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Isochromane "versus" O-Glycoside Synthesis. A Study of the Reaction of 2-Alkoxy-2-Fluoro-Glycosyl Fluorides with Alcohols.

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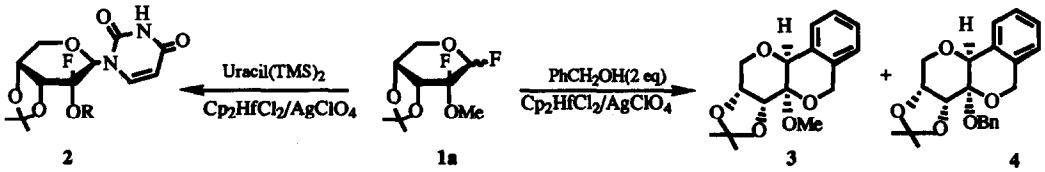
Abstract: 2-alkoxy-2-fluoro-glycosyl fluorides **1a** and **1b** react with benzyl alcohol derivatives in the presence of the fluorine activating system $Cp_2HfCl_2/AgClO_4$ giving isochromane or O-glycosides derivatives depending on the glycosyl fluoride/alcohol ratio. A mechanism of the consecutive reactions leading to the isochromane derivatives is proposed.

Glycosyl fluorides are useful glycosyl donors because of their stability with regard to other glycosyl halides, ease of handling and the availability of specific activation methods.[1] We recently reported[2] that methyl pyranosid-2-uloses react with diethylaminosulfur trifluoride (DAST) to give good yields of 2-alkoxy-2-fluoro-glycosyl fluorides. The 1,2-difluoro carbohydrate **1a**[2] is a stable compound and it behaves like a typical electrophilic glycosyl donor when it reacts with bis-(trimethylsilyl)uracile to give the 2-alkoxy-2-fluoronucleoside **2** (Scheme 1).[3] On the other hand, **1a** can also behave like a 1,2-dielectrophilic synthon. When activated[1f-j] by $Cp_2HfCl_2/AgClO_4$ it reacts with dinucleophilic compounds such as benzyl alcohol to give the isochromane derivatives **3** and **4**.[4] This reaction appeared to be dependent on the metallocene derivative used, on the reagents' molar ratio and on the solvent. The best results in the preparation of isochromane derivatives were obtained when a hafnocene dichloride/silver salt ratio of 1:2 and a sugar/benzyl alcohol ratio of 1:2 were used in dichloromethane as the solvent. When zirconocene dichloride was used as activator, principally non cyclized compounds were obtained. Various features of this reaction are oustanding, the stereospecificity, the exclusive formation of the C-C bond at C-1 position and not at C-2 and the obtention of compound **4** where the OMe group present in the starting material has been substituted by a OBn group.



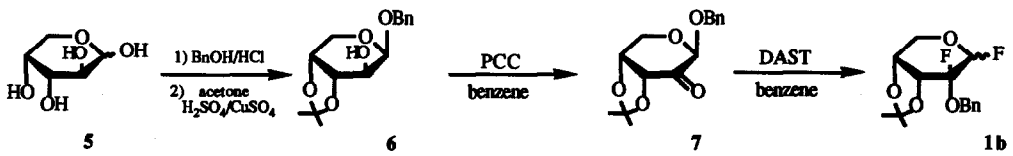
Scheme 1

In this article we describe the behaviour of this reaction with different alcohols and provide evidence of the structure of new compounds and for the mechanism of this process.

RESULTS

We considered that for mechanistic studies the benzyl derivative **1b** would be an appropriate starting material, since it would allow information to be obtained on the difference in reactivity between **1a** and **1b** and their influence on the stereochemistry of the products of the reaction. Moreover, a study of the reaction of **1b** in the absence of alcohols or with differently substituted benzyl alcohol would give information about the way the glycosylation reaction is produced.

As is shown in Scheme 2, compound **1b** was synthetized from D-arabinose (**5**) by reaction with HCl in benzyl alcohol and then with acetone/H_2SO_4/$CuSO_4$ to obtain compound **6**.[5] The treatment of **6** with PCC gave the ulose **7** in 56% yield. The reaction of **7** with DAST allowed 78% yield of compound **1b** to be obtained as an anomeric mixture ($\alpha/\beta = 3:1$).



