Carbohydrates to Carbocycles: Synthesis of the Densely Functionalized Carbocyclic Core of Tetrodotoxin by Radical Cyclization of an Anhydro Sugar Precursor[1]

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Abstract: The core of tetrodotoxin is a densely functionalized carbocycle for which an annulated pyranose can be envisaged as a retron. The carbocyclic ring is constructed upon a rigid 1,6-anhydro template which permits the early introduction of the key angular nitrogen, and concomitantly positions a trap for reaction with a carbon-centered radical generated chemospecifically at C6. The carbocyclic entity is elaborated in this process leading to a caged system with the capability for generating all of the stereogenic centers. A novel procedure using *tert*-butylhyponitrite is described for C6 dehydrogenation pursuant to the intramolecular radical cyclization.

Introduction

Recent publications from this laboratory have described the application of free radical methods for preparation of annulated sugars[4] which, in some cases, provide ready routes to densely functionalized carbocycles.[5,6] The core of the structurally unique molecule tetrodotoxin[7,8] (**1**) presents an awesome example of a densely functionalized cyclohexane. Disconnection of the hemiorthoester and guanidino moieties and reductive cleavage of the C6–C11 bond lead to the bicyclic entity **2a**, which when displayed as in **2b** emphasizes the relationship to an annulated pyranoside (Scheme I), which therefore fits into our ongoing research programs. Added significance comes from the immense folklore[9,10] and biological[7,11] importance of **1**, as well as the sustained challenges to synthesis of **1**[12,13] or any of its congeners.[14] In this manuscript, we describe synthetic transformations related to the annulated pyranoside **3**.

Retrosynthesis

Retron **2b** indicates the need for a functionalized two-carbon bridge between C3 and C6 of an hexopyranoside whose C5 configuration implies a D-sugar derivative existing in the unusual $^1C_4$ conformation.[15] The latter is locked into place in a 1,6-anhydro sugar, and hence retron **3** emerges from these considerations. If the C9 and C8 stereocenters of TTX are made to coincide with C2 and C4, respectively, of the sugar, the choice is limited to "D-altrosan" or "D-mannosan". The fact that the latter can be readily obtained by either pyrolysis[16a] or synthesis[16b] made it (**4**) the starting material of choice.

A major transformation would be required at C3, and this could probably be best accomplished *via* a trigonal center. This retrosynthetic idea would allow the unit representing C3a and C3b to be installed *via* an olefination reaction of a 3-keto sugar. In addition, we would be able to simultaneously address the challenge of the angular nitrogen at the outset through the *cis* oxyamination protocol that had been developed in these laboratories,[17] in which an allylic OH is utilized to deliver the *cis* vicinal nitrogen (e.g. **5** → **6**, Scheme IIa).

The choice of olefinating agent for this purpose would depend on the strategy for linking C3b and C6. Additional function-

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(4) See for example: Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065. Dickson, J. D., Jr.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1440. Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009.

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(15) Schwarz, J. C. P. *J. Chem. Soc., Chem. Commun.* **1973**, 505.

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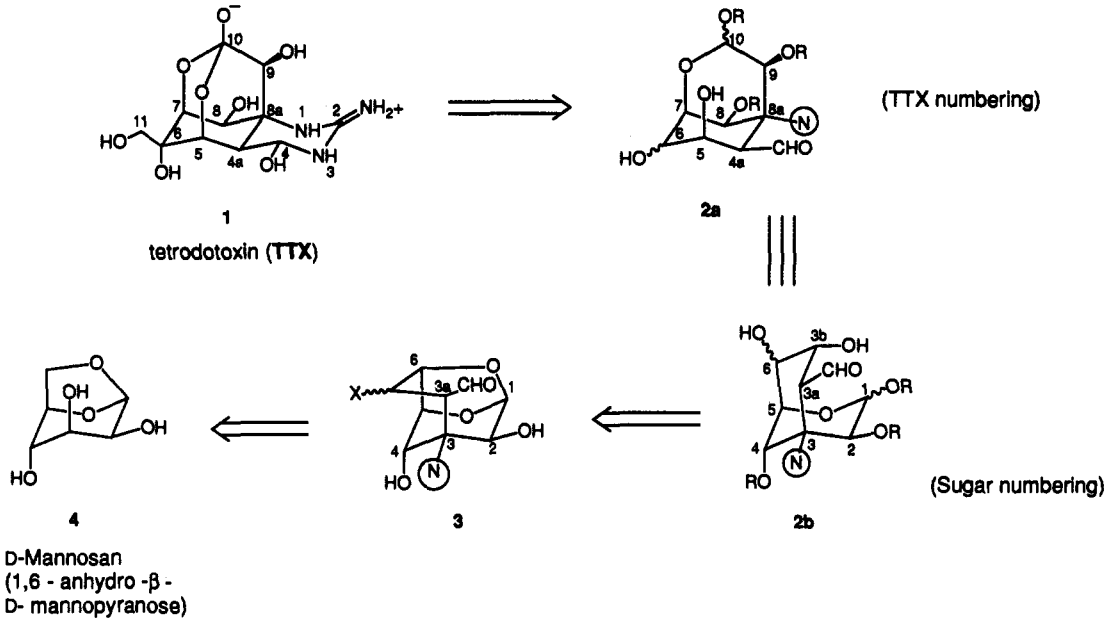
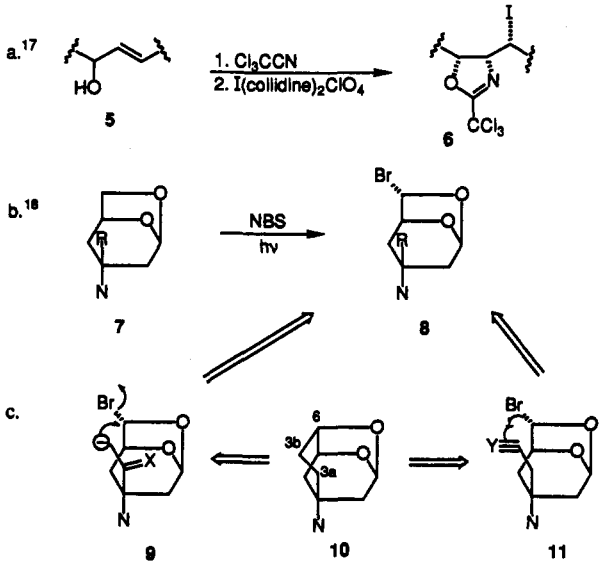
Scheme I



Scheme II



alization would probably be required at C6, and the elegant bromination of 1,6-anhydro sugars by Ferrier and Furneaux[18] (e.g. **7** → **8**, Scheme IIb) seemed ideal. An α-bromo ether such as **8** offered the attractive options of an intramolecular nucleophilic displacement or a radical cyclization, as depicted in **9** and **11**, respectively (Scheme IIc). Ideally, the substituent "R" in **8**, resulting from the olefination, should allow both pathways to **10** to be explored.

Exploratory Studies Toward Synthon 10 (Scheme III)

With this plan in mind, the known acetonide **12a**[16a] was processed routinely to give the diol **13a**, the stannylene derivative (**14**) of which allowed regioselective protection of the equatorial hydroxyl.[19] The product **15** was then oxidized to ketone **16a**, Dess–Martin periodinane[20] being found to give the best result.

With the 3-keto sugar in hand, the stage was set for introduction of the two-carbon unit *via* an olefination reaction. Use of the Wittig reagent, $Ph_3P{=}CHCO_2Et$, for introduction of the two-carbon unit either left **16a** unchanged or caused epimerization at C2 and/or C4. This was an unexpected result since this reagent usually works well with carbohydrate substrates.[6,21] On the other hand, a more nucleophilic reagent, triethyl phosphonoacetate, gave a virtually quantitative reaction, the *E*-isomer **16b** predominating. Reduction with diisobutylaluminum hydride or L-selectride then gave diol **17a**, the primary hydroxyl group of which was silylated as in **17b**.

Application of the oxyamination procedure[17] to **17b** involved conversion to the trichloroacetimidate **18** and treatment of the crude product with iodonium dicollidinium perchlorate, the latter reaction proceeding with high efficiency to give **19** in 85% yield.

