



## Fluorinated Analogues of Nojirimycin and Mannojirimycin from a non-Carbohydrate Precursor

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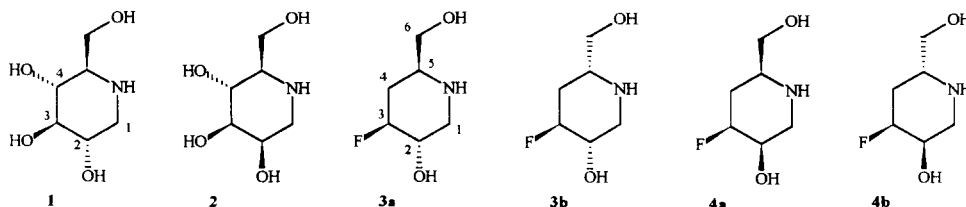
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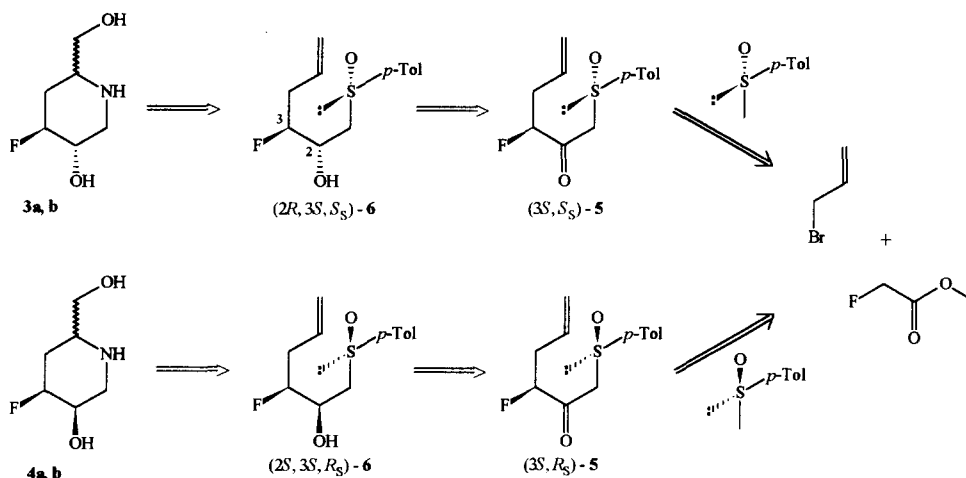
**Abstract:** 1,3,5-Trideoxy-3-fluoronojirimycin **3a** and its 5-*epi* isomer **3b** have been synthesized in enantiomerically pure form starting from the fluorohydroxysulfinylhexene (2*R*,3*S*,*S<sub>G</sub>*)-**6**. The nitrogen atom of the target bioactive compounds is introduced by replacing the sulfinyl group with an hydroxylamine residue and an intramolecular aminomercuration reaction builds up the desired piperidine ring. Finally, an oxidative demercuration affords the hydroxymethyl moiety. The same synthetic sequence allows to obtain 1,3,5-trideoxy-3-fluoromannojirimycin **4a** and its 5-*epi* isomer **4b** starting from the benzyloxy-fluorosulfinylhexene (2*S*,3*S*,*R<sub>G</sub>*)-**7**.

The study of glycosidases dates back to the time of Liebig and Wohler<sup>1</sup> and recent interest on these enzymes is due to their involvement in key cellular functions such as recognition, adhesion, and transport.<sup>2</sup> Glycosidase inhibitors are useful tools for probing the details and intricacies of catalytic mechanisms and could be of therapeutic value for the treatment of metabolic diseases, the inhibition of tumor metastasis, the control of infections of fungi and viruses.<sup>3</sup> Polyhydroxylated piperidines are a well known class of glycosidase inhibitors and 1-deoxynojirimycin **1** and 1-deoxymannojirimycin **2** are two particularly noteworthy specimens of the class.<sup>4</sup> They are the azasugar analogues of glucose and mannose and work as potent inhibitors of glucosidases and mannosidases,<sup>5</sup> respectively. Notably, 1-deoxynojirimycin **1** and some of its analogues interfere with HIV-induced syncytium formation and viral infectivity.<sup>6</sup>

Structure-activity studies on polyhydroxylated piperidine inhibitors have shown that strong enzyme recognition and binding by the inhibitors require that they contain, as part of their structures, electronegative atoms which are the topographical equivalent of the sugar C-2 and C-3 hydroxyl groups and ring heteroatom. The absence of a topographical analogue of the C-4 hydroxyl group of the sugar appears to



Scheme 1



have little effect on the binding and activity of inhibitors.<sup>7</sup> We have therefore decided to prepare piperidine derivatives **3a,b** and **4a,b** which are analogues of 1,3,4-trideoxynojirimycin and 1,3,4-trideoxymannojirimycin bearing a fluorine atom on C-3.<sup>8</sup> Fluorine is in fact well known to be able to mimic an hydroxyl group as it can interact significantly with proton donors also in enzymatic sites.<sup>9</sup> Another aspect of the rationale underlying the synthesis of analogues **3** and **4** is that fluorine is a non-protic substituent and more hydrophobic glycoside inhibitors are more potent inhibitors of HIV infections.<sup>10,6d</sup> The preparation of some piperidine and pyrrolidine glycoside inhibitors in which a fluorine atom substitutes for an hydroxy group has already been described.<sup>11</sup>

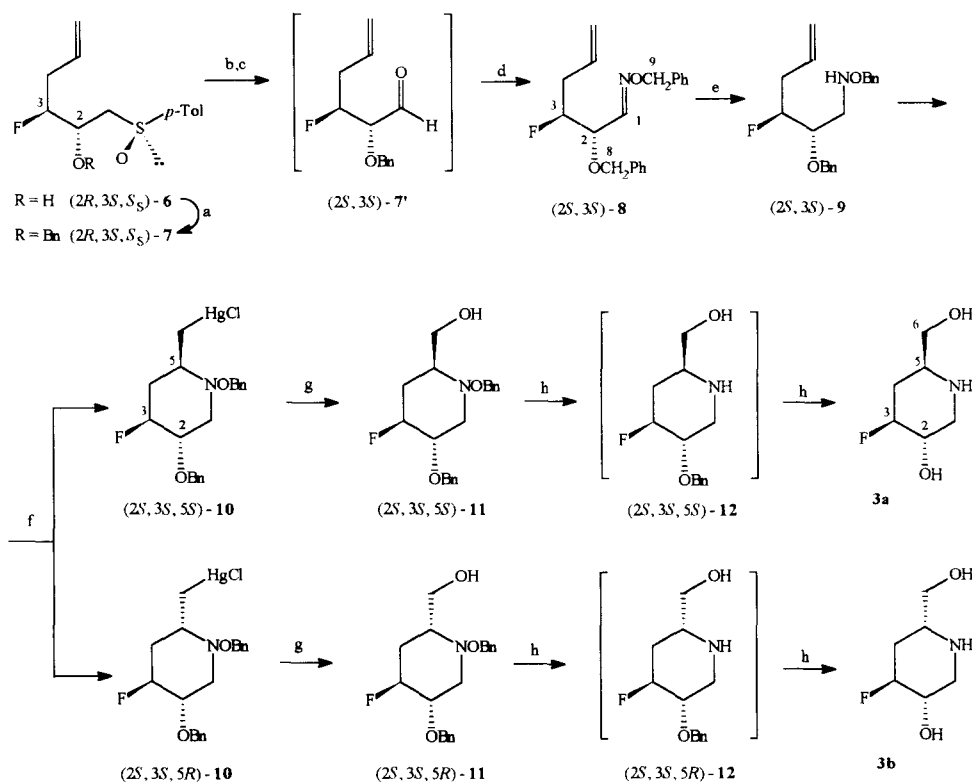
## Results and Discussion

A program on going in our laboratory has shown how enantiomerically pure fluorinated sulfoxides are useful chiroins for the syntheses of several polyfunctional fluorinated compounds<sup>12</sup> and can be used also in effective preparations of bioactive and fluoro substituted products.<sup>13</sup> Recently, other groups have been exploiting the synthetic potential of fluorinated sulfoxides<sup>14</sup> and using them as intermediates towards fluorinated analogues of natural substances.<sup>15</sup>

