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Neighboring-group participation in benzylidene acetal ring-opening of a 2-cyano-2-deoxypyranoside derivative by diethylaluminum cyanide

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Dedicated to Professor Dr Edmundo A. Rúveda (Rosario, Argentina) on the occasion of his 70th birthday

Abstract

The oxirane ring-opening of an anhydro sugar with diethylaluminum cyanide (Et_2AlCN) is a direct approach for obtaining a cyano derivative. Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside showed anomalous chemical behavior when treated with Et_2AlCN. The reaction afforded the corresponding β-cyanohydrin as the minor component from a mixture of compounds resulting from the benzylidene acetal ring-opening caused by the attack of ethyl or cyano groups.

Keywords: Benzylidene acetal; 2-Cyano-2-deoxypyranoside; Diethylaluminum cyanide

1. Introduction

Cyano sugars constitute versatile intermediates in natural product[1–5] and nucleoside synthesis.[6–8] Some naturally occurring monosaccharides are branched-chain sugars, whose side chain generally contains one or more carbon atoms. Such branched-alkyl, -formyl, or -amino sugars are part of many compounds that have important biological activities.[9]

The oxirane ring-opening of an anhydro sugar is a straightforward approach for regioselective introduction of a nucleophile into a pyranoside ring. Usually, this procedure affords a *trans*-diaxial substitution pattern. Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) is a useful starting material,[10] although it is reluctant to undergo a nucleophilic epoxide ring-opening under mild conditions.[11]

Inch and Lewis[12] studied the reactivity problems of some 2,3-anhydro sugars with several Grignard and alkyl-(or aryl)-lithium reagents and reported their tendency to afford reduction or elimination by-products. Gero and co-workers[13,14] developed a procedure for introducing a 1,3-dithianyl residue, but this required several days of reaction at low temperature, imposing certain operative difficulties. Kazmi and co-workers[15] reported the oxirane ring-opening of the same anhydro sugars, giving moderate yields, by using cyanotrimethylsilane and a catalytic amount of aluminum chloride.

Based on these precedents, we decided to reexamine Guthrie's procedure[16,17] for the introduction of a cyano group into a pyranose skeleton, and found that treating epoxide **1** with diethylaluminum cyanide (Et_2AlCN) in dichloromethane at room temperature afforded the corresponding β-cyanohydrin **2** in high yield.[18] Simultaneously, Bobek and co-workers[19] reported the epoxide ring-opening of pentofuranoside derivatives with the same reagent, observing variable yields and regioselectivities (Scheme 1).

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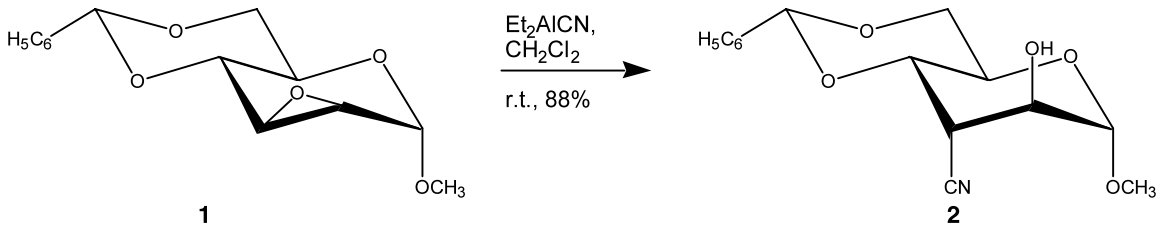


Scheme 1.

These conditions were very efficient for obtaining the 3-cyano-3-deoxy derivative, and we envisaged the same approach for synthesizing the 2-cyano-2-deoxy derivative from methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**3**), according to the Fürst–Plattner rule.[20]

2. Results and discussion

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was converted into methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**3**) by the literature procedure.[21] However, when **3** was treated with Et_2AlCN, the reaction was very slow and the β-cyanohydrin **4** was isolated as only a minor component from a mixture of two more polar products by thin layer chromatography (TLC) analysis.

Similar reactivity problems with this substrate had been reported by Guthrie and co-workers,[17] but the by-products were not identified and the reaction was not further studied. It was suggested that this behavior was related to the more complicated nature of the reaction with the anhydro-alloside because of further reaction of the expected 2-cyano-2-deoxy-*altro* product. An explanation then offered was the fact that the carbon–oxygen bonds in the ring and the methoxy group are β to the cyano group and therefore labile to base. This explanation is in agreement with Inch and Lewis' results[12] and a precedent in other reports.[1,15,22,23]

Our synthetic interest in substrate **4** led us to reinvestigate this reaction to find a suitable way of optimizing it. The spectroscopic data of compound **4** were consistent with the expected chemical structure.

