Asymmetric Synthesis of Fluorinated Analogues of 1-Deoxynojirimycin

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Two epimeric 1,3,4-trideoxy-3-fluoronojirimycins are obtained through a total asymmetric synthesis starting from a non-carbohydrate precursor; two key-steps of the synthetic sequence are an intramolecular aminomercuration reaction and an oxidative demercuration process.

The natural product 1-deoxynojirimycin **1** and some of its stereoisomers represent a particularly interesting class of glycosidase inhibitors having a basic nitrogen in place of the pyranose oxygen.[1,2] They have been used, or suggested, as antihyperglycaemic compounds, inhibitors of tumour metastasis, antiobesity drugs, fungistatic compounds, insect antifeedants and antiviral agents.[3] The observation that many glycosidase inhibitors show antiviral activity has suggested that these compounds exhibit activity against HIV, the causative agent of AIDS.

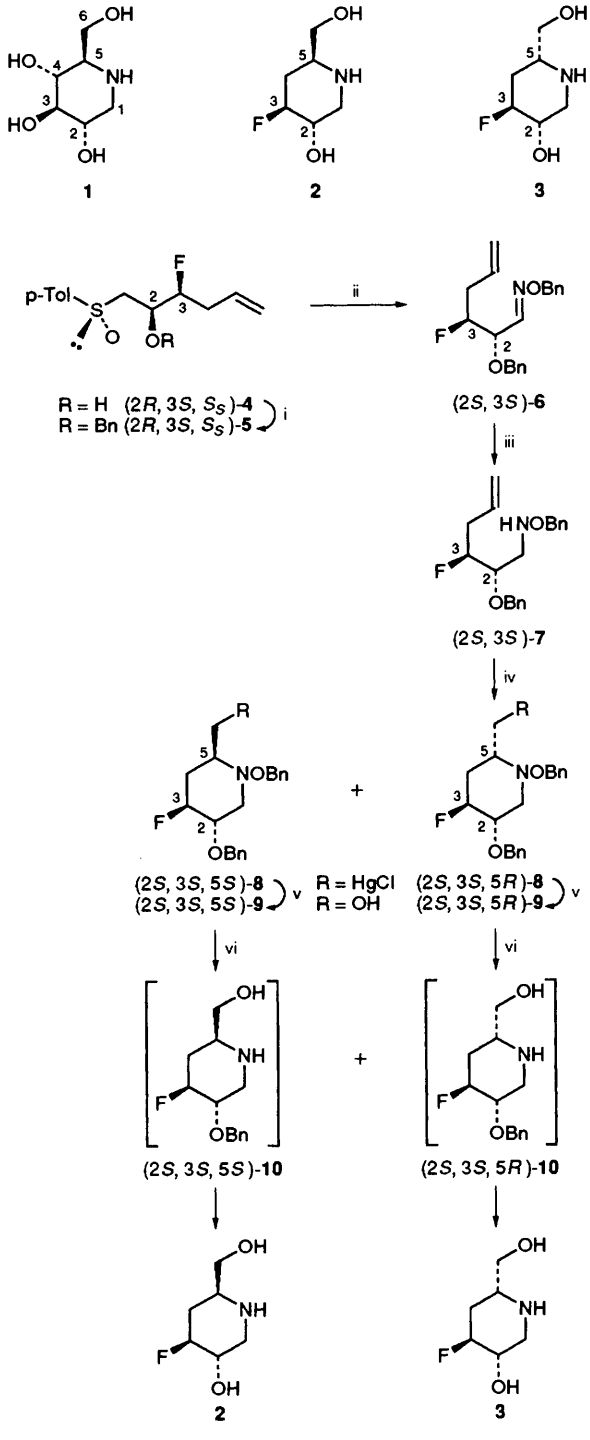
The substitution of a fluorine atom for a hydroxy group in a drug often results in improved pharmacological properties. This is often related to the ability of this halogen to mimic the hydroxy.[4]

The synthesis of 1,2-dideoxy-2-fluoro-[5] and 1,6-dideoxy-6-fluoro-nojirimycin[6] analogues has been reported recently. Here we describe an asymmetric synthesis of the new fluorinated analogues of 1,3,4-trideoxynojirimycin **2** and **3** with a fluorine atom at C-3.†