The retrosynthetic analysis of target molecules is sketched in Scheme 1. The six carbon framework of **3** and **4** is assembled starting from three building blocks: a one carbon unit (corresponding to the nitrogen substituted methylene), a two carbon unit (bearing the fluorine atom and the cyclic hydroxy group), and a three carbon unit (on which the heterocyclic nitrogen and the exocyclic hydroxy substituent will be inserted). These three pieces are furnished by methyl tolyl sulfoxide, ethyl fluoroacetate, and allyl bromide, respectively. The sulfinyl moiety of methyl tolyl sulfoxide works also as the chiral auxiliary group from which all the carbon stereocentres are obtained in enantiomerically pure form. 1-Deoxymannojirimycin **2** differs from 1-deoxynojirimycin **1** for the stereochemistry of the hydroxy group at C-2 and this difference occurs also in our target molecules **3** and **4**. In our synthetic approach this stereocentre is formed through the diastereoselective reduction of the carbonyl precursor **5**, the configuration at sulphur determining that at carbon [an (*S*) sulfoxide affords an (*R*) alcohol]. Methyl tolyl sulfoxide having the (*S*) and (*R*) absolute configurations have therefore to be used as starting materials for the synthesis of nojirimycin analogues **3** and mannojirimycin analogues **4**, respectively. Both these enantiomers are commercially available or, alternatively, can be easily prepared in two steps from the two antipodes of menthol.<sup>16</sup> The described synthesis of target compounds **3** and **4** thus shows the stereochemical flexibility of our approach.

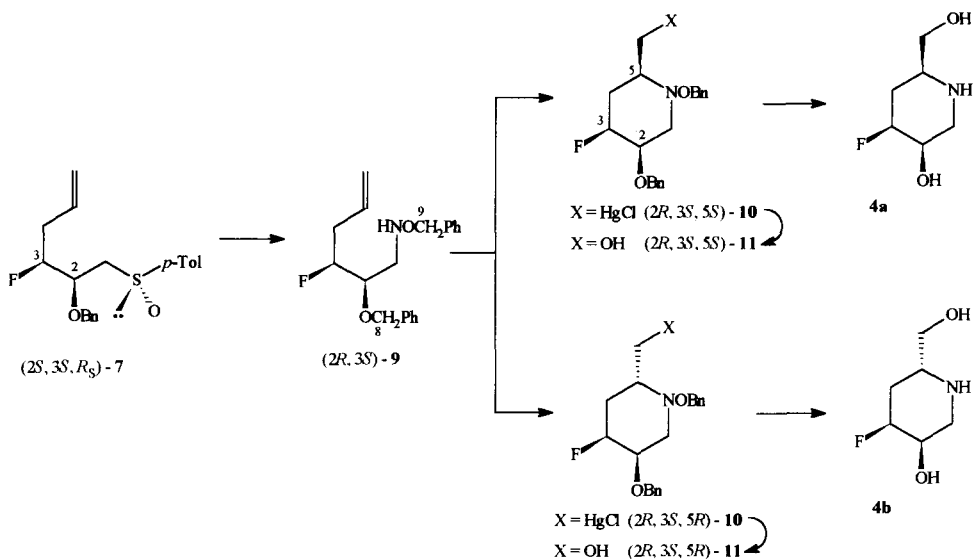
**Synthesis of nojirimycin analogues 3.** The synthesis of nojirimycin analogues **3** starts from the fluoro-sulfinyl-hexenol ( $2R,3S,S_S$ )-**6**, an intermediate in the preparation of muscarine analogues.<sup>13d</sup> The corresponding benzyl ether **7** was formed in quantitative yields under standard reaction conditions and treated with trifluoroacetic anhydride and 2,4,6-trimethylpyridine. A clean Pummerer rearrangement of the sulfoxide group occurred to give a geminal dithioltrifluoroacetoxy moiety. This masked aldehyde was not isolated, but hydrolysed *in situ* by treatment with copper(II) chloride in basic medium to give the fluoro-benzyloxyhexenal **7'** (Scheme 2).  $\alpha$ -Alkoxyaldehydes are known to have a marked proclivity for becoming hydrated and so crude aldehyde **7'** was treated with *O*-benzylhydroxylamine to afford the *O*-benzyl oximes ( $2S,3S$ )-**8** as a 10 : 1 mixture of the (*E*) and (*Z*) isomers in 65% overall yield from sulfinyl precursor **7**. The two oximes were separated into pure isomers, but their mixture could also be directly reduced to corresponding hydroxylamine ( $2S,3S$ )-**9** and high yields were obtained when sodium cyanoborohydride<sup>12d</sup> was used at pH  $\approx$  3.5.

The piperidine ring of target compounds **3a,b** was built through intramolecular cyclization of  $\delta$ -hydroxylaminohexene **9**. Both radical<sup>17</sup> and electrophilic<sup>18</sup> processes have been used for realizing this type of reaction. Some reagents frequently used when this latter approach is followed are bromine,<sup>19</sup> iodine,<sup>18</sup> selenium,<sup>20</sup> palladium<sup>21</sup> derivatives, but we have preferred mercury(II) salts<sup>22</sup> as they require very mild reaction conditions and give stable, easy to handle products in quantitative yields. Specifically, mercury(II)



**Scheme 2:** (a) NaH, BnBr, THF, DMF, 0 °C; (b)  $(CF_3CO)_2O$ , 2,4,6-trimethylpyridine, acetonitrile, 0 °C; (c)  $CuCl_2$ ,  $K_2CO_3$ , water, r. t.; (d)  $BnONH_2 \cdot HCl$ ,  $Na_2CO_3$ , molecular sieves (4 Å), EtOH, r. t.; (e)  $NaCNBH_3$ , dil. HCl, methanol, r. t.; (f)  $(CF_3COO)_2Hg$ , THF, r. t.; then: KCl, water, r. t.; (g)  $NaBH_4$ ,  $(CF_3)_2CHOH$ , perfluorotributylamine,  $O_2$ , r. t.; (h)  $H_2/Pd(C)$ , 4 atm,  $CF_3COOH$ , r. t.

Scheme 3



trifluoroacetate afforded exclusively the 5-chloromercuriomethylpiperidines 10 thus showing that the 6-*exo* process was favoured over the 7-*endo* one. This complete regioselectivity contrasts with the low diastereoselectivity. The two piperidines 10 epimeric at the newly formed carbon stereocentre were both produced and the isomer having the (2*S*,3*S*,5*S*) configuration, i.e. bearing all the ring substituents in equatorial position, was produced with slight preference over the (2*S*,3*S*,5*R*) product (d. e. 24%).