With the angular nitrogen now in place, connection of C6 and C3b was addressed and the alkylation option in Scheme IIc was first examined. A route to a methyl ketone (e.g. **9**, X=O) could conceivably involve Wacker oxidation[22] of an olefin, and with this objective in mind, iodide **19** was treated with activated zinc which afforded alkene **20a** in 83% yield (Scheme III). However, the Wacker oxidation took an anomalous course that gave traces of the aldehyde **25**[23] but none of the desired ketone **22b**.

We therefore resorted to a more circuitous route involving low-temperature ozonolysis of **20a** to give aldehyde **21**. Reaction of the latter with methyllithium or methylmagnesium bromide led only to modest amounts of **22a**. However, careful reaction with magnesium chlorotetramethylaluminate[24] gave the desired material in 72% yield as a 4:1 mixture of C3a epimers. Swern oxidation[25] then completed the route to **22b**.

Since a *p*-methoxybenzyl ether would not be expected to survive the conditions of the Ferrier bromination[18] (see Scheme IIb), the benzoate **22d** was prepared by routine transformations. Irradiation with a sun lamp in the presence of NBS gave the somewhat labile bromide **23** in 74% yield. Attempts to convert **23** into the tetracylic molecule **24** by a variety of procedures[26] were unfruitful.

Two developments now caused a change in our strategy. First was a molecular dynamics study which showed that ring closure

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(23) The abnormal course of this reaction, in giving an aldehyde rather than a methyl ketone, may be due to the presence of the proximal oxygens and/or the allylic acetamide group. Experiments are underway to seek clarification.
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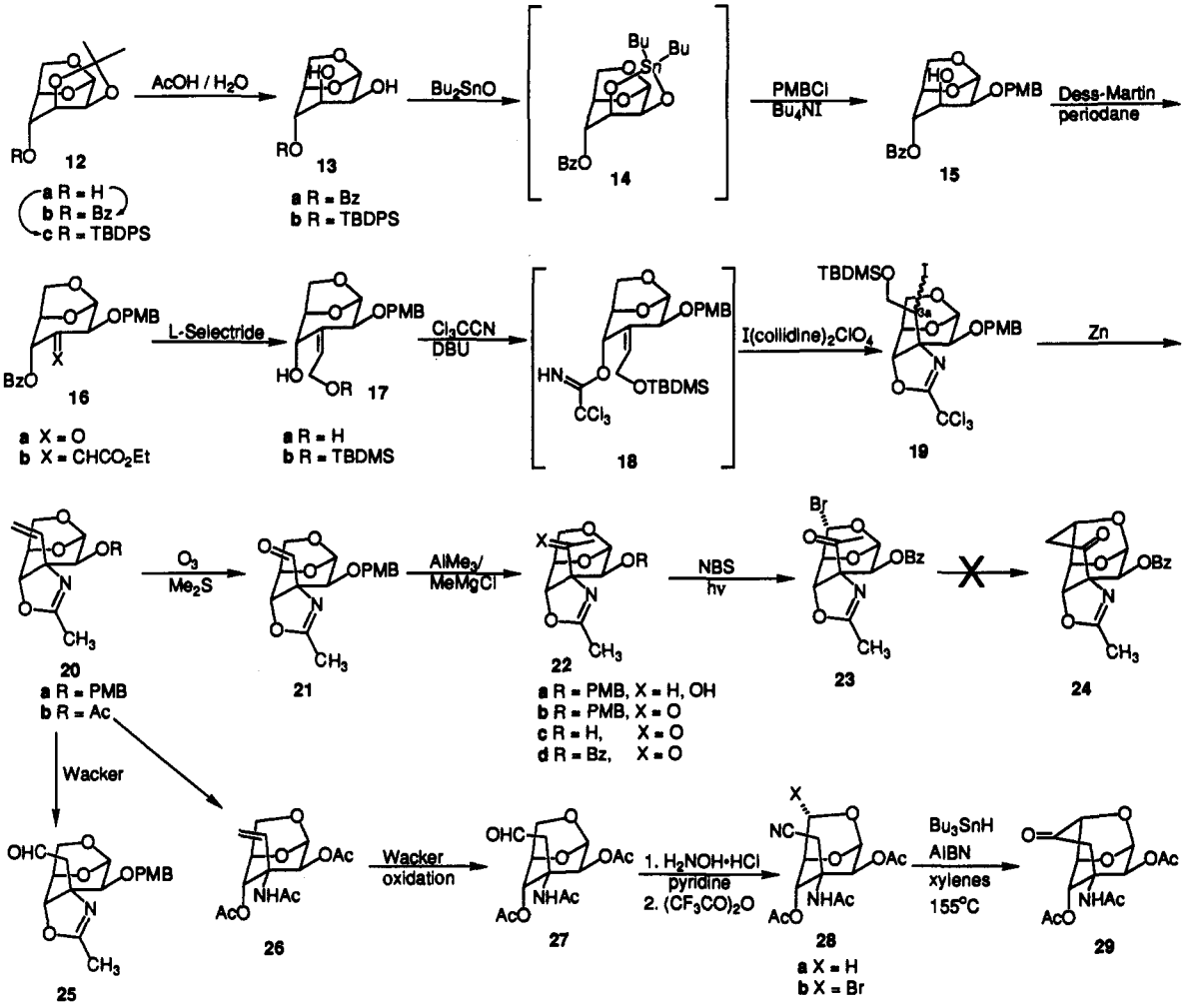
(26) Treatment of **23** with LDA, LiHMDS, and even K_2CO_3 in various solvents gave only intractable materials.

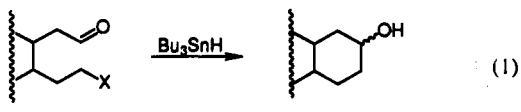
Scheme III



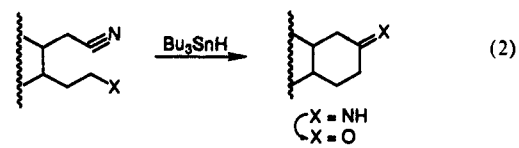
of **23** was being inhibited by the oxazoline ring. Second was formation of aldehyde **25** in the Wacker reaction of **20a** which prevented a concise route to methyl ketone **22b** (*vide supra*).

In order to profit from both observations, the oxazoline ring of **20a** had to be hydrolyzed. Experimentally, it was found best to use the corresponding acetate **20b** for this hydrolysis, followed by direct acetylation to give **26**. Wacker oxidation of the resulting material now gave aldehyde **27**[23] as a clear oil, albeit in only 21% yield (Scheme III).

Recent work in our laboratory has shown that radical cyclization of an ϵ-haloaldehyde can be an efficient method for forming a cyclohexanol[27] (eq 1), and with the aldehyde **27** in hand, this



(1)



(2)

possibility seemed tempting. However, such an approach was complicated by the fact that protection of the *aldehydo* group would be necessary[28] during the bromination at C6. On the other hand, cyclization of a halonitrile offered an alternative (eq 2). Although the pioneering work of Clive[29] and our own[4] experience had been limited to δ-halonitriles for the formation of cyclopentanones, we believed that the rigidity of the 1,6-anhydro scaffolding would facilitate ring closure by presenting the nitrile to the radical in a highly-ordered six-centered boatlike transition state.

Accordingly the aldehyde **27** was converted to nitrile **28a** under standard conditions, and the α-bromoether **28b** was prepared without event. Treatment with tri-*n*-butyltin hydride and AIBN in refluxing xylene now did produce ketone **29** in 77% yield.

An Expeditious Route to Ketone 29

The formation of the tricyclic ketone **29** seemed an important plateau. However, in order to properly evaluate its potential, a more expeditious route to the key intermediate **28a** was needed. The first improvement was based on the elegant procedure of Hanessian and David for regioselective oxidation of stannylene derivatives of vicinal diols.[30] The substrate required for this test, was the known diol **13b**[31] (Scheme IV). The stannylene derivative **30** underwent bromine oxidation very smoothly to give ketone **31a** in 88% overall yield. Oxidation of the axial hydroxyl had been expected on the basis of literature precedents,[30] and acetylation of the resulting acyloin gave **31b** without event.

