the physical method.

At room temperature the ^{31}P n.m.r. spectrum showed the disappearance of the signal due to the ATDP salt and the appearance of a signal due to hexamethylphosphoric triamide (HMPA) at +24.3 p.p.m. ^1H N.m.r. monitoring showed that besides HMPA, both the α- and β-glycosyl chlorides (3) and (4), respectively, were present as characterized by their 1-H signals: α, 6.30 (s); β, 6.20 (d, $J = 2$ Hz). Owing to the great sensitity of these compounds, they were not isolable. However after 24 h in solution the mixture composition shifted to 100% of (3).



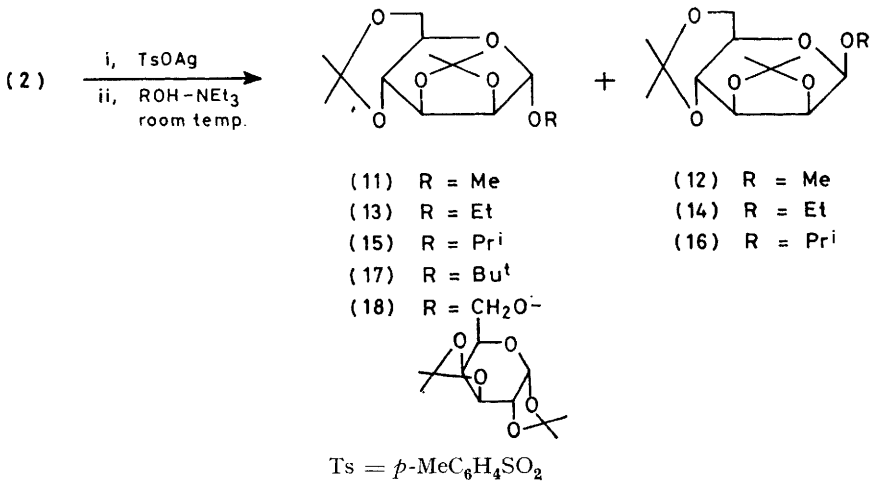
(1) (2) (3) (4)

The anomeric configuration of the salt (2) was determined by its reaction with thiols, which has been shown to proceed by an S_N2 process,[6] with complete inversion of configuration. The reaction with benzene-



(5) (6) a; R = H b; R = Me (7)

(8) X = O (9) X = S (10)



Ts = p-$MeC_6H_4SO_2$

thiol afforded only one product (5) whose β-configuration was assigned from its 1-H n.m.r. signal [δ 5.6, doublet ^3J (1-H, 2-H) 2.7 Hz] and from its optical rotation [−132°, $c = 1$, $CHCl_3$]. The α-configuration was

TABLE 1

Compound	$\lambda_{max.}$/nm (MeOH)
(8)	275, 225, 200
(6b)	280, 224
(10)	298, 255, 212, 200
3-Methylbenzoxazole-2(3*H*)-thione	310, 280, 240

assigned to the salt, confirming a general 1,2-*trans* relationship of ADTP salts.[6]

In a similar way, the heterocyclic thiols (6) and (7) afforded the corresponding thioglycosides (8) and (9).

TABLE 2

Reaction of (2) with thiols [a]

Thiol	Product [% yield]
PhSH	(5) [65%]
(6a)	(8) [50%] + (10) [15%]
(7)	(9) [65%]

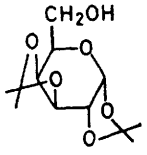
[a] RSH + NEt_3 in CH_2Cl_2 at room temp.; total yield 65% in each case.

In the case of (6), the product (8) was accompanied by 15% of the isomeric nucleoside (10) resulting from nitrogen alkylation. Compounds (8) and (10) were characterized by comparison of their u.v. spectra with those of the corresponding *S*- and *N*-methyl heterocyclic derivatives [7] (Table 1). The results of these condensations are in Table 2.

