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Mild Synthesis of Disaccharidic 2,3-Enopyranosyl Cyanides and 2-C-2-Deoxy Pyranosyl Cyanides with $Hg(CN)_2/HgBr_2/TMSCN$†

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Lewis acid-catalyzed dimerization of mono- and disaccharidic per-O-acetylated glycals gave di- and tetrasaccharidic O-acetylated C-glycosides, respectively. 2,3-Enopyranosyl cyanides were obtained from per-O-acetylated glycals by a new, mild anomeric S_N'-acetoxy displacement with $Hg(CN)_2/HgBr_2/TMSCN$. Per-O-acetylated 2-C-2-deoxy-pyranoses were converted into pyranosyl cyanides by the same reagent. An unprecedented acetic acid elimination from dimers with D-galacto- and L-fuco-configurations accompanied the S_N-displacement under those conditions. A new set of ^1H NMR coupling constants for 2,3-enopyranosyl systems was used for configurational assignment of complicated tetrasaccharide mimics.

Introduction

Synthetic oligosaccharides derived from glycals have been tested as antigens in anticancer vaccination.[1,2] The role of oligosaccharides in biological systems has become evident within the past decade.[3−8] The potential informational content of oligosaccharides due to monosaccharide sequence and permutations of glycosidic linkages most likely exceeds that of proteins. However, a distinct disadvantage of O-glycosidically linked oligosaccharides is their metabolic instability and limited lifetime in biological systems. Therefore, much effort has been spent in the past two decades on the development of feasible pathways towards C-glycosidic sugars, many of which exhibit biological activities similar to their O-glycosidic counterparts.

Results and Discussion

Synthesis of Glycals. Glycals are versatile chiral building blocks in the synthesis of natural products and biologically relevant oligosaccharides[2] because of the ease of their chemical transformation.

All literature procedures for the preparation of glycals via glycosyl bromides have several problems. For example, **1** had been synthesized from per-O-acetylated D-glucose in a one-pot, two-step sequence by the method of Roth/Pigman[9] in 60−70% yield. Shafizadeh[10] had synthesized **3** from the O-acetylated glycosyl bromide in 32% yield. To purify **3**, a vacuum distillation was described, which might contribute to the overall low yield. Compound **5** had been obtained from the O-acetylated starting material in 40% yield by the method of El Khadem and co-workers.[11] Most problematic in the above methods had been the solvolysis of the intermediate glycosyl bromides during elimination.

In published procedures,[9−20] the formation of glycosyl bromides involved the formation of HBr in situ of a glacial acetic acid solution of the per-O-acetylated starting material. Red phosphorus had been treated with elemental bromine to give PBr_3, which was hydrolyzed with H_2O. Already here, a substantial amount of the glycosyl bromide may have been lost due to solvolysis. The elimination step usually had been performed in aqueous medium (AcOH/NaOAc buffer) adding unwanted hydrolysis of the intermediate bromide. The zinc-promoted elimination of acetylated glycosyl bromides, as

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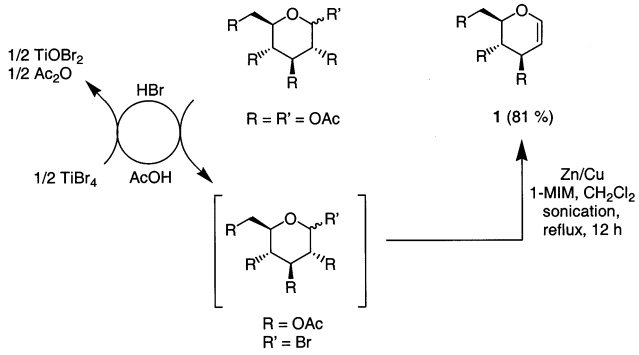
SCHEME 1. Typical Synthesis of a Glycal (Tri-*O*-acetyl-D-glucal)



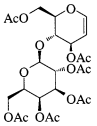
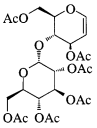
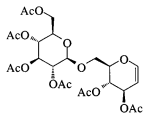
described by Somsák and Németh,[21] avoided the possibility of their hydrolysis. However, Somsák and Németh still found it necessary to isolate the notoriously unstable glycosyl bromides as starting materials.

In the present work we describe a new two-step synthesis of glycals in an aprotic solvent followed by a simple workup procedure, with good to excellent yields. Side products are minor. The intermediate glycosyl bromide does not need to be isolated. Commercially available D-glucose, D-galactose, and L-fucose were per-O-acetylated according to standard literature procedures. Some of the per-O-acetylated saccharides are commercially available.

In our procedure (see Experimental Section), $TiBr_4$ in CH_2Cl_2 was chosen as a brominating reagent because of titanium's tendency to form a stable titanyl TiO^{2+} cation, which is a well-known aspect of titanium chemistry.[22] The reaction was run with 0.6 equiv of $TiBr_4$ (20% excess). We reasoned that the bromination would be based on a catalytic cycle (Scheme 1). Small-scale reactions were run solely with $TiBr_4$. Residual traces of water on the surface of small containers caused hydrolysis of $TiBr_4$ and furnished HBr. Upon scale-up, yields of the intermediate bromides decreased. However, addition of a catalytic amount of glacial acetic acid overcame this problem. In the overall balance, Ac_2O is produced as a byproduct instead of potentially solvolytic AcOH.

The inertness of CH_2Cl_2 toward $TiBr_4$ in our procedure and the high solubility of starting materials, intermediates, and products in combination with the ease of removal of byproducts from CH_2Cl_2 made it possible to directly use glycosyl bromides in CH_2Cl_2. Running the elimination at the boiling point of CH_2Cl_2 (40 °C) favored the reaction entropically. Lower temperatures resulted in no reaction. We found none of the reported inconsistencies when we used freshly activated zinc dust.[35]

TABLE 1. Glycals Synthesized under Aprotic Conditions

Cpd. #	Structure	Yield (%)	Mp (°C)	Rf (Hex/ EtOAc)	Lit. Ref. $[\alpha]_D$ values
1		81	52-53 (from Et_2O/ pentane)	0.68 (5:2)	lit[9,12,13] $[\alpha]_D^{25}$ -59° (c 1, EtOH), lit. $[\alpha]_D^{20}$ -60° (c 1, EtOH) [32]
3		65	Oil	0.70 (5:2)	lit[10,13,14] $[\alpha]_D^{22}$ -14.5° (c 3), lit. $[\alpha]_D^{20}$ -15° (c 3) [32]
5		70	50-51 (from Et_2O/ pentane); lit. mp 49-50[15]	0.71 (5:2)	lit[11,15-17] $[\alpha]_D^{25}$ 12° (c 1), lit. $[\alpha]_D^{19}$ 9.9° (c 1, acetone) [15]
9		75	112-114 (from EtOH/ water); lit. mp 116[32]	0.75 (3:7)	lit[19,20] $[\alpha]_D^{19}$ -15.9° (c 1), lit. $[\alpha]_D^{20}$ -18° (c 0.8) [32]
11		73	129-130 (from EtOH/ water); lit. mp 131-133[32]	0.81 (3:7)	lit[18] $[\alpha]_D^{25}$ +73.4° (c 1.25), lit. $[\alpha]_D^{25}$ +68° (c 0.8) [32]
12		95	Oil	0.71 (3:7)	$[\alpha]_D^{25}$ +34° (c 1)

Per-O-acetylated D-galactose, L-fucose, D-maltose, D-lactose, and D-gentiobiose were treated analogously to penta-O-acetyl-D-glucose (see Table 1). Compounds **1**, **3**, and **5** crystallized at −20 °C from a minimal amount of warm Et_2O (~2.5 mL/g), with pentane added (~8 mL/g) to opalescence. Compounds **9** and **11** crystallized from a minimal amount of hot ethanol (~5 mL/g), with water added (~12 mL/g) to opalescence at 0 °C. Compound **12** was further purified by flash column chromatography on silica gel by gradient elution with hexane with increasing amounts of EtOAc. All glycals were obtained in >90% purity prior to purification, as estimated by NMR.