The target **28a** dictated the use of an olefinating reagent containing the cyano group and indeed the unsaturated nitrile **32** was obtained in 91% yield from treating **31b** with diethyl

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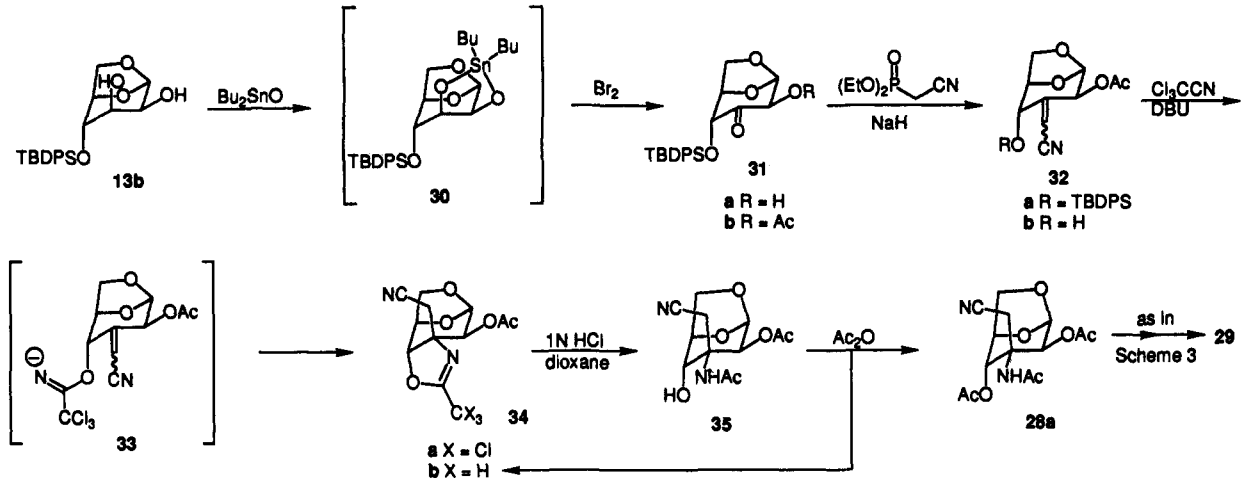
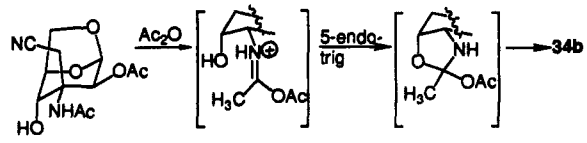
Scheme IV



cyanomethylphosphonate as an inseparable (5:1) mixture of *E*/*Z* isomers. Desilylation with HF/pyridine, which proceeded in 94% yield, did permit chromatographic separation, the *Z* and *E* isomers of **32b** being obtained in a ratio of 5:1 as crystalline materials.

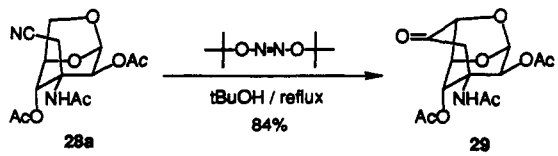
Fortunately, separation of the isomers was not necessary for the next step. Our standard oxyamination procedure (Scheme IIa) requires the use of an electrophile to trigger oxazoline formation. However, in the case of nitrile **32b**, the intermediate imidate anion **33** from reaction with trichloroacetonitrile underwent efficient conjugate addition affording the crystalline oxazoline **34a** in 97% yield. Catalytic hydrogenolysis of the trichloromethyl group then gave **34b** in 95% yield.

Two seemingly simple steps, hydrolysis and acetylation, now stood between **34b** and **28a**, and the procedure used above for converting **20b** into **26** was again applied. Hydrolysis of **34b** was followed on TLC, and the crude alcohol **35** was obtained. However, acetylation regenerated oxazoline **34b** in amounts which varied with the conditions used. This unexpected occurrence can be rationalized by invoking unfavorable 5-*endo*-trig ring closure[32] of the iminium ion **36** (eq 3). Patient experimentation yielded



optimum conditions (see the Experimental Section) in which the ratio of **28a**:**34b** was 4:1, these being separable by chromatography. On the basis of recovered starting material, the yield of **28a** was 95%.

The success of the exploratory route from **13** → **29** in Scheme III encouraged the development of the more concise pathway shown in Scheme IV. Thus the new route from **13b** to **28a** requires seven steps instead of 17 as shown in Scheme III. Additional saving came from the exciting observation that compound **28a** could be converted directly and in excellent yield into **29** (based on recovered **28a**) by use of *tert*-butylhyponitrite in refluxing *tert*-butyl alcohol[33] (eq 4). Formation of bromide **28b** can



(4)

therefore be avoided.

Summary

Tricyclic ketone **29** comprises the entire skeletal framework of tetrodotoxin (**1**), including the critical angular nitrogen. Ketone **29**, which corresponds to synthon **3** (Scheme I), can be visualized as an annulated pyranoside[4] with a two-carbon bridge linking C3 and C6 of a 1,6-anhydro-β-D-pyranose, the central core of which is a densely functionalized carbocycle.[5,6] The desire to transfer the C2 and C4 stereocenters intact from the sugar to tetrodotoxin makes readily available D-mannosan[16] (1,6-anhydro-β-D-mannopyranose) the logical choice as the starting material. The two-carbon unit is attached to C3 *via* an exocyclic olefin, and the resulting allylic C4–OH can then be utilized to deliver the vicinal angular nitrogen by employing the *cis* oxyamination protocol developed in these laboratories.[17] This process simultaneously erects the C3 carbon substituent, bringing it within bonding distance of C6. Functionalization of the latter site, readily achieved by Ferrier's photochemical bromination,[18] then paves the way for radical cyclization with a nitrile, thereby establishing the bridge connecting C3 and C6.

Experimental Section

All the reactions were performed under argon atmosphere and monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator (5554, Merck). Anhydrous Na_2SO_4 was used to dry the organic solutions during workups, and the removal of the solvents was done under vacuum with a rotavapor. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, Merck). Melting points were determined in capillary tubes and are uncorrected. Optical rotations were determined at the sodium D line. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian XL-300 and GE QE-300 spectrometers, using $CDCl_3$ as the internal standard and as the solvent. Chemical shifts are reported in δ values, and coupling constants (*J*, Hz), where specifically assigned, were determined by double-irradiation experiments. Chemical ionization mass spectroscopy was done with 10% NH_3 in methane with a source temperature of 150 °C. High-resolution mass spectra were recorded using NH_3 as the reagent gas and PFK for calibration. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

1,6-Anhydro-4-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-mannopyranose (12b). To a stirred solution of the anhydromannose **12a**[16] (11.0 g, 54.40 mmol) in pyridine (55 mL) cooled to 0 °C in an ice–water bath were added a catalytic amount of DMAP and benzoyl chloride (7.0 mL, 60 mmol) *via* a dropping funnel. The reaction mixture was stirred at 0 °C for 1 h then diluted with ether (250 mL). The resulting suspension was washed with 100 mL of water (2×), 100 mL of a saturated $CuSO_4$ solution (6×), 100 mL of a 1 N HCl solution (1×), 100 mL of a saturated $NaHCO_3$ solution (2×), and followed by 100 mL of brine (2×). The organic layer was separated, dried, and filtered, and the volatiles were removed to give **12b** as a white crystalline solid (15.61 g, 97%): mp (hexane/ether) 131–133 °C; ^1H NMR δ 8.1 (m, 2H, ArH), 7.7–7.4 (m, 3H, ArH), 5.43 (d, J = 2.8, 1H, H1), 5.20 (br s, 1H, H4), 4.70 (m, 1H, H5), 4.30 (m, 1H, H3), 4.17 (dd, J_1 = 6.4, J_2 = 2.8, 1H, H2), 4.12 (dd, J_1 = 7.3, J_2 = 1.3, 1H, H6′), 3.83 (dd, J_1 = 7.3, J_2 = 6.4, 1H, H6), 1.58 (s, 3H), 1.34 (s,

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(33) Rao, B. V.; Chan, J. B.; Moskowtiz, N.; Fraser-Reid, B. *Bull. Soc. Chim. Fr.*, in press.

3H); GC/CIMS (NH_3) m/z 325 $(M + NH_4)^+$. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.76; H, 5.99.

