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# An Enantiospecific Entry to Fluoro Substituted Aminocyclopentanols through Intramolecular Nitrile Oxide, Nitrone, and Oxime Cycloaddition Reactions

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**Abstract:** Starting from (2*R*,3*S*)-2-benzyloxy-3-fluoro-5-hexenale **2** and its (2*R*,3*R*) epimer, cyclopentanoisoxazolidines **4** and **7** are obtained with complete diastereoselectivity through nitrone and oxime intramolecular cycloaddition reactions. In contrast, cyclopentanoisoxazolines **6** are formed with only medium stereoselectivity through intramolecular nitrile oxide cycloaddition reactions. Further elaboration of these bicyclic compounds affords fluoro substituted aminocyclopetanols **8** and **10** in enantiomerically and diastereoisomerically pure form.

A fluorine atom is well known to be able to mimic a hydroxy group of a bioactive substance.[1] Over the last few years we have been studying this "isopolar substitution" and we have synthesized, for instance, various 4-deoxy-4-fluoromuscarines in enantiomerically pure form. In vitro and in vivo tests on these compounds have shown that substitution of fluorine for hydroxyl does not greatly influence the pharmacological profile of the parent drug, minor changes occurring only in some of the receptor-ligand interactions.[2]

Recently, we have reported the asymmetric synthesis of some deoxy-fluoro analogues of nojirimycin,[3] a particularly interesting glycosidase inhibitor characterized, from the structural point of view, by the presence of an amino group and various hydroxy residues. These structural features play an important role in securing a high affinity to the target enzyme and in conferring a high inhibitory activity to the molecule by mimicking the glycosyl cation, or its protonated polysaccharide precursor. It has been observed recently that the most potent and specific competitive inhibitors of some glycoside-processing enzymes belong to the general class of the polyhydroxylated aminocyclopentanes.[4] This is the case, for instance, of mannostatin A (α-D mannosidase inhibitor),[5] allosamidin (chitinase inhibitor),[6] trehazolin (α, α-trehalase inhibitor).[7] The same holds for other structurally related natural[8] and synthetic[9] compounds, all of which are polyhydroxylated cyclopentanes carrying an amino and/or hydroxymethyl residue.

As a continuation of our interest in the inhibitors of glycoprotein processing enzymes, we have achieved an enantiospecific synthesis of fluorinated aminocyclopentanols **8** and **10**. In our compounds one of the hydroxy groups on the cyclopentane ring of the parent inhibitors has been replaced by a fluorine atom, while other structural features have remained unchanged. The key-step in the synthetic sequences here described is an intramolecular 1,3-dipolar cycloaddition reaction of nitrile oxides,[10] nitrones,[10a,b, 11] or oximes.[12] These approaches are very powerful tools for the synthesis of highly functionalized systems in a regio and stereocontrolled manner.

## Results and Discussion

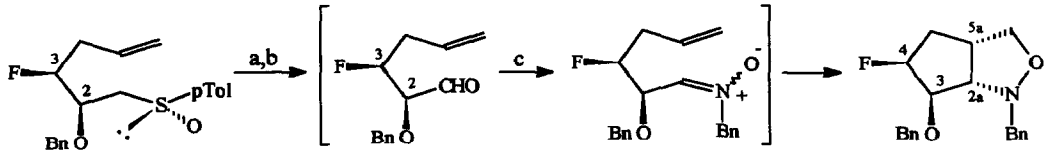
*Cycloaddition Reactions.* Several examples are reported in the literature describing the synthesis of five-membered carbocycles starting from 5-enals through formation of nitrones or nitrile oxides which are intramolecularly trapped in situ by the alkene group to give cyclopentanoisoxazolidines and cyclopentanoisoxazolines, respectively.[13]

By treating the (2*S*,3*S*,$R_S$)-1-*p*-tolylsulfinylhexene **1**[14] with trifluoroacetic anhydride and 2,4,6-trimethylpyridine a clean Pummerer rearrangement occurs[15] and gives an intermediate 1-((trifluoroacetyl)oxy)-1-toluenesulfenyl-5-hexene. This masked aldehyde is reacted with copper(II) chloride in basic medium to afford the crude free (2*R*,3*S*)-2-benzyloxy-3-fluorohexenal **2** which is the hey intermediate in our intramolecular cyloaddition reactions. On treatment of this aldehyde with *N*-benzyl-hydroxylamine in refluxing methanol, the intermediate nitrone **3** is formed and isoxazolidine (2a*S*,3*R*,4*S*,5a*S*)-**4** is isolated exclusively in 68% overall yield from **1**. Similarly, the cyclopentano-isoxazolidine (2a*S*,3*R*,4*R*,5a*S*)-**4**, having a *cis* ring junction and bearing the large group on C-3 located on the less congested convex side of the bicyclic product **4**, is the unique product formed (64% isolated yield) starting from the sulfinyl-hexene **1** having the (2*S*,3*R*,$R_S$) absolute configuration (Schemes 1, 4).

It is interesting to observe that the intramolecular cycloaddition reactions of *N*-methyl nitrones of 5-hexenals derived from glucose,[16] mannose,[9,17] galactose,[18] and ribose[19] always occur with a stereochemical course strictly similar to that described above (*cis* ring fusion, the isoxazolidine cycle *trans* to the protected hydroxyl group on C-2 of the starting hexenal), as if the configuration at C-3, and possibly on C-4, of the starting aldehyde has no effect on the stereoselectivity of the process which is strictly controlled by the stereochemistry at C-2.

