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Synthesis of 3-Substituted (Azido, Acylthio, Chloro or Fluoro)-2,3-dideoxy-D-*erythro*-pentoses and 3-Methyl-3-substituted-2,3-dideoxy-D-*erythro*-pentoses

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Abstract: The enantioselective synthesis of 3-substituted and 3-methyl-3-substituted 2,3-dideoxy-D-*erythro*-pentoses from (3*R*,4*R*)-1,1-diethoxy-3,4-epoxypentane-5-ol, (3*R*,4*R*)-1,1-diethoxy-3,4-epoxy-3-methylpentane-5-ol and (2*R*,3*R*)-2,3-epoxy-5-hexen-1-ol is reported. The key step is cleavage of the oxirane ring by Ti(O-*i*-Pr)$_3$X class reagents followed by selective cyclization of the acyclic acetals to the furanosides. Fluorination with the complex of titanium (IV) *iso*-propoxide - titanium (IV) fluoride provides an enantioselective synthesis of 3-fluoro-2,3-dideoxy-D-*erythro*-pentose and 3-fluoro-3-methyl-2,3-dideoxy-D-*erythro*-pentose.

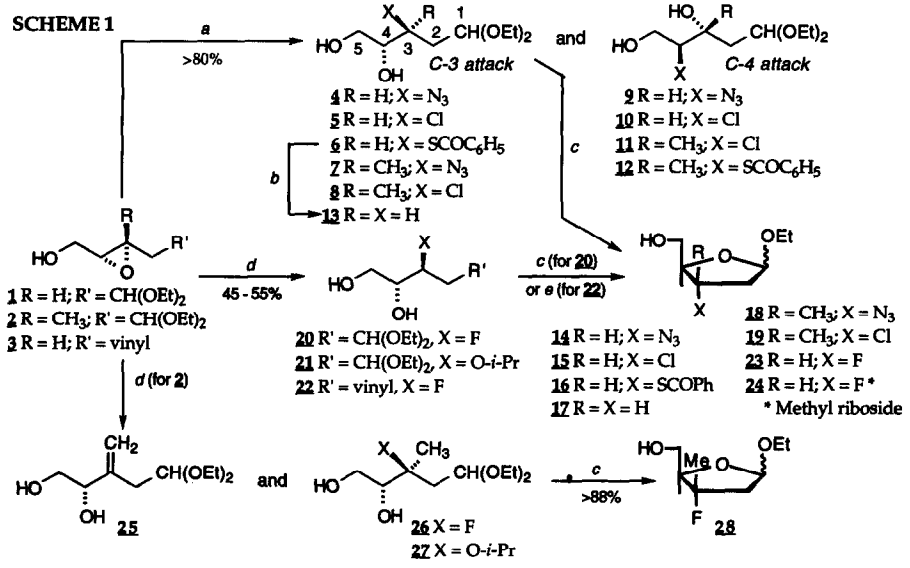
The identification of the antiretroviral activity[1] of azidothymidine[2], dideoxycytidine[3], dideoxyinosine[3], 3'-fluorothymidine[4] and 2',3'-dideoxypurine nucleosides[5] has resulted in increased interest in 3'-modified-2'-deoxynucleosides. While these nucleosides are typically synthesized by the modification of natural nucleosides, the complementary process of coupling unique carbohydrates with nucleoside bases allows for access to compounds not readily available by modification of the natural nucleosides. The application of this method, however, is limited by the availability of 3-modified-2,3-dideoxypentoses. Notably, lengthy syntheses of 2,3-dideoxy-D-pentose, 3-azido-2,3-dideoxy-D-*erythro*-pentose, 3-fluoro-2,3-dideoxy-D-*erythro*-pentose and 3-cyano-2,3-dideoxy-D-*erythro*-pentose from D-xylose[6], D-ribonolactone[7] and glutamic acid[7] have been reported. Further, the synthesis of fluorinated carbohydrates continues to be a major challenge.[8] Thus, expedient methods for the synthesis of 3-substituted-2,3-dideoxypentoses from non-carbohydrate precursors is desired.

We and others have focused on a strategy for the synthesis of deoxysugars based on the sequential asymmetric epoxidation of 5-hydroxy-3-enal acetals (1-2) and regioselective opening of the resultant α-epoxy alcohols with various nucleophiles.[9-10] From our studies, we found that introduction of soft nucleophiles (X = SCOR, OCOR, N_3) was efficiently accomplished with modified titanium alkoxides [Ti(O-*i*-Pr)$_3$X]. These reagents are readily obtained from titanium (IV) isopropoxide and the corresponding acids (*e.g.*, C_6H_5COSH or HN_3) in crystalline form and easy to manipulate. This

communication describes further applications of this strategy for the synthesis of 3-substituted-2,3-dideoxy-D-pentoses, including 3-azido-2,3-dideoxy-D-*erythro*-pentose (for azidothymidine), 3-fluoro-2,3-dideoxy-D-*erythro*-pentose (for FLT), 2,3-dideoxy-D-pentose (for dideoxycytidine), as well as 3-methyl-3-substituted-2,3-dideoxy-D-*erythro*-pentoses.

Both (3*R*,4*R*)-1,1-diethoxy-3,4-epoxypentane-5-ol (**1**)[10a] and (3*R*,4*R*)-1,1-diethoxy-3-methyl-3,4-epoxypentane-5-ol (**2**)[10b] were prepared in 4 steps (*ee* >96%) from crotonaldehyde (37%) or 3-methyl-2-butenal (23%), respectively. Similarly, (2R,3R)-epoxy-5-hexen-1-ol (**3**) was obtained from hex-5-en-2-yn-1-ol in two steps in >60% overall yield. The cleavage reactions were carried out with the titanium reagents (1.5 eq) in benzene (or chloroform), at ambient temperature, to afford mixtures of 3- and 4-substituted acetals (Scheme 1). The individual acetals **4-12** were isolated by column chromatography and their structure established by NMR spectroscopy. The experimental and calculated ^{13}C chemical shift values were comparable. The calculated values were based on shift increments on exchange of a hydroxyl group to azido (8 ppm for substituent-bearing carbon; -1.5 ppm for α-carbon), chloro (-8 ppm; +0.5 ppm), benzoylthio (-26 ppm; -1 ppm) and hydrogen (-40 ppm; -5 ppm).[11]

SCHEME 1



a) $Ti(O\text{-}i\text{-}Pr)_3X$ (X = Cl, N_3, $SCOC_6H_5$); b) Raney nickel; c) 1% EtOH - HCl; d) $Ti(O\text{-}i\text{-}Pr)_4$ - TiF_4; e) O_3 - CH_3OH

As shown in Table 1, the opening of epoxide **1** with various titanium reagents proceeds with moderate to high levels of C-3 attack. However with epoxide **2**, the reaction times are longer, and there is variable regioselectivity. As the steric bulk of nucleophile X increases, amounts of C-4 cleavage products increase. Thus, there is a preponderance for C-3 attack with tris(*iso*-propoxy)titanium azide *vs.* C-4 attack with the bulkier tris(*iso*-propoxy)titanium (IV) thiobenzoate [3-methyl-4-benzoylthio-2,4-dideoxy-L-*erythro*-pentose (**12**)]. With the latter example, electronic considerations are offset by the steric interaction between the X substituent and the C-3 methyl group in epoxide **2**. Further, acetal **6**

derived from epoxide **1** and tris(*iso*-propoxy)titanium thiobenzoate was converted to 2,3-dideoxy-D-pentose acetal (**13**) by reduction with Raney nickel.