Condensations with alcohols were carried out after treatment of the solution of (2) with silver tosylate, in order to avoid the formation of the glycosyl chlorides (3)

TABLE 3

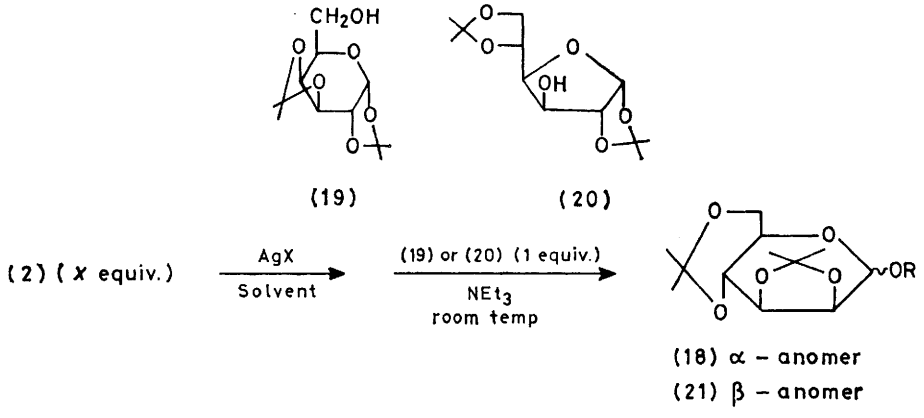
Reaction of (2) with alcohols

Alcohol	Anomer proportions α	Anomer proportions β	Total yield (%)
MeOH	(11) 57%	(12) 43%	90
EtOH	(13) 62%	(14) 38%	70
Pr^iOH	(15) 60%	(16) 40%	80
Bu^tOH	(17) 100%	0%	50
	(18) 100%	0%	20

and (4). The reaction intermediate was presumably the tosylmannoside.[8,9]

The alcohol was introduced in the presence of a stoicheiometric amount of triethylamine. The results of these reactions are in Table 3.

The enhancement of the stereoselectivity with increase in steric hindrance of the aglycone indicates a mechanism involving an oxenium cation.



A number of experiments were performed under different conditions with the single aglycone 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (19). Silver salts were again used to avoid the formation of chlorides and non-nucleophilic anions were introduced in order to test the reactivity of the ATDP salt itself.[9] Silver perchlorate and hexafluoroantimonate were chosen and triethylamine was used as the base (Table 4). The reactivity was increased considerably and the total yield was improved but the selectivity decreased. No solvent participation [10] was observed as the same results were obtained in methylene chloride as in THF.

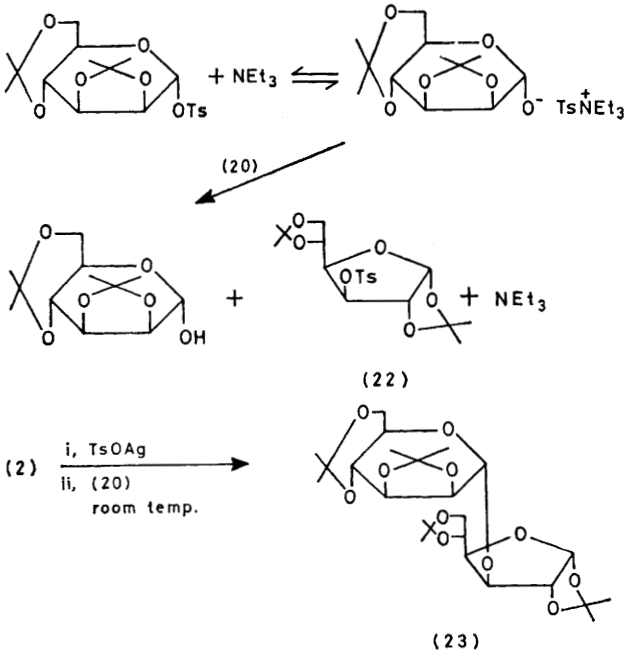
TABLE 4

Reaction of (2) with the aglycones (19) and (20)

ROH	x	Solvent	X	% Yield α-Anomer (18)	% Yield β-Anomer (21)	Total yield (%)
(19)	3	CH_2Cl_2	TsO	45		45
	3	CH_2Cl_2	SbF_6	50	16	66
	2.6	THF [a]	SbF_6	45	28	73
	3	THF [a]	SbF_6	50	12	62
	1	THF [a]	ClO_4	22	6	28
(20)	3	CH_2Cl_2	TsO			

[a] THF = tetrahydrofuran.

