C-Glycoside Syntheses. 1. Glycosyl Cyanides and Isocyanides from Glycosyl Fluorides with Full Acetal Protection

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2,3:5,6-Di-O-isopropylidenemannofuranose, 2,3:4,6-di-O-isopropylidenemannopyranose, and 2,3,4,6-tetra-O-benzylglucopyranose each have been converted with 2-fluoro-1-methylpyridinium tosylate into anomerically pure pairs of glycosyl fluorides. Reaction of each anomeric mannopyranosyl and mannofuranosyl fluoride with Et_2AlCN in THF gave only the two (four component) anomeric mixtures of mannopyranosyl, respectively mannofuranosyl cyanides and isocyanides. The pyranosidic four component mixture (α-CN, α-NC, β-CN, and β-NC) was completely separated by a combination of flash chromatography, crystallization, and/or preparative HPLC to give the individual components; in the furanose series, only the crystalline two component mixture of α-furano cyanide and isocyanide could not be resolved. Isocyanides show two absorption maxima in their UV spectra (195 and 230 nm) while cyanides show only the first. Cyanides, being C-glycosides, char more slowly on heated TLC plates than isocyanides.

Introduction

Cyclic C-glycosides are important as enzyme inhibitors[1a] and as chiral synthons, suitable for the synthesis of many natural products.[1b] Specifically, C-glycopyranosyl cyanides could be reduced to aminomethyl C-glycosides that could be widely elaborated at the amino function.

Similarly, isocyanides may be converted into a wide variety of products,[2] which all still contain the C–N σ bond. Thus, they are useful as precursors of N-glycosidic, nucleotide-type compounds.

Various C-glycopyranosyl nitromethanes were treated with PCl_3 and pyridine to give the corresponding C-glycopyranosyl cyanides in yields of 40–80%.[3] No anomerization was observed in this transformation.

2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl bromide with mercuric cyanide gave the acetylated galactopyranosyl β-cyanide in 83% yield.[4] Similarly, the per-O-acetylglycopyranosyl cyanides of D-glucose, D-mannose, L-fucose, as well as D-galactose were obtained in 21%, 40%, 79%, and 82% yields, respectively,[5] with up to 40% side product (1,2-O-[1-cyanoethylidene)-per-O-acetylglycopyranose) which was minimized at slightly higher temperatures (35–37 °C).[6] When the 1,2-O-(1-cyanoethylidene)-α-D-gluco-, -α-D-galacto-, and -β-D-mannopyranosides were treated with BF_3, the anomerically inverted tetra-O-acetyl-D-glycopyranosyl cyanides were obtained in yields of 17%, 77%, and 67%, respectively.[7] Thus the 1,2-O-(1-cyanoethylidene) compound appears to be the kinetic product, whereas the thermodynamic product, the glycopyranosyl cyanide, is formed with strong Lewis acid and at higher temperatures. Reduction of the tetra-O-acetylgluco-[8] and galactopyranosyl[4] cyanides to the corresponding deacetylated aminomethyl glycosides was accomplished with $LiAlH_4$.

Glycosyl isocyanides,[9] not cyanides, resulted in good yields from the reaction of glycosyl halides with silver cyanide in dichloromethane.[10] The reaction proceeded faster in polar solvents, such as nitromethane, but yields were drastically reduced due to the formation of byproducts.

The use of silver cyanide also gave the 1,2-O-(1-cyanoethylidene) compound believed to be formed by neighboring group participation of the 2-O-acetyl group. The 1,2-O-(1-cyanoethylidene) compounds could have been formed via an isocyanide intermediate.[11]

Various C-glycopyranosyl cyanides have been obtained from their per-O-acetyl, benzoyl, and benzyl precursors and Me_3SiCN/BF_3 in yields from 40 to 86%.[12] 2-Deoxy-, 3-deoxy-,[13] and unsaturated[14] glycopyranosyl cyanides have been similarly prepared.

While acetylated, benzylated, or benzoylated glycosyls have been used, glycosyl cyanides, fully protected by cyclic acetals, were not obtained in any of the investigations described above. For acetylated derivatives, neighboring group participation is possible. Conformationally mobile benzylated carbohydrates are often difficult to crystallize and purify. The use of conformationally rigid cyclic acetals permits protection of the glycosyl moiety with a base-stable, but acid-labile protecting group. The hydrophobic character of the protected glycosyl moiety benefits workup procedures, e.g. allowing extractions of the products from aqueous solutions, and separations by adsorption chromatography.

The method presented in this paper completely avoids acidic conditions on the pathway to glycosyl cyanides and isocyanides and is therefore compatible with acid-sensitive blocking groups. Also, neighboring group participation is completely excluded.

