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IMPROVED PREPARATIONS OF SOME PER-*O*-ACETYLATED ALDOHEXOPYRANOSYL CYANIDES*

ROBERT WALTER MYERS** AND YUAN CHUAN LEE***
Department of Biology and the McCollum-Pratt Institute, The Johns Hopkins University, Baltimore, Maryland 21218 (U.S.A.)

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ABSTRACT

3,4,6-Tri-*O*-acetyl-1,2-*O*-[1-(*exo*-, *endo*-cyano)ethylidene]-α-D-galacto- (**1a/b**), -α-D-gluco- (**2a/b**), and -β-D-manno-pyranose (**3a/b**) were stereoselectively isomerized to the corresponding per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides in 75, 16, and 62% yield, respectively, by treatment with boron trifluoride etherate in dry nitromethane. The corresponding per-*O*-acetylated 1,2-*cis*-aldohexopyranosyl cyanides were obtained concurrently in respective yields of 1.9, 0.9, and 4.8%. The per-*O*-acetylaldohexopyranosyl cyanide products were found stable to the reaction conditions and were readily isolated following completion of the rearrangement. It had previously been proved that reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-manno- and -gluco-pyranosyl bromide with mercuric cyanide in nitromethane generates, in the ratio of ~1:1, the desired 1,2-*trans*-glycosyl cyanides and the corresponding 1,2-*O*-(1-cyanoethylidene) isomers (**3a/b** and **2a/b**, respectively). Treatment of these reaction-mixtures with boron trifluoride etherate in nitromethane effected the rearrangement of **3a/b** and **2a/b**, thereby facilitating the isolation, and increasing the overall yields, of the per-*O*-acetylated 1,2-*trans*-D-manno- and -gluco-pyranosyl cyanides (58 and 30% total yield, respectively) relative to the earlier procedures. The boron trifluoride etherate-mediated reaction of per-*O*-acetyl-α- and -β-D-galacto-, -α- and -β-D-gluco-, -α-D-manno-, and -2-deoxy-2-phthalimido-β-D-gluco-pyranoses with trimethylsilyl cyanide in nitromethane was also investigated. This reaction provides a "one-flask" synthesis of the corresponding per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides in which 1,2-*O*-(1-cyanoethylidene) derivatives are isomerized *in situ*. Finally, improved preparations of the (not readily accessible) per-*O*-acetylated 1,2-*cis*-D-manno- and

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**Supported by NIH National Research Service Award GM 07231. Current address: Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254, U.S.A.
***To whom all correspondence should be addressed.

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-gluco-pyranosyl cyanides are described. Thus, 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-mannopyranosyl cyanide (48 and 16% total yield, respectively) and -α- and -β-D-glucopyranosyl cyanide (12 and 39% total yield, respectively) were synthesized by fusion of the corresponding α-D-glycosyl bromides with mercuric cyanide.

INTRODUCTION

In an earlier article[2], we described the synthesis and characterization of the anomeric pairs of the per-*O*-acetylaldohexopyranosyl cyanides of D-galactose, L-fucose, D-glucose, and D-mannose, as well as 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl cyanide. These compounds were prepared *via* reaction of the corresponding, readily available, per-*O*-acetylaldohexopyranosyl bromides with mercuric cyanide in nitromethane. In the products of these *C*-glycosylation reactions, 1,2-*trans*-glycosyl cyanides preponderated over the corresponding 1,2-*cis* anomers, in part because glycosyl bromides having a neighboring-group-active substituent (*i.e.*, acetoxyl or phthalimido) at C-2 were used. Unfortunately, per-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene]aldohexopyranoses, resulting from cyanide ion attack on the dioxolanium carbon atom of a 1,2-acetoxonium ion intermediate, were also products of some of these reactions. In certain instances, co-production of these acetals, which are stable to the reaction conditions employed, significantly lowered the yields of the desired glycosyl cyanides, or complicated their isolation, or both.

A parallel between these results and the well documented production of per-*O*-acyl-1,2-*O*-(1-alkoxy-ethylidene and -benzylidene)glycose (1,2-orthoesters) *via* reaction of per-*O*-acylglycosyl halides with alcohols and other alkoxyl donors in neutral or basic media (conditions of kinetic control)[3] was obvious. Moreover, the chemistry of 1,2-*O*-(1-cyanoethylidene)glycoses was expected to be analogous to that of 1,2-orthoesters. Carbohydrate 1,2-orthoesters can be converted stereoselectively into 1,2-*trans*-glycosides by treatment with electrophilic (acid) catalysts[3]. Application of this transformation has yielded several effective methods for the stereoselective synthesis of 1,2-*trans*-glycosides[3].

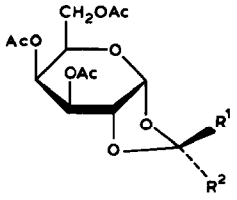
1,2-*O*-(1-Cyanoethylidene) derivatives appear to be much more stable to both protic and aprotic (Lewis) acids than are 1,2-orthoester derivatives (ref. 2, and unpublished results). However, Kochetkov[4] demonstrated that, under catalysis by the powerful electrophile triphenylcarbenium perchlorate, 1,2-*O*-(1-cyanoethylidene)glycoses react with tritylated alcohols to give triphenylacetonitrile and the corresponding 1,2-*trans*-glycosides. It therefore seemed possible that treatment of 1,2-*O*-(1-cyanoethylidene)glycoses with an appropriate electrophile, in the absence of alternative nucleophiles, would result in their rearrangement to the corresponding glycosyl cyanides.

We now report a method for the stereoselective isomerization of some per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses to the corresponding per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides using the "hard" Lewis acid boron

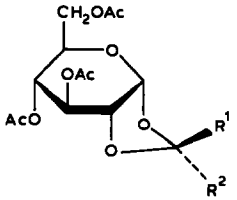
trifluoride etherate ($BF_3 \cdot OEt_2$) in nitromethane. Application of this BF_3-mediated rearrangement has led to significantly improved preparations of certain per-*O*-acetylaldohexopyranosyl cyanides.

RESULTS AND DISCUSSION

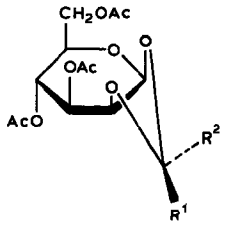
*Rearrangement of per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses by boron trifluoride.* — 3,4,6-Tri-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene]-α-D-galacto- (**1a** and **1b**), -α-D-gluco- (**2a** and **2b**), and -β-D-manno-pyranose (**3a** and **3b**) were prepared by a modification of the method of Kochetkov and co-workers[5]. In pilot experiments, **1a, 1b, 2a, 2b, 3a**, and **3b** were individually



1a R^1 = CN, R^2 = Me
1b R^1 = Me, R^2 = CN
D-*galacto*



2a R^1 = CN, R^2 = Me
2b R^1 = Me, R^2 = CN
D-*gluco*



3a R^1 = Me, R^2 = CN
3b R^1 = CN, R^2 = Me
D-*manno*

a = *exo*-cyano, b = *endo*-cyano

treated under anhydrous conditions with one equivalent of 0.5M $BF_3 \cdot OEt_2$ in nitromethane at room temperature (*i.e.*, with a potent Lewis acid in a polar aprotic solvent, in the absence of an exogenous source of cyanide or alternative nucleophiles). The reactions were closely monitored by t.l.c. (solvent *A*), which revealed the rapid formation of *exo/endo* mixtures (**1a/b, 2a/b**, or **3a/b**) from each diastereomerically pure 1,2-*O*-(1-cyanoethylidene) acetal. The resulting *exo/endo* mixtures were subsequently converted into the corresponding per-*O*-acetylaldohexopyranosyl cyanides[2].