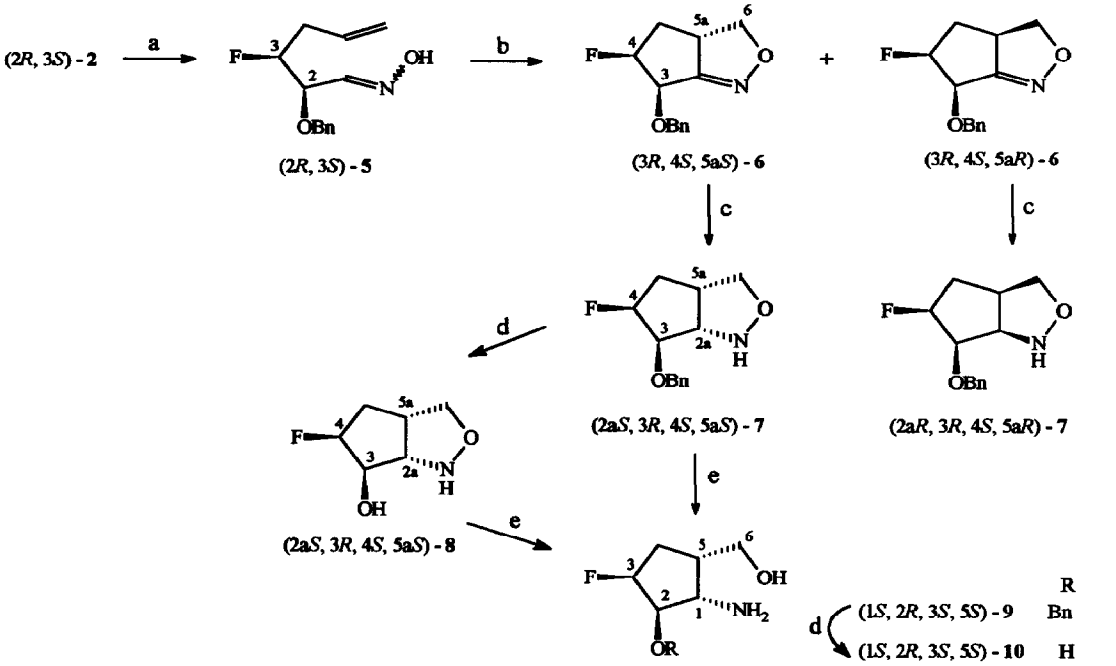
When the (2*R*,3*S*)-aldehyde **2** is reacted with hydroxylamine hydrochloride a 1 : 1 mixture of the corresponding *E* and *Z* oximes (2*R*,3*S*)-**5** is formed. Single diastereoisomers can be easily separated by

**Scheme 1:** (a) trifluoroacetic anhydride, 2,4,6-trimethylpyridine, acetonitrile; (b) copper(II) chloride, water; (c) *N*-benzyl hydroxylamine hydrochloride, sodium carbonate, methanol, reflux.




(2*S*, 3*S*, $R_S$) - **1** (2*R*, 3*S*) - **2** **3** (2a*S*, 3*R*, 4*S*, 5a*S*) - **4**

**Scheme 2:** (a) hydroxylamine hydrochloride, sodium carbonate, ethanol; (b) sodium hypochlorite, triethylamine, dichloromethane; (c) sodium cyanoborohydride, hydrochloric acid, methanol; (d) hydrogen, palladium on activated charcoal, trifluoroacetic acid; (e) hydrogen, platinum(II) oxide, methanol.

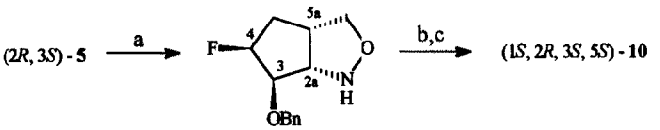



flash chromatography, but further reactions can be performed directly on the *E/Z* mixture. For instance, the oxidation with sodium hypochlorite and catalytic triethylamine affords the corresponding nitrile oxide[20] which undergoes an intramolecular nitrile oxide cycloaddition process (INOC) (Scheme 2). The two cyclopentanoisoxazolines (3*R*,4*S*,5a*S*)-**6** and (3*R*,4*S*,5a*R*)-**6** are formed in high yields and in a 4 : 1 ratio, the diastereoisomer having the benzyloxy residue on C-3 *trans* to the oxymethylene C-6 residue being formed preferentially.

The INOC reaction performed starting from the epimeric aldehyde (2*R*,3*R*)-**2** follows a similar stereochemical course. The isoxazoline with the benzyloxy group on C-2 *trans* to the oxymethylene C-6 residue is the product formed preferentially, but the diastereoselectivity of the process is lower than that previously observed ((3*R*,4*R*,5a*S*)-**6** : (3*R*,4*R*,5a*R*)-**6** ratio is 7 : 3). The same stereochemical preference has been observed in the INOC reaction of 2-methyl-[21] and 2-phthalimido-[22] hexenals and a force field model has been employed to account for the observed product ratios.[23]

Finally, unsaturated oximes have been reported to undergo intramolecular oxime-olefin cycloaddition reactions (IOOC).[12] An initial proton transfer from oxygen to nitrogen has been postulated to occur giving an intermediate NH nitrone species which is trapped via an intramolecular cycloaddition reaction.[24] When (2*R*,3*S*)-oximes **5** are heated in acetonitrile-dimethylformamide solution, the clean formation of the (2a*S*,3*R*,4*S*,5a*S*)-cyclopentanoisoxazolidine **7** is observed and similarly the (2*R*,3*R*)-oximes **5** afford the corresponding bicyclic product (2a*S*,3*R*,4*R*,5a*S*)-**7** (Schemes 3, 4). For both

**Scheme 3:** (a) dimethylformamide-acetonitrile, reflux; (b) hydrogen, palladium on activated charcoal (10%), trifluoroacetic acid; (c) hydrogen, platinum(II) oxide, methanol.