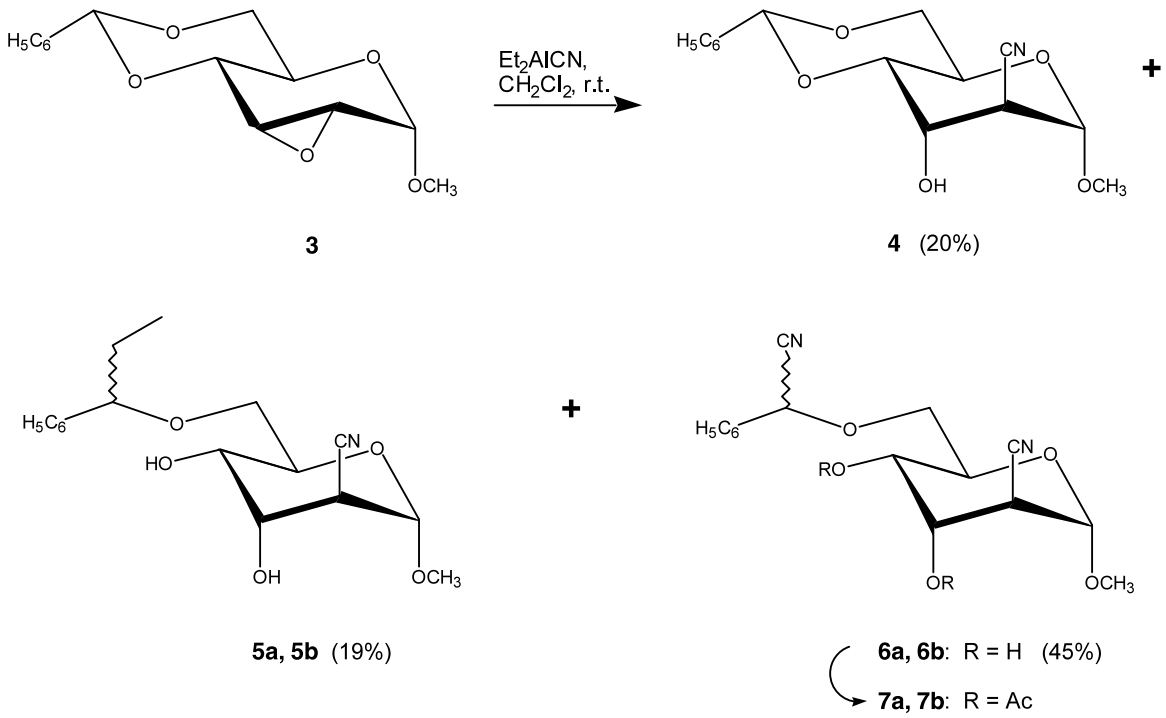
The ^{1}H NMR spectra of products **5** and **6** revealed that both had two very close sets of signals of equal intensity, with similar chemical shifts and coupling constants. This observation indicated that each sample was a mixture of epimers, which were not separable by standard flash chromatographic procedures.

It was evident from the ^{1}H NMR spectrum of the epimeric mixture of **5a** and **5b** that the epoxide had undergone the expected nucleophilic opening, but the benzylidene acetal ring had also been cleaved with concomitant alkylation of the benzylic carbon by an ethyl group. In the case of **6a** and **6b,** the ^{1}H NMR spectra showed that they had undergone similar ring-opening, but the ^{13}C NMR spectrum indicated that another cyano group was attached at the benzylic position (Scheme 2).

The ^{1}H and ^{13}C NMR signals of **5a**,**b** and **6a**,**b** were assigned based on homo and heteronuclear 2D NMR techniques. The ^{1}H NMR spectrum of **5a**,**b** showed a CH_3 triplet at 0.90 ppm, a complex multiplet for CH_2 at 1.80 ppm, and the benzylic proton signal was shifted upfield at 4.26 ppm and appears as a multiplet. The pyranose backbone was confirmed by the anomeric proton singlet at 4.97 ppm, and two methoxy groups, one for each epimer, as sharp singlets at 3.41 and 3.43 ppm. The ^{13}C NMR spectrum indicated an extra methyl group at 10.1 ppm and two methylene groups, one for each epimer, at 30.7 and 30.8 ppm, respectively. The signals for the benzylic carbons were shifted upfield in both epimers and appeared at 84.6 and 85.0 ppm. A very characteristic peak at 116.3 ppm was assigned to the cyano group introduced by oxirane ring-opening, and the signal for C-2 appeared at 36.6 ppm showing the shielding effect of the cyano group, and confirming the regioselectivity of the attack on the epoxide. The IR spectrum also showed an absorption peak at 2260 cm^{-1} corresponding to the cyano group.