1,6-Anhydro-4-*O*-benzoyl-β-D-mannopyranose (13a). A rapidly stirring suspension of **12b** (15.55 g, 50.77 mmol) in 20% HOAc (150 mL) was warmed to 100 °C. After 5 h, the hydrolysis of the acetonide was complete, as judged by TLC. The solution was concentrated, the resulting oil was diluted with toluene (200 mL), and the volatiles were again removed. The oil was then placed under high vacuum overnight. During that time, the oil **13a** crystallized and was used without further purification (13.47 g, 100%): mp (benzene) 108 °C; ^{1}H NMR δ 8.2–7.1 (m, 5H, ArH), 5.49 (s, 1H, H1), 5.18 (s, 1H, H4), 4.69 (m, 1H, H5), 4.34 (br s, 1H, H3), 4.14 (br s, 1H, H2), 3.83 (m, 2H, H6, H6′). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.56; H, 5.52.

1,6-Anhydro-4-*O*-benzoyl-2-*O*-(*p*-methoxybenzyl)-β-D-mannopyranose (15). To a flask containing a stirred suspension of diol **13a** (26.6 g, 100 mmol) and dibutyltin oxide (24.9 g, 100 mmol) in benzene (1.1 L) was attached a Dean–Stark trap fitted with a reflux condenser. The reaction mixture was heated to reflux, and the water was removed as an azeotrope with benzene. When no further water was produced (~2 h), the reaction mixture was cooled to room temperature to obtain **14**. To the crude stannylene **14** were added tetrabutylammonium iodide (36.9 g, 100 mmol) and *p*-methoxybenzyl chloride (14.3 mL, 105 mmol). The Dean–Stark trap was removed and replaced by a reflux condenser. The reaction mixture was heated to reflux. After 40 h, the reaction was complete as judged by TLC. It was cooled to room temperature and washed wtih 50-mL portions of water followed by brine (2×). The organic layer was separated, dried and filtered, and the volatiles were evaporated. The resulting brown oil was triturated with ether. The desired product precipitated out as a fine white powder which was filtered off and washed with ether. The filtrate was rotary evaporated to obtain a brown oil. This trituration protocol was repeated until no further product precipitated (29.9 g, 78%). The sample of **15** so obtained was analytically pure. NMR analysis revealed that less than 5% of the desired product remained in the oil: mp (ether/hexane) 96 °C; ^{1}H NMR δ 8.1–6.8 (m, 9H, Ar*H*), 5.47 (br s, 1H, H1), 5.21 (br s, 1H, H4), 4.69 (m, 1H, H5), 4.61 (ABq, J = 11.4, Δδ = 0.12, 2H, ArCH_2), 4.39 (dd, J_1 = 7.4, J_2 = 0.9, 1H, H6′), 4.15 (m, 1H, H3), 3.81 (s, 3H, CH_3O), 3.80 (m, 1H, H6), 3.66 (dd, J_1 = 5.1, J_2 = 1.7, 1H, H2), 3.23 (d, J = 2.6, 1H, OH); ^{13}C NMR δ 55.2, 65.1, 67.4, 70.8, 72.9, 73.2, 74.0, 100.2, 113.9, 128.4, 129.0, 129.5, 129.6, 129.7, 133.3, 159.6, 165.3.

1,6-Anhydro-4-*O*-benzoyl-2-*O*-(*p*-methoxybenzyl)-β-D-*arabino*-hexopyran-3-ulose (16a). To a stirred solution of alcohol **15** (10.52 g, 27.2 mmol) and Dess–Martin periodinane[20] (15.0 g, 35.4 mmol) in methylene chloride (100 mL) was added *tert*-butyl alcohol (2.57 mL, 27.2 mmol) *via* syringe. The reaction was usually complete within 2 h as judged by TLC. The reaction mixture was then diluted with additional methylene chloride and was washed with 100-mL portions of 1:1 saturated $Na_2S_2O_4$/saturated $NaHCO_3$ (3×) followed by 50 mL of brine. The organic layer was separated, dried, filtered, and concentrated. The white solid obtained was dissolved in a minimal amount of methylene chloride and filtered through a short pad of silica gel using ethyl acetate as the eluent. Rotary evaporation of the volatiles afforded 10.41 g (98%) of analytically pure ketone **16a**: ^{1}H NMR δ 8.0 (m, 2H, Ar*H*), 7.6–6.9 (m, 7H, Ar*H*), 5.62, (d, J = 2.2, 1H, H1), 5.22 (d, J = 1.7, 1H, H4), 4.98 (ddd, J_1 = 5.1, J_2 = J_3 = 1.7, 1H, H5), 4.78 (ABq, J = 11.5, Δδ = 0.3, 2H, ArCH_2), 4.24 (d, J = 2.2, 1H, H2), 3.93 (dd, J_1 = 8.6, J_2 = 5.1, 1H, H6′), 3.88 (dd, J_1 = 8.6, J_2 = 1.7, 1H, H6), 3.80 (s, 3H, CH_3O). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.63; H, 5.23. Found: C, 65.42; H, 5.44.

(*E*/*Z*)-1,6-Anhydro-4-*O*-benzoyl-3-deoxy-3-(*C*-(ethoxycarbonyl)methylene)-2-*O*-(*p*-methoxybenzyl)-β-D-*arabino*-hexopyranose (16b). To a stirred suspension of sodium hydride (2.46 g, 107 mmol) (washed three times with hexanes) in THF (100 mL), cooled to 0 °C, was added triethyl phosphonoacetate (24.1 mL, 121 mmol) *via* syringe. After the addition was complete, the reaction was stirred at 0 °C for 1 h. After 1 h, this solution was introduced, *via* cannula, to a −78 °C solution of ketone **16a** (27.6 g, 71.4 mmol) in THF (600 mL). The transfer required 10 min. Although TLC analysis revealed that the reaction was essentially complete after addition, the reaction mixture was stirred an additional 1 h at −78 °C. The reaction mixture was diluted with ethyl acetate (200 mL) and washed copiously with water. The organic layer was then washed with 100 mL of saturated $NaHCO_3$ (3×) and 100 mL of brine, dried, and filtered, and the volatiles were removed. The pale yellow oil was chromatographed on a silica gel column with 30% EtOAc/hexanes as the eluent. Upon concentration by rotary evaporation, 29.6 g (91%) of the α,β-unsaturated ester **16b** was obtained: ^{1}H NMR δ 8.10–6.92 (m, 9H, Ar*H*), 6.78 (d, J = 2.2, 1H, H4), 6.50 (d, J = 2.4, 1H, vinyl proton), 5.52 (d, J = 1.6, 1H, H1), 4.91 (m, 1H, H5), 4.70 (ABq, J = 11.7, Δδ = 0.03, 2H, ArCH_2), 4.33 (m, 1H, H2), 4.21 (m, 2H, OCH_2CH$_3$), 3.87 (d, J = 3.3, 1H, H6′), 3.84 (m, 4H, H6, OCH_3), 1.30 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3); GC/CIMS (NH_3) m/z 472 $(M + NH_4)^+$, 455 (MH^+). Anal. Calcd for $C_{25}H_{26}O_8$: C, 66.07; H, 5.77. Found: C, 66.00; H, 5.79.

(*E*/*Z*)-1,6-Anhydro-3-(*C*-2-(*tert*-butyldimethylsiloxy)ethylidene)-3-deoxy-2-*O*-(*p*-methoxybenzyl)-β-D-*arabino*-hexopyranose (17b). To a stirred solution of **16b** (32 g, 70.6 mmol) in THF (1 L), cooled to −78 °C, was added, *via* syringe, a 1 M solution of L-selectride (300 mL, 300 mmol) over the course of 30 min. The reaction mixture was stirred for an additional 2 h, after which TLC showed complete consumption of the starting material. The reaction was quenched with methanol (50 mL), and the volatiles were removed. The resulting foam was dissolved in methanol and re-evaporated. The brown oil was chromatographed on a silica gel column, with 65% EtOAc/hexanes as the eluent. Concentration of the appropriate fractions afforded 20.1 g (92%) of diol **17a**. To a stirred solution of the crude material (19.8 g, 64.2 mmol) and imidazole (6.12 g, 90 mmol) in DMF (200 mL), cooled to 0 °C, was added *tert*-butyldimethylsilyl chloride (11.6 g, 77 mmol). The reaction mixture was stirred for 4 h. The solution was then diluted with ether and washed with 50-mL portions of 1 N HCl (2×), saturated $NaHCO_3$ (2×), and brine. The organic layer was separated, dried, filtered, and concentrated. The resulting white oil was chromatographed on a silica gel column, with 50% EtOAc/hexanes as the eluent. Concentration of the appropriate fractions afforded 18.3 g of silyl ether **17b** (68%): ^{1}H NMR δ 7.30–6.90 (m, 4H, Ar*H*), 6.20 (m, 1H, vinyl proton), 5.38 (d, J = 2.0, 1H, H1), 4.64 (s, 2H, ArCH_2), 4.58 (m, 1H, H5), 4.49 (br s, 1H, H4), 4.35 (ddd, J_1 = 13.0, J_2 = 6.5, J_3 = 2.0, 1H, C*H*O(TBS)), 4.22 (ddd, J_1 = 13.0, J_2 = 6.5, J_3 = 2.0, 1H, C*H*′O(TBS)), 4.11 (br s, 1H, H2), 3.81 (m, 4H, OCH_3, H6), 3.68 (dd, J_1 = 7.6, J_2 = 1.1, 1H, H6′), 0.90 (s, 9H, (CH_3)$_3$CSi), 0.08 (s, 6H, (CH_3)$_2$Si); ^{13}C NMR δ −5.3, 25.9, 55.3, 58.9, 66.4, 68.2, 72.3, 75.8, 76.9, 100.5, 113.9, 129.6, 129.8, 129.9, 136.0, 159.4; GC/CIMS (NH_3) m/z 440 $(M + NH_4)^+$. Anal. Calcd for $C_{22}H_{34}O_6Si$: C, 62.53; H, 8.11. Found: C, 62.43; H, 8.11.