The length of time required to complete these reactions (as judged by the total disappearance of **1a/b, 2a/b**, or **3a/b**), as well as the yields of the glycosyl cyanides so obtained, was characteristic of the aldohexopyranose examined (*vide infra*). Additional studies demonstrated that per-*O*-acetyl-α- and -β-D-aldohexopyranosyl cyanides are stable to the aforementioned reaction conditions for fourteen weeks, showing no evidence of conversion into 1,2-*O*-(1-cyanoethylidene) derivatives or of anomerization. Because there is no cyanide ion elimination from glycosyl cyanides under these conditions, the BF_3-mediated rearrangement must be irreversible, and the anomeric ratio of the glycosyl cyanides produced must be kinetically controlled.

These rearrangements were scaled-up in order to isolate the glycosyl cyanides

TABLE I

RESULTS OF THE REARRANGEMENT OF VARIOUS PER-*O*-ACETYL-1,2-*O*-(1-CYANOETHYLIDENE)ALDOHEXOPYRANOSES BY $BF_3 \cdot OEt_2$ IN NITROMETHANE[a]

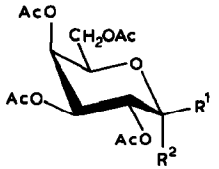
Starting 1,2-O-(1-cyanoethylidene)glycose		*Reaction time (h)*	*Per-O-acetylaldohexopyranosyl cyanides obtained*				
Parent sugar	*Compound*		*Compound*	*Anomer*	*Yield[b] (%)*	*1,2-trans/1,2-cis*	*Total yield (%)*
α-D-Gal	**1a/b** (3.4:1)[c]	1.5	**4**	α	1.9	40:1	77
			5	β	75		
α-D-Glc	**2a/b** (1.1:1)[c]	6	**9**	α	0.9	18:1	17
			10	β	16		
β-D-Man	**3a**	10	**16**	α	62	13:1	67
			17	β	4.8		

[a]Reaction conditions: one equivalent of $BF_3 \cdot OEt_2$, 2 mL of CH_3NO_2/mmol of acetal, room temperature. [b]Yield of crystalline product. [c]Mole ratio of *exo*-cyano to *endo*-cyano.

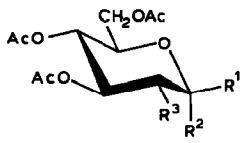
produced and to determine their yields. The results (see Table I) demonstrated that per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses **1a/b, 2a/b**, and **3a/b** were stereoselectively isomerized to the corresponding per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides by treatment with $BF_3 \cdot OEt_2$ in nitromethane. Crystalline 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-galactopyranosyl cyanide (**4** and **5**) were obtained in 1.9 and 75% yield, respectively, from **1a/b** *via* this reaction, whereas crystalline 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-mannopyranosyl cyanide (**16** and **17**) were obtained in respective yields of 62 and 4.8% from **3a**.

These data indicated that the BF_3-mediated isomerization-reaction proper is an intrinsically effective method for synthesizing 1,2-*trans*-glycosyl cyanides, and that glycosyl isocyanides[6] are, at most, minor by-products. Nevertheless, the combined yield of crystalline 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosyl cyanide (**9** and **10**) from **2a/b** was very low (17%). Preliminary results (unpublished) indicated that penta-*O*-acetyl-α-D-glucopyranose is a major by-product of this reaction (*cf.* ref. 2); the mechanism of its formation is obscure. Numerous polar by-products were also generated in relatively high proportions. It is suggested that many of these compounds may result from intramolecular rearrangements of the solvent-separated, "all-*trans*-oriented", per-*O*-acetylated 1,2-acetoxonium ion of D-glucopyranose[7]. Finally, it is notable that the rearrangement of **1a/b** (D-*galacto*) was significantly faster than that of **2a/b** (D-*gluco*) and **3a/b** (D-*manno*) under identical conditions.

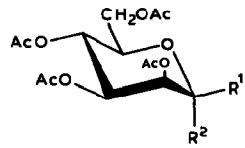
While this work was in progress, Utimoto and co-workers[8] independently demonstrated the Lewis acid-mediated conversion of 3,5-di-*O*-benzoyl-1,2-*O*-(1-



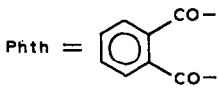
4 $R^1 = H, R^2 = CN$
5 $R^1 = CN, R^2 = H$
6 $R^1 = H, R^2 = Br$
7 $R^1 = H, R^2 = OAc$
8 $R^1 = OAc, R^2 = H$
D-*galacto*



9 $R^1 = H, R^2 = CN, R^3 = OAc$
10 $R^1 = CN, R^2 = H, R^3 = OAc$
11 $R^1 = H, R^2 = Br, R^3 = OAc$
12 $R^1 = H, R^2 = OAc, R^3 = OAc$
13 $R^1 = OAc, R^2 = H, R^3 = OAc$
14 $R^1 = CN, R^2 = H, R^3 = NPhth$
15 $R^1 = OAc, R^2 = H, R^3 = NPhth$
D-*gluco*



16 $R^1 = H, R^2 = CN$
17 $R^1 = CN, R^2 = H$
18 $R^1 = H, R^2 = Br$
19 $R^1 = H, R^2 = OAc$
D-*manno*



cyanobenzylidene)-α-D-ribofuranose and its *O*-acetyl analog into the corresponding per-*O*-acyl-β-D-ribofuranosyl cyanides using neat trimethylsilyl cyanide as an exogenous cyanide source (and solvent). These investigators also found $BF_3 \cdot OEt_2$ to be a superior reagent for effecting this transformation. However, our results showed that trimethylsilyl cyanide is not required for effective conversion of per-*O*-acylated 1,2-*O*-(1-cyanoethylidene)glycoses into the corresponding 1,2-*trans*-glycosyl cyanides.

For the most part, per-*O*-acetylaldohexopyranosyl cyanides synthesized *via* the BF_3-mediated isomerization-reaction are isolated more readily (see *Experimental* section) than those prepared by the mercuric cyanide-mediated cyanation reaction[2], as there are no isomeric 1,2-*O*-(1-cyanoethylidene) acetals present in the products of the rearrangement. However, by the rearrangement, only α-D-*manno* cyanide **16** was obtained in significantly improved yield, as compared to the referenced procedures[2]. This fact, coupled with the necessity of preparing the per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses (from the corresponding glycosyl bromides[5]), with the difficulties that we encountered in reproducing the published results[5], and with certain other considerations makes this route to per-*O*-acetylated 1,2-*trans*-glycosyl cyanides impractical. The following sections describe some practical applications of the BF_3-mediated rearrangement which, in combination with other cyanation reactions, provide improved syntheses of certain glycosyl cyanides.