The two piperidines 10 were separated through flash chromatography and oxidatively demercurated with sodium borohydride under oxygen to give hydroxymethyl products (2*S*,3*S*,5*S*)-11 and (2*S*,3*S*,5*R*)-11 without any epimerization at the  $\alpha$ -stereogenic centre. Good yields in these compounds were obtained when perfluorotributylamine/hexafluoroisopropanol were used as solvent mixture while under the standard reaction conditions, with dimethylformamide as solvent, 2-benzoyloxy-3-fluoro-5-methyl-*N*-benzoyloxypiperidines 13 and hexenylhydroxylamine 9 were main reaction products, desired hydroxymethyl piperidine 11 being formed in trace amounts, if any. In the oxidative demercuration, sodium borohydride induces the homolytic cleavage of the carbon-mercury bond to give an intermediate radical which is trapped by dioxygen to afford a peroxide successively reduced to the final alcohol.<sup>23</sup> Alternatively, the intermediate alkyl radical can also be directly reduced to give the corresponding hydrocarbon. Clearly the use of fluorinated solvents favours the first pathway and this may be due either to the higher solubility of oxygen in fluorinated solvents<sup>24</sup> or to the specific properties of alkoxyborohydride which probably form *in situ* on reaction of isopropanol and sodium borohydride.<sup>25</sup>

On treatment of (2*S*,3*S*,5*S*)-11 with hydrogen and palladium on charcoal (1 atm), hydrogenolysis of the N,O bond occurred first and (2*S*,3*S*,5*S*)-2-benzoyloxy-3-fluoro-5-hydroxymethylpiperidine 12 was isolated. Under more severe reaction conditions (4 atm), also debenzoylation of the hydroxy group on C-2 occurred and the nojirimycin analogue 3a was directly isolated as its trifluoroacetate (81% yield). Similarly, hydrogenolysis of (2*S*,3*S*,5*R*)-11 afforded the trideoxymonofluoronojirimycin 3b (80% yield).

**Synthesis of mannojirimycin analogues 4.** The sulfinyl residue of (2*S*,3*S*)-2-benzoyloxy-3-fluoro-1-(*R*) [(4-methylphenyl)sulfinyl]-5-hexene 7, the starting material in the synthesis of anti AIDS drugs,<sup>13e</sup> was transformed into an *O*-benzoyloxime group through a Pummerer rearrangement and reaction of the formed aldehyde with *O*-benzylhydroxylamine. Reduction of this oxime (sodium borohydride in acidic medium) afforded the (2*R*,3*S*)-*N*-(2-benzoyloxy-3-fluoro-5-hexenyl)-*O*-benzylhydroxylamine 9 in 63% overall yield

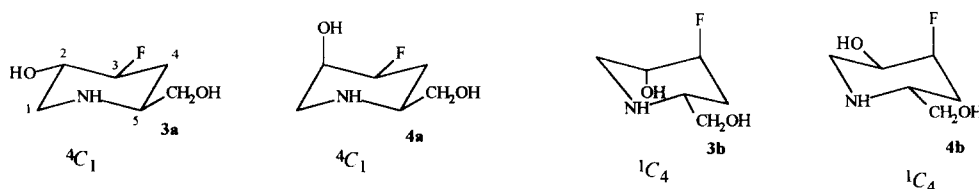
from **7** (Scheme 3). The aminomercuration reaction of (2*R*,3*S*)-**9** gave results similar to those described above for the (2*S*,3*S*) epimer **9**. The 6-*exo* cyclization process occurred exclusively and the formation of the piperidine (2*R*,3*S*,5*S*)-**10**, bearing the chloromercuriomethyl group in equatorial position, was slightly preferred [(2*R*,3*S*,5*S*)-**10** to (2*R*,3*S*,5*R*)-**10** ratio 64 : 36]. These two diastereoisomeric piperidines **10** were isolated in pure form through flash chromatography and substitution of hydroxy for chloromercurio to give 5-hydroxymethylpiperidines (2*R*,3*S*,5*S*)-**11** and (2*R*,3*S*,5*R*)-**11**, was best performed, once again, in a fluorinated solvent. Cleavage of the N,O bond and debenzoylation (H<sub>2</sub>/Pd on charcoal) afforded 1,3,4-trideoxy-3-fluoromannojojirimycin **4a** and its 5-*epi* isomer **4b** in enantiomerically and diastereoisomerically pure form.

**Structural analyses.** The absolute configuration at C-2 and C-3 of all the reported compounds comes from that of starting materials (2*R*,3*S*,5*S*)-**6**<sup>13d</sup> and (2*S*,3*S*,5*R*)-**7**.<sup>13e</sup> The stereochemistry at the newly formed C-5 carbon centre of piperidine derivatives **3**, **4**, and **10** - **13** as well as the preferred conformations of the heterocyclic ring were determined through an analysis of the coupling constants reported in the Table and in the Experimental.

The four target compounds **3a,b** and **4a,b** adopt preferentially the chair conformation reported in the Figure. Specifically, nojirimycin analogue **3a** and mannojirimycin analogue **4a** both adopt the <sup>4</sup>C<sub>1</sub> conformation which disposes the *cis* located fluorine and hydroxymethyl residues in equatorial position. Being these two compounds epimeric at C-2, the hydroxy group on this carbon is disposed equatorially in the former product and axially in the latter one. For **3a** this conformational preference is indicated by the magnitude of the vicinal couplings exhibited by H-2 $\beta$  with H-1 $\alpha$  (10.4 Hz) and by H-4 $\beta$  with H-3 $\alpha$  and H-5 $\alpha$  (11.3 and 11.6 Hz, respectively). For **4a** the coupling between H-1 $\alpha$  and H-2 $\alpha$  is of 1.7 Hz implying a *gauche* interaction and the high value of the couplings between H-4 $\beta$  and H-3 $\alpha$  and H-5 $\alpha$  indicates a *trans* diaxial relationship between involved nuclei.

The remaining target compounds **3b** and **4b**, again epimeric at C-2, adopt the <sup>1</sup>C<sub>4</sub> conformation so that the *trans* disposed fluorine and hydroxymethyl groups are located axially and equatorially in both products and the hydroxy on C-2 is axial in **3b** and equatorial in **4b**. In fact, the coupling between F-3 $\beta$  and H-4 $\alpha$  (43.8 and 42.9 Hz) and H-4 $\alpha$  and H-5 $\beta$  (11.6 and 11.1 Hz) require an axial-axial relationship while the  $J_{1\beta,2\beta}$  = 1.8 Hz of **3b** and the  $J_{1\beta,2\alpha}$  = 10.4 Hz of **4b** imply *gauche* and axial-axial interactions, respectively. Analogous arguments allowed the <sup>4</sup>C<sub>1</sub> and <sup>1</sup>C<sub>4</sub> conformations to be assigned to (2*S*,3*S*,5*S*)- and (2*S*,3*S*,5*R*)-*O*-benzyl piperidines **12**.

An interesting observation was that chemically and diastereoisomerically pure *N*-benzyloxy piperidine derivatives (2*S*,3*S*,5*S*)-**10**, -**11**, and (2*S*,3*S*,5*R*)-**13** and (2*R*,3*S*,5*R*)-**10** and -**11**, all bearing, in the preferred conformation, the substituents on C-2 and C-5 in equatorial position, showed broad signals in <sup>1</sup>H NMR spectra and two resonances attributable to F-3 in <sup>19</sup>F NMR spectra. This might be due to slow inversion either of the piperidine ring or of the nitrogen atom. However, <sup>19</sup>F NMR signals appeared as broad doublets of ~50 Hz in the former series of compounds showing that the fluorine atoms were invariably equatorially disposed. Differently, in the latter series, having the (2*R*,3*S*,5*R*) stereochemistry, fluorine signals were larger multiplets (due to the presence of additional axial-axial F,H couplings) and this was implying that fluorine



**Figure.** Preferred conformations of nojirimycin and mannojirimycin analogues **3a,b** and **4a,b**.

**Table.** Selected  $^1\text{H}$  and  $^{19}\text{F}$  NMR chemical shifts ( $\delta$ ) and coupling constants ( $J/\text{Hz}$ ) for compounds **3a,b**, **4a,b**, and (2*S*,3*S*,5*S*)- and (2*S*,3*S*,5*R*)-**12**. Numbering is shown in Schemes 2, 3 and Figure.

