Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 1029-1040, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00133-2

A Highly Stereocontrolled Synthetic Approach to 1,6-Dideoxy-6,6-difluoroazasugar Derivatives

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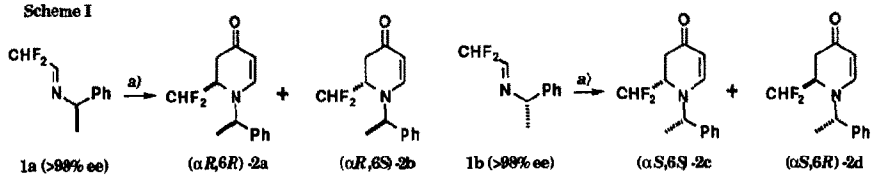
Abstract: The synthetic utility of (αR, $6R$)- or (αR, $6S$)-N-(methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone **2**, which was produced from the reaction of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene and (αR)- or (αS)-N-(2,2-difluoroethylidene)methylbenzylamine **1**, is described. These materials are found to be potential intermediates for a highly stereocontrolled synthesis of 1,6-dideoxy-6,6-difluoroazasugar analogues.

Since the discovery of the glycosidase inhibitors 1-deoxymannojirimycin[1] and 1-deoxynojirimycin,[2] research into the removal of the anomeric hydroxy group from a pyranose sugar and the replacement of the ring oxygen by a nitrogen atom, thus generating effective inhibitors of the corresponding glycosidases[1-5], have been extensive in recent years. Recent research has shown such derivatives to be active against human immunodeficiency virus (HIV) in cultured cells by α-glucosidase inhibition.[6] As a continuation of our interest in the synthesis of fluoro analogues of sugars and their derivatives,[7] which often exhibit unique physiochemical properties, we were intrigued by difluoromethyl substitution of sugars. The difluoromethyl group is favoured due to its ability to act as a hydrogen bond donor, potentially allowing interaction with solvent and biological molecules. Particularly, in the glycoside chemistry, site specific replacement of an oxygen atom, possessing stereochemically significant lone pairs, by the larger difluoromethylene unit would provide compounds which would still retain hydrogen bonding potential. In this field, fluorinated azasugars are interesting not only because of their potential pharmaceutical utility but also for their versatility as precursors for inhibitors of HIV virus. Accordingly, we have been studying new synthetic approaches to 1,6-dideoxy-6,6-difluoroazasugar analogues where the C6 hydroxyl group and hydrogen atom are replaced by a fluorine atom. Our basic strategy is based on the concept that CHF_2-containing molecules with multiple stereocenters might be constructed more easily by employing chiral building blocks with appropriate functionalities.[8]

Results and Discussion

Based on the recent impressive progress made on asymmetric aza-Diels-Alder reactions,[9-12] we designed our starting chiral building block (*R*)- or (*S*)-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone **2**, which was prepared via a cycloaddition reaction of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene and (α*R*)- or (α*S*)-N-(2,2-difluoroethylidene)(α-methylbenzyl)amine **1** derived from difluoro-acetaldehyde ethyl hemiacetal[13] and (*R*)- or (*S*)-(α-methylbenzyl)amine (>98% ee). The final purification of epimers was carried out by using column chromatography on silica gel to give (α*R*, 6*R*)- or (α*R*, 6*S*)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2a**: $[\alpha]^{19}_D$ +523.7 (*c* 1.07, MeOH), >99% de; **2b**: $[\alpha]^{18}_D$ -236.1 (*c* 0.72, MeOH), >99% de)(see Experimental Section). The epimeric purities of **2** determined by ^{19}F NMR (470 MHz) intensities were >99% de, respectively. Furthermore, (α*S*, 6*S*)- or (α*S*, 6*R*)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2c**: $[\alpha]^{19}_D$ -475.6 (*c* 1.07, $CHCl_3$), >99% de; **2d**: $[\alpha]^{19}_D$ +332.7 (*c* 0.30, $CHCl_3$), >99% de) were separated from the corresponding epimers in the same manner. Several Lewis acids, such as BF_3, $ZnCl_2$, $AlCl_3$ etc., were used in the above aza-Diels-Alder reaction, with BF_3 being found to be an most effective catalyst to achieve the highly diastereoselective addition.

Scheme I



1a (>98% ee) (α*R*,6*R*)-2a (α*R*,6*S*)-2b 1b (>98% ee) (α*S*,6*S*)-2c (α*S*,6*R*)-2d

a) 1-methoxy-3-trimethylsiloxy-1,3-butadiene,Lewis acid

Table 1 Aza-Diels-Alder Reaction Mediated by Lewis Acid

Entry No	Lewis Acid	Solvent	Temp. (°C)	Time (hr)	Yield (%)	Ratio 2a : 2b
1	$ZnCl_2$	THF	rt	4	70	48 : 52
2		THF	-78	5	0	
3		CH_2Cl_2	-78	5	50	46 : 54
4	$BF_3 \cdot Et_2O$	CH_2Cl_2	-78	5	82	19 : 81
5	$TiCl_4$	CH_2Cl_2	-78	5	61	41 : 59
6	$AlCl_3$	CH_2Cl_2	-78	5	21	35 : 65
7	$B(OPh)_3$	CH_2Cl_2	-78 → rt	24	65	25 : 75
8	$LiClO_4$	Et_2O	rt	22	85	53 : 47

The absolute configuration on C2 of a*R*-**2b** was determined by X-ray analysis. The result shown in Figure **1** shows that *R*-**2b** is the (αR, $6R$)-epimer.

