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RECENT ADVANCES IN GLYCOSYLATION REACTIONS

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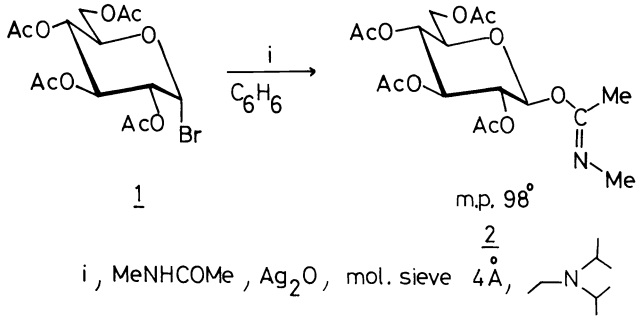
Abstract - Secondary amides react smoothly with benzylated glycosyl chlorides in the presence of a silver salt to give a new class of imidates which can be used in a novel method of α-glycoside synthesis. A practical and stereospecific approach to a variety of α-D-glucosides, α-D-galactosides, and α-L-fucosides is thereby provided. Applications of the method in the synthesis of several human blood group antigenic determinants is described together with other synthetic uses of sugar imidates.

INTRODUCTION

Much effort has been devoted (Ref. 1) in the last decade to the development of efficient and stereocontrolled syntheses of glycosides with the substituents at positions 1 and 2 in cis- or trans-relationship (1,2-cis and 1,2-trans-glycosides). The subject is of paramount importance in relation to the synthesis of biologically and clinically active substances such as carbohydrate antigens and oligosaccharide-containing antibiotics. Although there is now a variety of methods for the selective activation of the anomeric centre of carbohydrates, the long-established reaction using a glycosyl chloride or bromide remains one of the few methods of choice. This type of activation has been investigated widely since its introduction by Koenigs and Knorr (Ref. 2) and has recently been developed to provide important procedures for the synthesis of 1,2-cis-disaccharides (Refs. 1c, 3). The halide ion-catalyzed glycosylation reaction has been successfully applied by Lemieux et al. (Refs. 1c, 4) to the synthesis of several blood group antigenic determinants. Recent results obtained in the author's laboratory in this field are now summarised.

DISCUSSION

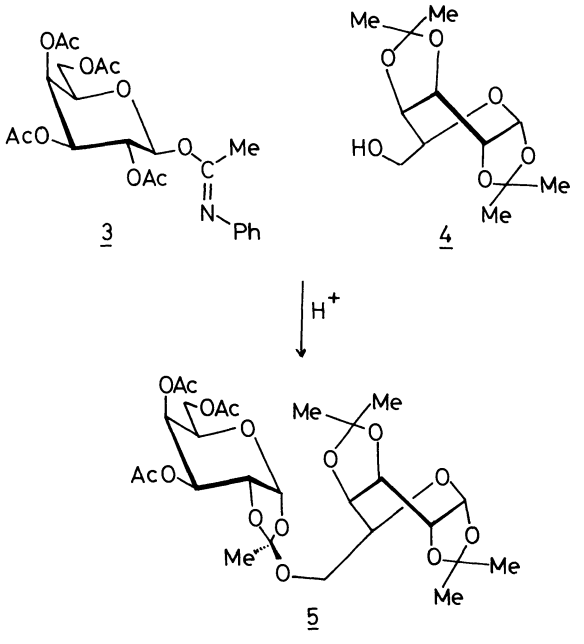
Although the alkylation of amides in the presence of silver salts to provide imidates is a well established process, no application to halogeno sugars has been reported so far. When a benzene solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1) was stirred at room temperature in the presence of N-methylacetamide, silver oxide, di-isopropylethylamine, and a molecular sieve (4 Å), the imidate 2 (m.p. 98°) was obtained (80%). The $^5J_{H,H}$ coupling constant (0.5 Hz) for the two methyl groups in 2 indicates the E-configuration. This reaction is general and a family of imidates has been prepared.



1 m.p. 98° 2

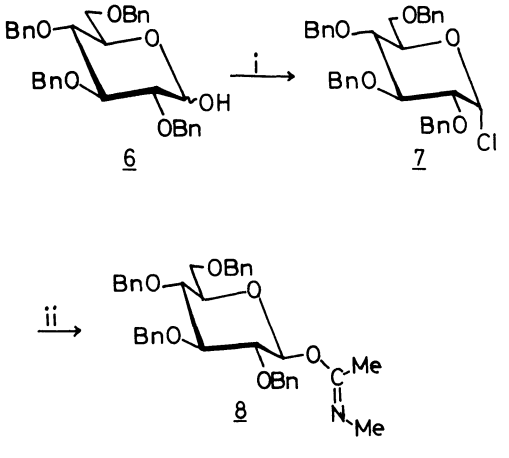
i , MeNHCOMe , Ag_2O , mol. sieve 4Å,

As might be expected, condensation of these acetylated imidates with alcohols in the presence of acid gave mainly orthoesters. For example, 2,3,4,6-tetra-O-acetyl-1-O-(N-phenylacetimidyl)-β-D-galactopyranose (3) was condensed at room temperature with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4) in benzene and in the presence of toluene-p-sulphonic acid to provide the orthoester 5.



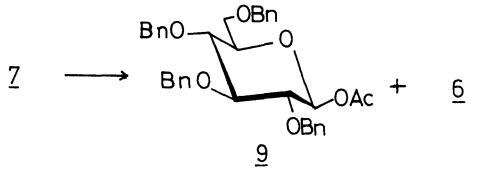
Such an orthoester can then be converted into a 1,2-trans-disaccharide by the procedure of Kochetkov et al. (Ref. 5).

A nonparticipating group at C-2 is necessary if a 1,2-cis-disaccharide is to be obtained. Easily available 2,3,4,6-tetra-O-benzyl-D-glucopyranose (6) was transformed in one step (85%) into 2,3,4,6-tetra-O--benzyl-α-D-glucopyranosyl chloride (7) using N,N-dimethylchloroformiminium chloride. When a benzene solution of 7 was stirred at room temperature with N-methylacetamide, silver oxide, di-isopropylethylamine,and a molecular sieve (4 Å), the imidate 8 was obtained.