Determination of the regioselectivity of the 1,3-dioxane ring-opening was achieved by a C–H correlation via long-range coupling (COLOC)[24] that clearly showed a cross peak between the benzylic proton and C-6. This evidence allows us to postulate the formation of the primary benzyl ether.

Analysis of the proton NMR spectrum of the mixture **6a**,**b** also showed duplicated singlet peaks at: 3.4/3.5, 4.99, 5.02 and 5.49 ppm corresponding to the methoxy groups, anomeric, and benzylic protons, respectively, for each isomer. The ^{13}C NMR showed two different sets of peaks at 115.7/115.8 and 117.0/117.1 ppm assigned to the cyano groups attached at C-2 and C-7. The signals for both carbons are also shifted upfield by the shielding effect of the cyano group, C-2 resonated at 36.7 ppm for both epimers and C-7 at 71.3 and 71.4 ppm for each of them. The IR spectrum showed a distinctive absorption band at 2230 cm^{-1} for the cyano group. The C–H correlation via long-range coupling, performed to determine the course of the benzylidene ring-opening,



Scheme 2.

was not conclusive and it was necessary to prepare the corresponding acetates **7a**,**b**.

In the ^{1}H NMR spectrum of **7a**,**b**, the H-4 protons have a chemical shift of 5.35 ppm whereas the same protons in **6a**,**b** appear at 3.73–4.24 ppm, this deshielding effect is indicative of the position occupied by the free hydroxyl group.

It could be assumed that the lack of stereoselectivity in the benzylidene ring-opening may be due to the attack of the nucleophile through an open-chain oxonium ion or through a hydrogen-bonded carbene model, like the one proposed by Frejd and co-workers[25] with no facial selectivity. We did not consider an isomerization process induced by base during the reaction work up for the cyano derivatives **6a**,**b**, because this process could not explain the same result for the ethyl derivatives **5a**,**b**.

We did not detect any by-product resulting from β-elimination, nor the benzylidene acetal ring-cleavage without the corresponding epoxide ring-opening. This observation led us to consider that the presence of the aluminum β-alkoxy-nitrile was necessary to cause the benzylidene ring-opening.

In order to secure evidence of the intervention of chelated species, we treated in parallel experiments the pure methyl 4,6-*O*-benzylidene-2-cyano-2-deoxy-α-D-altropyranoside (**4**) and methyl 4,6-*O*-benzylidene-3-cyano-3-deoxy-α-D-mannopyranoside (**2**) with Et_2AlCN. With the first one we again obtained the 1:1 epimeric mixture of compounds **5a**,**b** and **6a**,**b**, whereas with the latter, the starting material was recovered completely after work up.

While it is premature to propose a mechanism taking into account our observations, particularly because of the presence of multiple coordinating sites in the substrate, the results suggest that chelation of the aluminum center of the alkoxide with O-4 plays an important role in promoting nucleophilic attack on the benzylic carbon and determining the regiochemistry of the ring cleavage. The affinity of the Lewis acid for this site in the aluminum alkoxide derivative **8** is probably attributable to the favorable spatial disposition of O-4 (Fig. 1).

To test this hypothesis, we chose to block the free hydroxyl group present in compound **4** as the corresponding benzyl ether **9** and acetate **10**. Both compounds were treated with Et_2AlCN under the same conditions previously mentioned, but no reaction was observed (Scheme 3).

In order to determine whether this chemical behavior could be extended to other, related methyl 4,6-*O*-benzylidene-glycopyranosides, compounds **11**–**15** were