Discussion

Isopropylidenation usually gives the thermodynamically more stable 1,3-dioxolane ring systems,[15] e.g. 2,3:5,6-di-O-isopropylidene-D-mannofuranose (2), which avoid axial positioning of a methyl group in a potential 1,3-dioxane ring system. However, D-mannose can react with 2-

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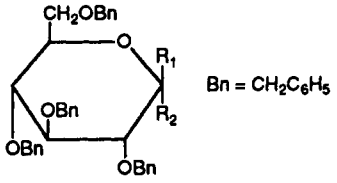
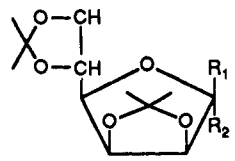
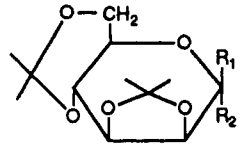
Scheme I



1a: R_1 = H; R_2 = F
b: R_1 = F; R_2 = H



2: R_1 = H; R_2 = OH
4b: R_1 = H; R_2 = F
b: R_1 = F; R_2 = H
6a: R_1 = H; R_2 = CN
b: R_1 = CN; R_2 = H
8a: R_1 = H; R_2 = NC
b: R_1 = NC; R_2 = H



3: R_1 = OH; R_2 = H
5b: R_1 = H; R_2 = F
b: R_1 = F; R_2 = H
7a: R_1 = H; R_2 = CN
b: R_1 = CN; R_2 = H
9a: R_1 = H; R_2 = NC
b: R_1 = NC; R_2 = H

methoxypropene/*p*-toluenesulfonic acid under kinetic control to give 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranose (**3**). In our hands, this preparation did not proceed as described in the literature,[16] and our modified procedure gave better results. After di-*O*-isopropylidenation was maximized, unreacted mannose was removed by aqueous extraction.

Glycosyl fluorides[17] have been used as synthetic intermediates for C-glycosylations,[18,19f] O-glycosylations,[19] S-glycosylations,[19a] and N-glycosylations.[19a] Various heterocyclic systems have been bonded to the anomeric carbon via glycosyl fluorides.[20] Preparations of glycosyl fluorides have involved HF/KF with acetylated aldoses,[21] HF/pyridine with glycosyl acetates,[22] AgF_2 with acetylated glycosyl halides,[23] XeF_2[24] or HF[25] with glycals, and (diethylamino)sulfur trifluoride (DAST),[26] hexafluoropropyl amine,[27] HF/pyridine,[28] or 2-fluoro-1-methylpyridinium tosylate[29] with glycosyls having open anomeric positions.

Table I

starting fluoride	β-CN + β-NC	α-CN + α-NC
α-furanose (**4a**)	84%[a] (**6b** + **8b**)	7%[b] (**6a** + **8a**)
β-furanose (**4b**)	95% (**6b** + **8b**)	2%[b] (**6a** + **8a**)
α-pyranose (**5a**)	54%[c] (**7b** + **9b**)	α-CN: 6% (**7a**) α-NC: 8% (**9a**)
β-pyranose (**5b**)	37%[c] (**7b** + (**b**)	α-CN: 3.3% (**7a**) α-NC: 4.5% (**9a**)

[a] CN/NC ratio = 1:9. [b] Not separated; CN/NC ratio estimated by ^1H NMR = 1:1. [c] CN/NC ratio = 3:7.

We found 2-fluoro-1-methylpyridinium tosylate to be a mild fluorinating agent for sugars with acid-sensitive blocking groups and an open glycosidic center. High acidity is generally the problem encountered with other fluorinating agents. For the preparation of 2-fluoro-1-methylpyridinium tosylate, no experimental details were given,[30] therefore we present such detail. Simple reflux of 2-fluoropyridine and methyl *p*-toluenesulfonate in absolute toluene gives the desired product which can be stored for up to 1 year with very little loss of reactivity.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl fluoride (**1b**) has been reported with (mp 48–48.5 °C; $[\alpha]^{22}_D$ +38° in $CHCl_3$ at c = 0.8)[26c] and without (mp 42–44 °C; $[\alpha]^{24}_D$ +31° in $CHCl_3$ at c = 1.03)[19d] experimental procedural detail. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (**1a**) has been reported.[19c,26c,28] Are anomeric mixtures of products[18b,19a–d] derived from compounds, such as **1a** and **1b**, possibly due to the anomeric fluoride mixtures? Anomerically pure glycosyl fluorides are needed to answer this question. In our procedure, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with 2-fluoro-1-methylpyridinium tosylate gave **1a** in good yield and in purer form than previously reported (mp 74 °C; $[\alpha]^{20}_D$ −4.0° in $CHCl_3$ at c = 1). The β-anomer could not be detected by TLC since it has the same R_f value as the α-anomer. However, flash chromatography with an oversized column gave the pure β-anomer (**1b**). Our α-fluoride (**1a**) is anomerically purer than previously reported, as shown by its *lower* rotation (Scheme I).

Reactions of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**2**) or 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranose (**3**) with 2-fluoro-1-methylpyridinium tosylate in the presence of triethylamine gave anomeric mixtures (**4a**/**4b** and **5a**/**5b**, respectively), which can be separated by flash chromatography to give the anomerically pure glycosyl fluorides in good yield (Scheme I).

2,3:5,6-Di-*O*-isopropylidene-D-mannofuranosyl fluoride has been reported,[19e,26b] although little experimental detail was given and no physical characteristics were listed.