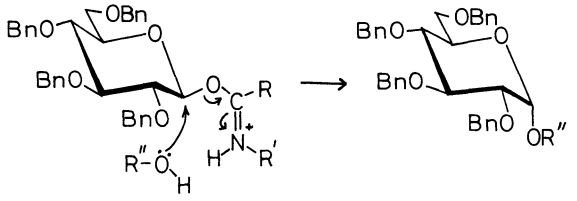
i $(Me_2\overset{+}{N}=CHCl)\,Cl^-$; ii MeNHCOMe, Ag_2O ,  , mol. sieve 4Å .

When Hünig's base was omitted, 1-O-acetyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (9) and 6 were isolated from the reaction mixture. The role of the non-nucleophilic base is to trap the hydrochloric acid, thus avoiding acid hydrolysis of the imidate 8. The stereospecificity of this reaction may be attributed to

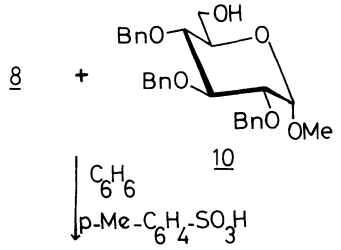


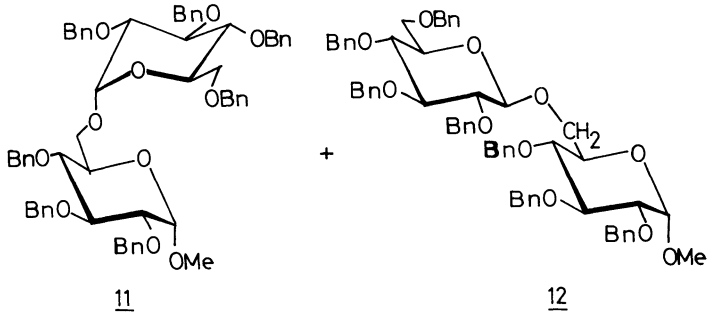
a push-pull mechanism at the surface of the insoluble silver oxide. The condensation is general for a variety of β-imidates and this new class of carbohydrate derivatives displayed interesting chemistry.

It was considered that 1-O-imidyl-β-D-sugars might be useful precursors of α-D-glycosides, according to the following scheme:

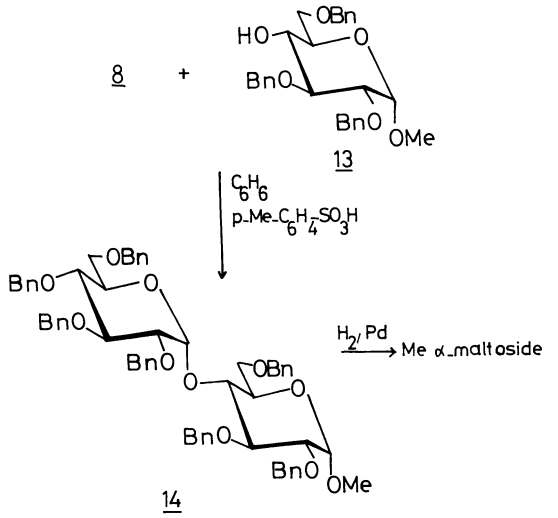


In order to study the parameters of this glucosidation reaction and to develop standard conditions for α-glycoside synthesis, methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (10) was selected as an alcohol. An optimum yield of α-glucoside was obtained using 8 in anhydrous benzene (ethyl ether or nitromethane provide similar results) with one equivalent of anhydrous toluene-p-sulphonic acid. An excellent yield (90%) of disaccharides 11 + 12 was obtained at room temperature (α:β ratio, 84:16, determined by g.l.c.). In this example, the imidate procedure compares well with the halide ion-catalysed reaction (75%, α:β ratio, 90:10).

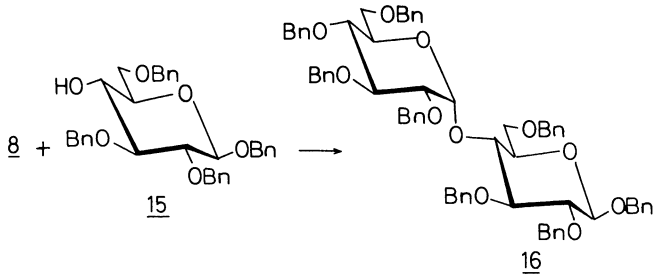




Having established the general conditions required for α-glucosylation, syntheses of various di- and oligosaccharides were attempted to investigate the scope of this new procedure. In order to avoid side reactions, a series of partially benzylated sugar derivatives was used. Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside (13) was chosen as a crucial model compound because of the difficulty of glucosidation of HO-4 of a hexopyranoside derivative ($^4C_1$ chair form). The disaccharide 14 was obtained in 85% yield and it was not possible to isolate any β-isomer from the reaction mixture. Catalytic hydrogenolysis of 14 gave methyl α-maltoside. It is only recently that a practical synthesis (44%) of a maltose derivative has been



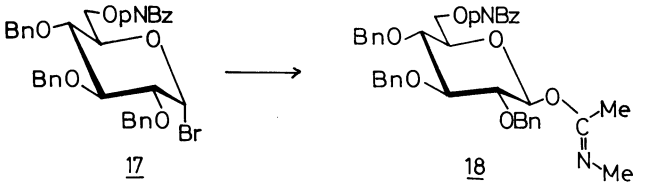
described (Ref. 1d). When 13 was reacted with 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide according to the method of Lemieux et al. (Ref. 1c), no disaccharide had been formed after one week. This result strikingly emphasises the potentiality of the imidate procedure. Condensation of 8 with benzyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside (15) gave the fully benzylated maltoside 16 (80%), catalytic hydrogenolysis of which yielded maltose, free of any trace of cellobiose (g.l.c.).