Table 1. Ring Opening of Epoxyalcohol Acetals 1-2 With Ti(O-*i*-Pr)$_3$X

		Reaction conditions			Composition of mixture,%	
Alcohol	X	time (hr)	solvent	Yield, %*	*C-3* attack	*C-4* attack
1	N_3	1.5	chloroform	95	91	9
1	Cl	1	benzene	85	60	40
1	SCOPh	1	chloroform	80	>98	<2
2	N_3	7	benzene	90	>98	<2
2	Cl	6	benzene	80	46**	34
2	SCOPh	8	benzene	83	<3	>97

*A summary yield of acetals after workup

Third component is the product of epoxide allylic rearrangement, 3-methylene-2,3-dideoxy-D-pentose diethyl acetal (25**)

Regioselective cyclization of acetals **4-8**, **13** afforded mixtures of α/β-ethyl furanosides **14-19** (95% yield) with little pyranoside content (3-4%). The spectral data of the confirmationally-rigid ethyl furanosides provided further support of the assigned stereochemistry for the acyclic acetals. Additionally, spectral correlations between ^{13}C NMR resonances, the ring size and anomeric configuration were also obtained. Formation of the furanosides leads to a downfield shift of the C-4 resonance in the ^{13}C NMR spectra *ca.* 8-10 ppm *vs.* the appropriate acyclic acetal, while in the pyranosides the difference is no more than 3-4 ppm.[12]

The anomeric configuration of the furanosides was determined by analysis of a) the spin-spin coupling constants (SSCC) of H-1, H-2, H-2', H-3 and b) the chemical shifts of the carbon atoms in the ring.[12] In accordance with earlier observations, the α-anomers are characterized by two small SSCC for H-2 or H-2' with H-1 and H-3, thus the anomeric assignment **14-19** was completed. Further, the ^{13}C chemical shifts of the ring carbons of the β-anomers are located downfield of those for the corresponding α-anomers. Table 3 shows the chemical shift differences of the carbon atoms for various pairs of anomers **14-19** *vs.* the observed average values for the corresponding 2-deoxyribose derivatives.[12] It can also be concluded that the determination of anomeric configuration of 2-deoxyribose derivatives, using C-3, C-4 and C-5 carbon shifts, is more reliable because the shift increments for C-1 and C-2 have smaller value and sometimes have the opposite sign.

The successes obtained in opening of the epoxy alcohols with the titanium reagents prompted us to further study the reaction of epoxide **1** with tris(*iso*-propoxy)titanium fluoride (**A**). Unpredictably, acetal **21** was the major product with traces of fluorohydrin **20** (<5%). Since the nucleophilicity of fluoride is appreciably lower, the isopropoxy groups on the titanium compete effectively in the epoxide cleavage, albeit undesirably. We thus considered the higher order, more Lewis acidic alkoxyfluorotitaniums, *e.g.* Ti(O-*i*-Pr)$_2$F$_2$ (**B**) and Ti(O-*i*-Pr)F$_3$ (**C**), which were initially prepared by reacting titanium (IV) isopropoxide with benzoyl fluoride (2 or 3 equiv). However, elemental analyses of the complexes indicated that they were mixtures of **B** and **C** (*ca.* 2.2 and 2.7 molar equiv of fluoride, respectively).

Indeed, increasing the fluoride ratio from 1 to 2.2 resulted in increased yields of fluorohydrin **20**, but further increases afforded either lower yields or none (TiF_4). While **B** afforded workable quantities of **20**, the crude products were typically admixed with mainly ethyl α,β-3-(O-*iso*-propyl)-2,3-dideoxy-*erythro*-pentofuranosides due to preferential acid-catalyzed cyclization of **21**.[13]

In contrast, the *in situ* generated complex of titanium (IV) isopropoxide and titanium (IV) fluoride in the presence of anhydrous potassium carbonate was effective in forming acetal **20** (47%). Similarly, vinyl epoxide **3** was transformed to the corresponding fluorohydrin **22** in 55% yield. However with acetal **2**, three concommitant reactions occurred with two of the products due to nucleophilic ring cleavage: a) 3-fluoro-3-methyl-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (**26**) and b) 3-methyl-3-(O-isopropyl)-2-deoxy-D-*erythro*-pentose diethyl acetal (**27**). The other product, 2,3-dideoxy-3-methylene-D-*glycero*-pentose diethyl acetal (**25**)[10b], is due to epoxide-allylic rearrangement (Scheme 1). As shown in Table 2, the yield of acetal **25** is almost independent of reaction conditions; however, the ratio of acetals **26** and **27** is dependent on reaction temperature. Thus, optimal yields (40%) of fluorohydrin **26** occur at high temperatures. In the absence of additional information, the exact nature of the *in situ* fluorinating reagent *vs.* the preformed reagents **B-C** can not be established. Conceivably, several possible "ate" complex-mediated fluorination mechanisms could also be operational. Further conversion of fluorohydrins **20**, **22** or **26** to the respective furanosides **23-24** or **28** was accomplished with mild acidic catalyst.

Table 2. Cleavage of Epoxy Alcohol 2 with $Ti(O\text{-}i\text{-}Pr)_4$ - TiF_4 in Benzene

Reaction Conditions				Composition of mixture, %		
Acetal -Ti-Reagent Ratio	Temp (C°)	Time (hrs)	Conversion (%)	(25)	(26)	(27)
1	10	1.5	94	16	14	70
1.5	15	1.0	96	29	19	52
2	20	1.0	>98	30	25	45
2	30	1.0	>98	31	28	40
2	80	0.5	>98	20	38	42

In summary, the $Ti(O\text{-}i\text{-}Pr)_3X$-class reagents (X = Cl, N_3, C_6H_5COS) are highly effective in transforming α-epoxy alcohols to functionalized 1,2-diols under mild conditions. Similar fluorinative-epoxide transformations were accomplished with an equimolar complex of titanium (IV) isopropoxide and titanium (IV) fluoride, albeit in lesser efficiency. The resultant functionalized 1,2-diols are easily transformed to 3-substituted-2,3-dideoxyribosides in high yields, as illustrated for the syntheses of 3-azido-2,3-dideoxy-D-*erythro*-pentosides, 3-halo-2,3-dideoxy-D-*erythro*-pentosides and 3-(acylthio)-2,3-dideoxy-D-pentosides.

EXPERIMENTAL

Thin-layer chromatography (TLC) was conducted on either Silufol UV_{254} (Kavalier, Czechoslovakia) or Analtech Uniplates in chloroform-methanol (10:1) with spot detection by either heat or phosphomolybdate spray reagent. Column chromatography was conducted over Silica Gel Merck 60. Optical rotations

were determined with a Perkin-Elmer 141 spectropolarimeter. NMR spectra were recorded with a Bruker CXP-200 (200 MHz, ^{1}H; 50 MHz, ^{13}C) or AM-360 (360 MHz ^{1}H; 90MHz, ^{13}C) spectrometers in acetone-d_6 and resonance values listed as δ (ppm) and coupling constants (*J*) in Hz. Where designated by an asterisk (*) in the nmr chemical shift listings, the signals due to the ethoxy unit have not been tabulated. All reagents were obtained from Aldrich Chemicals and used as is.

(3*R*,4*R*)-1,1-Diethoxy-3,4-epoxypentane-5-ol (1) and (3*R*,4*R*)-1,1-Diethoxy-3,4-epoxy-3-methylpentane-5-ol (2) were obtained by literature procedures.[10]

2,5-Hexadien-1-ol. A suspension of lithium aluminum hydride (8.0 g, 210 mmol) in anhydrous tetrahydrofuran (200 ml) was treated dropwise (0°C) with a solution of hex-5-en-2-yn-1-ol (16.1g, 170 mmol)[9b] in anhydrous tetrahydrofuran (200 ml). The reaction mixture was then stirred at 40°C for 3 hours, cooled to 0°C and treated dropwise with sat. ammonium chloride (FOAMING!). The resultant precipitate was filtered and washed well with tetrahydrofuran (200 ml). The organic phase was dried over anhydrous magnesium sulfate, concentrated *in vacuo* and distilled to afford diene alcohol (12.8 g, 80%): bp 70.0-71.0°C/15 mmHg; n_D^{20} 1.4530; ^{1}H NMR (360 MHz) δ 2.74 (m, 2H, H-4), 3.81 (bt, 1H, OH), 4.01 (d, 2H, H-1), 4.94 (m, 1H, H-6'), 5.03 (m, 1H, H-6), 5.62 (m, 2H, H-2 and H-3), 5.80 (m, 1H, H-5); ^{13}C NMR (90 MHz) δ 36.8 (C-4), 63.0 (C-1), 115.4 (C-6), 128.9 (C-2), 132.0 (C-3), 137.6 (C-5). Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.14; H, 10.01.