As mentioned in the introduction, glycosyl cyanides are often formed with the aid of a Lewis acid,[7,12–14] which was precluded because of our acid-sensitive isopropylidene blocking groups. The affinity of fluorine for silicon, aluminum, and certain other metals is well known.[31] Presumably, glycosyl fluorides have been activated by SiF_4,[20b] $AlMe_3$,[19a] $MgBr_2/Et_2O$,[19a] and $AgClO_4$.[19d] It has been shown that various organoaluminum reagents react with glycosyl fluorides to form *C*-glycosides in good yields.[18a] This prompted us to use diethylaluminum cyanide as a reagent. 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl fluoride (**4a**) with diethylaluminum cyanide (procedure A) gave a mixture of *C*-glycofuranosyl cyanides and iso-

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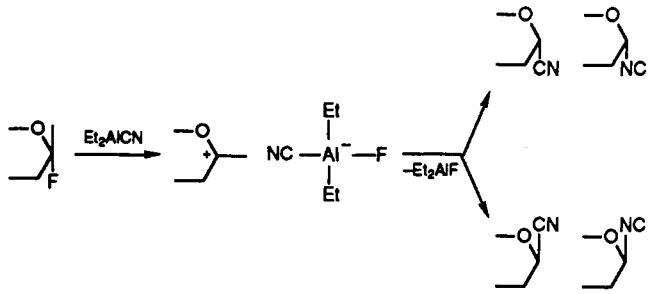
Scheme II



cyanides (Scheme I). Flash chromatography of the four component product mixture led to the isolation of two two-component mixtures: 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl cyanide and isocyanide (**6b**/**8b**; 84%) and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl cyanide and isocyanide (**6a**/**8a**; 7%) (Table I). Both mixtures were homogeneous on silica gel TLC. Separation of the β-mixture (**6b**/**8b**) by preparative HPLC afforded the pure β-cyanide (**6b**) and β-isocyanide (**8b**). Attempts to separate the α-mixture (**6a**/**8a**) were not successful.

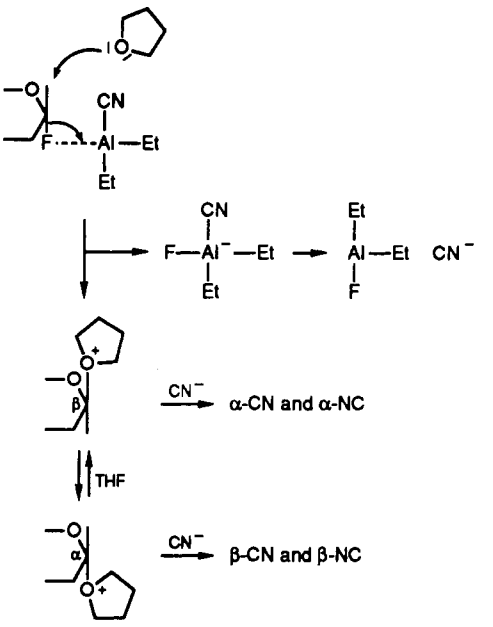
In procedure B, 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl fluoride (**4b**) was allowed to react with diethylaluminum cyanide to give, after flash chromatography, a β-mixture (**6b**/**8b**; 95%) and an α-mixture (**6a**/**8a**; 2%) (Table I).

2,3:4,6-Di-*O*-isopropylidene-α-D-mannopyranosyl fluoride (**5a**) with diethylaluminum cyanide (procedure A) gave similar results (Scheme I). After flash chromatography, a β-cyanide/β-isocyanide (**7b**/**9b**; 54%) mixture was found, but the α-cyanide (**9a**; 6%) and the α-isocyanide (**7a**; 8%) were separated by flash chromatography. Separation of the β-mixture (**7b**/**9b**) by preparative HPLC afforded the pure β-cyanide (**7b**) and β-isocyanide (**9b**). Reaction of 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranosyl fluoride (**5b**) with diethylaluminum cyanide (procedure B) also gave a β-mixture (**7b**/**9b**; 37%) and an α-mixture (**7a**/**9a**; 10%) that was separated by a second flash chromatography affording pure, crystalline **7a** (3.3%) and **9a** (4.5%) (Table I).

The mechanistic pathway of the reaction between the glycosyl fluoride and diethylaluminum cyanide is not clear. A concerted mechanism is not likely for steric reasons and, indeed, the product mixture formed could not come about through a concerted pathway since inversion, or possibly retention (S_Ni reaction) would be expected. The starting fluoride is not important since similar results are found for both α- and β-fluorides. Two possible explanations are given here. The formation of an ion pair (an oxonium ion and a tetra valent aluminum/fluoro complex) can lead to product mixtures (Scheme II). Also, THF can participate and give numerous inversions before cyanide, by an irreversible displacement of the THF, also gives product mixtures (Scheme III).

There are some noticeable differences between our glycosyl cyanides and glycosyl isocyanides. It has been reported that acetylated glycosyl cyanides do not exhibit IR absorptions.[4,8] In fact, strong IR absorptions were found for our glycosyl cyanides. IR absorptions for α-isocyanides tend to be lower (~20 cm^{-1}) than those for the corresponding β-isocyanides[11] although our compounds do not follow this trend. Upon visualization on the TLC plates by spraying with 10% H_2SO_4 in methanol followed by heating, glycosyl cyanides charred noticeably slower than glycosyl isocyanides. Ultraviolet spectra of cyanides and isonitriles are very different and are therefore useful for the detection of glycosyl cyanides and glycosyl isocyanides in conjunction with HPLC. Cyanides had one peak (λ_{max} = 195 nm), whereas isocyanides had two peaks (λ_{max} = 195 nm and λ_{max} = 230 nm).