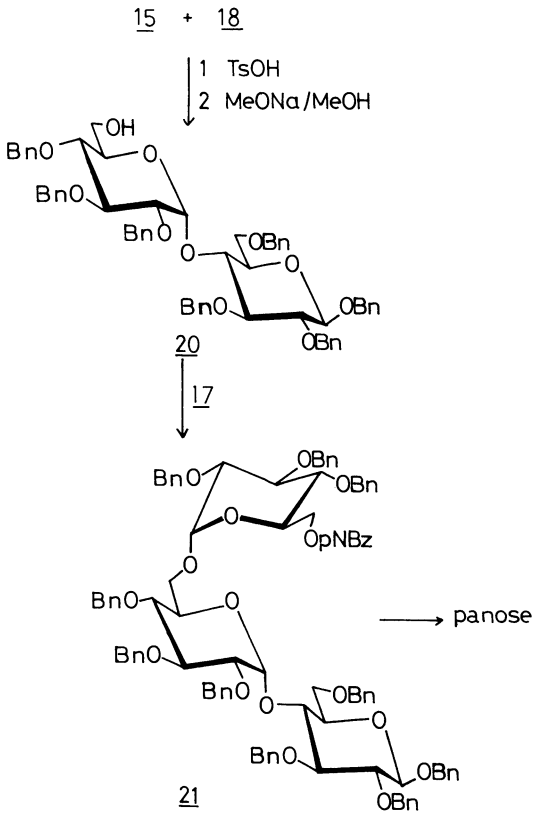


2,3,4-Tri-O-benzyl-6-O-p-nitrobenzoyl-1-O-(N-methylacetimidyl)-β-D-glucopyranose (18, m.p. 111-112.5°), prepared in the usual way (Ref. 6) from 2,3,4-tri-O-benzyl-6-O-p-nitrobenzoyl-α-D-glucopyranosyl bromide (17) was next used in a synthesis of the trisaccharide panose. Glucosidation of 15 with 18 proceeded smoothly to give the disaccharide 19 (80%) which was converted into the alcohol 20, then α-glucosylated using 17 to provide the panoside 21. Deacylation and catalytic hydrogenolysis of 21 then gave panose.

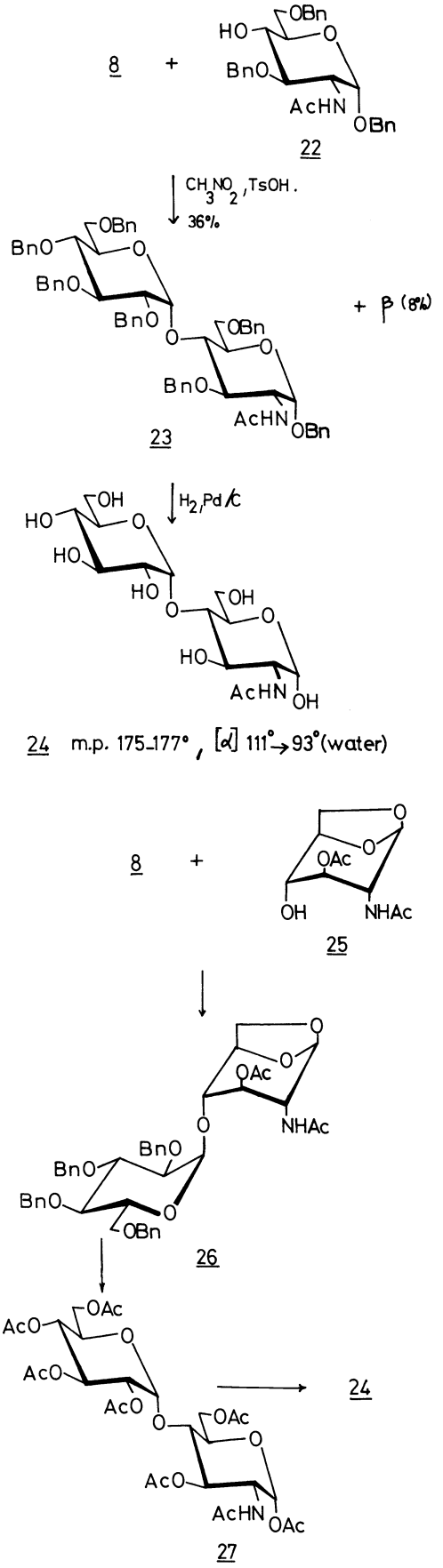
The disaccharide, 2-amino-2-deoxy-4-O-(α-D-glucopyranosyl)-D-glucopyranose has been isolated from carboxyl-reduced heparin and synthesised in extremely low yield from maltose (Ref. 7) and characterised as the N-acetate 24 {m.p. 144.5-146°, $[\alpha]_D^{19}$ +85° (1 min) → +39° (equil., water)}. The imidate 8 slowly condensed with benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside (22) in

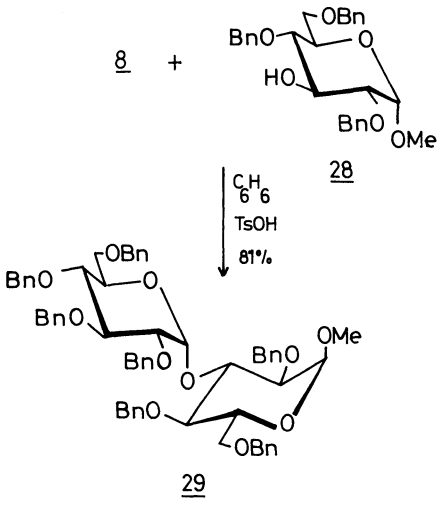
nitromethane to give the disaccharide 23 (36%). Some β-anomer (8%) was also isolated. The physical data for 24 obtained by the imidate route differed considerably from those reported by Wolfrom et al. (Ref. 8). The disaccharide 24 was also obtained by another route. When 8 was condensed with the 1,6-anhydro derivative 25, the expected disaccharide 26 was obtained in quantitative yield and converted (three steps) into the fully acetylated disaccharide 27 (m.p. 225°) and thence into 24 {m.p. 175-177° (decomp.), $[\alpha]_D^{20}$ +111° (1 min) → +93° (equil., water)}.