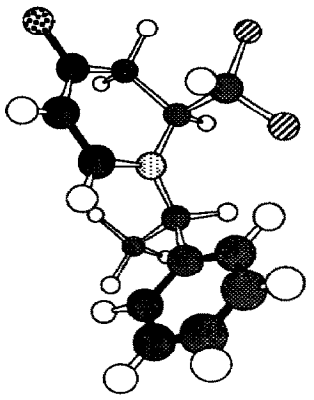
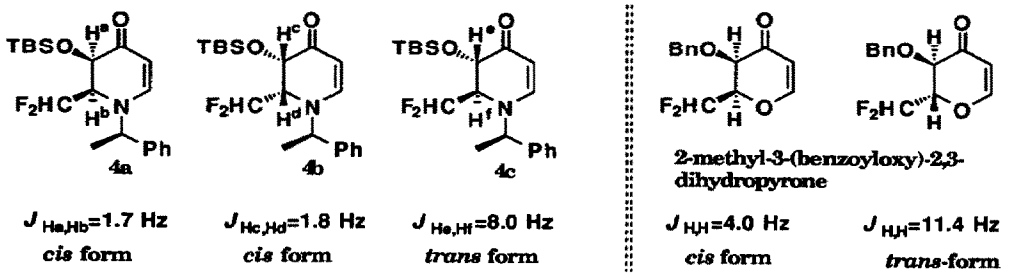


Fig. 1

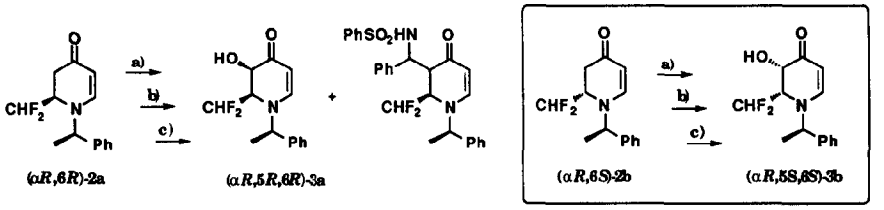
Next, the stereocontrolled hydroxylation onto the optically active 6-difluoro-methyl-5,6-dihydro-4-pyridone **2a** and **2b** was investigated in detail. Hydroxylation at this position was possible by trapping the enolate with Davis' oxazolidine.[14] Although various bases such as LDA, $NaN(TMS)_2$, $KN(TMS)_2$ and $Li(TMS)_2$, were examined, the system of $NaN(TMS)_2$ with 2-sulfonyloxazolidine in THF was found to afford 5,6-*syn* isomer in the best yields. The configuration of 6-difluoromethyl-5,6-dihydro-5-hydroxy-4-pyridone **3** was determined by the comparison of the ^1H NMR coupling constants of *cis*- and/or *trans*-2-methyl-3-(benzoyloxy)-2,3-dihydro-pyrone[15] and molecular mechanics calculations.

MM 2 calculations through multiconformer analysis of pyridone **3** gave global minimum conformations for *trans*- and *cis*-6-difluoromethyl-5,6-dihydro-5-hydroxy-4-pyridone **3**. The comparison of the calculated coupling constants for *vic*-proton is *trans* > *cis*. The observed ^1H NMR coupling constants of the products (**4a** and **4b**) indicates $J_{Ha,Hb}$=1.7 Hz (**4a**) and $J_{Hc,Hd}$=1.8 Hz (**4b**). Furthermore, ^1H NMR coupling constants of the compound (**4c**) derived from compound (**4a**) by epimerization was $J_{He,Hf}$=8.0 Hz. From these results, the products (**4a** and **4b**) were assigned the *cis*-configuration. (Figure 2).

Figure 2



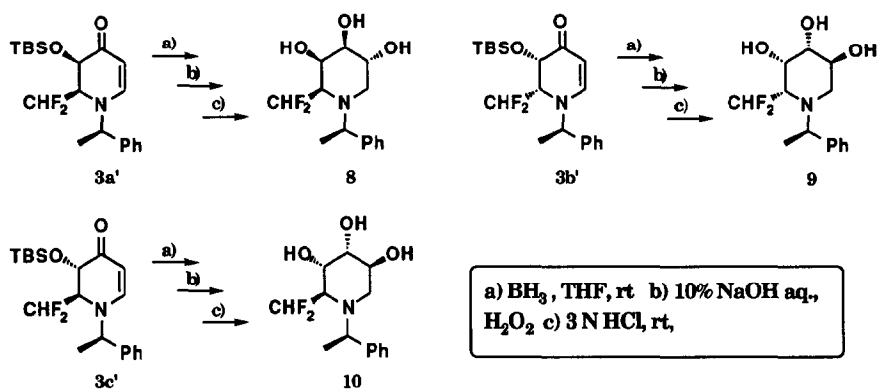
Scheme II



a) 1.0 M sodium bis(trimethylsilyl)amide in THF, -18 °C b) N-phenylsulfonyl 2-phenyloxazolidine, THF, -78 °C c) *p*-toluene sulfonic acid, Et_2O, CH_2Cl_2, 1 N HCl

