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SYNTHESIS OF FOUR HOMOCHIRAL 3,4-DIDEOXY-3-FLUORO-HEXOSES FROM A NON-CARBOHYDRATE PRECURSOR

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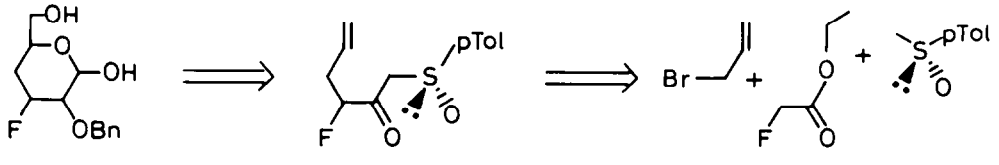
Abstract - The asymmetric synthesis of the 2-O-benzyl-3,4-dideoxy-3-fluoro-[*a*]-D-lyxo-hexopyranose (**11**), the -L-ribo-, the -D-arabino-, and the -L-xylo- analogues (**12** - **14**) has been realized through dihydroxylation of the double bond of (5S)-5-benzyloxy-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hex-1-ene (**4**) followed by oxidative removal of the chiral auxiliary sulphinyl group. A detailed spectroscopic analysis of the four fluorocarbohydrates **11** - **14** has also been performed.

The synthesis of fluorinated carbohydrates[1] is a topic of interest as a consequence of the manifold applications of these compounds as drug constituents,[2] tools for biochemical studies,[3] and tracers in clinical investigations and diagnosis.[4]

We have already reported[5] the asymmetric synthesis of the 2,3-dideoxy-3-fluoro-D-erythro-pentofuranose and the D-threo analogue, constituents of anti-retroviral nucleosides,[2d-f] starting from the 4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hex-5-en-2-ones (**2**).

We would like to report here the synthesis of four homochiral 3,4-dideoxy-3-fluoro-hexoses **1** starting from the same precursors **2** which are derived from (R)-methyl p-tolyl sulphoxide, ethyl fluoroacetate, and allyl bromide as sketched in the retrosynthetic Scheme reported below.



1 2

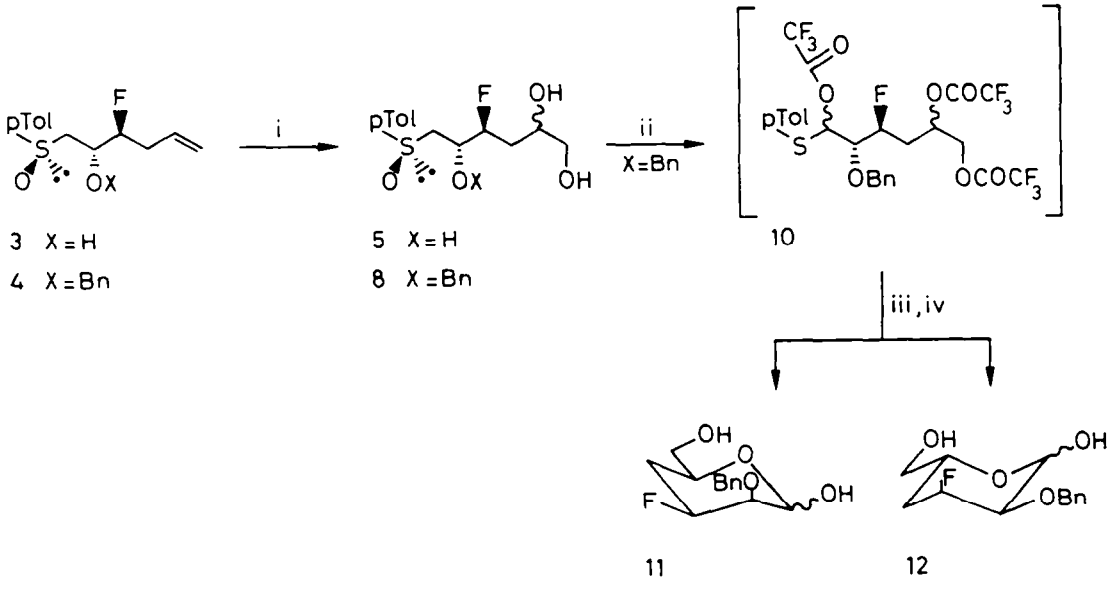
Results and Discusssion

Synthesis of fluorosugars **11** - **14**.- The (4S,5S)-4-fluoro-5-hydroxy-6-[(R)-(4-methylphenyl)sulphinyl]-hex-1-ene (**3**) and the epimer (4R,5S,R_S)-**3** had been obtained[5] by

stereoselective reduction, with diisobutylaluminium hydride, of (4S,R_S)-2 and (4R,R_S)-2, respectively. The absolute configuration at the hydroxyl group of these alcohols had been established through the chemical shift differences of the diastereoisomeric 2-phenylpropionic esters.[5,6]