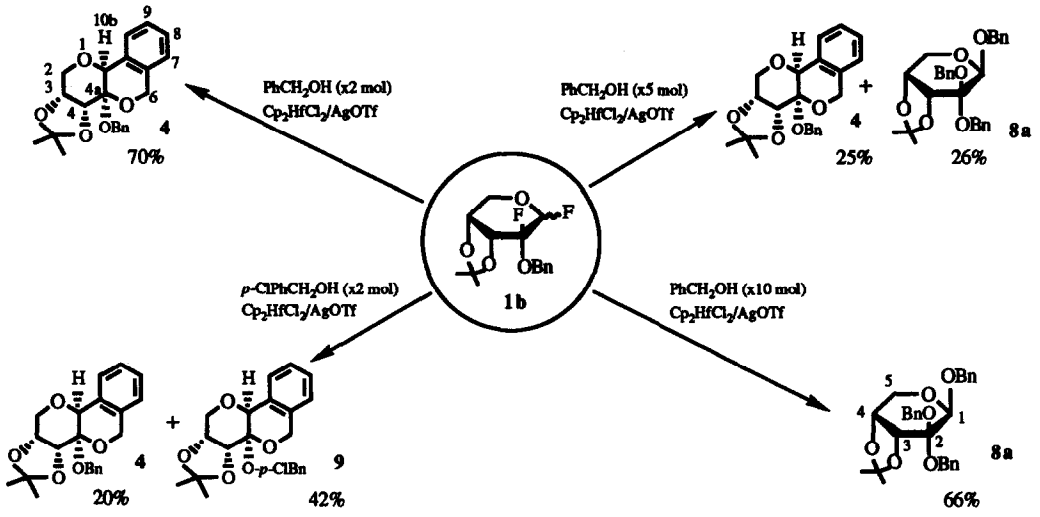
5 6 7 1b

Scheme 2

The most significant spectroscopic data supporting structure **1b** were: 1) In the ^1H, ^{13}C and ^{19}F NMR spectra it was possible to observe two closely related sets of signals in a 3:1 ratio. 2) Chemical shifts and coupling constants for protons H-1 (major isomer: d, $^2J_{H1,F1} = 63.9$ Hz; minor isomer: dd, $^2J_{H1,F1} = 64.1$ Hz, $^3J_{H1,F2} = 2.5$ Hz) indicated that a F-H geminal relation exists.[6] 3) Four different groups of signals (double doublets) in the ^{13}C NMR spectrum appeared in the 104-115 ppm region corresponding to C-1 and C-2 of the two isomers, the high value (~225 Hz) for $^1J_{F,C}$ coupling constants suggested a fluoroalkoxy substitution for these carbons[7]. 4) Coupling constants $J_{F2,F1} = J_{F2,H3} = 13$Hz observed in the ^{19}F NMR spectrum indicated that F-2 must be equatorial.[8]

When **1b** was treated with benzyl alcohol (2 mol) in the presence of Cp_2HfCl_2/AgOTf in benzene, only compound **4** was obtained in 70% yield after 1.5 hours (Scheme 3). However, when a greater excess of benzyl alcohol (5 mol) was used a mixture of the tribenzyl derivative **8a** and the tricyclic derivative **4** were obtained in yields of 26% and 25% respectively. That is to say, in the presence of a great excess of alcohol the intermolecular attack of a second benzyl alcohol molecule competes with the intramolecular Friedel-Craft cyclization. This must imply that a carbocation is produced at the anomeric position when two OBn groups are present at position 2. Anyway, the reaction leading to compound **4** is stereospecific, the cyclization product being obtained through the upper face (exo face in the bicyclic starting material). In spite of the presence of a benzyloxy group on the lower face of the starting glycosyl fluoride, a cyclization product was not detected through the lower face. When a tenfold excess of benzyl alcohol was used only compound **8a** was obtained in a yield of 66%. Also in this case, only one anomeric derivative was detected.

The structure of compound **4** was established by ^1H and ^{13}C NMR spectroscopy on the basis of the following facts: 1) In the ^1H NMR spectrum two sets of double doublets at 4.8-4.9 ppm showed that two AB systems, corresponding to two benzyl groups were present with coupling constants of 12 Hz and 14.5 Hz; this last value indicated that one benzylic CH_2 group is integrated in a cycle.[9] 2) In the acetal region (~100 ppm) of the ^{13}C NMR spectrum only two signals appeared, probably corresponding to the quaternary acetalic isopropylidene and to th C-4a carbons. 3) A HETCOR experiment allowed the signal at 72.5 ppm to be assigned to C-10b, indicating that it is not an anomeric carbon. 4) The absolute configuration of C-10b and



Scheme 3

C-4a was readily established on the basis of a NOESY experiment, observing that H-10b was correlated with the exocyclic benzyl protons and one of the methyl groups of the isopropylidene group, which suggests that H-10b, the exocyclic benzyl group and the isopropylidene group are on the same face of the molecule. 5) This correlation also suggests a twist boat conformation for the sugar ring.

The structure of compound **8a** was attributed taking into account the presence in the ^1H NMR spectrum of three AB systems between 4-5 ppm with J ~ 12 Hz; this was confirmed in the ^{13}C NMR spectrum by the presence of 4 CH_2 groups (3 from the benzyloxy groups plus C-5). Moreover, 3 signals (1 CH and 2 C) appeared at 100-110 ppm showing the presence of 3 acetal carbons (C-1, C-2 and the C-isopropylidene).

O.R. Martin[10a-d] has shown that the intramolecular reaction of the 2-OBn in pyranoid derivatives is slower than in furanoid ones, and that the presence of activating or withdrawing groups, such as m-OMe or Cl, in the aromatic ring of benzyl alcohol respectively increases or decreases the reaction rate.

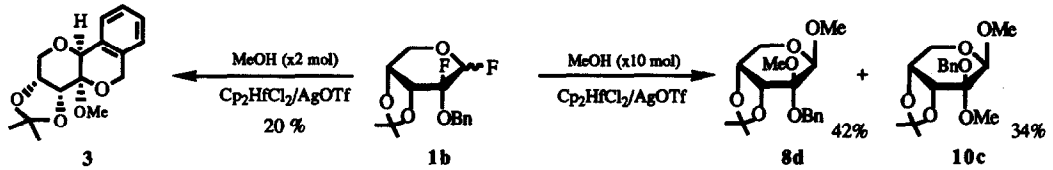
In order to find out the origin of the cyclized benzyl group and the factors controlling the stereochemistry of the cyclization reaction, we performed the reaction with differently substituted alcohols such as *m*-methoxybenzyl alcohol (activated ring) and *p*-chlorobenzyl alcohol (deactivated ring). This less reactive benzyl alcohol should allow the cyclization to take place through the benzyloxy group present on the lower face of starting glycosyl fluoride. The use of *m*-methoxybenzyl alcohol in the reaction with **1b** gave rise to a complex mixture of products. However, when *p*-chlorobenzyl alcohol (**1b**/*p*-ClBnOH ratio 1:2) was used an inseparable mixture of compounds **4** and **9** was obtained in 20% and 42% yields respectively (Scheme 3).