*Improved preparations of the per-*O*-acetylated 1,2-*trans*-*D-*manno- and -gluco-pyranosyl cyanides.* — Previously, we reported that reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-manno- and -gluco-pyranosyl bromides (**18** and **11**, respectively) with mercuric cyanide in nitromethane affords the desired per-*O*-acetylaldohexo-

TABLE II

EFFECT OF SUBSEQUENT $BF_3 \cdot OEt_2$ TREATMENT ON THE YIELDS OF PER-*O*-ACETYL-D-MANNO- AND -GLUCO-PYRANOSYL CYANIDES FROM THE REACTION OF THE CORRESPONDING α-D-GLYCOSYL BROMIDES WITH MERCURIC CYANIDE IN NITROMETHANE

Treatment[a]	D-*Mannopyranosyl cyanides obtained*[b]				D-*Glucopyranosyl cyanides obtained*[b]			
	Yield of α anomer **16** *(%)*	*Yield of β anomer* **17** *(%)*	*1,2*-trans/ *1,2*-cis	*Total yield (%)*	*Yield of α anomer* **9** *(%)*	*Yield of β anomer* **10** *(%)*	*1,2*-trans/ *1,2*-cis	*Total yield (%)*
A	37	3.3	11:1	40[c]	1.1	20	18:1	21[d]
B	61	4.3	14:1	65	1.3	26	20:1	27
C	58	3.8	15:1	62	1.2	24	20:1	25
D	—	—	—	—	2.3	30	13:1	32

[a]Following reaction and work-up as described in ref. 2, the products from the mercuric cyanide-mediated cyanation reactions were: A, purified without $BF_3 \cdot OEt_2$ treatment, as described in ref. 2; B, purified by gel filtration, treated with $BF_3 \cdot OEt_2$, and then purified; C, directly treated with $BF_3 \cdot OEt_2$ and then purified; D, directly treated with $BF_3 \cdot OEt_2$, acetylated, and then purified. [b]Yield of crystalline products. [c]Also produced were 1,2-*O*-(1-cyanoethylidene) derivatives **3a/b** in a combined yield of ~40%, as determined by gel filtration. [d]Also produced were 1,2-*O*-(1-cyanoethylidene) derivatives **2a/b** in a combined yield of ~25%, as determined by gel filtration.

pyranosyl cyanides (**16** and **17**, and **9** and **10**, respectively) in sub-optimal yields, as per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses **3a/b** and **2a/b**, respectively, were also major products (see Table II, Treatment A)[2]. By contrast, 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-galactopyranosyl cyanide (**4** and **5**) were obtained in 2.9 and 79% yield, respectively, from 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**6**) using this *C*-glycosylation reaction, **1a/b** being generated in only ~5% yield[2].

We now demonstrate that the BF_3-mediated rearrangement can be employed to increase the yields, and facilitate the purification, of the per-*O*-acetylated 1,2-*trans*-D-manno- and -gluco-pyranosyl cyanides from the corresponding, mercuric cyanide-mediated, cyanation reactions.

In our first experiments, each of bromides **18** and **11** was treated with one equivalent of mercuric cyanide in dry nitromethane at room temperature; then, after removal of the mercury salts by extraction, the products of each reaction were purified by gel filtration[2] prior to $BF_3 \cdot OEt_2$ treatment. Syrupy product-mixtures which consisted almost exclusively of glycosyl cyanides (**16** and **17**, and **9** and **10**, respectively) and the corresponding 1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene] isomers (**3a/b** and **2a/b**, respectively), in the ratio of ~1:1 (see Table II, Treatment A), were obtained in ~85 (D-*manno*) and ~50% (D-*gluco*) yield*. Recovery of these nitriles following gel filtration was almost quantitative. These

*The relatively low overall yield of **9**, **10**, and **2a/b** from this reaction (see ref. 2) may, in part, be a consequence of intramolecular rearrangements[7] of the intermediate, per-*O*-acetylated 1,2-acetoxonium ion of D-glucopyranose.

mixtures were then treated with $BF_3 \cdot OEt_2$ essentially as already described (~0.25M **3a/b** or **2a/b** in dry nitromethane, using one mol of $BF_3 \cdot OEt_2$ per mol of acetal, the reaction times being 10 and 6 h, respectively, for the D-*manno* and D-*gluco* mixtures). After purification, 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-mannopyranosyl cyanide (**16** and **17**) were obtained in 61 and 4.3% overall yield (from bromide **18**), respectively, whereas 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosyl cyanide (**9** and **10**) were obtained in 1.3 and 26% overall yield (from bromide **11**), respectively (see Table II, Treatment B). The yields of 1,2-*trans*-glycosyl cyanides **16** and **10** from this reaction sequence are an improvement, particularly in the case of **16**, over those obtained by the previous method[2] (see Table II; compare Treatments A and B). The increases in the yields of **16** and **10** agree well with the expected increases calculated from the estimated amounts of 1,2-*O*-(1-cyanoethylidene) isomers present and the yields from the rearrangements.

When gel filtration preceding $BF_3 \cdot OEt_2$ treatment was omitted, the overall yields of glycosyl cyanides **16** (and **17**) and (**9** and) **10** were only slightly lower (see Table II, Treatment C). Thus, by-products of the mercuric cyanide-mediated cyanation reactions do not interfere significantly with the outcome of the rearrangement, and consequently, the preliminary purification by gel filtration is unnecessary.

It seemed reasonable that partially deacetylated glycosyl cyanides might be by-products of the mercuric cyanide-mediated cyanation of bromide **11** and, in particular, of the BF_3-mediated rearrangement of **2a/b**. Therefore, an experiment was performed in which the products from reaction of **11** with mercuric cyanide in nitromethane were, after removal of the mercury salts by extraction, treated directly with $BF_3 \cdot OEt_2$ in nitromethane, subsequently acetylated with pyridine–acetic anhydride, and then purified. In this way, glycosyl cyanides **9** and **10** were indeed isolated in improved yields of 2.3 and 30%, respectively (see Table II, Treatment D).

*The boron trifluoride etherate-mediated reaction of per-*O*-acetylaldohexopyranoses with trimethylsilyl cyanide.* — In 1982, de las Heras and Fernàndez-Resa[9] reported the efficient conversion of per-*O*-acyl-β-D-ribofuranoses, -β-D-ribopyranose, -α- and -β-D-arabinopyranoses, and -β-D-galactopyranose into the corresponding per-*O*-acylated 1,2-*trans*-glycosyl cyanides using trimethylsilyl cyanide (Me_3SiCN) and $BF_3 \cdot OEt_2$ in nitromethane. Concurrently, Utimoto and coworkers[8] reported that per-*O*-acyl-α- and -β-D-ribofuranoses are transformed into the corresponding -β-D-ribofuranosyl cyanides in good yield by treatment with neat Me_3SiCN and a Lewis acid ($SnCl_2$, or $BF_3 \cdot OEt_2$). Having demonstrated that per-*O*-acetylaldohexopyranosyl cyanides are stable to $BF_3 \cdot OEt_2$ in nitromethane, whereas per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses are stereoselectively isomerized to the corresponding per-*O*-acetylated 1,2-*trans*-glycosyl cyanides, it was anticipated that the BF_3-mediated reaction of per-*O*-acetylaldohexopyranoses with Me_3SiCN in nitromethane would provide an alternative, one-flask synthesis of the corresponding per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl

TABLE III

RESULTS OF THE $BF_3 \cdot OEt_2$-MEDIATED REACTION OF VARIOUS PER-*O*-ACETYLALDOHEXOPYRANOSES WITH Me_3SiCN IN NITROMETHANE[a]

Starting acetate		*Me_3SiCN (equiv.)*	*Reaction time (h)*	*Per-O-acetylated 1,2-trans-aldohexopyranosyl cyanide obtained*[b]		
Parent sugar	*Compound*			*Compound*	*Anomer*	*Yield (%)*[c]
α-D-Gal	**7**	2	4.5	**5**	β	67
		4	1.5	**5**	β	43
β-D-Gal	**8**	2	1.5	**5**	β	77[d]
α-D-Glc	**12**	2	24	**10**	β	10[e]
		4	6	**10**	β	15
β-D-Glc	**13**	2	24	**10**	β	15[f,g]
		4	6	**10**	β	18
α-D-Man	**19**	2	24	**16**	α	56
		4	8	**16**	α	32
β-D-GlcNPhth	**15**	2	2	**14**	β	68

[a]Reaction conditions: one equivalent of $BF_3 \cdot OEt_2$, 2 or 4 mL of CH_3NO_2/mmol of sugar, room temperature. [b]In most cases, the corresponding 1,2-*cis* anomers were detected (by t.l.c.) as very minor products; however, no attempt was made to isolate them. [c]Yield of crystalline product. [d]De las Heras and Fernàndez-Resa[9] obtained **5** in 71% yield by a similar procedure. [e]Preliminary results indicate that **12** is a major component in the isolated reaction-mixture. [f]Preliminary results indicate that **12** is a major co-product. [g]Acetylation prior to purification failed to increase the yield of **10**.

cyanides. The results (see Table III) clearly indicated that this is, indeed, the case.

