Synthesis of Ligands Related to the O-Specific Antigen of Type 1 *Shigella dysenteriae*. 3. Glycosylation of 4,6-O-Substituted Derivatives of Methyl 2-Acetamido-2-deoxy-α-D-glucopyranoside with Glycosyl Donors Derived from Mono- and Oligosaccharides

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Methyl *O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside, obtained by silver trifluoromethanesulfonate-mediated condensation of methyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranoside and 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (**3**), was cleaved with dichloromethyl methyl ether (DCMME) to give *O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl chloride (**9**). Condensations of 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose with **3** and **9**, followed by treatment of the products with DCMME yielded, respectively, glycosyl chlorides **12** and **17**. Each of these, as well as 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride was condensed with 4,6-*O*-substituted (benzylidene, tetraisopropyldisiloxane-1,3-diyl, or benzyl) derivatives of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, using CH_2Cl_2, ether, or a mixture thereof as the solvent. The formation of the desired α-D-galactopyranosyl linkage was favored when ether was the solvent. Under these conditions, however, the combined yield of the condensation products decreased, especially when less reactive synthons were used. The α-linked products obtained were deprotected to give the methyl α-glycosides of the tetra, tri-, and the disaccharide related to the chemical repeating unit of the O-specific side chain of the lipopolysaccharide of *Shigella dysenteriae* type 1. Synthesis of methyl α-glycosides of three other constituents of the same polymeric antigen [α-L-Rha-(1→3)-α-L-Rha, α-L-Rha-(1→2)-α-D-Gal, and α-L-Rha-(1→3)-α-L-Rha-(1→2)-α-D-Gal] are also described.

Introduction

This laboratory (at the NIH) has studied the interaction of carbohydrate antigens with antibodies for nearly 20 years. Using natural or synthetic oligosaccharides, some of which were specificaly deoxygenated or fluorinated at certain positions, we have mapped the subsites in the combining area of, among others, (1→6)-β-D-galactan- and (1→6)-α-D-glucan-specific monoclonal immunoglobulins.[2-5] In studying systems involving carbohydrate *homo*polymers we have developed a rational process for obtaining highly detailed information, on the molecular level, on the mode of binding. As a logical next step, we would like to apply this proven approach to a more complex system, such as one involving a *hetero*polysaccharide antigen of which the determinant-epitope is a repeating unit made up of several different sugar moieties. The *chemical* repeating units of many heteropolysaccharide antigens are known, but the nature of the *immunological* repeating unit—which can be any sequential permutation of the chemical repeating unit or even a larger species—need not necessarily be the same. The determination of the immunological repeating unit, a simple task in the case of a homopolysaccharide, is more complicated when the chemical repeating unit is a heterooligosaccharide. This information can be important in developing a *synthetic* vaccine conceivably better than that based on the natural, polymeric antigen.

The nature of the antigen–antibody interaction can be deduced best by analysis of all epitope contributions to that interaction. Such an analysis involves the determination of affinities of a series of constituents as well as analogues of the chemical repeating unit. As part of such a study involving an existing infectious disease, we synthesize oligosaccharides related to the antigenic determinant of the O-specific side chain of the bacterial polysaccharide of *Shigella dysenteriae* type 1. Our future goal is to describe, in molecular detail, the interactions of that antigen with its homologous antibody. In addition, the ligand suggested by the binding studies as the one having the best potential for eliciting the desired immunoresponse could be incorporated in a synthetic vaccine. It has been pointed out[6] that "the severe clinical syndrome caused by *S. dysenteriae* 1 (Shiga's bacillus), its propensity to pandemic spread, and its resistance to most clincally relevant antibiotics make a vaccine to prevent Shiga dysentery a high priority". Thus, in addition to addressing a fundamental problem, this work may have a practical outcome.

→[3-α-L-Rha_p-(1→3)-α-L-Rha_p-(1→2)-α-D-Gal_p-(1→3)-α-D-Glc_pNAc-1]$_n$→

A B C D

Figure 1. Chemical repeating unit of the O-specific antigenic polysaccharide of *S. dysenteriae* type 1.

The chemical repeating unit for this antigen has been determined[7] (Figure 1). Elsewhere,[8] it was found that the sugar linked to the core region of the lipopolysaccharide is D-galactose, thereby suggesting that the nonreducing end group of the O-antigen would be the *N*-acetyl-D-glucosaminyl group. Some fragments of the structure shown in Figure 1 have been synthesized.[9-11] Here, we report on a synthesis of the tetrasaccharide sequence ABCD, as well as of the complete series of its fragments.

(1) (a) NIDDK. (b) Eastman Kodak.
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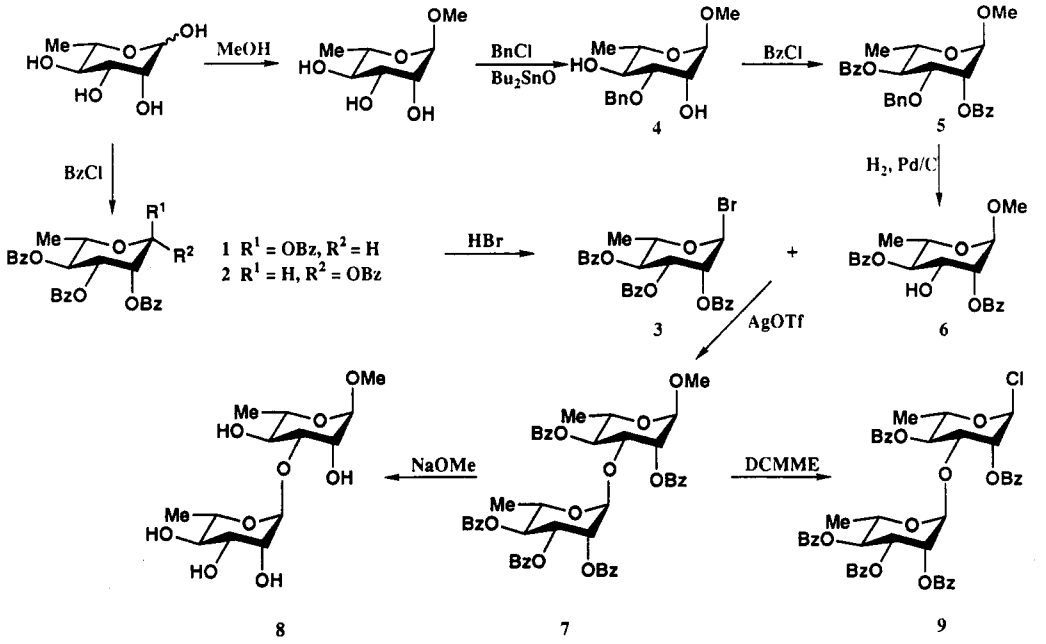
Scheme I



Results and Discussion

The oligosaccharides related to the sequence ABCD were prepared as their methyl glycosides having the same ring structure and anomeric configuration as occurs in the polysaccharide antigen at that locus. The advantage of such structures in solution-binding studies, as compared to free oligosaccharides, has been discussed.[2] Our efforts were targeted primarily toward the three *N*-acetyl-D-glucosamine-containing oligosaccharides (CD, BCD, ABCD, Figure 1) but prompted by the need of ligands for future binding studies; the complete series of ligands related to the sequence ABCD was also prepared during this work. Of these, i.e., the unsubstituted methyl α-glycosides of oligosaccharides AB, BC, CD, ABC, BCD, and ABCD, only the disaccharide AB, **8**, has been previously obtained by a chemical synthesis: Lipták et al.[12] obtained **8** by deprotection of its fully acetylated analogue, synthesized by condensation of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide with methyl 2,4-di-*O*-benzyl-α-L-rhamnopyranoside. Here, the rhamnobioside **8** was synthesized from benzoylated intermediates (Scheme I). L-Rhamnose was benzoylated[13] to give a mixture of 1,2,3,4-tetra-*O*-benzoyl-α- (**1**) and -β-L-rhamnopyranose (**2**) which was then converted[13] to the glycosyl bromide **3**. Methyl 3-*O*-benzyl-α-L-rhamnopyranoside[14] (**4**), now obtained in an improved yield, was benzoylated and the fully protected derivative[15] **5**, here obtained crystalline, was hydrogenolyzed to give the known[16,17] derivative **6**. Condensation of **3** and **6** under the conditions of base-deficient silver trifluoromethanesulfonate (triflate) glycosylation gave the disaccharide **7** in 96% yield. Subsequent debenzoylation of **7** gave the rhamnobioside **8** in a virtually theoretical yield, indistinguishable (^{13}C-NMR) from the independently synthesized[12] substance. The fully protected methyl glycoside **7** was readily converted, by treatment[18] with dichloromethyl methyl ether (DCMME), to the useful building block **9** (Scheme I). An analogous treatment of methyl 3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside with dibromomethyl methyl ether gave[16] the corresponding glycosyl halide in lower yield (50 vs 73% in the present case), due to more extensive cleavage of the interglycosidic linkage. We used **9** as a glycosyl donor (cf. below, syntheses of trisaccharides **16** and **23**), rather than the fully acetylated rhamnobiosyl glycosyl bromide,[19] to avoid the extensive transesterification known to occur[20] with 2-*O*-acetylated glycosyl halides under the conditions of silver trifluoromethanesulfonate (triflate)-mediated glycosylation reactions.

In our original strategy to synthesize the methyl α-glycosides of the disaccharide (BC) and trisaccharide (ABC) sequences (Figure 1), the readily obtainable[21] 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**10**) was used as the starting material. The plan was to treat each of **3** and **9** with **10** and treat the resulting oligosaccharides **11** and **16**, respectively, with DCMME to give the corresponding glycosyl chlorides (**12** and **17**) having a nonparticipating glycosyloxy group at C-2. Subsequent reaction thereof with MeOH was expected to take place with a stereoselective formation of 1,2-cis glycosidic linkage giving predominantly the desired methyl α-glycosides. The respective conversions (Scheme II) gave **12** and **17** in excellent yields. However, the reaction of **12** with MeOH under conditions reported[22] to give methyl α-glucosides nearly exclusively from glucosyl chlorides having at O-2 a nonparticipating group showed no such stereoselectivity. This was rather unexpected since we have, in the past,[23-27] been able to confirm the remarkable utility of the method[22] in highly stereoselective syntheses of 1,2-cis glycosidic linkages.