Synthesis of Dimers. One way to render carbohydrate-derived structures metabolically more stable is the

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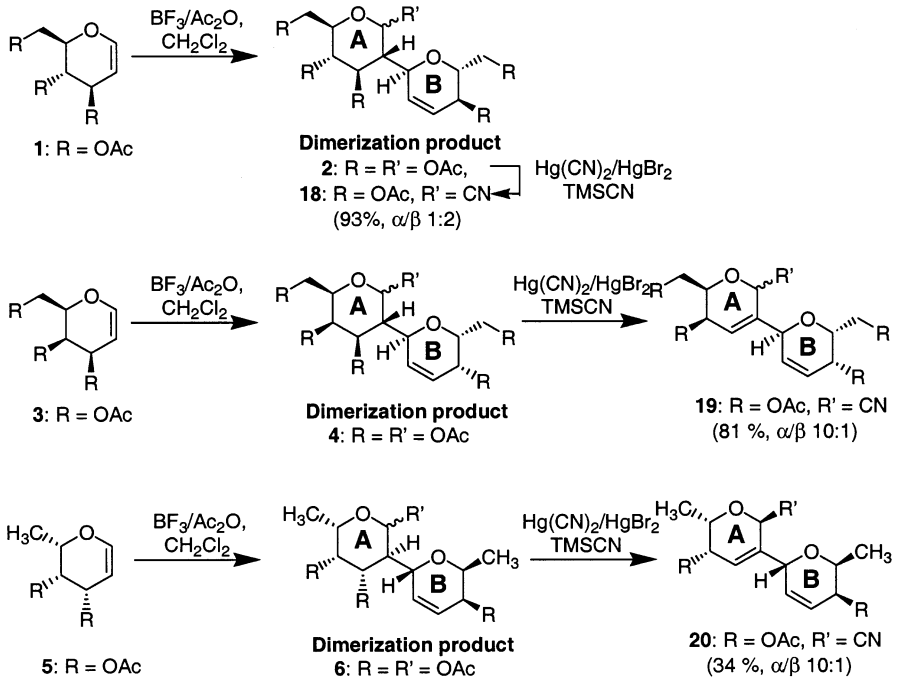
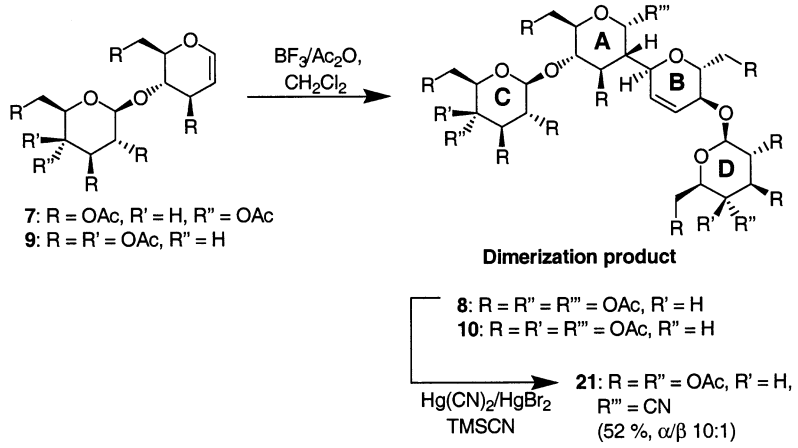
(33) Advantageous for the handling of $TiBr_4$ is a glovebox. In the method described herein, an "atmosbag" (Aldrich) was used to maintain an inert gas atmosphere and solid $TiBr_4$ was employed.
(34) A system 4:6 hexane/EtOAc was used (R_f starting material = 0.54, R_f bromide = 0.71). Before spotting the glycosyl bromides on the TLC plate, it was necessary to prespot with THF to prevent their hydrolysis due to local heat of adsorption. Prolonged exposure to air humidity (>3 h) resulted in complete hydrolysis of the bromide on the plate. TLC detection was done by spraying with 10% H_2SO_4/MeOH and charring at 150 °C.
(35) Inconsistencies due to different grades of zinc reported by E. Erdik (*Tetrahedron* **1987**, *43*, 2203) were not noted if a large excess of zinc powder (i.e., 8 g, Aldrich, 98+%, <10 μm) was activated properly prior to use as follows. The zinc was suspended in water (10 mL). With stirring was added dropwise $CuSO_4$ (10% solution, 5 mL). After the mixture was stirred for 10 min, the Zn/Cu couple was filtered off, washed with water (2 × 10 mL), ethanol (2 × 10 mL), and diethyl ether (3 × 10 mL), subsequently dried in vacuo over P_2O_5 for 6 h, and used promptly, as it may loose its activity by aging in air over several days.

SCHEME 2. Structures of Products from Glycal Dimerization and Cyanation[a]



[a] Ring A (nucleophile) and ring B (electrophile) are used throughout the text. The molecular structure of **20** was unambiguously established by X-ray crystallography, details of which will be published.

SCHEME 3. Dimerization of Per-*O*-acetyl-cellobial and Per-*O*-acetyl-lactal[a]



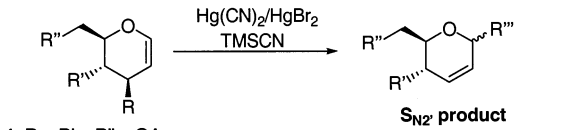
[a] (i) $BF_3/Ac_2O/CH_2Cl_2$; (ii) $Hg(CN)_2/HgBr_2$/TMSCN, 2:3 THF/H_3CCN.

dimerization of glycals, which has been described first for per-O-acetylated glucal by Ferrier and Prasad.[23] We synthesized similar products (Scheme 2), which are directly C-linked. We also applied an improved dimerization method[24] with BF_3/Ac_2O catalyst to disaccharidic glycals in order to obtain tetrasaccharidic glycomimetics (Scheme 3). Such compounds may potentially show altered and/or enhanced bioactivity due to a well-documented[5] cluster effect. The nonphysiological nature of the new C−C-linkages of our compounds may transfer metabolic stability also to O-glycosidic bonds still present in their structures. Dimerizations that lead from disaccharidic glycals to tetramers gave much lower yields. Their syntheses required careful optimization of the reaction to minimize cleavage of the disaccharidic bonds by the BF_3-catalyst.