(2*R*,3*R*)-2,3-Epoxy-5-hexen-1-ol (3). A cold, stirred mixture (-20°C) of powdered, activated 4Å sieves (3.0 g) and anhydrous methylene chloride (300 ml) was treated sequentially with D-(-)-diisopropyl tartrate (2.81g, 12.0 mmol), titanium (IV) isopropoxide (2.84 g, 10.0 mmol) and *tert*-butyl hydroperoxide (29.5 ml, 4.4M in methylene chloride). After stirring for 30 minutes, a solution of *2,5-hexadien-1-ol* (9.8 g, 100 mmol) in anhydrous methylene chloride (20 ml) was added dropwise and the mixture stirred at -20°C for 12 hours. The reaction was quenched at -20°C with 10% sodium hydroxide saturated with sodium chloride (8 ml). After warming to +10°C, additional ether was added followed by anhydrous magnesium sulfate (8.0 g) and Celite (1.0 g) and the mixture was stirred for 15 minutes and allowed to stand for 1 hour. The resultant suspension was filtered through a bed of Celite and washed well with ether. The combined filtrate was dried over anhydrous magnesium sulfate, concentrated and distilled to afford alcohol **3** (8.9 g, 78%): Bp 85-87°C/10 mmHg; n_D^{20} 1.4458; $[\alpha]_D^{20}$ +23.2° (*c* 10, methanol); ^{1}H NMR (360 MHz) δ 2.27 (m, 2H, H-4), 2.83 (ddd, 1H, H-2), 2.86 (ddd, 1H, H-3), 3.49 (dd, 1H, H-1'), 3.70 (m, 1H, H-1), 3.88 (t, 1H, OH), 5.03 (m, 1H, H-6a), 5.11 (m, 1H, H-6b), 5.82 (m, 1H, H-5); ^{13}C NMR (90 MHz) δ 36.5 (C-4), 55.1 (C-3), 58.6 (C-2), 62.7 (C-1), 117.3 (C-6), 134.5 (C-5). Anal. Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 62.88; H, 8.49.

Tris(*iso*-propoxy)titanium thiobenzoate was obtained from titanium (IV) isopropoxide (28.4 g, 0.1 mol) and thiobenzoic acid (13.8 g, 0.1 mol) in 100 ml of pentane. After 30 min., the yellow crystalline solid was collected (28.9 g, 80%), mp 100-105°C. Anal. Calcd. for $C_{16}H_{26}O_4STi$: C, 53.04; H, 7.23; Ti, 13.22; S, 8.85. Found: C, 52.65; H, 7.01; Ti, 13.60; S, 9.02.

Tris(*iso*-propoxy)titanium azide was obtained from titanium (IV) isopropoxide (28.4 g, 0.1 mol) and 0.6 M HN_3 in pentane (160 ml, 96 mmol) as a green-yellow crystalline solid (19.8 g, 68%), mp 67-70°C. Anal. Calcd. for $C_9H_{21}N_3O_3Ti$: C, 40.46; H, 7.92; Ti, 17.92; N, 15.73. Found: C, 40.17; H, 7.73; Ti, 18.03; N, 15.98.

General Procedure for Oxirane Ring Opening by Titanium Reagents. 3-Azido-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (4). A solution of (3*R*,4*R*)-1,1-diethoxy-3,4-epoxy-pentane-5-ol (**1**) (1.9 g, 10 mmol) in dry chloroform (100 ml) was treated with tris(*iso*-propoxy)titanium azide (3.2 g, 12 mmol). The reaction mixture was stirred with a magnetic stirrer at 20°C for 0.5 h; then sat. sodium bicarbonate (10 ml) was added, and the reaction mixture was stirred vigorously for 3 h. The precipitate was filtered, washed thoroughly with diethyl ether (5 x 30 ml), the combined organic phase was dried (K_2CO_3) and concentrated *in vacuo*. The crude acetal was purified by column chromatography using chloroform-methanol (30:1) as eluent to give acetal (**4**) (1.9 g, 82%) [n_D^{20} 1.4650; R_f 0.37; $[\alpha]_D^{20}$ -17.0° (*c* 3.6, methanol); ^1H NMR* (360 MHz) δ 1.69 (m, 1H, $J_{2,3}$ = 10.3 Hz, $J_{2,2'}$ = 14.3 Hz, H-2), 2.00 (m, 1H, $J_{2',3}$ = 2.8 Hz, H-2'), 3.60-3.68 (m, 4H, H-3, H-4, CH_2OH), 4.68 (m, 1H, $J_{1,2}$ = 3.8 Hz, $J_{1,2'}$ = 7.8 Hz, H-1); ^{13}C NMR* (90 MHz) δ 35.0 (C-2), 61.8 (C-3), 63.7 (C-5), 74.8 (C-4), 101.5 (C-1)] and ***4-azido-2,4-dideoxy-L-erythro-pentose diethyl acetal*** (**9**) (0.2 g, 9%) [n_D^{20} 1.4606; R_f 0.45; $[\alpha]_D^{20}$ +22.2° (*c* 2.7, methanol); ^1H NMR* (360 MHz) δ 1.69 (m, 1H, $J_{2,3}$ = 9.6 Hz; $J_{2,2'}$ = 14.1 Hz, H-2), 1.85 (m, 1H, $J_{2',3}$ = 2.8 Hz, H-2'), 3.60 (m, 1H, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 3.9 Hz, H-4), 3.66 (m, 1H, $J_{5,5'}$ = 11.3 Hz, H-5), 3.81 (m, 1H, $J_{3,4}$ = 5.9 Hz, H-3), 3.84 (m, 1H, H-5'), 4.75 (m, 1H, $J_{1,2}$ = 4.2 Hz, $J_{1,2'}$ = 7.0 Hz, H-1); ^{13}C NMR* (90 MHz) δ 38.2 (C-2), 62.7 (C-5), 68.8 (C-3), 69.1 (C-4), 101.8 (C-1)] as syrups. Anal. Calcd. for $C_9H_{19}N_3O_4$: C, 46.34; H, 8.21; N, 18.02. Found for **4**: C, 46.42; H, 8.15; N, 17.91. Found for **9**: C, 46.28; H, 8.18; N, 18.14.

3-Chloro-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (5) (1.7 g, 72%) was obtained from epoxide **1** (1.9 g, 10 mmol) and tris(*iso*-propoxy)titanium chloride (3.4 g, 13 mmol) using benzene as solvent: n_D^{20} 1.4620; R_f 0.38; $[\alpha]_D^{20}$ -20.8° (*c* 1.5, methanol); ^1H NMR* (360 MHz) δ 1.84 (m, 1H, $J_{2,3}$ = 10.7 Hz, $J_{2,2'}$ = 14.6 Hz, H-2), 2.32 (m, 1H, $J_{2',3}$ = 2.6 Hz, H-2'), 3.72 (m, 1H, H-4), 3.68 (m, 2H, CH_2OH), 4.09 (m, 1H, $J_{3,4}$ = 5.3 Hz, H-3), 4.76 (m, 1H, $J_{1,2}$ = 3.0 Hz, $J_{1,2'}$ = 8.41 Hz, H-1); ^{13}C NMR* (90 MHz) δ 38.5 (C-2), 60.6 (C-3), 63.7 (C-5), 75.8 (C-4), 101.3 (C-1). ***4-Chloro-2,4-dideoxy-L-erythro-pentose diethyl acetal*** (**10**) was obtained as the minor component: ^1H NMR* (360 MHz) δ 1.73 (m, 1H, $J_{2,3}$ = 7.5 Hz, $J_{2,2'}$ = 14.2 Hz, H-2), 2.03 (m, 1H, $J_{2',3}$ = 2.4 Hz, H-2'), 3.93 (m, 1H, $J_{4,5}$ = 5.5 Hz, $J_{4,5'}$ = 6.9 Hz, H-4), 3.85 (m, 2H, CH_2OH), 3.97 (m, 1H, $J_{3,4}$ = 5.0 Hz, H-3), 4.76 (m, 1H, $J_{1,2}$ = 3.8 Hz, $J_{1,2'}$ = 9.2 Hz, H-1); ^{13}C NMR* (90 MHz) δ 38.3 (C-2), 64.3 (C-5), 67.7 (C-4), 70.0 (C-3), 101.8 (C-1). Anal. Calcd. for $C_9H_{19}ClO_4$: C, 47.68; H, 8.45; Cl, 15.64. Found for **5**: C, 47.49; H, 8.20; Cl, 15.81.