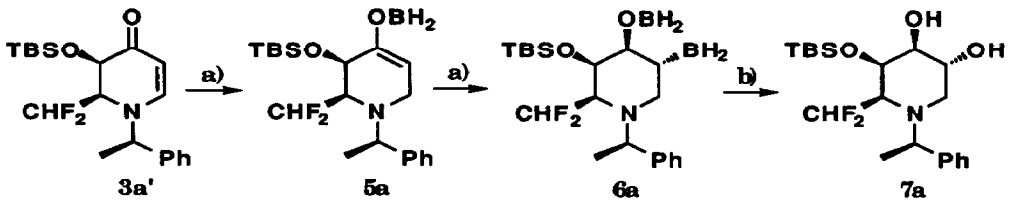
The next step is the transformation from compounds **3** to 1,6-dideoxy-6-difluoroazasugar derivatives. The desired reaction was eventually realized by utilization of BH_3 using the method developed by Klein and co-workers. These conditions gave highly diastereoselective bishydroxylation, which produced to the *trans*-2,3-diol stereoisomer. In the above transformation, more than 2 equiv of BH_3 per mole of compound **3** were required. Obviously, 1 equiv of BH_3 was consumed by the generation of the boron enolate **5** in situ (Scheme IV).

Scheme III



a) BH_3, THF, rt b) 10% NaOH aq., H_2O_2 c) 3 N HCl, rt,

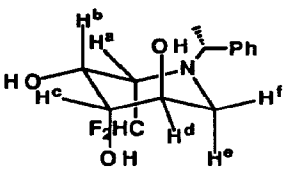
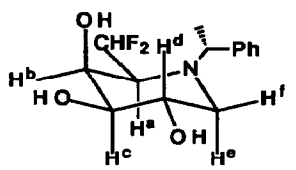
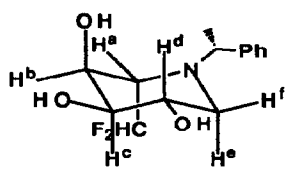
Scheme IV



a) BH_3, THF b) 10% NaOH aq., H_2O_2

The configuration of (α*R*)-N-(α-methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxy-piperidine (**8**, **9**, **10**) was assigned by ^1H NMR coupling constants.

Table 2 ^1H NMR Coupling Constants (Hz) of Products (8,9,10)

Compound	Product	Coupling constants (Hz)
8		$J_{Ha,Hb}$ = 2.81, $J_{Hb,Hc}$ = 2.81 $J_{Hc,Hd}$ = 9.40, $J_{Hd,He}$ = 9.64 $J_{Hd,Hf}$ = 5.05
9		$J_{Ha,Hb}$ = 3.66, $J_{Hb,Hc}$ = 3.90 $J_{Hc,Hd}$ = 8.06, $J_{Hd,He}$ = 8.55 $J_{Hd,Hf}$ = 1.95
10		$J_{Ha,Hb}$ = 3.18, $J_{Hb,Hc}$ = 2.44 $J_{Hc,Hd}$ = 8.30, $J_{Hd,He}$ = 8.50 $J_{Hd,Hf}$ = 4.39

To determine the inhibitory effect of compounds (**8**, **9**, **10**) on cell-to-cell transmission of HIV, CD4+ HTLV-1-transformed clonal T cells, ATHS cells were cultured containing various concentrations of the compounds. The pretreated HIV-1I, AI(IIIB) were mixed with uninfected cells, and then cultured at the final cell density of 3 x 10^5 cells/l. The viable cells were counted. In this assay system, no antiviral activity of any of the compounds (**8**, **9**, **10**) was detected at concentrations of up to 100 μM.

Experimental Section

General Procedures. All commercially available reagents were used without further purification. Infrared spectra were obtained by using a JASCO A-102 or a Jasco FT/IR-5000 spectrometer and KBr pellets. Nuclear magnetic resonance (NMR) spectra were recorded at 200 MHz or 500 MHz for ^{1}H NMR (internal Me_4Si) and at 470 MHz for ^{19}F NMR (internal C_6F_6) at 125 MHz for ^{13}C NMR in $CDCl_3$. Yields were those of isolated products.