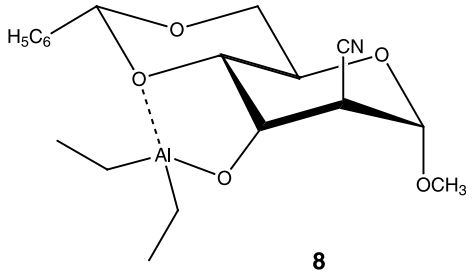
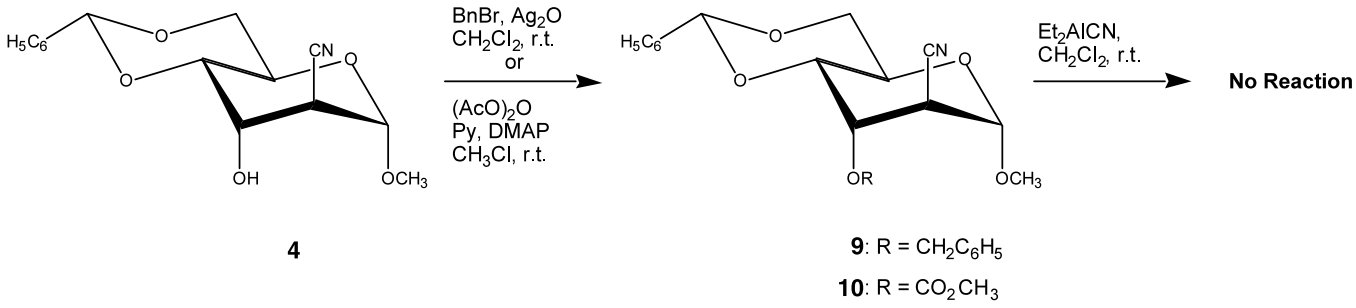


Fig. 1. Possible chelated intermediate.



Scheme 3.

treated with Et_2AlCN under standard conditions. These experiments could provide information regarding the effect of the stereochemistry at C-3, the relative position of the hydroxyl group, and the substituents at C-2 (Fig. 2).

Substrates **11**–**14** did not react with Et_2AlCN even after longer reaction times than those used with compound **4**, whereas bromohydrin **15** underwent intramolecular nucleophilic substitution, affording the corresponding epoxide **3** in 20% yield and recovering 77% of the starting material. Nagata and co-workers[26] assumed the intermediacy of the corresponding epoxide in the direct conversion of β-bromohydrins into β-cyanohydrins when treating the former with hydrogen cyanide–triethylaluminum. In our case, the rate of oxirane ring-closure must be higher than the corresponding ring-opening, allowing isolation of the epoxide without its further transformation into the cyanohydrin derivative. This result clearly demonstrated the reactivity of the aluminum alkoxide and the stability of compound **3**. On the other hand, full analysis of the results do not provide a conclusive explanation for the observed chemical phenomenon; however, it demonstrates that formation of the O-3 aluminum alkoxide is a requirement, but not the unique one, for the benzylidene acetal cleavage.

The NMR spectra of the aluminum alkoxides prepared from the reaction of alcohols **2**, **4** and **12** with trimethylaluminum add further evidence in favor of the formation of the aluminum alkoxide chelate with O-4 and its probable effects on the aromatic portion of the molecule, as it is evident by the chemical-shift differences ($\Delta\delta$) in Table 1.

The ^{13}C NMR spectrum of the aluminum alkoxide derived from the β-cyanohydrin **4** shows that the benzylic carbon (C-7) suffers higher deshielding than the equivalent carbon in the other two substrates, and a similar effect is observed with C-4. The difference in the shielding effect observed in C-*ipso* is also remarkable. These observations support the formation of an aluminum chelated species **8**.

Several literature reports are in agreement with our investigations. De las Heras and co-workers[22] used trimethylsilyl cyanide, in combination with a Lewis