3-(Benzoylthio)-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (6) (2.6 g, 80%) was obtained from epoxide **1** (1.9 g, 10 mmol) and tris(*iso*-propoxy)titanium thiobenzoate (4.0 g, 11 mmol) using chloroform as solvent: n_D^{20} 1.5090; R_f 0.35; $[\alpha]_D^{20}$ -13.6° (*c* 2.0, methanol); ^1H NMR* (360 MHz)

δ 1.60 (m, 1H, $J_{2,3}$ = 9.8 Hz; $J_{2,2'}$ = 13.0 Hz, H-2), 1.91 (m, 1H, $J_{2',3}$ = 2.6 Hz, H-2'), 3.45 (m, 1H, $J_{3,4}$ = 5.5 Hz, H-3), 3.60 (m, 2H, CH_2OH), 3.75 (m, 1H, $J_{4,5}$ = 6.5 Hz, $J_{4,5'}$ = 6.0 Hz, H-4), 4.68 (m, 1H, $J_{1,2}$ = 4.0 Hz, $J_{1,2'}$ = 7.5 Hz, H-1); ^{13}C NMR* (90 MHz) δ 34.7 (C-2), 43.9 (C-3), 64.8 (C-5), 75.3 (C-4), 102.1 (C-1). Anal. Calcd. for $C_{16}H_{26}O_5S$: C, 58.16; H, 7.93. Found: C, 58.30; H, 7.69.

3-Azido-3-methyl-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (7) (2.2 g, 90%) was obtained from epoxide **2** (2.0 g, 10 mmol) and tris(*iso*-propoxy)titanium azide (4.0 g, 15 mmol) using benzene as a solvent: n_D^{20} 1.4628; R_f 0.33; $[\alpha]_D^{20}$ -10.0° (*c* 3.5, methanol); ^1H NMR* (360 MHz) δ 1.32 (s, 3H, C(3)-CH_3), 1.80 (dd, 1H, $J_{2,2'}$ = 14.6 Hz, H-2), 1.94 (dd, 1H, H-2'), 3.52 (m, 1H, H-5'), 3.61 (m, 1H, $J_{5,5'}$ = 11.8 Hz, H-5), 3.65 (m, 1H, $J_{4,5}$ = 6.6 Hz, $J_{4,5'}$ = 6.0 Hz, H-4), 4.71 (m, 1H, $J_{1,2}$ = 5.6 Hz, $J_{1,2'}$ = 4.8 Hz, H-1); ^{13}C NMR* (90 MHz) δ 21.7 (CH_3), 40.3 (C-2), 63.3 (C-5), 65.0 (C-3), 76.9 (C-4), 101.0 (C-1). Anal. Calcd. for $C_{10}H_{21}N_3O_4$: C, 48.57; H, 8.56; N, 16.99. Found: C, 48.52; H, 8.60; N, 17.03.

3-Chloro-3-methyl-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (8). A mixture of epoxide **2** (2.0 g, 10 mmol) and tris(*iso*-propoxy)titanium chloride (3.9 g, 15 mmol) in benzene was stirred for 6 h to afford a mixture of acetals **8**, **11** and **25**.[10b] After chromatography, acetal **8** was isolated as a syrup (1.6 g, 68%): n_D^{20} 1.4635; R_f 0.38; $[\alpha]_D^{20}$ -15.0° (*c* 1.2, methanol); ^1H NMR* (360 MHz) δ 1.32 (s, 3H, C(3)-CH_3), 1.75 (dd, 1H, $J_{2,2'}$ = 13.9 Hz, H-2), 1.96 (dd, 1H, H-2'), 3.65 (m, 2H, $J_{5,5'}$ = 12.0 Hz, CH_2OH), 3.85 (m, 1H, $J_{4,5}$ = 5.5 Hz, $J_{4,5'}$ = 5.5 Hz, H-4), 4.85 (m, 1H, $J_{1,2}$ = 5.2 Hz, $J_{1,2'}$ = 4.6 Hz, H-1); ^{13}C NMR* (90 MHz) δ 23.4 (CH_3), 43.5 (C-2), 62.7 (C-5), 63.7 (C-3), 78.1 (C-4), 101.8 (C-1). **4-Chloro-3-methyl-2,4-dideoxy-L-*erythro*-pentose diethyl acetal (11)** was the minor component: ^1H NMR* (360 MHz) δ 1.17 (s, 3H, C(3)-CH_3), 1.68 (dd, 1H, $J_{2,2'}$ = 14.0 Hz, H-2), 1.88 (dd, 1H, H-2'), 3.75 (m, 1H, H-5'), 3.80 (m, 1H, $J_{1,2}$ = 5.8 Hz, $J_{1,2'}$ = 5.3 Hz, H-1), 3.85 (m, 1H, $J_{5,5'}$ = 11.6 Hz, H-5), 4.05 (m, 1H, $J_{4,5}$ = 5.6 Hz, $J_{4,5'}$ = 6.0 Hz, H-4); ^{13}C NMR* (90 MHz) δ 22.9 (CH_3), 43.3 (C-2), 64.0 (C-5), 69.5 (C-4), 73.7 (C-3), 101.0 (C-1). Anal. Calcd for $C_{10}H_{21}ClO_4$: C, 49.90; H, 8.73; Cl, 14.77. Found for **8**: C, 49.86; H, 8.76; Cl, 14.75. Found for **11**: C, 50.10; H, 8.78; Cl, 14.79.

3-Methyl-4-(benzoylthio)-2,4-dideoxy-L-*erythro*-pentose diethyl acetal (12) (2.7 g, 83%) was obtained from epoxide **2** (2.0 g, 10 mmol) and tris(*iso*-propoxy)titanium thiobenzoate (5.4 g, 15 mmol) in benzene: R_f 0.78; $[\alpha]_D^{20}$ -14.0° (c 2.0, methanol); ^1H NMR* (360 MHz) δ 1.29 (s, 3H, C(3)-CH_3), 2.01 (d, 2H, *J* = 5.5 Hz, $\mathbf{CH_2}$CH), 3.52 (m, 2H, CH_2OH), 3.61 (m, 1H, H-4), 4.81 (t, 1H, H-1); ^{13}C NMR* (90 MHz) δ 25.6 (C(3)-CH_3), 44.7 (C-2), 54.8 (C-4), 63.5 (C-5), 74.2 (C-3), 101.4 (C-1). Anal. Calcd for $C_{17}H_{27}O_5S$: C, 63.15; H, 8.36; S, 9.91. Found: C, 63.20; H, 8.30; S, 9.87.

2,3-Dideoxy-D-pentose diethyl acetal (13). To a solution of 3-(benzoylthio)-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (**6**, 2.8 g) in methanol (10 ml) was added 2.0 g of Raney nickel. The reaction was stirred for 5 h at 20°C, then the precipitate was filtered, solvent was evaporated *in vacuo*

and the residue was purified by column chromatography with chloroform-methanol (30:1) as an eluent to afford acetal **13** (1.1 g, 57%) as a yellow oil: n_D^{20} 1.4480; R_f 0.37; $[\alpha]_D^{20}$ -3.3° (*c* 3.2, methanol); ^1H NMR* (360 MHz) δ 1.45 (m, 2H, *J* = 5.5 Hz, H-3), 1.62 (m, 1H, $J_{2'3}$ = 4.5 Hz, H-2'), 1.71 (m, 1H, $J_{2,2'}$ = 10.5 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 3.35 (m, 1H, $J_{5,5'}$ = 10.7 Hz, H-5), 3.45 (m, 1H, H-5'), 3.90 (m, 1H, $J_{4,5}$ = 4.3 Hz, $J_{4,5'}$ = 4.0 Hz, H-4), 4.47 (t, 1H, *J* = 5.5 Hz, H-1); ^{13}C NMR* (90 MHz) δ 29.3 (C-3), 30.6 (C-2), 67.3 (C-5), 72.5 (C-4), 103.7 (C-1). Anal. Calcd. for $C_9H_{20}O_4$: C, 56.22; H, 10.49. Found: C, 56.20; H, 10.45.