(α*R*)-*N*-(2,2-Difluoroethylidene)(α-methylbenzyl)amine (**1a**). To a solution of (*R*)-(α-methylbenzyl)amine (1.15 mL, 9.0 mmol, >96% ee) in toluene, difluoroacetaldehyde ethyl hemiacetal (1.26 g, 10 mmol) was added at 0 °C, and then the mixture was sirred at 100 °C for 3 h. After removing water and ethanol under reduced pressure, the residual oil was purified by distillation to afford (α*R*)-N-(2,2-difluoroethylidene)(α-methylbenzyl)amine (**1a**) in 85% yield, bp 55-56 °C(5 mmHg):$[\alpha]^{19}_D$ +90.8 (c 1.06, MeOH);^{1}H NMR ($CDCl_3$):δ 1.54 (d, 3 H, $J_{H,H}$ = 6.68 Hz), 4.49 (d, 1H, $J_{H,H}$ = 6.88 Hz), 6.02 (td, 1H, $J_{H,H}$ = 5.29, $J_{H,F}$ = 55.0 Hz), 7.20~7.40 (m, 5H, Ar-H), 7.68 (dtd, 1H, $J_{H,H}$ = 0.8, 2.1, 5.2 Hz);^{13}C NMR ($CDCl_3$): δ 24.0 (t, J= 1.4Hz), 69.11 (s), 113.1 (t, J = 238Hz), 126.6 (s), 127.5, 128.7, 142.8 (s), 153.9 (t, J = 32.0Hz);^{19}F NMR ($CDCl_3$):δ 38.9 (ddd, 1F, $J_{F,H}$ = 4.58, 54.9, $J_{F,F}$ = 330 Hz), 39.6 (ddd, 1F, $J_{F,H}$ = 4.57, 54.9, $J_{F,F}$ = 330 Hz);IR (cm^{-1}): 1390 (C=N); Analysis: Calcd. for $C_{10}H_{11}NF_2$: C, 65.56; H, 6.05; N, 7.65%. Found: C, 65.88; H, 5.89; N, 7.94%.

(α*S*)-*N*-(2,2-Difluoroethylidene)(α-methylbenzyl)amine (**1b**). (*S*)-(α-Methylbenzyl)amine (1.15 mL, 9.0 mmol, >96% ee) and difluoroacetaldehyde ethyl hemiacetal (1.26 g, 10 mmol) were used and worked up similarly. (α*S*)-N-(2,2-difluoroethylidene)(α-methylbenzyl)amine (**1b**) was obtained. $[\alpha]^{22}_D$ -70.43 (c 0.72, $CHCl_3$).

(α*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2**). To a solution of zinc chloride (0.80 g, 5.9 mmol), (α*R*)-N-(2,2-difluoroethylidene)(α-methylbenzyl)amine (**1a**) (1.0 g, 5.9 mmol) and 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (1.51 g, 8.8 mmol) in THF (50 mL) were added. After 3 h of stirring at room temperature, the whole was added into the water, and then oily materials were extracted with ethyl acetate. The extracts were dried over magnesium sulfate. On removal of the solvent, crude epimers (1:1 mixture), (α*R*)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2**) was isolated in 83% yield. Epimers were separated by the column chromatography on silica gel using by a mixture of *n*-hexane and ethyl acetate (1: 3) as eluent, giving compound (**2a**) (43% yield) and compound (**2b**) (40% yield).

(α*R*, 6*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2a**); $[\alpha]^{19}_D$ +523.7 (c 1.07, MeOH);R_f 0.35 (AcOEt : Hexane = 3 : 1);^{1}H NMR ($CDCl_3$): δ 1.68 (d, 3 H, $J_{H,H}$ = 6.84 Hz), 2.55 (d, 1 H, $J_{H,H}$ = 17.3 Hz), 2.79 (ddd, 1 H, $J_{H,H}$ = 2.20, 7.57, 17.3 Hz), 3.58 (m, 1 H), 4.65 (q, 1 H, $J_{H,H}$ = 7.08 Hz), 5.13 (dd, 1 H,$J_{H,H}$ = 0.73, 7.57 Hz), 5.97 (dt, 1 H, $J_{H,H}$ = 6.59, $J_{H,F}$=55.9 Hz), 7.20-7.40 (m, 5H, Ar-H),

7.48 (dd, 1 H, $J_{H,H}$= 0.98, 7.57 Hz);^{13}C NMR ($CDCl_3$):δ 21.29 (s), 34.39 (t, J=3.8 Hz), 58.49 (t, J =23.8 Hz), 62.93 (t, J=1.6 Hz), 99.52 (s), 113.09 (t, J=246.6 Hz), 125.77 (s), 128.39 (s), 129.28 (s), 142.21 (s), 147.89 (s), 188.58 (s);^{19}F NMR($CDCl_3$): δ 34.91 (ddd, 1F, $J_{F,H}$=7.4, 54.93, $J_{F,F}$ = 288 Hz), 35.50 (ddd, 1F, $J_{F,H}$ = 9.16, 54.9, $J_{F,F}$ = 288 Hz);IR(cm^{-1}):1650 (C=O); high-resolution mass calcd for $C_{14}H_{15}NOF_2$ $(M)^+$ 251.1122, found 251.1120.