Scheme III



Experimental Section

Infrared spectra were recorded with a Perkin-Elmer spectrophotometer Model 283 using potassium bromide pellets. Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus, Model 6404H. Optical rotations were measured at the sodium D line with an O. C. Rudolph and Sons polarimeter, Model 956, in chloroform (c = 1) unless otherwise specified. All compounds synthesized were homogeneous by thin-layer chromatography analysis, on plates coated with 0.25 mm of silica gel GF from Analtech, Inc. *Glycosyl fluoride preparations were monitored by TLC.* Plates were developed with methylcyclohexane containing tetrahydrofuran (20%). Suitable compounds were visualized under UV light, and all by spraying the plates with 10% sulfuric acid in methanol, and by heating them for 10 min at 150 °C. For flash chromatography,[32] 40-μm silica gel was used. Column sizes were 5 cm i.d. × 45 cm (200 g of SiO_2) or 1.9 cm i.d. × 45 cm (30 g of SiO_2), unless otherwise specified. All HPLC was done on a Waters 600E multisolvent delivery system equipped with a 990 photodiode array detector and a Bondapak C18 preparative column (19 mm × 30 cm, 15–20 μm, 125 A). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 FTNMR spectrophotometer using deuterated chloroform with 1% tetramethylsilane as the internal standard, unless otherwise specified. Elemental analyses were done by Beller Microanalytisches Laboratorium, Goettingen, West Germany. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose by Pfanstiehl Chemical Company was used as supplied.

2-Fluoro-1-methylpyridinium Tosylate. A solution of 2-fluoropyridine (30.2 ml, 0.35 mol) and methyl *p*-toluenesulfonate (65.3 g, 0.35 mol) in absolute toluene (80 mL) was heated at reflux (1.5 h). At room temperature, the bottom phase of the resulting two-phase mixture crystallized. The top phase was decanted. The crystalline mass was digested with hexane (150 mL) and was filtered off to give 88.0 g (89%); mp 130–131 °C (lit.[33a] mp 130–134 °C; lit.[33b] mp 132 °C).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl Fluoride (1a). 2-Fluoro-1-methylpyridinium tosylate (6.3 g, 22.2 mmol) was added slowly to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucose (10.0 g, 18.5 mmol) in CH_2Cl_2 (50 mL) and triethylamine (3.35 mL, 24.0 mmol). The mixture was magnetically stirred at room temperature

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(33) (a) *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich: Milwaukee, 1988–1989; p 755. (b) *TCI-American Organic Chemicals Catalog*; Tokyo Kasei Kogyo Co.: Tokyo, Japan, 1988–1989; p 616.

(23 h) and was extracted with H_2O (5 × 50 mL), citric acid (10%; 2 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL), and H_2O (50 mL). The organic phase was dried (Na_2SO_4) and was concentrated in vacuo. The solution of the residue in CH_2Cl_2 (50 mL) was run over a short column of SiO_2 (25 g) and was concentrated in vacuo. The addition of $CHCl_3$/hexane and cooling (−20 °C) overnight gave **1a**: 4.0 g (40%); mp 74 °C; $[\alpha]^{20}_D$ −4.0° [lit.[26c] mp 71–72 °C, $[\alpha]^{22}_D$ +11° (*c* = 0.9); lit[28a] mp 68–69 °C, $[\alpha]^{22}_D$ +8.3°; lit.[28b] mp 64–64.5 °C, $[\alpha]_D$ +9.7°]; TLC R_f 0.63; IR 1455 (CH_2), 1080 (CF), 690, 740 (C_6H_5) cm^{-1}; ^1H NMR δ 5.56 (d, $J_{1,F}$ = 53.2 Hz, $J_{1,2}$ = 2.6 Hz, H^1), 3.57 (ddd, $J_{2,F}$ = 25.7 Hz, $J_{2,3}$ = 9.6 Hz, H^2), 3.99 (t, H^3), 3.70 (m, H^4), 3.94 (m, H^5), 3.65 (m, H^6), 4.45–4.98 (m, four CH_2), 7.15, 7.31 (m, four C_6H_5); ^{13}C NMR δ 104.15 (C^1), 79.23 (C^2), 81.54 (C^3), 77.00 (C^4), 72.74 (C^5), 67.91 (C^6), 72.80, 73.65, 75.27, 75.93 (four CH_2), 127.82–128.66 (four C_6H_5). Anal. Calcd for $C_{34}H_{35}O_5F$ (542.65): C, 75.26; H, 6.50; F, 3.50. Found: C, 75.27; H, 6.61; F, 3.70.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl Fluoride (1b). The mother liquor from **1a** was subjected to flash chromatography (275 g SiO_2, 5 cm i.d. × 45 cm) with toluene as the base solvent. Fractions of 100–125 mL were collected. After 200 mL of toluene, the column was eluted with toluene/ethyl acetate/CH_2Cl_2 (18:1:1). Fractions 14–16 gave a syrup that was crystallized from methylcyclohexane/hexane by cooling (−20 °C) overnight to give a mixture containing **1a** and **1b**: 1.5 g (15%); mp 42–58 °C. Fractions 12–13 gave a syrup that was crystallized from methylcyclohexane/hexane by cooling (−20 °C) overnight to give **1b**: 2.3 g (23%); mp 42–44 °C; $[\alpha]^{20}_D$ +35.2° [lit.[26c] mp 48–48.5 °C, $[\alpha]^{22}_D$ +38° (*c* = 0.8); lit.[19d] mp 42–44 °C, $[\alpha]^{22}_D$ +31° (*c* = 1.03)]; TLC R_f 0.63; IR 1455 (CH_2), 1080 (CF), 690, 740 (C_6H_5) cm^{-1}; ^1H NMR δ 5.26 (dd, $J_{1,F}$ = 52.5 Hz, $J_{1,2}$ = 6.3 Hz, H^1), 3.55 (m, H^2), 3.99 (t, H^3), 3.70 (m, H^4), 3.94 (m, H^5), 3.70 (m, H^6), 4.45–4.99 (m, four CH_2), 7.15, 7.32 (m, four C_6H_5); ^{13}C NMR δ 107.15 (C^1), 79.47 (C^2), 81.83 (C^3), 77.73 (C^4), 75.13 (C^5), 68.63 (C^6), 73.54, 73.62, 75.20, 75.83 (four CH_2), 127.82–128.66 (four C_6H_5). Anal. Calcd for $C_{34}H_{35}O_5F$ (542.65): C, 75.26; H, 6.50; F, 3.50. Found: C, 75.27; H, 6.61; F, 3.70.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose (2). **2** was prepared according to the method described by Schmidt:[15] mp 124–125 °C; $[\alpha]^{20}_D$ +6.3° → −23.9° ($CHCl_3$, final, 48 h), +25.6° → +18.7° (acetone, final, 48 h); TLC R_f 0.32 (lit.[15] mp 122–123 °C; $[\alpha]^{14}_D$ +38° → +17° (acetone, final)).