General Procedure for the Regioselective Cyclization of Acetals (4-8, 13). The cyclization of acetal **4** is described as an illustrative case. A solution of acetal **4** (1.2 g, 5 mmol) in absolute ethyl alcohol (15 ml) was treated with 1% ethanolic hydrogen chloride (0.1 ml). The reaction mixture was stirred at ambient temperature for 1.5 h and neutralized with dry K_2CO_3 (0.1 g). After filtration and evaporation *in vacuo*, the residue was chromatographed over silica gel (chloroform) to yield ***ethyl 3-azido-2,3-dideoxy-α-D-erythro-pentofuranoside*** (**14a**) (0.4 g, 43%) [R_f 0.70; $[\alpha]_D^{20}$ +122.1° (*c* 6.4, methanol); ^1H NMR* (360 MHz) δ 1.18 (m, 1H, $J_{2,3}$ = 3.3 Hz, $J_{2,2'}$ = 14.1 Hz, H-2), 2.42 (m, 1H, $J_{2',3}$ = 8.5 Hz, H-2'), 3.62 (m, 2H, CH_2OH), 3.93 (m, 1H, $J_{4,5} = J_{4,5'}$ = 4.4 Hz, H-4), 3.99 (m, 1H, $J_{3,4}$ = 5.1 Hz, H-3), 5.13 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{1,2'}$ = 5.3 Hz, H-1); ^{13}C NMR* (90 MHz) δ 39.30 (C-2), 61.1 (C-3), 62.8 (C-5), 83.7 (C-4), 103.9 (C-1)] and β-anomer (**14b**) (0.5 g, 52%) [R_f 0.57; $[\alpha]_D^{20}$ -78.5° (*c* 8.3, methanol); ^1H NMR* (360 MHz) δ 2.04 (m, 1H, $J_{2,3}$ = 6.6 Hz, $J_{2,2'}$ = 13.4 Hz, H-2), 2.24 (m, 1H, $J_{2',3}$ = 7.3 Hz, H-2'), 3.52 (m, 1H, $J_{5,5'}$ = 11.1 Hz, H-5), 3.63 (m, 1H, H-5'), 3.94 (m, 1H, $J_{4,5}$ = 6.6 Hz, $J_{4,5'}$ = 5.0 Hz, H-4), 4.20 (m, 1H, $J_{3,4}$ = 4.3 Hz, H-3), 5.14 (m, 1H, $J_{1,2}$ = 5.3 Hz, $J_{1,2'}$ = 2.0 Hz, H-1); ^{13}C NMR* (90 MHz) δ 39.5 (C-2), 62.8 (C-3), 64.3 (C-5), 85.4 (C-4), 104.2 (C-1)] as syrups. Anal. Calcd. for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found for **14a**: C, 44.82; H, 6.92; N, 22.47. Found for **14b**: C, 44.80; H, 6.96; N, 22.53.

Ethyl 3-chloro-2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (15a,b). Acetal **5** (1.1 g, 5 mmol) afforded α-anomer (**15a**) (0.49 g, 55%) [R_f 0.48; $[\alpha]_D^{20}$ +158.6° (*c* 2.2, methanol); ^1H NMR* (360 MHz) δ 1.99 (m, 1H, $J_{2,3}$ = 5.7 Hz, $J_{2,2'}$ = 14.1 Hz, H-2), 2.73 (m, 1H, $J_{2',3}$ = 9.0 Hz, H-2'), 3.60 (m, 1H, $J_{5,5'}$ = 12.0 Hz, H-5), 3.73 (m, 1H, H-5'), 4.02 (m, 1H, $J_{4,5}$ = 3.9 Hz, $J_{4,5'}$ = 3.0 Hz, H-4), 4.21 (m, 1H, $J_{3,4}$ = 6.9 Hz, H-3), 5.14 (dd, 1H, $J_{1,2}$ = 2.4 Hz, $J_{1,2'}$ = 5.6 Hz, H-1); ^{13}C NMR* (90 MHz) δ 43.5 (C-2), 54.5 (C-3), 61.3 (C-5), 86.2 (C-4), 103.7 (C-1)] and β-anomer (**15b**) (0.36 g, 40%) [R_f 0.72; $[\alpha]_D^{20}$ -91.0° (*c* 1.6, methanol); ^1H NMR* (360 MHz) δ 2.29 (m, 1H, $J_{2,3}$ = 6.4 Hz, $J_{2,2'}$ = 13.8 Hz, H-2), 2.42 (m, 1H, $J_{2',3}$ = 6.9 Hz, H-2'), 3.58 (m, 2H, CH_2OH), 4.08 (m, 1H, $J_{4,5} = J_{4,5'}$ = 5.2 Hz, H-4), 4.47 (m, 1H, $J_{3,4}$ = 4.5 Hz, H-3), 5.22 (dd, 1H, $J_{1,2}$ = 5.3 Hz, $J_{1,2'}$ = 2.7 Hz, H-1); ^{13}C NMR* (90 MHz) δ 43.8 (C-2), 57.3 (C-3), 63.6 (C-5), 88.8 (C-4), 104.1 (C-1)] as syrups. Anal. Calcd. for $C_7H_{13}ClO_3$: C, 46.54; H, 7.25; Cl, 19.63. Found for **15a**: C, 46.42; H, 7.38; Cl, 19.70. Found for **15b**: C, 46.60; H, 7.31; Cl, 19.89.

Ethyl 3-(benzoylthio)-2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (16a,b). Acetal **6** (1.6 g, 5 mmol) afforded α-anomer (**16a**) (0.70 g, 50%) [R_f 0.68; $[\alpha]_D^{20}$ +129.8° (*c* 4.3, methanol); ^{1}H NMR* (360 MHz) δ 1.90 (m, 1H, H-2), 2.48 (m, 1H, H-2'), 3.55 (m, 1H, H-5), 3.60 (m, 1H, H-5'), 3.80 (m, 1H, H-3), 3.95 (m, 1H, H-4), 5.07 (dd, 1H, H-1); ^{13}C NMR* (90 MHz) δ 40.7 (C-3), 40.8 (C-2), 63.9 (C-5), 85.5 (C-4), 103.8 (C-1)] and β-anomer (**16b**) (0.59 g, 42%) [R_f 0.50; $[\alpha]_D^{20}$ -67.6° (*c* 2.1, methanol); ^{1}H NMR* (360 MHz) δ 1.97 (m, 1H, $J_{2,3}$ = 9.3 Hz, $J_{2,2'}$ = 13.1 Hz, H-2), 2.34 (m, 1H, $J_{2',3}$ = 7.1 Hz, H-2'), 3.57 (m, 1H, $J_{5,5'}$ = 12.0 Hz, H-5), 3.63 (m, 1H, H-5'), 3.91 (m, 1H, $J_{4,5}$ = $J_{4,5'}$ = 5.5 Hz, H-4), 3.92 (m, 1H, $J_{3,4}$ = 5.7 Hz, H-3), 5.11 (dd, 1H, $J_{1,2}$ = 5.2 Hz, $J_{1,2'}$ = 1.2 Hz, H-1)] as syrups. Anal. Calcd. for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09. Found for **16a**: C, 59.01; H, 7.20. Found for **16b**: C, 58.98; H, 7.24.

Ethyl 2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (17a,b). Acetal **13** (1.9 g, 10 mmol) afforded α-anomer (**17a**) (0.80 g, 55%) [R_f 0.60; $[\alpha]_D^{20}$ +51.6° (*c* 2.1, methanol); ^{13}C NMR* (90 MHz) δ 26.1 (C-3), 32.6 (C-2), 65.0 (C-5), 79.4 (C-4), 104.7 (C-1)] and β-anomer (**17b**) (0.55 g, 38%) [R_f 0.55; $[\alpha]_D^{20}$ -12.5° (*c* 3.9, methanol); ^{13}C NMR* (90 MHz) δ 26.2 (C-3), 33.4 (C-2), 66.7 (C-5), 81.6 (C-4), 104.4 (C-1)] as syrups. Anal. Calcd. for $C_7H_{14}O_3$:C, 57.51; H, 9.65. Found for **17a**: C, 57.49; H, 9.64. Found for **17b**: C, 57.45; H, 9.60.