From these examples, it may be reasonably anticipated that α-glucosylation of secondary hydroxyl groups at other positions should not be difficult. Indeed, α-glucosylation of methyl 2,4,6-tri-O-benzyl-α-D-glucopyranoside (28) gave 81% of the disaccharide derivative 29. It was not possible to isolate any trace of the β-anomer from the reaction mixture. Another (1→3)-α-linked disaccharide derivative (31, m.p. 90-91°) was likewise obtained after α-glucosylation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (30). A minute amount of the crystalline β-anomer was also isolated.


8 +
22
CH3NO2, TsOH.
36%
+ β (8%)
23
H2, Pd/C
24 m.p. 175-177°, [α] 111°→93°(water)
8 +
25
26
24
27



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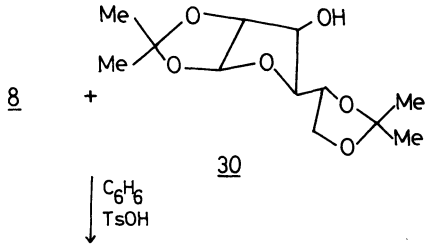
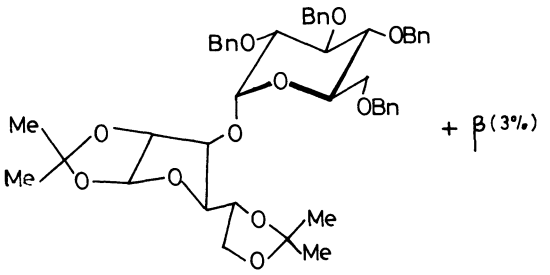
For D-galactopyranoside, HO-2 has been glucosylated in poor yield (25%) using either 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl chloride (Ref. 1b) or 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide under halide ion-catalysed conditions (Ref. 9). When benzyl 3,4,6-tri-O-benzyl-β-D-galactopyranoside (32) was glucosylated with 8, 90% of the disaccharide derivative 33 was obtained.



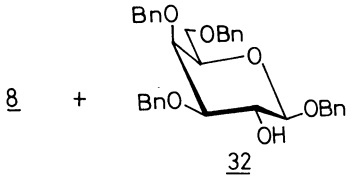


m.p. 90-91°

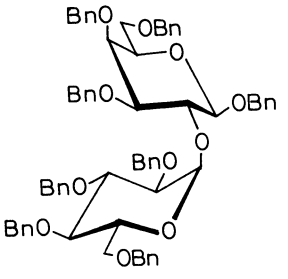
31

The new glycosylation reaction was next explored for the stereospecific and high-yielding syntheses of complex natural oligosaccharides. The human blood group B antigenic determinant was selected for synthesis and the imidate procedure was first applied to a variety of stereospecific α-L-fucosylations and α-D-galactosylations.

Using N,N-dimethylchloroformiminium chloride, 2,3,4-tri-O-benzyl-α-L-fucopyranose (34) was conveniently transformed into 2,3,4-tri-O-benzyl-α-L-fucopyranosyl chloride (35, m.p. 72-73°), which, in turn, was converted into 2,3,4-tri-O-benzyl-1-O-(N-methylacetimidyl)-β-L-fucopyranose (36, m.p. 89-90°). The stable imidate 36 has been used successfully for the preparation of various protected

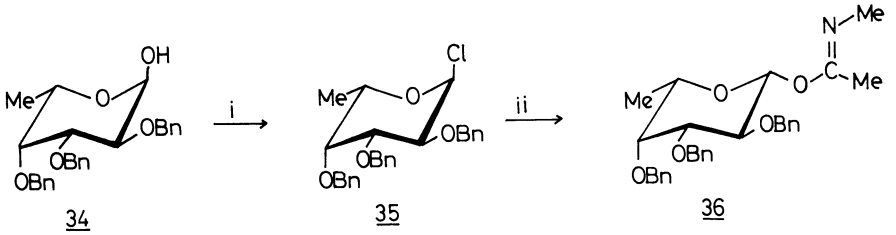


8 + 32



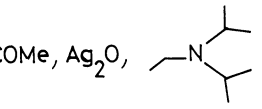
33

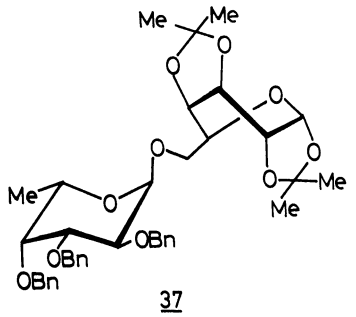
di- and tri-saccharides. The disaccharide 37 (m.p. 116-117°) was thus obtained in 92% yield. Alcohols 13 and 22 were likewise smoothly converted, respectively, into disaccharides 38 and 39. No evidence for the formation of β-anomer was obtained in any of the experiments. These results indicate that the imidate 36 is a very useful α-L-fucosylating agent.



34 35 36

i $(Me_2\overset{+}{N}=CHCl)Cl^-$; ii MeNHCOMe, Ag_2O,





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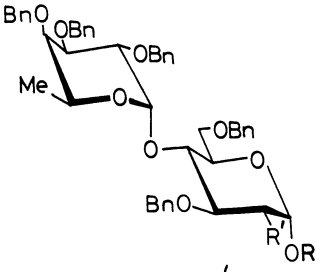
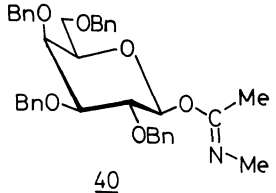


38 R = Me, R' = Bn
39 R = Bn, R' = NHAc

Not unexpectedly, it was found also that 2,3,4,6-tetra-O-benzyl-1-O-(N-methylacetimidyl)-β-D-galactopyranose (40) was an outstanding α-D-galactosylating agent. The disaccharides 41 and 42 were obtained (~80%) by reaction of the respective alcohols 4 and 30 with 40.