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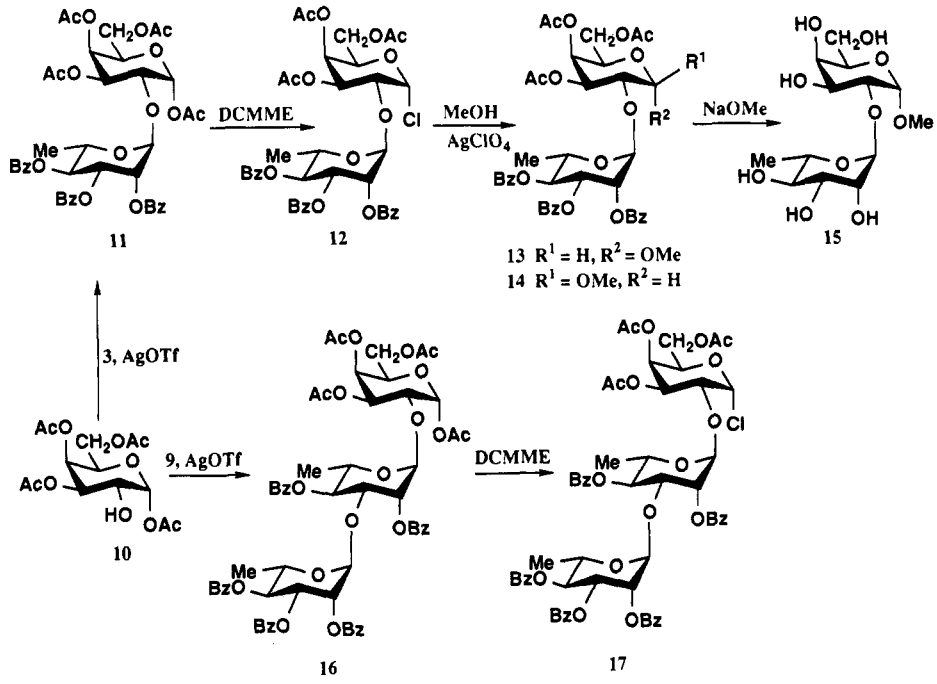
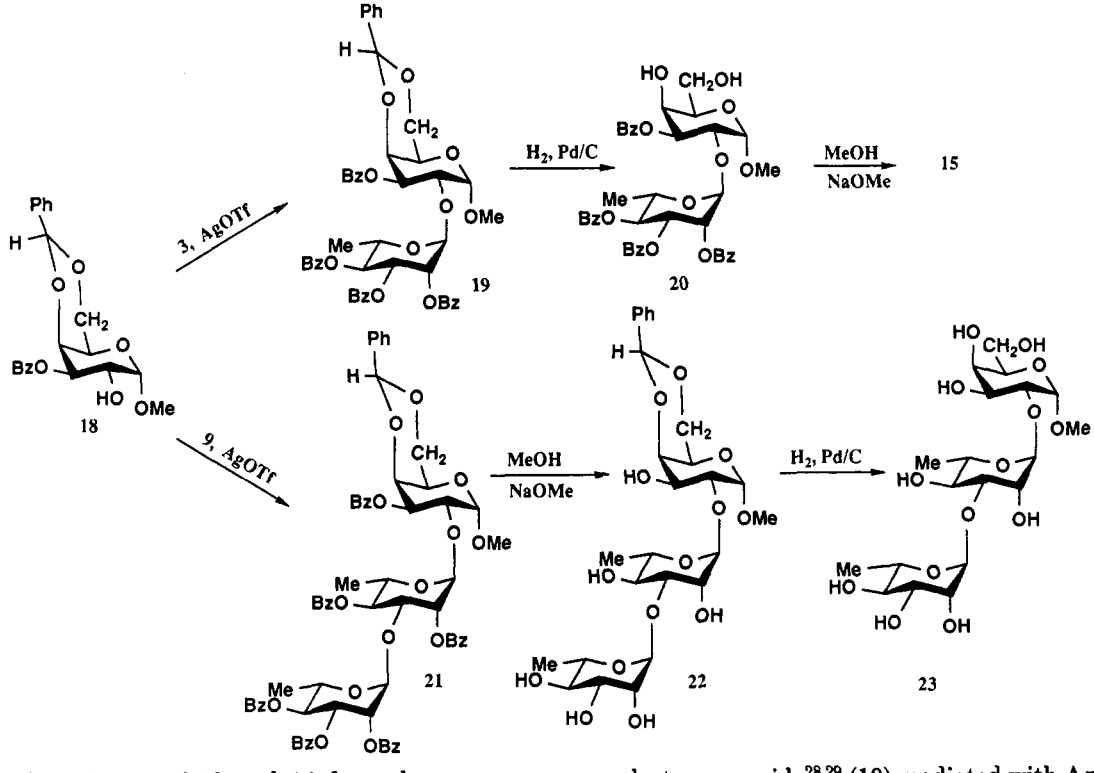
Scheme II



Scheme III



Moreover, the mixture of **13** and **14** formed was very difficult to separate, making this preparation of **15** impractical. Similar problems were anticipated during the reaction of **17** with MeOH, and therefore, alternative pathways for the synthesis of **15** and **23** were sought, starting with a derivative of methyl α-D-galactopyranoside. Accordingly (Scheme III), condensation of the glycosyl bromide **3** with methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-galactopyranoside[28,29] (**18**) mediated with AgOTf under the base-deficient conditions readily gave the fully protected disaccharide **19** which was deprotected by successive hydrogenolysis and catalytic debenzoylation. The methyl glycoside **15** thus obtained was identical (NMR) with the substance synthesized independently as described above. Analogously (Scheme III), using the disaccharide glycosyl chloride **9** as the glycosyl donor and **18** as the glycosyl acceptor, we obtained the desired trisaccharide **23**. The condensation product **21** was obtained in high yield (~

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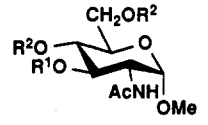
80%) even though no excess of the labor-intensive glycosyl donor **9** was used.

The synthesis of oligosaccharides containing the methyl 2-acetamido-2-deoxy-α-glucopyranoside residue required the formation of the α-(1→3)-linkage between D-galactose and methyl 2-acetamido-2-deoxy-α-D-glucopyranoside. An available alternative, i.e., the preparation of a suitable derivative of 2-azido-2-deoxy-D-glucose and its transformation to the corresponding 2-acetamido derivative after the formation of an oligosaccharide, would be more laborious regardless of the stage at which the azido compound would be converted to the methyl α-glycoside. Numerous examples for the formation of the β-D-galactopyranosyl linkage to the position 3 of methyl 2-acetamido-2-deoxy-α-D-glucosamine can be found in the literature,[30] but no synthesis targeted toward **37** or higher analogues possessing the methyl 2-acetamido-2-deoxy-α-D-glucopyranoside residue has been reported. The closest example of such a preparation was described by Bovin et al.[31] They isolated the α-linked disaccharide as a byproduct of the condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with benzyl 2-acetamido-6-*O*-acetyl-4-*O*-(chloroacetyl)-α-D-glucopyranoside.

Successful glycosylations at O-3 of *N*-acetyl-α-D-glucosamine derivatives have most often been carried out at an elevated temperature, in benzene or in benzene–nitromethane (or acetonitrile) as the solvent, with catalysis by mercuric salts. However, these conditions are unfavorable for the stereoselective formation of a 1,2-cis interglycosidic linkage. The logical glycosyl acceptor in the synthesis of **37** (or its extended analogues, using glycosyl halides derived from oligosaccharides such as, e.g., **12** or **17**) appears to be methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**27**). Due to its insolubility in ether we anticipated that this readily obtainable substance would not be a suitable substrate for the above-mentioned method[22] of 1,2-cis glycosylation. We have, therefore, prepared new 4,6-O-substituted derivatives of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (**24**). Two of them, **26** and **31**, as well as the derivative **27** were used in subsequent glycosylations. The isolation of the pure, crystalline 4,6-*O*-tetraisopropyldisiloxane-1,3-diyl derivative **26**, prepared conventionally,[32] did not require



	R^1	R^2
24	H	H
25	H	-Ip-
26	H	-TIPS-
27	H	-PhCH-
28	MBn	-PhCH-
29	MBn	H
30	MBn	Bn
31	H	Bn

chromatography of the crude product. In order to obtain methyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**31**), the benzylidene derivative **27** was *p*-methoxybenzylated to give the fully protected substance **28**. Selective removal of the 4,6-*O*-benzylidene group in the foregoing compound by acid hydrolysis with dilute acetic acid failed due to simultaneous, extensive cleavage of the *p*-methoxybenzyl group. The pronounced acid lability of a *p*-methoxybenzyl group as compared to that of a benzyl group has been documented.[33] The desired, selective deprotection was readily achieved by the treatment of **28** with methanolic iodine[34] to give crystalline **29** in 86% yield. Benzylation[35] of **29** with benzyl bromide–KOH in dimethyl sulfoxide (DMSO), followed by de-*p*-methoxybenzylation[36] of the formed **30** with ceric ammonium nitrate (CAN), gave the target nucleophile **31**.

Glycosylations targeted toward the disaccharide **37** were carried out using glycosyl acceptors **26**, **27**, and **31**, and 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride[37] (**32**) as the glycosyl donor. Due to the low reactivity of HO-3 in derivatives of *N*-acetylglucosamine,[31] and poor solubility of nucleophiles used here, we have not been able to carry out glycosylations at subzero temperatures. This may account for somewhat poor stereoselectivities observed for reactions yielding synthetic precursors of **37** (Scheme IV and Table I) in which the very reactive glycosyl halide **32** was used. In these situations, unlike the preparations of higher oligosaccharides described below, the use of ether

Table I. Disaccharide Formations Using Chloride 32 as the Glycosyl Donor and 4,6-O-Substituted Methyl 2-Acetamido-2-deoxy-α-D-glucopyranosides as the Glycosyl Acceptors[a]

acceptor	solvent	donor–acceptor	yield (α + β, %)	stereoselectivity (α/β)
26	CH_2Cl_2–Et_2O[b]	2	34	3
26	CH_2Cl_2	2	91[c]	2
27	CH_2Cl_2–Et_2O[b]	2	92	3
31	CH_2Cl_2–Et_2O[b]	1.5	89	2
31	Et_2O	1.5	88	3

[a] Unless otherwise stated, reactions were carried out at room temperature with $AgClO_4$ as the promoter. For further details, see the Experimental Section. [b] Ethereal $AgClO_4$ was added to a solution of reactants in dichloromethane. [c] In a separate experiment, almost no reaction was observed during the first 15 min when the reaction was started at −5 °C. Continuing the reaction at room temperature resulted in a largely incomplete conversion of the nucleophile into the desired products.

Table II. Yields and Stereoselectivities Observed during Glycosylations of Various Nucleophiles with Glycosyl Halides 12 and 17 Derived from Oligosaccharides[a]

acceptor	donor	solvent	donor–acceptor	yield (α + β, %)	stereoselectivity (α/β)
methanol[b]	12	Et_2O	0.75	95	1
26	12	CH_2Cl_2	1	17	7
26	12	CH_2Cl_2–Et_2O[c]	1	~5[d]	*e*
26	12	toluene[f]	1	15	20
27	12	CH_2Cl_2–Et_2O[c]	1	63	8
31	12	CH_2Cl_2	1	55	6
31	12	CH_2Cl_2–Et_2O[c]	1	52	6
31	12	Et_2O	1	37	48
31	17	Et_2O	1	35	38

[a] Unless stated otherwise, reactions were carried out at room temperature with $AgClO_4$ as the promoter. For further details, see the Experimental Section. [b] Reaction carried out at −20 °C. [c] Ethereal $AgClO_4$ was added to a solution of reactants in dichloromethane. [d] Estimated visually from TLC. [e] Traces of the β-linked isomer were formed. [f] Reaction carried out at 60 °C with $Hg(CN)_2$–$HgBr_2$ as the promoter.

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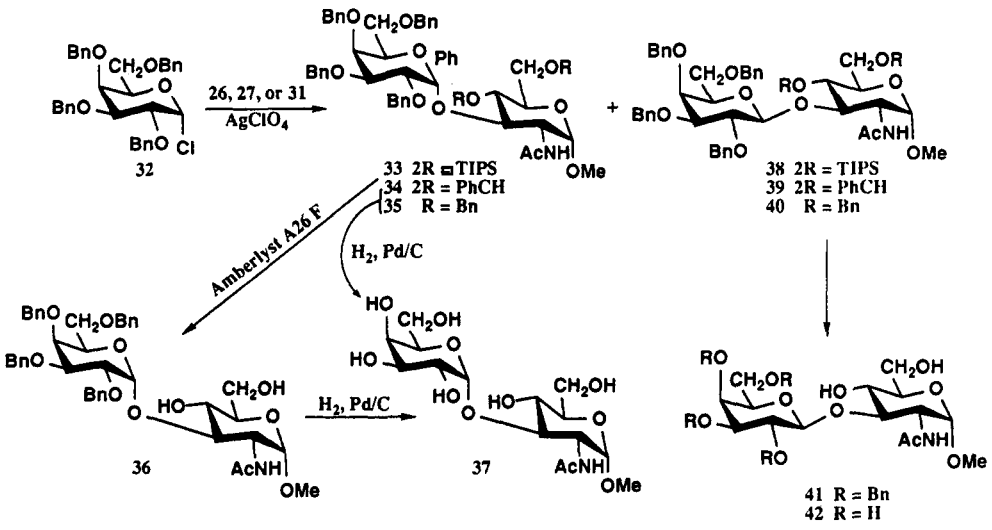
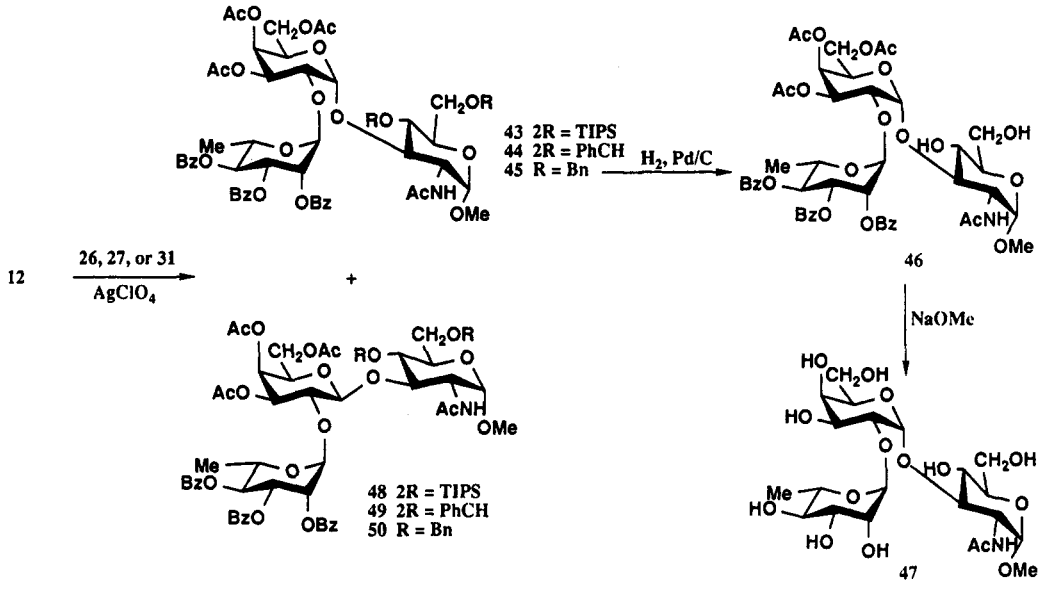
Scheme IV