Cyanation Products. Another way to render carbohydrate-derived structures metabolically more stable is introducing a C-glycosidic cyanide functionality into glycals by the S_N'-reaction (Scheme 4). The complex stereospecificity, if any, of such reactions has been discussed by March.[25]

In an experimental procedure investigated previously in this laboratory with tri-*O*-acetyl-D-glucal,[26] a mixture of $Hg(CN)_2$, $HgBr_2$, and TMSCN was used as a mild source of cyanide in a mixture of dry THF and MeCN (2:3). We could use this reagent not only to convert O-glycosidic glycals into 2,3-enopyranosyl cyanides (Scheme 4) but also to obtain anomeric cyanides from glycal dimers and tetramers (Schemes 2 and 3), which are 2-C-2-deoxy-sugars. The reagent was compatible with 1,4- and 1,6-O-glycosidic linkages, which are normally

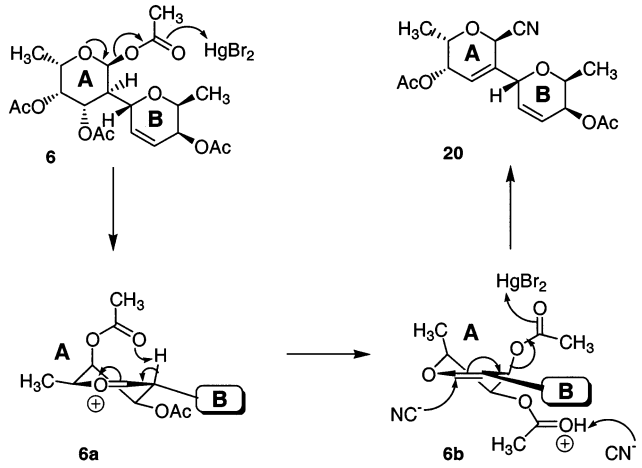
SCHEME 4. Cyanation of Per-*O*-acetyl-glucal and Disaccharidic Per-*O*-acetyl-glycals



1: R = R' = R" = OAc
7: R = R" = OAc,
R' = Per-O-acetyl-β-D-glucopyranosyl
9: R = R" = OAc,
R' = Per-O-acetyl-β-D-galactopyranosyl
11: R = R" = OAc,
R' = Per-O-acetyl-α-D-glucopyranosyl
12: R = R' = OAc,
R" = Per-O-acetyl-β-D-glucopyranosyl

$S_{N2'}$ product
13: R"' = CN, R' = R" = OAc
14: R"' = CN, R" = OAc
R' = Per-O-acetyl-β-D-glucopyranosyl
(52 %, α/β < 1:20)
15: R"' = CN, R" = OAc,
R' = Per-O-ac-β-D-galactopyranosyl
(65 %, α/β 3:1)
16: R"' = CN, R" = OAc,
R' = Per-O-ac-α-D-glucopyranosyl
(52 %, α/β 1:1)
17: R"' = CN, R' = OAc,
R" = Per-O-ac-β-D-glucopyranosyl
(62 %, α/β 4:1)

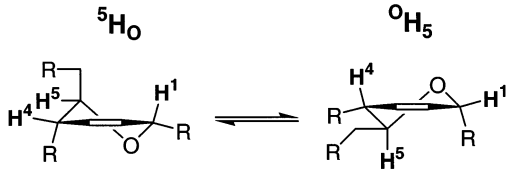
SCHEME 5. Possible Mechanism for the Formation of 19 and 20



prone to cleavage in the presence of BF_3.[27] In contrast to the sequence **2** → **18**, the introduction of the cyanide group at the anomeric center of ring A in the galactal and fucal dimers (**4** and **6**, respectively) introduced also a double bond into ring B for either anomer (Scheme 2).

The example **6** → **20** (Scheme 5) shows a possible mechanism for the formation of **19** or **20** from **4** or **6**, respectively. Initial activation of the anomeric acetate from **6** results in a partially flattened oxonium ion (**6a**). The axial acetoxy group at $C4^A$ helps to stabilize the positive charge at $C1^A$–O. The increased lifetime of **6a** allows CN^- to react as a base, removing $H2^A$ to give an intermediate glycal (**6b**). This removal may be aided by the carbonyl oxygen of the 4-acetoxy group acting as an intramolecular base, transporting the proton into the medium, like a "molecular crane". Subsequently, **6b** and cyanide react in an S_N2' reaction.

For **2** → **18**, the acetoxy group at $C4^A$ is in an equatorial position and, therefore, cannot stabilize the oxonium ion. The nucleophilic cyanide traps the oxonium ion prior to proton abstraction.



$^3J_{1,2}$ = 0 - 2 Hz	$^3J_{1,2}$ = 2.2 Hz
$^4J_{1,3}$ = 0 - 2.5 Hz	$^4J_{1,3}$ = < 0.3 Hz
$^3J_{3,4}$ = 4.8 - 5.7 Hz	$^3J_{3,4}$ = 2.2 Hz
$^4J_{2,4}$ = 0 - 1.5 Hz	$^4J_{2,4}$ = n. det. Hz
$^3J_{4,5}$ = < 1.0 Hz	$^3J_{4,5}$ = 6.3 - 9.0 Hz

FIGURE 1. Coupling constants for ^5H_O-[28] and $^OH_5$-conformations[29,31] of 2,3-dideoxy-2-enopyranose systems (ring "**B**").

NMR Proof of Structure. The assignment of configuration and conformation of the obtained dimers was accomplished by NMR spectroscopy. Small coupling constants (0–2 Hz) between the allylic protons and the vinylic protons in ring B of products **2**, **4**, and **6** were indicative of an ~80° angle. Larger coupling constants (3–5 Hz) indicated a ~40° angle (Figure 1).[28]

Compound **18** was obtained from **2** as a 1:2 α/β mixture. A sample of the β-anomer could be obtained by flash chromatography. In the ^1H NMR spectrum and in ^1H–^1H COSY correlation of the β-anomer, $H2^A$ showed coupling constants of $^3J_{2,1}$ = 5.1 Hz, $^3J_{2,3}$ = 11.4 Hz, and $^3J_{2,1B}$ = 5.1 Hz. In turn, the equatorial $H1^A$ showed a coupling constant of $^3J_{1,2}$ = 4.8 Hz at a chemical shift of δ = 4.88 ppm. The values of the coupling constants for the remainder of ring A are consistent with the gluco-configuration as assigned previously.[24] The signal of $H1^B$ is well exposed as a double doublet at δ = 4.39 ppm with values of $^3J_{1,2}$ < 1 Hz, $^4J_{1,3}$ = 2.1 Hz, and $^3J_{1,2A}$ = 4.8 Hz. Ring B was assigned a $^5H_0$ conformation on the basis of a set of standard coupling constants for 2,3-enopyranosyl systems published by us.[28]