2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranose (3). 2-Methoxypropene (5.7 mL, 60 mmol) was added dropwise to a cooled (≈0 °C), magnetically stirred solution of D-mannose (5.4 g, 30 mmol) and *p*-toluenesulfonic acid monohydrate (0.5 g, 2.6 mmol) in dimethylformamide (DMF, 20 mL). After 3 h, another portion of 2-methoxypropene (5.7 mL, 60 mmol) was added dropwise. After a total of 6 h, the resulting solution was neutralized with $NaHCO_3$ (2 g), filtered, and concentrated in vacuo. Traces of DMF were removed by codistillation with H_2O from the residual oil, which was distributed between CH_2Cl_2 (30 mL) and H_2O (5 × 30 mL). The organic layer was dried (Na_2SO_4) and was concentrated in vacuo. **3** crystallized from ethyl acetate: 5.0 g (64%); mp 153–154 °C; $[\alpha]^{20}_D$ −112.6° → −55.5° (final, 48 h); TLC R_f 0.26 (lit.[16] for α-anomer: mp 139–141 °C; $[\alpha]^{20}_D$ −39° (initial) → −50° (final, 48 h; *c* = 1, $CHCl_3$).

2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl Fluoride (4b). 2-Fluoro-1-methylpyridinium tosylate (21.3 g, 75 mmol) was added slowly to a stirred solution of **2** (15.0 g, 57 mmol) in CH_2Cl_2 (150 mL) and triethylamine (10.9 mL, 78 mmol). The mixture was magnetically stirred at room temperature (91 h) and was extracted with H_2O (5 × 50 mL), citric acid (10%; 2 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL), and H_2O (50 mL). The organic phase was dried (Na_2SO_4) and was concentrated in vacuo. Addition of petroleum ether gave **4b**: 8.13 g (54%); total yield of **4b** including material from the chromatographic purification of **4a** 8.43 g (56%); mp 114–115 °C; $[\alpha]^{20}_D$ −21.4°; TLC R_f 0.43; IR 2950 (CH), 1370 (CF) cm^{-1}; ^1H NMR δ 5.51 (d, $J_{1,F}$ = 66.7 Hz, $J_{1,2}$ = 3.6 Hz, H^1), 4.65–4.75 (m, $J_{2,F}$ = 15.4 Hz, $J_{2,3}$ = 5.9 Hz, H^2), 4.85 (t, H^3), 4.19 (m, H^4), 4.48 (q, H^5), 4.3 (d, H^6). Anal. Calcd for $C_{12}H_{19}O_5F$ (262.28): C, 54.95; H, 7.30; F, 7.24. Found: C, 55.09; H, 7.37; F, 7.30.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl Fluoride (4a). The mother liquor from **4b** was subjected to flash chromatography with $CHCl_3$ as the solvent. Fractions of 100–125 mL were collected. Fractions 26–31 gave **4b**: 0.30 g (2%). Fraction 4–17 gave a syrup that crystallized from methylcyclohexane at −50 °C to give **4a**: 2.60 g (17%); mp 27–28 °C; $[\alpha]^{20}_D$ −3.6°; TLC R_f 0.69; IR 2990, 2940 (CH), 1375 (CF) cm^{-1}; ^1H NMR δ 5.68 (d, $J_{1,F}$ = 59.2 Hz, $J_{1,2}$ = <0.2 Hz, H^1), 4.77 (t, $J_{2,F}$ = 6.2, $J_{2,3}$ = 6.0 Hz, H^2), 4.85 (t, H^3), 4.16 (m, H^4), 4.40 (q, H^5), 4.06, 4.11 (m, H^6). Anal. Calcd for $C_{12}H_{19}O_5F$ (262.28): C, 54.95; H, 7.30; F, 7.24. Found: C, 56.51; H, 7.45; F, 7.30.

