3-Vinyloxymethyl-1-methyl-2-pyridone (7) was prepared from 6 and ethyl vinyl ether using mercuric acetate as catalyst,[12] yield 34% as a yellow oil: gc on 5% QF-1 on Chromosorb W 80/100, 10 ft × 0.25 in., 168°, retention time 6.4 min; nmr (CCl_4) δ 7.00–7.43 (crude t, 2 H), 6.43 (d, J_{cis} = 7 Hz, of d, J_{trans} = 14 Hz, 1 H), 6.02 (t, J = 7 Hz, 1 H), 4.59 (s, 2 H), 4.25 (d, J_{gem} = 2 Hz, of d, J_{trans} = 14 Hz, 1 H), 4.00 (d, J_{gem} = 2 Hz, of d, J_{cis} = 7 Hz, 1 H), 3.47 (s, 3 H); ir (film) 1651, 1600, 1561, 1407, 1198, 766 cm^{-1}; mass spectrum m/e 165 (P), 137, 122, 94.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.1; H, 6.4; N, 8.4.

Registry No.—**1**, 6456-92-4; **3**, 51417-13-1; **4**, 51417-14-2; **5**, 51417-15-3; **6**, 36721-61-6; **7**, 51417-16-4; **8**, 500-22-1; **9**, 100-55-0; NBS, 128-08-5.

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Steric and Electrostatic Interactions in Reactions of Carbohydrates. II.[1] Stereochemistry of Addition Reactions to the Carbonyl Group of Glycopyranosiduloses. Synthesis of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-mannopyranoside[2]

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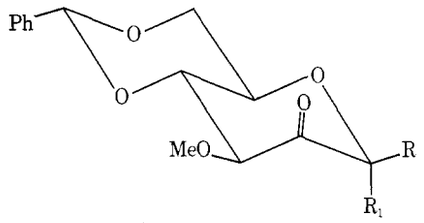
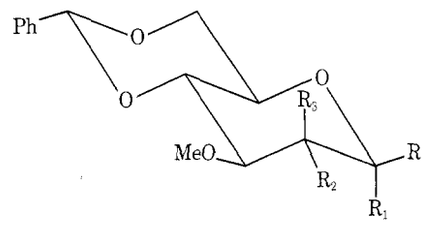
It has been reported that the reduction of benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-*lyxo*-hexopyranosid-2-ulose with lithium aluminum hydride gave benzyl 4,6-*O*-benzylidene-β-D-talopyranoside[3] (73%) whereas the reduction of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino*-hexopyranosid-2-ulose with lithium aluminum hydride gave methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-glucopyranoside as the only product.[4] These observations, and our earlier observation on the dependence upon the anomeric configuration of the stereochemistry of the methyllithium and Grignard reagent additions to the C-4 carbonyl carbon atom of glycopyranosid-4-uloses,[1] prompted us to investigate the influence of the anomeric configuration on the stereochemical course of metal-hydride reduction of the C-2 carbonyl group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α- and -β-*arabino*-hexopyranosid-2-ulose (**1** and **2**).[10] The following were the reasons for undertaking this investigation.

Presently, a view has been adopted that the transition-state geometry for reactions of metal hydrides (and organometalic reagents) with carbonyl groups resembles the geometry of the starting ketone, and that nonbonded steric interactions, torsional strain, and electrostatic interactions (dipole–dipole repulsions) are decisive factors in determining the direction from which a nucleophile will approach a carbonyl group.[5] In the case of D-glycopyranosid-2-uloses of the β series, *e.g.*, **2**, the axial approach of the metal hydride anion to the C-2 carbonyl carbon atom, resulting in the formation of the transition state **3**, requires that the negatively charged metal hydride ion approaches the C-2 carbonyl carbon atom from a direction bisecting the C_1–O_1 and C_1–O_5 torsional angle. Since the C_1–O_1 and C_1–O_5 bonds are polarized and act as two equally oriented dipoles, an approach which will apposition a negatively charged ion between them should be energetically unfavorable owing to electrostatic interactions. An "equatorial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of **2**, resulting in the formation of the transition state **4**, will be, however, not only free from the electrostatic interactions, but the torsional strain and nonbonding steric interactions will be at a minimum as well.