(2a*S*, 3*R*, 4*S*, 5a*S*) - 7

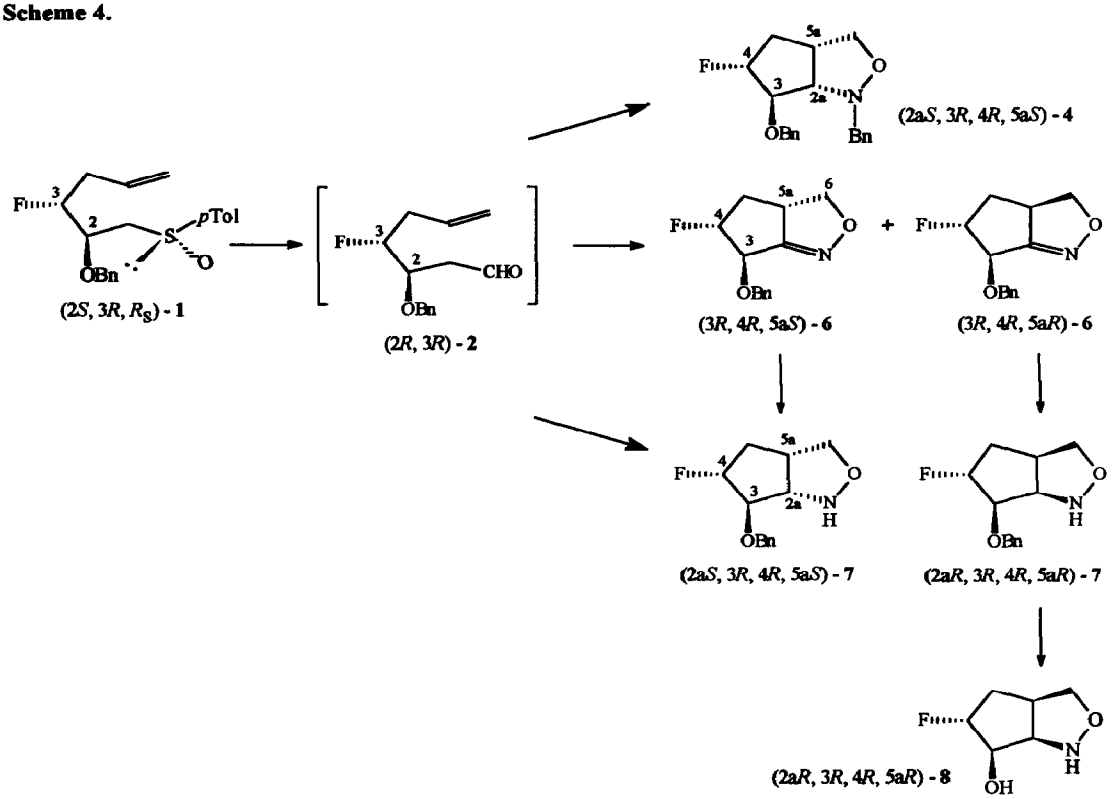
substrates a unique product is formed and the diastereoselectivity of the process is that observed previously in the 1,3-dipolar cycloaddition reaction of corresponding *N*-benzyl-nitrones (Schemes 1, 4). The same preference for a *cis* ring fusion and a *trans* relationship between the substituent on C-3 and the isoxazolidine ring has been reported for IOOC reactions of other 2-substituted-5-enals.[24]

*Synthesis of aminocyclopentanols.* On treatment of isoxazolines **6** with sodium cyanoborohydride at pH 3[25] a stereospecific reduction of the C=N double bond occurs in quantitative yields and, independently from the chirality at C-3 and C-4, the four different diastereoisomeric precursors **6** give exclusively the corresponding *cis* ring fused cyclopentanoisoxazolidines **7**. Target aminocyclopentanols **10** are best obtained by performing debenzylation and hydrogenolysis of the oxygen-nitrogen bond of compounds **7** in two different steps. For instance, on treatment of (2a*S*,3*R*,4*S*,5a*S*)-3-benzyloxyisoxazolidine **7** with hydrogen and Pd on activated charcoal, the (2a*S*,3*R*,4*S*,5a*S*)-3-hydroxyisoxazolidine **8** is isolated, while when hydrogen and $Pt_2O$ are employed, the (1*S*,2*R*,3*S*,5*S*)-2-benzyloxyaminocyclopentanol **9** is formed. When applied successively, the two hydrogenolyses afford the fluoro substituted aminocyclopentanol (1*S*,2*R*,3*S*,5*S*)-**10** in enantiomerically and diastereoisomerically pure form. Similarly, (2a*R*,3*R*,4*R*,5a*R*)-**8** is obtained through debenzylation of (2a*R*,3*R*,4*R*,5a*R*)-**7**.

*Structural analyses.* The structures and the stereochemistries of compounds **4**, **6-10** were determined by analyses of their $^1H$, $^{13}C$, and $^{19}F$ NMR spectra (Tables 1 and 2) and $^1H$-{$^1H$} and $^1H$-{$^{19}F$} NOE difference experiments. The absolute configurations of these compounds were assigned by establishing the relative stereochemistries between the newly formed stereocentres and those already present in starting materials **1**.[14] The configurations at the oxygenated and fluorinated carbons of compounds **1** remained unchanged throughout the performed reactions, no epimerization was in fact occurring during the cyclization step or in successive ones. This was proven, among others, by the fact that in all cyclization products **4**, **6 - 8** obtained from *anti*[26] (2*S*,3*S*,$R_S$)-**1** the fluorine atom resonates at higher fields than in corresponding epimers obtained starting from *syn* (2*S*,3*R*,$R_S$)-**1**. It has already been observed on strictly related cyclic fluorhydrins[27] that in the *cis* array fluorine is shifted upfield with respect to the *trans* one and it is interesting to observe that, as we have already discussed,[28] this trend is reversed in acyclic precursors **1**.

The (*S*) absolute configuration at C-2a and C-5a of cyclopentanoisoxazolidines (2a*S*,3*R*,4*S*,5a*S*)-**4** and (2a*S*,3*R*,4*R*,5a*S*)-**4**, that is to say the *cis* ring junction, was revealed by the NOEs observed for both H-2a and H-5a upon irradiation of F-4β and H-4β, respectively. An analogous behaviour was observed for (3*R*,4*S*,5a*S*)-**6** and (2a*S*,3*R*,4*S*,5a*S*)-**7**, both bearing F-4β and H-5a, and possibly H-2a, in a *cis* relationship, and for (3*R*,4*R*,5a*R*)-**6** and (2a*R*,3*R*,4*R*,5a*R*)-**7** in which the 1,3-*cis* related nuclei are F-4α, H-5a, and possibly H-2a.