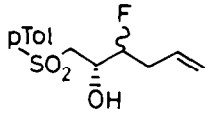
Trimethylamine N-oxide in the presence of catalytic amounts of osmium tetroxide[7] has been utilized for the dihydroxylation of the olefinic double bond of alcohols 3. This oxidizing system had already been employed for the stereoselective dihydroxylation of cyclic α-hydroxy-β-sulphoximine-olefins,[8] α-amido-γ-sulphinyl-olefins,[9] and α-hydroxy-(or α-acetoxy-)-β-sulphinyl olefins.[10]

When a tetrahydrofuran (THF) solution of the N-oxide was added to a THF-H_2O solution of crystalline osmium tetroxide and (4S,5S,R_S)-3, having a β-fluoro-γ-hydroxy-δ-sulphinyl-olefin moiety, the dihydroxylation of the double bond took place at a comparable rate with the undesired oxidation of the sulphoxide group to the corresponding sulphone.[9,10] The desired (4S,5S,R_S)-4-fluoro-6-p-tolylsulphinyl-hexan-1,2,5-triols 5 were thus obtained along with the corresponding sulphonyl-triols 7 and the sulphonyl analogue 6 of the starting olefin 3. A higher chemoselectivity in the oxidation of the double bond was obtained by using a water solution of osmium tetroxide and by protecting the secondary alcohol of the substrate. Thus, the (4S,5S,R_S)-5-benyloxy-4-fluoro-6-sulphinyl-1-hexene 4, obtained through benzylation of (4S,5S,R_S)-3 under standard conditions, afforded the corresponding 1,2-diols 8 in yields higher than 75% of isolated products. Under all the examined reaction conditions the dihydroxylation of the double bond of 3 and 4 occurred



3 X = H
4 X = Bn
5 X = H
8 X = Bn
10

SCHEME 1: i, OsO_4/Me_3N:O-2:H_2O/THF/H_2O; ii, $(CF_3CO)_2O$/2,4,6-trimethylpyridine/CH_3CN; iii, $CuCl_2$/K_2CO_3/H_2O; iv, flash chromatography.



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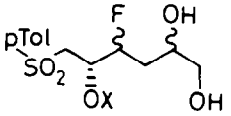


7 X = H

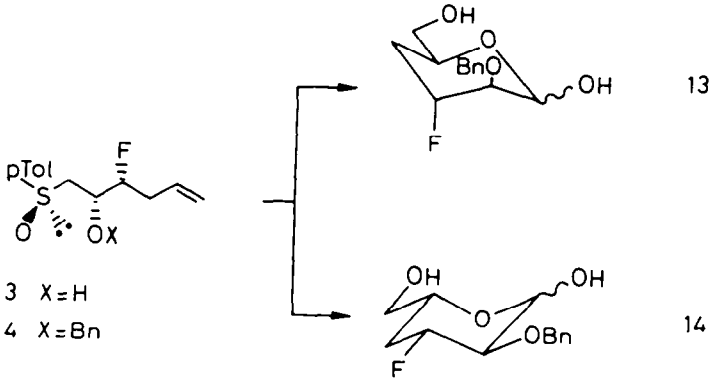
9 X = Bn

with low diastereoselectivity as shown by ^{13}C n.m.r. spectra of the isolated mixtures of **5** and **8**.

The removal of the sulphinyl residue from the nearly equimolar mixture of diastereoisomeric 5-benzyloxy-1,2-diols **8** with concomitant oxidation of the sulphinylated carbon was realized cleanly through a Pummerer rearrangement (trifluoroacetic anhydride/2,4,6-trimethylpyridine).[5,11] The formyl group of the intermediate α-trifluoroacetyloxy-α-tolylthio derivative **10** was unmasked by treatment with copper(II) chloride. Flash chromatography of the crude reaction mixture afforded the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-D-lyxo-hexopyranose (**11**) and the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-L-ribo-hexopyranose (**12**) in 50% overall yield from (4S,5S,R_S)-**4** (Scheme 1).

Dihydroxylation of the carbon-carbon double bond of the (4R,5S)-4-fluoro-5-hydroxy-6-[(R)-(4-methylphenyl)sulphinyl]-hex-1-ene (**3**) and the O-benzyl derivative (4R,5S,R_S)-**4** gave results similar to those reported above for the (4S,5S,R_S)-epimers **3** and **4**. The sulphinyl group of the so obatined 5-benzyloxy-4-fluoro-6-sulphinyl-hexan-1,2-diols (**8**) having the (2S,4R,5S,R_S) and (2R,4R,5S,R_S) configurations was removed through a Pummerer rearrangement and the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-D-arabino-hexopyranose (**13**) and the α,β-L-xylo-hexopyranose **14** were obtained in pure form by flash chromatography in 56% yield from (4R,5S,R_S)-**4** (Scheme 2).

The lyxo- and the arabino-hexopyranoses **11** and **13** were isolated as liquid mixtures of



3 X = H

4 X = Bn

13

14

SCHEME 2

the α and β anomers, while crystallization (from diisopropyl ether/ethyl acetate) of the ribo- and xylo-hexopyranoses **12** and **14**, respectively, afforded the pure anomers (m.p. 139-140°C and 105-107°C, respectively).