Compounds **19** and **20** showed a close resemblance to each other in their NMR spectra (Figure 2). However, significant differences compared to **18** were discovered. In the ^1H NMR spectrum of **19** only four signals for the acetyl groups were observed. On the basis of ^1H–^1H COSY correlation and an unusually large chemical shift, the double triplet at δ = 6.06 ppm was assigned to a vinylic $H3^A$. The absence of an $H2^A$ signal showed that one molecule of acetic acid had been eliminated between $C2^A$ and $C3^A$. The signal at 5.19 ppm was assigned to $H4^A$ with vinylic coupling of 5.7 Hz to $H3^A$, consistent with a pseudoequatorial orientation. The signal at δ = 5.39 ppm represents $H1^A$ with allylic coupling to $H3^A$ of 1.2 Hz. The configuration at $C1^A$ was inferred by NOEDIF experiments. Selective irradiation of $H1^A$ gave a NOE at $H1^B$ and $H5^B$. No other transannular NOEs were observed, consistent with both $H1^A$ and $H1^B$ being pseudoequatorial. The configuration at $C1^A$ was concluded to be α. In ring B, $H1^B$ showed a coupling constant of $^3J_{1,2}$ = 3.3 Hz and $H4^B$ a coupling constant of $^3J_{4,3}$ = 5.1 Hz, which put both protons into a pseudoequatorial position.[28] It was concluded that ring B favored the $^5H_0$ conformation.

In the very similar ^1H NMR spectrum of **20**, the region at δ = 3.8–4.5 ppm was greatly simplified due to the low

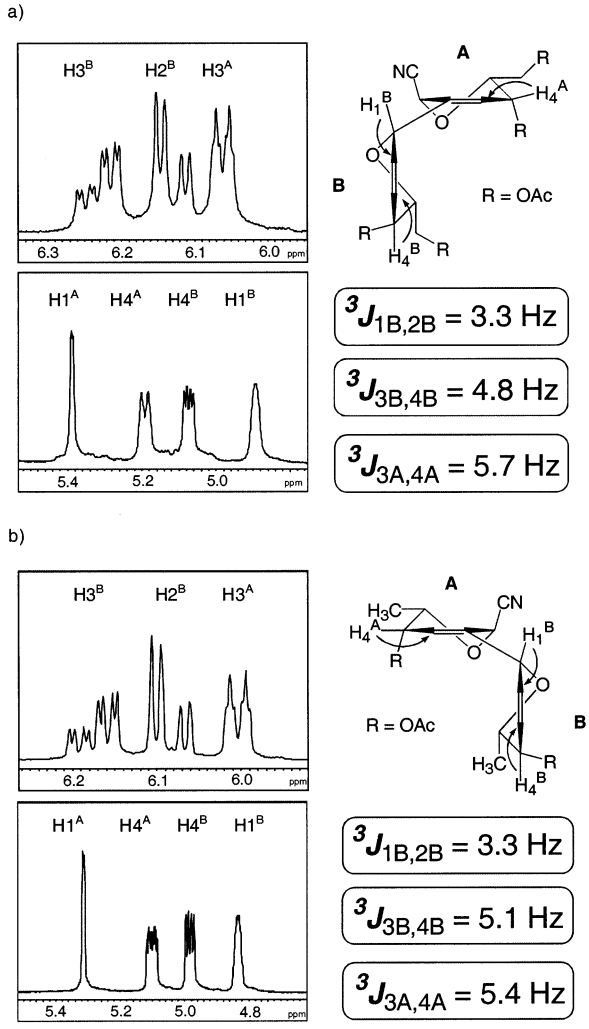


FIGURE 2. Compounds **19** (a) and **20** (b): ^{1}H NMR spectrum (detail).

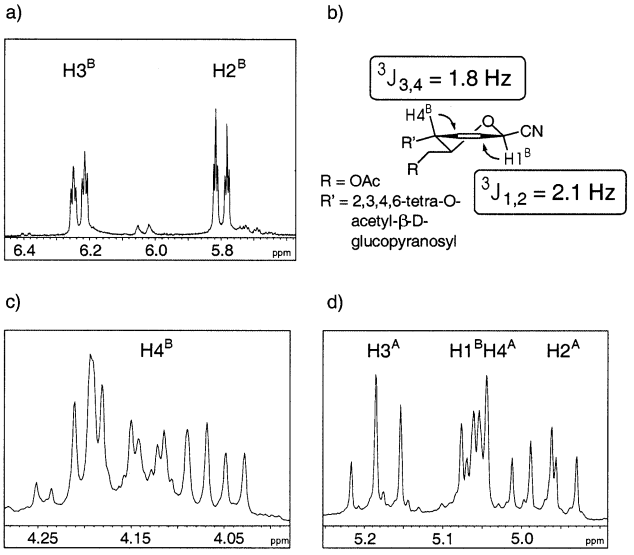


FIGURE 3. Compound **14**: (a) ^{1}H NMR spectrum (detail); (b) configuration and conformation; (c and d) unusual five-bond coupling between H1^B and H4^B.

TABLE 2. Coupling Constants (hertz), Configurations (C1), and Preferred Conformations for 2,3-Enopyranosyl Rings ($CDCl_3$)

compd	$^3J_{1,2}$	$^3J_{3,4}$	configuration at C1^B	conformation of ring B[c]
2	<1	5.1	α	^5H_O (D-config)
4[a]	3.3	4.5	α	$^OH_5$ (D-config)
6[a]	3.3	5.1	α	^5H_O (L-config)
8	3.0	1.8	α	$^OH_5$ (D-config)
10	3.0	1.8	α	$^OH_5$ (D-config)
14	2.4	2.1	β	$^OH_5$ (D-config)
15a[b]	3.3	1.8	α	$^OH_5$ (D-config)
15b[b]	1.8	2.1	β	$^OH_5$ (D-config)
16	2.5	1.5	α	$^OH_5$ (D-config)
17	2.1	1.5	α	$^OH_5$ (D-config)
18	< 1	4.8	α	^5H_O (D-config)
19	3.3	4.8	α	$^OH_5$ (D-config)
20	− (ring A)	5.4 (ring A)	−	^5H_O (L-config)
	3.5 (ring B)	5.1 (ring B)	α	^5H_O (L-config)
21	1.5	3.3	α	^5H_O (D-config)

[a] Measured in acetone-d_6. [b] Fractions of both α- and β-anomer were isolated in pure form. [c] Conformation symbol convention as shown in Figure 1.

δ-values of H6 (CH_3 group). Only two acetyl signals were observed. Also here, the signal for H2^A was absent, and **20** had a double bond between C2^A and C3^A. Assignments of both rings in **20** were completely analogous. The axial disposition of the sterically demanding ring A in **19** and **20** is possible because the acetyl group at C-4 is on the opposite side of the ring compared to that in the gluco-configuration of **18**.