Specifically, the fluorosulfinylhexenol (2*R*,3*S*,S_S)-**4** has been prepared in three steps from (−)-(*S*)-methyl *p*-tolyl sulfoxide[7] and has been transformed into the corresponding benzyl ether (2*R*,3*S*,S_S)-**5** under standard reaction conditions and in quantitative yields. On treating this sulfinylbenzyloxy-fluorohexene with trifluoroacetic anhydride and 2,4,6-trimethylpyridine[8] a geminal tolylthiotrifluoroacetyloxy moiety was formed through a clean Pummerer rearrangement of the sulfoxide group. This masked aldehyde was not isolated but directly hydrolysed by treatment with copper(II) chloride. The so-formed crude α-benzyloxy-β-fluorohexenal was reacted with O-benzylhydroxylamine[9] to afford the *O*-benzyl oximes (2*S*,3*S*)-**6** as a 10 : 1 mixture of (*E*) and (*Z*) isomers in 65% overall yield from **5**. These two oximes could be separated into pure isomers [(*E*,2*S*,3*S*)-**6**, $[\alpha]_D^{20}$ + 35.1 (*c* 1, $CHCl_3$); (*Z*,2*S*,3*S*)-**6**, $[\alpha]_D^{20}$ + 48.1 (*c* 0.3, $CHCl_3$)] but the mixture of isomers could also be directly reduced to hydroxylamine (2*S*,3*S*)-**7** (sodium cyanoborohydride, 86% yield).[10]

Intramolecular aminomercuration[11] allowed the assembly of the piperidine ring of the target compounds **2** and **3**. The two 5-chloromercuriomethyl piperidines **8** epimeric at the newly formed carbon stereocentre were formed [(2*S*,3*S*,5*S*)-**8**/(2*S*,3*S*,5*R*)-**8** ratio 1 : 1] and easily separated by flash chromatography (n-hexane–ethyl ether 1 : 1).‡

Oxidative demercuration of these two piperidines **8** to afford 5-hydroxymethyl piperidines **9** was performed with sodium borohydride and bubbling dioxygen in the reaction solution. Typically, dimethylformamide (DMF) is the solvent of choice for this reaction, but when it was used with our substrates, reductive demercuration products, *i.e.* *N*-benzyloxy-2-benzyloxy-3-fluoro-5-methylpiperidines,† were formed nearly exclusively (*ca.* 70% isolated yields). It was thought that the trapping of the intermediate radical by dioxygen could



Scheme 1 *Reagents and conditions*: i, NaH, BnBr, THF, DMF, 0 °C; ii, (a) $(CF_3CO)_2O$, 2,4,6-trimethylpyridine, MeCN, 0 °C; (b) $CuCl_2$ K_2CO_3, room temp; (c) $BnONH_2$–HCl, Na_2CO_3, molecular sieve (4 Å), EtOH, room temp.. iii, $NaCNBH_3$ dil.HCl MeOH, room temp.; iv, (a) $(CF_3COO)_2Hg$ THF, room temp.; (b) KCl, H_2O, room temp.; v, $NaBH_4$ $(CF_3)_2CHOH$, O_2, room temp.; vi, H_2/Pd(C), 4 atm, CF_3CO_2H, room temp. (Bn = $PhCH_2$, *p*-Tol = *p*-MeC_6H_4)

† The piperidine ring of compounds **2**, **3**, **8**, **9** and **10** has been numbered as indicated in the formulae and in Scheme 1. This non-systematic nomenclature has been used as it is commonly employed for nojirimycin analogues. Furthermore, consistency is obtained in numbering systems of acyclic and cyclic compounds.

‡ All compounds gave expected ^1H and ^{19}F NMR, IR, and mass spectra. The compounds were also characterized through their optical rotations and satisfactory microanalyses (C, H) were obtained.