^{1}H, ^{13}C, And ^{19}F NMR analyses of fluoro-sugars **11** - **14**.- A detailed analyses of the ^{1}H, ^{13}C, and ^{19}F NMR spectra has been carried out for the structural determination as well as for the conformational analyses of the 2-O-benzyl-3,4-dideoxy-3-fluoro-hexoses **11** - **14**.

The relative stereochemistry of ring substituents has been determined from the values of the proton-proton vicinal coupling constants (Table). A set of empirical additivity constants have been developed[12] which are valid for the prediction of ^{3}J's for the pyranose ring in the chair conformation. The values of these constants depend on the electronegativity and the orientation of the substituents. The application of such additivity rules reproduces reasonably well (within 1 Hz) the values of experimental ^{3}J's in the 3-F-3,4-dideoxyhexoses **11** - **14**. A few examples are reported here: J(3e,4a) ranges from 2.0 to 2.6 Hz in good agreement with the predicted value of 1.9 Hz, J(3e,4e) from 3.5 to 3.9 Hz (predicted value 3.3 Hz), J(3a,4e) from 5.0 to 5.7 Hz (predicted value 5.1 Hz).

Fluorine and carbon chemical shifts together with proton-fluorine and carbon-fluorine coupling constats are also useful source of structural informations. Fluorine chemical shifts are known[13,14] to be very sensitive to any structural modification of the molecule. Some general trends along the strictly related series of the 3-F-3,4-dideoxy-hexoses under study can be outlined as follows. The orientation of the anomeric hydroxyl induces large chemical shift variations on fluorine nucleus. Changing from the β to the α configuration the equatorial fluorine is shifted upfield by ca. 3-5 ppm (compounds **11** and **14**) while an axial fluorine is shifted downfield by ca. 4 ppm (compounds **12** and **13**). The origin of the downfield shift of the axial fluorine is probably the same which causes generally the deshielding by 0.2-0.5 ppm of protons in syn 1,3-diaxial interaction with a substituent. The observed effects can be useful for the assignment of both the anomeric configuration and the stereochemistry at C-3 in 3-fluorosugars. The fluorine chemical shift is shifted upfield by ca. 2-8 ppm when the benzyloxy substituent at C-2 changes from the axial to the equatorial orientation. The major effect was found for the axial fluorine, which is shifted upfield by ca. 8 ppm changing the orientation of $-OCH_2Ph$ group from the anti (isomer **13**) to the gauche one (isomer **12**). Such a shielding pruduced by the benzyloxy substituent on the fluorine at C-3 is in good agreement with the effect found for a gauche interaction (-9 ppm) exerted by a carbon on a fluorine nucleus.[15]

The values of the vicinal proton-fluorine coupling constants depend on the dihedral angle and the electronegativity of the substituents.[13,14] In the present series of conformationally pure pyranose rings the trans $^{3}J(2a,Fa)$ is about 15 Hz smaller than $^{3}J(4a,Fa)$ due to the influence of the oxygen atom at C-2. The gauche vicinal coupling

TABLE. ^{1}H, ^{13}C, and ^{19}F NMR data for the 2-O-benzyl-3,4-dideoxy-3-fluoro-hexoses.[a]