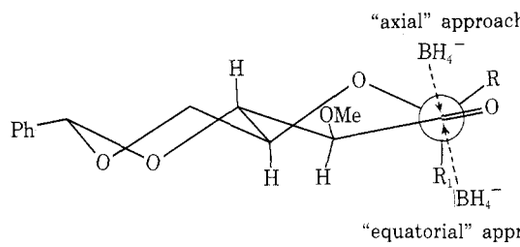
In the transition state **5**, which results from an "axial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of D-glycopyranosid-2-uloses of the α series, *e.g.*, **1**, the electrostatic interactions of the type described for the transition state **3** are not present. Furthermore, there will be no torsional strain. The only interaction present in **5** is one 1,3-nonbonding steric interaction between the axially oriented C-4 hydrogen atom and the incoming metal hydride anion. An "equatorial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of **1** resulting in the formation of the transition state **6** should give rise to generation of considerable torsional strain and dipolar interaction between the axially oriented C-1 methoxy group and the approaching metal hydride anion. Furthermore, in the transition state **6**, there will be two nonbonding steric interac-



1, R = H; R_1 = OCH_3
2, R = OCH_3; R_1 = H



7, R = R_3 = H; R_1 = OCH_3; R_2 = OH
8, R = OCH_3 R_1 = R_2 = H; R_3 = OH
9, R = OCH_3; R_1 = R_3 = H; R_2 = OH



3, R = OCH_3; R_1 = H ("axial" approach)
4, R = OCH_3; R_1 = H ("equatorial" approach)
5, R = H; R_1 = OCH_3 ("axial" approach)
6, R = H; R_1 = OCH_3 ("equatorial" approach)

tions between the approaching metal hydride anion and the axially oriented hydrogens at C-3 and C-5.

As a consequence, the metal hydride reduction of **1** should give methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**7**) as the preponderant, if not the only, product, whereas the metal hydride reduction of **2** should yield methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**8**) as the preponderant product.

The results of our studies are reported in this paper.

Methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose (**2**) was prepared by DMSO–Ac_2O oxidation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**9**)[6] at room temperature. The reduction of **2** was effected with sodium borohydride in methanol. The reason for using sodium borohydride for reduction of **2** rather than lithium aluminum hydride was based on the observation that sodium borohydride produces more axial alcohol than lithium aluminum hydride in reductions of alicyclic ketones, indicating a greater effective size of the borohydride species.[7] The crude reduction product, as expected, consisted almost exclusively of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**8**) [the ratio of D-manno (**8**) to D-gluco derivative (**9**) was 19:1].

The sodium borohydride reduction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**) in methanol, which was obtained by DMSO–Ac_2O oxidation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**7**),[6] afforded the D-gluco derivative **7** as the only product.

It is interesting to note that Ekborg, *et al.*,[8] have recently reported the synthesis of methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside by catalytic hydrogenation of methyl 3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosid-2-ulose. The high stereoselectivity (D-manno to D-gluco ratio was 19:1) in catalytic hydrogenation of the C-2 carbonyl group of β-D-*arabino*-hexopyranosid-2-uloses observed first by Theander[9] and confirmed by Ekborg, *et al.*,[8] is probably due to steric interactions exclusively.

The observed high stereoselectivity in the sodium borohydride reduction of **2** not only provides a very convenient synthetic route for the preparation of a wide variety of alkyl and/or aryl β-D-mannopyranosides, but also makes the C-2 tritium- and deuterium-labeled β-D-mannopyranoside derivatives readily available.

Experimental Section

General. The silica gel used for all column chromatography was E. Merck (Darmstadt, Germany) silica gel, grain size <0.08 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267; the nmr spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in parts per million.

Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose (2). A solution of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**9**, 520 mg) in 2:1 methyl sulfoxide–acetic anhydride mixture (12 ml) was kept at room temperature for 17 hr. The solvents were removed *in vacuo* (bath temperature was 60°), and the crystalline residue was chromatographed on silica gel (50 g). Elution with 50:75:1 acetone–hexane–water afforded pure **2** (413 mg, 80%), which after recrystallization from acetone–isopropyl ether (needles) showed mp 167–169° dec; $[\alpha]^{27}D$ −73° (*c* 1.17, $CHCl_3$); ir ($CHCl_3$) 1753 cm^{-1} (C=O stretch); nmr ($CDCl_3$) δ 7.7–7.2 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.82 (s, 1, H-1), 4.6–3.7 (m, 5, H-3, H-4, H-5, H-6, H-6′), 3.63 (s, 3, methyl from C-1 methoxy group), 3.60 (s, 3, methyl from C-3 methoxy group).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 60.94; H, 6.05.

Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-mannopyranoside (8). To a solution of **2** (116 mg) in methanol (15 ml) a methanolic solution (10 ml) of sodium borohydride (50 mg) was added dropwise. After the reduction was finished (10 min; monitored by tlc using 95:5 benzene–2-propanol as eluent), the excess of sodium borohydride was destroyed with acetic acid, and the resulting solution was evaporated *in vacuo* to dryness. The solid residue was extracted with boiling ethyl acetate (3 × 30 ml) and combined extracts were evaporated *in vacuo*. The crude product (127 mg) was chromatographed on silica gel (20 g). Elution with 3:2 hexane–acetone gave three fractions. The first fraction (3.5 mg) was pure methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**9**) identical with an authentic sample (mixture melting point and ir spectra). The second fraction (18 mg) was a mixture of **8** and **9** (monitored by tlc using 95:5 benzene–2-propanol as eluent), whereas the third fraction (82 mg) was pure methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside (**8**). Rechromatography of the second fraction (18 mg) on silica gel (5 g) afforded 1.5 mg of **9** and 14.5 mg of **8**. Therefore, the total isolated amounts of **8** and **9** by sodium borohydride reduction of **2** were 96.5 mg of **8** (82%) and 5 mg of **9** (4%). The overall yield of reduction was 86%. Recrystallization of the methyl β-D-manno derivative **8** from acetone–isopropyl ether gave very fine needles: mp 187–188°; $[\alpha]^{27}D$ −70° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 3575 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.9–7.2 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.45 (d, $J_{1,2} \leq 1$ Hz, 1, H-1), 3.53 (s, 6, C-1 and C-3 methoxy groups), 2.53 (broad s, 1, OH).

Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 60.59; H, 6.79.

Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1). Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**7**, 537 mg) was dissolved in 2:1 methyl sulfoxide–acetic anhydride mixture (12 ml) and the solution was kept at room temperature for 6 hr. The solvents were evaporated *in vacuo* (bath temperature was 60°) and the crystalline residue was chromatographed on silica gel (50 g). Elution with 120:80:1 hexane–acetone–water gave pure **1** (484 mg, 90%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether (needles): mp 133.5–134.5°; $[\alpha]^{27}D$ +42° (*c* 1.0, $CHCl_3$); ir ($CHCl_3$) 1750 cm^{-1} (C=O stretch); nmr ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 4.73 (s, 1, H-1), 4.5–3.7 (m, 5, H-3, H-4, H-5, H-6, H-6′), 3.59 (s, 3, methyl from C-3 methoxy group), 3.47 (s, 3, methyl from C-1 methoxy group).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.05; H, 6.14.