Scheme V



as the (co)solvent did not markedly affect the distribution of the anomers formed (Tables I and II). On the other hand, the presence of ether did adversely affect the combined yield of the coupling products in the case of less reactive nucleophiles. Of the nucleophiles used here, compound **26** showed the least reactivity. As shown in Table I, practically the same yields of the requisite disaccharides were obtained from **31** using ether or an ether–CH_2Cl_2 mixture as the solvent. In contrast to this, the conversion of the less reactive **26** into the coupling products was noticeably decreased when the condensation was run in the presence of ether. Higher reactivity of the benzylated compound **31** as compared with that of the disiloxane derivative **26** is also apparent from the observation that when **31** is used as a glycosyl acceptor, a lesser amount of the glycosyl donor is necessary to drive the reaction to a combined yield of coupling products in the 90% range (Table I).

Higher stereoselectivities of α-glycosylation were generally observed in condensations of the less reactive halides derived from oligosaccharides, **12** and **17**, with the relatively poorly reactive nucleophiles derived from **24**. The low reactivity of the disiloxane derivative **26** is noticeable again when comparing (Table II, Scheme V) glycosylations of **26**, **27**, and **31** with the glycosyl donor **12** carried out in CH_2Cl_2–ether as the solvent. While the combined yields of the α- and β-linked trisaccharides formed from **27** and **31** were, respectively, 63 and 52% (Table II), hardly any desired product was formed from **26** (TLC, Table II). The presence of ether in the system again markedly decreased the yield of the condensation, an effect which may not be readily recognized with very reactive reagents. Such were the synthons used in the original study[22] where ether was found to be the best solvent for α-glycosylations even with such a reactive nucleophile as MeOH. On the other hand, when less reactive reactants are used, the presence of ether in the reaction system appears to cause enhanced stereoselectivity of α-glycosylation (cf. the decreased yield vs increased α-stereoselectivity in the reactions of **31** with **12**, Table II). The same trend is noted in the increased stereoselectivity of α-glycosylation effected with the less powerful promoter, $Hg(CN)_2$–$HgBr_2$. Regarding the yield and the desired stereoselectivity in CH_2Cl_2–ether as the solvent, the best results were obtained with the benzylidene derivative **27**. However, owing to the insolubility of **27** in ether, the α-stereoselectivity could not be enhanced by conducting the reaction in that solvent, as would clearly be suggested by data in Table I and II. Therefore, to eventually obtain the tetrasaccharide **52**, the conditions most favorable for the formation of α-D-glycosidic linkage

were applied in the reaction of the benzylated nucleophile **31** with **17**, notwithstanding the anticipated lower yield of the coupling reaction.

Glycosylations with the disaccharide glycosyl donor **12** to yield (a) the mixture of methyl glycosides **13** and **14** and (b) the trisaccharides **43–45** and **48–50** also deserve a comparison. As described in the Experimental Section, for economic reasons, excess of the synthetically more valuable glycosyl halide **12** was not used in these condensations, and the yields of trisaccharides were not impressive. That these low yields resulted more from the low reactivity of the nucleophiles used than from the low reactivity of **12** can be deduced from the high combined yield of **13** and **14**, resulting from the condensation of **12** with MeOH, a very reactive nucleophile. Consequently, glycosyl chloride **12** is not unreactive per se and may be more useful in other situations.

Removal of the disiloxane group from **33** was conveniently done using an anion exchange resin (F^--form) as the fluoride ion source[38] in the presence[32] of H_2O. Subsequent hydrogenolysis of **36** formed, or hydrogenolysis of **34** or **35**, gave the target, hitherto unknown disaccharide **37**. The β-linked disaccharide **38**, formed along with **33**, was treated in the same way, to give the methyl glycoside **42**. The deprotection of the synthetic precursors of the trisaccharide **47** (Scheme V) and the tetrasaccharide **52** (Scheme VI) were done conventionally, to yield the desired substances in high yields. Their structures were fully supported by spectral (NMR and MS) data.

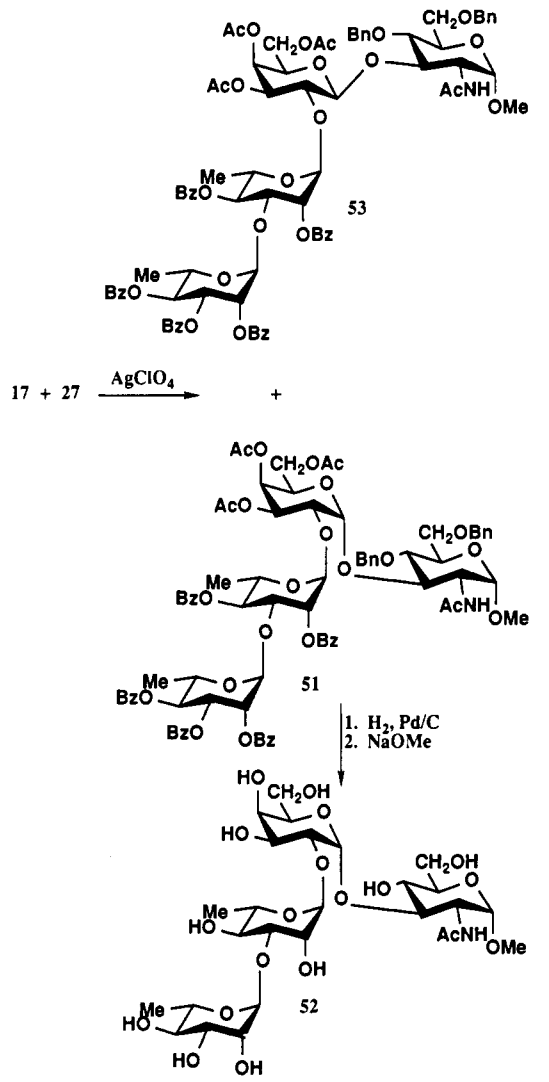
Conclusions

Further examples are presented of the utility[39-41] of the DCMME-$ZnCl_2$ reagent for the preparation of glycosyl chlorides derived from oligosaccharides, which are useful as glycosyl donors for blockwise synthesis of complex oligosaccharides. The series of reactions leading to *N*-acetyl-D-glucosamine-containing oligosaccharides described here include condensations of very reactive and moderately reactive glycosyl halides (**32**, and **12** and **17**, respectively) with nucleophiles of relatively low reactivity. They have put to a test, and fully confirmed, the empirical guidelines[42] regarding the stereoselectivity of 1,2-cis glycosylation vs the reactivity of the synthons and the strength of the promoter. Low stereoselectivity of the formation of the α-D-glycosidic linkage, largely unaffected by solvent (CH_2Cl_2 vs ether), was observed for reactions involving the highly reactive glycosyl donor **32**. Condensations involving the same nucleophiles but less reactive glycosyl donors, or a weak promoter, showed generally higher stereoselectivities. In these cases, stereoselectivity could be further enhanced, at the expense of the combined yield of the oligosaccharides formed—particularly evident in the case of less reactive synthons—by conducting the reactions in, or in the presence of, ether rather than in neat CH_2Cl_2.

Experimental Section

General Methods. General experimental methods not referred to in this section were as described previously.[9] Unless stated otherwise, optical rotations were measured at 25 °C for solutions in $CHCl_3$. Thin-layer chromatography (TLC) was performed with

Scheme VI



solvent mixtures of appropriately adjusted polarity consisting of A, carbon tetrachloride–acetone; B, toluene–acetone; C, carbon tetrachloride acetate; D, toluene–ethyl acetate; E, $CHCl_3$–MeOH; F, CH_2Cl_2–acetone; G, $CHCl_3$–ethyl acetate; and H, $CHCl_3$–acetone. When necessary, streaking on TLC plates of substances containing *N*-acetyl-D-glucosamine was suppressed by addition to the elution solvent of concentrated, aqueous ammonia (5–10% of the polar component, v/v). For preparative chromatography of glycosyl chlorides, the silica gel was dried at 160 °C for 16 h. Assignments of NMR signals (Tables III and IV, see also Tables SI–SIII in Supplementary Material), obtained at 300 MHz for ^1H and 75 MHz for ^{13}C at 25 °C, were made by homonuclear and heteronuclear 2-dimensional correlation spectroscopy using commercial software. When tabulating data for oligosaccharides, the data in the first row of each entry refer to the first sugar residue, data in the second, third, and fourth row, if present, refer to the sugar residues 2, 3, and 4, respectively. NMR data presented in the Experimental Section were obtained under the same conditions, and assignments of proton signals were supported by homonuclear decoupling experiments. Carbon signal assignments found therein were made by mutual comparison of the spectra and by comparison with spectra of related substances. Sugar residues in oligosaccharides are serially numbered, beginning with the one bearing the aglycon, and identified by a superscript in listings of signal assignments. Chemical ionization mass spectra (CIMS) were measured using ammonia as the reactive gas. Fast-atom bombardment mass spectra (FAB) were obtained using *m*-nitrobenzyl alcohol as the matrix. Reactions requiring anhydrous conditions were performed under Ar, and reagents and solvents were handled with gas-tight syringes. Silver trifluoromethanesulfonate (AgOTf), purchased from Aldrich Chemical Co.,

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Table III. ^{1}H NMR Chemical Shifts (δ)