The very hindered aglycone (20) gave no reaction using our standard conditions with silver tosylate and 3 equiv. of (2). Surprisingly the tosylate (22) was obtained on increasing the temperature, suggesting the intervention of triethylamine as an agent to transfer the tosyl unit from the tosylmannoside to the aglycone (20).



When triethylamine was omitted, the reaction gave the α-disaccharide (23) in 40% yield.

EXPERIMENTAL

U.v. spectra were recorded in methanol on a Beckman DK 2A spectrometer. ^{1}H N.m.r. spectra were recorded on Perkin-Elmer R 12B (60 MHz) or CAMECA 250 (250 MHz) spectrometers in deuteriochloroform with tetramethylsilane as internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. M.p.s were measured in capillary tubes; t.l.c. was performed with Kieselgel H (Merck) and Kieselgel 70—285 mesh (Merck) was used for column chromatography.

Preparation of the ATDP Salts.—A solution of the sugar (1 mmol) in dry dichloromethane (15 ml) containing carbon tetrachloride (308 mg, 2 mmol) was cooled to −40 °C under an inert atmosphere. The mixture was stirred magnetically and a solution of hexamethylphosphoric triamide (200 mg, 1.23 mmol) in dry dichloromethane (5 ml) was added dropwise during 1 h with a motor-driven syringe.

Condensation with Thiols.—An excess of the thiol (3 mmol) and triethylamine (1 ml) was added to a cooled solution of the ATDP salt. The mixture was allowed to warm to room temperature during 2 or 3 h. The mixture was then washed with water (3 × 20 ml). The organic layer was dried ($MgSO_4$) and then evaporated.

Phenyl 2,3:4,6-*di*-O-*isopropylidene*-1-*thio*-β-D-*mannopyranoside* (5) (240 mg, 65% yield) was purified by chromatography, with hexane–ethyl acetate (3 : 2) as eluant, m.p. 142 °C (from ethanol), $[\alpha]_D^{25}$ −132° (*c* 1, $CHCl_3$), δ 1.4 (3 H, s), 1.6 (3 H, s), 1.6 (6 H, s) (all CMe_2), 3.97 (6 H, m), 5.06 (1 H, d, *J* 2.7 Hz, 1-H), and 7.4 (5 H, m, ArH) (Found: C, 61.6; H, 6.7; S, 9.0. $C_{18}H_{24}O_5S$ requires C, 61.3; H, 6.9; S, 9.1%).

Benzoxazol-2-*yl* 2,3:4,6-*di*-O-*isopropylidene*-1-*thio*-β-D-*mannopyranoside* (8) and 3-(2,3:4,6-*di*-O-*isopropylidene*-β-D-*mannopyranosyl*)*benzoxazole*-2(3H)-*thione* (10) were purified by chromatography, with hexane–ethyl acetate (3 : 2) as eluant, to yield (8) (190 mg, 50%) and (10) (60 mg, 15%). Compound (8) had m.p. 166 °C, $[\alpha]_D^{25}$ −111° (*c* 0.91, $CHCl_3$), δ 1.49 (12 H, CMe_2), 3.95 (6 H, m), 6.18 (1 H, d, *J* 2.7 Hz, 1-H), and 7.48 (4 H, m, ArH) (Found: C, 58.5; H, 5.9; N, 3.5; S, 7.9. $C_{19}H_{23}NO_6S$ requires C, 58.0; H, 5.9; N, 3.55; S, 8.1%). Compound (10) had m.p. 144 °C, δ 1.26, 1.47, 1.58, 1.62 (each 3 H, s, CMe_2), 4 (6 H, m), 6.53 (1 H, d, *J* 2.7 Hz, 1-H), and 7.51 (4 H, m, ArH) (Found: C, 58.5; H, 5.9; N, 3.5; S, 7.9%).