Ethyl 3-azido-3-methyl-2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (18a,b). Acetal **7** (2.0 g, 8 mmol) afforded α-anomer (**18a**) (1.14g, 71%) [R_f 0.46; $[\alpha]_D^{20}$+60.0° (*c*, 1.2, methanol); ^{1}H NMR* (360 MHz) δ 1.33 (s, 3H, CH_3), 2.00 (m, 1H, $J_{2,2'}$ = 13.7 Hz, H-2), 2.27 (m, 1H, H-2'), 3.60 (m, 1H, $J_{5,5'}$ = 11.5 Hz, H-5), 3.64 (m, 1H, H-5'), 3.98 (dd, 1H, $J_{4,5}$ = 6.0 Hz, $J_{4,5'}$ = 5.3 Hz, H-4), 5.13 (dd, 1H, $J_{1,2}$ = 2.5 Hz, $J_{1,2'}$ = 5.8 Hz, H-1); ^{13}C NMR* (90 MHz) δ 20.0 (CH_3), 61.5 (C-5), 67.4 (C-3), 84.1 (C-4), 102.7 (C-1)] and β-anomer (**18b**) (0.22 g, 14%) [R_f 0.61; $[\alpha]_D^{20}$ -36.0° (*c* 1.0, methanol); ^{1}H NMR* (360 MHz) δ 1.46 (s, 3H, CH_3), 1.97 (m, 1H, $J_{2,2'}$ = 14.2 Hz, H-2), 2.37 (m, 1H, H-2'), 3.60 (m, 2H, CH_2OH), 3.90 (m, 1H, $J_{4,5}$ = $J_{4,5'}$ = 5.0 Hz, H-4), 5.18 (dd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{1,2'}$ = 6.1 Hz, H-1); ^{13}C NMR* (90 MHz) δ 19.1 (CH_3), 45.9 (C-2), 62.9 (C-5), 70.2 (C-3), 87.0 (C-4), 104.1 (C-1)] as syrups. Anal. Calcd. for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88. Found for **18a**: C, 47.50; H, 7.70; N, 21.10. Found for **18b**: C, 47.58; H, 7.65; N, 21.00.

Ethyl 3-chloro-3-methyl-2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (19a,b). Acetal **8** (1.2 g, 5 mmol) afforded α-anomer (**19a**) (0.37 g, 38%) [R_f 0.41; $[\alpha]_D^{20}$ +78.0° (*c* 1.4, methanol); ^{1}H NMR* (360 MHz) δ 1.48 (s, 3H, CH_3), 2.27 (dd, 1H, $J_{2,2'}$ = 15.0 Hz, H-2), 2.64 (dd, 1H, H-2'), 3.60 (m, 1H, $J_{5,5'}$ = 11.5 Hz, H-5), 3.75 (m, 1H, H-5'), 4.26 (dd, 1H, $J_{4,5}$ = 4.5 Hz, $J_{4,5'}$ = 6.0 Hz, H-4), 5.13 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{1,2'}$ = 6.0 Hz, H-1); ^{13}C NMR* (90 MHz) δ 26.1 (CH_3), 51.2 (C-2), 60.8 (C-5), 68.8 (C-3), 86.5 (C-4), 102.4 (C-1)] and β-anomer (**19b**) (0.41 g, 42%) [R_f 0.54; $[\alpha]_D^{20}$ -42.0° (*c* 1.1, methanol); ^{1}H NMR* (360 MHz) δ 1.70 (s, 3H, CH_3), 2.18 (dd, 1H, $J_{2,2'}$ = 14.0 Hz, H-2), 2.50 (dd, 1H, H-2'), 3.56 (m, 1H, $J_{5,5'}$ = 12.0 Hz, H-5), 3.75 (m, 1H, H-5'), 4.15 (dd, 1H, $J_{4,5}$ = 5.0 Hz, $J_{4,5'}$ = 5.5 Hz, H-4), 5.31 (dd, 1H, $J_{1,2}$ = 4.6 Hz, $J_{1,2'}$ = 6.0 Hz, H-

1); ^{13}C NMR* (90 MHz) δ 25.5 (CH_3), 50.4 (C-2), 61.7 (C-5), 75.2 (C-3), 90.5 (C-4), 104.3 (C-1)] as syrups. Anal. Calcd. for $C_8H_{15}ClO_3$: C, 49.36; H, 7.71; Cl, 18.25. Found for **19a**: C, 49.40; H, 7.56; Cl, 18.13. Found for **19b**: C, 49.30; H, 7.80; Cl, 18.31.

Table 3. ^{13}C NMR Chemical Shift Increments of α- and β-Anomers

Compound	C-1	C-2	C-3	C-4	C-5
14	+0.4	+0.2	+1.7	+1.8	+1.5
15	+0.4	+0.3	+2.8	+2.7	+2.3
16	+0.4	+0.1	+0.9	+0.9	+1.0
17	-0.3	+0.8	+0.1	+2.2	+1.7
18	+1.4	-0.7	+2.8	+2.5	+1.4
19	+1.9	-0.8	+6.3	+4.0	+0.9
Aver. value[12]	+0.4	+0.3	+1.3	+1.1	+0.9

3-Fluoro-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (20). To a 3 l four-necked round bottom flask equipped with a mechanical stirrer, pressure equalizing addition funnel, condenser, argon inlet and thermometer was charged anhydrous benzene (1.8 L), powdered anhydrous potassium carbonate (100g) and titanium (IV) fluoride (34.7 g, 280 mmol). Titanium (IV) isopropoxide (34g, 280 mmol) was added and the stirred reaction mixture was heated to reflux and (3*R*,4*R*)-5-hydroxy-3,4-epoxypentanal diethyl acetal (**1**) (53.5g, 280 mmol) was added dropwise over a 15 min period. After 5 min at reflux, the reaction mixture was cooled to 10°C and treated dropwise with a solution of sodium chloride-sodium hydroxide (30 g of sodium hydroxide, 5 g of sodium chloride and 200 ml of water). The suspension was filtered, after 3 h, through a bed of Celite and the filter bed throughly extracted with warm ethyl acetate. The combined extracts was concentrated *in vacuo* and chromatographed to afford the fluorohydrin acetal **20** (27.6 g, 47%) as a light yellow syrup: R_f 0.35; $[\alpha]_D^{20}$ -30.7° (*c* 3.0, methanol); ^1H NMR* (360 MHz) δ 1.91 (m, 1H, $^3J_{HF}$ = 16.3 Hz, $J_{2',3}$ = 9.5 Hz, H-2'), 2.06 (m, 1H, $^3J_{HF}$ = 39.0 Hz, $J_{2,2'}$ = 14.8 Hz, $J_{2,3}$ = 2.5 Hz, H-2), 3.57 (m, 1H, H-5), 3.66 (m, 1H, H-5'), 3.70 (m, 1H, H-4), 4.59 (m, 1H, $^2J_{HF}$ = 48.5 Hz, $J_{3,4}$ = 5.7 Hz, H-3), 4.70 (dd, 1H, $J_{1,2}$ = 8.5 Hz, $J_{1,2'}$ = 3.6 Hz, H-1); ^{13}C NMR (90 MHz) δ 15.5 and 15.6 (OCH_2CH_3's), 36.2 (d, $^2J_{CF}$ = 20.1Hz, C-2), 61.5 and 61.8 (OCH_2's), 63.2 (d, $^3J_{CF}$ = 6.0Hz, C-5), 73.7 (d, $^2J_{CF}$ = 23.1Hz, C-4), 91.6 (d, $^1J_{CF}$ = 168.6Hz, C-3), 100.5 (d, $^3J_{CF}$ = 3.5Hz, C-1). Anal. Calcd for $C_9H_{19}FO_4$: C, 51.41; H, 9.11; F, 9.04. Found: C, 51.19; H, 8.88; F, 8.61.