Interestingly, close monitoring with t.l.c. (solvent *A*) revealed that the BF_3-mediated reaction of penta-*O*-acetyl-α-D-manno- (**19**), -β-D-gluco- (**13**), and -β-D-galacto-pyranose (**8**) (1,2-*trans* pentaacetates) with Me_3SiCN in nitromethane rapidly generated per-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-cyano)ethylidene]aldohexopyranoses **3a/b, 2a/b**, and **1a/b**, respectively, as the preponderant, initial products. Subsequently, BF_3-mediated rearrangement of these acetals was found to occur *in situ,* as expected, to give the corresponding, stable, per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides (**16, 10**, and **5**, respectively). The times required for completion of the reaction (*i.e.*, no remaining acetals), and the product distributions from these reactions (including the overall yields of **16, 10**, and **5**), are similar to those found for the rearrangement of pure **3a/b, 2a/b**, and **1a/b** (*cf.*, Tables I and III).

These results indicated that the overall yields for the conversion of per-*O*-acetylated 1,2-*trans*-glycoses into the corresponding 1,2-*trans*-glycosyl cyanides *via* the Me_3SiCN procedure are governed largely by the yields of the secondary, Lewis acid-mediated rearrangement (a possibility also suggested by the data of Utimoto *et al.*[8]). The observed reaction-pathway readily explains the isolation of 1,2-*O*-(1-cyano-ethylidene and -benzylidene)glycoses from similar Me_3SiCN procedures employed by others[8,9] (*i.e.*, apparently, the conditions employed did not allow for

complete rearrangement of these kinetic products). Furthermore, these results suggested that the Me_3SiCN method, under appropriately controlled conditions (accomplished perhaps by using "weaker" Lewis acids[8], or lower temperatures, or both) may provide an efficient synthesis of 1,2-*O*-(1-cyanoethylidene)glycoses, which are useful as 1,2-*trans* *O*-glycosylating reagents[4]. In support of this notion, Utimoto and co-workers[8] obtained **2** (isomer not specified) in 64% yield, and the 3,5-di-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-α-D-ribofuranoses in 96% yield, *via* reaction of the corresponding 1,2-*trans* peracetates with neat Me_3SiCN using a relatively weak Lewis acid, $SnCl_2$, as the catalyst. In contrast to our results, these workers reported that **2** was recovered unchanged after prolonged treatment with Lewis acids (and Me_3SiCN).

Banoub and Bundle[10] concluded that the stannic chloride-mediated conversion of per-*O*-acetylated 1,2-*trans*-glycoses into the corresponding 1,2-*trans*-glycosides proceeds *via* 1,2-orthoester intermediates which are stereoselectively rearranged *in situ*.

The 1,2-*trans* derivative 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**15**) gave 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl cyanide (**14**) in 68% yield *via* the Me_3SiCN method. In sharp contrast to the reaction course exhibited by the 1,2-*trans* pentaacetates **19**, **13**, and **8**, no intermediates analogous to 1,2-*O*-(1-cyanoethylidene) derivatives could be detected (by t.l.c.) in the conversion of **15** into **14**, nor was the production of the corresponding 1,2-*cis*-glycosyl cyanide observed. It is notable that reaction of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide with mercuric cyanide in nitromethane was also highly stereoselective, providing the 1,2-*trans*-glycosyl cyanide **14** in the same yield as the Me_3SiCN procedure[2].

Penta-*O*-acetyl-α-D-galacto- (**7**) and -gluco-pyranose (**12**) (1,2-*cis* pentaacetates) gave somewhat lower yields of glycosyl cyanides **5** and **10**, respectively, *via* the Me_3SiCN procedure than did the corresponding 1,2-*trans* pentaacetates **8** and **13** (see Table III); the reason(s) for this are unknown. Monitoring by t.l.c. (solvent *A*) established that per-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)aldohexopyranoses **1a/b** and **2a/b** were not generated efficiently from **7** and **12** during the course of these reactions. Furthermore, **12** was observed to be considerably less reactive to coupling than was 1,2-*trans* anomer **13** (however, **7** was only slightly less reactive than **8**). Thus, a considerable proportion of **12** remained after prolonged reaction (4 months) with two equivalents of Me_3SiCN under our standard conditions. The use of four equivalents of Me_3SiCN resulted in rapid and complete consumption of **12**, but an only slightly improved overall yield of **10** (numerous more-polar species of unknown structure were co-produced). Even more surprising was the observation that 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranose was unreactive to treatment (15 h) with Me_3SiCN and $BF_3 \cdot OEt_2$ in nitromethane under our standard conditions. Previous studies of Me_3SiCN reactions demonstrated no disadvantage in the use of the 1,2-*cis* anomers of tetra-*O*-acetyl-arabinopyranose[9] and -ribofuranose[8] *versus* the corresponding 1,2-*trans* anomers.

In summary, the results clearly demonstrated that the BF_3-mediated reaction of per-*O*-acetylaldohexopyranoses with Me_3SiCN in nitromethane provides a one-flask synthesis of the corresponding per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides, so long as *in situ* rearrangement of the 1,2-*O*-(1-cyanoethylidene) acetals is permitted to proceed to completion. However, a comparative examination revealed that the yields of glycosyl cyanides from the mercuric cyanide-mediated cyanation reactions, especially when followed by BF_3-mediated rearrangement, and acetylation as required (D-*manno* and D-*gluco* products), are better than, or comparable to, those obtained from the Me_3SiCN reactions (*cf.* ref. 2 and Tables II and IV with Table III; unpublished results). This fact, coupled with the increased yield of many glycosyl bromides from the parent aldohexopyranoses (relative to the corresponding 1,2-*trans* peracylated derivatives), the considerably lower expense of mercuric cyanide (relative to Me_3SiCN), and certain other considerations, explains why the (modified) mercuric cyanide procedures are our method of choice for the (preparative-scale) synthesis of per-*O*-acetylaldohexopyranosyl cyanides having the β-D-*galacto*, 6-deoxy-β-L-*galacto*, β-D-*gluco*, 2-deoxy-2-phthalimido-β-D-*gluco*, and α-D-*manno* configurations, *i.e.*, all those that we have examined to date.

Fusion of per-O-acetyl-α-D-glycosyl bromides with mercuric cyanide. — Despite the aforementioned improvements, the preparation of 1,2-*trans*-glycosyl cyanide **10** in good yield remained problematic in our hands. By contrast, Fuchs and Lehmann[11] reported that fusion of D-*gluco* bromide **11** with two equivalents of mercuric cyanide (for 20 min at 85°) gave **10** in 30% isolated yield (80% "yield" by gas–liquid chromatographic analysis). Although details for the purification of **10** so prepared were not provided, the crude reaction-product was converted into 2,6-anhydro-D-*glycero*-D-*gulo*-heptonic acid (β-D-glucopyranosylformic acid) in 73% overall yield (based on **11**).