Benzothiazol-2-*yl* 2,3:4,6-*di*-O-*isopropylidene*-1-*thio*-β-D-*mannopyranoside* (9) (260 mg, 65%) was purified by chromatography, with hexane–ethyl acetate (3 : 2) as eluant, m.p. 162 °C, $[\alpha]_D^{25}$ −123° (*c* 0.83, $CHCl_3$), δ 1.41 (3 H, s), 1.51 (3 H, s), 1.6 (6 H, s) (all CMe_2), 3.87 (6 H, m), 6.00 (1 H, d, *J* 2.5 Hz, 1-H), and 7.40 (4 H, m, ArH) (Found: C, 55.7; H, 5.6; N, 3.4; S, 16.1. $C_{19}H_{23}NO_5S_2$ requires C, 55.7; H, 5.7; N, 3.4; S, 15.65%).

Condensation with Alcohols.—Silver toluene-*p*-sulphonate (418 mg; 1.5 mmol) was poured into a cooled solution (−40 °C) of the ATDP salt. After silver chloride had

precipitated, an excess of the alcohol (1 ml) and triethylamine (1 ml) was added at −40 °C. The mixture was allowed to warm to room temperature during 3 or 4 h. The silver salts were then filtered off and the organic layer was washed with water, dried ($MgSO_4$), and evaporated.

Methyl 2,3:4,6-*di*-O-*isopropylidene*-α-D-*mannopyranoside* (11) and *methyl* 2,3:4,6-*di*-O-*isopropylidene*-β-D-*mannopyranoside* (12) were purified by chromatography, with ether–light petroleum (1 : 1) as eluant, to yield (11) (140 mg, 51%) and (12) (105 mg, 38%). Compound (11) was a gum, $[\alpha]_D^{25}$ +75° (*c* 1.52, $CHCl_3$), δ 1.35, 1.41, 1.51, 1.53 (each 3 H, s, CMe_2), 3.35 (3 H, s, OMe), 3.92 (6 H, m), and 4.87 (1 H, s, 1-H) (Found: C, 56.8; H, 8.15. $C_{13}H_{22}O_6$ requires C, 56.9; H, 8.1%); compound (12) was a gum $[\alpha]_D^{25}$ −0.86 (*c* 1.98, $CHCl_3$), δ 1.38, 1.42, 1.51, 1.58 (each 3 H, s, CMe_2), 3.55 (3 H, s, OMe), 3.69 (6 H, m), and 4.73 (1 H, d, *J* 2.5 Hz, 1-H) (Found: C, 57.0; H, 8.05. $C_{13}H_{22}O_6$ requires C, 56.9; H, 8.1%).

Ethyl 2,3:4,6-*di*-O-*isopropylidene*-α-D-*mannopyranoside* (13) and *ethyl* 2,3:4,6-*di*-O-*isopropylidene*-β-D-*mannopyranoside* (14) were purified by chromatography, with ether–light petroleum (1 : 1) as eluant to yield (13) (130 mg, 45%) and (14) (80 mg, 28%). Compound (13) had m.p. 56—57 °C, $[\alpha]_D^{25}$ +7° (*c* = 1.05, $CHCl_3$), δ 1.20 (3 H, t, *J* 7 Hz, OEt), 1.33, 1.41, 1.51, 1.53 (each 3 H, s, CMe_2), 3.74 (8 H, m), and 4.98 (1 H, s, 1-H) (Found: C, 58.2; H, 8.4. $C_{14}H_{24}O_6$ requires C, 58.3; H, 8.4%); compound (14) had m.p. 42—43 °C, $[\alpha]_D^{25}$ −84.2° (*c* 1, $CHCl_3$), δ 1.26 (3 H, t, *J* 7 Hz, OEt), 1.39, 1.42, 1.51, 1.58 (each 3 H, s, CMe_2), 3.67 (8 H, m), and 4.80 (1 H, d, *J* 2.5 Hz, 1-H) (Found: C, 58.5; H, 8.5. $C_{14}H_{24}O_6$ requires C, 58.3; H, 8.4%).