	11α	11β	12α	12β	13α	13β	14α	14β
H-1	5.23	4.60	5.31	5.14	5.22	4.96	5.27	4.63
H-2	3.80	3.89	3.46	3.20	3.55	~3.55	3.48	3.30
H-3	5.02	4.73	5.12	5.02	4.88	4.90	4.98	4.64
H-4ax	2.08	2.04	1.83	1.69	2.04	1.92	1.64	1.65
H-4eq	1.79	1.81	2.05	1.94	1.78	1.71	2.07	2.01
H-5	4.05	3.48	4.27	4.00	4.28	3.90	4.11	b
H-6	3.63	3.68	3.75	3.71	3.66	3.69	3.64	b
H-6'	3.60	3.63	3.54	3.53	3.58	3.56	3.54	b
Ha(Bn)	4.81	4.97	4.72	4.82	4.66	4.69	4.84	b
Hb(Bn)	4.63	4.61	4.69	4.77	4.60	4.67	4.68	b
F	-192.3	-186.6	-197.7	-201.0	-189.3	-193.7	-187.5	-184.0
J(1,2)	2.0	1.5	4.0	8.0	~1	1.5	4.0	7.5
J(2,3)	3.0	3.0	2.5	2.5	3.5	3.6	9.0	8.5
J(3,4ax)	12.0	12.0	2.0	2.1	2.6	2.5	11.5	11.5
J(3,4eq)	5.0	5.0	3.9	3.5	3.5	3.5	5.5	5.7
J(4ax,4eq)	12.0	12.0	14.2	13.4	14.5	14.5	12.5	12.6
J(5,4ax)	12.0	12.0	11.7	11.7	12.7	12.5	12.0	12.0
J(5,4eq)	2.5	2.3	2.4	2.3	2.5	2.5	2.3	1.8
J(5,6)	6.5	3.5	3.1	3.0	3.0	3.0	2.8	b
J(5,6')	3.3	6.0	5.4	6.0	6.5	6.2	6.5	b
J(6,6')	12.0	12.0	11.9	12.0	11.8	12.0	11.5	b
J(Ha,Hb)	12.0	11.5	12.0	12.0	12.0	12.0	12.0	b
J(2,4eq)	~1	1.3	-	-	1.0	1.0	-	-
J(1,F)	5.5	2.3	b	1.1	b	2.9	3.8	b
J(2,F)	6.0	6.5	30.5	28.5	8.0	6.0	12.2	16.0
J(3,F)	47.0	46.5	50.5	50.4	46.6	46.1	52.0	50.5
J(4ax,F)	8.5	8.5	44.5	43.5	45.5	46.0	12.0	12.0
J(4eq,F)	5.5	5.0	11.5	11.0	13.5	13.0	5.5	3.8
C-1	94.24	93.38	b	94.40	92.93	91.92	92.31	96.42
C-2	74.32	75.53	b	77.79	72.38	73.70	78.53	82.08
C-3	88.38	90.88	b	88.25	87.33	87.23	89.98	91.90
C-4	28.65	27.61	b	32.08	27.73	27.50	32.81[c]	32.73[c]
C-5	68.90	71.52	b	70.86	64.06	70.96	67.85	71.26
C-6	65.27	64.79	b	64.66	65.18	64.98	64.89[c]	64.68[c]
C-OBn	73.58	75.02	b	72.51	72.77	74.0	74.50[c]	73.20[c]
J(1,F)	9.0	10.7	b	3.0	-	-	10.8	12.0
J(2,F)	15.0	15.0	b	17.0	24.5	27.2	15.5	17.0
J(3,F)	182.0	185.0	b	175.5	172.5	172.0	179.0	182.0
J(4,F)	20.0	20.0	b	20.0	20.0	18.4	18.0	18.0
J(5,F)	11.0	11.0	b	-	-	-	11.0	11.0
J(6,F)	3.0	3.0	b	-	-	-	2.5	2.5
J(F,C-OBn)	3.0	4.0	b	-	-	-	1.6	1.6

(a) Proton and carbon chemical shifts in ppm from internal TMS; fluorine chemical shifts in ppm from C_6F_6 (ϕ_F = -162.9). Coupling constant in Hz, solvent $CDCl_3$+D_2O.
(b) Not determined. (c) Assignments in horizontal line may be interchanged.

constants fall in the range 3.8-16.0 Hz and their rationalization in terms of the electronegativity and orientation of the substituents is more difficult.[13]

^{3}J(Fa,He) varies from 6.0 to 13.5 Hz; in this case an oxygen atom which is trans diaxial to the coupled fluorine decreases[16] the value of ^{3}J by about 6 Hz (cfr. ^{3}J(F,4e) vs ^{3}J(F,2e) for compound **13**). The coupling constants ^{3}J(Fe,Ha) and ^{3}J(Fe,He) range from 8.5 to 16.0 Hz and 3.8 to 6.5 Hz respectively showing markedly the trend that an equatorial-equatorial coupling is smaller than an axial-equatorial one.

Previous studies in the field of carbohydrates[17] have shown the usefulness of ^{3}J(F,C) and ^{2}J(F,C) for the ring substituent stereochemical assignments.

The magnitude of ^{3}J(F,C) for the pyranose ring is highly stereospecific varying from 8-11 Hz for trans oriented nuclei to 0-3 Hz for gauche coupled nuclei. In the present case of the 3-F-3,4-dideoxyhexoses ^{3}J(F,C-5) and ^{3}J(F,C-1) changes from 11.0 and 9-12.0 Hz, respectively for compounds **11** and **14** to 0.0-3.0 Hz for compounds **12** and **13** allowing a rapid and safe assignment of the stereochemistry at C-3. ^{2}J(F,C) depends on the electronegativity and orientation of the substituents.[17] In particular it increases significantly when the fluorine atom and the electronegative substituents are trans diaxial. In our case the increase of ^{2}J(F,C-2) from 15.0-17.0 Hz, observed for compounds **11**, **12** and **14**, to 24.5 and 27.0 Hz, respectively, for the isomers **13**α and **13**β allows to determine unequivocally the trans relationship betweent the fluorine atom and the benzyloxy substituent for compound **13**.