2,3:4,6-Di-*O*-isopropylidene-α-D-mannopyranosyl Fluoride (5a). The method described for **4b** was applied to **3** (15.0 g, 57 mmol) to give a dry CH_2Cl_2 solution that was concentrated in vacuo and was subjected to flash chromatography with THF/methylcyclohexane (2:8) as the solvent. Fractions of 100–125 mL were collected. Fractions 13–14 gave a mixture of **5a** and **5b** that was saved to be rechromatographed: 4.05 g (27%). Fractions 3–12 gave **5a** (a syrup): 7.65 g (51%); $[\alpha]^{20}_D$ −53.2°; TLC R_f 0.75; IR 2940, 3000 (CH), 1385 (CF) cm^{-1}; ^1H NMR δ 5.76 (d, $J_{1,F}$ = 49.3 Hz, $J_{1,2}$ = <0.2 Hz, H^1), 4.31 (m, $J_{2,F}$ = 6.7 Hz, $J_{2,3}$ = 6.1 Hz, H^2) 4.22 (m, H^3), 3.75 (m, H^4), 3.68 (m, H^5), 3.75, 3.95 (m, H^6). Anal. Calcd for $C_{12}H_{19}O_5F$ (262.28): C, 54.95; H, 7.30; F, 7.24. Found: C, 56.21; H, 7.50; F, 7.2.

2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosyl Fluoride (5b). Fractions 15–22 of the preceding flash chromatography (**5a**) gave a syrup that crystallized from methylcyclohexane at −50 °C to give **5b**: 1.86 g (13%); mp 72–73 °C; $[\alpha]^{20}_D$ −63.6°; TLC R_f 0.63; IR 2940, 3000 (CH), 1375 (CF) cm^{-1}; ^1H NMR δ 5.60 (d, $J_{1,F}$ = 60.1 Hz, $J_{1,2}$ = 2.3 Hz, H^1), 4.27 (d, $J_{2,F}$ = 28.1 Hz, $J_{2,3}$ = 7.7 Hz, H^2), 4.37 (m, H^3), 4.32 (m, H^4), 3.53 (m, H^5), 3.76, 3.98 (m, H^6). Anal. Calcd for $C_{12}H_{19}O_5F$ (262.28): C, 54.95; H, 7.30; F, 7.24. Found: C, 54.90; H, 7.13; F, 6.8.

2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl Cyanide (6b) and 2,3:5,6-Di-*O*-isopropylidene-β-D-mannofuranosyl Isocyanide (8b). Procedure A. Diethyl aluminum cyanide (1 M in toluene, 22.9 mL, 22.9 mmol) was added to a cooled (≈−3 °C), magnetically stirred solution of **4a** (5.0 g, 19.1 mmol) in THF (80 mL). Stirring was continued for 1 h, and the solution was allowed to come to room temperature. After 17 h, the solution was extracted with saturated aqueous KCl/saturated aqueous $NaHCO_3$ (1:1, 4 × 50 mL), dried (Na_2SO_4), concentrated in vacuo, and subjected to flash chromatography with THF/methylcyclohexane (2:8) as the solvent. Fractions of 100–125 mL were collected. Fractions 7–12 gave **6b** and **8b** (a syrup): 4.3 g (84%); $[\alpha]^{20}_D$ −42.3°; TLC R_f 0.56; IR 2940, 3000 (CH), 2130 (CN/NC) cm^{-1}. Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 58.84; H, 7.06; N, 5.07.

Procedure B. The method described in procedure A was applied to **4b** (5.0 g, 19.1 mmol) to give a syrup containing **6b** and **8b**: 4.9 g (95%).