2′-Methyl-(1,6-anhydro-3-deoxy-2-*O*-(*p*-methoxybenzyl)-3-*C*-vinyl-β-D-altropyranosido)-[3,4:4′,5′]-Δ$^{2'}$-oxazoline (20a). In keeping with the published procedure,[17] a solution of alcohol **17b** (24 g, 57 mmol) was converted to the imidate **18** (>70%), which was directly dissolved in acetonitrile and treated with solid I(Coll)$_2$ClO$_4$ (1.5 equiv). After heating at 55 °C for 1 h, diethyl ether was added, and standard processing[17] afforded **19** as an epimeric mixture (1:1) (86%). The crude iodohydrin **19** (21.6 g) in ethanol (300 mL) was warmed to reflux. Careful portionwise addition of freshly activated zinc (11.1 g, 180 mmol) kept the reaction mixture at reflux. After 4 h, TLC analysis revealed the complete consumption of the starting material. The reaction mixture was concentrated to afford a thick brown oil. This oil was diluted with ethyl acetate and filtered through a pad of Florisil to remove the unreacted zinc and zinc salts present. The filtrate was concentrated to a dark oil, dissolved in a minimum amount of methylene chloride, and chromatographed on a silica gel column using 50% EtOAc/hexanes as the eluent to afford 8.1 g of vinyl oxazoline **20a** (70% for 2 steps): ^{1}H NMR δ 7.27–6.85 (m, 4H, Ar*H*), 6.35 (dd, J_1 = 17.3, J_2 = 10.6, 1H, *H*C═C), 5.45 (dd, J_1 = 17.3, J_2 = 1.6, 1H), 5.37 (d, J = 2.2, 1H, H1), 5.28 (dd, J_1 = 10.6, J_2 = 1.6, 1H), 4.81 (m, 1H, H5), 4.54 (ABq, J = 11.5, Δδ = 0.37, 2H, ArCH_2), 3.97 (s, 1H, H4), 3.86 (d, J = 4.2, 2H, H6, H6′), 3.79 (s, 3H, OCH_3), 3.28 (d, J = 2.2, 1H, H2), 2.10 (s, 3H, CH_3); CIMS (isobutane) m/z 332 (M + 1). HRMS Calcd for $C_{18}H_{21}O_5$: 331.141 97. Found: 331.142 10, Δ = 0.39 ppm.

2′-Methyl-(1,6-anhydro-3-deoxy-3-*C*-formyl-2-*O*-(*p*-methoxybenzyl)-β-D-altropyranosido)-[3,4:4′,5′]-Δ$^{2'}$-oxazoline (21). A solution of olefin **20a** (406 mg, 1.22 mmol) in dry methyl alcohol (25 mL) was cooled to −78 °C and ozonolyzed until the solution was blue in color (3 min). The solution was purged with argon, and dimethyl sulfide (0.2 mL) was added. The solution was warmed to room temperature over 2 h and then concentrated. Flash chromatography (50% EtOAc/petroleum ether) provided aldehyde **21** (335 mg, 82%) as a colorless oil: ^{1}H NMR δ 9.80 (s, 1H, C*H*O), 7.06 (ABq, J = 8.7, Δδ = 0.21, 4H, Ar*H*), 5.24 (d, J = 2.6, 1H, H1), 4.82 (d, J = 5.4, 1H, H5), 4.70 (ABq, J = 11.5, Δδ = 0.07, 2H, ArCH_2), 4.52 (br s, 1H, H4), 4.06 (d, J = 7.8, 1H, H6′), 3.80 (dd, J_1 = 7.8, J_2 = 5.4, 1H, H6), 3.78 (s, 3H, ArOCH_3), 3.61 (d, J = 2.6, 1H, H2), 2.03 (s, 3H, CH_3); ^{13}C NMR δ 14.1, 55.2, 65.5, 72.8, 73.1, 79.1, 79.4, 82.7, 98.1, 113.9, 129.1, 129.6, 159.5, 165.8, 197.6; IR (neat) 1725, 1655, 1610 cm^{-1}; $[\alpha]_D^{19}$ = −28.4° (*c* 2.22, $CHCl_3$); GC/CIMS (NH_3) m/z 334 (MH^+). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.28; H, 5.76; N, 4.16.

2′-Methyl-(3-*C*-acetyl-1,6-anhydro-3-deoxy-2-*O*-(*p*-methoxybenzyl)-β-D-altropyranosido)-[3,4:4′,5′]-Δ$^{2'}$-oxazoline (22b). Magnesium chlo-

rotetramethylaluminate was prepared according to the method of Webb.[24] To trimethylaluminum (1 mL, 2 M in toluene) at 0 °C was added methylmagnesium chloride (0.5 mL, 3 M in THF). The mixture was stirred for 10 min at 0 °C prior to use. To a solution of aldehyde **21** (50.2 mg, 0.151 mmol) in dry CH_2Cl_2 (2 mL) at −78 °C was added the magnesium chlorotetramethylaluminate mixture (0.75 mL). The reaction contents were stirred for 1 h at −78 °C, warmed to −40 °C, and treated with acetone (0.1 mL). After stirring the mixture for 5 min, saturated aqueous sodium bicarbonate (2 mL) was added dropwise. The mixture was warmed to room temperature and extracted with CH_2Cl_2 (25 mL). Drying and rotary evaporation of the solvent provided the mixture of epimeric alcohols **22a** (50.2 mg). Flash chromatography afforded 37.9 mg (72%, 4:1), which typically were combined for further use. To a solution of oxalyl chloride (0.21 mL, 2.4 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added dropwise dry DMSO (0.23 mL, 3.2 mmol). The solution was stirred for 20 min, and a solution of alcohol **22a** (566 mg, 1.62 mmol) in dry CH_2Cl_2 (10 mL) was added. The mixture was stirred for 1 h at −78 °C and then treated with dry triethylamine (0.8 mL). The mixture was warmed to 0 °C over 2 h, diluted with CH_2Cl_2 (30 mL), and washed with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL). The organic layer was dried, and the solvent was evaporated to give a yellow oil (0.62 g). Flash chromatography (50–100% EtOAc/petroleum ether) provided **22b** (433 mg, 77%) as a pale yellow oil: ^{1}H NMR δ 7.27–7.22 (m, 2H, Ar*H*), 6.86–6.81 (m, 2H, Ar*H*), 5.17 (d, J = 3.2, 1H, H1), 4.73 (d, J = 5.7, 1H, H5), 4.60 (ABq, J = 11.5, $\Delta\delta$ = 0.03, 2H, ArCH_2), 4.49 (br s, 1H, H4), 4.29 (d, J = 7.4, 1 H, H6′), 3.86 (d, J = 7.4, 1H, H6), 3.77 (s, 3H, ArOCH_3), 3.54 (d, J = 3.2, 1 H, H2), 2.31 (s, 3H, CH_3C), 2.00 (s, 3H, CH_3CO); ^{13}C NMR δ 14.0, 29.0, 55.2, 64.9, 72.9, 73.6, 80.8, 81.6, 81.9, 97.6, 113.9, 129.1, 129.8, 159.5, 164.7, 207.4; IR (neat) 1720, 1670, 1615 cm^{-1}; $[\alpha]_D^{19}$ = −77.4° (*c* 1.49, $CHCl_3$); GC/CIMS (NH_3) m/z 348 (MH^+). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.16; H, 6.13; N, 4.00.