Atom <sup>a</sup>	<b>3a</b> <sup>b</sup>	<b>3b</b> <sup>b</sup>	<b>4a</b> <sup>c</sup>	<b>4b</b> <sup>c</sup>	(2 <i>S</i> ,3 <i>S</i> ,5 <i>R</i> )- <b>12</b> <sup>c</sup>	(2 <i>S</i> ,3 <i>S</i> ,5 <i>R</i> )- <b>12</b> <sup>b</sup>
H-1 $\alpha$	2.96	3.75	2.69	3.10	2.83	3.52
H-1 $\beta$	3.70	3.66	3.22	2.86	3.48	3.34
H-2 $\alpha$			4.04	3.67		
H-2 $\beta$	4.25	4.38			~4.1	3.72
H-3 $\alpha$	4.82	5.10	4.61	4.91	4.63	5.07
H-4 $\alpha$	2.31	2.58	1.82	1.55	2.25	2.19
H-4 $\beta$	1.85	2.13	1.72	2.03	1.94	2.07
H-5 $\alpha$	3.15		2.71		3.30	
H-5 $\beta$		3.82		3.01		3.51
H-6a	3.98	4.16	3.66	3.66	~4.1	3.99
H-6b	3.90	3.98	3.51	3.43	~4.1	3.88
F-3 $\beta$	-181.08	-188.28	-182.56	-205.22	-183.75	-189.05
OH-2, -6	5.9	7.60	2.10	1.85	~4.1	5.70
<i>J</i> <sup>d</sup>						
1 $\alpha$ ,1 $\beta$	12.0	13.3	13.8	11.7	12.5	14.0
1 $\alpha$ ,2 $\alpha$			1.7	5.2		
1 $\alpha$ ,2 $\beta$	10.4	~2.5			10.2	e
1 $\beta$ ,2 $\alpha$			3.3	10.4		
1 $\beta$ ,2 $\beta$	5.3	1.8			5.1	2.3
2 $\alpha$ ,3 $\alpha$			2.9	2.5		
2 $\beta$ ,3 $\alpha$	8.4	4.3			8.3	4.1
3 $\alpha$ ,4 $\alpha$	5.3	2.4	5.5	2.2	5.3	2.4
3 $\alpha$ ,4 $\beta$	11.3	3.8	11.2	4.5	11.0	3.5
4 $\alpha$ ,4 $\beta$	12.1	14.6	11.5	14.5	12.6	14.6
4 $\alpha$ ,5 $\alpha$	2.5		3.0		2.5	
4 $\alpha$ ,5 $\beta$		11.6		11.1		11.5
4 $\beta$ ,5 $\alpha$	11.6		12.3		11.5	
4 $\beta$ ,5 $\beta$		3.5		3.0		e
5,6a	4.3	4.2	3.8	3.6	3.6	4.3
5,6b	6.8	6.2	7.8	7.1	7.8	6.2
6a,6b	10.7	11.0	10.9	10.7	11.0	10.8
F,1 $\alpha$	1.2	~1	1.7	<1	1.0	~1
F,1 $\beta$	5.8	3.0	7.9	1.8	5.5	3.2
F,2 $\alpha$			8.2	29.2		
F,2 $\beta$	12.6	5.5			11.0	6.0
F,3 $\alpha$	51.3	47.1	47.2	51.0	50.6	46.8
F,4 $\alpha$	5.5	43.8	5.5	42.9	7.7	43.5
F,4 $\beta$	9.9	11.5	10.0	10.8	10.3	e
F,5 $\alpha$	2.0		2.0		1.5	

<sup>a</sup>The amine protons resonates at the same chemical shifts of the hydroxyl protons; in compounds **3a,b**, (2*S*,3*S*,5*S*)-**12**, and (2*S*,3*S*,5*R*)-**12** the fluorine atoms of trifluoroacetate anion resonates at -75.87, -75.52, -76.91, and -75.67 ppm, respectively; in the latter two compounds the 2-*O*-Bn protons resonate at 4.66, 4.77, and 7.2-7.5 and 4.59, and 7.2-7.5 ppm, respectively. <sup>b</sup>In pyridine-*d*<sub>5</sub>. <sup>c</sup>In CDCl<sub>3</sub>. <sup>d</sup>In compounds (2*S*,3*S*,5*S*)-**12** and (2*S*,3*S*,5*R*)-**12**  $J_{8a,8b}$  = 11.7 and 11.8 Hz, respectively. <sup>e</sup>Not assigned.

atoms were axially located. These observations allowed the explanation based on ring inversion to be excluded and the couples of  $^{19}\text{F}$  NMR signals have thus been attributed to the two epimers bearing the benzyloxy residue on nitrogen in equatorial and axial position and having the above discussed  $^4\text{C}_1$  and  $^1\text{C}_4$  conformations, respectively. Similar slow inversions at nitrogen have already been reported for *N*-alkoxy substituted piperidines and pyrrolidines.<sup>26</sup>

In the remaining N-OBn derivatives (2*R*,3*S*,5*S*)-10 and -11, (2*S*,3*S*,5*R*)-10 and -11, and (2*S*,3*S*,5*S*)-13 the fluorine resonances appeared as single but unresolved, or broadened, signals. This indicates that the temperature of coalescence of the signals of the two forms due to nitrogen inversion is lower than that of the other N-OBn derivatives discussed above.<sup>27</sup>

## Experimental

**General.** Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon; acetonitrile was freshly distilled from  $\text{P}_2\text{O}_5$  under argon; dimethylformamide was stored over molecular sieves (4 and 13 Å). All spectral and physical characterisations of new compounds, chromatographic separations, and solvent purifications were made as already described.<sup>13a</sup> A detailed procedure is described for compounds obtained starting from (2*R*,3*S*,5*S*)-6 (Scheme 2), the same experimental procedure was used for elaboration of (2*S*,3*S*,5*R*)-7 (Scheme 3).

**(2*R*,3*S*)-2-Benzoyloxy-3-fluoro-1-(*S*)-[(4-methylphenyl)sulfinyl]-5-hexene (7).** A solution of (2*R*,3*S*,5*S*)-fluorosulfinylhexenol 6 (4.74 g, 18.5 mmol) in DMF (15 mL) was added dropwise into a suspension of oil-free sodium hydride (672 mg, 28 mmol) and benzyl bromide (3.33 mL, 28 mmol) in THF (15 mL) with stirring under argon at 0 °C. After 0.5 h at 25 °C diluted hydrochloric acid was added. The usual work up and flash chromatography (*n*-hexane/ethyl acetate 7 : 3) gave (2*R*,3*S*,5*S*)-7 in 94% yield.  $[\alpha]_{\text{D}}^{22}$  -274 (*c* 1.10,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.6-7.2 (9H, m, ArH), 5.77 (1H, m, H-5), 5.14 and 5.10 (2H, m, H<sub>2</sub>-6), 4.90 and 4.78 (2H, d, *J* = 12 Hz, H<sub>2</sub>-8), 4.47 (1H, dm, *J* = 47 Hz, H-3), 4.21 (1H, m, H-2), 2.5-2.3 (2H, m, H<sub>2</sub>-4), and 2.99 and 2.94 (2H, m, H<sub>2</sub>-1). Anal. calcd for  $\text{C}_{20}\text{H}_{23}\text{FO}_2\text{S}$ : C, 69.34; H, 6.70; S, 9.26. Found: C, 69.51; H, 6.88; S, 9.10.