Finally, just dissolved samples of the crystallized ribo- and xylo-pyranoses **12** and **14** showed exclusively the presence of the β anomers, but in solution all compounds **11** - **14** exist at equilibrium as mixtures of α and β forms. The β anomer dominates (ca. 78%) for the isomers **12** and **13** bearing an axial fluorine atom in position 3. Clearly in these compounds the 1,3-diaxial interaction between fluorine and the anomeric hydroxyl group destabilizes the α anomer. On the contrary the α anomer is more abundant (abt. 65%) for compounds **11** and **14** bearing an equatorial fluorine at C-3. In this case the configuration of the anomeric carbon is stabilized by the "anomeric effect".[12]

Conclusions

The commonly employed approach for the synthesis of fluorinated sugars resorts to the introduction of fluorine on a proper derivative of a naturally occcurring carbohydrate.[1] In the few examples of total synthesis of non racemic fluoro-deoxy-sugars the source of chirality is represented by a synthon from the pool of chirality which is incorporated in the fluorinated carbohydrate.[19]

The syntheses of the four 3,4-dideoxy-3-fluoro-hexopyranoses **11** - **14** here described show the feasibility of another approach, according to which no fragments from the chiral pool are incorporated in the fluoro-carbohydrate moiety, as the chiral centres and functional groups of the fluoro-sugar are built up around the chiral sulphinyl auxiliary group.[5]

Experimental

IR spectra were taken on a Perkin-Elmer 177 spectrophotometer. ^{1}H, ^{19}F, And ^{13}C NMR spectra were recorded with a Brucker CPX 300 or a Brucker AM 500 spectrometer; TMS was used as internal standard unless otherwise stated; $_{H,C,F}$ values are in ppm. Melting points are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} merck; column chromatographies were performed with silica gel 60 (60 - 200 µm, Merck). Osmium tetroxide (osmic acid, Aldrich), osmium tetroxide (4 wt% solution in water, Aldrich), and trimethylamine N-oxide dihydrate (Fluka) were used. Commercially available reagent grade solvents were employed without purification.

(5S)-4-Fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hexan-1,2,5-triols (5).- Osmium tetroxide (4 wt % solution in water, 1.8 mL) was added at 0°C into a solution of (4S,5S)-4-fluoro-5-hydroxy-6-[(R)-(4-methylphenyl)sulphinyl]-hex-1-ene (3) (600 mg, 2.34 mmol) in THF/H_2O (20 : 1 mixture, 4 mL) and the solution was stirred in the dark for 5 min. The colour of the solution turned to brown and trimethylamine N-oxide dihydrate (250 mg, 2.34 mmol) in THF (5 mL) was added. After 90 min at room temperature a saturated aqueous solution of sodium sulphite was added (10 mL). Citric acid was added to reach pH = 5 and after stirring 1 h at room temperature the mixture was extracted with ethyl acetate (5 x 30 mL). The collected organic phases were dried with anhydrous sodium sulphate, evaporated under reduced pressure and flash chromatographed (methylene chloride/ethyl acetate/methanol 35 : 55 : 10) to give 373 mg (55 % yield) of (4S,5S)-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hexan-1,2,5-triols (5) (nearly equimolecular mixtures of the two diastereoisomers having the (2S) and (2R) absolute configurations) and 172 mg (24 % yield) of (4S,5S)-4-fluoro-6-[(4-methylphenyl)sulphonyl]-hexan-1,2,5-triols (7) (nearly equimolar mixtures of the two diastereoisomers having the (2S) and (2R) absolute configurations); only trace amounts (< 2 % yield) of the (4S,5S)-4-fluoro-5-hydroxy-6-[(4-methylphenyl)sulphonyl]-hex-1-ene (6) could be detected through TLC. (4S,5S,R_S)-5 (epimer mixture at C-2): R_f (methylene chloride/ethyl acetate/methanol 35 : 55 : 10): 0.33; ^{1}H n.m.r. (MeOD): 1.5 - 2.0 (m, 2H, H_2-3); 2.45 (s, 3H, Me); 2.85 and 3.05 (m, 2H, H_2-6); 3.47 (m, 2H, H_2-1); 3.80 (m, 1H, H-2); 4.20 (m, 1H, H-5); 7.41 and 7.60 (m, 4H, ArH). ^{13}C N.m.r. (MeOD): 21.44 (Me); 35.66 and 35.74 (C-3, J(C,F) = 21 Hz); 62.19 (C-6); 66.76 and 67.64 (C-1); 68.13 and 68.46 (C-5, J(C,F) = 20 Hz); 69.03 and 70.04 (C-2); 93.83 and 94.60 (C-4, J(C,F) = 173.6 Hz); 125.25 and 131.36 (ArCH). (4S,5S)-7 (epimer mixture at C-2): R_f (methylene chloride/ethyl acetate/methanol 35 : 55 : 10): 0.42; ^{1}H n.m.r. (MeOD): 1.5-2.0 (m, 2H, H_2-3); 2.46 (s, 3H, Me); 3.3-3.5 (m, 4H, H_2-6 and H_2-1); 3.74 (m, 1H, H-2); 4.13 (m, 1H, H-5); 7.42 and 7.85 (m, 4H, ArH). ^{13}C N.m.r. (MeOD): 21.61 (Me); 34.40 and 35.44 (C-3, J(C,F) = 21 Hz); 59.58 and 59.66 (C-6); 66.74 and 67.61 (C-1); 68.79-69.98 (C-2 and C-5); 93.85 and 94.14 (C-4, J(C,F) = 173.0 Hz and 173.6 Hz); 129.27 and 130.92 (ArCH).