Purification of 6b and 8b via Preparative HPLC. With a programmed gradient from 40% methanol (60% water) to 30% methanol and the UV detector set at 207 nm, a mixture containing **6b** and **8b** (1 g in 2 mL of methanol) was injected onto a Bondapak C18 preparative HPLC column. Earlier fractions containing **6b** and later fractions containing **8b** were collected, freed from methanol in vacuo, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated in vacuo to give pure **6b** and **8b**. **6b**: 0.2; $[\alpha]^{20}_D$ −36.4; IR (in $CHCl_3$) 3000 (CH), 2130 (CN); ^1H NMR δ 4.76 (s, H^1), 4.99 (d, H^2), 4.88 (m, H^3), 3.92 (m, H^4), 4.41 (m, H^5), 4.01 (m, H^6), 1.35, 1.39, 1.47, 1.48 (s, four CH_3); ^{13}C NMR 87.63 (C^1), 85.46 (C^2), 80.90 (C^3), 84.01 (C^4), 73.49 (C^5), 67.62 (C^6), 110.5, 114.9 (two $C(CH_3)$), 25.61, 26.13, 26.82, 27.87 (four CH_3), 117.1 (CN). **8b**: 0.5 g; $[\alpha]^{20}_D$ −58.7°; IR (in $CHCl_3$) 3000, 3120 (CH), 2130 (NC); ^1H NMR δ 5.23 (s, H^1), 4.99 (d, H^2), 4.88 (m, H^3), 4.05 (m, H^4), 4.41 (m, H^5), 3.91, 4.10 (m, H^6), 1.35, 1.38, 1.47, 1.48 (s, four CH_3); ^{13}C NMR 87.86 (C^1), 85.46 (C^2), 80.18 (C^3), 83.30 (C^4), 73.43 (C^5), 67.62 (C^6), 110.5, 114.8 (two $C(CH_3)$), 25.57, 26.13, 26.75, 27.87 (four CH_3), 162.5 (NC).

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl Cyanide (6a) and 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl Isocyanide (8a). Procedure A. Fractions 22–27 from the flash chromatography of **6b**/**8b** (procedure A) gave a crystalline mass that was recrystallized from THF/petroleum ether to give a mixture of **6a** and **8a** that could not be separated: 0.35 g (7%); mp 115–116 °C; $[\alpha]^{20}_D$ +48.7°; TLC R_f 0.32; IR 2940, 3000 (CH), 2130 (CN/NC) cm^{-1}; ^1H NMR δ 4.9 (d, H^1), 4.34 (d, H^2), 4.80 (m, H^3), 3.57 (q, H^4), 4.42 (m, H^5), 4.05, 4.3 (m, H^6), 1.36, 1.37, 1.42,

1.57 (s, four CH_3); ^{13}C NMR δ 114.6 (CN), 162.5 (NC). Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.16; N, 5.19.

Procedure B. Fractions 22-24 from the flash chromatography of **6b/8b** (procedure B) gave a crystalline mass that was recrystallized from THF/petroleum ether to give a mixture of **6a** and **8a**: 0.3 g (2%).

2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosyl Cyanide (7b) and 2,3:4,6-Di-*O*-isopropylidene-β-D-mannopyranosyl Isocyanide (9b). Procedure A. The method described for **6b/8b** was applied to **5a** (5.0 g, 19.1 mmol) to give fractions 5-11 containing **7b** and **9b** (a syrup): 2.8 g (54%); $[\alpha]^{20}_D$ -36.3°; TLC R_f 0.73; IR 2950, 3000 (CH), 2125 (CN/NC) cm^{-1}. Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.46; H, 7.03; N, 4.99.

Procedure B. The method described in procedure A was applied to **5b** (5.0 g, 19.1 mmol) and gave a syrup containing **7b** and **9b**: 1.9 g (37%).

Purification of 7b and 9b via Preparative HPLC. The method described for the purification of **6b** and **8b** was applied to **7b** and **9b** (1 g in 2 mL of methanol). Earlier fractions containing **7b** and later fractions containing **9b** were collected, freed from methanol in vacuo, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated in vacuo to give pure **7b** and **9b**. **7b**: 0.2 g; $[\alpha]^{20}_D$ -36.4°; IR (in $CHCl_3$) 2950, 3000 (CH), 2130 (CN) cm^{-1}; ^1H NMR δ 5.53 (d, H^1), 4.38 (d, H^2), 4.27 (m, H^3), 3.77 (m, H^4), 3.60 (m, H^5), 3.71, 3.97 (m, H^6), 1.39, 1.45, 1.52, 1.56 (s, four CH_3); ^{13}C NMR δ 67.36 (C^1), 74.22 (C^2), 74.89 (C^3), 72.13 (C^4), 64.83 (C^5), 61.42 (C^6), 18.79, 26.26, 28.08, 28.89 (four CH_3), 100.01, 110.78 (two $C(CH_3)_2$), 115.53 (CN). **9b**: 0.5 g; $[\alpha]^{20}_D$ -58.7°; IR (in $CHCl_3$) 2945, 3000 (CH), 2125 (NC) cm^{-1}; ^1H NMR δ 5.28 (d, H^1), 4.36 (d, H^2), 4.26 (m, H^3), 3.76 (m, H^4), 3.60 (m, H^5), 3.71, 3.94 (m, H^6), 1.37, 1.43, 1.50, 1.54 (s, four CH_3); ^{13}C NMR δ 65.70 (C^1), 74.67 (C^2), 74.34 (C^3), 72.15 (C^4), 64.84 (C^5), 61.40 (C^6), 18.81, 26.38, 28.12, 28.93 (four CH_3), 100.1, 110.8 (two $C(CH_3)_2$), 163.1 (NC).