The 500 MHz ^1H NMR spectrum of the mixture has two almost identical sets of signals in the aliphatic region. In the aromatic region it is possible to observe a double doublet characteristic of *para*-substituted aromatic rings, corresponding to the main product **9**. Neither the doublet or the double doublet indicating the cyclization on the chlorophenyl ring were detected. Nevertheless, the stereochemistry of both products was the same, the cyclization having been produced exclusively through the upper face of the sugar ring. This would imply that a transacetalization equilibrium was produced in such a way that the benzyloxy group present in the starting material left the molecule to then enter through the upper face and/or is epimerized.

This equilibrium process was confirmed by the reaction of **1b** with 5 mol of $PhCD_2OH$ (α,α-dideuterio benzyl alcohol), which gave a 73% yield of a mixture of partially deuterated compounds after 48 hours. The

^1H and ^{13}C NMR spectra of this mixture are identical to the spectra of compound **8a**, except the benzylic CH_2 signals. In the ^1H NMR spectrum the total disappearance of an AB system and the modification of the two others is observed. This is confirmed by the ^{13}C NMR (DEPT) spectrum where three CH_2 signals show a relatively different intensity with regard to the one observed in the spectrum of compound **8a**. Thus the signal at 64.6 ppm completely disappeared and the the signals at 67.0 and 71.1 have a third and a half of the intensity of the other carbons (Figure 1). This clearly demonstrates that deuterated benzyl alcohol is also present in the position occupied by the OBn group in the starting material. The integration in the ^1H NMR spectrum showed a 70% ratio of deuterium incorporation in the final mixture of products. This ratio corresponds quite well with the ratio $PhCD_2OH/PhCH_2OH$ present in the reaction solution. Curiously, the reaction of **1b** with 2 mol $PhCD_2OH$ did not gave the expected cyclized product, but a mixture of partially deuterated compounds **8b** and **10a** (see scheme 5) was slowly obtained.

We have shown above that the reaction of glycosyl fluoride **1a** with benzyl alcohol gave a mixture of **3** and **4** (Scheme 1). In the last product the OMe present in the starting material had been substituted by a benzyloxy group coming from the reactive alcohol. We think that reversing the process, that is to say, making **1b** react with methanol could give additional information about the cyclization and the substituent exchange. The reaction of **1b** with 2 mol of methanol in standard conditions gave 20% of a compound that after spectroscopical elucidation turned out to be identical to compound **3**. A tenfold excess of methanol allowed a mixture of compounds **8d** and **10c** to be obtained in a yield of 42% and 34% respectively. Also in this case the ratio MeO/BnO in the reaction products was in agreement with their ratio in the reagents (Scheme 4).



3 **1b** **8d** **10c**

Scheme 4

The almost identical NMR spectra of both compounds, together with the presence of two methyl and one benzyl groups with a ^2J=12 Hz (exocyclic) seemed to indicate the presence of an anomeric mixture. However, nOe experiments showed that the irradiation of H-3 in the main product **8d** produced an small increase in the signals of the two methyl groups; in the same way, only one methyl group increased when H-3 and H-5a of the minor product **10c** were irradiated, which implies that it must be at the anomeric position. The fact that substituents at the anomeric position are always ß, together with the obtention of an epimeric mixture at C-2, seems to confirm that the reaction starts by the activation of C-1, being the glycosylation governed by the anomeric effect. In a second step the C-2 activation would take place to give the acetalization. The $Cp_2HfCl_2/AgOTf$ system is also able to catalyze the transacetalization reaction. This was confirmed by treatment in benzene of compound **10c** with the above catalytic system, resulting a mixture of compounds **3** and **4** in absence of alcohol, and compound **8a** in the presence of benzyl alcohol.

We mentioned in the introduction that the reaction of glycosyl fluoride **1a** with bis-(trimethylsilyl)uracil led to nucleoside **2** which conserved the fluorine at position 2 (Scheme 1). On the other hand, in all the cases discussed above, the reaction of **1b** with benzyl alcohol derivatives and methanol gave compounds where the configuration of carbons 10b and 4a was the same. Compounds with the opposite stereochemistry (cyclized through the lower face) were not observed. With the aim of trying to conserve the fluorine at position 2 and force the cyclization through the lower face, compound **1b** was treated with the fluorine activator $Cp_2HfCl_2/AgOTf$ in the absence of alcohol. Curiously, only compound **4** was isolated in 26% yield, together with other minor unidentified products; this confirms that the $Cp_2HfCl_2/AgOTf$ system not only activates the