4-O-(α-D-Galactopyranosyl)-D-galactose has been recently synthesised from 1,6-anhydro-β-D-galactopyranose derivatives (Refs. 10, 11). When benzyl 2,3,6-tri-O-benzyl-β-D-galactopyranoside (43) was condensed at room temperature in nitromethane with the imidate 40, the disaccharide 44 was obtained (~75%).



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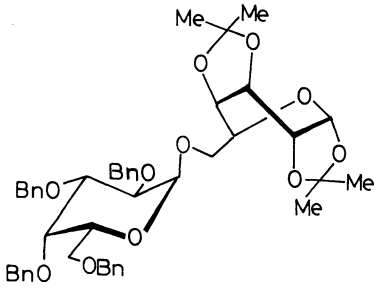

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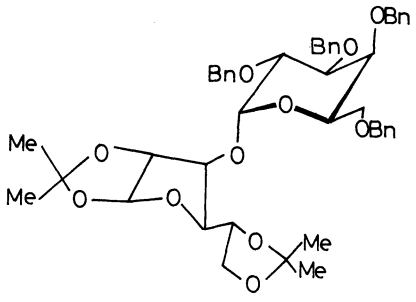

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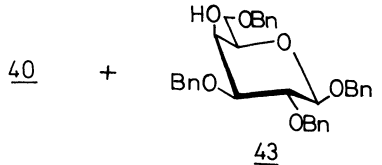

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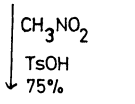

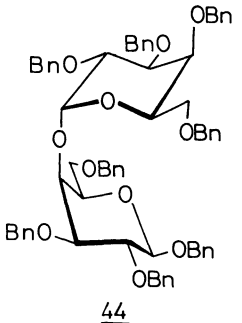

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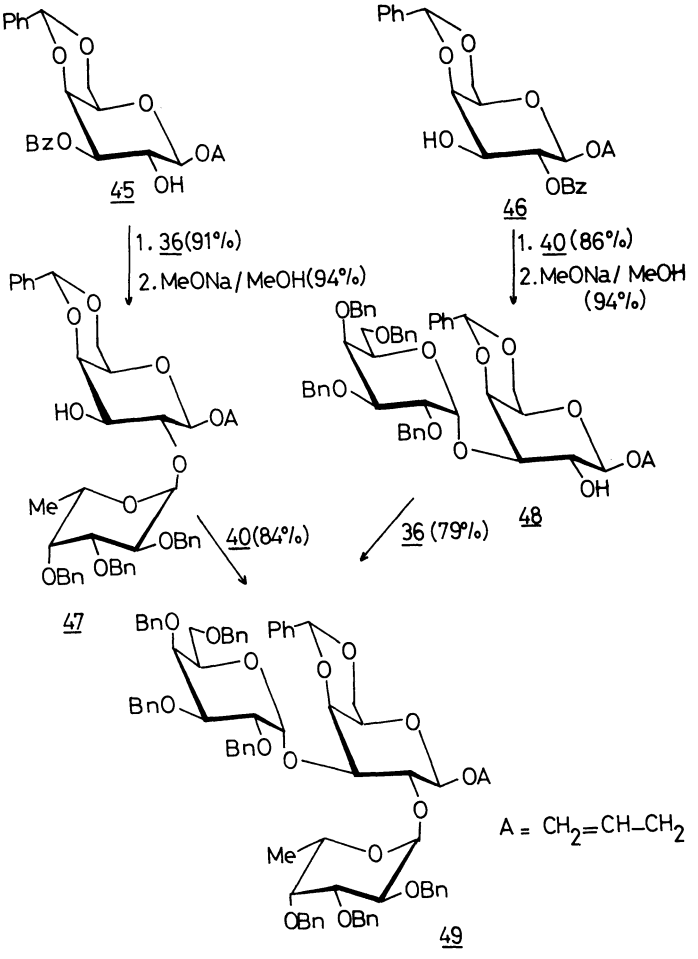
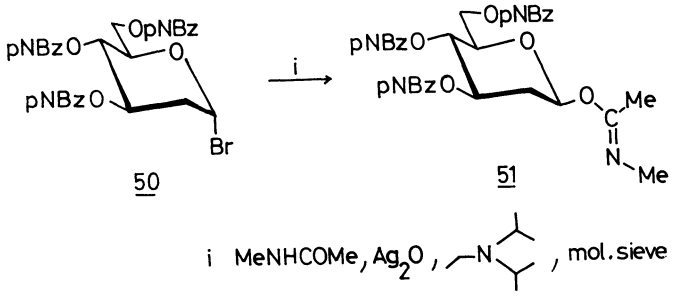
The successful application of the imidate procedure to the stereospecific chemical synthesis in high yield of the human blood group B antigenic determinant is illustrated in the annexed scheme. The crystalline protected trisaccharide 49 was obtained in two ways starting from each of the benzoates 45 and 46. The choice of the allyl glycoside allows flexibility. Thus, the trisaccharide 49 may be converted into the free trisaccharide or transformed into a variety of functional derivatives useful for attachment to a protein

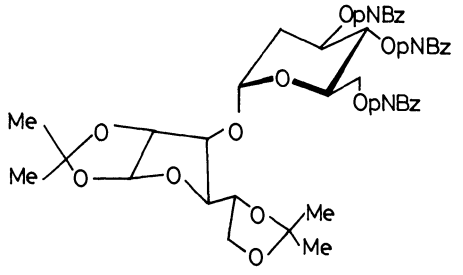


(artificial antigen) or an insoluble matrix (immunoabsorbent).