**Scheme 4.**




Finally, the mutual NOEs observed in cyclopentanoisoxazolidines (2a*R*,3*R*,4*S*,5a*R*)-7 and (2a*S*,3*R*,4*R*,5a*S*)-7 between H-2a and both H-4 and H-5a established their stereochemistries and, as a consequence, those of the starting compounds (3*R*,4*S*,5a*R*)-4 and (3*R*,4*R*,5a*S*)-4.

## Experimental

**General.** $^{1}H$, $^{13}C$, $^{19}F$ NMR spectra were recorded on a Bruker CPX-300 or a Bruker AC 250L spectrometer in $CDCl_3$ unless otherwise stated. $C_6F_6$ was used as internal standard ($\delta_F$ -162.90 ppm) for $^{19}F$. Optical rotations were determined on a Jasco DIP-181 polarimeter. Mps are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 $F_{254}$ Merck; flash column chromatographies were performed with silica gel 60 (60-200 μm, Merck). A detailed procedure is described for compounds obtained starting from (2*S*,3*S*,$R_S$)-1 (Schemes 1-3). The same experimental procedure was used for elaboration of (2*S*,3*R*,$R_S$)-1 (Scheme 4).

**Pummerer Rearrangement of (2*S*,3*S*)-2-Benzyloxy-3-fluoro-1(*R*)-[(4-methyphenyl)sulfinyl]5-hexene (1) to give (2*R*,3*S*)-2-Benzyloxy-3-fluoro-5-hexenal (2).** A solution of trifluoroacetic anhydride (5.64 mL, 40.0 mmol) in acetonitrile (160 mL) was added dropwise into a solution of (2*S*,3*S*,$R_S$)-1 (6.92 g, 20.0 mmol) and of 2,4,6-trimethylpyridine (7.94 mL, 60.0 mmol) in the same solvent (400 mL) with stirring at 0 °C under argon. After 30 min at room temperature a solution of copper (II) chloride (4.04 g, 30.0 mmol) and of potassium carbonate (4.14 g, 30.0 mmol) in water (150 mL) was added. The resulting

**Table 1.** $^{1}H$ and $^{19}F$ NMR Chemical Shifts (δ, ppm) of Compounds **4**, **6** and **7** in $CDCl_3$; Coupling Constants ($J_{H,H}$ and $J_{H,F}$, Hz) for Spectra in $CDCl_3$.

| Atom no. | (2a*S*,3*R*,4*S*,5a*S*)-**4** | (2a*S*,3*R*,4*R*,5a*S*)-**4** | (3*R*,4*S*,5a*S*)-**6** | (3*R*,4*S*,5a*R*)-**6** | (3*R*,4*R*,5a*S*)-**6**[a] | (3*R*,4*R*,5a*R*)-**6** | (2a*S*,3*R*,4*S*,5a*S*)-**7**[b] | (2a*R*,3*R*,4*S*,5a*R*)-**7**[b] | (2a*S*,3*R*,4*R*,5a*S*)-**7**[b,c] | (2a*R*,3*R*,4*R*,5a*R*)-**7**[b,d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 2a | 3.80 | 3.48 | | | | | 4.05 | 4.00 | 3.79 | 3.88 |
| 3 | 3.89 | 3.95 | 4.47 | 4.58 | 4.51 | 4.61 | 3.75 | 3.90 | 3.91 | 3.90 |
| 4 | 5.04 | 4.86 | 5.25 | 5.09 | 5.22 | 5.32 | 5.03 | 5.08 | 4.88 | 5.08 |
| 5α | 1.68 | 1.85 | 1.78 | 2.39 | 1.72 | 2.33 | 1.56 | 1.85 | 1.76 | 1.97 |
| 5β | 2.34 | 2.33 | 2.43 | 1.96 | 2.65 | 1.98 | 2.36 | 2.03 | 2.35 | 1.93 |
| 5a | 3.37 | 3.12 | 4.13 | 3.65 | 3.89 | 4.08 | 3.26 | 3.10 | 2.98 | 3.07 |
| 6α | 3.62 | 3.68 | 3.79 | 4.65 | 3.96 | 4.63 | 3.87 | 4.36 | 3.86 | 3.75 |
| 6β | 4.13 | 4.12 | 4.65 | 3.90 | 4.69 | 3.87 | 3.44 | 3.56 | 3.55 | 3.65 |
| 7a[e] | 4.56 | 4.48 | 4.79 | 4.97 | 4.68 | 4.95 | 4.71 | 4.78 | 4.72 | 4.72 |
| 7b[e] | 4.48[f] | 4.36[g] | 4.67 | 4.81 | 4.56 | 4.73 | 4.71 | 4.69 | 4.69 | 4.72 |
| F-4 | -200.83 | -186.08 | -196.41 | -188.71 | -177.41 | -177.65 | -201.32 | -191.11 | -188.50 | -188.32 |
| *J* | | | | | | | | | | |
| 2a,3 | 5.5 | 4.8 | | | | | 6.5 | 6.5 | 5.8 | 7.0 |
| 2a,5a | 8.7 | 9.0 | | | | | 8.9 | 8.4 | 9.0 | 7.5 |
| 3,4 | 2.8 | 5.8 | 4.4 | 4.8 | 2.5 | 1.5 | 3.2 | 3.4 | 7.3 | 6.6 |
| 4,5α | 3.5 | 7.9 | 5.8 | 5.2 | 5.7 | 1.5 | 3.3 | 4.0 | 9.7 | 8.7 |
| 4,5β | 2.5 | 6.4 | 3.8 | 3.2 | 6.6 | 5.2 | 1.8 | 1.9 | 6.9 | 7.1 |
| 5α,5β | 14.6 | 13.5 | 14.0 | 14.9 | 13.6 | 14.2 | 14.7 | 15.3 | 12.7 | 13.4 |
| 5α,5a | 7.8 | 7.0 | 8.5 | 9.5 | 8.9 | 7.9 | 8.8 | 8.6 | 9.3 | 7.8 |
| 5β,5a | 8.9 | 8.5 | 9.0 | 6.4 | 8.6 | 10.9 | 8.7 | 2.1 | 8.6 | 3.4 |
| 5a,6α | 2.7 | 3.4 | 12.6 | 9.8 | 12.0 | 9.7 | 1.0 | 8.8 | 1.7 | 7.2 |
| 5a,6β | 7.1 | 7.5 | 9.8 | 13.3 | 10.2 | 12.5 | 6.3 | 7.9 | 6.1 | 2.6 |
| 6α,6β | 9.0 | 8.7 | 8.2 | 8.0 | 8.2 | 7.8 | 8.9 | 8.1 | 8.5 | 8.2 |
| 7a,7b[e] | 11.6 | 11.5 | 11.9 | 12.0 | 11.7 | 11.6 | h | 11.9 | 12.2 | 11.8 |
| F,3 | 24.0 | 14.8 | 9.6 | 17.0 | 15.0 | 21.5 | 26.4 | 25.5 | 15.2 | 15.6 |
| F,4 | 53.5 | 53.1 | 50.6 | 52.0 | 50.5 | 49.5 | 53.8 | 53.8 | 54.2 | 55.4 |
| F,5α | 38.4 | 18.0 | 24.8 | 26.3 | 25.9 | 19.5 | 41.9 | 39.9 | 16.8 | 17.6 |
| F,5β | 18.0 | 13.1 | 19.0 | 26.3 | 14.0 | 36.5 | 17.5 | 19.2 | 4.3 | 9.7 |