Prompted by this report, we repeated the published synthesis[11]. Following the fusion, dry nitromethane was added, and the mixture was stirred under anhydrous conditions at room temperature to allow reaction of the small proportion of **11** that remained (extended fusion-times appeared to increase by-product formation). After purification, glycosyl cyanides **9** and **10** were isolated in 12 and 39% yield, respectively (see Table IV). The yields of 1,2-*trans* anomer **10** and of the difficultly accessible 1,2-*cis* anomer **9**, as well as their combined yield, were the highest we have obtained to date (*cf.* Tables I–III). Preliminary results (unpublished) indicated that penta-*O*-acetyl-D-glucopyranose is a major by-product from the fusion (*cf.*, ref. 2).

Application of the fusion method to D-*manno* bromide **18** (for 25 min at 60°) gave, after purification, glycosyl cyanides **16** and **17** in 48 and 16% yield, respectively (see Table IV). Notably, the yield of the 1,2-*cis* anomer **17** was considerably greater than that obtained by other methods, whereas the combined yield of **16** and **17** was among the highest we have obtained to date (*cf.*, Tables I–III).

TABLE IV

RESULTS OF THE FUSION OF VARIOUS PER-*O*-ACETYLALDOHEXOPYRANOSYL BROMIDES WITH MERCURIC CYANIDE (TWO EQUIVALENTS)

Starting bromide		*Reaction conditions*		*Per-O-acetylaldohexopyranosyl cyanides obtained*[a]				
Parent sugar	*Compound*	*Time (min)*	*Temp. (degrees)*	*Compound*	*Anomer*	*Yield (%)*	*1,2-trans/ 1,2-cis*	*Total yield (%)*
α-D-Man	**18**	25	60	**16**	α	48	3:1	64
				17	β	16		
α-D-Glc	**11**	20	85	**9**	α	12	3:1	51
				10	β	39		
α-D-Gal	**6**	20	80	**4**	α	4.2	13:1	59
				5	β	55		

[a]Yield of crystalline product.

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**6**) was also fused with mercuric cyanide for 20 min at 80°, to furnish, after purification, glycosyl cyanides **4** and **5** in 4.2 and 55% yield, respectively (see Table IV). Unfortunately, as compared with other methods, the yield of 1,2-*cis* anomer **4** was only slightly improved, whereas the yield of the 1,2-*trans* anomer **5** was notably decreased (*cf.*, ref. 2 and Tables I and III). The fusion method is, therefore, of limited value in this instance. These and other results (see Tables I and IV, as well as ref. 2) indicate that, under identical reaction-conditions, per-*O*-acetylaldohexopyranosyl cyanides having the D-*galacto* configuration are consistently generated in somewhat higher 1,2-*trans*:1,2-*cis* ratios than are the corresponding derivatives having the D-*manno* and D-*gluco* configurations. A major by-product from the fusion appears to be penta-*O*-acetyl-D-galactopyranose (unpublished result).

Thus, the fusion method provides a facile synthesis of the per-*O*-acetylated 1,2-*trans*-D-gluco- and -manno-pyranosyl cyanides in moderate yield, and the corresponding 1,2-*cis* anomers in low, but synthetically useful, yield.

As indicated in Table IV, the fusions gave per-*O*-acetylaldohexopyranosyl cyanides in considerably lower 1,2-*trans*:1,2-*cis* ratios than did other cyanation reactions (*cf.*, ref. 2 and Tables I–III). In addition, we observed that each of the fusions (including, notably, the reactions employing bromides **11** and **18**) apparently generated low proportions of the per-*O*-acetylated 1,2-*O*-(1-cyanoethylidene)aldohexopyranoses (*cf.*, ref. 2 and Table II). Anomerization of glycosyl cyanides under the conditions of the melts is highly unlikely. Furthermore, in view of the need for relatively high concentrations of strong Lewis acids and prolonged reactions times

in order to effect facile rearrangement of **1a/b, 2a/b**, and **3a/b**, any such acetals formed during mercuric cyanide-mediated fusions should be stable to the reaction conditions employed (*i.e.*, not subject to rearrangement). Collectively, these results suggest that cationic intermediates generated by reaction of per-*O*-acetylaldohexopyranosyl bromides with mercuric cyanide in a melt possess high "glycosyl oxocarbenium ion character" and low "1,2-acetoxonium ion character" (*i.e.*, the acetoxyl substituent on C-2 is clearly less effective at participation). Kozikowski and Sorgi[12] reported that the zinc bromide-mediated reaction of per-*O*-acylaldopento-furanoses and -pyranoses with neat allyltrimethylsilane at 110° furnishes high yields of allylated *C*-glycosyl compounds with low 1,2-*trans* stereoselectivity. Thus, it seems likely that, at the higher temperatures used in these *C*-glycosylation reactions, the equilibrium between the 1,2-acetoxonium ion and glycosyl oxocarbenium ion intermediates favors the latter cation, so that it becomes the predominant species determining product-formation. A lessened proportion of the D-*gluco* 1,2-acetoxonium ion intermediate could account for the improved overall yield of cyanides **9** and **10** from the fusion method, as intramolecular acetoxonium ion rearrangements[7] leading to by-product formation would be suppressed.

EXPERIMENTAL

Materials. — Boron trifluoride etherate (Aldrich Chem. Co.) was redistilled from an excess of diethyl ether and calcium hydride. Nitromethane (99%) and acetonitrile (99%) (Aldrich Chem. Co.) were dried over molecular sieves Type 4Å (Davison Chem.). Potassium cyanide (J. T. Baker Chem. Co.) and tetrabutylammonium bromide (99%, Aldrich Chem. Co.) were vacuum-dried for 12 h at 25°. Mercuric cyanide (99.7%, Alfa Products) was vacuum-dried over sodium hydroxide for 18 h at 100°. The following materials were obtained from the sources indicated, and used without further treatment: trimethylsilyl cyanide (Aldrich Chem. Co.), 1,2,3,4,6-penta-*O*-acetyl-β-D-galacto- and -gluco-pyranose (Koch–Light Lab., Ltd. and Pfanstiehl Lab., Inc., respectively), and 1,2,3,4,6-penta-*O*-acetyl-α-D-galacto- and -gluco-pyranose (Sigma Chem. Co.). All other commercial products were of reagent grade and were used without further treatment.

General methods. — The general methods used in this investigation have been described[2]. All reactions were performed under anhydrous conditions (dried glasswater, argon atmosphere). Where indicated, compounds were purified by gel-filtration chromatography using Sephadex LH-20 (Pharmacia), preparative liquid chromatography (p.l.c.) using silica gel 60, 15–40 μm (E. Merck), and conventional silica-gel chromatography using silica gel 60, 15–40 μm (E. Merck) as previously described[2]. T.l.c. was conducted on layers (0.20 mm) of silica gel 60 F_{254} precoated on aluminum sheets (E. Merck), and the components were detected with u.v. irradiation and by charring with sulfuric acid[2]. The following solvent systems were employed for chromatography: (*A*) 3:1 (v/v) diethyl ether–petroleum ether (b.p. 30–75°), (*B*) 100:1 (v/v) chloroform–methanol, and (*C*) 3:1 (v/v) toluene–ethyl

acetate. The progress of all purifications was most effectively monitored by t.l.c. using solvent *A* for development. In this way, the per-*O*-acetylated anomeric glycosyl cyanides and diastereomeric 1,2-*O*-(1-cyanoethylidene) acetals of D-galacto-, -gluco-, and -manno-pyranose were all resolved, the order of mobilities being: (1) **1a** > **4** > **1b** > **5**; (2) **2a** > **9** > **2b** > **10**; and (3) **16** > **3a** > **17** > **3b**. All preparations of per-*O*-acetylaldohexopyranosyl cyanides described in this report were crystallized (and recrystallized as necessary) to homogeneity, as judged by m.p., t.l.c., and 80-MHz, ^{1}H-n.m.r. data[2]. Unless otherwise indicated, per-*O*-acetylaldohexopyranosyl cyanides **4**, **9**, **10**, **16**, and **17** were crystallized and recrystallized (with high recovery) by dissolution in hot ethanol (~2 mL/mmol), rapid filtration, and gradual cooling to 4°; crystalline **14** and **5** were similarly obtained using ethanol (~10 mL/mmol) and methanol (~5 mL/mmol), respectively.