2-Deoxy-α-D-glycosides are biologically important as structural units in many natural products, especially sugar-containing antibiotics such as the macrolides and the anthracycline group. Preliminary studies on 2-deoxy-D-arabino-hexose (2-deoxy-D-glucose) indicate that the imidate procedure might again be the technique of choice. 2-Deoxy-3,4,6-tri-O-p-nitrobenzoyl-α-D-arabino-hexopyranosyl bromide (50, Ref. 12) was converted into crude 2-deoxy-1-O-(N-methylacetimidyl)-3,4,6-tri-O-p-nitrobenzoyl-β-D-arabino-hexopyranose (51) which was used for glycosylation reactions without further purification. Condensation of 51 with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4) at room temperature (benzene, 8 h) gave an excellent yield (95%) of disaccharides (α:β ratio, 2:1). This reaction represents a



considerable improvement compared to that involving oxymercuration of D-glucal triacetate (Ref. 13). Although the stereoselectivity is poor, the yield is an encouraging feature, as we may expect better selectivity with less reactive secondary hydroxyl groups. Indeed, condensation of 51 with 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (30) gave the disaccharide 52 (88%) and only a minute amount (<5%) of β-disaccharide was isolated. Furthermore, the alcohol 22 reacted stereospecifically in one hour at room temperature with crude 51 to give the disaccharide 53 (83%, yield not optimised).



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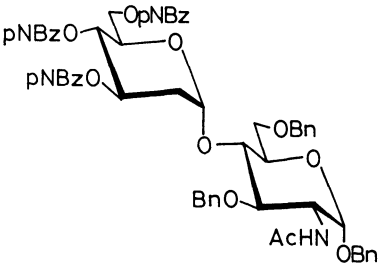
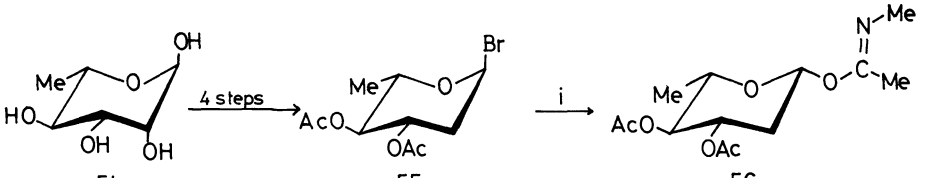
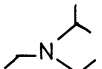


53

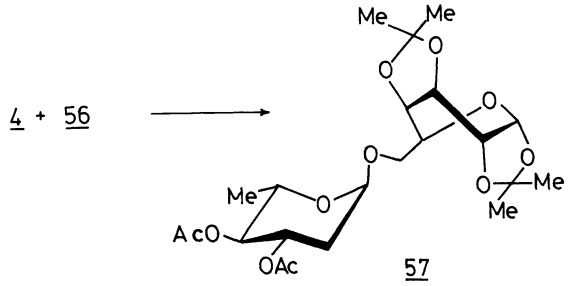
The alcohol 22 was largely recovered when treated for several days with the imidate 8. A stereospecific synthesis of α-glycosides of 2,6-dideoxysugars would establish a route to adriamycin-like antitumour compounds. The crystalline bromide 55 was recently prepared (Ref. 14) from L-rhamnose 54 and converted into the imidate 56 using our standard treatment.



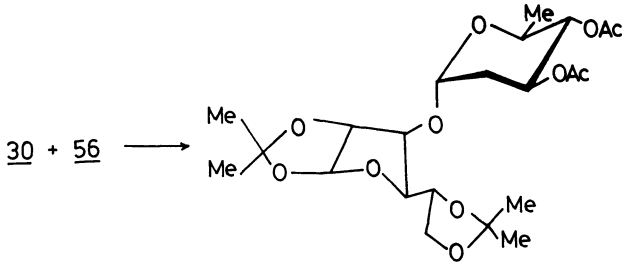
54 55 56

i MeNHCOMe, Ag_2O,  , mol. sieve 4Å.

The imidate 56 condensed (4 h at room temperature in benzene) with the alcohol 4 to give the disaccharide 57 (91%) and with the alcohol 30 to give the disaccharide 58 (83%); no β-disaccharide was isolated from either of these two condensations.

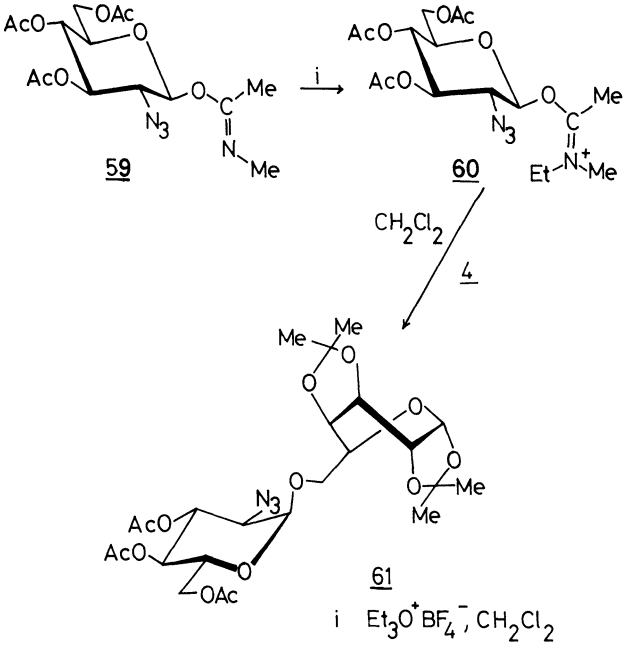


57

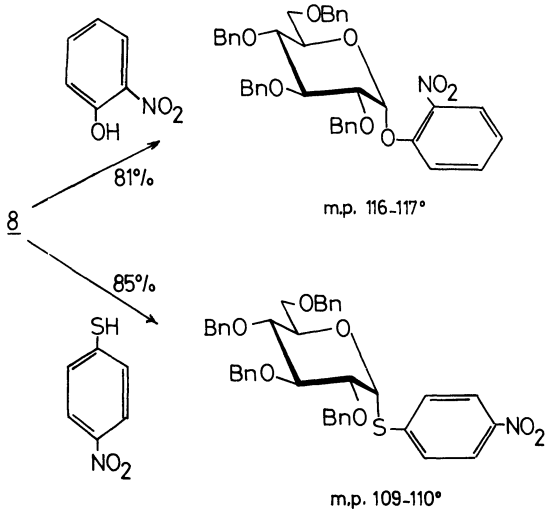


58

Only limited results have been obtained so far using the imidate procedure for the synthesis of α-glycosidically linked 2-acetamido-2-deoxy sugars. The imidate 59 was alkylated to give the sensitive salt 60 which, in turn, without isolation, was condensed with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4) to provide, stereospecifically, the disaccharide 61 in satisfactory yield (60%), Unfortunately, secondary hydroxyl groups are not sufficiently reactive.