[a]Coupling constants for spectrum in benzene-$d_6$. [b]NH Protons resonate at 5.1 - 5.8. [c]Coupling constants for spectrum in pyridine-$d_5$. [d]Coupling constants for spectrum in benzene-$d_6$/pyridine-$d_5$ 1:1. [e]Correspond to $OCH_2Ph$. [f]$NCH_2Ph$ resonate at 4.06 and 3.81. [g]$NCH_2Ph$ resonate at 4.07 and 3.74. [h]Not determined.

**Table 2.** Selected $^{13}C$ NMR Chemical Shifts (δ, ppm) of Compounds **6** in $CDCl_3$; $J_{C,F}$ (Hz) are reported in parentheses when higher than 0.5 ppm.

| Carbon | (3*R*,4*S*,5a*S*)-**6** | (3*R*,4*S*,5a*R*)-**6** | (3*R*,4*R*,5a*S*)-**6** | (3*R*,4*R*,5a*R*)-**6** |
|---|---|---|---|---|
| 2a | 166.15 | 166.85 | 165.29 (5) | 169.06 (4) |
| 3 | 70.75 (16) | 73.07 (17.5) | 75.13 (29.5) | 76.39 (31.5) |
| 4 | 94.72 (197) | 97.79 (195) | 99.81 (187.5) | 101.67 (183) |
| 5 | 33.03 (23) | 31.27 (21) | 33.82 (24.5) | 34.16 (24) |
| 5a | 49.54 | 47.36 | 49.22 | 51.43 |
| 6 | 75.52 | 76.23 | 76.22 | 74.74 |
| $OCH_2Ph$ | 72.02 | 72.35 | 71.72 | 72.43 |

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) and extracted with ethyl acetate (3x100 mL), and the collected organic phases were dried ($Na_2SO_4$). Evaporation under reduced pressure gave a residue containing the crude, hygroscopic[29] (2*R*,3*S*)-2-benzyloxy-3-fluorohexenal **2** which was used in successive reactions without further purification. Similarly, the hexenal (2*R*,3*R*)-**2** was obtained starting from the hexenylsulfoxide (2*S*,3*R*,$R_S$)-**1**.

**(2a*S*,3*R*,4*S*,5a*S*)-2-Benzyl-3-benzyloxy-4-fluorocyclopentano[c]isoxazolidine (4).** A solution of the crude aldehyde (2*R*,3*S*)-**2** (obtained as described above starting from 1.38 g (4.0 mmol) of (2*S*,3*S*,$R_S$)-hexene **1**) in methanol (10.0 mL) was added to a suspension of *N*-benzyl hydroxylamine hydrochloride (1.92 g, 12.0 mmol) and sodium carbonate (1.66 g, 12.0 mmol) in the same solvent (10.0 mL) under nitrogen. The reaction mixture was refluxed for 1.5 h, then it was evaporated under reduced pressure. The residue was dissolved in water (20.0 mL) and extracted with ethyl acetate (3x50 mL). Collected organic phases were dried ($Na_2SO_4$), evaporated under reduced pressure, and the resulting oil was flash chromatographed (toluene/diisopropyl ether 90 : 10) to give 0.89 g (68% yield) of pure (2a*S*,3*R*,4*S*,5a*S*)-**4**: $[\alpha]_D^{22}$ +26 (c 1.23, MeOH); NOE experiments: irradiated nucleus {F-4}, affected protons (enhancement %): 2a (1.5), 4 (1.5), 5β (2.5), 5a (1.5), OC*H*aPh (0.5), OC*H*bPh (0.5). Anal. calcd for $C_{20}H_{22}FNO_2$: C, 73.37; H, 6.77. Found: C, 73.56; H, 6.58.

**(2a*S*,3*R*,4*R*,5a*S*)-2-Benzyl-3-benzyloxy-4-fluorocyclopentano[c]isoxazolidine (4).** Eluting system for flash chromatography *n*-hexane/ethyl acetate (8 : 2); isolated yield 485 mg, 64%; $[\alpha]_D^{22}$ -4.8 (c 2.06, MeOH); NOE experiments: irradiated nucleus {H-2a}, affected protons (enhancement %): 4 (2), 5a (3), NC*H*aPh (1.5), NC*H*bPh (4), OC*H*aPh (0.5), OC*H*bPh (1); {H-4}: 2a (2), 5β (4), 5a (2), OC*H*aPh (0.5), OC*H*bPh (0.5); {H-5a}: 2a (3), 4 (1.5), 5β (3), 6β (3.5). Anal. calcd for $C_{20}H_{22}FNO_2$: C, 73.37; H, 6.77. Found: C, 73.60; H, 6.49.