3,4,6-Tri-O-*acetyl-1,2*-O-[*1-(*exo-, endo-*cyano)ethylidene*]-α-D-*galactopyranoses* (**1a/b**)[5]. — To a vigorously stirred suspension of well-ground potassium cyanide (16.3 g, 250 mmol) and tetrabutylammonium bromide (16.1 g, 50 mmol) in acetonitrile (150 mL) was added freshly prepared 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[13] (**6**; 20.6 g, 50 mmol) at room temperature. After 15 days, t.l.c. (solvent *A*) indicated that ~70% of **6** had reacted, and the mixture was filtered through Celite. Water (10 mL) was added to the filtrate, and the solution was stirred for 8 h at room temperature, when t.l.c. (solvent *A*) indicated that remaining **6** had been completely hydrolyzed. The solution was then evaporated, the residue was extracted with chloroform (200 mL), and the extract successively washed with chilled water (twice), saturated aqueous sodium hydrogencarbonate, and water (50 mL each), dried (Na_2SO_4), and evaporated. Purification of the resulting residue by p.l.c. (solvent *B* as eluant) gave a mixture of **1a/b**, which was homogeneous in t.l.c. (solvent *A*, *B*, or *C*). The purity of this product was further insured by subjecting it to gel filtration, which failed to provide any additional purification. In this way, syrupy **1a/b** (6.92 g, 39%) was obtained as a 3.4:1 *exo–endo* mixture as determined by 80-MHz, ^{1}H-n.m.r. analysis[5]; R_F 0.39 and 0.31 (**1a** and **1b**, respectively, solvent *A*) and R_F 0.51 (solvent *B*).

3,4,6-Tri-O-*acetyl-1,2*-O-[*1-(*exo-, endo-*cyano)ethylidene*]-α-D-*glucopyranoses* (**2a/b**)[5]. — To a vigorously stirred suspension of well-ground potassium cyanide (8.14 g, 125 mmol) and tetrabutylammonium bromide (4.03 g, 12.5 mmol) in acetonitrile (75 mL) was added freshly prepared 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[13] (**11**; 10.3 g, 25 mmol) at room temperature. After 4 days, t.l.c. (solvent *A*) indicated that the reaction was complete. The mixture was then filtered through Celite, the filtrate evaporated, the resulting residue extracted with chloroform (125 mL), and the extract successively washed with chilled water (twice), saturated aqueous sodium hydrogencarbonate, and water (30 mL each), dried (Na_2SO_4), and evaporated. Purification of the resulting residue by p.l.c. (solvent *B* as eluant) gave a mixture of **2a/b**, which was homogeneous by t.l.c. (solvent *A*, *B*, or *C*). The purity of this product was further insured by subjecting

it to gel filtration, which failed to provide any additional purification. In this way, syrupy **2a/b** (5.64 g, 63%) was obtained as a 1.1:1 *exo–endo* mixture, as determined by 80-MHz, ^{1}H-n.m.r. analysis[5]; R_F 0.38 and 0.27 (**2a** and **2b**, respectively, solvent *A*) and R_F 0.50 (solvent *B*).

*2,3,4,6-Tetra-*O*-acetyl-α- and -β-*D*-galactopyranosyl cyanide* (**4** *and* **5**). — *Method a. By $BF_3 \cdot OEt_2$ treatment of* **1a/b**. A solution of **1a/b** (6.92 g, 19.4 mmol; *exo–endo* ratio 3.4:1) in nitromethane (80 mL) was concentrated until ~40 mL of solvent had been distilled. Boron trifluoride etherate (2.39 mL, 19.4 mmol) was added to the resulting solution under argon, with stirring, at room temperature. After 1.5 h, t.l.c. (solvent *A*) indicated that the rearrangement was complete (no remaining **1a/b**). The solvent was then removed by evaporation, and a solution of the residue in chloroform (100 mL) was washed with chilled water (twice), saturated aqueous sodium hydrogencarbonate, and water (20 mL each), dried (Na_2SO_4), and evaporated. The product crystallized from methanol; recrystallization from methanol gave **5** (4.62 g, 67%); m.p. 169–171° (lit.[2] m.p. 169–170°). The mother liquors were combined, concentrated, and purified by conventional silica-gel column chromatography (solvent *B* as eluant) to give, first, impure **4** (devoid of **5**), and later, **5** (0.57 g, 8.2%); m.p. 167–169°. Further purification by gel filtration and subsequent crystallization gave **4** (0.13 g, 1.9%); m.p. 93–94° (lit.[2] m.p. 93–94°).

Method b. By fusion of **6** *with mercuric cyanide.* A well-ground mixture of freshly prepared bromide **6** (41.1 g, 100 mmol; prepared according to ref. 13) and mercuric cyanide (50.5 g, 200 mmol), evenly distributed on the bottom of a 1-L Erlenmeyer flask and under a constant stream of dried argon, was heated at 80° while being occasionally stirred with a glass rod. After 20 min, the melt was quickly cooled to near room temperature; nitromethane (200 mL) was added, and the mixture was stirred for 48 h at room temperature with exclusion of moisture. Solvent and mercury salts were then removed as previously described[2]. The resulting product crystallized upon addition of diethyl ether (200 mL); recrystallization from methanol gave **5** (17.3 g, 48%); m.p. 169–171° (lit.[2] m.p. 169–170°). The mother liquors were combined, concentrated, and purified by gel filtration, to give a mixture of **4** and **5**, contaminated with traces of **1a** and **1b**. The mixture (9.3 g, 26 mmol) was then treated with $BF_3 \cdot OEt_2$ in the usual manner (see *Method a*). Purification of the product so obtained by p.l.c. (solvent *B* as eluant) gave, first, impure **4** (devoid of **5**), and later, **5** (2.44 g, 6.8%); m.p. 167–170°. Further purification by gel filtration and subsequent crystallization gave **4** (1.50 g, 4.2%); m.p. 91–93° (lit.[2] m.p. 93–94°).