Compound **14** (Scheme 3) was obtained almost exclusively as the β-anomer (>20:1). The values of the three bond couplings in ring A of **14** were all in agreement with a β-D-gluco-configuration and a $^4C_1$-conformation. The trans-diaxial couplings for the 1−5 had values of 8.1−9.9 Hz. The β-configuration at C1 in ring B was supported by coupling constants of $^3J_{1B,2B}$ = 2.4 Hz and $^3J_{3B,4B}$ = 2.1 Hz (Table 2).[28] Protons 1^B and 4^B showed a five-bond coupling with a value of $^5J_{1,4}$ = 1.8−2.4 Hz. Proton 1^B caused a quartet at δ = 5.06 ppm (Figure 3). Proton 4^B caused a double quartet at δ = 4.13 ppm. Allylic interproton coupling has been thoroughly reviewed.[30]

Both, the α- and β-anomers of **15** could be isolated by flash chromatography. The values of optical rotation for **15** are consistent with the Casiraghi rule, which predicts for the β-anomer of monosaccharidic 2,3-enopyranose cyanides higher absolute optical rotations than for the α-anomers. The Casiraghi rule also states that the anomer with the greater $^3J_{4,5}$ coupling constant (8.7−10 Hz) in the unsaturated ring has the β-configuration as opposed to the α-configuration (3−9 Hz).[31] However, in our experiments, the values of $^3J_{1,2}$ in ring B were a more reliable indicator. The coupling constants are generally on the order of 3.3 and 1.8 Hz for the α- and β-anomers, respectively (Figure 4).[28]

The obvious change of the splitting pattern of H2^B (α-anomer) with one large coupling constant $^3J_{2,3}$ = 10.2 Hz, one medium constant $^3J_{2,1}$ = 3.3 Hz, and one small constant $^4J_{2,4}$ = 1.8 Hz is evidence that H1^B is in a pseudoequatorial position. The coupling pattern of H3^B did not change. Therefore, the configuration was assigned as α. The ring is in a $^OH_5$ conformation. The unusual coupling pattern observed for H1^B and H4^B in the β-anomer of **14** was observed here also (Figure 4). H1^B generates a quartet at δ = 5.08 ppm with a five-bond coupling of 2.4 Hz toward H4^B, which could not be

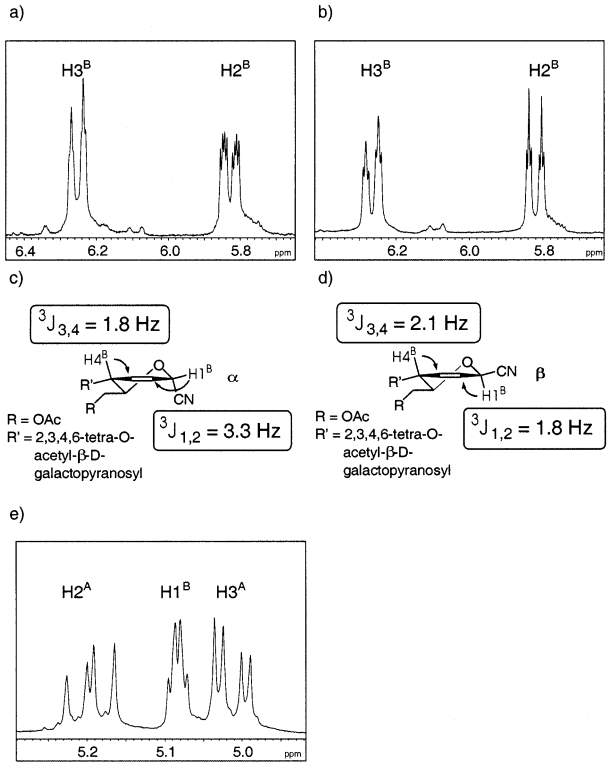


FIGURE 4. Compound **15**: (a) ^{1}H NMR spectrum (detail, α); (b) ^{1}H NMR spectrum (detail, *β*); (c) configuration and conformation (α); (d) configuration and conformation (*β*); (e) unusual five-bond coupling between H1^B and H4^B (*β*-anomer).

investigated because its signal at ~4.1 ppm heavily overlaps with other signals.

Compound **16** was obtained as a 1:1 mixture of α- and *β*-anomers. The coupling constants for H2^B and H3^B are virtually identical to those of **15**. The unusual coupling pattern observed for H1^B and H4^B in the *β*-anomer of **14** was observed here also. H1^B causes a quartet at $\delta = 5.05$ ppm including a five-bond coupling of 2.1 Hz toward H4^B, which could not be investigated because its signal at ~4.26 ppm heavily overlaps with other signals.

Compound **17** was assigned the α-configuration analogously. The unusual coupling pattern observed for H1^B and H4^B in the *β*-anomer of **14** was observed here also (Figure 5). H1^B generates a quartet at $\delta = 5.06$ ppm with a five-bond coupling of 2.1 Hz toward H4^B. Proton 4^B gave a double quartet at $\delta = 5.32$ ppm, which is shifted downfield because the OH group at carbon 4^B is acetylated.

The NMR values found for vinylic and allylic coupling constants in the 2,3-enopyranosyl systems of **2**, **6**, **14**−**17**, **19**, and **20** subsequently allowed us to assign the configuration of the C−C linkage and conformation of rings **A** and **B** in **8** and **10**. The NMR spectra of the tetramers that resulted from dimerization of per-*O*-acetyl cellobial and per-*O*-acetyl lactal were characterized by heavily overlapped signals except for H1^A, H2^A, H2^B, and H3^B.

The signal of H2^A in **8** showed coupling constants of $^3J_{2,1} = 3.6$ Hz, $^3J_{2,3} = 11.1$ Hz, and $^3J_{2,1B} = 9.6$ Hz (Figure 6). This was consistent with an α-configuration at C1^A and a $^4C_1$-conformation of ring **A**. The vinylic protons H2^B and H3^B displayed a double double doublet ($\delta = 5.63$ ppm) and a double triplet ($\delta = 5.91$ ppm), respectively. The coupling constants of H2^B were measured with $^3J_{2,1} = 3.0$ Hz, $^3J_{2,3} = 10.8$ Hz, and $^4J_{2,4} = 1.8$ Hz. The values for H3^B were $^4J_{3,1} = 1.8$ Hz, $^3J_{2,3} = 10.8$ Hz, and $^3J_{3,4} = 1.8$ Hz. The coupling constants of H2^B ($^3J_{2,1}$ and $^4J_{2,4}$) and H3^B ($^4J_{3,1}$ and $^3J_{3,4}$) were compared to vinylic and allylic coupling constants found in **2**, **6**, **14**−**17**, **19**, and **20**. The configuration at C1^B in **8** was assigned as α with a $^OH_5$-conformation of ring B.