**(*E*,2*S*,3*S*)-2-Benzoyloxy-3-fluoro-5-hexenal *O*-benzyloxime (8) and (*Z*,2*S*,3*S*)-8.** A solution of trifluoroacetic anhydride (2.82 mL, 20.0 mmol) in acetonitrile (30 mL) was added dropwise into a solution of the sulfinyl derivative (2*R*,3*S*,5*S*)-7 (3.46 g, 10.0 mmol) and of 2,4,6-trimethylpyridine (3.97 mL, 30.0 mmol) in the same solvent (50 mL) with stirring at 0 °C under argon. After 30 min at room temperature a solution of copper(II) chloride (2.02 g, 15.0 mmol) and of potassium carbonate (2.07 g, 15.0 mmol) in water (40 mL) was added. The obtained mixture was stirred at room temperature for 2.0 h and then evaporated under reduced pressure. The resulting solution was diluted with water (50 mL), extracted with ethyl acetate and the collected organic phases were dried (anhydrous  $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. The resulting oil, containing the crude 2-benzoyloxy-3-fluoro-5-hexenal (2*S*,3*S*)-7', was dissolved in ethanol (40 mL) and added to a suspension of *O*-benzylhydroxylamine hydrochloride (4.79 g, 30.0 mmol),  $\text{Na}_2\text{CO}_3$  (3.18 g, 30 mmol), and molecular sieves (25 mL, beads 4 Å) in the same solvent (100 mL). The reaction mixture was stirred under argon and at room temperature for 16 h, then it was filtered on a celite pad, evaporated under reduced pressure and the residue was dissolved in water and extracted with ethyl acetate. Combined organic phases were dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), evaporated under reduced pressure and purified through flash chromatography (*n*-hexane/ethyl ether 93 : 7) to give 2.13 g (65% overall yield from 7) of pure (*E*,2*S*,3*S*)-8 and (*Z*,2*S*,3*S*)-8 in 10 : 1 ratio. (*E*,2*S*,3*S*)-8: higher *R*<sub>f</sub> isomer;  $[\alpha]_{\text{D}}^{22}$  +35.1 (*c* 0.89,  $\text{CHCl}_3$ ); IR (liq. film) 1215, 1030, 1010, 760;  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 7.46 (1H, dd, *J* = 8.1 and 1.2 Hz, H-1), 5.70 (1H, m, H-5), 5.13 (2H, s, H<sub>2</sub>-9), 5.07 and 5.06 (2H, m, H<sub>2</sub>-6), 4.61 and 4.36 (2H, d, *J* = 11.9 Hz, H<sub>2</sub>-8), 4.56 (1H, dddd, *J* = 47.0, 7.7, 5.2, and 4.0 Hz, H-3), 3.98 (1H, ddd, *J* = 21.1, 8.1, and 4.0 Hz, H-2), and 2.49, 2.42 (2H, m, H<sub>2</sub>-4);  $^{19}\text{F}$  NMR,  $\delta$ : -194.84 (br dddd, *J* = 47.0, 26.9, 21.1, and 17.5 Hz, F-3). Anal. calcd for  $\text{C}_{20}\text{H}_{22}\text{FNO}_2$ : C, 73.38; H, 6.77; N, 4.28. Found: C, 73.42; H, 6.94; N, 4.02. (*Z*,2*S*,3*S*)-8: lower *R*<sub>f</sub> isomer;  $[\alpha]_{\text{D}}^{22}$  +48.1 (*c* 0.3,  $\text{CHCl}_3$ ); IR (liq. film) 1215, 1030, 1010, 690;  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 6.86 (1H, br d, *J* = 6.5 Hz, H-1), 5.70 (1H, m, H-5), 5.12 (2H, s, H<sub>2</sub>-9), 5.08 and 5.06 (2H, m, H<sub>2</sub>-6), 4.70 (1H, ddd, *J* = 24.6, 6.5, and 3.3 Hz, H-2), 4.64 (1H,

dddd,  $J = 46.8, 8.2, 5.2,$  and  $3.3$  Hz, H-3), 4.63 and 4.39 (2H, d,  $J = 11.9$  Hz, H<sub>2</sub>-8), and 2.57 and 2.41 (2H, m, H<sub>2</sub>-4);  $^{19}\text{F}$  NMR,  $\delta$ : -194.55 (br dddd,  $J = 46.8, 27.5, 24.6,$  and  $15.2$  Hz, F-3). Anal. calcd for  $\text{C}_{20}\text{H}_{22}\text{FNO}_2$ : C, 73.38; H, 6.77; N, 4.28. Found: C, 73.51; H, 6.60; N, 4.18.

**(*E*,2*R*,3*S*)-2-Benzyl-3-fluoro-5-hexenal *O*-benzyloxime (8) and (*Z*,2*R*,3*S*)-8.** Eluting system for flash chromatography *n*-hexane/diisopropyl ether 90 : 10; isolated yield 2.03 g [67 % overall yield from (*2S*,3*S*,*R*<sub>S</sub>)-7] of pure (*E*,2*R*,3*S*)-8 and (*Z*,2*R*,3*S*)-8 in 14 : 1 ratio. (*E*,2*R*,3*S*)-8: higher  $R_f$  isomer;  $[\alpha]_{\text{D}}^{22}$  -54.7 ( $c$  1.3,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 7.42 (1H, dd,  $J = 7.8$  and  $1.1$  Hz, H-1), 5.76 (1H, m, H-5), 5.14 (2H, s, H<sub>2</sub>-9), 5.10 and 5.09 (2H, m, H<sub>2</sub>-6), 4.65 (1H, dddd,  $J = 47.6, 6.3, 6.0,$  and  $4.7$  Hz, H-3), 4.58 and 4.38 (2H, d,  $J = 11.8$  Hz, H<sub>2</sub>-8), 3.99 (1H, dddd,  $J = 15.8, 7.8,$  and  $4.7$  Hz, H-2), and 2.45 and 2.40 (2H, m, H<sub>2</sub>-4);  $^{19}\text{F}$  NMR,  $\delta$ : -193.53 (br dddd,  $J = 47.6, 26.6, 22.0,$  and  $15.8$  Hz, F-3). Anal. calcd for  $\text{C}_{20}\text{H}_{22}\text{FNO}_2$ : C, 73.38; H, 6.77; N, 4.28. Found: C, 73.12; H, 6.46; N, 4.06. (*Z*,2*R*,3*S*)-8: lower  $R_f$  isomer;  $[\alpha]_{\text{D}}^{22}$  -35.2 ( $c$  0.32,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 6.76 (1H, dd,  $J = 6.5$  and  $2.0$  Hz, H-1), 5.77 (1H, m, H-5), 5.13 (2H, s, H<sub>2</sub>-9), 5.12 and 5.11 (2H, m, H<sub>2</sub>-6), 4.87 (1H, ddd,  $J = 17.6, 6.5,$  and  $3.3$  Hz, H-2), 4.70 (1H, dddd,  $J = 47.6, 8.5, 4.6,$  and  $3.3$  Hz, H-3), 4.58 and 4.49 (2H, d,  $J = 11.9$  Hz, H<sub>2</sub>-8), and 2.49 and 2.35 (2H, m, H<sub>2</sub>-4);  $^{19}\text{F}$  NMR,  $\delta$ : -190.02 (br dddd,  $J = 47.6, 30.4, 17.6,$  and  $16.8$  Hz, F-3).