Oxidation of (4S,5S,R_S)-3 under the above described reaction conditions, but by using

crystalline OsO_4 in catalytic amounts (instead of the 4 wt % water solution) required longer reaction times (2.5 h) and afforded, after flash chromatography (n-hexane/ethyl acetate 7 : 3; then chloroform/ethyl acetate/methanol 45 : 45 : 10) the (4S,5S,R_S)-sulphinyl triols 5 (ca. 1 : 1 mixture of the two epimers at C-2) in 35 % yield, the (4S,5S)-sulphonyl triols 7 (ca. 1 : 1 mixture of the two epimers at C-2) in 23 % yield, and the (4S,5S)-4-fluoro-5-hydroxy-6-[(4-methylphenyl)sulphony]-hex-1-ene (6) in 28 % yield: R_f (n-hexane/ethyl acetate 7 : 3): 0.35; $[\alpha]_D^{20}$ +22.8° (c 1.7 in $CHCl_3$); ^1H n.m.r. ($CDCl_3$): 2.3-2.6 (m, 2H, H_2-3); 2.46 (s, 3H, Me); 3.23 (dd, 1H, H-6, J(H,H) = 14.0 and 10.0 Hz); 3.34 (dt, 1H, H-6, J(H,F) = 1.5 Hz); 4.15 (m, 1H, H-5); 4.39 (m, 1H, H-4, J(H,F) = 47 Hz); 5.12 and 5.13 (m, 2H, H_2-1); 5.78 (m, 1H, H-2); 7.39 and 7.82 (m, 4H, ArH).

Similarly, the oxidation of (4R,5S,R_S)-3 under the reaction conditions described above and by using a 4 wt % water solution of OsO_4, afforded, after flash chromatography (methylene chloride/ethyl acetate/methanol 45 : 45 : 10) the (4R,5S,R_S)-sulphinyl-triols 5 (ca. 1 : 1 mixture of the two epimers at C-2) in 51 % yield and the (4R,5S)-sulphonyl-triol 7 (ca. 1 : 1 mixture of the two epimers at C-2) in 38 % yield. (4R,5S,R_S)-5 (epimer mixture at C-2): R_f (methylene chloride/ethyl acetate/methanol 45 : 45 : 10): 0.33; ^1H n.m.r. ($CDCl_3$/MeOD 1:1): 1.6-2.1 (m, 2H, H_2-3); 2.43 (s, 3H, Me); 2.87 (ddd, 1H, H-6, J(H,H) = 13.5, 8.5 Hz; J(H,F) = 3.5 Hz); 3.10 (dd, 1H, H-6); 3.44 and 3.63 (m, 2H, H_2-1); 3.88 (m, 1H, H-2); 4.27 (m, 1H, H-5); 4.62 (m, 1H, H-4); 7.34 and 7.53 (m, 4H, ArH). ^{13}C N.m.r. ($CDCl_3$): 21.45 (Me); 34.23 and 34.43 (C-3, J(C,F) = 21 Hz); 61.22 and 61.61 (C-6); 66.10 and 66.74 (C-1); 65.6-66.5 (C-5); 67.98 and 68.50 (C-2); 92.51 and 93.02 (C-4, J(C,F) = 175 Hz); 124.04 and 130.35 (ArCH). (4R,5S)-7 (epimer mixture at C-2): R_f (methylene chloride/ethyl acetate/methanol 45 : 45 : 10): 0.45; ^1H n.m.r. ($CDCl_3$/MeOD 1:1): 1.5-2.0 (m, 2H, H_2-3); 2.47 (s, 3H, Me); 3.3-3.6 (m, 4H, H_2-6 and H_2-1); 3.87 (m, 1H, H-2); 4.2-4.4 (m, 1H, H-5); 4.69 (m, 1H, H-4, J(H,F) = 47 Hz); 7.38 and 7.82 (m, 4H, ArH). ^{13}C N.m.r. ($CDCl_3$/MeOD 1 : 1): 21.88 (Me); 34.51 and 34.88 (C-3, J(C,F) = 23 Hz); 59.62 (C-6); 66.37 and 67.09 (C-1); 67.65 and 68.01 (C-5, J(C,F) = 23 Hz); 68.48 and 69.17 (C-2); 92.46 and 93.13 (C-4, J(C,F) = 175 Hz); 128.59 and 130.47 (ArCH).