(α*R*, 6*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2b**); mp 107-108 °C: $[\alpha]^{18}_D$ -236.1 (c 0.72, MeOH);^{1}H NMR ($CDCl_3$):δ 1.64 (d, 3 H, $J_{H,H}$ = 7.08 Hz), 2.44 (dt, 1 H, $J_{H,H}$ = 1.22, 17.6 Hz), 2.71 (dd, 1 H, $J_{H,H}$ = 7.57, 17.3 Hz), 3.83 (m, 1 H), 4.71 (q, 1 H, $J_{H,H}$ = 6.83 Hz), 4.96 (dd, 1 H, $J_{H,H}$ = 0.73, 7.56 Hz), 5.97 (dt, 1 H, $J_{H,H}$ = 6.59, $J_{H,F}$ = 55.9 Hz), 6.90 (dd, 1 H, $J_{H,H}$ = 1.22, 7.81 Hz), 7.2-7.4 (Ar-H); ^{13}C NMR ($CDCl_3$):δ 21.29 (t, J = 1.1 Hz), 35.22 (dd, J = 2.2, 4.9 Hz), 57.92 (dd, J = 22.1, 25.8 Hz), 63.10 (s), 99.93 (s), 113.56 (dd, J = 245.2, 247.8 Hz), 128.10 (s), 129.23 (s), 129.65 (s), 139.21 (s), 150.73 (s), 189.30 (s);^{19}F NMR($CDCl_3$):δ 35.1 (ddd, 1F, $J_{F,H}$ = 12.2, 56.5, $J_{F,F}$ = 288 Hz), 36.9 (ddd, 1F, $J_{F,H}$ = 7.63, 54.9, $J_{F,F}$ = 288 Hz);IR(cm^{-1}): 1650 (C=O). Anal. Calcd for $C_{14}H_{15}NOF_2$: C, 66.92; H, 6.02; N, 5.57%. Found: C, 66.37; H, 6.31; N, 5.46%.

(α*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone. In the above reaction, zinc chloride (0.80 g, 5.9 mmol), (α*S*)-N-(2,2-difluoroethylidene) (α-methylbenzyl)amine (**1b**) (1.0 g, 5.9 mmol) and 1-methoxy-3-[(trimethylsilyl)-oxy]-1,3-butadiene (1.51 g, 8.8 mmol) in THF (50 mL) were used, and then worked up similarly. (α*S*)-N-(α-methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone was obtained in 40% yield.

(α*S*, 6*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2c**); $[\alpha]^{19}_D$ -475.9 (c 1.07, $CHCl_3$). (α*S*, 6*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-5,6-dihydro-4-pyridone (**2d**); $[\alpha]^{19}_D$ +332.7 (c 0.30, $CHCl_3$).

(α*R*, 5*R*, 6*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-5-[(*t*-butyldimethyl-silyl)oxy]-5,6-dihydro-4-pyridone (**3a'**). To a mixture solution of THF (4 mL) and sodium bis(trimethylsilyl)amide (3 mL, 3 mmol; 1.0 M in THF) under an atmosphere of nitrogen, a solution of (α*R*, 6*R*)-N-(α-methylbenzyl)-6-difluoro-methyl-5,6-dihydro-4-pyridone (640 mg, 2.5 mmol) in THF (4 mL) was added at -18 °C, and then the whole was stirred for 30 min at that temperature. After the mixture was cooled to -78 °C, the cooled solution of 2-sulfonyloxazolidine (990 mg, 3.8 mmol) in THF (4 mL) was added to the above mixture at -78 °C. After 1 h of stirring at that temperature, the reaction mixture was quenched with aq. *p*-toluene sulfonic acid (20 mL, 0.5 mol/L). The mixture was poured into a solution of diethyl ether (15 mL) and methylene chloride (5 mL). The whole was washed with water (3 x 10 mL), 1N HCl (1 x 10 mL) and brine (1 x 10 mL), and then the organic layer was dried over magnesium sulfate. On removal of the solvent, (α*R*, 5*R*, 6*R*)-N-(α-methylbenzyl)-6-difluoromethyl-5-hydroxy-5,6-dihydro-4-pyridone (**3a**) was isolated by the column chromatography on silica gel by using

a mixture solution of hexane and ethyl acetate (1 : 2) as eluent in 18% yield. To a solution of above obtained (**3a**) in methylene chloride (10 mL), imidazole (143 mg, 2.0 mmol) and *t*-butyldimethylsilylchloride (300 mg, 2.0 mmol) were added at room temperature. After 30 min of stirring, the whole was poured into water and the organic layer was dried over magnesium sulfate. On removal of the solvent, the title material was isolated in 96% yield by column chromatography on silica gel using by a mixture of hexane and ethyl acetate (1 : 1) as eluent. mp 106-107 °C; $[\alpha]^{22}_{D}$ +275.2 (c 0.24, $CHCl_3$); R_f 0.50 (AcOEt : Hexane = 1:2); ^1H NMR ($CDCl_3$):δ 0.40 (s, 9 H), 0.75 (s, 6 H), 1.66 (d, 3 H, $J_{H,H}$ = 7.04 Hz), 3.60 (m, 1 H, $J_{H,H}$ = 1.22, 1.70, 6.10, $J_{H,F}$ = 10.98, 15.13 Hz), 3.86 (dd, 1 H, $J_{H,H}$ = 1.69 Hz), 4.62 (q, 1 H, $J_{H,H}$ = 7.06 Hz), 5.04 (dd, 1 H, $J_{H,H}$ = 1.51, 7.78 Hz), 5.73 (ddt, 1 H, $J_{H,H}$ = 0.61, 6.23 Hz, $J_{H,F}$ = 55.42 Hz), 7.26 (dd, 1 H, $J_{H,H}$ = 1.34, 7.32 Hz), 7.30-7.45 (Ar-H); ^{13}C NMR ($CDCl_3$): δ -4.55 (s), -4.36 (s), 18.64 (s), 21.76 (s), 26.16 (s), 63.14 (s), 66.83 (t, J = 22.7 Hz), 69.16 (dd, J = 3.5, 5.0 Hz), 96.55 (s), 113.14 (t, J = 246.4 Hz), 126.99 (s), 128.56 (s), 129.47 (s), 141.33 (s), 148.41 (s), 188.07 (s); ^{19}F NMR ($CDCl_3$):δ 38.7 (dddd, 1F, $J_{F,H}$ = 1.53, 8.39, 57.98, $J_{F,F}$ = 296.8 Hz), 39.6 (ddd, 1F, $J_{F,H}$ = 9.06, 54.16, $J_{F,F}$ = 297 Hz); IR(cm^{-1}): 1640 (C=O).