(6*S*)-2′-Methyl-(3-*C*-acetyl-1,6-anhydro-2-*O*-benzoyl-6-bromo-3-deoxy-β-D-altropyranosido)-[3,4:4′,5′]-Δ$^{2'}$-oxazoline (23). To a solution of **22b** (433 mg, 1.25 mmol) in CH_2Cl_2 (30 mL) were added water (0.5 mL) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (397 mg, 1.75 mmol). The mixture was stirred vigorously overnight and then quenched with *p*-methoxybenzyl alcohol (0.15 mL) and stirred for an additional 20 min. The mixture was flushed through Florisil (20–80% EtOAc/petroleum ether), affording alcohol **22c** (231 mg, 81%). Without further purification, the alcohol was dissolved in pyridine (5 mL) at 0 °C and treated with benzoyl chloride (0.23 mL, 2.0 mmol). The mixture was stirred at room temperature for 3 h, diluted with diethyl ether (50 mL), and washed with saturated aqueous sodium bicarbonate (3 × 25 mL). The organic layer was dried and concentrated. Flash chromatography (EtOAc; 5% CH_3-OH/EtOAc) of the residue afforded benzoate **22d** (267 mg, 79%) as a yellowish solid. A portion of ketone **22d** (25.5 mg, 0.0880 mmol) in carbon tetrachloride (3 mL) was degassed with argon. *N*-Bromosuccinimide (NBS) (27.4 mg, 0.14 mmol) was added, and the resulting suspension was irradiated (250-W sunlamp) for 10 min. TLC indicated that the starting ketone had not been consumed. Irradiation was continued for 10 min, NBS (8.4 mg) was added, and the mixture was irradiated for an additional 10 min. TLC indicated that the reaction was complete. The mixture was filtered through silica gel and eluted with 50% EtOAc/petroleum ether to provide bromide **23** (24.3 mg, 74%): ^{1}H NMR δ 7.98–7.88 (m, 2H, Ar*H*), 7.64–7.54 (m, 1H, Ar*H*), 7.50–7.38 (m, 2H, Ar*H*), 6.71 (s, 1H, H6), 5.93 (d, J = 2.8, 1H, H2), 5.16 (s, 1H, H5), 5.14 (d, J = 2.8, 1H, H1), 4.65 (s, 1H, H4), 2.28 (s, 3H, CH_3), 2.10 (s, 3H, CH_3); GC/CIMS (NH_3) m/z 410, 412 (MH^+).

3-Acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-3-*C*-vinyl-β-D-altropyranose (26). To a portion of the oxazoline **20a** (1.0 g, 3 mmol) in methylene chloride (10 mL) was added triphenylcarbenium tetrafluoroborate (1.3 g, 4 mmol). After 1.5 h, TLC analysis revealed the complete consumption of the starting material. The mixture was diluted with methylene chloride and washed with 50-mL portions of water (2×), saturated $NaHCO_3$ (2×), and brine. The organic layer yielded the crude alcohol which was dissolved in methylene chloride (5 mL) and acetylated (DMAP (380 mg)/Ac_2O (1 mL)). After 1 h, the reaction mixture was diluted with ethyl acetate and processed in the usual way. Chromatography on a silica gel column with 40% EtOAc/hexanes as the eluent afforded 726 mg of the acetate **20b** (91%) as a white oil. To a stirred solution of this material (532 mg, 2 mmol) in THF (10 mL), cooled to 0 °C, was added 1 N HCl (1 mL, 1 mmol) dropwise. The cooling bath was then removed, and the reaction mixture was slowly allowed to come to room temperature. After 3 h (TLC), the reaction mixture was neutralized with saturated sodium bicarbonate solution, volatiles were removed, and residual water was removed as its azeotrope with toluene. The crude alcohol, dried under high vacuum, was taken up in CH_2Cl_2 and acetylated as described above. Chromatography on silica gel with 40% EtOAc/hexanes as the eluent afforded 350 mg of triacetate **26** (64%) as a white oil: ^{1}H NMR δ 6.68 (br s, 1H, N*H*), 6.16 (dd, J_1 = 11.0, J_2 = 17.3, 1H), 5.57 (d, J = 2.0, 1H, H4), 5.52 (dd, J_1 = 17.3, J_2 = 1.0, 1H), 5.40 (d, J = 1.9, 1H, H1), 5.33 (d, J = 11.0, 1H), 4.90 (d, J = 1.9, 1H, H2), 4.70 (dd, J_1 = 5.1, J_2 = 2.0, 1H, H5), 4.11 (d, J = 8.2, 1H, H6′), 3.73 (dd, J_1 = 8.2, J_2 = 5.1, 1H, H6), 2.18 (s, 3H, CH_3-CO), 2.10 (s, 3H, CH_3CO), 1.92 (s, 3H, CH_3CO).

3-Acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-deoxy-3-(*C*-formylmethyl)-β-D-altropyranose (27). To a vigorously stirred suspension of copper(II) acetate (720 mg, 4 mmol), palladium(II) chloride (340 mg, 2 mmol), and triacetate **26** (3.13 g, 10 mmol) in 20 mL of a mixture of DMF/water (3:1) was bubbled in oxygen. During the next 7 days, periodic additions of copper(II) acetate were made. After 8 days, TLC analysis revealed the reaction was complete. The reaction mixture was filtered through a pad of Florisil to remove the metal salts. The Florisil pad was copiously washed with ethyl acetate. When the green copper salts began to elute, the washings were stopped. The filtrate was concentrated, and the resulting oil chromatographed on a silica column using 40% EtOAc/hexanes as the eluent to obtain 650 mg (21%) of aldehyde **27** as a clear oil: ^{1}H NMR δ 9.51 (m, 1H, C*H*O), 6.48 (br s, 1H, N*H*), 5.29 (d, J = 2, 1H, H1), 5.26 (d, J = 1.7, 1H, H4), 4.78 (d, J = 2, 1H, H2), 4.57 (dd, J_1 = 5.4, J_2 = 1.7, 1H, H5), 3.98 (d, J = 8.6, 1H, H6′), 3.73 (dd, J_1 = 8.6, J_2 = 5.4, 1H, H6), 3.44 (dd, J_1 = 16.2, J_2 = 1.3, 1H, C*H*C), 3.19 (dd, J_1 = 16.2, J_2 = 1.3, 1H, C*H*C), 2.04 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 1.81 (s, 3H, CH_3CO). Anal. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 50.90; H, 5.83; N, 4.23.

3-Acetamido-2,4-di-*O*-acetyl-1,6-anhydro-3-(*C*-cyanomethyl)-3-deoxy-β-D-altropyranose (28a). (a) A vigorously stirred solution of aldehyde **27** (600 mg, 1.8 mmol) and hydroxylamine hydrochloride (140 mg, 2 mmol) in pyridine (5 mL) was warmed to 110 °C. After 15 min at 110 °C, TLC analysis revealed complete consumption of the aldehyde. The reaction mixture was concentrated, and the resulting oil was taken up in CH_2Cl_2 (5 mL). To this stirred solution was added $(CF_3CO)_2O$ (0.280 mL, 2 mmol) *via* syringe. After 6 h, consumption of the oxime was complete as judged by TLC. The reaction mixture was diluted with CH_2Cl_2 and washed with 50-mL portions of 10% $CuSO_4$ (2×) and brine. The organic layer was separated, dried, filtered, and concentrated, and the residue was chromatographed on a silica gel column with 70% EtOAc/hexanes as the eluent to afford 473 mg (85%) of nitrile **28a** as a white solid: mp 194–196 °C; ^{1}H NMR δ 6.70 (s, 1H, NH), 5.43 (m, 1H), 5.34 (br s, 1H), 4.89 (m, 1H), 4.69 (m, 1H), 3.83–3.80 (m, 2H, H6, H6′), 3.65 (d, J = 15.8, 1H, H3b′), 3.33 (d, J = 15.8, 1H, H3a′), 2.29 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO); ^{13}C NMR δ 20.77, 23.17, 24.45, 58.33, 65.23, 72.61, 73.11, 74.87, 99.96, 116.81, 169.30, 170.20, 172.81; $[\alpha]_D^{20}$ = −69° (*c* 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 344 ($M + NH_4$)$^+$, 327 (MH^+). Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.53; H, 5.56; N, 8.59. Found: C, 51.64; H, 5.60; N, 8.60.