*2,3,4,6-Tetra-*O*-acetyl-α- and -β-*D*-glucopyranosyl cyanide* (**9** *and* **10**). — *Method a. By $BF_3 \cdot OEt_2$ treatment of* **2a/b**. A solution of **2a/b** (5.64 g, 15.8 mmol; *exo–endo* ratio 1.1:1) in nitromethane (50 mL) was concentrated until ~20 mL of solvent had been distilled. Boron trifluoride etherate (1.94 mL, 15.8 mmol) was added to the resulting solution under argon, with stirring, at room temperature. After 6 h, t.l.c. (solvent *A*, *B*, and *C*) indicated that the rearrangement was complete

(no remaining **2a/b**). The solvent was then evaporated, and a solution of the residue in chloroform (100 mL) was washed with chilled water, saturated aqueous sodium hydrogencarbonate, and water (20 mL each), dried (Na_2SO_4), and evaporated. Purification of the resulting residue by gel filtration gave a mixture containing **10** and traces of **9**, as well as several more-polar contaminants of unknown structure. The product crystallized from ethanol; recrystallization from ethanol gave **10** (0.71 g, 13%); m.p. 114–115° (lit.[2] m.p. 114–115°). The mother liquors were combined, concentrated, and purified by conventional, silica-gel column chromatography (solvent *B* as eluant) and subsequent crystallization, to give **9** (50 mg, 0.9%); m.p. 109–111° (lit.[2] m.p. 111–112°), and additional **10** (0.20 g, 3.5%), m.p. 112–114°.

Method b. By $BF_3 \cdot OEt_2$ treatment of the products from the reaction of **11** *with mercuric cyanide in nitromethane (Table II, Treatment D).* The syrupy product remaining after work-up of the reaction of bromide **11** (20.6 g, 50 mmol; prepared according to ref. 13) with mercuric cyanide in nitromethane[2] was dissolved in nitromethane (100 mL), and the solution was concentrated until ~50 mL of solvent had been distilled. Boron trifluoride etherate (1.54 mL, 12.5 mmol) was added to the resulting solution under argon, with stirring, at room temperature. After 6 h, t.l.c. (solvent *A*, *B*, and *C*) indicated that the rearrangement was complete (no remaining **2a/b**). The solvent was then evaporated, and a solution of the residue in chloroform (200 mL) was washed with chilled water (twice), saturated aqueous sodium hydrogencarbonate, and water (40 mL each), dried (Na_2SO_4), and evaporated. The product was acetylated by dissolution in pyridine (40.5 mL, 0.50 mol)–acetic anhydride (23.6 mL, 0.25 mol). After 24 h, the solution was evaporated, and a solution of the residue in chloroform (200 mL) was washed with chilled 1.2N sulfuric acid, water, saturated aqueous sodium hydrogencarbonate, and water (50 mL each), treated with Norit, dried (Na_2SO_4), and evaporated. Purification of the resulting residue by gel filtration gave a mixture containing **10** and traces of **9**. The product crystallized from ethanol; recrystallization from ethanol gave **10** (4.62 g, 26%); m.p. 113–115° (lit.[2] m.p. 114–115°). The mother liquors were combined, concentrated, and further purified by p.l.c. (solvent *B* as eluant) and subsequent crystallization, to give **9** (0.41 g, 2.3%); m.p. 110–111° (lit.[2] m.p. 111–112°), and additional **10** (0.78 g, 4.4%), m.p. 113–115°.

Method c. By fusion of **11** *with mercuric cyanide.* The procedure reported here is an extension of the method of Fuchs and Lehmann[11]. A well-ground mixture of freshly prepared bromide **11** (41.1 g, 100 mmol; prepared according to ref. 13) and mercuric cyanide (50.5 g, 200 mmol), evenly distributed on the bottom of a 1-L Erlenmeyer flask and under a constant stream of dried argon, was heated at 85° while being occasionally stirred with a glass rod. After 20 min, the melt was quickly cooled to near room temperature; nitromethane (200 mL) was added, and the mixture was stirred for 48 h at room temperature, with exclusion of moisture. Solvent and mercury salts were then removed as previously described[2]. The resulting residue was dissolved in ethanol (100 mL), and a seed crystal of **10** was added. The

product, a thick gum, embedded with crystals that developed with time, was recrystallized sequentially from ethanol (125 mL at 25°), chloroform (10 mL)–diethyl ether (50 mL), and ethanol (twice), to give **10** (3.93 g, 11%); m.p. 114–115° (lit.[2] m.p. 114–115°). The mother liquors from the second, third, and fourth recrystallizations, still highly enriched in **10**, were combined, concentrated, and purified by conventional silica-gel column chromatography (solvent *C* as eluant; sample loaded in chloroform), to give a mixture containing mainly **10**, contaminated with a by-product tentatively identified as penta-*O*-acetyl-D-glucopyranose. The product crystallized from ethanol; recrystallization from ethanol gave **10** (1.50 g, 4.2%); m.p. 113–115°. All of the remaining mother liquors were then combined, concentrated, and purified by gel filtration, to give a mixture containing mainly **10** and **9**, contaminated with a trace of **2a** and **2b** (but devoid of penta-*O*-acetyl-D-glucopyranose, which was eluted earlier). Purification of the mixture by p.l.c. (solvent *B* as eluant) and subsequent crystallization gave **9** (3.37 g, 9.4%); m.p. 109–111° (lit.[2] m.p. 111–112°), and additional **10** (7.64 g, 21%); m.p. 113–115°. The mother liquors were combined, and concentrated, and the residue (5.4 g, 15 mmol) was treated with $BF_3 \cdot OEt_2$ in the usual manner (see *Method a*). The resulting product was then purified by p.l.c. (solvent *B* as eluant) and subsequent crystallization, to give further **9** (0.88 g, 2.5%); m.p. 109–111°, and **10** (0.88 g, 2.5%); m.p. 113–115°. Additional experiments indicated that **10** and **9** can be more readily purified from the fusion products by using the following scheme: (*1*) $BF_3 \cdot OEt_2$ treatment to rearrange **2a/b**; (*2*) acetylation; (*3*) p.l.c. (solvent *B* as eluant), to separate **9** from **10**; (*4*) crystallization of the separated anomers; and (*5*) gel filtration and subsequent crystallization of the resulting, individual, mother liquors.

*2,3,4,6-Tetra-*O*-acetyl-α- and -β-*D*-mannopyranosyl cyanide* (**16** *and* **17**). — *Method a. By $BF_3 \cdot OEt_2$ treatment of* **3a**. To a stirred solution of 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*-cyano)ethylidene]-β-D-mannopyranose[5] (**3a**; 7.14 g, 20.0 mmol; m.p. 155–156°, lit.[5] m.p. 154–155°) in nitromethane (40 mL) was added $BF_3 \cdot OEt_2$ (2.46 mL, 20.0 mmol) at room temperature. After 10 h, t.l.c. (solvent *A*, *B*, and *C*) indicated that the rearrangement was complete (no remaining **3a/b**). The solvent was then removed by evaporation and a solution of the residue in chloroform (100 mL) was washed with chilled water, saturated aqueous sodium hydrogencarbonate, and water (20 mL each), dried (Na_2SO_4), and evaporated. Purification of the resulting residue by gel filtration gave a mixture containing **16** and traces of **17**, as well as a contaminant of unknown structure. The product crystallized from ethanol on addition of a seed crystal of **16**; recrystallization from ethanol gave **16** (2.36 g, 33%); m.p. 58–60° (lit.[2] m.p. 58–60°). The mother liquors were combined, concentrated, and purified by conventional silica-gel column chromatography (solvent *B* as eluant), to give, first, **16** (1.72 g, 24%); m.p. 58–60°, and later, **17** (0.34 g, 4.8%); m.p. 143–144° (lit.[2] m.p. 142–144°). The mother liquor from crystallization of **16** was concentrated, and further purified by conventional silica-gel column chromatography (solvent *C* as eluant) and subsequent crystallization, to give additional **16** (0.34 g, 4.8%); m.p. 58–60°.