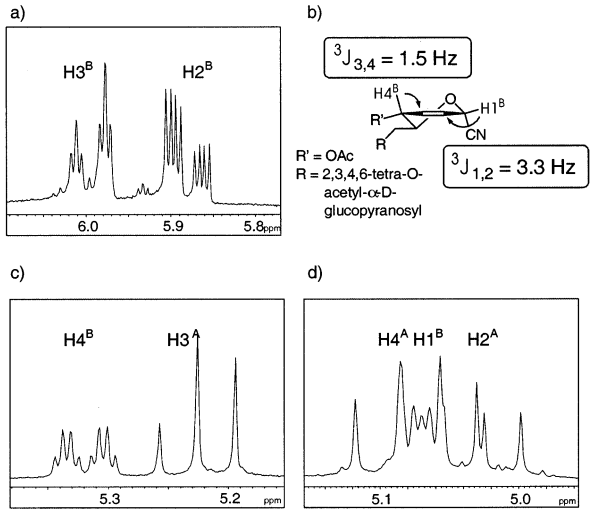


FIGURE 5. Compound **17**: (a) ^{1}H NMR spectrum (detail); (b) configuration and conformation; (c and d) unusual five-bond coupling between H1^B and H4^B (α-anomer)

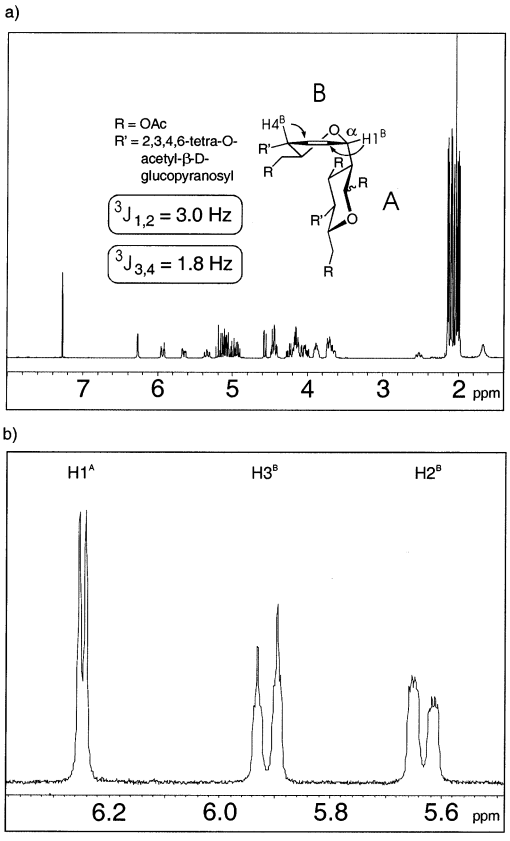


FIGURE 6. Compound **8** (a and b): ^{1}H NMR spectrum, details, and conformation. Compare splitting patterns of H3^B and H2^B to Figure 4a.

Similarly, **10** showed coupling constants for H2^B (δ = 5.66 ppm) with $^3J_{2,1}$ = 3.0 Hz, $^3J_{2,3}$ = 10.8 Hz, and $^4J_{2,4}$ = 1.5 Hz. The signal of H3^B (δ = 5.96 ppm) was split into a double triplet with coupling constants of $^4J_{3,1}$ = 1.8 Hz, $^3J_{2,3}$ = 10.8 Hz, and $^3J_{3,4}$ = 1.8 Hz. On the basis of the same arguments outlined above, the configuration at C1^B in **10** was α and the conformation of ring B was $^OH_5$.

Conclusions

New and mild methods for the dimerization of acetylated glycals and for the introduction of a cyanide functionality into acetylated glycals and into acetylated 2-C-2-deoxy pyranoses have been developed. 2,3-Enopyranosyl cyanides and 2-C-2-deoxy pyranosyl cyanides were isolated in moderate to excellent yields. The reagent $Hg(CN)_2/HgBr_2$/TMSCN is compatible with 1,4- and 1,6-O-glycosidic bonds contrary to the method published by DeLas Heras.[27] The unprecedented additional elimination of acetic acid in **19** and **20** as opposed to a plain displacement of the anomeric acetate in **18** may be attributed to a delicate balance of nucleophilicity and basicity of the cyanide anion on one hand and the steric position of the C4^B-acetoxy group as a potential internal base on the other hand. NMR analysis of the vinylic and allylic coupling constants in the 2,3-enopyranosyl rings of the products gave a new diagnostic tool for the assignment of configuration and conformation of such ring systems.

Experimental Section

Flash chromatography was performed on silica gel from J. T. Baker (40 μm, ρ = 0.5 g/cm^3). Solvents of HPLC grade were used without further purification unless stated otherwise. TLC was done on SiO_2 plates from Analtech with the same solvents, unless stated otherwise. ^{1}H NMR and ^{13}C NMR data were acquired at 300 MHz. Melting points are uncorrected. Optical rotations were measured against the sodium 589 nm line in $CHCl_3$, unless stated otherwise. Elemental analysis was done by Desert Analytics, Tucson, AZ.

Mass spectral data were obtained with an infusion pump in positive and negative atmospheric pressure chemical ionization mode. Solutions of c = 100 nM in MeCN were prepared. A 250 μL syringe was used for continuous injection at a rate of 0.3 mL/h. N_2 was used as a desolvating gas at a pressure of 700 psi. Protonated, sodiated, and potassiated molecules are abbreviated as $(M + H)^+$, $(M + Na)^+$ and $(M + K)^+$, respectiveley. Radical anions are abbreviated as $(M^{\bullet -})$.

Chemicals were purchased commercially and used without further purification unless specified.

General Procedure for Preparation of Glycals (1, 3, 5, 7, 9, 11, 12). A 500 mL round-bottom flask was charged under nitrogen with CH_2Cl_2 (100 mL, previously dried over 4 Å molecular sieves overnight) and $TiBr_4$ (3.23 g, 0.6 equiv).[33] Glacial acetic acid (10 drops) was added with stirring followed, after 10 min, by the dropwise addition of D-cellobiose-octaacetate (10 g, 14.7 mmol) in CH_2Cl_2 (100 mL) over 0.5 h. The solution was stirred at rt for 24 h. Emergence of the glycosyl bromide was monitored by TLC.[34] The reaction was quenched with portions of $NaHCO_3$ (5 × 1 g). Each portion was followed by H_2O (5 mL) over the course of 0.5 h. Vigorous stirring (CO_2 evolution) was continued for 2 h. The separated organic layer was filtered through a pad of Celite. The filter cake was washed with CH_2Cl_2 (2 × 20 mL), and the combined CH_2Cl_2 solutions were dried (Na_2SO_4) with stirring for 2 h.

In a three-necked 500 mL round-bottom flask, a Zn/Cu couple (8 g, 8 equiv)[35] was suspended in CH_2Cl_2 (20 mL, previously dried over 4 Å molecular sieves overnight). The slurry was heated to reflux in an ultrasonic bath; 1-methyl imidazole (1.4 mL, 1.2 equiv) and molecular sieves (4 Å, 1 g) were added, and the slurry was kept at reflux in the ultrasonic bath for another 0.5 h. The solution of the glycosyl bromide in CH_2Cl_2 was added via dropping funnel into the refluxing mixture over the course of 1 h. After the mixture had been sonicated at reflux for 12 h, the reaction was normally complete.[36] The mixture, cooled to rt, was filtered through a pad of Celite. Evaporation of the solvent in vacuo and crystallization of the residue from the minimal amount of hot MeOH (~20 mL) gave 3,6-di-*O*-acetyl-4-[2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl]-2-deoxy-D-*arabino*-hex-1-enopyranose (hexa-*O*-acetyl-D-cellobial, **7**, 7.4 g, 90%, mp 135−137 °C (lit.[32] 137 °C), TLC system 4:6 hex/EtOAc, R_f 0.72, $[\alpha]^{18}_D$ −19° (*c* 1.2; lit.[32] −20°).[37]

Other glycals (**1**, **3**, **5**, **9**, **11**, **12**) synthesized under aprotic conditions along with yields and physical properties are listed in Table 1.