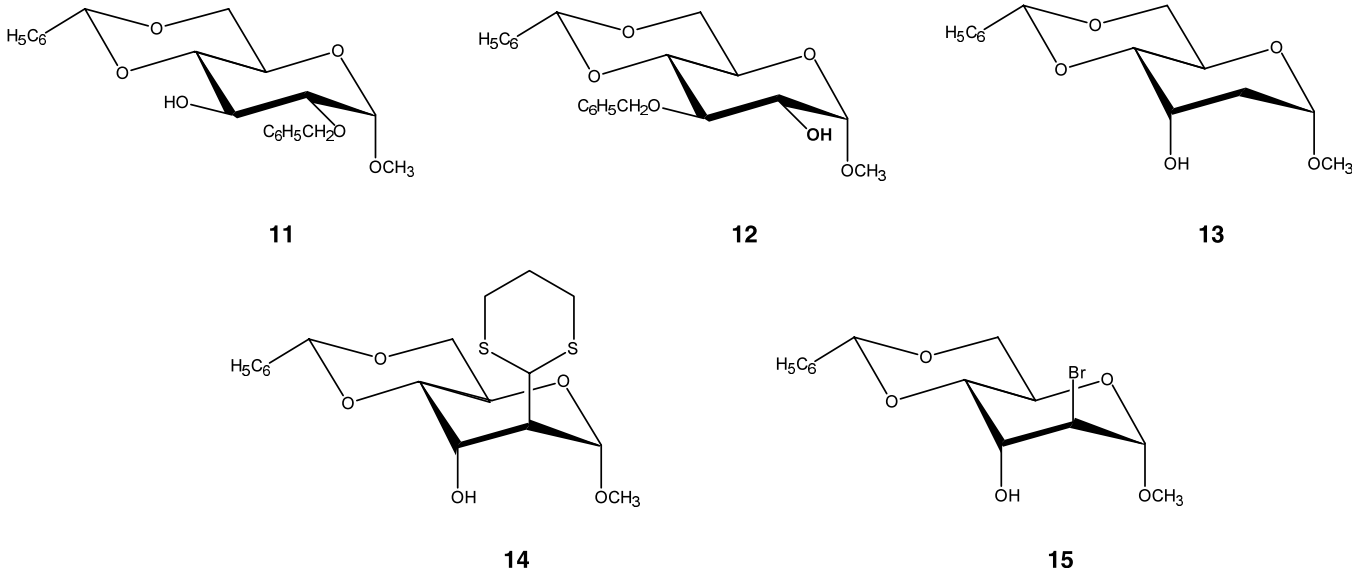


Fig. 2. Other substrates tested.

Table 1
Selected 13C NMR data [a]

Carbon	$\Delta\delta$: **2**	$\Delta\delta$: **4**	$\Delta\delta$: **13**
1	−1.6	−0.5	−0.3
2	1.8	−0.6	−0.3
3	−0.3	0.6	0.3
4	−1.2	0.2	0.2
5	0.4	−0.2	0.1
6	−0.6	0.1	0.2
7	0.3	0.6	0.3
Ipso	−0.4	−1.0	−0.4
OCH_3	0.6	0.1	+0.3
CN	−1.6	−0.3	

$\Delta\delta$: $\delta_{R-OAl(Et)_2} - \delta_{R-OH}$ ppm.

[a] We could not use the alkoxide formed with Et_2AlCN because this reagent caused the transformation of **4** into **5a**,**b** and **6a**,**b** during the time the measurements were made, making the spectra difficult to analyze because of the complex mixture of compounds present in solution.

acid, to obtain mandelonitrile ethers, by opening of the 1,3-dioxane benzylidene ring of **3** with low regioselectivity at room temperature, yielding a mixture of the 6-*O*- and 4-*O*-(cyanophenylmethyl) regioisomers of the anhydro derivative. The regioselectivity was greatly enhanced when methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside was used as the starting material, affording methyl 6-*O*-(cyanophenylmethyl)-2,3-di-*O*-tosyl-α-D-glucopyranoside in 80% yield as the only product. This is a clear precedent, because the product obtained, and the regioselectivity observed with a substrate that has an adequate coordination site vicinal to the benzylidene acetal ring, is comparable to our work. These assumptions are also in accord with the results reported by Frejd and co-workers.[27] They studied the substituent effects on the alkylative cleavage of glycosides with organoaluminun reagents, and noted the importance of aluminum alkoxide formation in some of their examples in allowing the reaction to proceed. In another report, they also mentioned the difficulties encountered when the primary alcoholate, product of the oxirane ring-openings of 2,3-anhydropentopyranosides with trimethylaluminum, underwent subsequent reaction with trimethylaluminum to give unknown compounds[23] thus constituting another coincidence with our example. Finally, Davis and co-workers[28] have shown that addition of 2-propanol to Et_2AlCN resulted in the irreversible formation of ethylaluminum cyanide alkoxide, which is capable of coordinating and activating the imine double bond and ultimately delivering cyanide to the C=N double bond. This result is applicable to alkoxide **8**, which could be the intermediate responsible for delivering the ethyl group intermolecularly.

3. Conclusions

We were able to isolate and identify the reaction by-products from the reaction of **3** with Et_2AlCN and prove that they did not originate from a β-elimination process. Instead they were the products of benzylidene acetal cleavage with concomitant nucleophilic attack by an ethyl or cyano group.

Interpretation of the results obtained from the benzylidene acetal cleavage with different substrates is not straightforward, however, some speculations are possible: the process may be induced by the neighboring aluminum alkoxide that coordinates with O-4, yielding a chelate structure **8**. This coordination could enhance the liability of the C-7–O-4 bond, thus making the C-7 susceptible to nucleophilic attack, but it still remains unclear as to the role of the cyano group at C-2 compared with other substituents at the same position.