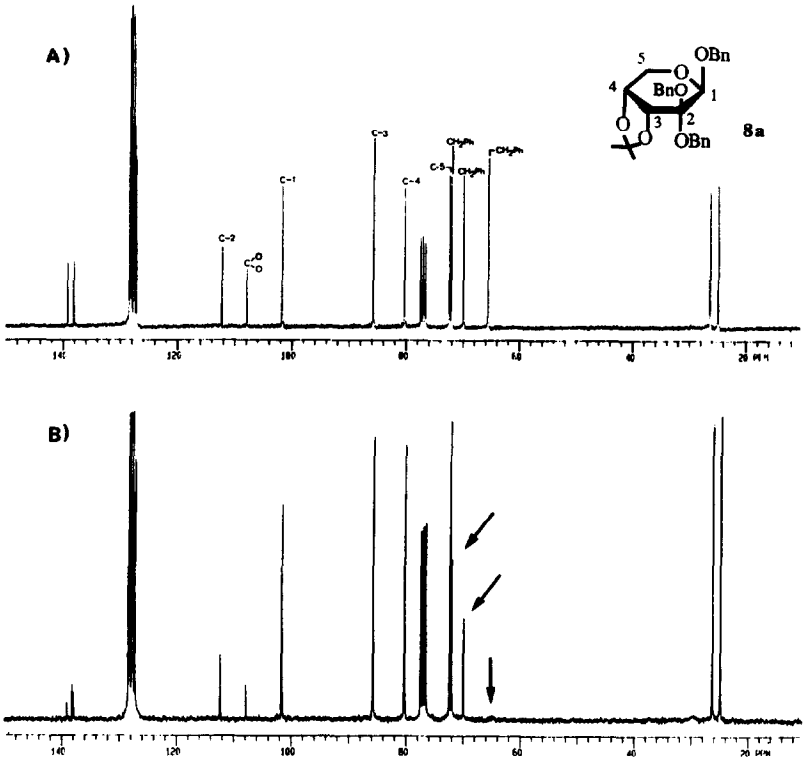


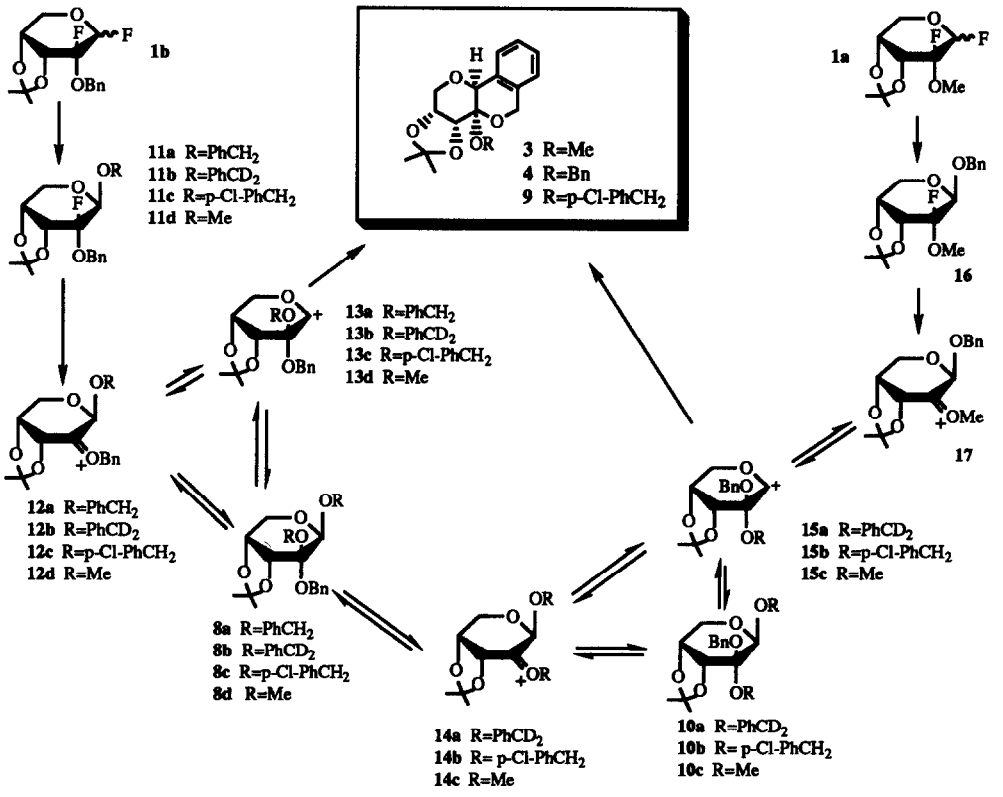
Figure 1: ^{13}C NMR spectra of A) compound **8a** and B) mixture of deuterated compounds **8b+ 10a**.

two fluorine atoms but also the departure of the OBn group. Another fluorine activator, Tf_2O,[11] also gave the same product in a similar yield. The use of $BF_3{\cdot}Et_2O$[1c-d] or TMSOTf[1b] led to a mixture of products where no cyclized products were present.

Mechanism of the reaction

A mechanism trying to explain this reaction must account for the following facts: a) the observed stereochemistry of the final products, isochromane derivatives as well as normal glycosides, particularly the configuration of position 1 and 2 (sugar numeration); b) a new C-C bond is formed exclusively at carbon C-1, via a Friedel-Craft reaction, which means that a carbocation has been generated at this carbon; c) compound **4** is obtained from **1a** and **9** from **1b**, which supposes that there has been a reaction affecting the OMe and OBn groups respectively present in the starting materials; d) employing *p*-Cl-$PhCH_2OH$ no cyclization involving the chlorine containing ring was produced; e) when $PhCH_2OH$ is used, isochromane derivatives or normal glycosides can be obtained depending on the sugar/alcohol ratio; f) the reaction of **1b** with $PhCD_2OH$ and with MeOH (10 mol) give rises to an epimeric mixture at C-2, but neither anomeric mixtures nor mixtures of differently substituted compounds at C-1.