Improved Procedure for Glycal Dimerization (8 and 10). A fresh solution of CH_2Cl_2 (5 mL), Ac_2O (1.0 equiv), and $BF_3{\cdot}Et_2O$ (0.1 equiv) was stirred at 0 °C for 15 min with a solution of the glycal (1.0 g) in CH_2Cl_2 (5 mL) and took on a deep purple color when allowed to reach rt over the next hour. The color changed to light yellow when the solution was stirred vigorously with saturated aqueous $NaHCO_3$ (2 equiv) for 0.5 h. The separated organic phase was dried (Na_2SO_4). After removal of the solvent in vacuo, flash chromatography as specified gave the products.

1,3,6-Tri-*O*-acetyl-2-C-[6-*O*-acetyl-2,3-dideoxy-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-α-D-*erythro*-hex-2-enopyranosyl]-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-2-deoxy-α-D-glucopyranose (8). Obtained from **7** (0.5 g, 0.89 mmol) by dimerization, the product was isolated by flash chromatography (20 g SiO_2, EtOAc/hexane: [2:3] 250 mL, [2:1] 2 × 250 mL) and crystallized from the solvent after 1 day. Colorless crystals: yield 20%, mp > 250 °C, no decomposition, R_f (7:3 EtOAc/hexane) 0.56, $[\alpha]^{25}_D$ −51° (*c* 1).

1,3,6-Tri-*O*-acetyl-2-C-[6-*O*-acetyl-2,3-dideoxy-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-α-D-*erythro*-hex-2-enopyranosyl]-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-2-deoxy-α-D-glucopyranose (10). Obtained from **9** (1.0 g, 1.78 mmol) by dimerization, the product was isolated by flash chromatography (40 g SiO_2, EtOAc/hexane: [2:3] 250 mL, [2:1] 2 × 250 mL). R_f (4:3 EtOAc/hexane) = 0.42 and 0.29. Crystallization from 1:1 THF/(i-Pr)$_2$O gave colorless crystals (mp 103−105 °C, yield 40 mg, 4%), which were a mixture of four compounds (1:1:1:1). The NMR spectrum revealed eight vinylic carbons, four C2^B, and four C1^B. Careful crystallization of the remainder from THF/(i-Pr)$_2$O (added to turbidity) gave

(36) All glycals char noticeably faster than the starting material or bromides. The acetylated glycals of the monosaccharides run faster on TLC than the bromides. The acetylated glycals of the disaccharides run only slightly faster than the bromides, possibly leading to misinterpretations of TLC data. Incomplete conversion from disaccharidic bromides to glycals could be detected as follows. A TLC plate was spotted with the reaction mixture. After moistening the plate with water vapor, it was allowed to sit for 3 h on the benchtop. In case of incomplete reaction, any remaining bromide was hydrolyzed and showed up after development and charring with a lower R_f-value than the glycal. The acetylated glycals of the disaccharides, when isolated as syrups, were not stable for a long time. If possible, they should be used directly in subsequent chemical transformations. However, they can be stored in a freezer for several days without serious decomposition. In crystalline form they can be stored for prolonged times at rt.

(37) Spectral properties are as follows: ^{1}H NMR (300 MHz, $CDCl_3$, primed protons refer to the unsaturated ring) δ 2.00 (s, 3H, $CH_3{}^{ac}$), 2.02 (s, 3H, $CH_3{}^{ac}$), 2.05 (s, 3H, $CH_3{}^{ac}$), 2.06 (s, 3H, $CH_3{}^{ac}$), 2.10 (s, 3H, $CH_3{}^{ac}$), 2.13 (s, 3H, $CH_3{}^{ac}$), 3.69 (ddd, 1H, H5), 3.97−4.22 (m, 4H), 4.32 (dd, 1H, H4′), 4.45 (dd, 1H, H6a′), 4.69 (d, 1H, H1), 4.83 (dd, 1H, H2′), 4.98 (dd, 1H, H2), 5.09 (t, 1H, H3), 5.19 (t, 1H, H4), 5.43 (ddd, 1H, H3′), 6.41 (dd, 1H, H1′); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.99, 21.10, 21.27, 21.42, 62.14, 68.41, 68.93, 71.70, 72.35, 73.08, 74.67, 74.99, 99.35, 100.83, 145.63, 169.35, 169.45, 170.42.

colorless crystals after several days: yield 100 mg, 10% with respect to starting material, mp 186−188 °C, $[\alpha]^{25}_D$ + 43° (*c* 0.5).

4,6-Di-*O*-acetyl-2,3-dideoxy-α/*β*-D-erythro-hex-2-enopyranosyl cyanide (13). To a mixture of $Hg(CN)_2$ (25.1 g, 97.6 mmol) and $HgBr_2$ (2.14 g, 5.94 mmol) in MeCN (60 mL) and THF (30 mL) at 0 °C was added TMS−CN (8 mL, 60.0 mmol) followed by 3,4,6-tri-*O*-acetyl-D-glucal **1** (4.0 g, 14.7 mmol). The colorless suspension was stirred at room temperature under N_2 for 20 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to a brown residue that was extracted with CH_2Cl_2 (100 mL). The extract was washed with saturated aqueous $KHCO_3$ (100 mL), H_2O (100 mL), and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), and concentrated in vacuo to an oil. The residual oil was crystallized from THF and $(i\text{-}Pr)_2O$ to give **13**: yield 1.51 g (6.3 mmol, 43%), mp 58−86 °C, $[\alpha]^{20}_D$ −14.5° (*c* 1).

The mother liquor from the crystallization was evaporated. The residue was subjected to column chromatography (100 g SiO_2, 1:2 EtOAc/hexane) to give the *β*-anomer: yield 1.4 g (5.7 mmol, 39%). Recrystallization from $(i\text{-}Pr)_2O$ at −78 °C afforded colorless crystals: mp 60−60.5 °C, $[\alpha]^{20}_D$ +192° (*c* 1).

General Synthetic Procedure for 2,3-Enopyranosyl Cyanides (14−17). The suspension of the glycal (7.6 mmol), $Hg(CN)_2$ (9.7 g, 38 mmol), $HgBr_2$ (0.2 g, 0.6 mmol), and TMSCN (1.4 mL, 10 mmol) in absolute THF (16 mL) and absolute acetonitrile (30 mL) was warmed (60 °C bath) for 4 h. The solvents were removed in vacuo. The suspension of the residue in CH_2Cl_2 (20 mL) was filtered through Celite to give the products' solution, which was subjected to flash chromatography on silica gel with hexane/EtOAc gradients specified for the individual preparations.