Method b. By $BF_3 \cdot OEt_2$ treatment of the products from the reaction of **18** *with mercuric cyanide in nitromethane (Table II, Treatment C).* The syrupy product remaining after work-up of the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**18**; prepared[14] from penta-*O*-acetyl-α-D-mannopyranose[15], 19.5 g, 50 mmol) with mercuric cyanide in nitromethane[2] was dissolved in dry toluene (75 mL). The solvent was evaporated, and the residue was dissolved in nitromethane (100 mL). Boron trifluoride etherate (3.07 mL, 25.0 mmol) was added under argon, with stirring, at room temperature. After 10 h, t.l.c. (solvent *A*, *B*, or *C*) indicated that the rearrangement was complete (no remaining **3a/b**). The solvent was evaporated, and a solution of the residue in chloroform (150 mL) was washed with chilled water (twice), saturated aqueous sodium hydrogencarbonate, and water (30 mL each), dried (Na_2SO_4), and evaporated. Purification of the residue by gel filtration gave a mixture containing **16** and traces of **17**, as well as a contaminant of unknown structure. The product crystallized from ethanol on addition of a seed crystal of **16**, to give **16** (7.62 g, 43%); m.p. 57–59° (lit.[2] m.p. 58–60°). The mother liquor was concentrated, and purified by p.l.c. (solvent *B* as eluant), to give, first, **16** (1.84 g, 10%); m.p. 57–59°, and later, **17** (0.67 g, 3.8%); m.p. 142–144° (lit.[2] m.p. 142–144°). The mother liquor from crystallization of **16** was concentrated, and further purified by conventional, silica-gel, column chromatography (solvent *C* as eluant) and subsequent crystallization, to give additional **16** (0.88 g, 4.9%); m.p. 59–60°.

Method c. By fusion of **18** *with mercuric cyanide.* A suspension of freshly prepared, syrupy bromide **18** (prepared[14] from penta-*O*-acetyl-α-D-mannopyranose[15], 19.5 g, 50 mmol) and mercuric cyanide (25.3 g, 100 mmol) in petroleum ether (b.p. 30–75°; 50 mL) in a 1-L, round-bottomed flask was quickly evaporated to dryness. The residue was then immediately heated at 60° while under a constant stream of dry argon and while being occasionally stirred with a glass rod. After 25 min, the melt was quickly cooled to near room temperature; nitromethane (100 mL) was added, and the mixture was stirred for 48 h at room temperature with exclusion of moisture. Solvent and mercury salts were then removed as previously described[2]. Treatment of the resulting, crude product with $BF_3 \cdot OEt_2$ in the usual manner (see *Method b*) effected the rearrangement of **3a** and **3b**. The product so obtained was then purified by gel filtration, to give a mixture of **16** and **17** containing a minor contaminant of unknown structure. The product crystallized from diethyl ether (70 mL) on addition of a seed crystal of authentic **17**; recrystallization from ethanol gave **17** (2.01 g, 11%); m.p. 142–144° (lit.[2] m.p. 142–144°). The mother liquors were combined, concentrated, and further purified by p.l.c. (solvent *B* as eluant), to give, first, **16** (6.76 g, 38%); m.p. 57–60° (lit.[2] m.p. 58–60°), and later, **17** (0.83 g, 4.7%), m.p. 143–144°. The mother liquor from crystallization of **16** was concentrated, and further purified by conventional silica-gel column chromatography (solvent *C* as eluant) and subsequent crystallization, to give additional **16** (1.88 g, 11%); m.p. 56–60°.

*Preparation of per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides via the*

trimethylsilyl cyanide (Me_3SiCN) method. General procedure. — The procedures reported here constitute a modification of the method of de las Heras and Fernàndez-Resa[9]. To a stirred solution of the appropriate per-*O*-acetylaldohexopyranose (5–20 mmol) and Me_3SiCN in nitromethane was added $BF_3 \cdot OEt_2$ at room temperature, under the conditions specified in Table III. After the reaction was complete, the solvent was removed by evaporation, and a solution of the residue in chloroform (5–10 mL/mmol of sugar) was washed four times with 1/4 vol. of chilled water, dried (Na_2SO_4), and concentrated. A black tar, which frequently developed during work-up, did not contain glycosyl cyanides. Purification of the resulting syrup by chromatography on silica gel (solvent *B* as eluant for **5** and **14**; solvent *C* as eluant for **10** and **16**), followed by gel filtration (**10** and **16** only) and subsequent crystallization, provided the per-*O*-acetylated 1,2-*trans*-aldohexopyranosyl cyanides in the yields indicated. No attempt was made to isolate the per-*O*-acetylated 1,2-*cis*-aldohexopyranosyl cyanides generated as very minor products of most of these reactions.

*2,3,4,6-Tetra-*O*-acetyl-β-*D*-galactopyranosyl cyanide* (**5**). — Reaction of penta-*O*-acetyl-α-D-galactopyranose (**7**; 1.95 g, 5.0 mmol) with two equivalents of Me_3SiCN in nitromethane (20 mL) gave **5** (1.20 g, 67%); m.p. 169–171° (lit.[2] m.p. 169–170°). Reaction of **7** (1.95 g, 5.0 mmol) with four equivalents of Me_3SiCN in nitromethane (10 mL) gave **5** (0.76 g, 43%); m.p. 168–170°. Reaction of penta-*O*-acetyl-β-D-galactopyranose (**8**; 1.95 g, 5.0 mmol) with Me_3SiCN in nitromethane (20 mL) gave **5** (1.38 g, 77%); m.p. 170–171°.

*2,3,4,6-Tetra-*O*-acetyl-β-*D*-glucopyranosyl cyanide* (**10**). — Reaction of penta-*O*-acetyl-α-D-glucopyranose (**12**; 3.90 g, 10.0 mmol) with two equivalents of Me_3SiCN in nitromethane (20 mL) for 24 h (after 6 h, no further change in the mixture was detected by t.l.c.) gave **10** (0.37 g, 10%); m.p. 113–115° (lit.[2] m.p. 114–115°). The use of four equivalents of Me_3SiCN afforded, after 6 h (no further change in the mixture was detected by t.l.c. after 3 h), **10** in 15% yield (0.55 g); m.p. 113–115°. Reaction of penta-*O*-acetyl-β-D-glucopyranose (**13**; 3.90 g, 10.0 mmol) with two equivalents of Me_3SiCN in nitromethane (20 mL) for 24 h (after 6 h, no further change in the mixture was detected by t.l.c.) gave **10** (0.55 g, 15%); m.p. 113–115°. The use of four equivalents of Me_3SiCN afforded, after 6 h (no further change in the mixture was detected by t.l.c. after 3 h), **10** in 18% yield (0.63 g); m.p. 113–115°.

*2,3,4,6-Tetra-*O*-acetyl-α-*D*-mannopyranosyl cyanide* (**16**). — Reaction of penta-*O*-acetyl-α-D-mannopyranose[15] (**19**; 3.90 g, 10.0 mmol) with two equivalents of Me_3SiCN in nitromethane (40 mL) for 24 h furnished, in two crops, **16** (2.01 g, 56%); m.p. 56–60° (lit.[2] m.p. 58–60°). Reaction of **19** (3.90 g, 10.0 mmol) with four equivalents of Me_3SiCN in nitromethane (20 mL) for 8 h (after 4 h, no further change in the mixture was detected by t.l.c.) furnished, in two crops, **16** (1.14 g, 32%); m.p. 57–60°.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl cyanide* (**14**). — Reaction of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose[16]

(**15**; 4.77 g, 10.0 mmol) with Me_3SiCN in nitromethane (40 mL) gave **14** (3.01 g, 68%); m.p. 176–178° (lit.[2] m.p. 176–178°).

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