In accordance with these events a proposed mechanism is shown in Scheme 5. From compound **1b** the reaction starts with the activation of F-1 and subsequent alcohol glycosylation. The isolation of a 2-fluoro nucleoside (Scheme 1), the fluoroglycosides **11a-d** were not isolated, supports this assumption. Then, the



Scheme 5

activation of F-2 generates the oxonium cations **12a-d** which may evolve to compounds **8a-d** by the attack of a second alcohol molecule, or to oxonium cations **13a-d** by 1,2-rearrangement of the anomeric substituents.

From **13a-d** tricyclic compounds or O-glycosides can be obtained, via a intramolecular Friedel-Craft reaction or by reaction with alcohol, respectively. These are competitive reactions, and the formation of tryciclic compounds or glycosides depends on the alcohol concentration and on the activation of the aromatic ring. Thus, the cyclization reaction is observed from **13a** (R=Bn) to give **4**, but when an excess of benzyl alcohol is used only **8a** is obtained, while from **13c** (deactivated ring) no cyclization products were produced. From **13d** the tricyclic product should have been formed, but the cyclization reaction was probably limited by the high steric crowding in the transition state.

Since no mixtures at C-1 have been detected neither in the glycosides nor in the cyclized products, the reactions affecting this position (glycosylation from **1b** or from **13a-d**) have to be stereoselectives. The factors controlling the stereochemistry can be stereoelectronics (anomeric effect) and/or conformationals (attack by the exo face).

When $PhCD_2OH$ was used a mixture of epimers **8b** and **10a**, and probably also the tri-[(α,α-dideuterio)benzyl derivative was obtained. Formation of **10a** can be explained considering that in the reaction medium compound **8b** can generate the oxonium cations **12b** and **13b** or lead to the new one **14a**, from which compound **10a** (reaction with benzyl alcohol) can be obtained through a transacetalization reaction. The ^{13}C spectrum (Figure 1) of the final products matches quite well with this situation, since a CH_2 has completely

disappeared (the anomeric one), and the different intensity of two other CH_2 carbons indicates the different ratio of compounds **8b** and **10a**.

The obtention of cyclized products **4** and **9** by reaction of **1b** with *p*-Cl-$PhCH_2OH$ can be explained taken into account the above comments. Compounds **4** and **9** must be formed from cations **13a** and **15b**, respectively. However, similarly when $PhCH_2OH$ was used, cations **12c** and **13c**, and hence compound **8c**, must be initially formed. A transacetalization process, similar to the observed for $PhCD_2OH$, can be invoked to justify the formation of **13a** and **15b** from **8c**.

The reaction of **1b** with methanol lead to compound **3** or to the mixture **8d** plus **10c** depending on the methanol excess. When twice mol of methanol were used, the initially formed cation **12d** evolve to **13d** and to **8d**, from which cyclized product **3** can be obtained through consecutive transacetalization, intramolecular 1,2-rearrangement and Friedel-Craft reaction. In a great excess of methanol the intermolecular reactions from **12d** and **13d** or from **14c** and **15c**, leading to **8d** or **10c**, respectively, are faster.

Similarly, starting from **1a** the oxonium cation **17** would also be obtained by reaction with benzyl alcohol, which would evolve to the oxonium cation **15c** and then to the tricyclic compound **3** by intramolecular cyclization.

In conclusion, the glycosyl fluorides **1a** and **1b** react with alcohols through glycosylation, 1,2-migrations, transacetalization and/or Friedel-Craft reactions catalysed by the $Cp_2HfCl_2/AgOTf$ system to give the isochromane derivatives **3**, **4** and **9** or the diacetals of pyranoside-2-uloses **8a**, **8b**, **8d**, **10a** and **10c**. These reactions take place through different intermediates in equilibrium, being the determining step the competition between intramolecular cyclization and glycosilation, which depends on the activation of the aromatic ring towards electrophilic substitution reaction and on the alcohol concentration. The resulting stereochemistry is determined by stereoelectronic and/or conformational effects.

EXPERIMENTAL SECTION

General Procedures. Melting points were measured in a Büchi 510 apparatus and appear uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 300 instrument (300MHz, 75 MHz and 288 MHz respectively), using Me_4Si, the central peak at δ 77 ppm and $CFCl_3$, respectively as internal reference. Elemental analyses were determined using a Carlo Erba apparatus. Flash column chromatography was performed on silicagel 60 A CC. Preparative thin layer chromatography was performed on silicagel 60. All the reactions were carried out under an atmosphere of dry argon in oven-dried glassware. Reaction temperatures were recorded as bath temperatures. Solvents for chromatography were distilled at atmospheric pressure prior to use. Anhydrous CH_2Cl_2 was distilled from CaH_2. Benzene was dried by distillation from Na ribbon and stored over 4Å molecular sieves and under argon. Reported yields refer to chromatographically and spectroscopically homogeneous material.