Reduction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Sodium Borohydride in Methanol. To a vigorously stirred methanolic solution (15 ml) of **1** (96 mg), a methanolic solution (8 ml) of sodium borjhydride (40 mg) was added drpwise. After the reaction was finished (5 min, monitored by tlc using 95:5 benzene–2-propanol as eluent), acetic acid was added to destroy the excess of sodium borohydride, and the resulting solution was evaporated *in vacuo* to dryness. The solid residue was extracted with three 30-ml portions of boiling ethyl acetate, and combined extracts were evaporated *in vacuo*. The crude reaction product (108 mg) was chromatographed twice on silica gel. Elution with 95:5 benzene–2-propanol gave pure **7** (80 mg, 82%), which after recrystallization from acetone–isopropyl ether (needles) showed mp 147–148° and was identical with an authentic sample[6] (mixture melting point and ir spectra). Even traces of methyl α-D-manno derivative were not present in the crude reaction mixture (examined by tlc using 95:5 benzene–2-propanol as eluent).

Registry No.—**1**, 29774-59-2; **2**, 29774-60-5; **7**, 20770-95-0; **8**, 51364-57-9; **9**, 35775-68-9.

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Reactions of Naphthalene and Anthracene Derivatives with Trifluoromethyl Hypofluorite

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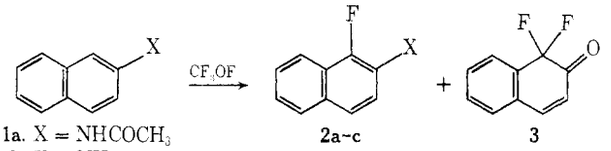
The recent discoveries that trifluoromethyl hypofluorite (CF_3OF) is useful in the fluorination of aromatic compounds[2,3] coupled with our interests in preparing fluoroaromatic compounds[4] led us to investigate the reaction of CF_3OF with some naphthalene and anthracene derivatives. Barton and coworkers'[2] report on the preparation of 1-fluoro-2-acetylaminonaphthalene (**2a**) from reaction of CF_3OF with 2-acetylaminonaphthalene (**1a**) led us to reinvestigate this reaction as a starting point for our own work.

Reaction of **1a** with CF_3OF was carried out in chloroform solution at room temperature. The reaction was performed until all **1a** was consumed as discerned from glpc and tlc analyses of the reaction progress. When all **1a** had been consumed two major products were present, 1-fluoro-2-acetylaminonaphthalene (**2a**) and 1,1-difluoro-2-naphthone (**3**), in 25 and 43% yields, respectively. The structure of **2a** was confirmed by conversion to 1-fluoro-2-aminonaphthalene (**2b**). Compound **3** was identified by its spectral and elemental analyses and by spectral analysis of its hydrogenation product.



1a, X = $NHCOCH_3$
b, X = NH_2
c, X = OH

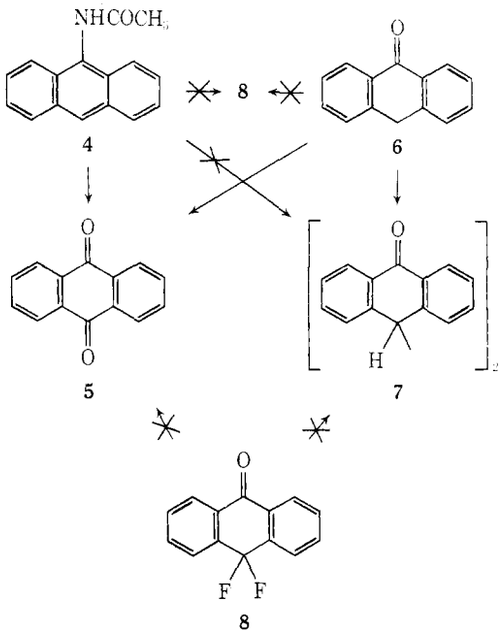
2a–c **3**

Reaction of 2-naphthylamine (**1b**) with CF_3OF produced a mixture from which 1-fluoro-2-naphthylamine (**2b**) was obtained in 9% yield and **3** was obtained in 19% yield. Facile decomposition of **2b** on exposure to air may account partially for its low yield. 2-Naphthol (**1c**) reacted with CF_3OF to yield 1-fluoro-2-naphthol (**2c**) in 14% yield and **3** in 20% yield. Analytical data established the composition of **2c**, but analogy with reaction products from **1a** and **1b** was used to determine the orientation of the fluorine atom. The hydroxyl proton showed long-range coupling to the fluorine atom, giving further evidence that the fluoro and hydroxyl groups are adjacent.[5] Attempts to prepare **2c** unambiguously from 1-amino-2-naphthol failed.