(b) The oxazoline **34b** (2.95 g, 11.1 mmol) was dissolved in dioxane (59 mL), and 1 N HCl (22.1 mL, 22.1 mmol) was added. The solution was stirred for 2 h and then saturated with solid NaCl. This slurry was diluted with CH_2Cl_2 and the layers were separated. The aqueous layer was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 (3×) and $CHCl_3$ (8×). All of the organic layers were combined, dried, and concentrated to give **35**. The crude alcohol was suspended in CH_2Cl_2 (200 mL), and Et_3N (8.6 mL, 61.9 mmol), Ac_2O (7.3 mL, 77.6 mmol), and DMAP (cat.) were added. This reaction mixture was stirred at room temperature overnight, concentrated, rediluted with toluene, and concentrated (2×). The crude triacetate **28a** was adsorbed onto silica gel and flash chromatographed using 10–30% acetone/petroleum ether to afford 2.76 g (76%) of product as a white solid and 550 mg (19%) of recovered starting material (95% total yield).

(6*S*)-3-Acetamido-2,4-di-*O*-acetyl-1,6-anhydro-6-bromo-3-(*C*-cyanomethyl)-3-deoxy-β-D-altropyranose (28b). A degassed suspension of nitrile **28a** (200 mg, 0.61 mmol), NBS (110 mg, 0.61 mmol), and benzoyl peroxide (10 mg), in CCl_4 (15 mL), was exposed to a 250-W heat lamp. As the reaction progressed, the starting material went into solution. After 1 h, 1 mol equiv of NBS (110 mg, 0.61 mmol) was added and the solution was again exposed to the heat lamp. After an additional 1 h, TLC analysis showed no starting material. The reaction was diluted with $CHCl_3$, washed with H_2O, dried, and concentrated. This residue was immediately chromatographed on silica gel using 55% EtOAc/hexanes as the eluent. Concentration of appropriate fractions yielded 202 mg (81%) of bromide **28b** as a white solid: mp 124–140 °C (decomposition); ^{1}H NMR δ 6.65 (br s, 1H, NH), 6.26 (s, 1H, H6′), 5.79 (d, J = 2.0, 1H, H1), 5.39 (d, J = 1.8, 1H, H4), 4.95 (d, J = 2.0, 1H, H2), 4.88 (d, J = 1.8, 1H, H5),

3.61 (d, J = 15.8, 1H, H3b'), 3.13 (d, J = 15.8, 1H, H3a'), 2.27 (s, 3H, CH_3CO), 2.12 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO); ^{13}C NMR δ 20.56, 20.60, 23.08, 24.01, 58.10, 70.39, 71.33, 77.80, 84.75, 102.61, 116.34, 169.16, 170.46, 172.33; $[\alpha]_D^{20}$ = −186° (c 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 422, 424 ($M + NH_4$)$^+$, 405, 407 (MH^+).

(1*S*,3*S*,6*R*,7*S*,8*S*,10*S*)-6-Acetamido-7,10-diacetoxy-2,9-dioxatricyclo-[4.3.1.0^{3,8}]deca-4-one (29). (a) A stirred solution of bromide **28b** (488 mg, 1.20 mmol) and AIBN (10 mg), in xylenes (60 mL), was degassed by bubbling argon through the solution for 20 min. The reaction vessel was then heated to 155 °C. To this solution was added Bu_3SnH (0.41 mL, 1.50 mmol) dropwise over 10–20 min. The reaction mixture was heated at the same temperature for 1 h, after which time TLC analysis revealed the total absence of starting material. The solution was cooled to room temperature and concentrated. The resulting oil was chromatographed on a silica gel column, using 20% EtOAc/hexanes followed by 80% EtOAc/hexanes as the eluent to afford 300 mg (77%) of ketone **29** as a white solid: mp 183–186 °C; ^1H NMR δ 6.18 (br s, 1H, NH), 5.54–5.50 (m, 2H, H1, H7), 5.10 (s, 1H, H10), 5.04 (dd, J_1 = 3.2, J_2 = 6.4, 1H, H8), 4.18 (d, J = 6.4, 1H, H3), 3.35 (d, J = 18.0, 1H, H5'), 3.20 (d, J = 18.0, 1H, H5), 2.24 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 1.89 (s, 3H, CH_3CO); ^{13}C NMR δ 20.70, 21.02, 23.88, 40.65, 57.71, 69.83, 73.00, 73.38, 78,71, 101.05, 169.44, 169.82, 172.24, 200.95; $[\alpha]_D^{20}$ = −81° (c 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 328 (MH^+). Anal. Calcd for $C_{14}H_{17}NO_8$: C, 51.38; H, 5.24; N, 4.28. Found: C, 51.30; H, 5.26; N, 4.23.

(b) Compound **28a** (100 mg, 0.3 mmol) in *tert*-butyl alcohol (3 mL) was flushed with argon for 20 min and then heated to 85 °C. Small amounts of *tert*-butylhyponitrite[33] (~3 mg) were added from time to time (~15 min), progress of the reaction being constantly monitored by TLC. After 3 h, there seemed to be no further progress. The reaction mixture was evaporated to dryness, redissolved in methylene chloride, and washed with water. The material was recovered in the usual way, and column chromatography on silica gel gave 50 mg of starting material **28a** and 42 mg of ketone **29** (84% yield based on recovered **28a**) as a white solid.

1,6-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-β-D-*arabino*-hexopyran-3-ulose (31a). To a stirred solution of diol **13b**[31] (20 g, 50 mmol), in benzene (250 mL), was added dibutyltin oxide (12.94 g, 52 mmol). The reaction mixture was then processed as described above for diol **13a**. The solution of stannylene **30** was then cooled to room temperature, and bromine (2.56 mL, 50 mmol), in methylene chloride (30 mL), was added dropwise so that the next drop was added as the previous one has decolorized. TLC analysis revealed complete consumption of the starting material after 1 h of additional stirring. Excess bromine was quenched with cyclohexene. The volatiles were removed by rotary evaporation to afford a thick white oil. The compound was loaded onto a silica gel column using hexanes followed by 20% EtOAc/hexanes as the eluent to afford 17.6 g (88%) of ketone **31a** as a white solid: mp 100–102 °C; ^1H NMR δ 7.76–7.69 (m, 2H, Ar*H*), 7.63–7.56 (m, 2H, Ar*H*), 7.50–7.36 (m, 6H, Ar*H*), 5.64 (d, J = 2.1, 1H, H1), 4.65 (dd, J_1 = 6.3, J_2 = 2.1, 1H, H2), 4.45 (ddd, J_1 = 5.7, J_2 = 2.2, J_3 = 1.0, 1H, H5), 4.07 (d, J = 2.2, 1H, H4), 3.64 (dd, J_1 = 8.4, J_2 = 5.7, 1H, H6), 3.39 (dd, J_1 = 8.4, J_2 = 1.0, IH, H6'), 3.28 (d, J = 6.3, 1H, OH), 1.08 (s, 9H, $(CH_3)_3CSi$); ^{13}C NMR δ 19.31, 26.70, 65.01, 76.26, 77.66, 78.23, 103.62, 128.02, 130.36, 131.71, 132.72, 135.70, 203.41; $[\alpha]_D^{20}$ = −108° (c 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 416 ($M + NH_4$)$^+$. Anal. Calcd for $C_{22}H_{26}O_5Si$: C, 66.30; H, 6.58. Found: C, 66.18; H, 6.61.