compd	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	CH_3	OCH_3 ($PhOCH_3$)	OH	CHPh
7	5.00	5.61	4.58	5.69	4.13			1.46	3.57		
	5.29	5.37	5.68	5.57	4.21			1.26			
8	4.55	3.89	3.65	3.40	3.59			1.18	3.36		
	4.91	3.94	3.71	3.33	3.68			1.15			
11	6.48	4.30	5.40	5.56	4.38	4.11	4.14				
	5.26	5.49	5.67	5.68	4.22			1.35			
13	4.98	4.04	5.40	5.47	4.17	4.07	4.09		3.48		
	5.13	5.56	5.77	5.66	4.28			1.33			
14	4.47	3.97	5.07	5.41	3.94	4.11	4.19		3.62		
	5.22	5.44	5.77	5.66	4.44			1.30			
15	4.80	3.69	3.76	3.89	3.77	3.61	3.65		3.32		
	4.81	3.94	3.63	3.34	3.59			1.20			
16	6.43	4.29	5.40	5.54	4.37	4.10	4.15				
	5.26	5.41	4.27	5.57	4.09			1.37			
	5.21	5.32	5.61	5.49	4.06			1.13			
19	5.10	4.50	5.53	4.70	3.85	4.10	4.31		3.54		5.29
	5.53	5.54	5.82	5.62	4.29			1.33			
21	5.11	4.42	5.51	4.66	3.83	4.31	4.09		3.51		5.10
	5.26	5.38	4.43	5.57	4.19			1.33			
	5.53	5.21	5.51	5.33	3.88			0.73			
23	4.85	3.70	3.79	3.91	3.79	3.65	3.67		3.35		
	4.83	4.08	3.71	3.45	3.67			1.24			
	4.95	3.99	3.72	3.37	3.74			1.21			
31[a]	4.72	4.13	3.82	3.57	3.69	3.71	3.75		3.36 (3.81)	3.22	
33[b]	4.83	4.10	4.02	4.05	4.34	3.62	3.92		3.27		
	5.31	3.91	3.96	3.95	3.48	3.90	4.13				
34[c]	4.71	4.33	4.22	3.87	4.13	3.38	3.64		3.32		5.39
	5.57	3.39	3.85	3.74	3.76	3.77	4.24				
35[d]	4.66	4.27	4.12	3.79	4.23	3.40	3.66		3.26		
	5.61	4.07	3.98	3.80	3.70	3.62	3.67				
37[e]	4.63	3.94	3.78	3.62	3.72	3.62	3.71		3.29		
	5.32	3.68	3.67	3.87	3.66	3.62	3.75				
38[f]	4.76	4.34	3.92	3.86	3.48	3.87	4.13		3.33		
	4.43	3.76	3.42	3.86	3.46	3.57	3.62				
39[g]	4.81	4.23	3.79	4.17	3.81	3.76	4.19		3.36		5.54
	4.62	3.82	3.47	3.87	3.37	3.40	3.58				
40[h]	4.78	4.32	4.17	3.62	3.78	3.73	3.83		3.33		
	4.58	3.83	3.49	3.91	3.46	3.42	3.48				
42[i]	4.65	4.02	3.79	3.51	3.62	3.71	3.76		3.31		
	4.33	3.42	3.54	3.82	3.59	3.67	3.67				
43[j]	4.78	4.27	3.99	4.16	3.52	3.92	4.18		3.32		
	5.37	4.12	5.36	5.54	4.46	4.13	4.32				
	5.28	5.63	5.78	5.68	4.43			1.33			
44[k]	4.73	4.55	4.12	4.04	3.87	3.93	4.27		3.41		5.68
	5.77	4.17	5.27	5.52	4.52	4.14	4.18				
	5.23	5.50	5.88	5.49	3.91			0.77			
45[l]	4.68	4.48	4.04	3.92	3.85	3.67	3.73		3.37		
	5.54	4.19	5.43	5.52	4.57	4.17	4.57				
	5.26	5.48	5.78	5.60	4.28			1.19			
47[m]	4.62	3.98	3.84	3.75	3.61	3.67	3.67		3.30		
	5.48	3.81	3.77	3.90	3.60	3.65	3.71				
	4.96	3.96	3.66	3.36	3.72			1.19			
48[n]	4.70	4.46	3.97	3.85	3.52	3.88	4.17		3.38		
	4.72	4.03	5.02	5.41	3.90	3.96	4.22				
	5.29	5.57	5.92	5.70	4.57			1.28			
49[o]	4.89	4.14	3.83	4.16	3.35	3.73	3.99		3.33		5.56
	4.73	3.82	5.03	5.30	3.81	3.81	4.26				
	5.26	5.65	5.68	5.75	4.48			1.52			
50[p]	4.73	4.43	4.23	3.69	3.76	3.67	3.75		3.36		
	4.93	3.94	5.05	5.41	3.82	4.09	4.09				
	5.23	5.65	5.90	5.75	4.70			1.43			
51[q]	4.63	4.46	4.01	3.83	3.81	3.52	3.57		3.32		
	5.42	4.19	5.49	5.50	4.56	4.11	4.20				
	5.28	5.43	4.04	5.45	3.99			1.06			
	5.08	5.28	5.55	5.48	4.18			1.22			
52[r]	4.62	3.99	3.84	3.60	3.62	3.61	3.65		3.24		
	5.48	3.81	3.63	3.75	*s*	3.74	3.76				
	4.95	4.05	3.75	3.45	3.77			1.18			
	4.97	3.96	3.73	3.36	3.71			1.21			
53[t]	4.64	4.50	4.20	3.56	3.75	3.67	3.76		3.35		
	4.77	4.00	5.04	5.39	3.88	4.04	4.13				
	5.31	5.33	4.94	5.61	4.66			1.38			
	5.50	5.35	5.60	5.44	4.06			1.13			

[a] δ_{CH_2Ph} 4.87, 4.57, ^2J 11.5 Hz; 4.63, 4.53, ^2J 12.1 Hz; δ_{NH} 5.94; δ_{NHCOCH_3} 2.03. [b] δ_{CH_2Ph} 4.47, 4.59, ^2J 11.4 Hz; 4.62 (2-proton singlet); 4.52, 4.72, ^2J 12.1 Hz; 4.75 (2-proton singlet); δ_{NH} 6.31; δ_{NHCOCH_3} 1.84. [c] δ_{CH_2Ph} 4.30, 4.52, ^2J 12.0 Hz; 4.42, 4.62, ^2J 10.8 Hz; 4.53, 4.88, ^2J 11.4 Hz; 4.68, 4.90, ^2J 12.0 Hz; δ_{NH} 6.17. [d] δ_{CH_2Ph} 4.42, 4.62, ^2J 11.4 Hz; 4.46, 4.62, ^2J 11.4 Hz; 4.71, 4.76, ^2J 11.4 Hz; 4.48, 4.82, ^2J 12.0 Hz; 4.54, 4.90, ^2J 12.0 Hz; 4.32, 4.94, ^2J 12.6 Hz. [e] A resonance due to the NH proton was not observed; δ_{NHCOCH_3} 1.94. [f] δ_{CH_2Ph} 4.41, 4.72 (3-proton singlet), 4.63, 4.92, 4.48, 4.93; δ_{NH} δ 5.65; δ_{NHCOCH_3} 1.89. [g] δ_{CH_2Ph} 4.25, 4.21, ^2J 11.7 Hz; 4.59, 4.66, ^2J 11.7 Hz; 4.76, 4.82, ^2J 11.9 Hz; 4.56, 4.91, ^2J 11.3 Hz; δ_{NH} 5.75; δ_{NHCOCH_3} 1.62. [h] δ_{CH_2Ph} 4.25, 4.40, ^2J 11.5 Hz; 4.54, 4.66, ^2J 12.7 Hz; 4.72s, 4.74, 4.93, ^2J 12.1 Hz; 4.45, 4.97, ^2J 12.1 Hz; 4.40, 5.02, ^2J 10.9 Hz; δ_{NH} 5.77; δ_{NHCOCH_3} 1.79. [i] A resonance due to the NH proton was not observed; δ_{NHCOCH_3} 1.93. [j] δ_{NH} 5.92; δ_{NHCOCH_3} 2.03. [k] δ_{NH} 6.02; δ_{NHCOCH_3} 2.09. [l] δ_{CH_2Ph} 4.50, 4.58, ^2J 11.5 Hz, δ 4.66, 5.06, ^2J 11.5 Hz; δ_{NH} 5.87; δ_{NHCOCH_3} 2.06. [m] A resonance due to the NH proton was not observed; δ_{NHCOCH_3} 1.93. [n] δ_{NH} 5.60; δ_{NHCOCH_3} 2.04. [o] A resonance due to the NH proton was not observed; δ_{NHCOCH_3} 1.72. [p] δ_{CH_2Ph} 4.45, 5.02, ^2J 10.8 Hz, and δ 4.49, 4.63, ^2J 12.1 Hz. [q] δ_{CH_2Ph} 4.29, 4.39, ^2J 12.1 Hz; 4.64, 5.02, ^2J 11.3 Hz; δ_{NH} 5.80; δ_{NHCOCH_3} 2.05. [r] A resonance due to the NH proton was not observed; δ_{NH} 2.04. [s] Not determined due to overlap of signals. [t] δ_{CH_2Ph} 4.35, 5.02, ^2J 9.7 Hz; 5.30, 5.47, ^2J 9.3 Hz.

Table IV. ^{13}C-NMR Chemical Shifts (δ)[a]

compd	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3 ($PhOCH_3$)	$NCOCH_3$
7	98.41	72.25	76.25	73.12	66.59	17.55	55.20	
	99.36	70.66	69.30	71.52	67.38	17.15		
8	101.01	69.97	78.15	71.57	68.72	16.66	54.88	
	102.55	70.29	70.26	72.17	69.22	16.69		
11	90.85	71.33	69.64	67.68	68.77	61.14		
	98.70	70.76	69.17	71.30	67.54	17.40		
13	99.16	75.34	68.50	68.46	66.20	61.79	55.42	
	99.45	70.79	69.51	71.64	67.28	17.56		
14	102.76	74.12	73.25	67.31	70.50	61.22	57.02	
	98.19	71.07	69.55	71.71	67.02	16.97		
15	103.05	77.51	68.64	69.45	70.78	61.34	54.98	
	99.01	70.17	70.25	72.03	69.36	16.84		
16	90.94	71.54	69.36	67.63*	68.61	61.10		
	98.87	71.99	75.90	72.50	67.60*	17.45		
	99.25	70.52	69.28	71.33	67.42	17.05		
19[b]	99.94	75.01	70.78	74.23	62.09	69.17	55.50	
	100.69	70.68	69.43	71.89	67.14	17.51		
21[c]	99.89	75.76	70.30	74.37	62.05	69.15	55.42	
	99.77	72.31	75.76	72.97	67.34	17.66		
	100.78	70.50	69.24	71.46	67.14	16.64		
23	98.91	77.51	68.54	69.42	70.75	61.31	54.96	
	102.84	69.89	78.62	71.27	69.42	16.92		
	102.60	70.26	70.19	72.12	69.26	16.71		
31[d]	98.08	54.14	75.11	78.47	70.12	68.62	54.97	23.23
33[e]	98.48	52.95	76.40	71.14	72.13*	60.90	55.00	23.26
	97.11	75.62	78.01	74.55	72.45*	68.66		
34[f]	98.86	52.16	72.24	82.80	62.38	71.18	55.21	22.81
	97.07	75.42	78.72	75.48	70.72	69.09		
35[g]	98.34	52.24	75.22	79.17	69.96	68.50*	54.92	22.94
	98.57	75.30	79.94	75.10	70.57	71.39*		
37	98.38	52.06	77.50	70.93	71.60	60.45	55.24	22.17
	99.29	68.65	69.40	69.06	70.86	60.58		
38[h]	98.80	53.85	76.78	68.27*	72.66	60.80	54.90	23.44
	104.12	78.73	82.48	73.87*	73.45	68.96		
39[i]	98.69	53.15	81.22	75.28	62.66	69.01	55.24	22.84
	102.92	79.84	82.58	72.94	73.16	68.55		
40[j]	98.30	53.49	77.20	76.69	70.64	68.75	54.92	23.22
	103.48	80.06	82.36	73.61	73.55	68.75		
42	98.35	52.55	80.48	68.78	71.51	60.69	55.27	22.10
	103.61	70.82	72.67	68.68	75.36	61.14		
43	98.78	52.84	78.53	70.28	72.77	60.45	55.10	23.44
	96.63	74.89	68.32	67.11	68.27	60.84		
	98.35	70.94	69.24	71.77	67.77	17.94		
44[k]	99.14	51.46	70.39	83.13	62.39	68.93	55.26	22.89
	96.63	70.90	69.71	72.21	65.59	62.73		
	97.09	71.07	68.71	68.20	67.51	17.41		
45[l]	98.81	51.89	76.58	78.52	70.84	68.61	55.05	23.16
	97.97	73.48	68.98	68.22	66.35	61.93		
	98.30	70.84	69.15	71.80	67.58	17.68		
47	98.26	52.12	74.94	70.96	71.76	60.72	55.22	22.12
	97.64	73.81	69.08	69.52	71.83	60.40		
	101.69	69.97	70.20	72.00	69.33	16.70		
48	98.96	53.09	76.82	68.01	72.51	60.79	55.01	23.46
	101.55	73.00	74.44	67.20	70.00	60.79		
	98.26	70.96	70.00	71.47	66.88	17.08		
49[m]	98.35	53.26	75.72	82.42	62.53	69.20	55.39	22.45
	102.45	79.78	71.03	66.89	70.33	60.71		
	99.71	70.06	69.40	70.81	68.87	17.63		
50[n]	98.61	52.81	77.07	76.89	70.62	68.45	54.95	23.18
	101.26	76.40	73.16	66.98	70.28	60.72		
	99.07	70.71	69.86	71.14	67.56	17.32		
51[o]	98.85	52.09	78.48	77.79	70.69	68.59	55.07	23.29
	98.93	73.69	72.82	68.22	66.70	61.50		
	98.69	72.22	76.09	69.12	67.37	17.29		
	98.93	70.45	69.49	71.44	67.59	17.89		
52	98.27	52.13	75.11	71.79	69.05	60.72	55.23	22.13
	97.68	73.91	71.44	70.97	69.53	60.51		
	101.59	69.73	78.10	71.53	69.44	16.80		
	102.39	70.32	70.22	72.21	69.24	16.82		
53[p]	98.80	52.81	77.20	76.20	70.48	68.43	54.96	23.52
	100.96	72.99	73.77	67.07	70.28	60.56		
	98.01	72.99	75.18	72.80	67.42	17.49		
	99.29	70.53	69.54	71.78	67.07	17.42		