Oxidation of (4R,5S,R_S)-3 by using crystalline OsO_4 in catalitic amounts under the standard reaction conditions (room temperature, 2.5 h) afforded after flash chromatography (n-hexane / ethyl acetate 7 : 3; then chloroform/ethyl acetate/methanol 45:45:10) the (4R,5S,R_S)-sulphinyl triols 5 (1:1 mixture of epimers at C-2) in 35% yield, the (4R,5S)-sulphonyl triol 7 (1:1 mixture of epimers at C-2) in 28% yield, and the (4R,5S)-4-fluoro-5-hydroxy-6-[(4-methylphenyl)sulphonyl]-hex-1-ene 6 in 24% yield: R_f (n-hexane/ethylacetate 7:3) 0.35; $[\alpha]_D^{20}$ + 17.2° (c 2.1 in $CHCl_3$); ^1H n.m.r. ($CDCl_3$) : 2.4-2.6 (m, 2H, H_2-3); 2.47 (s, 3H, Me); 3.28 (dd, 1H, H-6, J(H,H) = 14.5, 2.5 Hz); 3.41 (dd, 1H, H-6, J(H,H) = 9.5 Hz); 4.28 (ddt, 1H, H-5, J(H,H) = 9.0, 2.5, 2.5 Hz, J(H,F) = 22 Hz); 4.45 (m, 1H, H-4, J(H,F) = 47 Hz); 5.05-5.25 (m, 2H, H_2-1); 5.79 (m, 1H, H-2); 7.40 and 7.83 (m, 4H, ArH).

(5S)-5-Benzyloxy-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hexan- 1,2-diols (8). The (4S,5S)-5-benzyloxy-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hex-1-ene (4) was oxidized with catalytic amounts of OsO_4 (4 wt % in water)and $Me_3NO{\cdot}2H_2O$ following the procedure described above for the (4S,5S)-5-hydroxy-1-hexene 3. The flash chromatography (toluene/ethyl acetate/methanol 9:9:1) of the crude reaction mixture afforded the (4S,5S)-5-benzyloxy-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hexan-1,2-diols (8) (approximate 1:1 mixture of the (2S) and (2R) diastereoisomers) in 75% yield and the (4S,5S)-5-benzyloxy-4-fluoro-6-[(4-methylphenyl)sulphonyl]-hexan-1,2-diols (9) (approximate 1:1 mixture of the (2S) and (2R) diastereoisomers) in 14% yield. (4S,5S,R_S)-8 (epimer mixture at C-2): R_f (toluene/ethylacetate/methanol 9:9:1): 0.35; ^1H n.m.r. ($CDCl_3$): 1.5-2.0 (m, 2H, H-3); 2.42 (s, 3H, Me); 2.8-2.9 (m, 2H, H_2-6); 3.3-3.7 (m, 2H, H_2-1); 3.94 (m, 1H, H-2); 4.2-4.4 (m, 1H, H-5); 4.86 (m, 1H, H-4); 4.82 (m, 2H, CH_2Ph); 7.2-7.6 (m, 9H, ArH). ^{13}C N.m.r. ($CDCl_3$): 21.42 (Me); 33.89 and 33.93 (C-3, J(C,F) = 20 Hz); 60.05 and 60.09 (C-6); 66.05 and 66.88 (C-1); 68.01 and 68.89 (C-2); 73.80 and 74.04 (CH_2Ph); 75.11 and 75.26 (C-5); 91.37 and 92.54 (C-4, J(C,F) = 175 Hz). (4S,5S)-9 (epimer mixture at C-2): R_f (toluene/ethylacetate/methanol 9:9:1): 0.55; ^1H n.m.r. ($CDCl_3$): 1.5-2.0 (m, 2H, H_2-3); 2.43 (br s, 3H, Me); 3.3-3.5 (m, 2H, H_2-6); 3.5-4.0 (m, 3H, H_2-1 and H-2); 4.26 (m, 1H, H-5); 4.48, 4.53 and 4.60, 4.62 (m, 2H, CH_2Ph); 4.87 (m, 1H, H-4); 7.2-7.4 and 7.77 (m, 9H, ArH). ^{13}C N.m.r. ($CDCl_3$): 21.62 (Me); 33.55 and 33.60 (C-3, J(C,F) = 21 Hz); 57.53 and 57.57 C-6); 65.97 and 66.78 (C-1); 67.99 and 68.81 (C-2); 73.00 and 73.25 (CH_2Ph); 75.09 and 75.45 (C-5, J(C,F) = 22 Hz); 91.23 and 92.22 (C-4, J(C,F) = 176 Hz).