A gray solid (mp 295–298°) was formed in the reactions of **1a**, **1b**, and **1c** with CF_3OF. This material was insoluble in most organic solvents except dimethyl sulfoxide. The composition of the solid was not determined owing to slow continuous decomposition and our inability to obtain a pure sample. The infrared spectrum showed absorbances characteristic of an amine salt[6] at 2200 and 1800 cm^{-1} if the spectrum was obtained on freshly prepared material. On standing, these absorbances disappeared.

Treatment of pure samples of **2a**, **2b**, **2c**, and **3** with CF_3OF produced a complex mixture of at least seven components (tlc and glpc). We could therefore not show that **3** was formed by further fluorination of **2a**, **2b**, and **2c**. Yields of products are based on a parallel reaction scheme: **1** → **2**; **1** → **3**.

Reaction between 9-acetylaminoanthracene (**4**) and CF_3OF yielded anthraquinone (**5**) in 95% yield. No other compound was detected by tlc or glpc. Attempts to determine a mechanism for this reaction were made by treating feasible intermediates with CF_3OF. Anthrone (**6**) produced both **5** (55%) and 10,10-bianthronyl (**7**, 30%) on reaction with CF_3OF. 10,10-Difluoroanthrone (**8**) and **7** are reported products from the reaction of **6** with sulfur tetrafluoride in the presence of radical scavengers.[7] We were unable to detect either **5** or **7** on reaction of **8** with CF_3OF. Our detection methods (tlc and glpc) could have detected at least 0.1% of the components as determined from standard solutions of **5** and **7**. Careful reexamination of the products from **4** failed to show any **7**. These results are presently taken as evidence against the intermediacy of either **6** or **8**. Investigations which should provide useful information regarding the mechanism and synthetic potential of these and similar reactions are in progress.



Experimental Section

All temperature reading are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were determined on a Varian T-60 spectrometer using tetramethylsilane (δ 0.0) as an internal standard. Molecular weights were determined from mass spectra obtained on a Varian MAT-111 spectrometer. Infrared spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer using polystyrene for calibration. Trifluoromethyl hypofluorite was obtained from PCR, Inc., Gainesville, Fla. Aldrich spectroquality chloroform was used as the solvent in all reactions with CF_3OF. Glpc analyses were performed on a Varian 1440 flame ionization gas chromatograph using a 5 ft × 0.13 in. stainless steel column of 3% SE-30 on Chromosorb W and helium flow rate of 60 ml/min.

Reactions with Trifluoromethyl Hypofluorite (CF_3OF). 2-Acetylaminonaphthalene (1a). A solution of 1.5 g (7.2 mmol) of **1a** in 25–30 ml of chloroform was treated with CF_3OF at room temperature. The reaction mixture became dark. The course of the reaction was followed by glpc and tlc (silica gel). Two major products were formed and all **1a** was consumed within 40–60min. Nitrogen was bubbled through the reaction mixture to assist in the removal of residual CF_3OF. The mixture was filtered to give 0.7 g of gray material, mp 295–298° dec. *Anal.* Found: C, 75.2; H, 4.7; N, 7.9; F, 3.6. This material was not identified because its properties (ir, nmr, melting point) continuously changed.

The filtrate was concentrated on a rotary evaporator, giving 1.8 g of brown oil. Trituration with petroleum ether (bp 40–60°) gave