Benzyl 3,4-O-isopropylidene-ß-D-*erythro*-pentopyranosid-2-ulose (7). In a light protected flask, 14.7 g (68.4 mmol) of pyridinium chlorochromate, 5.6 g (68.4 mmol) of anhydrous sodium acetate, 34 g of 4Å molecular sieves (previously activated) and benzene (10 ml) were introduced and stirred under argon atmosphere for 10 minutes. A solution of benzyl 3,4-O-isopropylidene-ß-D-*arabino*-pentopyranoside (8 g, 28.5 mmol) in 120 ml of benzene was added to the suspension obtained and then the resulting reaction mixture was heated to reflux for two hours. When the reaction finished, it was diluted with 200 ml of ethyl ether and filtered through a silicagel pad to separate the chromiun salts formed. The remaining solution was evaporated to dryness and coevaporated with toluene three times to eliminate traces of pyridine. The remaining residue was purified by flash chromatography (hexane/ethyl acetate 3:1) obtaining 4.5 g (56%) of compound **7** as an oil. (**7**): $[\alpha]_D$=-179.4° (c 0.78, $CHCl_3$). ^1H NMR δ, 7.30-7.20 (s, 5H, Ph), 4.79 (s, 1H, H-1),

4.69 (d, 1H, J=11.7 Hz, CH_2Ph), 4.60 (d, 1H, $J_{3,4}$=5.5 Hz, H-3), 4.49 (d, 1H, CH_2Ph), 4.41 (dd, 1H, $J_{4,5ax}$=2.1 Hz, H-4), 4.18 (dd, 1H, $J_{5ax,5eq}$=13.5 Hz, H-5ax), 3.99 (d, 1H, H-5eq), 1.35 (s, 3H, CH_3isopr), 1.28 (s, 3H, CH_3isopr). ^{13}C NMR δ 198.9 (C-2), 128.2 (Ph), 110.6 (Cisopr), 99.3 (C-1), 77.8-75.6 (C-3, C-4), 58.9 (C-5), 27.4 (CH_3isopr), 26.4 (CH_3isopr). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.72; H, 6.53. Found: C, 64.20; H, 6.59.

2-O-Benzyl-2-fluoro-3,4-O-isopropylidene-α and ß-D-*ribo*-pento-pyranosyl Fluoride (1b). To a solution of the ulose 7 (0.5g, 1.8 mmol) in anhydrous benzene (5 ml) DAST (0.53 ml, 3.9 mmol) was added dropwise at room temperature. After 24 hours the reaction mixture was poured into cold saturated aqueous $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml); then, the combined organic layers were dried ($MgSO_4$) and evaporated. The crude oil was purified by flash chromatography (ethyl acetate/hexane 1:2) giving the glycosyl fluoride **1b** (420mg, 78%) as an α/ß anomeric mixture. Major isomer (ß, axial F in C_1): ^1H NMR δ 7.36 (m, 5H, Ph), 5.31 (d, 1H, $J_{1,F1}$=63.9 Hz, H-1), 4.93-4.60 (m, 5H, H-2, H-3, H-4, CH_2Ph), 4.22-4.13 (m, 2H, H-5ax, H-5eq), 1.58 (s, 3H, CH_3isopr), 1.38 (s, 3H, CH_3isopr). ^{13}C NMR δ , 128.7-128.3 (Ph), 115.4 (Cisopr), 112.2 (dd, $J_{C2,F2}$=239.9 Hz, $J_{C2,F1}$=28.0 Hz, C-2), 106.8 (dd, $J_{C1,F1}$=223.0 Hz, $J_{C1,F2}$=45.0 Hz, C-1), 79.3 (d, $J_{C3,F2}$=19.6 Hz, C-3), 78.3 (C-4), 72.4 (C-5), 71.6 (CH_2Ph), 25.9 (CH_3isopr), 25.6 (CH_3isopr). ^{19}F NMR δ -123.5 (m, F_2), -143.7 (dd, $J_{F,H1}$=63.9 Hz, $J_{F,F}$=3.1 Hz, F-1). Minor isomer (α, equatorial F in C_1): ^1H NMR δ 7.5-7.3 (m, 5H, Ph), 5.4 (dd, $J_{1,F1}$=64.1 Hz, $J_{1,F2}$=2.5 Hz, H-1), 4.9-4.6 (m, 5H, H-2, H-3, H-4, CH_2Ph), 4.2-4.1 (m, 2H, H-5ax, H-5eq), 1.6 (s, 3H, Me), 1.4 (s, 3H, Me). ^{13}C NMR δ 128.7-128.3 (Ph), 115.3 (Cisopr), 112.4 (dd, $J_{C2,F2}$=236.6 Hz, $J_{C2,F1}$=34.3 Hz, C-2), 107.1 (dd, $J_{C1,F1}$=223.8 Hz, $J_{C1,F2}$=45.6 Hz, C-1), 79.1 (d, $J_{C3,F2}$=19.2 Hz, C-3), 78.3 (C-4), 72.5 (C-5), 71.8 (CH_2Ph), 25.9 (CH_3isopr), 25.6 (CH_3isopr). ^{19}F NMR δ -123.3 (td, $J_{F2,F1}$=$J_{F2,H3}$=13.0 Hz, $J_{F2,H1}$=2.5 Hz, F-2), 141.6 (dd, $J_{F1,H1}$=64.1 Hz, $J_{F1,F2}$=13.0 Hz, F-1).