2,3:5,6-Di-*O*-isopropylidene-α-D-mannopyranosyl Isocyanide (9a). Procedure A. Fractions 18-19 from the flash chromatography of **7b/9b** (procedure A) gave a crystalline mass that was recrystallized from THF/petroleum ether to give **9a**: 0.4 g (8%); mp 121-122 °C; $[\alpha]^{20}_D$ -55.0°; TLC R_f 0.37; IR 2960, 3000 (CH), 2140 (NC) cm^{-1}; ^1H NMR δ 5.19 (d, H^1), 4.30 (m, H^{2-4}), 3.38 (m, H^5), 3.83, 3.96 (m, H^6), 1.40, 1.43, 1.55, 1.64 (s, four CH_3); ^{13}C NMR δ 78.13 (C^1), 72.82 (C^2), 70.51 (C^3), 75.52 (C^4), 67.50 (C^5), 62.40 (C^6), 18.94, 25.56, 26.97, 28.91 (four CH_3), 100.0, 112.0 (two $C(CH_3)_2$), 163.0 (NC). Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.16; N, 5.19.

Procedure B. Fractions 18-19 from the flash chromatography of **7b/9b** (procedure B) gave a crystalline mass that was recrystallized from THF/petroleum ether to give a mixture of **7a** and **9a**: 0.5 g (10%). This mixture was subjected to further flash chromatography with THF/methylcyclohexane (2:8) as the solvent. Fractions of 40-50 mL were collected. Fractions 7-8 gave pure **9a**: 0.23 g (4.5%); mp 121-122 °C.

2,3:5,6-Di-*O*-isopropylidene-α-D-mannopyranosyl Cyanide (7a). Procedure A. Fractions 20-23 from the flash chromatography of **7b/9b** (procedure A) gave a mixture of **7a** and **9a** that was saved to be rechromatographed: 0.2 g (4%). Fractions 24-26 of the preceding flash chromatography gave a crystalline mass that was recrystallized from THF/petroleum ether to give **7a**: 0.3 g (6%); mp 148-149 °C; $[\alpha]^{20}_D$ -55.2°; TLC R_f 0.29; IR 2950, 3000 (CH), 2140 (CN) cm^{-1}; ^1H NMR δ 4.70 (d, H^1), 4.50 (d, H^2), 4.13 (q, H^3), 3.76 (t, H^4), 3.19 (m, H^5), 3.89 (m, H^6), 1.39, 1.40, 1.51, 1.60 (s, four CH_3); ^{13}C NMR δ 65.49 (C^1), 73.02 (C^2), 75.50 (C^3), 71.75 (C^4), 69.94 (C^5), 61.54 (C^6), 18.80, 26.25, 28.98, 28.92 (four CH_3), 111.3, 114.8 (two $C(CH_3)_2$), 114.8, (CN). Anal. Calcd for $C_{13}H_{19}O_5N$ (269.29): C, 57.98; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.16; N, 5.19.

Procedure B. Fraction 9 of the second chromatographic purification of **9a** (procedure B) gave a mixture of **7a** and **9a** that was saved to be rechromatographed: 0.1 g (2%). Fractions 10-12 gave pure **7a**: 0.17 g (3.3%); mp 148-149 °C.

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Registry No. **1a**, 89025-46-7; **1b**, 78153-79-4; **2**, 14131-84-1; **3**, 130495-48-6; **4a**, 94898-41-6; **4b**, 96089-62-2; **5a**, 130495-46-4; **5b**, 130495-47-5; **6a**, 130468-51-8; **6b**, 130468-52-9; **7a**, 130495-49-7; **7b**, 130495-50-0; **8a**, 130468-53-0; **8b**, 130468-54-1; **9a**, 130495-51-1; **9b**, 130495-52-2; Et_2AlCN, 5804-85-3; 2-fluoro-1-methylpyridinium tosylate, 58086-67-2; 2,3,4,6-tetra-*O*-benzyl-D-glucose, 38768-81-9; D-mannose, 3458-28-4.

Enantioselective Syntheses of Vinblastine, Leurosidine, Vincovaline, and 20′-*epi*-Vincovaline

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The binary indole-indoline alkaloids vinblastine (**1**), leurosidine (**13**), 20′-*epi*-vincovaline (**14a**), and vincovaline (**14b**) were obtained by coupling of vindoline (**3**) to the tetracyclic intermediates **7a**, **7b** or **22a**, **22b**, followed by reduction and cyclization steps (60% overall yield for these reactions). The intermediates were obtained by enantioselective establishment of C20′ through a first-step Sharpless oxidation (**10a,b**) and followed by a subsequent diastereomeric separation (**20a,b** or **21a,b**). Alternatively, enantioselective control of the key secodine-type cyclization in the reaction sequence provided the tetracyclic intermediates **54** and **60** for coupling to vindoline. Selective generation of the natural (**1**, **13**, **14a,b**) or unnatural (**30**, **34**, **35a,b**) atropisomeric forms of the alkaloids was achieved through alternative closures of ring D′. The natural products were also obtained from the higher energy atropisomers by conformational inversion on heating. For the vinblastine synthesis, the overall yield was 22%.

Efforts directed toward the synthesis of vinblastine (**1**)[1] have a rich history, starting in 1967. Since there are adequate reviews of these studies,[2-4] we summarize here only their culmination for comparison with the results that are

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