4. Experimental

4.1. General methods

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage, Model 350 apparatus, and are uncorrected. Optical rotations were recorded with a Jasco DIP 1000 polarimeter. Infrared spectra were recorded on a Beckman Acculab 8 spectrometer. Nuclear magnetic resonance spectra were recorded on a Bruker AC-200 spectrometer with Me_4Si as the internal standard and chloroform-*d* as solvent.

Reactions were monitored by TLC on 0.25 mm E. Merck silica gel plates ($60F_{254}$), using UV light and anisaldehyde–H_2SO_4–AcOH as detecting agent. Flash column chromatography, using Merck silica gel 60H, was performed by gradient elution with mixtures of hexanes and increasing amounts of EtOAc.

Reaction were performed under argon with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

4.1.1. Methyl 4,6-*O*-benzylidene-2-*C*-cyano-2-deoxy-α-D-altropyranoside (4), methyl 2-*C*-cyano-2-deoxy-6-*O*-ethylphenylmethyl-α-D-altropyranoside (5a/b)- and methyl 2-*C*-cyano-6-*O*-cyanophenylmethyl-2-deoxy-α-D-altropyranoside (6a/b). Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**3**, 198.8 mg, 0.75 mmol) was azeotropically dried with anhydrous benzene under vacuum and dissolved in dry CH_2Cl_2 (3 mL) under argon. Diethylaluminum cyanide (1 M soln in toluene, 1.5 mL, 1.5 mmol) was added at room temperature (rt) to the magnetically stirred soln. Stirring was continued during 6 days at rt. The mixture was then diluted with

CH_2Cl_2 and poured onto ice–Na_2CO_3 soln. The organic layer was separated and the aqueous phase further extracted with CH_2Cl_2. The combined organic layers were washed with 10% aq NH_4Cl and brine and dried ($MgSO_4$). Concentration and purification by flash chromatography furnished **4** (43.9 mg, 20%) as a white crystalline solid and four other, more-polar products: **5a/b** (46.4 mg, 19%) and **6a/b** (108.1 mg, 45%); compound **4**: mp 198.5–200.0 °C (petroleum ether–$CHCl_3$); $[\alpha]_D$ +19.8 (*c* 0.71, $CHCl_3$); IR (KBr) ν_{max}: 3490, 2940, 2920, 2280 (CN), 1460, 1375, 1240, 1220, 1140, 1060, 1030, 990, 900, 820, 760 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.00 (broad, 1 H, OH), 3.29 (d, 1 H, $J_{2,3}$ 2.59 Hz, H-2), 3.46, (s, 3 H, OCH_3), 3.91 (t, 1 H, $J_{gem} = J_{5,6}$ 9.65 Hz, H-6ax), 4.34 (dd, 1 H, $J_{3,4}$ 2.89, $J_{4,5}$ 9.24 Hz, H-4), 4.20–4.45 (m, 3 H, H-3, H-5 and H-6eq), 4.97 (s, 1 H, H-1), 5.68 (s, 1 H, H-7), 7.30–7.50 (m, 5 H, aromatics); ^{13}C NMR ($CDCl_3$): δ 37.4 (C-2), 56.1 (OCH_3), 58.1 (C-5), 66.4 (C-3), 68.6 (C-6), 76.3 (C-4), 97.6 (C-1), 102.2 (C-7), 116.4 (C≡N), 126.1 (2 C, C_{ortho}), 128.3 (2 C, C_{meta}), 129.3 (C_{para}), 136.6 (C_{ipso}). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88, N, 4.81. Found: C, 61.69; H, 5.86; N, 4.78. Compounds **5a/b**: IR (NaCl) ν_{max}: 3480 (OH), 3030, 2940, 2260 (CN), 1460, 1390, 1230, 1115, 1080, 1010, 770, 710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (t, 3 H, $J_{16,17}$ 7.40 Hz, CH_2CH_3), 1.60–1.97 (m, 2 H, CH_2CH_3), 3.05 (s, 1 H, OH), 3.24 (dd, 1 H, $J_{1,2} = J_{2,3}$ 1.90 Hz, H-2), 3.41/3.43 (s, 3 H, OCH_3), 3.46–3.73 (m, 2 H, H-6ax and H-6eq), 3.73–4.00 (m, 2 H, H-3 and H-4), 4.05–4.33 (m, 2 H, H-5 and H-7) 4.97 (s, 1 H, H-1), 7.24–7.44 (m, 5 H, aromatics); ^{13}C NMR ($CDCl_3$): δ 10.1 (CH_2CH_3), 30.7/30.8 (CH_2CH_3), 36.6 (C-2), 55.8 (OCH_3), 66.0 (C-4), 67.7 (C-5), 67.8 (C-3), 68.6/68.8 (C-6), 84.5/85.0 (C-7), 97.0/97.1 (C-1), 116.3 (C≡N), 126.6 (2 C, C_{ortho}), 127.6 (C_{para}), 128.9 (2 C, C_{meta}), 141.5 (C_{ipso}); HRMS (CI): Calcd for $C_{17}H_{23}NO_5$: ($M+Na^+$) 344.147393. Found: ($M+Na^+$) 344.146854. Compounds **6a/b**: IR (NaCl) ν_{max}: 3470 (OH), 3020, 2930, 2230 (CN), 1705, 1480, 1440, 1260, 1175, 980, 735, 655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.67 (broad, 1 H, OH), 3.29 (m, 1 H, H-2), 3.41/3.45 (s, 3 H, OCH_3), 3.73–4.24 (m, 5 H, H-3, H-4, H-5, H-6ax and H-6eq), 4.99/5.02 (s, 1 H, H-1), 5.40/5.49 (s, 1 H, H-7), 7.40–7.58 (m, 5 H, aromatics); ^{13}C NMR ($CDCl_3$): δ 36.7 (C-2), 56.0/56.1 (OCH_3), 64.3/64.6 (C-4), 67.9 (C-3), 68.2 (C-5), 68.5/69.3 (C-6), 71.3/71.4 (C-7), 97.2/97.3 (C-1), 115.7/115.8 (C≡N), 117.0/117.1 (C≡N), 127.0/127.3 (2 C, C_{ortho}), 128.9 (2 C, C_{meta}), 129.8 (C_{para}), 133.1 (C_{ipso}). HRMS (CI): Calcd for $C_{16}H_{18}N_2O_5$: ($M+Na^+$) 383.128334. Found: ($M+Na^+$) 383.126684.