(α*R*, 5*S*, 6*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-5-[(*t*-butyldimethylsilyl) oxy]-5,6-dihydro-4-pyridone (**3b'**). In the above reaction, (α*R*, 6*S*)-N-(α-methyl-benzyl)-6-difluoro-methyl-5,6-dihydro-4-pyridone was used, and worked up similarly. Crude (α*R*, 5*S*, 6*S*)-N-(α-methylbenzyl)-6-difluoro-methyl-5,6-dihydro-4-pyridone (**3b**) was isolated by the column chromatography on silica gel using by a mixture solution of hexane and ethyl acetate (1: 2) as eluent in 42% yield. To a solution of crude (**3b**), imidazole and *t*-butyldimethylsilylchloride in methylene chloride were used in the above reaction, and worked up similarly. The title material was obtained in 99% yield by column chromatography on silica gel using by a mixture of hexane and ethyl acetate (1 : 1) as eluent. mp 106-107 °C; $[\alpha]^{26}_{D}$ -96.8 (c 0.24, $CHCl_3$); R_f 0.60 (AcOEt : Hexane = 1 : 2); ^1H NMR ($CDCl_3$):δ 0.10 (s, 6 H), 0.92 (s, 9 H), 1.64 (d, 3 H, $J_{H,H}$ = 6.83 Hz), 3.81 (dddt, 1 H, $J_{H,H}$ = 1.22, 1.85, 6.47 Hz, $J_{H,F}$ = 10.0 Hz), 3.90 (dd, 1 H, $J_{H,H}$ = 1.80 Hz), 4.66 (q, 1 H, $J_{H,H}$ = 7.10 Hz), 4.87 (dd, 1 H, $J_{H,H}$ = 1.51, 7.71 Hz), 5.84 (dt, 1 H, $J_{H,H}$ = 6.6, $J_{H,F}$ = 55.2 Hz), 6.75 (dd, 1 H, $J_{H,H}$ = 1.10, 7.53 Hz), 7.41 (Ar-H); ^{13}C NMR ($CDCl_3$):δ -4.29 (s), -3.10 (s), 19.48 (s), 26.15 (s), 26.21 (s), 62.90 (s), 66.90 (t, J = 21.9 Hz), 68.93 (t, J = 4.04 Hz), 97.17 (s), 112.91 (t, J = 245 Hz), 128.56 (s), 129.15 (s), 129.52 (s), 138.80 (s), 149.49 (s), 188.34 (s); ^{19}F NMR ($CDCl_3$) : δ 39.4 (ddd, 1F, $J_{F,H}$ = 10.7, 54.9, $J_{F,F}$ = 294 Hz), 40.0 (ddd, 1F, $J_{F,H}$ = 9.15, 54.9, $J_{F,F}$ = 294 Hz); IR(cm^{-1}): 1650 (C=O), 1580 (C=C).

(α*R*, 3*R*, 4*S*, 5*R*, 6*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxy-piperidine (**8**). (a) Reduction of compound (**3a'**). To a solution of compound (**3a'**) (1 mmol) in THF (3 mL), was added BH_3-THF (2.0 mL, 2.0 mmol; 1 M solution in THF) at 0 °C. After the solution was stirred at room temperature for 2 h, 10% NaOH aq (2.0 mL) and 35% H_2O_2 aq (2.0 mL) was added and the whole solution was allowed to warm to room temperature. After the whole was stirred at that