Isopropyl 2,3:4,6-*di*-O-*isopropylidene*-α-D-*mannopyranoside* (15) and *isopropyl* 2,3:4,6-*di*-O-*isopropylidene*-β-D-*mannopyranoside* (16) were purified by chromatography, with ether–light petroleum (1 : 1) as eluant to yield (15) (150 mg, 50%) and (16) (100 mg, 33%). Compound (15) had m.p. 59—60 °C, $[\alpha]_D^{25}$ +18° (*c* = 1, $CHCl_3$), δ 1.17 (6 H, dd, *J* 6.7 Hz, Pr^iO), 1.35, 1.42, 1.49, 1.53 (each 3 H, s, CMe_2), 3.98 (7 H, m), and 5.10 (1 H, s, 1-H) (Found: C, 59.4; H, 8.7. $C_{15}H_{26}O_6$ requires C, 59.6; H, 8.7%); compound (16) was a gum, δ 1.39 (18 H, m, all CMe_2 + Pr^iO), 3.93 (7 H, m), and 4.82 (1 H, d, *J* 2.5 Hz, 1-H) (Found: C, 59.9; H, 8.4. $C_{15}H_{26}O_6$ requires C, 59.6; H, 8.7%).

t-Butyl-2,3:4,6-*di*-O-*isopropylidene*-α-D-*mannopyranoside* (17) (160 mg, 50%) was purified by chromatography with ether–light petroleum (1 : 1) as eluant, m.p. 112 °C (from hexane), δ 1.24 (9 H, s, Bu^tO), 1.35, 1.42, 1.51, 1.55 (each 3 H, s, CMe_2), 4.25 (6 H, m), and 5.31 (1 H, s, 1-H) (Found: C, 60.5; H, 9.0. $C_{16}H_{28}O_6$ requires C, 60.7; H, 8.9%).

2,3:4,6-*Di*-O-*isopropylidene*-α-D-*mannopyranosyl*-(1 → 6)-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose* (18) and 2,3:4,6-*di*-O-*isopropylidene*-β-D-*mannopyranosyl*-(1 → 6)-1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose* (21) were purified by chromatography, with ether–light petroleum (1 : 1) as eluant to yield (18) (250 mg, 45%) and (21) (190 mg, 28%). Compound (18) was a gum, $[\alpha]_D^{25}$ −16.6° (*c* 1.47, $CHCl_3$), δ 1.40 (24 H, m, CMe_2), 4.04 (12 H, m), 5.02 (1 H, s, 1-H of mannose), and 5.51 (1 H, d, *J* 5.3 Hz, 1-H of galactose) (Found: C, 57.8; H, 7.25. $C_{24}H_{38}O_{11}$ requires C, 57.4; H, 7.6%); compound (21) was also a gum, δ 1.40 (24 H, m, CMe_2), 3.55—4.75 (12 H, m), 4.93 (1 H, d, *J* 2.6 Hz, 1-H of mannose), and 5.53 (1 H, d, *J* 5.3 Hz, 1-H of galactose) (Found: C, 37.2; H, 7.45%).

2,3:4,6-*Di*-O-*isopropylidene*-α-D-*mannopyranosyl*-(1 → 3)-1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose* (23) was purified by chromatography, with ether–light petroleum (3 : 7) as eluant and obtained (200 mg, 40%) as a gum, $[\alpha]_D^{25}$ +0.93° (*c* = 1.07, $CHCl_3$), δ (250 MHz) 1.3—1.58 (24 H, m, CMe_2), 3.5—4.22 (10 H, m), 4.32 (1 H, d, *J* 2.6 Hz), 4.54 (1 H, d, *J* 3.7 Hz, 2-H of glucose), 5.32 (1 H, s, 1-H of mannose), and 5.89 (1 H, d, *J* 3.7 Hz, 1-H of glucose) (Found: C, 57.9; H, 7.5. $C_{24}H_{38}O_{11}$ requires C, 57.4; H, 7.6%).

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