6-*O*-Acetyl-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1,2,3-trideoxy-*β*-D-2-enopyranosyl Cyanide (14). From **7** (4.25 g, 7.6 mmol). Flash-column chromatography (120 g SiO_2, EtOAc/hexane: [1:6] 300 mL, [3:4] 300 mL, [1:1] 300 mL) of the product solution gave the *β*-anomer, which crystallized upon removal of the solvent: yield 2.1 g (4.0 mmol, 52%), mp 142−144 °C, $[\alpha]^{25}_D$ +10° (*c* 1), R_f 0.55 (9:1 CH_2Cl_2/EtOAc).

6-*O*-Acetyl-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-1,2,3-trideoxy-α/*β*-D-2-enopyranosyl Cyanide (15). From **9** (2.3 g, 4.1 mmol). Flash-column chromatography (90 g SiO_2, EtOAc/hexane: [1:6] 300 mL, [3:4] 300 mL, [1:1] 300 mL) of the product solution gave an α/*β*-mixture: yield 1.42 g (2.7 mmol, 65%). The predominant *β*-cyanide (3:1, 0.3 g) could be crystallized from i-PrOH (3 mL): mp 147−149 °C, $[\alpha]^{25}_D$ +134° (*c* 1), R_f 0.73 (9:1 CH_2Cl_2/EtOAc). A later fraction gave the α-anomer as an oil (0.11 g): $[\alpha]^{25}_D$ +16° (*c* 1), R_f 0.69 (9:1 CH_2Cl_2/EtOAc).

6-*O*-Acetyl-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1,2,3-trideoxy-α/*β*-D-2-enopyranosyl Cyanide (16). From **11** (2.3 g, 4.1 mmol). Flash-column chromatography (90 g SiO_2, EtOAc/hexane: [1:6] 300 mL, [3:4] 300 mL, [1:1] 300 mL) of the product solution gave an α/*β*-mixture (1:1): yield 1.12 g (2.1 mmol, 52%). The α-anomer could be crystallized from i-PrOH: yield 120 mg (0.23 mmol, 5.5%), colorless crystals, mp 130−132 °C, $[\alpha]^{25}_D$ +105° (*c* 1), R_f 0.68 (9:1 CH_2Cl_2/EtOAc).

4-*O*-Acetyl-6-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1,2,3-trideoxy-α/*β*-D-2-enopyranosyl Cyanide (17). From **12** (1.2 g, 2.1 mmol). Flash-column chromatography (90 g SiO_2, EtOAc/hexane: [1:6] 300 mL, [3:4] 300 mL, [1:1] 300 mL) of the product solution gave a 4:1 α/*β* mixture: yield 0.68 g (1.3 mmol, 62%). The α-anomer was crystallized from i-PrOH: yield (α-anomer) 200 mg (0.72 mmol, 31%), colorless crystals, mp 165−167 °C, $[\alpha]^{25}_D$ −45° (*c* 1), R_f 0.57 (9:1 CH_2Cl_2/EtOAc).

General Synthetic Procedure for 2-C-2-Deoxy-pyranosyl Cyanides (18−21). The suspension of the Ferrier dimerization product (0.07 mmol), $Hg(CN)_2$ (0.1 g, 0.35 mmol), $HgBr_2$ (0.002 g, 0.006 mmol), and TMSCN (0.014 mL, 0.1 mmol) in absolute THF (0.3 mL) and absolute MeCN (0.6 mL) was stirred at rt for 24 h. After completion of the reaction (TLC), the solvent was removed in vacuo. The suspension of the residue in CH_2Cl_2 (20 mL) was filtered through Celite. Isolation and purification are described under the individual preparations.

3,4,6-Tri-*O*-acetyl-2-C-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-deoxy-α/*β*-D-glucopyranosyl Cyanide (18). Compound **2**[24] (80 mg, 0.147 mmol) was completely consumed after 36 h at rt [TLC (4:3 EtOAc/hexane)] and gave one apparent product, which was crystallized from EtOH (2 days at −20 °C): yield 70 mg (93%), mp 114−116 °C, $[\alpha]^{20}_D$ +225° (*c* 0.5). This product was an anomeric mixture (NMR). A sample of the *β*-anomer was isolated by flash chromatography (5 g SiO_2, EtOAc/hexane: [1:6] 20 mL, [3:4] 20 mL, [1:1] 20 mL) as an oil, which aided in the NMR spectroscopic assignment of both anomers in the mixture.

3,4,6-Tetra-*O*-acetyl-2-C-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-2-deoxy-α-D-galactopyranosyl Cyanide (19). Compound **4**[24] (3.0 g, 5.51 mmol) was completely consumed after 36 h at rt [TLC (4:3 EtOAc/hexane) and gave an anomeric mixture: yield 2.28 g (4.46 mmol, 81%, α/*β* ratio 10:1, R_f 0.74 and 0.54, 4:3 EtOAc/hexane) without apparent side products. The α-anomer was crystallized from i-PrOH to give white crystals: yield 2.0 g (79%), mp 94−96 °C, $[\alpha]^{25}_D$ −125° (*c* 1).

4-*O*-Acetyl-2-C-(4-*O*-acetyl-2,3-dideoxy-α-L-*threo*-hex-2-enopyranosyl)-2,3-dideoxy-2-eno-α-L-fucopyranosyl Cyanide (20). Crude **6**[24] (2.3 g, 5.37 mmol, α/*β* 4:1) was completely consumed after 36 h at rt. Two products [TLC (4:3 EtOAc/hexane)] were observed: yield 0.61 g (1.82 mmol, 34%, α/*β* 10:1). The α-anomer was crystallized from MeOH: yield 0.59 g (30%), mp 137−139 °C, $[\alpha]^{25}_D$ +413° (*c* 1).

3,6-Di-*O*-acetyl-2-C-[6-*O*-acetyl-2,3-dideoxy-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-α-D-*erythro*-hex-2-enopyranosyl]-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-1,2-dideoxy-α-D-glucopyranosyl Cyanide (21). Compound **8** (80 mg, 0.07 mmol) was completely consumed after 24 h [TLC (7:3 EtOAc/hexane)]. Removal of the solvent in vacuo gave a syrup, which was digested with dry Et_2O (5 mL) for 2 h at reflux to give the α-anomer as colorless, cotton-like crystals: yield 40 mg (52%), mp 173−175 °C, $[\alpha]^{25}_D$ −16° (*c* 1).

Acknowledgment. We thank Dr. Allen D. Hunter for helpful discussion of molecular structures. Financial support by the Chemistry Department of the University of the Pacific is gratefully acknowledged.

Supporting Information Available: Complete NMR assignment of compounds **8**, **10**, and **13**−**21**, elemental analyses, and mass spectrometric data. This material is available free of charge via the Internet at http://pubs.acs.org.

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