temperature for 1 h, the solution was cooled by an ice bath and then saturated $Na_2S_2O_3$ aq was added into the solution. The mixture was allowed to warm to room temperature, and then the whole was stirred at that temperature for 3 h. The whole solution was poured into water, and oily materials were extracted with ethyl acetate. On removal of the solvent, (α*R*, 3*R*, 4*S*, 5*R*, 6*R*)-N-(α-methylbenzyl)-6-difluoromethyl-5-[(*t*-butyldimethylsilyl)oxy]-3,4-dihydroxy-piperidine (**7a**) was obtained in 66% yield by column chromatography on silica gel using the mixture of hexane and ethyl acetate (5 : 1) as eluent. $[\alpha]^{27}_D$ +40.7 (c 0.22, $CHCl_3$); R_f 0.32 (AcOEt : Hexane = 1 : 5);^{1}H NMR ($CDCl_3$):δ 0.05 (s, 3 H), 0.13 (s, 3 H), 0.95 (s, 9 H), 1.41 (d, 3 H, $J_{H,H}$ = 6.59 Hz), 2.58 (dt, 1 H, $J_{H,H}$ = 1.46, 11.5 Hz), 2.94 (ddd, 1 H, $J_{H,H}$ = 0.73, 4.64, 12.9 Hz), 3.32 (ddt, 1 H, $J_{H,H}$ = 2.24, 12.7 Hz, $J_{H,F}$ = 10 Hz), 3.23 (m, 1 H), 3.84 (dt, 1 H, $J_{H,H}$ = 4.64, 9.28 Hz), 4.19 (q, 1 H, $J_{H,H}$ = 6.59 Hz), 4.22 (t, 1 H, $J_{H,H}$ = 3.18 Hz), 5.95 (dt, 1 H, $J_{H,H}$ = 3.42, $J_{H,F}$ = 55.7 Hz), 7.20-7.40 (m, 5H, Ar-H);^{13}C NMR ($CDCl_3$): δ -4.50 (s), -4.35 (s), 22.18 (s), 26.27 (s), 48.57 (s), 60.44 (s), 63.66 (t, J = 20.5 Hz), 67.71 (s), 69.44 (t, J = 2.1 Hz), 74.64 (s), 116.22 (t, J = 247 Hz), 127.64 (s), 127.76 (s), 128.96 (s), 144.87 (s);^{19}F NMR ($CDCl_3$) : δ 41.4 (ddd, 1F, $J_{F,H}$ = 10.6, 54.9, $J_{F,F}$ = 285 Hz), 43.1 (ddd, 1F, $J_{F,H}$ = 7.63, 53.4, $J_{F,F}$ = 285 Hz);IR(cm^{-1}): 3400 (OH).

(b) Deprotection (**7a**). The solution of the above compound (40 mg, 0.1 mmol) and 3 N HCl (10 mL) in methanol (3 mL) was stirred at room temperature for 24 h. The whole solution was poured into saturated $NaHCO_3$ aq, and then oily materials was extracted with ethyl acetate. On removal of the solvent, (α*R*, 3*R*, 4*S*, 5*R*, 6*R*)-N-(α-methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxypiperidine (**8**) was obtained in 60% yield by column chromatography on silica gel using the mixture of hexane and ethyl acetate (2 : 1) as eluent.$[\alpha]^{25}_D$ +55.8 (c 0.30, $CHCl_3$); R_f 0.09 (AcOEt : Hexane = 1 : 5);^{1}H NMR ($CDCl_3$):δ 1.40 (d, 3 H, $J_{H,H}$ = 6.35 Hz), 2.58 (t, He, $J_{He,Hf}$ = 11.48 Hz), 3.11 (dd, Hf, $J_{Hf,Hd}$ = 5.50, $J_{Hf,He}$= 12.58 Hz), 3.33 (tbr, Ha, $J_{H,F}$ = 14.9 Hz), 3.54 (dd, Hc, $J_{Hc,Hb}$ = 2.76, $J_{Hc,Hd}$ = 9.40 Hz), 3.86 (dt, Hd, $J_{Hd,Hf}$ = 5.05, $J_{Hd,He}$ = 9.64 Hz), 4.04 (tbr, Hb, $J_{Hb,Hc}$ = 2.81 Hz), 4.11 (q, 1 H, $J_{H,H}$ = 6.43 Hz), 6.13 (ddd, 1 H, $J_{H,H}$ = 4.15, $J_{H,F}$ = 54.7, 55.4 Hz), 7.20-7.40 (Ar-H);^{13}C NMR ($CDCl_3$):δ 21.86 (s), 48.12 (s), 60.26 (s), 61.90 (t, J = 20.5 Hz), 67.86 (s), 67.98 (s), 73.84 (s), 115.27 (t, J = 247 Hz), 127.03 (s), 127.42 (s), 128.75 (s), 144.37 (s); ^{19}F NMR ($CDCl_3$):δ 40.7 (ddd, 1F, $J_{F,H}$ = 18.3, 56.5, $J_{F,F}$ = 293 Hz), 44.2 (ddd, 1F, $J_{F,H}$ = 12.2, 54.9, $J_{F,F}$ = 293 Hz). Analysis: Calcd for $C_{14}H_{19}NO_3F_2$: C, 58.53; H, 6.67; N, 4.45%. Found: C,58.34; H, 6.99; N, 4.50%.

(α*R*, 3*S*, 4*R*, 5*S*, 6*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxypiperidine (**9**). (a) Reduction of compound (**3b'**). In the above reaction, compound (**3b'**) was used, and then worked up similarly. (α*R*, 3*S*, 4*S*, 5*S*, 6*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-5-[(*t*-butyldimethylsilyl)oxy]-3,4-dihydroxypiperidine was obtained in 40% yield by column chromatography on silica gel using the mixture of hexane and ethyl acetate (4 : 1) as eluent. $[\alpha]^{21}_D$ -23.8 (c 0.33, MeOH); R_f 0.20