**(2*R*,3*S*)-2-Benzyloxy-3-fluoro-5-hexenal Oximes (5).** A suspension of hydroxylamine hydrochloride (1.26 g, 18.2 mmol) and sodium carbonate (1.20 g, 11.4 mmol) in absolute ethanol (30 mL) was added to a solution of the crude (2*R*,3*S*)-2-benzyloxy-3-fluorohexenal **2** (from 1.58 g, 4.56 mmol of (2*S*,3*S*,$R_S$)-hexenylsulfoxide **1**) in the same solvent (30 mL). The mixture was left overnight over molecular sieves (4A) and under argon; the precipitate was removed by filtration, and washed with ethanol. Combined organic phases were evaporated under reduced pressure, and flash chromatography of the residue (toluene/diisopropyl ether 92 : 8) afforded 822 mg, (76% yield) of (2*R*,3*S*,*E*)-**5** and (2*R*,3*S*,*Z*)-**5** in 1:1 ratio. (2*R*,3*S*,*E*)-**5**: higher $R_f$ isomer; $[\alpha]_D^{22}$ -57 (c 0.4, $CHCl_3$); $^1H$ NMR, δ: 7.92 (1H, s, OH), 7.44 (1H, br d, $J$ = 7.7 Hz, H-1), 7.4 - 7.2 (5H, m, ArH), 5.78 (1H, m, H-5), 5.13 (2H, m, $H_2$-6), 4.68 (1H, ddt, $J$ = 47.7, 4.8, and 6.2 Hz, H-3), 4.67 and 4.46 (2H, d, $J$ = 11.8 Hz, $CH_2Ph$), 4.03 (1H, ddd, $J$ = 15.2, 7.7, and 4.8 Hz, H-2), and 2.6 - 2.2 (2H, m, $H_2$-4); $^{19}F$ NMR, δ: -193.39 (br dddd, $J$ = 47.7, 26.5, 22.5, and 15.2 Hz, F-3). Anal. calcd for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80. Found: C, 65.73; H, 6.50. (2*R*,3*S*,*Z*)-**5**: lower $R_f$ isomer; $[\alpha]_D^{22}$ -24.7 (c 0.2, $CHCl_3$); $^1H$ NMR, δ: 8.02 (1H, br s, OH), 7.5 - 7.2 (5H, m, ArH), 6.82 (1H, br dd, $J$ = 6.7 and 1.7 Hz, H-1), 5.81 (1H, m, H-5), 5.16 and 5.12 (2H, m, $H_2$-

6), 4.94 (1H, ddd, $J$ = 17.7, 6.7, and 3.3 Hz, H-2), 4.76 (1H, dddd, $J$ = 47.6, 8.4, 4.6, and 3.3 Hz, H-3), 4.65 and 4.54 (2H, d, $J$ = 11.7 Hz, $CH_2Ph$), and 2.6 - 2.1 (2H, m, $H_2$-4); $^{19}F$ NMR, δ: -190.59 (br dddd, $J$ = 47.6, 30.7, 17.7, and 16.5 Hz, F-3).

**(2*R*,3*R*)-2-Benzyloxy-3-fluoro-5-hexenal Oximes (5).** Eluting system for flash chromatography toluene/ethyl acetate (95 : 5); isolated yield 1.12 g, 74%. (2*R*,3*R*,*E*)-**5**: higher $R_f$ isomer; $[\alpha]_D^{22}$ -65 (c 1.0, $CHCl_3$); mp 55-57 °C; $^1H$ NMR, δ: 8.15 (1H, s, OH), 7.48 (1H, br d, $J$ = 7.8 Hz, H-1), 7.5 - 7.2 (5H, m, ArH), 5.72 (1H, m, H-5), 5.11 and 5.10 (2H, m, $H_2$-6), 4.69 and 4.44 (2H, d, $J$ = 11.9 Hz, $CH_2Ph$), 4.60 (1H, dddd, $J$ = 47.0, 7.8, 5.0, and 4.0 Hz, H-3), 4.02 (1H, ddd, $J$ = 20.6, 7.9, and 4.0 Hz, H-2), and 2.7 - 2.2 (2H, m, $H_2$-4); $^{19}F$ NMR, δ: -194.61 (br dddd, $J$ = 47.0, 26.8, 20.6, and 18.0 Hz, F-3). Anal. calcd for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80. Found: C, 65.63; H, 6.67. (2*R*,3*R*,*Z*)-**5**: lower $R_f$ isomer; $[\alpha]_D^{22}$ -34 (c 0.7, $CHCl_3$); mp 105-107 °C; $^1H$ NMR, δ: 8.13 (1H, br s, OH), 7.5 - 7.2 (5H, m, ArH), 6.91 (1H, br d, $J$ = 6.5 Hz, H-1), 5.74 (1H, m, H-5), 5.10 and 5.09 (2H, m, $H_2$-6), 4.78 (1H, ddd, $J$ = 25.2, 6.5, and 3.4 Hz, H-2), 4.70 (1H, dddd, $J$ = 46.5, 7.8, 5.5, and 3.4 Hz, H-3), 4.69 and 4.46 (2H, d, $J$ = 11.7 Hz, $CH_2Ph$), and 2.8 - 2.3 (2H, m, $H_2$-4); $^{19}F$ NMR, δ: -194.68 (br dddd, $J$ = 46.5, 27.3, 25.2, and 14.8 Hz, F-3).