Ethyl 2,3-dideoxy-3-fluoro-α,β-D-*erythro*-pentofuranosides (23). A solution of acetal **20** (18.0 g, 86 mmol) in methylene chloride (800 ml) was treated with 1M hydrogen chloride-diethyl ether (0.5ml) at ambient temperature. After 15 minutes, the solution was treated with anhydrous potassium carbonate (1.0 g) and stirred for 1 hr. The solid was filtered and washed well with ether; the combined filtrate and washings was concentrated *in vacuo* and chromatographed over silica gel (chloroform) to give initially the *beta-anomer* **23b** (4.1 g, 25%) [R_f 0.70; $[\alpha]_D^{20}$ -85.5° (*c* 2.03, methanol); ^1H NMR (360 MHz) δ 1.14 (t, 3H, OCH_2CH_3), 2.21 (m, 1H, $^3J_{HF}$ = 29.0 Hz, $J_{2,2'}$ = 15.1 Hz, $J_{2,3}$ = 5.9 Hz, H-2), 2.34 (m, 1H, $^3J_{HF}$ = 29.6 Hz, $J_{2',3}$ = 2.5 Hz, H-2'), 3.47 (m, 1H, $^4J_{HF}$ =

5.8 Hz, $J_{5,5'}$ = 11.4 Hz, H-5), 3.55 (q, 2H, OCH_2), 3.58 (m, 1H, $^4J_{HF}$ = 6.2 Hz, H-5'), 4.21 (m, 1H, $^3J_{HF}$ = 23.6 Hz, $J_{4,5}$ = 7.2 Hz, $J_{4,5'}$ = 5.1 Hz, H-4), 5.23 (m, 1H, $^2J_{HF}$ = 55.0 Hz, $J_{3,4}$ = 1.2 Hz, H-3), 5.28 (dd, 1H, $J_{1,2}$ = 3.4 Hz, $J_{1,2'}$ = 5.7 Hz, H-1); ^{13}C NMR (90 MHz) δ 15.5 (OCH_2CH_3), 40.4 (d, $^2J_{CF}$ = 21.1 Hz, C-2), 63.3 (OCH_2), 62.6 (d, $^3J_{CF}$ = 9.1 Hz, C-5), 85.5 (d, $^2J_{CF}$ = 25.1 Hz, C-4), 94.7 (d, $^1J_{CF}$ = 177.6 Hz, C-3), 104.6 (C-1)] and the *alpha-anomer* **23a** (9.8 g, 60%) [R_f 0.55; $[\alpha]_D^{20}$ +111.0° (*c* 2.5, methanol); ^{1}H NMR (360 MHz) δ 1.14 (t, 3H, OCH_2CH_3), 2.08 (m, 1H, $^3J_{HF}$ = 24.7 Hz, $J_{2,2'}$ = 14.8 Hz, $J_{2,3}$ = 1.0 Hz, H-2), 2.25 (m, 1H, $^3J_{HF}$ = 35.8 Hz, $J_{2',3}$ = 6.6 Hz, H-2'), 3.42 (q, 2H, OCH_2), 3.54 (m, 1H, $^4J_{HF}$ = 5.5 Hz, $J_{5,5'}$ = 11.7 Hz, H-5), 3.64 (m, 1H, $^4J_{HF}$ = 6.3 Hz, H-5'), 4.21 (m, 1H, $^3J_{HF}$ = 26.0 Hz, $J_{4,5}$ = $J_{4,5'}$ = 4.2 Hz, H-4), 5.09 (m, 1H, $^2J_{HF}$ = 56.4Hz, $J_{3,4}$ = 2.1 Hz, H-3), 5.19 (dd, 1H, $J_{1,2}$ = 0.8 Hz, $J_{1,2'}$ = 5.5 Hz, H-1); ^{13}C NMR (90 MHz) δ 15.4 (CH_3), 40.7 (d, $^2J_{CF}$ = 21.6 Hz, C-2), 64.0 (OCH_2), 63.3 (d, $^3J_{CF}$ = 10.5 Hz, C-5), 86.4 (d, $^2J_{CF}$ = 22.6 Hz, C-4), 95.6 (d, $^1J_{CF}$ = 176.1 Hz, C-3), 104.9 (d, $^3J_{CF}$ = 1.0 Hz, C-1)] as light yellow syrups. Anal. Calcd for $C_7H_{13}FO_3$: C, 51.21; H, 7.98; F, 11.57. Found for **23a**: C, 51.02; H, 7.78; F, 11.21. Found for **23b**: C, 51.24; H, 7.63; F, 11.32.

(2*R*,3*S*)-3-Fluoro-5-hexen-1,2-diol (22). A suspension of titanium (IV) fluoride (3.2 g, 26 mmol) in toluene (150 ml), at 20°C, was treated with titanium (IV) isopropoxide (7.4 g, 26 mmol). The mixture was heated to reflux and a solution of epoxy alcohol **3** (4.5 g, 40 mmol) in anhydrous toluene (20 ml) was added dropwise over a 5 minute period. After 10 minutes, the reaction was cooled to 10°C and saturated sodium bicarbonate solution (20 ml) was added. The mixture was stirred for 1.5 hr and the resultant precipitate was filtered and washed with ether (300 ml). The organic phase was dried over anhydrous magnesium sulfate, concentrated and chromatographed (chloroform-isopropanol, 50:1) to afford diol **22** (2.8g, 55%) as white crystals, mp 37.0-38.0°C; R_f 0.30; $[\alpha]_D^{20}$ -14.0° (*c* 1, methanol); ^{1}H NMR (360 MHz) δ 2.42 (m, 1H, $^3J_{HF}$ = 15.5 Hz, H-4), 2.52 (m, 1H, $^3J_{HF}$ = 34.0 Hz, H-4'), 3.57 (m, 1H, H-1), 3.65 (m, 1H, H-1'), 3.72 (m, 1H, $^3J_{HF}$ = 23.1 Hz, H-2), 4.48 (m, 1H, $^2J_{HF}$ = 48.5 Hz, H-3), 5.05 (dm, 1H, H-6), 5.11 (dm, 1H, H-6'), 5.88 (m, 1H, H-5); ^{13}C NMR (90 MHz) δ 36.0 (d, $^2J_{CF}$ = 21.1 Hz, C-4), 63.3 (d, $^3J_{CF}$ = 5.5 Hz, C-1), 73.3 (d, $^2J_{CF}$ = 23.1 Hz, C-2), 93.5 (d, $^1J_{CF}$ = 171.6 Hz, C-3), 117.6 (C-6), 134.9 (d, $^3J_{CF}$ = 3.5 Hz, C-5). Anal. Calcd for $C_6H_{11}FO_2$: C, 53.72; H, 8.27; F, 14.17. Found: C, 52.92; H, 8.01; F, 13.28.

Methyl 3-fluoro-2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (24). A solution of olefin **22** (6.3 g, 47 mmol) in methanol (300 ml) was cooled to -78°C and treated with ozone until a persistent blue color was observed. Excess ozone was purged from the reaction with oxygen and the reaction mixture was treated with palladium-on-carbon (0.3 g). The mixture was warmed to -5°C and hydrogen was bubbled through the solution for 3 hrs. The reaction mixture was warmed to ambient temperature, filtered and treated with 1.0 M hydrogen chloride - diethyl ether (0.2 ml). After 5 hr, the reaction mixture was neutralized with anhydrous potassium carbonate (1.0 g) and stirred for 1 hr. The solid was filtered, washed with ether (3 X 10 ml) and the filtrate concentrated and the residue