*These assignments may have to be interchanged. [a]Spectra taken at ambient temperature for solutions in $CDCl_3$ using tetramethylsilane as the internal standard, except for compounds 8, 15, 19, 25, 36, 44, and 49, the spectra of which were measured for solution in D_2O using methanol as the internal standard (δ_{MeOH} vs δ_{TMS} 49.0 ppm). [b]δ_{CHPh} 99.72. [c]δ_{CHPh} 99.20. [d]δ_{CH_2Ph} δ 74.76, and 73.46. [e]δ_{CH_2Ph} 73.19 (2 C) and 73.77 (2 C). [f]δ_{CH_2Ph} 74.23, 74.17, 73.82, and 71.67; δ_{CHPh} 101.91. [g]δ_{CH_2Ph} 74.30, 74.17 (2 C), 73.40 (2 C), and 73.06. [h]δ_{CH_2Ph} 74.94, 74.56, 73.71, and 72.76. [i]δ_{CH_2Ph} 74.38 (2 C) 73.48, and 72.34; δ_{CHPh} 101.36. [j]δ_{CH_2Ph} 75.05, 74.90, 74.61, 74.05 (2 C), and 72.78. [k]δ_{CHPh} 101.02. [l]δ_{CH_2Ph} 74.11 and 73.40. [m]δ_{CHPh} 102.09. [n]δ_{CH_2Ph} 73.45 and 74.40. [o]δ_{CH_2Ph} 74.29 and 73.19. [p]δ_{CH_2Ph} 75.00 and 73.44.

was dried at 140 °C. 2-Acetamido-2-deoxy-D-glucose was purchased from Sigma Chemical Co. and used as supplied. 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane and Amberlyst A26 F were purchased from Fluka Chemical Co. and used as supplied. DCMME was purchased from Aldrich Chemical Co. or Fluka Chemical Co. and used as supplied. It is a suspect carcinogen,[43] and all operations involving this reagent should be conducted in a well-ventilated hood. $AgClO_4$ was prepared as previously described.[25]

2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyanosyl Bromide (3). This compound was prepared and crystallized essentially as described.[13] A portion of the mixture of the intermediate 1,2,3,4-tetra-*O*-benzoyl-α- (1) and -β-L-rhamnopyranose (2) was resolved by chromatography (solvent A), to give pure 1, $[\alpha]_D$ +80° (*c* 1.5) (lit.[44] $[\alpha]_D$ +83°), and 2, $[\alpha]_D$ +137° (*c* 1.25) (lit.[44] $[\alpha]_D$ +135°), which were used for the NMR analysis. ^{1}H-NMR data obtained agreed with the literature values.[44]

Methyl 3-*O*-Benzyl-α-L-rhamnopyranoside (4). A mixture of methyl L-rhamnopyranoside[45] (19.6 g, 0.11 M) and dibutyltin oxide (27.5 g, 0.11 M) in toluene (550 mL) was refluxed for 2 h, in a Soxhlet apparatus, with the azeotropic removal of water. CsF[46] (33 g, 0.22 M) was added, and the mixture was concentrated to dryness. Benzyl bromide (26.4 mL, 0.22 M) was added with stirring to a suspension of the residue in DMF (550 mL), and the mixture was stirred at rt for 18 h. After concentration, the residue was partitioned between CH_2Cl_2 and aqueous NaCl solution, and the organic phase was dried and concentrated. Chromatography and crystallization gave 4 (25.7 g, 83%), identical in all respects with the previously described[14] substance; reported yields: lit.[14] 50%; lit.[47] 71%.

Methyl 2,4-Di-*O*-benzoyl-3-*O*-benzyl-α-L-rhamnopyranoside (5). The 3-*O*-benzyl derivative 4 (0.55 g, 2 mmol) was dissolved in pyridine (3 mL), and benzoyl chloride (0.75 mL, 6.45 mmol) was added. The mixture was stirred at rt until TLC (solvent B) showed that the reaction was complete (~3 h). The mixture was processed conventionally, and the crude product was eluted from a column of silica gel (solvent B) to give pure 5 (0.92 g, 95%), which solidified on standing. Crystallization from ethanol or cyclohexane–hexane, followed by recrystallization from 2-propanol, gave material showing mp 67–69 °C and $[\alpha]_D$ +119° (*c* 0.8), $[\alpha]_D$ +116° (*c* 1.1, CH_2Cl_2) (lit.[15] $[\alpha]_D$ +79.5° (*c* 1.58, CH_2Cl_2)) for the amorphous material: CIMS *m/z* 477 $(M + 1)^+$, 494 $(M + 18)^+$. The reported[15,16] NMR data for the independently synthesized substance were confirmed by 2 D NMR spectroscopy.

Anal. Calcd for $C_{28}H_{28}O_7$ (476.50): C, 70.57; H, 5.92. Found: C, 70.47; H, 5.92.

Methyl 2,4-Di-*O*-benzoyl-α-L-rhamnopyranoside (6). A mixture of 5 (2.9 g) and 5% palladium-on-charcoal catalyst (1 g) in EtOH (100 mL) was stirred in a H_2 atmosphere until hydrogen uptake ceased (~3 h). TLC (solvent B) showed that the reaction was complete and that one product was formed. Conventional processing afforded material (2.25 g, 96%) indistinguishable (NMR) from the independently synthesized[16,17] substance.

Methyl *O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (7). A solution of 6 (3.53 g, 9.1 mmol), 3 (6.9 g, 12.8 mmol), and 2,4,6-trimethylpyridine (1.52 mL, 11.5 mmol) in CH_2Cl_2 (50 mL) was added wth stirring at −20 °C to a suspension of AgOTf (3.94 g, 15.4 mmol) in CH_2Cl_2 (50 mL). Cooling was discontinued and, after 15 min, when the mixture became acidic to litmus, TLC (solvent B) showed that the starting materials were no longer present. One major product was formed, together with several very minor ones that resulted from the decomposition and/or side reactions of the starting glycosyl bromide which was used in excess. After filtration through Celite, the material in the filtrate was partitioned between CH_2Cl_2 and a mixture of aqueous solutions of $NaHCO_3$ and sodium thiosulfate. The organic phase was dried, and concentrated, finally at 133 Pa, to remove 2,4,6-trimethylpyridine. Chromatography of the residue gave pure 7 (7.4 g, 95.8%): $[\alpha]_D$ +184° (*c* 0.8); CIMS *m/z* 862 $(M + 18)^+$.

Anal. Calcd for $C_{48}H_{44}O_{14}$ (844.83): C, 68.23; H, 5.24. Found: C, 68.10; H, 5.27.

Methyl *O*-α-L-Rhamnopyranosyl-(1→3)-α-L-rhamnopyranoside (8). MeOH (50 mL) was added to a solution of compound 7 (1.69 g, 2 mmol) in toluene (10 mL), followed by 1 M methanolic sodium methoxide, until the solution became strongly alkaline to litmus. The solution was kept at 50 °C for 16 h. After cooling and neutralization with Amberlite IR 120 (H^+) resin, the solution was concentrated. A solution of the residue in MeOH was slowly added with stirring to ether, and the white precipitate was filtered, washed with ether, and dried at 50 °C to give 0.58 g (89.4%): $[\alpha]_D$ −83° (*c* 0.8, H_2O) (lit.[12] $[\alpha]_D$ −78°).

O-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl Chloride (9). Freshly fused $ZnCl_2$ (~100 mg) was added to solution of 7 (2 g) in $CHCl_3$–DCMME mixture (1:2, 12 mL), and the mixture was stirred under gentle reflux. After 2–3 h, TLC (solvent C) showed that almost all starting material was consumed and that one major product was formed. The mixture was concentrated by coevaporation with toluene and the residue was chromatographed to give pure 9 (1.47 g, 73.5%): $[\alpha]_D$ +157° (*c* 0.7).

Anal. Calcd for $C_{47}H_{41}ClO_{13}$ (849.25): C, 66.46; H, 4.85; Cl, 4.17. Found: C, 66.21; H, 4.85; Cl, 4.32.

O-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (11). A solution of 10 (ref 21, 0.435 g, 1.25 mmol), 2,4,6-trimethylpyridine (0.172 mL, 1.3 mmol), and 3 (0.81 g, 1.5 mmol) in CH_2Cl_2 (10 mL) was treated with a suspension of AgOTf (0.45 g, 1.75 mmol) in CH_2Cl_2 (5 mL), as described for the preparation of 7. TLC (solvent B) showed that both starting compounds reacted completely and that one major product was formed. After conventional processing, the crude product was chromatographed to give pure 11 (0.98 g, 97%). The substance crystallized on standing, and recrystallization from MeOH containing a few drops of CH_2Cl_2 gave material showing mp 181–182 °C and $[\alpha]_D$ +159° (*c* 1).

Anal. Calcd for $C_{41}H_{42}O_{17}$ (806.74): C, 61.03; H, 5.24. Found: C, 60.84; H, 5.20.

O-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl Chloride (12). A mixture of 11 (6.75 g) and DCMME (20 mL) in $CHCl_3$ (20 mL) was treated with $ZnCl_2$ (~100 mg) as described for the preparation of 9. After 1 h, TLC (solvent D) showed that the reaction was complete and that one product was formed. The mixture was processed as described above, and chromatography gave pure 12 (6.3 g, 96%): $[\alpha]_D$ +185° (*c* 1.1); CIMS *m/z* 800 $(M + 18)^+$.

Anal. Calcd for $C_{39}H_{39}ClO_{15}$ (783.15): C, 59,80; H, 5.01; Cl, 4.52. Found: C, 59.74; H, 5.05; Cl, 4.58.

Methyl *O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-3,4,6-tri-*O*-acetyl-α- (13) and -β-D-galactopyranoside (14). Ethereal $AgClO_4$ (0.08M, 18.2 mL, 2.4 mmol) was slowly added at −20 °C to a stirred solution of 12 (0.82 g, 1.05 mmol) and MeOH (56.5 μL, 1.4 mmol) in ether (5 mL). Shortly after the addition was complete (~2 min), the cooling was terminated and the mixture was allowed to warm slowly to room temperature at which it was kept for 30 min. On examination of the reaction mixture by TLC in various solvents, the major product appeared as a spot the shape of which indicated that it might represent two substances showing very close chromatographic mobilities. After concentration to a small volume, the mixture was diluted with CH_2Cl_2 and filtered through Celite, the solids were washed with CH_2Cl_2, and the filtrate was washed with a mixture of aqueous $NaHCO_3$ and sodium thiosulfate solution. The organic phase was dried and concentrated to dryness, and the residue was chromatographed (solvent D). First eluted was a mixture of 13 and 14 highly enriched in 13 (0.16 g). After the intermediate, mixed fraction containing approximately the same amount of both title compounds (0.446 g), a mixture of 13 and 14 highly enriched in 14 (0.165 g, total yield, 95%) was eluted. The enriched fractions were rechromatographed to give pure substances:

13: $[\alpha]_D$ +95° (*c* 0.9).

Anal. Calcd for $C_{40}H_{42}O_{16}$ (778.73): C, 61.69; H, 5.43. Found: C, 61.80; H, 5.51.

14: $[\alpha]_D$ +112° (*c* 0.6).

Anal. Calcd for $C_{40}H_{42}O_{16}$ (778.73): C, 61.69; H, 5.43. Found: C, 62.02; H, 5.70.

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Methyl O-α-L-Rhamnopyranosyl-(1→2)-α-D-galactopyranoside (15). (a) Compound **13** (0.13 g) was deacylated as described for the preparation of **8**. After chromatography of the crude product (solvent E), substance **15** (0.45 g, 79%) crystallized (twice) from ethanol as a hemihydrate, mp 122–127 °C, with evolution of vapors: $[\alpha]_D$ +66° (*c* 0.5, H_2O); CIMS *m/z* 358 (M + 18)$^+$.

Anal. Calcd for $C_{13}H_{24}O_{10}\cdot 0.5H_2O$ (349.33): C, 44.69; H, 7.21. Found: C, 44.49; H, 7.35.

(b) Compound **20**, when treated as described above, gave in a virtually theoretical yield material which, when crystallized from ethanol, melted broadly above 115 °C and was indistinguishable (CIMS, NMR) from **15** described above.

Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl)-(1→2)-3-O-benzoyl-4,6-O-benzylidene-α-D-galactopyranoside (19). A stirred solution of **18** (refs 28 and 29; 0.39 g, 1 mmol), **3** (0.755 g, 1.4 mmol), and 2,4,6-trimethylpyridine (0.166 mL, 1.26 mmol) in CH_2Cl_2 (5 mL) was treated at −20 °C with a suspension of AgOTf (0.411 g, 1.6 mmol) in CH_2Cl_2 (5 mL), as described for the preparation of **7**. The mixture became acidic to litmus after 2 min and, after a total reaction time of 5 min, it was neutralized by addition of 2,4,6-trimethylpyridine. TLC (solvent D) showed that the starting materials were completely converted to one major and several very minor products. After processing, as described above, the crude product was chromatographed to give pure **19** (0.8 g, 94%) as a foam: $[\alpha]_D$ +189° (*c* 1.2); CIMS *m/z* 862 (M + 18)$^+$.

Anal. Calcd for $C_{48}H_{44}O_{14}$ (844.82): C, 68.23; H, 5.24. Found: C, 68.13; H, 5.26.

Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyanosyl)-(1→2)-3-O-benzoyl-α-D-galactopyranoside (20). A solution of **19** (0.5 g) in acetone–MeOH (1:1, 20 mL) was hydrogenolyzed as described for the preparation of **6**. One product was formed, as shown by TLC (solvent F). After conventional processing, the product was eluted from a small column of silica gel, to remove the catalyst debris, to give pure **20** in a virtually theoretical yield: $[\alpha]_D$ +177° (*c* 1.2); CIMS *m/z* 774 (M + 18)$^+$.

Anal. Calcd for $C_{41}H_{40}O_{14}$ (756.73): C, 65.07; H, 5.33. Found: C, 64.85; H, 5.39.

Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl)-(1→3)-(2,4-di-O-benzoyl-α-L-rhamnopyranosyl)-(1→2)-3-O-benzoyl-4,6-O-benzylidene-α-D-galactopyranoside (21). A solution of **9** (1.95 g, 2.3 mmol), **18** (0.888 g, 2.3 mmol), and 2,4,6-trimethylpyridine (0.273 mL, 2.07 mmol) in CH_2Cl_2 (10 mL) was added at −5 °C to a stirred suspension of AgOTf (0.643 g, 2.5 mmol) in CH_2Cl_2 (10 mL). After a total reaction time of 5 min, when the mixture had been slightly acidic for ~3 min, the solution was processed as described for the preparation of **19**. Chromatography (solvent D) gave pure **21** (2.2 g, 79.8%): $[\alpha]_D$ +190° (*c* 1).

Anal. Calcd for $C_{68}H_{62}O_{20}$ (1199.17): C, 68.10; H, 5.71. Found: C, 68.26; H, 5.35.

Methyl O-α-L-Rhamnopyranosyl-O-(1→3)-α-L-rhamnopyranosyl-(1→2)-4,6-O-benzylidene-α-D-galactopyranoside (22) and Methyl O-α-L-Rhamnopyanosyl-(1→3)-O-α-L-rhamnopyranosyl-(1→2)-α-D-galactopyranoside (23). A solution of **21** (1.7 g, 1.4 mmol) was treated as described for the preparation of **8**. The crude product, a crystalline solid, was dissolved in hot acetone–H_2O mixture, the solution was filtered, concentrated to a small volume, and MeOH was added to effect crystallization. A portion of the crystalline **22** (0.15 g, 0.26 mmol) was saved for characterization: mp 290–292 °C; $[\alpha]_D$ +31° (*c* 0.6, H_2O); CIMS *m/z* 592 (M + 18)$^+$.

Anal. Calcd for $C_{26}H_{38}O_{14}$ (574.56): C, 54.35; H, 6.67. Found: C, 54.67; H, 6.79.

The rest of the crystalline **22** was combined with the material that remained in the mother liquor and concentrated. The solution of the residue in 2-methoxyethanol–water (4:1, 50 mL) was hydrogenolyzed as described above, to give one product, as shown by TLC (solvent E). After conventional workup, the crude product was eluted from a column of silica gel (solvent G) to give, after freeze-drying, **23** as a hygroscopic solid (0.45 g, 0.925 mmol, combined yield of **22** and **23**, 1.185 mmol, 84.6%): $[\alpha]_D$ +12° (*c* 1, H_2O); CIMS *m/z* 504 (M + 18)$^+$.

Methyl 2-Acetamido-2-deoxy-4,6-O-isopropylidene-α-D-glucopyranoside (25). 2-Acetamido-2-deoxy-D-glucose was converted[48,49] to methyl 2-acetamido-2-deoxy-α,β-D-glucopyranoside. Acetylation of the foregoing material with acetic anhydride in pyridine gave a product containing two substances readily separable by chromatography, as shown by TLC (solvent A). The faster moving compound, largely preponderating, was methyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranoside, as shown by comparison of ^{1}H-NMR data with those reported:[49] ^{13}C-NMR ($CDCl_3$) δ 98.36 (C-1), 71.37 (C-3), 68.29 (C-4), 67.72 (C-5), 62.11 (C-6), 55.42 (OCH_3), 51.91 (C-2), 23.15 ($NHCOCH_3$). The slower moving material was methyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranoside: CIMS *m/z* 362 (M + 1)$^+$, 379 (M + 18)$^+$; ^{1}H-NMR ($CDCl_3$) δ 5.84 (bd, 1 H, $J_{2,NH}$ 8.6 Hz, N*H*), 5.29, t, 1 H, $J_{2,3} = J_{3,4}$ 9.5 Hz, H-3), 5.08 (t, 1 H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 4.61 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 4.28 (dd, 1 H, $J_{5,6a}$ 4.7 Hz, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.14 (dd, 1 H, $J_{5,6b}$ 2.3 Hz, H-6b), 3.89 (dt, 1 H, H-2), 3.73 (ddd, 1 H, H-5), 3.50 (s, 3 H, OCH_3), 2.09, 2.04, 2.03, 1.96 (4 × s, 4 × 3 H, 4 × $COCH_3$); ^{13}C-NMR ($CDCl_3$) δ 101.64 (C-1), 72.56 (C-3), 71.88 (C-5), 68.83 (C-4), 62.23 (C-6), 56.71 (OCH_3), 54.61 (C-2), 23.26 ($NHCOCH_3$).

The foregoing methyl α-glycoside was deacetylated conventionally (Zemplén) to give chromatographically pure **24** whose ^{13}C-NMR data agreed with those reported;[50] mp 195–196 °C (from MeOH–acetone); $[\alpha]_D$ +127° (*c* 1, H_2O) (lit.[51] mp 187–188 °C; $[\alpha]_D$ +131°). Mps in the range of 188–191 °C and $[\alpha]_D$ values between 103 and 133° have been reported[49,52] for other preparations of **24**.

A mixture of **24** (0.47 g, 2 mmol), 2,2-dimethoxypropane (0.5 mL), and camphorsulfonic acid (~5 mg) in DMF (3 mL) was stirred for 16 h at rt. TLC (solvent F) showed that little starting material remained and that one product was formed. Aqueous $NaHCO_3$ was added, and the solvents were removed at 40 °C/133Pa. Chromatography of the residue gave pure **27** (0.4 g, 73%): CIMS *m/z* 276 (M + 1)$^+$. The compound formed a gel on concentration, but when a concentrated solution of **27** in ethanol was allowed to evaporate slowly at room temperature some crystalline material separated. It was collected and, after drying at 60 °C, it melted unsharply within 169–174 °C. The compound was recrystallized from MeOH–ether and dried at 110 °C to give material showing mp 173–174 °C, $[\alpha]_D$ +60° (*c* 0.5).

Anal. Calcd for $C_{12}H_{21}NO_6$ (275.29): C, 52.30; H, 7.68; N, 5.08. Found: C, 52.25; H, 7.69; N, 5.08.

Methyl 2-Acetamido-2-deoxy-4,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-glucopyranoside (26). 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (10 mL, 32 mmol) was added with the exclusion of atmospheric moisture to a stirred solution of **24** (4.7 g, 20 mmol) in pyridine (60 mL), while the reaction flask was immersed in an ice–H_2O mixture. Stirring was continued for 18 h, while the ice was allowed to melt. After concentration, the crude product was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ solution, and the organic phase was dried and concentrated at 40 °C/133Pa to give a solid residue. Crystallization from CH_2Cl_2–ether (twice) gave 7.24 g of pure **26**: mp 194–195 °C; $[\alpha]_D$ +24° (*c* 0.8); CIMS *m/z* 478 (M + 1)$^+$. Chromatography of the material that remained in the mother liquor afforded a further crop of the same substance (1.41 g, total yield 90%).

Anal. Calcd for $C_{21}H_{43}NO_7Si_2$ (477.75): C, 52.79; H, 9.07; N, 2.93. Found: C, 52.66; H, 9.01; N, 2.92.

Methyl 2-Acetamido-4,6-O-benzylidene-2-deoxy-3-O-(p-methoxybenzyl)-α-D-glucopyranoside (28). Methyl 2-acetamido-2-deoxy-α,β-D-glucopyranoside, obtained as described above, was converted[48] to methyl 2-acetamido-3-O-acetyl-4,6-O-benzylidene-2-deoxy-α,β-D-glucopyranoside. Chromatography (solvent F) gave pure 2-acetamido-3-O-acetyl-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside: mp 214–215 °C (lit.[48] mp 211–212 °C); ^{1}H-NMR data agreed with those reported;[48] ^{13}C-NMR ($CDCl_3$) δ 101.63 (C_6H_5CH), 99.10 (C-1), 79.07 (C-4), 70.37 (C-3), 68.93 (C-6), 62.83 (C-5), 55.34 (OCH_3), 52.65 (C-2), 23.17 ($NHCOCH_3$), 20.87 ($OCOCH_3$). To the solution of the

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foregoing acetyl derivative (13.3 g) in MeOH (700 mL) was added wet[53] Amberlite IRA 400 (OH^--form). The mixture was stirred until TLC (solvent F) showed that the deacetylation was complete (~4 h), while gentle heating (~40 °C) was applied to keep the carbohydrate components in solution. The mixture was filtered, the resin was washed with hot MeOH, and the filtrate was concentrated to give **27**, in virtually theoretical yield. The material was sufficiently pure for the next step. A portion, when recrystallized from MeOH, showed mp 258–260 °C lit.[52] mp 261–262 °C; lit.[54] mp 258–260 °C): ^{1}H-NMR ($CDCl_3$) δ 5.87 (bd, 1 H, $J_{2,NH}$ 8.4 Hz, NH), 5.56 (s, 1 H, PhC*H*), 4.72 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.32–4.25 (m, 1 H, H-6a), 4.21 (dd, partially overlapped, H-2), 3.90 (dt, 1 H, $J_{3,OH}$ 3.1 Hz, H-3), 3.84–3.72 (m, 2 H, H-5,6b), 3.40 (s, 3 H, OCH_3), 3.05 (d, 1 H, OH), 2.06 (s, 3 H, $NCOCH_3$); ^{13}C-NMR ($CDCl_3$) δ 101.97 (C_6H_5CH), 98.79 (C-1), 82.09 (C-4), 70.77 (C-3), 68.83 (C-6), 62.32 (C-5), 55.26 (OCH_3), 54.08 (C-2), 23.30 ($NHCOCH_3$).

Powdered KOH (4 g), followed by *p*-methoxybenzyl chloride (5.4 mL, 40 mmol), was added to a solution of **27** (8.7 g, 27 mmol) in dimethyl sulfoxide (100 mL) contained in a 1-L flask equipped with a mechanical stirrer. The mixture was stirred at room temperature for 1 h during which time the product **28** almost completely crystallized. Water (500 mL) was added, and the stirring was continued for 10 min. The product was filtered off and washed with H_2O until the washings were neutral and then with ether (thrice). The material obtained after drying (10.53 g, 88%) was sufficiently pure for the next step. A portion was recrystallized from ethanol to give needles: mp 245–247 °C; $[\alpha]_D$ +110° (*c* 0.9); CIMS *m/z* 444 $(M + 1)^+$, 461 $(M + 18)^+$.

Anal. Calcd for $C_{24}H_{29}NO_7$ (443.48): C, 64.99; H, 6.59; N, 3.15. Found: C, 65.04; H, 6.63; N, 3.16.