**(*2S*,3*S*)-*N*-1-(2-Benzyl-3-fluoro-5-hexenyl)-*O*-benzylhydroxylamine (9).** An aqueous solution of HCl (1 : 1 v/v) was added dropwise to a stirred solution of *O*-benzyloximes (*E*,2*S*,3*S*)-8 and (*Z*,2*S*,3*S*)-8 (2.13 g, 6.5 mmol), sodium cyanoborohydride (1.63 g, 26.0 mmol), and methyl orange (0.1% solution, 1 drop) in methanol (20 mL). The rate of addition was controlled so that the colour of the reaction mixture remained reddish-orange (pH 3-4) for 1 h, and then the reaction was quenched with HCl (7.0 mL). Methanol was removed under reduced pressure, the residue was treated with saturated  $\text{K}_2\text{CO}_3$  and the aqueous phase was extracted with ethyl acetate. Combined organic phases were dried ( $\text{K}_2\text{CO}_3$ ) and evaporated under reduced pressure. Flash chromatography of the residue (*n*-hexane/ethyl ether 80 : 20) gave pure *O*-benzyl-*N*-hexenylhydroxylamine (*2S*,3*S*)-9 (2.06 g, 96% yield):  $[\alpha]_{\text{D}}^{22}$  -50.2 ( $c$  1.0,  $\text{CHCl}_3$ ); IR (liq. film) 1215, 760;  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 5.85 (1H, br signal, NH), 5.79 (1H, m, H-5), 5.11 and 5.10 (2H, m, H<sub>2</sub>-6), 4.68 and 4.63 (2H, d,  $J = 11.4$  Hz, H<sub>2</sub>-8), 4.66 (2H, s, H<sub>2</sub>-9), 4.56 (1H, dddd,  $J = 47.5, 7.9, 4.9,$  and  $4.3$  Hz, H-3), 3.77 (1H, dddd,  $J = 18.9, 7.3, 4.9,$  and  $4.3$  Hz, H-2), 3.13 (1H, dd,  $J = 13.5$  and  $4.3$  Hz, H-1a), 2.97 (1H, dd,  $J = 13.5$  and  $7.3$  Hz, H-1b), and 2.45 and 2.39 (2H, m, H<sub>2</sub>-4);  $^{19}\text{F}$  NMR,  $\delta$ : -193.19 (br dddd,  $J = 47.5, 29.2, 20.1,$  and  $18.9$  Hz, F-3). Anal. calcd for  $\text{C}_{20}\text{H}_{24}\text{FNO}_2$ : C, 72.93; H, 7.34; N, 4.25. Found: C, 73.04; H, 7.18; N, 4.03.

**(*2R*,3*S*)-*N*-1-(2-Benzyl-3-fluoro-5-hexenyl)-*O*-benzylhydroxylamine (9).** Eluting system for flash chromatography *n*-hexane/ethyl ether 80 : 20; isolated yield 94%;  $[\alpha]_{\text{D}}^{22}$  +38.6 ( $c$  0.8,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.1 (10 H, m, ArH), 5.85 (1H, br signal, NH), 5.84 (1H, m, H-5), 5.15 and 5.13 (2H, m, H<sub>2</sub>-6), 4.70 and 4.59 (2H, d,  $J = 11.2$  Hz, H<sub>2</sub>-8), 4.68 (2H, s, H<sub>2</sub>-9), 4.61 (1H, dddd,  $J = 47.6, 8.4, 4.1,$  and  $4.0$  Hz, H-3), 3.91 (1H, dddd,  $J = 16.0, 8.0, 4.0,$  and  $3.6$  Hz, H-2), 3.14 (1H, dd,  $J = 13.7$  and  $3.6$  Hz, H-1a), 2.94 (1H, ddd,  $J = 13.7, 8.0,$  and  $1.0$  Hz, H-1b), and 2.50 and 2.41 (2H, m, H<sub>2</sub>-4);  $^{19}\text{F}$  NMR,  $\delta$ : -189.59 (br dddd,  $J = 47.6, 32.0, 18.4,$  and  $16.0$  Hz, F-3). Anal. calcd for  $\text{C}_{20}\text{H}_{24}\text{FNO}_2$ : C, 72.93; H, 7.34; N, 4.25. Found: C, 72.78; H, 7.51; N, 4.00.

**(*2S*,3*S*,5*S*)-2-Benzyl-5-chloromercurimethyl-3-fluoro-*N*-benzyloxypiperidine (10) and (*2S*,3*S*,5*R*)-10.** Solid mercury(II) trifluoroacetate (3.94 g, 9.2 mmol) was added to a solution of *O*-benzyl-*N*-5-hexen-1-yl-hydroxylamine (*2S*,3*S*)-9 (2.77 g, 8.4 mmol) in anhydrous THF (90 mL) under nitrogen. After 2.0 h at room temperature, saturated aqueous solutions of  $\text{NaHCO}_3$  and of KCl were added in the order and stirring was continued for 2.0 h. The aqueous phase was extracted with ethyl acetate, collected organic layers were dried ( $\text{K}_2\text{CO}_3$ ) and evaporated under reduced pressure. Flash chromatography of the residue (*n*-hexane/ethyl ether 50 : 50) afforded 4.55 g (96% yield) of chloromercurimethylpiperidines (*2S*,3*S*,5*S*)-10 and (*2S*,3*S*,5*R*)-10 in 62 : 38 ratio as diastereoisomerically pure compounds. (*2S*,3*S*,5*S*)-10: lower  $R_f$  isomer;  $[\alpha]_{\text{D}}^{22}$  -40.1 ( $c$  1.3,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 5.0-4.3 (5H, m, H-3, H<sub>2</sub>-8, H<sub>2</sub>-9), 4.1-3.4 (2H, m, H-1 $\beta$  and H-2), 3.02 (1H, m, H-5), and 2.6-1.7 (5H, m, H-1 $\alpha$ , H<sub>2</sub>-4, and H<sub>2</sub>-



6);  $^{19}\text{F}$  NMR,  $\delta$ : -177.36 and -184.69 (br d,  $J = 49.8$  Hz both, F-3 $\beta$ , 1 : 2 ratio);  $^{13}\text{C}$  NMR (DEPT),  $\delta$ : 129.34, 128.83, 128.62, 128.47, 127.82, and 127.80 (ArCH), 93.84 and 92.42 (C-3, 1 : 2), 76.37 and 73.52 (C-2, 2 : 1), 75.19 and 72.92 (C-8 and/or C-9), 62.17 and 61.08 (C-5, 2 : 1), 56.40 and 54.75 (C-1, 2 : 1), 38.55 and 34.11 (C-4, 2 : 1), and 36.99 and 35.02 (C-6, 2 : 1). Anal. calcd for  $\text{C}_{20}\text{H}_{23}\text{ClFHgNO}_2$ : C, 42.56; H, 4.11; N, 2.48. Found: C, 42.71; H, 4.30; N, 2.19. (2*S*,3*S*,5*R*)-10: higher  $R_f$  isomer;  $[\alpha]_{\text{D}}^{22} +74.4$  (c 0.53,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 4.70 (2H, s, H<sub>2</sub>-9), 4.60 (1H, m, H-3), 4.60 and 4.54 (2H, d,  $J = 12.2$  Hz, H<sub>2</sub>-8), 3.76 (1H, br s, H-2), 3.39 and 2.86 (2H, br d,  $J = 11.5$  Hz, H<sub>2</sub>-1), 3.25 (1H, m, H-5), and 2.5-1.5 (4H, m, H<sub>2</sub>-4 and H<sub>2</sub>-6);  $^{19}\text{F}$  NMR,  $\delta$ : -187.62 (br dd,  $J \sim 47$  and 40 Hz, F-3 $\beta$ );  $^{13}\text{C}$  NMR (DEPT),  $\delta$ : 129.34, 128.74, 128.56, 128.39, 127.88, and 127.66 (ArCH), 86.34 (C-3,  $J_{\text{C,F}} = 175$  Hz), 75.09 and 71.25 (C-8 and/or C-9), 74.60 (C-2,  $J_{\text{C,F}} = 26$  Hz), 59.28 (C-5), 52.69 (C-1), 37.20 (C-6), and 36.83 (C-4,  $J_{\text{C,F}} = 24$  Hz). Anal. calcd for  $\text{C}_{20}\text{H}_{23}\text{ClFHgNO}_2$ : C, 42.56; H, 4.11; N, 2.48. Found: C, 42.77; H, 4.31; N, 2.44.