4.1.2. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*C*-cyano-2-deoxy-α-D-altropyranoside (9). Methyl 4,6-*O*-benzylidene-2-cyano-2-deoxy-α-D-altropyranoside (**4**, 18.5 mg, 0.06 mmol) was azeotropically dried with anhydrous benzene under vacuum and dissolved in dry CH_2Cl_2 (0.5 mL) under argon. Silver oxide (freshly prepared, 52.2 mg, 0.22 mmol) and benzyl bromide (freshly distilled, 20 μL, 0.17 mmol) were added consecutively at rt to the magnetically stirred soln. Stirring was continued during 2 h at rt. The mixture was diluted with CH_2Cl_2 and filtered through a silica gel column and the organic layer was concentrated under vacuum. Purification by flash chromatography furnished **9** (24.2 mg, 100%) as a colorless oil. Compound **9**: $[\alpha]_D^{32}$ 13.7 (*c* 0.99, $CHCl_3$); IR (NaCl) ν_{max}: 2920, 2720, 2250 (CN), 1460, 1380, 1240, 1110, 1055, 920, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.26 (d, 1 H, $J_{2,3}$ 2.43 Hz, H-2), 3.41 (s, 3 H, OCH_3), 3.80 (t, 1 H, $J_{gem} = J_{5,6}$ 10.23 Hz, H-6ax), 4.00 (dd, 1 H, $J_{3,4}$ 2.77 , $J_{4,5}$ 8.70 Hz, H-4), 4.18 (t, 1 H, $J_{2,3} = J_{3,4}$ 2.53 Hz, H-3), 4.27–4.52 (m, 2 H, H-5 and H-6eq), 4.70 (d, 1 H, J_{gem} 12.40 Hz, CH_2 benzylic), 4.83 (d, 1 H, J_{gem} 12.40 Hz, CH_2 benzylic), 4.90 (s, 1 H, H-1), 5.60 (s, 1 H, H-7), 7.24–7.58 (m, 10 H, aromatics); ^{13}C NMR ($CDCl_3$): δ 36.5 (C-2), 55.6 (OCH_3), 58.3 (C-5), 66.6 (C-6), 72.1 (C-3), 73.0 (CH_2 benzylic), 77.0 (C-4), 97.3 (C-1), 102.2 (C-7), 117.2 (C≡N), 126.1 (2 C, $C_{aromatic}$), 127.5 (2 C, $C_{aromatic}$),127.7 (C_{para}), 128.2 (2 C, $C_{aromatic}$), 128.3 (2 C, $C_{aromatic}$), 129.1 (C_{para}), 137.2 (C_{ipso}), 137.4 (C_{ipso}).