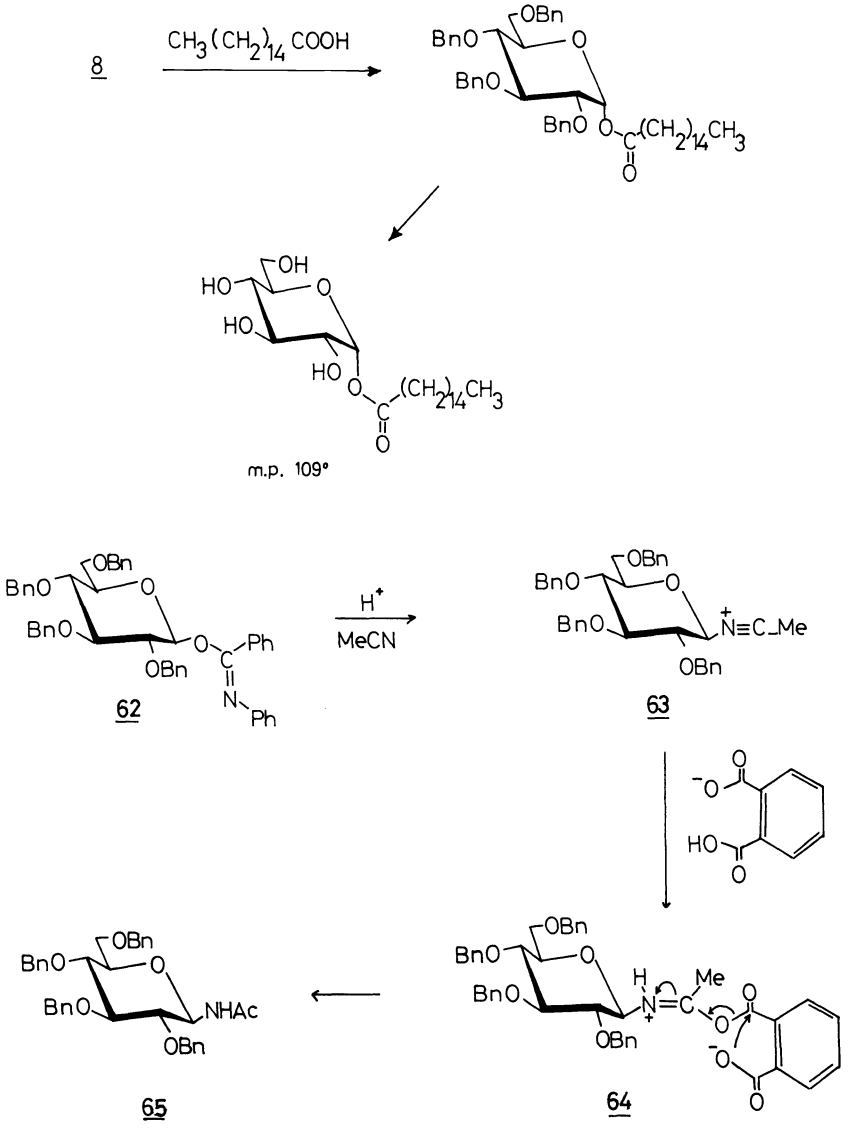


In concluding this general survey of the synthesis of 1,2-cis-glycosides using 1,2-trans-acetamidates it should be pointed out that acidic phenols react spontaneously with the imidate 8 to give α-glucosides in good yield.



Although the stereospecific conversion into O-glycosides is an outstanding property of 1-O-imidyl sugars, they display other interesting and related reactions. As may be anticipated, the imidate 8 stereoselectively reacts with carboxylic acids to give α-esters, which are catalytically reduced to 1-O-acyl-α-D-glucopyranoses. This reaction provides a route to 1-O-(fatty acyl)-D-glucoses which possess various interesting biological properties (Ref. 15).

In 1976 we described (Ref. 16) a peculiar reaction of 2,3,4,6-tetra-O-benzyl-1-O-(N-phenylbenzimidoyl)-β-D-glucopyranose (62) in the presence of a carboxylic acid in acetonitrile, the postulated intermediate being the β-nitrilium ion 63. When phthalic acid was used, 65 was obtained in a few minutes in quantitative yield from the dipolar intermediate 64.

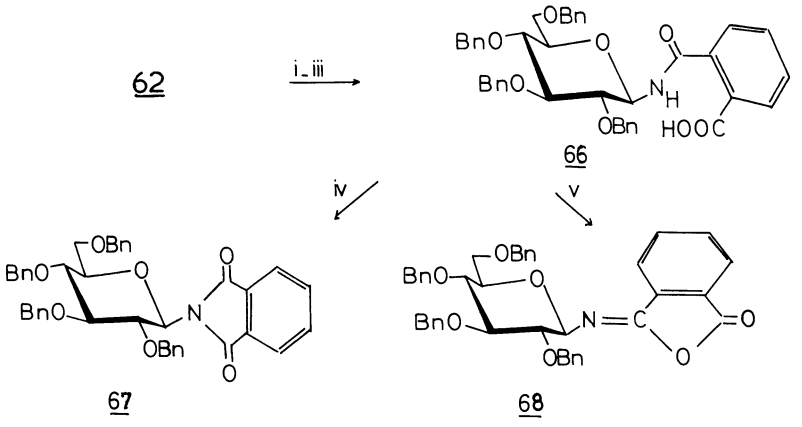


An application of this stereospecific reaction provides the phthalamide 66 which was used to produce either the β-imide 67 or the β-isoimide 68, depending on the dehydration conditions employed. Isoimides have been relatively little investigated in organic chemistry.