**(2*R*,3*S*,5*S*)-2-Benzoyloxy-5-chloromercuriomethyl-3-fluoro-*N*-benzyloxypiperidine (10) and (2*R*,3*S*,5*R*)-10.** Eluting system for flash chromatography toluene/ethyl acetate 95 : 5; isolated yield 3.89 g (95% yield) of pure (2*R*,3*S*,5*S*)-10 and (2*R*,3*S*,5*R*)-10 in 64 : 36 ratio. (2*R*,3*S*,5*S*)-10: higher  $R_f$  isomer;  $[\alpha]_{\text{D}}^{22} -59.8$  (c 1.1,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 4.70 and 4.66 (2H, br d,  $J = 12.3$  Hz, H<sub>2</sub>-8), 4.66 (2H, br s, H<sub>2</sub>-9), 4.66 (1H, br d,  $J = 48.0$  Hz, H-3), 3.91 (1H, m, H-2), 3.44 (1H, br ddd,  $J = 11.2$ , 5.6, and 4.9 Hz, H-1 $\beta$ ), 3.04 (1H, m, H-5), 2.60 (1H, br d,  $J = 11.2$  Hz, H-1 $\alpha$ ), 2.28 and 2.05 (2H, m, H<sub>2</sub>-4), and 2.10, 2.00 (2H, m, H<sub>2</sub>-6); NOE experiments (pyridine- $d_5$ ): irradiation of H-1 $\alpha$  enhanced, *inter alia*, H-3 $\alpha$  (3%) and H-5 $\alpha$  (1.5%);  $^{19}\text{F}$  NMR,  $\delta$ : -190.60 (br signal, F-3 $\beta$ );  $^{13}\text{C}$  NMR (DEPT),  $\delta$ : 129.36, 128.74, 128.47, 128.34, 127.80, and 127.63 (ArCH), 89.07 (C-3), 75.25 and 71.56 (C-8 and/or C-9), 73.27 (C-2), 61.75 (C-5), 53.90 (C-1), 37.25 (C-6), and 35.33 (C-4). Anal. calcd for  $\text{C}_{20}\text{H}_{23}\text{ClFHgNO}_2$ : C, 42.56; H, 4.11; N, 2.48. Found: C, 42.81; H, 4.34; N, 2.24. (2*R*,3*S*,5*R*)-10: lower  $R_f$  isomer;  $[\alpha]_{\text{D}}^{22} +44.1$  (c 0.46,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.1 (10H, m, ArH), 5.2-4.4 (5H, m, H-3, H<sub>2</sub>-8, and H<sub>2</sub>-9), 4.1-2.7 (4H, m, H-2, H-5, and H<sub>2</sub>-1), and 2.5-1.1 (4H, m, H<sub>2</sub>-4 and H<sub>2</sub>-6);  $^{19}\text{F}$  NMR,  $\delta$ : -201.99 and -204.73 (br dddd,  $J = 51.5$ , 42.5, 28.4, and 9.9 Hz and br ddd,  $J \sim 52$ , 45, and 32 Hz, respectively, F-3 $\beta$ , 2 : 1 ratio);  $^{13}\text{C}$  NMR (DEPT),  $\delta$ : 129.33, 128.84, 128.58, 128.47, 128.03, and 127.82 (ArCH), 87.28 and 85.52 (C-3, 1 : 2), 75.00, 74.89 and 71.16, 71.05 (C-8 and/or C-9, 1 : 2 and 2 : 1 ratio), 74.20 and 69.50 (C-2, 2 : 1), 58.75 and 56.60 (C-5, 2 : 1), 53.20 and 51.24 (C-1, 2 : 1), 38.38 and 33.37 (C-4, 2 : 1), and 37.26 and 35.35 (C-6, 2 : 1). Anal. calcd for  $\text{C}_{20}\text{H}_{23}\text{ClFHgNO}_2$ : C, 42.56; H, 4.11; N, 2.48. Found: C, 42.44; H, 4.25; N, 2.21.

**(2*S*,3*S*,5*S*)-2-Benzoyloxy-3-fluoro-5-hydroxymethyl-*N*-benzyloxypiperidine (11).** Sodium borohydride (45 mg, 1.19 mmol) was added to a solution of chloromercuriomethylpiperidine (2*S*,3*S*,5*S*)-10 (30 mg, 0.053 mmol) in a perfluorotributylamine/hexafluoroisopropanol mixture (3 mL, 3 : 2 v/v) where oxygen was bubbled. The reaction was stirred for 10 min, then saturated aqueous solution of  $\text{NH}_4\text{Cl}$  and of  $\text{Na}_2\text{CO}_3$  were added. The resulting heterogeneous system was extracted with ethyl acetate, collected organic phases were dried (anhydrous  $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. Flash chromatography of the residue (*n*-hexane/ethyl ether 20 : 80) afforded 14 mg (74% yield) of the hydroxymethylpiperidine (2*S*,3*S*,5*S*)-11 in pure form:  $[\alpha]_{\text{D}}^{22} -18.2$  (c 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 4.9-4.3 (5H, m, H-3, H<sub>2</sub>-8, and H<sub>2</sub>-9), 4.1-3.4 (4H, m, H-1 $\beta$ , H-2, and H<sub>2</sub>-6), 2.9-2.4 (2H, m, H-1 $\alpha$  and H-5), and 2.1-1.6 (3H, m, H<sub>2</sub>-4 and OH-6);  $^{19}\text{F}$  NMR,  $\delta$ : -177.60 and -184.91 (br d,  $J = 50.6$  and 51.4 Hz, F-3 $\beta$ , 1 : 1.5). Anal. calcd for  $\text{C}_{20}\text{H}_{24}\text{FNO}_3$ : C, 69.55; H, 7.00; N, 4.06. Found: C, 69.83; H, 7.34; N, 3.90. When dimethylformamide was used as solvent (2*S*,3*S*,5*R*)-2-benzoyloxy-3-fluoro-5-methyl-*N*-benzyloxypiperidine (13) and (2*S*,3*S*)-*N*-1-(2-benzoyloxy-3-fluoro-5-hexenyl)-*O*-benzylhydroxylamine (9) were formed in 78 and 18% yield, respectively. (2*S*,3*S*,5*R*)-13:  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 4.9-4.3 (5H, m, H-3, H<sub>2</sub>-8, and H<sub>2</sub>-9), 4.0-3.4 (2H, m, H-1 $\beta$  and H-2), 2.9-2.3 (2H, m, H-1 $\alpha$  and H-5), 2.2-1.8 (2H, m, H<sub>2</sub>-4), and 1.22 (3H, d,  $J = 6.3$  Hz, H<sub>3</sub>-6);  $^{19}\text{F}$  NMR,  $\delta$ : -177.20 and -184.94 (br dd,  $J = 50.5$  and 49.8 Hz, F-3 $\beta$ , 1 : 2).