Similarly, the oxidation of the (4R,5S)-5-benyloxy-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hex-1-ene (4) with catalytic amounts of OsO_4 (4 wt % in water) and $Me_3NO{\cdot}2H_2O$ according to the standard procedure described above afforded a crude reaction mixture which gave, after flash chromatography (toluene/ethyl acetate/methanol 40:45:8), the (4R,5S,R_S)-sulphinyl diols 8 (approximate 1:1 epimer mixture at C-2) in 77% yield and the (4R,5S)-sulphonyl diols 9 (approximate 1:1 epimer mixture at C-2) in 15% yield. (4R,5S,R_S)-8 (epimer mixture at C-2): R_f (toluene/ethylacetate/methanol 40:45:8): 0.35; ^1H n.m.r. ($CDCl_3$): 1.5-1.9 (m, 2H, H_2-3); 2.42 (s, 3H, Me); 2.9-3.1 (m, 2H, H_2-6); 3.35-3.70 (m, 2H, H_2-1); 3.87 (m, 1H, H-2); 4.22 (m, 1H, H-5); 4.6-4.9 (m, 3H, CH_2Ph and H_2-4); 7.25-7.55 (m, 9H, ArH). ^{13}C N.m.r. ($CDCl_3$): 21.42 (Me); 33.95 and 34.27 (C-3, J(C,F) = 20 Hz); 60.17 and 60.46 (C-6); 66.17 and 66.69 (C-1); 68.01 and 69.11 (C-2); 73.80 and 74.15 (C-5); 74.53 and 74.63 (CH_2Ph); 91.38 and 92.96 (C-4, J(C,F) = 175 Hz). (4R,5S)-9 (epimer mixture at C-2): R_f (toluene/ethylacetate/methanol 40:45:8): 0.55; ^1H n.m.r. ($CDCl_3$): 1.5-2.0 (m, 2H, H_2-3); 2.43 (br s, 3H, Me); 3.3-3.5 (m, 2H, H_2-6); 3.5-3.9 (m, 3H, H_2-1 and H-2); 4.17 (m, 1H, H-5); 4.5 and 4.6 (AB systems, 2H, CH_2Ph); 4.85 (m, 1H, H-4); 7.2-7.4 and 7.77 (m, 9H, ArH). ^{13}C N.m.r. : 21.64 (Me); 33.50 and 33.83 (C-3, J(C,F) = 21 Hz); 56.63 and 56.82 (C-6); 66.05 and 66.60 (C-1); 68.08 and 69.12 (C-2); 72.76 and 72.98 (CH_2Ph); 73.39 and 74.12 (C-5, J(C-F) = 21 Hz); 90.37 and 91.71 (C-4, J(C,F) = 163 and 175 Hz).

2-O-Benzyl-3,4-dideoxy-3-fluoro-hexopyranoses **11** - **14**. A solution of trifluoroacetic anhydride (0.85 mL, 6.00 mmol) in dry acetonitrile (6.0 mL) was dropped at 0° C into a stirred solution of the 5-benzyloxy-4-fluoro-6-[(R)-(4-methylphenyl)sulphinyl]-hexan-1,2-diols **8** (570 mg, 1.50 mmol) and 2,4,6-trimethylpyridine (0.40 mL, 3.00 mmol) in the same solvent (35 mL). After 40 min at the same temperature a solution of copper(II) chloride (403 mg, 3.00 mmol) and potassium carbonate (511 mg, 3.70 mmol) in water (8.0 mL) was added. After stirring at room temperature for 1 h the shy-blue mixture turned to green. Acetonitrile was removed under reduced pressure, the water residue was diluted (20 mL) and extracted with ethyl acetate (5x25 mL). The collected organic phases were dried over anhydrous sodium sulphate, evaporated under reduced pressure, and flash chromatographed (chloroform/ethyl acetate/methanol 50 : 50 : 1).

Starting from (4S,5S,R_S)-**8** (nearly equimolar mixture of epimers at C-2) the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-D-lyxo-hexopyranose (**11**) and the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-L-ribo-hexopyranose (**12**) were isolated in 66% overall yield.

Starting from (4R,5S,R_S)-**8** (nearly equimolar mixture of epimers at C-2) the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-D-arabino-hexopyranose (**13**) and the 2-O-benzyl-3,4-dideoxy-3-fluoro-α,β-L-xylo-hexopyranose (**14**) were isolated in 73% overall yield.

D-Lyxo-hexopyranose **11**: $[\alpha]_D^{20}$ +48.7° (c 1.1 in $CHCl_3$); found: C, 60.76; H, 6.78. $C_{13}H_{17}FO_4$ requires C, 60.92; H, 6.69%; IR (film): 3350, 2920, 1090, 1040, 750, 690 cm^{-1}.

L-Ribo-hexopyranose **12**: $[\alpha]_D^{20}$ +3.6° (c 1.2 in $CHCl_3$); found C, 60.80; H, 6.81. $C_{13}H_{17}FO_4$ requires C, 60.92; H, 6.69%; m.p. 139 - 140°C (i-Pr_2O/AcOEt); IR (KBr) 3400, 3200, 2960, 2920, 1110, 1040, 690 cm^{-1}.

D-Arabino-hexopyranose **13**: $[\alpha]_D^{20}$ +7.96° (c 1.1 in $CHCl_3$); found: C, 60.70; H, 6.86. $C_{13}H_{17}FO_4$ requires C, 60.92; H, 6.69%; IR (film): 3400, 2920, 1120, 750 cm^{-1}.

L-Xylo-hexopyranose **14**: $[\alpha]_D^{20}$ -35.1° (c 1.03 in $CHCl_3$); found: C, 60.81; H, 6.74. $C_{13}H_{17}FO_4$ requires C, 60.92; H, 6.69%; m.p. 105-107°C (i-Pr_2O/AcOEt); IR (KBr): 3450, 3250, 2920, 1140, 1120, 1030, 740 cm^{-1}.

^1H, ^{13}C, And ^{19}F n.m.r. data of the four fluorocarbohydrates **11** - **14** are reported in the Table.

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