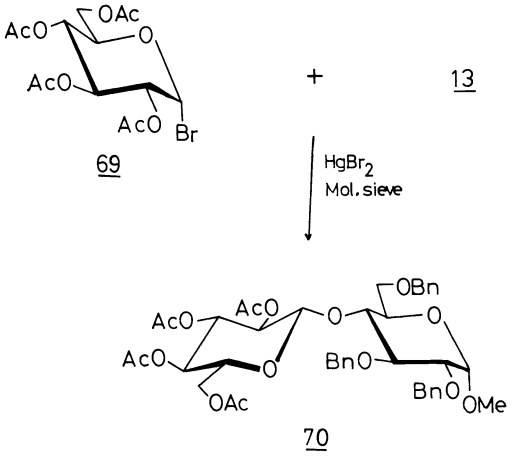
Thus, by the mediation of acetonitrile, aryl imidates provide a new stereospecific synthesis of N-glycosides of unusual types such as 65, 67, and 68. It is possible that 1-O-imidyl-β-D-sugars may be useful precursors of α-thioglycosides, sugar phosphates, and polysaccharides. Such reactions are currently under investigation in our laboratory.

During our current work on the chemical synthesis of human blood group antigenic determinants or structural units (Le^c and Le^d), it was necessary to develop a synthesis of appropriately substituted derivatives of N-acetyllactosamine using a coupling procedure. The low reactivity of HO-4 of 2-acetamido-2-deoxy-D-glucose derivatives ($^4C_1$ chair conformation) has hampered such syntheses in the past and required the use of the more reactive 1,6-anhydro derivatives (Ref. 17). We have solved this problem by selection of the glycosylation conditions and using an appropriately protected alcohol.

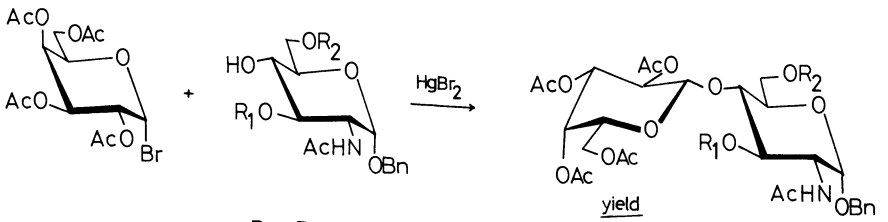
Glycosylation conditions were studied using acetobromogalactose and, from the foregoing comments, a side reaction would be expected if silver salts are used as a catalyst. On the other hand, mercuric cyanide, although satisfactory, is a concurrent nucleophile in the reaction. We found that acetobromogalactose (or acetobromoglucose) condensed with various alcohols in boiling dichloroethane, in the presence of mercuric bromide and a molecular sieve (4 Å), the yield of β-glycosides being >85% as a rule. A significant example is provided by the synthesis of the disaccharide 70 (84% from 13 and acetobromoglucose).



i , MeCN ; ii MeONa, MeOH ; iii NaOH ; iv Ac_2O, Et_3N ; v $(CF_3CO)_2O$



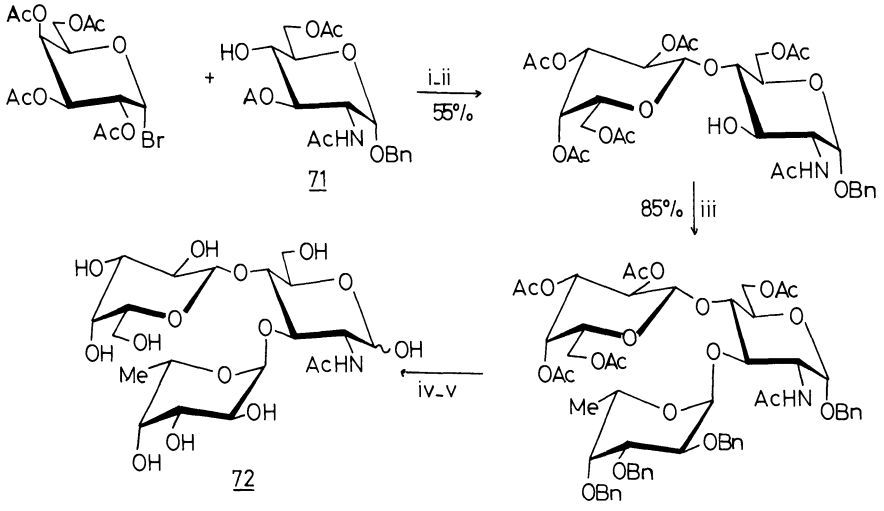
On the other hand, the critical influence of the nature of the substituents on the reactivity of HO-4 is illustrated in the next scheme, which demonstrates that ethers are very appropriate substituents resulting in an excellent yield of lactosamine and that acetylation of HO-6 does not hamper the reactivity of HO-4.



		yield
R_1 = Bn	R_2 = Bn	87%
R_1 = CH_2-CH=CH_2	R_2 = Bn	77%
R_1 = CH_2-CH=CH_2	R_2 = Ac	78%
R_1 = Ac	R_2 = Bn	5%
R_1 = Ac	R_2 = Ac	5%

The possibility of preparing N-acetyllactosamine derivatives in excellent yield, in combination with the imidate procedure, opens a route of synthesis to some oligosaccharides of biological significance. An example is provided by the high-yield synthesis of the trisaccharide 72 from the easily available alcohol 71.

This trisaccharide is located at the "non-reducing end" of numerous oligosaccharides or glycoconjugates of human origin (Ref. 18). In the same way we are currently working on a synthesis of the human blood group P_1 antigenic determinant Galα(1→4)Galβ(1→4)GlcNAc.



i $HgBr_2$; ii $(PPh_3)_3Rh^ICl$; iii Imidate Procedure ; iv MeONa ; v H_2 , Pd/C .

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