**(2*S*,3*S*,5*R*)-2-Benzoyloxy-3-fluoro-5-hydroxymethyl-*N*-benzyloxypiperidine (11).** Eluting system for flash chromatography *n*-hexane/ethyl ether 40 : 60; isolated yield 70%;  $[\alpha]_{\text{D}}^{22} +33.7$  (c 0.75,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 4.71 and 4.70 (2H, d,  $J = 11.0$  Hz, H<sub>2</sub>-9), 4.64 (1H, br d,  $J = 47.0$  Hz, H-

3), 3.79 (1H, dd,  $J = 11.4$  and  $2.9$  Hz, H-6a), 3.74 (1H, m, H-2), 3.56 (1H, br dd,  $J = 11.4$  and  $4.6$  Hz, H-6b), 3.42 (1H, dddd,  $J = 12.2, 3.4, 1.5$ , and  $1.0$  Hz, H-1 $\beta$ ), 2.95 (1H, m, H-5), 2.89 (1H, ddd,  $J = 12.2, 4.5$ , and  $2.5$  Hz, H-1 $\alpha$ ), 2.08 (1H, dddd,  $J = 42.7, 14.8, 11.2$ , and  $2.6$  Hz, H-4 $\alpha$ ), 2.00 (1H, br signal, OH-6), and 1.94 (1H, m, H-4 $\beta$ );  $^{19}\text{F}$  NMR,  $\delta$ : -188.32 (br dd,  $J \sim 47.0$  and  $42.7$  Hz, F-3 $\beta$ ). Anal. calcd for  $\text{C}_{20}\text{H}_{24}\text{FNO}_3$ : C, 69.55; H, 7.00; N, 3.85. Found: C, 69.71; H, 7.00; N, 4.03.

**(2*S*,3*S*,5*S*)-2-Benzoyloxy-3-fluoro-5-methyl-*N*-benzyloxypiperidine (13).** Eluting system for flash chromatography *n*-hexane/ethyl ether 90 : 10; isolated yield 80%;  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, m, ArH), 4.79 and 4.73 (2H, br d,  $J = 10.9$  Hz, H<sub>2</sub>-9), 4.57 and 4.54 (2H, d,  $J = 12.3$  Hz, H<sub>2</sub>-8), 4.56 (1H, br d,  $J \sim 47$  Hz, H-3), 3.72 (1H, m, H-2), 3.34 and 2.82 (2H, br d,  $J = 11.5$  Hz, H<sub>2</sub>-1), 2.94 (1H, m, H-5), 2.1-1.6 (2H, m, H<sub>2</sub>-4), and 1.27 (3H, d,  $J = 6.5$  Hz, H<sub>3</sub>-6);  $^{19}\text{F}$  NMR,  $\delta$ : -188.07 (br dd,  $J \sim 47$  and  $40$  Hz).

**(2*R*,3*S*,5*S*)-2-Benzoyloxy-3-fluoro-5-hydroxymethyl-*N*-benzyloxypiperidine (11).** Eluting system for flash chromatography *n*-hexane/ethyl ether 35 : 65; isolated yield 74%;  $[\alpha]_{\text{D}}^{22}$  -9.9 (*c* 0.50,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.4-7.2 (10H, m, ArH), 4.72 and 4.70 (2H, br d,  $J = 10.9$  Hz, H<sub>2</sub>-9), 4.70 (1H, dddd,  $J = 48.4, 10.0, 4.5$ , and  $2.9$  Hz, H-3), 4.66 and 4.61 (2H, br d,  $J = 12.3$  Hz, H<sub>2</sub>-8), 3.88 (1H, m, H-2), 3.70 (2H, br s, H<sub>2</sub>-6), 3.43 (1H, ddd,  $J = 12.0, 5.5$ , and  $5.0$  Hz, H-1 $\beta$ ), 2.84 (1H, m, H-5), 2.70 (1H, br d,  $J = 12.0$  Hz, H-1 $\alpha$ ), 2.23 (1H, dddd,  $J = 13.3, 10.0, 9.2$ , and  $9.0$  Hz, H-4 $\beta$ ), 2.20 (1H, br s, OH-6), and 1.97 (1H, m, H-4 $\alpha$ );  $^{19}\text{F}$  NMR,  $\delta$ : -191.44 (br m, F-3 $\beta$ ). Anal. calcd for  $\text{C}_{20}\text{H}_{24}\text{FNO}_3$ : C, 69.55; H, 7.00; N, 4.06. Found: C, 69.79; H, 7.31; N, 3.85.

**(2*R*,3*S*,5*R*)-2-Benzoyloxy-3-fluoro-5-hydroxymethyl-*N*-benzyloxypiperidine (11).** Eluting system for flash chromatography *n*-hexane/ethyl ether 20 : 80; isolated yield 73%;  $[\alpha]_{\text{D}}^{22}$  +21.9 (*c* 1.10,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR,  $\delta$ : 7.5-7.2 (10H, br m, ArH), 5.3-4.5 (5H, br m, H-3, H<sub>2</sub>-8, and H<sub>2</sub>-9), 4.1-2.7 (6H, br m, H-2 and H-5, and H<sub>2</sub>-1 and H<sub>2</sub>-6), and 2.1-1.5 (3H, br m, H<sub>2</sub>-4 and OH-6);  $^{19}\text{F}$  NMR,  $\delta$ : -203.34 and -205.76 (br m,  $J \sim 50, 40$ , and  $30$  Hz both, 1.5 : 1). Anal. calcd for  $\text{C}_{20}\text{H}_{24}\text{FNO}_3$ : C, 69.55; H, 7.00; N, 4.06. Found: C, 69.71; H, 7.24; N, 3.82.

**1,3,4-Trideoxy-3-fluoronojirimycin (3a).** A solution of dibenzylated piperidine (2*S*,3*S*,5*S*)-11 (385 mg, 1.11 mmol) in trifluoroacetic acid (5 mL) was shaken with palladium on activated charcoal (10%) under hydrogen (4 atm) for 24 h at room temperature. The reaction mixture was filtered, evaporated under reduced pressure, and flash chromatographed (ethyl acetate/methanol 85/15; then methanol) to give 181 mg (68% yield) of pure (2*S*,3*S*,5*S*)-2-benzyloxy-3-fluoro-5-hydroxymethylpiperidine (12) ( $^1\text{H}$  and  $^{19}\text{F}$  NMR are reported in the Table) and 28 mg (17% yield) of pure 1,3,4-trideoxy-3-fluoronojirimycin (3a),  $[\alpha]_{\text{D}}^{22}$  +21.3 (*c* 0.60,  $\text{CF}_3\text{COOH}$ );  $^1\text{H}$  and  $^{19}\text{F}$  NMR are reported in the table. On shaking the reaction mixture for 24 h at 4 atm, fluoronojirimycin 3a was exclusively isolated in 81% yield.

**1,3,4-Trideoxy-3-fluoro-5-*epi*-nojirimycin (3b).** Eluting system for flash chromatography ethyl acetate/methanol 80 : 20 then methanol; isolated yield 80%;  $[\alpha]_{\text{D}}^{22}$  +3.9 (*c* 1.00,  $\text{CF}_3\text{COOH}$ );  $^1\text{H}$  and  $^{19}\text{F}$  NMR are reported in the Table.

**1,3,4-Trideoxy-3-fluoromannojirimycin (4a).** Eluting system for flash chromatography ethyl acetate/methanol 60 : 40 then methanol; isolated yield 77%;  $[\alpha]_{\text{D}}^{22}$  -23.9 (*c* 0.60, acetone);  $^1\text{H}$  and  $^{19}\text{F}$  NMR are reported in the Table.

**1,3,4-Trideoxy-3-fluoro-5-*epi*-mannojirimycin (4b).** Eluting system for flash chromatography ethyl acetate/methanol 80 : 20 then methanol; isolated yield 84%;  $[\alpha]_{\text{D}}^{22}$  +33.0 (*c* 0.48, acetone);  $^1\text{H}$  and  $^{19}\text{F}$  NMR are reported in the Table.

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