**(3*R*,4*S*,5a*S*)-3-Benzyloxy-4-fluorocyclopentano[c]2-isoxazoline (6) and (3*R*,4*S*,5a*R*)-6.** A solution of sodium hypochlorite (4.8 mmol of available chlorine) was added slowly at 0 °C to a solution of (2*R*,3*S*)-oximes **5** (0.72 g, 3.0 mmol) and triethylamine (0.042 mL, 0.3 mmol) in dichloromethane (45 mL). After stirring overnight at room temperature, water was added (15 mL), the aqueous layer was extracted with chloroform (3x30 mL), and the collected organic phases were dried ($Na_2SO_4$). Solvent was removed under reduced pressure and flash chromatography of the residue (*n*-hexane/ethyl acetate 75 : 25) afforded 0.57 g, (81% yield) of (3*R*,4*S*,5a*S*)-**6** and (3*R*,4S,5a*R*)-**6** in 4 : 1 ratio as diastereoisomerically pure compounds. (3*R*,4*S*,5a*S*)-**6**: $[\alpha]_D^{22}$ -23.7 (c 0.7, $CHCl_3$); NOE experiments: irradiated nucleus {F-4}, affected protons (enhancement %): 4 (9), 5β (2.5), 5a (1.5). (3*R*,4S,5a*R*)-**6**: $[\alpha]_D^{22}$ -160 (c 0.4, $CHCl_3$). Anal. calcd for $C_{13}H_{14}FNO_2$: C, 66.37; H, 6.00. Found: C, 66.12; H, 6.23.

**(3*R*,4*R*,5a*S*)-3-Benzyloxy-4-fluorocyclopentano[c]2-isoxazoline (6) and (3*R*,4*R*,5a*R*)-6.** Eluting system for flash chromatography toluene/ethyl acetate (95 : 5); isolated yield 0.84 g, 77%, 7 : 3 mixture of (3*R*,4*R*,5a*S*)-**6** and (3*R*,4*R*,5a*R*)-**6**. (3*R*,4*R*,5a*S*)-**6**: $[\alpha]_D^{22}$ -19.2 (c 1.0, $CHCl_3$). (3*R*,4*R*,5a*R*)-**6**: $[\alpha]_D^{22}$ -206 (c 1.0, $CHCl_3$); NOE experiments: irradiated nucleus {F-4}, affected protons (enhancement %): 3 (5.5), 4 (9), 5α (2), 5a (1.5). Anal. calcd for $C_{13}H_{14}FNO_2$: C, 66.37; H, 6.00. Found: C, 66.19; H, 5.80.

**(2a*S*,3*R*,4*S*,5a*S*)-3-Benzyloxy-4-fluorocyclopentano[c]isoxazolidine (7). Reduction of (3*R*,4*S*,5a*S*)-6.** An aqueous solution of HCl (1 : 1 v/v) was added dropwise to a stirred solution of (3*R*,4*S*,5a*S*)-cyclopentano[c]2-isoxazoline (**6**) (1.56 g, 6.63 mmol), sodium cyanoborohydride (1.25 g, 20.0 mmol), and methyl orange (0.1% solution, 1 drop) in methanol (30 mL). The rate of addition was controlled so that the colour of the reaction mixture remained reddish-orange (pH 3-4). After 3 h the reaction was quenched with HCl (5.0 mL), methanol was removed under reduced pressure, the residue was treated with saturated potassium carbonate, and the aqueous phase was extracted with ethyl acetate (3x200 mL) Combined organic phases were dried ($K_2CO_3$) and evaporated under reduced pressure to give exclusively (2a*S*,3*R*,4*S*,5a*S*)-cyclopentano[c]isoxazolidine (**7**) in nearly pure form; isolated yield 1.45 g, 92%. An analytical sample was obtained through flash chromatography (*n*-hexane/ethyl acetate 45 : 55); $[\alpha]_D^{22}$ +120 (c 0.7, $CHCl_3$); NOE experiments: irradiated nucleus {F-4}, affected protons (enhancement %): 2a (1.5), 4 (9.5), 5β (3), 5a (1.5), OC*H*aPh (0.5), OC*H*aPh (0.5); mass spectrum (EI) m/e 237 (M), 161, 146, 131. Anal. calcd for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80. Found: C, 65.97; H, 6.98. **Heating of (2*R*,3*S*)-5.** A solution of (2*R*,3*S*)-oximes **5** (0.83 g, 3.5 mmol) in acetonitrile/ dimethylformamide (1 : 1, 20 mL) was refluxed for 24 h, acetonitrile was removed under reduced pressure, water was added, and organic products were extracted with ethyl ether (3x40 mL). Collected organic phases were dried ($Na_2SO_4$), the solvent was removed under reduced pressure, and flash chromatography afforded 0.59 g (71% yield) of pure (2a*S*,3*R*,4*S*,5a*S*)-cyclopentano[c]isoxazolidine (**7**).

**(2a*R*,3*R*,4*S*,5a*R*)-3-Benzyloxy-4-fluorocyclopentano[c]isoxazolidine (7). Reductive approach.** Eluting system for flash chromatography *n*-hexane/ethyl acetate (15 : 85); isolated yield 981 mg, 94%;

$[\alpha]_D^{22}$ -19.0 (c 0.7, $CHCl_3$); NOE experiments: irradiated nucleus {H-2a}, affected protons (enhancement %): 4 (2.5), 5α (1), 5a (4.5), OC*H*aPh (1), OC*H*bPh (1); {H-4}: 2a (1.5), 3 (1), 5α (2); {H-5a}: 2a (2.5), 3 (1), 5α (2.5), 5β (1), 6α (3); mass spectrum (EI) m/e 237 (M), 161, 146, 131.

**(2a*S*,3*R*,4*R*,5a*S*)-3-Benzyloxy-4-fluorocyclopentano[c]isoxazolidine (7). Reductive approach.** Eluting system for flash chromatography *n*-hexane/ethyl acetate (55 : 45); isolated yield 1.24 g, 90%; $[\alpha]_D^{22}$ +59.2 (c 0.5, $CHCl_3$); NOE experiments: irradiated nucleus {H-2a}, affected protons (enhancement %): 4 (1), 5a (5.5), OC*H*aPh (1), OC*H*bPh (1); {H-4}: 2a (2.5), 5β (3.5), 5a (2); {H-5a}: 2a (5.5), 4 (1), 5β (2.5), 6β (1.5); mass spectrum (EI) m/e 237 (M), 161, 146, 131. Anal. calcd for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80. Found: C, 66.04; H, 7.01. **Heating of (2*R*,3*R*)-5.** Isolated yield: 66%.