General Procedure for the Reaction of 2-O-Benzyl-2-fluoro-3,4-O-isopropylidene-α and ß-D-*ribo*-pento-pyranosyl Fluoride (1b) with Alcohols. A mixture of Cp_2HfCl_2 (1 mmol), AgOTf (2 mmol) and molecular sieves 4Å (1000 mg) in dichloromethane (3 ml), was stirred for 10 minutes. Then, the alcohol (2 mmol) in dichloromethane (1 ml) was added and, after 5 minutes at room temperature, the mixture was cooled to -50°C. Aftewards, 2-O-benzyl-2-fluoro-3,4-O-isopropylidene-α and ß-D-*ribo*-pento-pyranosyl fluoride (**1b**) (1 mmol) in dichloromethane (2 ml) was added and the temperature was left to rise to room temperature. When the reaction finished, the reaction mixture was poured into cold saturated aqueous $NaHCO_3$ solution, and filtered through a Cellite pad. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml) and the combined layers were dried ($MgSO_4$) and evaporated. The crude oil was purified by flash or thin layer chromatography.

Reaction of 2-O-Benzyl-2-fluoro-3,4-O-isopropylidene-α and ß-D-*ribo*-pento-pyranosyl Fluoride (1b) with Benzyl Alcohol.

a) Ratio **1b** / $PhCH_2OH$ 1:2. The general procedure was followed with Cp_2HfCl_2 (120 mg, 0.32 mmol), AgOTf (166 mg, 0.64 mmol) and molecular sieves 4Å (320 mg), benzyl alcohol (69 mg, 0.64 mmol) and compound **1b** (50 mg, 0.17 mmol) for 1.5 hours. The standard work-up gave a crude oil which was purified by flash chromatography (ethyl acetate/hexane 2:3) obtaining the compound **4** (46 mg, 70%) as a white oil.

[3R, 4R, 4aR, 10bS]-2,3,4,4a,6,10b-hexahydro-4a-benzyloxy-3,4-dihydroxy-3,4-O-isopropylidene-pyrano[3,2-c][2]benzopyran (**4**): $[\alpha]_D$=-149.6° (c 0.84, $CHCl_3$). ^1H NMR δ 7.50-7.00 (m, 9H, Ph), 4.95 (dd, 1H, $J_{3,4}$=5.8 Hz, $J_{3,2ax}$=3.8 Hz, H-3), 4.89 (d, 1H, J=15.3 Hz, H-6a), 4.82 (d, 1H, H-4), 4.75 (d, 1H, J=11.3 Hz, CH_2Ph), 4.74 (d, H-6b), 4.63 (d, 1H, J=11.5 Hz, CH_2Ph), 4.49 (s, 1H, H-10b), 3.99 (d, 1H, $J_{2eq,2ax}$=10.2 Hz, H-2eq), 3.92 (dd, 1H, H-2ax), 1.50 (s, 3H, CH_3), 1.41 (s, 3H, CH_3). ^{13}C NMR δ 134.3-124.8 (Ph), 112.4

(Cisopr), 107.6 (C-4a), 84.4 (C-4), 80.3 (C-3), 73.7 (C-2), 72.5 (C-10b), 65.2 (C-6), 26.3 (CH_3isopr), 25.0 (CH_3isopr). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.71; H, 6.58. Found: C, 71.11; H, 6.65.

b) Ratio **1b**/$PhCH_2OH$ 1:10: The general procedure was followed starting from compound **1b** (100 mg, 0.33 mmol), Cp_2HfCl_2 (124 mg, 0.33 mmol), AgOTf (137 mg, 0.66 mmol), molecular sieves 4Å (300 mg) and benzyl alcohol (350 mg, 3.3 mmol) in dichloromethane (5 ml). After 3 hours and the corresponding work-up, the resulting crude oil was purified by thin layer chromatography (hexane/ethyl acetate 3:1) to give compound **8a** (101 mg, 66%).

Benzyl 2,2-dibenzyloxy-3,4-O-isopropylidene-ß-D-*erythro*-pentopyranoside (**8a**): $[\alpha]_D$=-35.4° (c 0.90, $CHCl_3$). ^1H NMR δ 7.50-7.30 (m, 15 H, Ph), 5.03 (d, 1H, J=12.0 Hz, CH_2Ph), 4.97 (s, 1H, H-1), 4.86-4.77 (m, 4H, H-4, CH_2Ph(3)), 4.69 (d, 1H, J=11.9 Hz, CH_2Ph), 4.68 (d, 1H, J=11.9 Hz, CH_2Ph), 4.58 (d, 1H, $J_{3,4}$=5.8 Hz, H-3), 4.02 (d, 1H, $J_{5eq,5ax}$=10.4 Hz, H-5eq), 3.86 (dd, $J_{5ax,4}$=4.0 Hz, H-5ax), 1.40 (s, 3H, CH_3isopr), 1.28 (s, 3H, CH_3isopr). ^{13}C NMR δ 127.4-126.2 (Ph), 111.3 (Cisopr), 106.4 (C-2), 100.7 (C-1), 84.8 (C-3), 79.3 (C-4), 72.0 (C-5), 71.4, 69.9, 65.6 (CH_2Ph), 25.4 ($\underline{C}H_3$isopr), 23.9 ($\underline{C}H_3$isopr). Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.08; H, 6.78. Found: C, 72.44; H, 6.79.

Reaction of 2-O-Benzyl-2-fluoro-3,4-O-isopropylidene-α and ß-D-*ribo*-pento-pyranosyl Fluoride (1b) with Methanol.

a) Ratio **1b**/MeOH 1:2: Compound **1b** (53 mg, 0.17 mmol) in dichloromethane (1 ml) was treated with Cp_2HfCl_2 (64 mg, 0.17 mmol), AgOTf (87 mg, 0.34 mmol) and methanol (14 µL, 0.34 mmol) for 2 hours in accordance with the general procedure. The reaction crude was purified by thin layer chromatography (hexane/ethyl acetate 4:1) obtaining 11 mg (20% yield) of compound **3**.