Methyl 2-Acetamido-2-deoxy-3-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (29). A suspension of **28** (13 g) in 1% methanolic iodine (260 mL) was heated under reflux. A clear solution was obtained after 3–4 h and, after 6 h, TLC (solvent F) showed that the reaction was essentially complete and that one major product was formed. Solid $NaHCO_3$ (2 g) was added, and the solution was decolorized with 5% aqueous sodium thiosulfate solution. MeOH was evaporated, and the separated solid product was collected by filtration and washed with H_2O. The filtrate, combined with the washings, was extracted several times with $CHCl_3$, and the chloroform solution was combined with the bulk of the product. Chromatography gave pure **29** (8.9 g, 85.5%). A portion was dissolved in MeOH, and toluene was added. After concentration to remove almost all MeOH, the compound crystallized. The material was washed with toluene and ether to give, after drying, the analytical sample: mp 177–179 °C; $[\alpha]_D$ +89° (*c* 0.75, MeOH).

Anal. Calcd for $C_{17}H_{25}NO_7$ (355.38): C, 57.45; H, 7.09; N, 3.94. Found: C, 57.36; H, 7.11; N, 3.89.

Methyl 2-Acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(*p*-methoxybenzyl)-α-D-glucopyranoside (30). Powdered KOH (13 g) followed by benzyl bromide (9 mL, 78 mmol) was added to a solution of **29** (8.9 g, 26.5 mmol) in DMSO (85 mL). The mixture was stirred mechanically at room temperature. It thickened shortly and, after 4 h, it was diluted with H_2O (600 mL) and filtered, the solids were washed three times each with H_2O and hexane, and the washings were discarded. Recrystallization from ethanol gave pure **30** (10.25 g), and a further crop (1 g; total yield, 79.2%) of the same substance was obtained by chromatography of the material that remained in the mother liquor: mp 184–185 °C; $[\alpha]_D$ +86° (*c* 1.3).

Anal. Calcd for $C_{31}H_{37}NO_7$ (535.61): C, 69.51; H, 6.96; N, 2.61. Found: C, 69.62; H, 7.00; N, 2.63.

Methyl 2-Acetamido-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (31). To a stirred solution of **30** (10.3 g, 19.2 mmol) in acetonitrile–H_2O (9:1, 100 mL) was added CAN (21.15 g, 38.6 mmol), and the resulting solution was stirred at room temperature for 20 min, when TLC (solvent F) showed that the reaction was complete. The mixture was worked up as described,[36] and the crude product was chromatographed to give the title substance (7.65 g, 95%). The analytical sample was obtained by recrystallization of a portion from acetone–hexane, mp 140–141 °C, $[\alpha]_D$ +50° (*c* 0.6).

Anal. Calcd for $C_{23}H_{29}NO_7$ (415.47): C, 66.48; H, 7.03; N, 3.37. Found: C, 66.35; H, 7.04; N, 3.36.

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α- (33) and -β-D-galactopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-glucopyranoside (38). (a) An ethereal solution of $AgClO_4$ (0.08 M, 15 mL, 1.2 mmol) was added slowly at room temperature to a stirred solution of **26** (0.24 g, 0.5 mmol), **32**[37] (0.56 g, 1 mmol), and 2,4,6-trimethylpyridine (0.185 mL, 1.4 mmol) in CH_2Cl_2 (5 mL). After 24 h, TLC (solvent D) showed that the mixture contained several products and a large amount of unchanged **26**, but the glycosyl donor was no longer present. The mixture was filtered through Celite, the solids were washed with CH_2Cl_2, and the combined filtrates were washed with aqueous sodium thiosulfate solution. The organic phase was dried and concentrated, and the residue was chromatographed. The two substances showing mobilities closest to but faster than that of the unchanged **26** were isolated. The faster of these two was the desired α-linked product **33** (0.125 g, 25%): mp 83–84 °C (from hexane); $[\alpha]_D$ +63° (*c* 1.2); FABMS *m/z* 968 $(M - 31)^+$, 1000 $(M + 1)^+$, 1022 $(M + Na)^+$, 1038 $(M + K)^+$.

Anal. Calcd for $C_{55}H_{77}NO_{12}Si_2$ (1000.35): C, 66.03; H, 7.75; N, 1.40. Found: C, 65.82; H, 7.76; N, 1.39.

The material eluted next was the β-linked disaccharide **38** (0.045 g, 9%): mp 113–114 °C (from hexane); $[\alpha]_D$ +50° (*c* 1); FABMS *m/z* 968 $(M - 31)^+$, 1000 $(M + 1)^+$, 1022 $(M + Na)^+$, 1038 $(M + K)^+$.

Anal. Calcd for $C_{55}H_{77}NO_{12}Si_2$ (1000.35): C, 66.03; H, 7.75; N, 1.40. Found: C, 65.86; H, 7.80; N, 1.37.

(b) A solution of **32**[37] (3.36 g, 6 mmol) in CH_2Cl_2 (50 mL) was added slowly, at room temperature, to a stirred suspension of **26** (1.43 g, 3 mmol), $AgClO_4$ (1.25 g, 6 mmol, and 2,4,6-trimethylpyridine (0.86 mL, 6.5 mmol) in CH_2Cl_2 (25 mL). After 1 h, TLC showed that both starting materials were consumed and that two major products, which cochromatographed with **33** and **38**, were formed. The mixture was processed as described above and chromatographed to give **40** (1.8 g, 60%) and **34** (0.93 g, 31%).

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α- (34)- and -β-D-galactopyranosyl)-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (39). A solution of the glycosyl chloride **32**[37] (3.36 g, 6 mmol) in CH_2Cl_2 (20 mL), followed by ethereal $AgClO_4$ (0.08 M, 80 mL, 6.4 mmol), was added with stirring at room temperature to a solution of compound **27** (0.97 g, 3 mmol) in CH_2Cl_2 (250 mL) containing 2,4,6-trimethylpyridine (0.85 mL, 6.4 mmol). The mixture was stirred for 18 h, when TLC (solvent G) showed that both starting materials were consumed and that two major products were formed. The mixture was worked up as described above, and chromatography gave first **34** (1.77 g, 70%) mp 147–148 °C (from ethanol), $[\alpha]_D$ +58° (*c* 0.8); CIMS *m/z* 846 $(M + 1)^+$, 863 $(M + 18)^+$.

Anal. Calcd for $C_{50}H_{55}NO_{11}$ (845.95): C, 70.98; H, 6.55; N, 1.65. Found: C, 70.77; H, 6.57; N, 1.63.

Eluted next was **39** (0.56 g, 22%): mp 179–181 °C (from CH_2Cl_2–MeOH), $[\alpha]_D$ +32° (*c* 1); CIMS *m/z* 846 $(M + 1)^+$, 863 $(M + 18)^+$.

Anal. Calcd for $C_{50}H_{55}NO_{11}$ (845.95): C, 70.98; H, 6.55; N, 1.65. Found: C, 70.82; H, 6.61; N, 1.62.

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α- (35)- and -β-D-galactopyranosyl)-(1→3)-2-acetamido-4,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside (40). (a) A solution of **31** (0.208 g, 0.5 mmol), **32**[37] (0.42 g, 0.75 mmol), 2,4,6-trimethylpyridine (0.11 mL, 0.8 mmol) in CH_2Cl_2 (5 mL) was treated with ethereal $AgClO_4$ (0.08 M, 10 mL, 0.8 mmol), as described above. After 1 h, TLC (solvent D) showed that the reaction was complete and that two major products were formed. The mixture was processed conventionally, and chromatography afforded **35** (0.285 g, 61%): mp 104–105 °C (from ethanol); $[\alpha]_D$ +65° (*c* 0.7); CIMS *m/z* 906 $(M - 31)^+$, 938 $(M + 1)^+$, 955 $(M + 18)^+$.

Anal. Calcd for $C_{57}H_{63}NO_{11}$ (938.08): C, 72.97; H, 6.76; N, 1.49. Found: C, 72.81; H, 6.77; N, 1.44.

Subsequently eluted was the amorphous β-linked isomer **40** (0.131 g, 28%), $[\alpha]_D$ +55° (*c* 1.3); CIMS *m/z* 906 $(M - 31)^+$, 938 $(M + 1)^+$, 955 $(M + 18)^+$.

Anal. Calcd for $C_{57}H_{63}NO_{11}$ (938.08): C, 72.97; H, 6.76; N, 1.49. Found: C, 72.88; H, 6.77; N, 1.48.

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(b) Finely powdered **31** (0.831 g, 2 mmol) was dissolved in ether (500 mL). With stirring, a solution of **32**[37] (1.68 g, 3 mmol) and 2,4,6-trimethylpyridine (0.462 mL, 3.5 mmol) in ether (10 mL) followed by ethereal $AgClO_4$ (0.08 M, 37.5 mL, 3 mmol) was added. After 24 h, TLC (solvent D) showed that **32** was all consumed and that only a trace of **31** remained. After concentration to a small volume, CH_2Cl_2 was added to the residue, and the mixture was processed as described above. Chromatography yielded **35** (1.25 g, 67%) and **40** (0.39, 21%), identical (NMR) with compounds described above.

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (36). A stirred suspension of the fully protected disaccharide **33** (1 g) and Amberlyst A26 F (5 g) in acetonitrile–H_2O (10:1, 22 mL) was heated at 90 °C for 24 h, when TLC (solvent F) showed that the reaction was essentially complete. The mixture was filtered through Celite, and the solids were washed with hot acetonitrile. The filtrate combined with the washings was concentrated to give a solid residue. Crystallization (twice) from ethanol gave pure **36** (0.53 g). A further crop of the same substance (0.15 g, total yield, 90%) was obtained by chromatography of the material that remained in the mother liquor: mp 178–179 °C; $[\alpha]_D$ +75° (*c* 1); CIMS *m/z* 758 $(M + 1)^+$, 775 $(M + 18)^+$.

Anal. Calcd for $C_{43}H_{51}NO_{11}$ (757.83): C, 68.14; H, 6.78; N, 1.84. Found: C, 68.05; H, 6.65; N, 1.86.

Methyl *O*-α-D-Galactopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (37). (a) Compound **33** (1 g) was treated as described above for the preparation of **36**. A solution of the crude product in MeOH (70 mL) was stirred overnight at room temperature in a hydrogen atmosphere, at atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (0.5 g). The mixture was processed conventionally, and the crude product was eluted from a column of silica gel (solvent E) to give **37** as a white, hygroscopic solid (0.34 g, 85%): $[\alpha]_D$ +161° (*c* 0.8, H_2O); CIMS *m/z* 398 $(M + 1)^+$.

(b) Hydrogenolysis of **34** or **35**, as described above, gave in virtually theoretical yield material indistinguishable (MS, NMR, and $[\alpha]_D$) from the substance **37** described above.

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (41). Compound **38** (0.25 g) was treated with Amberlyst A26 F, essentially as described for the preparation of **36**. The product was crystallized from MeOH containing a few drops of CH_2Cl_2 and recrystallized from acetone to give **41** (0.145 g, 76.5%): mp 203–205 °C (sint. 199 °C); $[\alpha]_D$ +69° (*c* 0.5); CIMS *m/z* 758 $(M + 1)^+$.

Anal. Calcd for $C_{43}H_{51}NO_{11}$ (757.83): C, 68.14; H, 6.78; N, 1.84. Found: C, 68.05; H, 6.78; N, 1.82.

Methyl *O*-β-D-Galactopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (42). Compound **38** (0.25 g) was treated as described above for the preparation of **36**, and a solution of the crude product in MeOH (70 mL) was hydrogenolyzed as described for the preparation of **37** to give **42** (74 mg, 74.5%): mp 255–256 °C, $[\alpha]_D$ +67°; CIMS *m/z* 398 $(M + 1)^+$ (lit.[55] mp 236–239 °C, $[\alpha]_D$ +57°, for a monohydrate; lit.[56] mp 247–249 °C, $[\alpha]_D$ 86°).

Anal. Calcd for $C_{15}H_{27}NO_{11}$ (397.36): C, 45.33; H, 6.84; N, 3.45. Found: C, 45.17; H, 6.80; N, 3.45.