chromatographed over silica gel (chloroform) to afford the *beta anomer* **24b** (1.9 g, 28%) [Rf 0.68; $[\alpha]_D^{25}$ -98.3° (*c* 2, methanol); ^{1}H NMR (360 MHz) δ 2.18 (m, 1H,$^3J_{HF}$ = 29.0 Hz, $J_{2,2'}$ = 15.0 Hz, $J_{2,3}$ = 5.9 Hz, H-2), 2.34 (m, 1H, $^3J_{HF}$ = 29.6 Hz, $J_{2,3'}$ = 2.5 Hz, H-2'), 3.29 (s, 3H, OCH_3), 3.47 (m, 1H, $^4J_{HF}$ = 5.8 Hz, $J_{5,5'}$ = 11.4 Hz, H-5), 3.56 (m, 1H, $^4J_{HF}$ = 6.2 Hz, H-5'), 4.17 (m, 1H, $^3J_{HF}$ = 23.6 Hz, $J_{4,5}$ = 7.1 Hz, $J_{4,5'}$ = 5.1 Hz, H-4), 5.16 (dd, 1H, $J_{1,2}$ = 3.4 Hz, $J_{1,2'}$ = 5.7 Hz, H-1), 5.21 (m, 1H, $^2J_{HF}$ = 55.0 Hz, $J_{3,4}$ = 1.2 Hz, H-3); ^{13}C NMR (90 MHz) δ 40.4 (d, $^2J_{CF}$ = 21.6 Hz, C-2), 55.4 (OCH_3), 63.2 (d, $^3J_{CF}$ = 10 Hz, C-5), 86.3 (d, $^2J_{CF}$ = 22.6 Hz, C-4), 95.6 (d, $^1J_{CF}$ = 175.6 Hz, C-3), 106.3 (C-1)] and the *alpha anomer* **24a** (4.2 g, 60%) [R_f 0.55; $[\alpha]_D^{25}$ +85.0° (*c* 2, methanol); ^{1}H NMR (360 MHz) δ 2.06 (m, 1H, $^3J_{HF}$ = 26.1 Hz, $J_{2,2'}$ = 14.9 Hz, $J_{2,3}$ = 1.0 Hz, H-2), 2.24 (m, 1H, $^3J_{HF}$ = 35.9 Hz, $J_{2',3}$ = 6.7 Hz, H-2'), 3.28 (s, 3H, OCH_3), 3.53 (m, 1H, $^4J_{HF}$ = 5.5 Hz, $J_{5,5'}$ = 11.8 Hz, H-5), 3.63 (m, 1H, $^4J_{H,F}$ = 6.2 Hz, H-5'), 4.19 (m, 1H, $^3J_{HF}$ = 26.2 Hz, $J_{4,5}$ = 4.2 Hz, $J_{4,5'}$ = 4.2 Hz, H-4), 5.06 (dd, 1H, $J_{1,2}$ = 0.8 Hz, $J_{1,2'}$ = 5.5 Hz, H-1), 5.08 ($^2J_{HF}$ = 56.4 Hz, $J_{3,4}$ = 2.1 Hz, H-3); ^{13}C NMR (90 MHz) δ 40.1 (d, $^2J_{CF}$ = 21.1 Hz, C-2), 54.7 (OCH_3), 62.4 (d, $^3J_{CF}$ = 9.6 Hz, C-5), 85.5 (d, $^2J_{CF}$ = 23.6 Hz, C-4), 94.6 (d, $^1J_{CF}$ = 177.6 Hz, C-3), 105.8 (C-1)] as yellow oils.

3-Fluoro-3-methyl-2,3-dideoxy-D-*erythro*-pentose diethyl acetal (26). A suspension of titanium (IV) fluoride (7.44 g, 60 mmol) and powdered potassium carbonate (24 g) in dry benzene (200 ml) was treated with titanium (IV) isopropoxide (17.04 g, 60 mmol) and stirred at ambient temperature for 0.5 h. The resultant mixture was heated to reflux and a solution of epoxide **2** (6.12 g, 30 mmol) in dry benzene (20 ml) was added dropwise to the reaction. After stirring for 0.5 h, the reaction was cooled to 5-10°C and quenched with sat. aqueous potassium carbonate (100 ml). The precipitate was filtered and the filtercake washed thoroughly with diethyl ether (5 x 100 ml). The organic phase was dried (K_2CO_3) and concentrated *in vacuo*. NMR analysis of the crude mixture showed a composition of **25** (20%)[13b], **26** (42%) and **27** (38%) which was separated by column chromatography (CH_2Cl_2). Fluorohydrin **26** (2.3 g, 35%): $[\alpha]_D^{20}$ +15.2° (*c* 1.0, methanol); ^{13}C NMR (90 MHz) δ 15.5 (CH_3), 20.8 (d, $^2J_{CF}$ = 24.1 Hz, C(3)-CH_3), 41.5 (d, $^2J_{CF}$ = 21.6 Hz, C-2), 61.2 and 61.4 (OCH_2's), 62.7 (d, $^3J_{CF}$ = 5.0 Hz, C-5), 76.6 (d, $^2J_{CF}$ = 26.2 Hz, C-4), 97.1 (d, $^1J_{CF}$ = 170.6 Hz, C-3), 100.0 (d, $^3J_{CF}$ = 6.0 Hz, C-1). Anal. Calc. for $C_{10}H_{21}O_4F$: C, 53.56; H, 9.44; F, 8.47. Found: C, 53.38; H, 9.40; F, 8.55. ***2,3-Dideoxy-3-C-methylene-D-glycero-pentose diethyl acetal*** **(25)**: $[\alpha]_D^{20}$ +12° (*c* 2.2, methanol); ^{1}H NMR* (360 MHz) δ 2.31 (m, 1H, $J_{2,2'}$ = 14.8 Hz, H-2), 2.38 (m, 1H, H-2'), 3.42 (m, 1H, $J_{5,5'}$ = 11.2 Hz, H-5), 3.57 (m, 1H, H-5'), 4.12 (m, 1H, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 4.0 Hz, H-4), 4.63 (t, 1H, $J_{1,2}$ = $J_{1,2'}$ = 5.6 Hz, H-1), 4.99 (m, 1H, $=CH_a$), 5.14 (m, 1H, $=CH_b$); ^{13}C NMR (90 MHz) δ 15.5 (CH_3), 37.4 (C-2), 61.6 (OCH_2), 61.9 (OCH_2), 66.2 (C-5), 75.6 (C-4), 103.3 (C-1), 113.4 ($=CH_2$). Anal. Calc. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.83; H, 9.85. ***3-(O-Isopropyl)-3-methyl-2,3-dideoxy-D-erythro-pentose diethyl acetal*** **(27)**: ^{1}H NMR* (360 MHz) δ 1.08 (s, 3H, C(3)-CH_3), 1.78 (m, 1H, $J_{2,2'}$ = 14.8 Hz, H-2), 1.90 (m, 1H, H-2'), 3.5 (m,

3H, H-4, H-5, H-5'), 4.76 (m, 1H, $J_{1,2}$ = 3.3 Hz; $J_{1,2'}$ = 6.2 Hz, C**H**(OEt)$_2$); ^{13}C NMR (90 MHz) δ 19.5 (C(3)-CH_3), 41.3 (C-2), 63.4 (C-5), 76.2 (C-4), 79.0 (C-3), 100.7 (C-1).

Ethyl 3-fluoro-3-methyl-2,3-dideoxy-D-*erythro*-pentofuranosides (28). A solution of acetal **25** (0.63 g, 2.8 mmol) in dichloromethane (20 ml) was treated with 1% ethanolic hydrogen chloride (0.01 ml). The reaction, which was monitored by TLC, was complete in 0.5 h and neutralized with solid potassium bicarbonate. The precipitate was filtered and the filtrate was concentrated *in vacuo* and purified by column chromatography ($CHCl_3$). Furanoside **28** was obtained as an anomeric mixture (0.45 g, 90%): R_f 0.65 and 0.80. *Alpha anomer* **28a**: ^{13}C NMR (90 MHz) δ 15.5 (OCH_2CH_3), 20.5 (d, $^2J_{CF}$ = 26.6 Hz, C(3)-CH_3), 46.6 (d, $^2J_{CF}$ = 21.4 Hz, C-2), 61.9 (d, $^3J_{CF}$ = 8.8 Hz, C-5), 63.3 (OCH_2), 86.5 (d, $^2J_{CF}$ = 27.3 Hz, C-4), 101.5 (d, $^2J_{CF}$ = 175.5 Hz, C-3), 103.6 (d, $^3J_{CF}$ = 0.9 Hz, C-1). *Beta anomer* **28b**: ^{13}C NMR (90 MHz) δ 15.5 (OCH_2CH_3), 19.6 (d, $^2J_{CF}$ = 25.4 Hz, C(3)-CH_3), 46.3 (d, $^2J_{CF}$ = 22.0 Hz, C-2), 62.8 (d, $^3J_{CF}$ = 10.3 Hz, C-5), 64.3 (OCH_2), 87.8 (d, $^2J_{CF}$ = 24.1 Hz, C-4), 103.4 (d, $^2J_{CF}$ = 172.3 Hz, C-3), 104.5 (d, $^3J_{CF}$ = 0.9 Hz, C-1). Anal. Calc. for $C_8H_{15}O_3F$: C, 53.92; H, 8.49; F, 10.66. Found for **28a**: C, 54.03; H, 8.44; F, 10.58. Found for **28b**: C, 54.07; H, 8.24; F, 10.52.

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