[3R, 4R, 4aR, 10bS]-2,3,4,4a,6,10b-hexahydro-3,4-dihydroxy-3,4-O-isopropylidene-4a-Methoxy-pyrano[3,2-c][2]benzopyran (**3**): $[\alpha]_D$=-107.5° (c 0.40, $CHCl_3$). ^1H NMR δ 7.50-7.00 (m, 4H, Ph), 4.96 (td, $J_{3,4}$=$J_{3,2ax}$=5.9 Hz, $J_{3,2eq}$=3.0 Hz, H-3), 4.88 (d, 1H, J=15.2 Hz, H-6a), 4.74 (d, 1H, J=15.2 Hz, H-6b), 4.73 (d, 1H, H-4), 3.99 (d, 1H, $J_{2eq,2ax}$=10.4 Hz, H-2eq), 3.90 (dd, 1H, H-2ax), 3.42 (s, 3H, OCH_3), 1.54 (s, 3H, CH_3isopr), 1.39 (s, 3H, CH_3isopr). ^{13}C NMR δ 130.1-124.1 (Ph), 84.4 (C-4), 80.3 (C-3), 73.8 (C-2), 72.7 (C-10b), 62.6 (C-6b), 56.3 (OMe), 26.4 (CH_3isopr), 25.1 (CH_3isopr).

b) Ratio **1b**/MeOH 1:10: Following the experimental procedure, compound **1b** (100 mg, 0.33 mmol) was treated in dichloromethane with Cp_2HfCl_2 (132 mg, 0.35 mmol), AgOTf (179 mg, 0.70 mmol) and methanol (0.14 ml, 3.5 mmol) in accordance with the general procedure for 2 hours. The reaction crude was purified by thin layer chromatography (hexane/ethyl acetate 3:1) obtaining 45 mg (42% yield) of compound **8d** and 37 mg (34%) of compound **10c**.

Benzyl 2-benzyl-3,4-O-isopropylidene-2-methoxy-ß-D-*ribo*-pento-pyranoside (**8d**): $[\alpha]_D$=-60° (c 0.99, $CHCl_3$). ^1H NMR δ 7.50-7.00 (m, 5H, Ph), 4.76 (dd, 1H, $J_{4,3}$=5.8 Hz, $J_{4,5ax}$=3.9 Hz, H-4), 4.75 (d, 1H, J_{AB}=11.7 Hz, CH_2Ph), 4.67 (d, 1H, J_{AB}=11.7 Hz, CH_2Ph), 4.57 (s, 1H, H-1), 4.38 (d, 1H, H-3), 3.96 (d, 1H, $J_{5eq,5ax}$=10.3 Hz, H-5eq), 3.75 (dd, 1H, H-5ax), 3.42 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 1.41 (s, 3H, CH_3isopr), 1.25 (s, 3H, CH_3isopr). ^{13}C NMR δ 140.0-128.0 (Ph), 112.4 (Cisopr), 107.1 (C-2), 103.7 (C-1), 85.7, 80.3 (C-3, C-4), 72.2,72.1 (CH_2Ph, C-5), 56.2 (OMe), 51.5 (OMe), 26.3 (CH_3isopr), 24.9 (CH_3isopr).

Benzyl 2-methoxy-3,4-isopropylidene-2-benzyloxy-ß-D-*ribo*-pento-pyranoside (**10c**): $[\alpha]_D$=-67° (c 0.70, $CHCl_3$). ^1H NMR δ 7.40-7.10 (m, 5H, Ph), 4.80 (d, 1H, J_{AB}=12.0 Hz, CH_2Ph), 4.75 (dd, 1H, $J_{4,3}$=5.8 Hz, $J_{4,5ax}$=3.9 Hz, H-4), 4.60 (d, 1H, J_{AB}=12.0 Hz, CH_2Ph), 4.62 (s, 1H, H-1), 4.39 (d, 1H, H-3), 3.93 (d, 1H, $J_{5eq,5ax}$=10.3 Hz, H-5eq), 3.74 (dd, 1H, H-5ax), 3.41 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 1.35 (s, 3H, CH_3isopr), 1.23 (s, 3H, CH_3isopr). ^{13}C NMR δ 130.0-128.0 (Ph), 104.1 (C-1), 85.5, 80.2 (C-3, C-4), 72.3 (CH_2Ph), 70.5 (C-5), 58.1 (OMe), 51.4 (OMe), 25.3 (CH_3isopr), 24.9 (CH_3isopr). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.96; H, 7.47. Found: C, 62.90; H, 7.50.

Reaction of 2-O-Benzyl-2-fluoro-3,4-O-isopropylidene-α and ß-D-*ribo*-pento-pyranosyl Fluoride (1b) with Cp_2HfCl_2/AgOTf in the absence of alcohol.

Following the general procedure for the reaction of the glycosyl fluoride **1b** with alcohols, compound **1b** (34 mg, 0.1 mmol) was treated in dichloromethane (0.5 ml) with Cp_2HfCl_2 (41.8 mg, 0.11 mmols), AgOTf (56 mg, 0.22 mmol) and 4Å molecular sieves (140 mg) for 4 hours. Thin layer chromatography (hexane/ethyl acetate 3:1) allowed 11 mg (26%) of pure compound **4** to be obtained.

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