2-*O*-Acetyl-1,6-anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-β-D-*arabino*-hexopyran-3-ulose (31b). To a stirred solution of ketone **31a** (12 g, 30 mmol) and Ac_2O (4 mL, 42 mmol), in methylene chloride (100 mL), was added DMAP (100 mg, 1.5 mmol). The reaction mixture was stirred for 2 h, after which time TLC analysis revealed the total consumption of the starting alcohol. The solution was diluted with ethyl acetate and washed with 50-mL portions of 1 N HCl, saturated $NaHCO_3$ (3×), and brine. The organic layer was separated, dried, filtered, and concentrated. Chromatography on a silica gel column with 15% EtOAc/hexanes as the eluent afforded 12.4 g (94%) of acetate **31b** as a white oil: ^1H NMR δ 7.78–7.71 (m, 2H, Ar*H*), 7.64–7.59 (m, 2H, Ar*H*), 7.51–7.36 (m, 6H, Ar*H*), 5.69 (d, J = 2.0, 1H, H1 or H2), 5.66 (d, J = 2.0, 1H, H1 or H2), 4.46 (m, 1H), 4.00 (d, J = 2.0, 1H, H4), 3.70 (dd, J_1 = 8.4, J_2 = 5.8, 1H, H6), 3.43 (d, J = 8.4, 1H, H6'), 2.23 (s, 3H, CH_3CO), 1.04 (s, 9H, $(CH_3)_3CSi$); ^{13}C NMR δ 19.30, 20.53, 26.64, 65.09, 76.14, 77.82, 78.10, 101.63, 127.96, 130.23, 130.30, 131.54, 132.87, 135.67, 135.81, 169.52, 196.80; $[\alpha]_D^{20}$ = −35.4° (c 1.01, $CHCl_3$); GC/CIMS (NH_3) m/z 458 ($M + NH_4$)$^+$, 441 (MH^+). Anal. Calcd for $C_{24}H_{28}O_6Si$: C, 65.43; H, 6.41. Found: C, 65.54; H, 6.45.

(*E*/*Z*)-2-*O*-Acetyl-1,6-anhydro-3-(*C*-cyanomethylene)-3-deoxy-β-D-*arabino*-hexopyranose (32b). To a suspension of sodium hydride (1.02 g, 34 mmol) (washed three times with hexanes) in THF (100 mL), cooled to 0 °C, was added diethyl cyanomethylphosphonate (5.5 mL, 34 mmol) *via* syringe. After the addition was complete, the reaction was stirred at 0 °C for 0.5 h. This solution was introduced, *via* cannula, to a −40 °C solution of ketone **31b** (12.0 g, 28 mmol) in THF (50 mL). The transfer required 15 min. The reaction mixture was stirred an additional 6 h at −40 °C. The yellow reaction mixture was diluted with ethyl acetate and washed copiously with water. The organic layer was then washed with 100 mL of saturated $NaHCO_3$ (2×) and 100 mL of brine. The organic layer was separated, dried, and filtered, and the volatiles were removed. The pale yellow oil was chromatographed on a silica gel column with 25% EtOAc/hexanes as the eluent. Upon concentration by rotary evaporation, 11.85 g (91%, colorless oil) of the unsaturated nitrile **32a** was obtained as an inseparable mixture of isomers (~5:1 by NMR). To a stirred solution of the unsaturated nitrile **32a** (30.4 g, 65.6 mmol), in THF (400 mL), was added HF·pyridine (24 mL) followed by neat pyridine (48 mL). The reaction mixture was heated at reflux for 6 h, after which time TLC analysis revealed consumption of the starting material. The solution was cooled to room temperature and neutralized by adding solid $NaHCO_3$. It was then filtered, concentrated, dissolved in toluene, and concentrated again (2×). The resulting residue was chromatographed on a silica gel column by eluting with 30% EtOAc/hexanes then 50% EtOAc/hexanes followed by 100% EtOAc. Obtained were 11.4 g (51.4 mmol) of the major isomer **32b** and 2.4 g (10.7 mmol) of the minor isomer **32b** (94% total yield). Major isomer: mp 116–117 °C; ^1H NMR δ 5.60 (br s, 2H), 5.52 (br s, 1H), 4.79–4.72 (m, 2H, H4 and H5), 3.89 (dd, J_1 = 8.2, J_2 = 5.4, 1H, H6'), 3.70 (dd, J_1 = 8.2, J_2 = 1.1, 1H, H6'), 3.05 (d, J = 7.1, 1H, OH), 2.21 (s, 3H, CH_3CO); ^{13}C NMR δ 20.72, 66.16, 70.56, 71.63, 77.43, 99.48, 100.28, 114.72, 155.97, 169.54; $[\alpha]_D^{20}$ = −172° (c 0.50, $CHCl_3$). HRMS Calcd: 225.063 723. Found: 225.063 203, Δ = 2.3 ppm. Minor isomer: mp 121–123 °C; ^1H NMR δ 5.75 (m, 1H), 5.62 (br d, J = 2.5, 1H), 5.46 (br d, J = 2.0, 1H), 4.72 (ddd, J_1 = 5.7, J_2 = 2.0, J_3 = 1.1, 1H, H5), 3.90 (dd, J_1 = 8.1, J_2 = 5.7, 1H, H6'), 3.72 (dd, J_1 = 8.1, J_2 = 1.1, 1H, H6), 3.18 (br s, 1H, OH), 2.28 (s, 3H, CH_3CO); ^{13}C NMR δ 20.57, 65.97, 70.79, 74.04, 77.17, 100.33, 101.27, 114.74, 155.02, 170.54; $[\alpha]_D^{20}$ = −161° (c 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 243 ($M + NH_4$)$^+$. Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.93; N, 6.22. Found: C, 53.28; H, 4.92; N, 6.16.

2'-Trichloromethyl-(2-*O*-acetyl-1,6-anhydro-3-(*C*-cyanomethyl)-3-deoxy-β-D-altropyranosido)-[3,4:4',5']-Δ$^{2'}$-oxazoline (34a). To a solution of alcohol (*E*/*Z*) **32b** (11.4 g, 51.4 mmol) and trichloroacetonitrile (6.7 mL, 66.8 mmol) in CH_2Cl_2 (275 mL), at 0 °C, was added dropwise *via* syringe DBU (1.54 mL, 10.3 mmol). No starting material remained 10 min after the addition of DBU, as judged by TLC. The reaction mixture was filtered with EtOAc through a short pad of silica gel to remove the trichloroacetonitrile. The resulting filtrate was concentrated to afford the crude oxazoline. The crude product was again filtered through silica gel using 10% acetone/CH_2Cl_2 as a solvent to afford 18.3 g (97%) of **34a** as a white solid: mp 157–159 °C; ^1H NMR δ 5.58 (m, 1H), 5.03 (m, 1H), 4.79–4.75 (m, 2H), 3.95–3.92 (m, 2H, H6, H6'), 3.23 (d, J = 17.5, 1H, H3a'), 2.90 (d, J = 17.5, 1H, H3b'), 2.19 (s, 3H, CH_3CO); ^{13}C NMR δ 20.82, 26.00, 65.60, 70.66, 72.85, 74.43, 77.32, 86.34, 97.04, 115.83, 163.57, 169.13; $[\alpha]_D^{20}$ = −68° (c 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 369 (MH^+). Anal. Calcd for $C_{12}H_{11}Cl_3N_2O_5$: C, 39.00; H, 3.00; N, 7.58. Found: C, 38.89; H, 2.99; N, 7.48.

2'-Methyl-(2-*O*-acetyl-1,6-anhydro-3-(*C*-cyanomethyl)-3-deoxy-β-D-altropyranosido)-[3,4:4',5']-Δ$^{2'}$-oxazoline (34b). The trichloroxazoline **34a** (18 g, 48.7 mmol) was partially dissolved (with heating) in absolute EtOH (325 mL) and Et_3N (30.4 mL, 219 mmol). After an inert atmosphere had been created over the solution with argon, 5% Pd/C catalyst (2.1 g) was added. This solution was hydrogenated on a Parr apparatus at 55 psi overnight. The solution was filtered through Celite and rinsed copiously with acetone. The filtrate was concentrated and chromatographed with 70% acetone/petroleum ether as the eluent to afford 12.2 g (94%) of **34b** as a white solid: mp 177 °C; ^1H NMR δ 5.48 (d, J = 2.3, 1H), 4.91 (m, 1H), 4.71 (d, J = 2.4, 1H), 4.35 (s, 1H), 3.91–3.87 (m, 2H, H6, H6'), 3.10 (d, J = 17.2, 1H, H3b'), 2.76 (d, J = 17.2, 1H, H3a'), 2.15 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR δ 13.99, 20.80, 26.27, 65.82, 69.53, 73.07, 75.79, 83.07, 97.36, 116.73, 166.51, 169.35; $[\alpha]_D^{20}$ = −75° (c 1.0, $CHCl_3$); GC/CIMS (NH_3) m/z 267 (MH^+). Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.10; H, 5.35; N, 10.40.