The ^1H NMR spectra of the two piperidines **8** showed broad signals because of nitrogen and/or ring slow inversion. A similar behaviour has already been observed for *N*-benzyloxypyrrolidines and piperidines.[12]

2: δ_H ([$^2H_5$]pyridine): 4.82 (1H, dddd, *J* 51.3, 11.3, 8.4, and 5.3 Hz, 3-H), 4.25 (1H, m, 2-H), 3.90 and 2.90 (2H, m, 6-H_2), 3.70 (1H, m, 1-H_β), 3.15 (1H, m, 5-H), 2.96 (1H, ddd, *J* 12.0, 10.4 and 1.2 Hz, 1-H_α), 2.31 (1H, m, 4-H_α) and 1.85 (1H, dddd, *J* 12.1, 11.6, 11.3, and 9.9 Hz, 4-H_β). δ_F ([$^2H_5$]pyridine): −75.87 (3F, s, CF_3), −181.08 (1F, m, 3-F). The coupling constants observed between 1-H_α and 2-H_β, 2-H_β and 3-H_α, 3-H_α and 4-H_β, and 4-H_β and 5-H_α (10.4, 8.4, 11.3 and 11.6 Hz, respectively) indicate that all these protons are axially disposed. The absolute configuration at C-5 in compound **2** and its precursors **8** and **9** is thus established from the known configuration[7] at C-2 and C-3. Furthermore, it follows that the piperidine ring of this isomer preferentially adopts a chair conformation in which all the substituents are equatorially disposed.

3: δ_H ([$^2H_5$]pyridine): 5.09 (1H, m, 3-H), 4.21 (1H, m, 2-H), 4.05 and 3.92 (2H, m, 6-H_2), 3.57 (1H, m, 5-H), 3.51 and 3.49 (2H, m, 1-H_2), 2.44 (1H, dddd, *J* 43.8, 14.6, 11.6, and 2.4 Hz, 4-H_α) and 2.08 (1H, m, 4-H_β). δ_F ([$^2H_5$]pyridine): −74.25 (3F, s, CF_3), −187.16 (1F, m, 3-F). The value of the coupling constants observed between 4-H_α and 5-H_β (11.6 Hz) and between 3-F_β and 4-H_α (43.8 Hz) requires that these atoms are axially disposed. The coupling of 5.5 Hz observed between 2-H_β and 3-F_β is indicative of a gauche relationship. As the absolute configuration at C-2 and C-3 is already known,[7] the data reported above allow unequivocal assignment of the absolute configuration at C-5 of **3** and its precursors **8** and **9**.

be favoured by using a solvent in which dioxygen has a particularly high solubility. Various fluorinated hydrocarbons, amines and alcohols were tried and the best results were obtained when hexafluoroisopropyl alcohol was employed.§ In this way the desired 5-hydroxymethylpiperidines **9** were formed in quantitative yields and no epimerization at the α-carbon stereocentre was observed.

Hydrogenolysis of the N–O bond of the (2*S*,3*S*,5*R*)-**9** could be performed selectively (H_2 1 atm/Pd-C, CF_3CO_2H, room temp.) (1 atm = 101.3 kPa) to give the corresponding (2*S*,3*S*,5*R*)-2-benzyloxy-3-fluoro-5-hydroxymethylpiperidine **10**. However, isolation of this intermediate was not necessary as by using more severe reaction conditions [H_2 (4 atm)/Pd-C, CF_3CO_2H, room temp. both N–O bond cleavage and debenzylation of the hydroxy group on C-2 occurred to give compound **3** which was isolated as its trifluoroacetate (50% yield; $[\alpha]_D^{20}$ + 3.9, *c* 1, CF_3CO_2H). Similarly, hydrogenolysis of (2*S*,3*S*,5*S*)-**9** afforded the trideoxymonofluoronojirimycin **2** (75% yield; $[\alpha]_D^{20}$ + 21.3, *c* 0.6, CF_3CO_2H).

The 3-fluoro-2-hydroxy-1-sulfinylhex-5-ene **4** having the (2*R*,3*R*,*S*$_S$) absolute configuration is also easily available.[7] Starting from this compound, we are presently synthesizing the two epimers of **2** and **3** which have opposite configuration at the fluorinated stereocentre.

§ This behaviour was shown to be quite general and other examples will be reported in the near future.

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