**(2a*R*,3*R*,4*R*,5a*R*)-3-Benzyloxy-4-fluorocyclopentano[c]isoxazolidine (7). Reductive approach.** Eluting system for flash chromatography *n*-hexane/ethyl acetate (30 : 70); isolated yield: 94%; $[\alpha]_D^{22}$ -81.6 (c 0.7, $CHCl_3$); NOE experiments: irradiated nucleus {F-4}, affected protons (enhancement %): 2a (1.5), 3 (3), 4 (10.5), 5α (2.5), 5β (1), 5a (1); mass spectrum (EI) m/e 237 (M), 161, 131.

**(2a*S*,3*R*,4*S*,5a*S*)-3-Hydroxy-4-fluorocyclopentano[c]isoxazolidine (8).** A solution of (2a*S*,3*R*,4*S*,5a*S*)-7 (324 mg, 1.36 mmol) in trifluoroacetic acid (5.0 mL) was shaken with palladium on activated charcoal (10% ) under hydrogen at 20 psi for 8 h. Ethanol was added, the reaction was filtered, the solvent was removed under reduced pressure, and flash chromatography of the residue (ethyl acetate/methanol 95 : 5) afforded 154 mg (78% yield) of pure (2a*S*,3*R*,4*S*,5a*S*)-**8**; $[\alpha]_D^{22}$ +46 (c 1.0, MeOH); $^1$H NMR, δ: 5.62 (2H, br signal, NH-2 and OH-3), 5.00 (1H, br d, $J$ = 53.8 Hz, H-4), 4.2-3.5 (4H, m, H-2a, H-3, and $H_2$-6), 3.28 (1H, m, H-5a), 2.34 and 1.66 (2H, m, $H_2$-5); $^{19}$F NMR, δ: -202.04 (m, F-4).

**(2aR,3R,4R,5aR)-3-Hydroxy-4-fluorocyclopentano[c]isoxazolidine (8).** Eluting system for flash chromatography ethyl acetate/*n*-hexane/triethylamine 95:5:1; isolated yield 78%; $^1$H NMR, δ: 5.45 (2H, br signal, NH-2 and OH-3), 4.88 (1H, br d, $J$ = 54.0 Hz, H-4), 4.1-3.5 (4H, m, H-2a, H-3, and $H_2$-6), 3.22 (1H, m, H-5a), 2.07 and 1.85 (2H, m, $H_2$-5); $^{19}$F NMR, δ: -190.79 (m, F-4).

**(1*S*,2*R*,3*S*,5*S*)-2-Benzyloxy-3-fluoro-5-hydroxymethylcyclopentylamine (9).** A solution of (2a*S*,3*R*,4*S*,5a*S*)-7 (285 mg, 1.20 mmol) in methanol (5.0 mL) was stirred with $Pt_2O$ under hydrogen for 1 h. The catalyst was filtered off, the solvent was removed under reduced pressure, and the residue was flash chtomatographed (ethyl acetate/methanol/triethyl amine 90 : 5 : 5) to give 241 mg (84% yield) of pure (1*S*,2*R*,3*S*,5*S*)-**9**; $[\alpha]_D^{22}$ +93 (c 1.6, MeOH); $^1$H NMR, δ: 7.5-7.2 (5H, m, ArH), 5.00 (1H, br ddd, $J$ = 55.0, 4.0, and 3.2 Hz, H-3), 4.77 and 4.52 (2H, d, $J$ = 11.5 Hz, $OCH_2Ph$), 3.78 (1H, dd, $J$ = 11.5 and 3.3 Hz, H-6a), 3.70 (1H, ddd, $J$ = 9.8, 9.6, and 2.5 Hz, H-1), 3.54 (1H, br ddd, $J$ = 25.7, 9.8, and 3.2 Hz, H-2), 3.45 (1H, dd, $J$ = 11.5 and 5.2 Hz, H-6b), 2.40 (3H, br signal, $NH_2$-1 and OH-6), 2.38 (1H, ddddd, $J$ = 9.6, 9.2, 7.7, 5.2, and 3.3 Hz, H-5), 2.10 (1H, br dddd, $J$ = 23.4, 15.4, 9.2, and 1.0 Hz, H-4β), and 1.83 (1H, br dddd, $J$ = 42.9, 15.4, 7.7, and 4.0 Hz, H-4α); $^{19}$F NMR, δ: -194.36 (m, F-3).

**(1*S*,2*R*,3*S*,5*S*)-2-Hydroxy-3-fluoro-5-hydroxymethylcyclopentylamine (10).** From (1*S*,2*R*,3*S*,5*S*)-**9** by treatment with palladium on charcoal. Eluting system for flash chromatography: ethyl acetate/methanol 1 : 1; isolated yield 62%; $[\alpha]_D^{20}$ +53 (c 0.12, MeOH), $^1$H NMR, δ: 4.91 (1H, br dddd, $J$ = 55.2, 4.3, 3.6, and 1.0 Hz, H-3), 3.79 (1H, dd, $J$ = 11.5 and 3.4 Hz, H-6a), 3.77 (1H, br ddd, $J$ = 24.9, 9.2, and 3.6 Hz, H-2), 3.51 (1H, dd, $J$ = 11.5 and 5.5 Hz, H-6b), 3.51 (1H, br dd, $J$ = 9.3 and 9.2 Hz, H-1), 2.50 (1H, ddddd, $J$ = 9.3, 9.2, 7.0, 5.5, and 3.4 Hz, H-5), 2.25 (4H, br signal, $NH_2$-1, OH-2, and OH-6), 2.10 (1H, br dddd, $J$ = 25.0, 15.5, 9.3, and 1.0 Hz, H-4β), and 1.90 (1H, br dddd, $J$ = 43.0, 15.5, 7.0, and 4.3 Hz, H-4α); $^{19}$F NMR, δ: -184.41 (m, F-3).

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