4.1.3. Methyl-3-*O*-acetyl-4,6-*O*-benzylidene-2-*C*-cyano-2-deoxy-α-D-altropyranoside (10). Methyl 4,6-*O*-benzylidene-2-cyano-2-deoxy-α-D-altropyranoside (**4**, 18.1 mg, 0.06 mmol) was dissolved in dry $CHCl_3$ (0.8 mL) and cooled at 0 °C under argon atmosphere. Dry pyridine (35 μL, 0.43 mmol), 4-(dimethylamino)pyridine (2.5 mg, 0.02 mmol) and Ac_2O (25 μL, 0.26 mmol) were successively added to the stirred soln at 0 °C. The cooling bath was then removed and stirring was continued during 4 h at rt. The mixture was diluted with EtOAc, washed with 10% aq $CuSO_4$, water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography to furnish pure **10** (17.7 mg, 86%) as a colorless oil. Compound **10**: $[\alpha]_D^{20}$ 64.6 (c 0.59, $CHCl_3$); IR (NaCl) ν_{max}: 2935, 2250 (CN), 1740 (C=O), 1380, 1230, 1130, 1050, 1020, 915, 800, 690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (s, 3 H, CH_3CO), 3.39 (s, 3 H, OCH_3), 3.49 (d, 1 H, $J_{2,3}$ 2.58 Hz, H-2), 3.82 (t, 1 H, Jgem $= J_{5,6}$ 12.30 Hz, H-6ax), 4.07 (dd, 1 H, $J_{3,4}$ 2.95, $J_{4,5}$ 9.14 Hz, H-4), 4.25–4.40 (m, 2 H, H-5 and H-6eq), 4.91 (s, 1 H, H-1), 5.31 (t, 1 H, $J_{2,3}$ 2.68 Hz, H-3), 5.63 (s, 1 H, H-7), 7.30–7.55 (m, 5 H, aromatics); ^{13}C NMR ($CDCl_3$): δ 20.8 (CH_3CO), 35.2 (C-2), 55.7 (OCH_3), 58.7 (C-5), 66.3 (C-3), 68.8 (C-6), 74.4 (C-4), 97.2 (C-1), 102.1 (C-7), 116.1 (C≡N), 126.0 (2 C, C_{ortho}), 128.2 (2 C, C_{meta}), 129.2 (C_{para}), 136.7 (C_{ipso}), 170.2 (C=O).

4.1.4. Methyl 3,4-di-*O*-acetyl-2-*C*-cyano-6-*O*-cyanophenylmethyl-2-deoxy-α-D-altropyranoside (7a/b). Compound **6a/b** (61.3 mg, 0.19 mmol) was dissolved in

dry $CHCl_3$ (1.9 mL) and cooled at 0 °C under argon. Dry pyridine (156 μL, 1.93 mmol), 4-(dimethylamino)pyridine (11.8 mg, 0.10 mmol) and Ac_2O (109 μL, 1.16 mmol) were successively added to the stirred soln at 0 °C. The cooling bath was then removed and stirring continued during 15 h at rt. The mixture was diluted with EtOAc, washed with 10% aq $CuSO_4$, water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography to furnish pure **7a/b** (70.0 mg, 90%) as a colorless oil. Compounds **7a/b**: IR (NaCl) ν_{max}: 3020, 2950, 2250 (C≡N), 1760 (C=O), 1500, 1455, 1380, 1250, 1185, 1070, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.98/2.10 (s, 3 H, CH_3CO), 3.29 (m, 1 H, H-2), 3.40/3.44 (s, 3 H, OCH_3), 3.70–3.93 (m, 2 H, H-6), 4.25 (m, 1 H, H-5), 4.97 (m, 1 H, H-1), 5.24 (m, 1 H, H-3), 5.30–5.55 (m, 2 H, H-4 and H-7), 7.40–7.65 (m, 5 H, aromatics); ^{13}C NMR ($CDCl_3$): δ 20.4 (CH_3CO), 34.9 (C-2), 56.1/56.2 (OCH_3), 65.1/65.4 (C-3), 66.18/66.22 (C-4), 67.9/68.6 (C-5), 67.6/68.5 (C-6), 71.0/71.1 (C-7), 97.5 (C-1), 115.8 (2C, C≡N), 116.5 (2C, C≡N), 127.1/127.3 (2 C, C_{ortho}), 129.0 (2 C, C_{meta}), 129.9 (C_{para}), 132.4 (C_{ipso}), 169.1/169.3/169.4/169.5 (C=O).

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