Methyl *O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-acetyl-α- (43) and -β-D-galactopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-glucopyranoside (48). (a) A solution of **26** (0.24 g, 0.5 mmol), **12** (0.39 g, 0.5 mmol), and 2,4,6-trimethylpyridine (0.092 mL, 0.7 mmol) in CH_2Cl_2 (10 mL) was added at room temperature to a stirred suspension of $AgClO_4$ (0.125 g, 0.6 mmol) in CH_2Cl_2 (5 mL). After 24 h, TLC (solvent D) showed that the glycosyl donor was all consumed. TLC (solvent B) showed that a large amount of **26** was still present and that several products were formed. The reaction mixture was processed as described above and chromatographed. The two products showing closest chromatographic mobility to but faster than **26** were isolated. The one eluted first exhibited spectral data consistent with its being the β-linked trisaccharide **48** (12 mg, 2%): FABMS *m/z* 1224 $(M + 1)^+$, 1246 $(M + Na)^+$.

Eluted next was the desired α-linked product **43** (92 mg, 15%): $[\alpha]_D$ +98° (*c* 1.1); FABMS *m/z* 1224 $(M + 1)^+$, 1246 $(M + Na)^+$, 1262 $(M + K)^+$.

Anal. Calcd for $C_{60}H_{81}NO_{22}Si_2$ (1224.44): C, 58.85; H, 6.66; N, 1.14. Found: C, 58.92; H, 6.67; N, 1.19.

(b) When synthons in a were allowed to react for 24 h in the manner described above for the preparation of **33** (a), TLC showed that only very little of **43** and only a trace of **48** were formed (Table II).

(c) A solution of **26** (0.24 g, 0.5 mmol) and **12** (0.39 g, 0.5 mmol) in toluene–nitromethane (10:1) was concentrated to ~3 mL. Mercuric cyanide (65 mg, 0.25 mmol) and mercuric bromide (~20 mg) was added, and the mixture was stirred, at 60 °C, with the exclusion of moisture for 10 days, when TLC showed that all **12** was consumed and that a large amount of unchanged **26** remained. The mixture was filtered, the filtrate was concentrated, and the solution of the residue in dichloromethane was washed with aqueous KBr solution, the organic phase was concentrated, and chromatography yielded **48** (4.4 mg, 0.7%) and **43** (87.5 mg, 14.3%).

Methyl *O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-acetyl-α- (44) and -β-D-galactopyranosyl)-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (49). Ethereal $AgClO_4$ (0.08 M, 15 mL, 1.2 mmol) was added at rt to a stirred solution of **27** (0.323 g, 1 mmol), **12** (0.783 g, 1 mmol), and 2,4,6-trimethylpyridine (0.15 mL, 1.13 mmol) in CH_2Cl_2 (100 mL). After 18 h, TLC (solvent H) showed that all of **12** was consumed and that some unchanged **27** was still present. The two products showing chromatographic mobility closest to, but faster than, **27** were isolated by chromatography of the crude product, obtained after the reaction mixture had been processed as described above. First eluted was the β-linked trisaccharide **49** (75 mg, 7%): $[\alpha]_D$ +68° (*c* 0.9); FABMS *m/z* 1070 $(M + 1)^+$, 1092 $(M + Na)^+$, 1108 $(M + K)^+$.

Anal. Calcd for $C_{55}H_{59}NO_{21}$ (1070.03): C, 61.73; H, 5.55; N, 1.30. Found: C, 61.49; H, 5.58; N, 1.35.

Eluted next was the desired trisaccharide **44** (602 mg, 56.3%): $[\alpha]_D$ +91° (*c* 0.9); FABMS *m/z* 1070 $(M + 1)^+$, 1092 $(M+ Na)^+$, 1108 $(M + K)^+$. The NMR spectral data were consistent with the anticipated structure. The substance tenaciously retained residual solvent and elemental analysis within ±0.4% could not be obtained.

Methyl *O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-*O*-(3,4,6-tri-*O*-acetyl-α- (45) and -β-D-galactopyranosyl)-(1→3)-2-acetamido-4,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (50). (a) A solution of **31** (0.208 g, 0.5 mmol), **12** (0.392 g, 0.5 mmol), and 2,4,6-trimethylpyridine (80 μL, 0.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise at rt to a stirred suspension of $AgClO_4$ (140 mg, 0.67 mmol). After 4 h, TLC (solvent B) showed that the glycosyl donor **12** was consumed and that several products were formed, but that a large amount of unchanged nucleophile **31** remained. The mixture was worked up as described above for similar preparations, and the crude product was chromatographed to isolate two substances that showed chromatographic mobility closest to, but faster than **31**. Isolated first was **50** (45 mg, 7.8%): $[\alpha]_D$ +75° (*c* 0.6); FABMS *m/z* 1162 $(M + 1)^+$, 1184 $(M + Na)^+$, 1200 $(M + K)^+$.

Anal. Calcd for $C_{62}H_{67}NO_{21}$ (1162.16): C, 64.07; H, 5.81; N, 1.20. Found: C, 63.96; H, 5.85; N, 1.20.

Subsequently eluted was the desired, α-linked trisaccharide **45** (276 mg, 47.5%): $[\alpha]_D$ +109° (*c* 1.1); FABMS *m/z* 1162 $(M + 1)^+$, 1184 $(M + Na)^+$, 1200 $(M + K)^+$.

Anal. Calcd for $C_{62}H_{67}NO_{21}$ (1162.16): C, 64.07; H, 5.81; N, 1.20. Found: C, 64.13; H, 5.76; N, 1.21.

(b) Ethereal $AgClO_4$ (0.08 M, 20 mL, 1.6 mmol) was added at rt to a stirred solution of **31** (0.52 g, 1.25 mmol), **12** (0.978 g, 1.25 mmol), and 2,4,6-trimethylpyridine (0.2 mL, 1.5 mmol) in CH_2Cl_2 (75 mL). Stirring was continued for 18 h, and the mixture was worked up as described above. Chromatography of the crude product afforded **50** (110 mg, 7.6%) and **45** (0.65 g, 44.8%), indistinguishable (NMR) from the compounds described above.

(c) A reaction performed on the same scale using ether (310 mL) as the solvent, in the manner described for the preparation of **35** (b), yielded, after chromatography, **50** (11 mg, 0.75%) and **45** (0.53 g, 36.5%), indistinguishable (NMR) from the compounds described above.

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Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl)-(1→2)-O-(3,4,6-tri-O-acetyl-α-D-galactopyranosyl)-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (46) and Methyl O-α-L-Rhamnopyranosyl-(1→2)-O-α-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (47). A solution of the fully protected trisaccharide **45** (1 g, 0.86 mmol) in MeOH (50 mL) was hydrogenolyzed, as described above. A portion of the crude product was eluted from a column of silica gel (solvent F) to give **46** (0.17 g, 0.173 mmol): mp 210–211 °C (from ethanol), $[\alpha]_D$ +175° (*c* 0.6); FABMS *m/z* 982 $(M + 1)^+$, 1004 $(M + Na)^+$, 1020 $(M + K)^+$.

Anal. Calcd for $C_{48}H_{55}NO_{21}$ (981.92): C, 58.70; H, 5.64; N, 1.42. Found: C, 58.74; H, 5.70; N, 1.39.

The rest of the material was deacylated, as described above for the preparation of **15**. The crude product was eluted from a column of silica gel (solvent E) to afford, after freeze-drying, **47** (0.32 g, 0.59 mmol, total yield based on **45**, 88%) as a white hygroscopic solid: $[\alpha]_D$ +98° (*c* 0.7, H_2O); FABMS *m/z* 544 $(M + 1)^+$, 566 $(M + Na)^+$, 582 $(M + K)^+$.

Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl)-(1→3)-O-(2,4-di-O-benzoyl-α-L-rhamnopyranosyl)-(1→2)-O-(3,4,6-tri-O-acetyl-α-D-galactopyranosyl)-(1→3)-2-acetamido-4,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside (51). Compound **17** (1.138 g, 1 mmol), **31** (0.416 g, 1 mmol), 2,4,6-trimethylpyridine (0.15 mL, 1.13 mmol), and $AgClO_4$ (0.08 M, 14 mL, 1.12 mmol) were allowed to react as described for the preparation of **35** (b). After conventional processing, as described above, the crude product was chromatographed (solvent B) to isolate two substances that showed chromatographic mobility closest to but faster than **31**. The material eluted first showed spectral data consistent with its being the β-linked substance **53** (14 mg, 0.9%): FABMS *m/z* 1516 $(M + 1)^+$.

Eluted next was the target tetrasaccharide **51** (0.52 g, 34.3%): $[\alpha]_D$ +158° (*c* 0.9); FABMS *m/z* 1516 $(M + 1)^+$, 1538 $(M + Na)^+$, 1555 $(M + K)^+$.

Anal. Calcd for $C_{82}H_{85}NO_{27}$ (1516.51): C, 64.93; H, 5.64; N, 0.92. Found: C, 65.22; H, 5.77; N, 0.87.

Methyl O-α-L-Rhamnopyranosyl-(1→3)-O-α-L-rhamnopyranosyl-(1→2)-O-α-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (52). A solution of **51** (0.42 g) in 2-methoxyethanol (50 mL) was stirred in a hydrogen atmosphere at rt for 16 h. The mixture was processed as before, and to the solution of the crude product in MeOH (50 mL) was added M sodium methoxide in MeOH until the solution was strongly alkaline to litmus. After 16 h at 50 °C and conventional processing, the crude product was chromatographed (solvent E). Solutions of the purified material were made successively in MeOH and H_2O, and each of the solutions was filtered through a syringe membrane filter (pore size, 0.2 μm). After freeze-drying, compound **52** was obtained (168 mg, 88%) as a white, hygroscopic solid, $[\alpha]_D$ +52° (*c* 1.4, H_2O); FABMS *m/z* 690 $(M + 1)^+$, 712 $(M + Na)^+$, 770 $(M + K)^+$.

Supplementary Material Available: ^{13}C-NMR spectra of compounds **23**, **37**, **44**, **47**, and **52** and Tables SI, SII (extension of Tables III and IV, containing complete sets of ^1H- and ^{13}C-NMR chemical shifts for compounds **1–17**, **19–23**, **25**, **27–31**, **33–40**, and **42–53**), and SIII (containing ^1H-NMR coupling constants) (18 pages). Ordering information is given on any current masthead page.

Notes

Unprecedented Tandem Michael–Ene Reaction of 2-Formylcyclohexa-2,5-dienone and Subsequent Unusual Autoxidation

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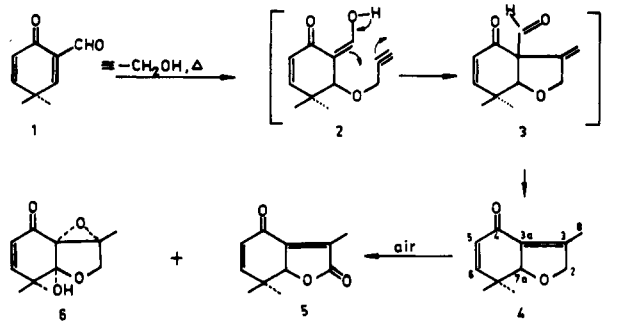
Intramolecular ene reactions of unsaturated carbonyl compounds have been widely used in the synthesis of an enormous variety of monocyclic, bicyclic, and bridged compounds.[1,2] The carbonyl group serves either as the enophile or, via its enol tautomer, as the ene unit. The pronounced enolic character of β-dicarbonyl compounds allows ene cyclization at temperatures as low as 200 °C.[3] We report herein an unprecedented one-pot heteroannulation through the tandem Michael–ene reaction of 2-formyl-4,4-dimethylcyclohexa-2,5-dien-1-one (**1**)[4] with propargyl alcohol.

A toluene solution of **1** and an excess of propargyl alcohol (10 equiv) was heated in a sealed tube for 4 h at 160–165 °C. Silica gel column chromatographic purification of crude products gave nonpolar liquid product **4** (67%), in addition to the dipropargyl acetal of **1** (10%). In the ^1H-NMR spectrum of **4**, the signal at 2.12 (3 H, six-line multiplet) indicates the presence of a methyl group situated on the β-carbon atom of an α,β-enone. The multiplicity of this signal is due to long-range coupling between H-8 and H-2, in addition to expected homoallylic coupling[5] between H-8 and H-7a. The signals for geminally coupling C-2 methylene protons appear at δ 4.75 (ddq, 1 H, *J* = 1.4, 4.3, 14.8 Hz) and 4.64 (ddq, 1 H, *J* = 1.2, 6.2, 14.8 Hz). The observed multiplicity of these signals confirms the coupling between H-2 and H-8. The signal for H-7a appears at δ 4.90 as a nine-line multiplet, which is due to the long-range homoallylic coupling between H-7a

Scheme I



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