(AcOEt : Hexane = 1 : 3);^{1}H NMR ($CDCl_3$):δ 0.00 (s, 6 H), 0.80 (s, 9 H), 1.20 (d, 3 H, $J_{H,H}$ = 6.59 Hz), 2.26 (dt, 1 H, $J_{H,H}$ = 5.62, 12.5 Hz), 2.63 (dd, 1 H, $J_{H,H}$ = 2.93, 12.5 Hz), 3.10 (dddd, 1 H, $J_{H,H}$ = 4.89, 10.0, $J_{H,F}$ = 18.1 Hz), 3.20 (s, 1 H), 3.43 (t, 1 H, $J_{H,H}$ = 4.15 Hz), 3.69 (dt, 1 H, $J_{H,H}$ = 0.37, 4.89 Hz), 6.24 (dt, 1 H, $J_{H,H}$ = 4.88, $J_{H,F}$ = 55.7 Hz), 7.00-7.20 (Ar-H);^{13}C NMR ($CDCl_3$):δ -4.65 (s), -4.01 (s), 17.58 (s), 26.31 (s), 47.23 (s), 59.51 (s), 62.91 (t, J = 19.0 Hz), 70.34 (s), 71.24 (t, J = 5.0 Hz), 74.18 (s), 116.03 (t, J = 243 Hz), 127.43 (s), 127.89 (s), 128.78 (s), 145.42 (s);^{19}F NMR ($CDCl_3$) : δ 34.42 (dd, 1F, $J_{F,H}$ = 55.7, $J_{F,F}$ = 296 Hz), 38.72 (ddd, 1F, $J_{F,H}$ = 6.10, 54.9, $J_{F,F}$ = 296 Hz); IR(cm^{-1}): 3400 (OH).

(b) Deprotection (**7b**). The solution of the above compound (280 mg, 0.7 mmol) and 3 N HCl (10 mL) in methanol (3 mL) was stirred at room temperature for 24 h, and then worked up similarly. (α*R*, 3*S*, 4*R*, 5*S*, 6*S*)-N-(α-Methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxy-piperidine (**9**) was obtained in 70% yield by column chromatography on silica gel using the mixture of hexane and ethyl acetate (2 : 1) as eluent.$[\alpha]^{14}_D$ -9.2 (c 0.29, MeOH);R_f 0.12 (AcOEt : Hexane = 1 : 1); ^{1}H NMR ($CDCl_3$):δ 1.38 (d, 3 H, $J_{H,H}$ = 6.59 Hz), 2.47 (dd, He, $J_{He,Hd}$= 8.54, $J_{He,Hf}$ = 12.7 Hz), 2.94 (dd, Hf, $J_{Hf,Hd}$= 4.40, $J_{Hf,He}$ = 12.9 Hz), 3.42 (tt, Ha, $J_{Ha,Hb}$ = 3.66, $J_{H,F}$ = 14.2 Hz), 3.63 (ddd, Hc, $J_{H,H}$ = 0.49, $J_{Hc,Hb}$ = 3.17, $J_{Hc,Hd}$ = 8.06 Hz), 3.71 (dt, Hd, $J_{Hd,Hf}$ = 3.95,$J_{Hd,He}$ = 8.55 Hz), 4.07 (t, Hb, $J_{Hb,Hc}$ = 3.90 Hz), 4.26 (q, 1 H, $J_{H,H}$ = 6.35 Hz), 6.06 (dt, 1 H, $J_{H,H}$ = 3.41 Hz, $J_{H,F}$ = 55.2 Hz), 7.20-7.40 (Ar-H);^{13}C NMR ($CDCl_3$):δ 20.78 (s), 49.63 (s), 61.20 (s), 63.24 (t, J = 19.7 Hz), 67.85 (s), 69.29 (t, J = 3.1 Hz), 74.68 (s), 117.94 (t, J = 244 Hz), 128.21 (s), 128.46 (s), 129.53 (s), 147.36 (s); ^{19}F NMR ($CDCl_3$):δ 37.0 (d, 1F, $J_{F,F}$ = 313 Hz), 40.7 (ddd, 1F, $J_{F,H}$ = 15.3, 54.9, $J_{F,F}$ = 313 Hz). Analysis: Calcd for $C_{14}H_{19}NO_3F_2$: C, 58.53; H, 6.67; N, 4.45%. Found: C,58.42; H, 6.98; N, 4.45%.

(α*R*, 3*S*, 4*R*, 5*S*, 6*R*)-N-(α-methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxy-piperidine (**10**). (a) (α*R*, 5*S*, 6*R*)-N-(Methylbenzyl)-6-difluoromethyl-5-[(*t*-butyl-dimethylsilyl)oxy]-5,6-dihydro-4-pyridone (**3c'**). (α*R*, 5*R*, 6*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-5-[(*t*-butyldimethylsilyl)oxy]-5,6-dihydro-4-pyridone (**3a'**) and lithium diisopropylamine (LDA) in tetrahydrofuran was stirred for 5 hr at room temperature. The whole was poured into water and the organic layer was extracted with dichloromethane. On removal of the solvent, the title material was isolated; $[\alpha]^{20}_D$ +324.9 (c 0.81, $CHCl_3$); R_f 0.53 (AcOEt : Hexane = 1 : 3);^{1}H NMR ($CDCl_3$): δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.78 (s, 9 H), 1.65 (d, 3 H, $J_{H,H}$ = 6.84 Hz), 3.54 (dtt, 1 H, $J_{H,H}$ = 1.95, 6.84, $J_{H,F}$ = 22.2 Hz), 4.46 (dd, 1 H, $J_{H,H}$ = 1.9, 8.0 Hz), 4.59 (q, 1 H, $J_{H,H}$ = 7.1 Hz), 4.86 (d, 1 H, $J_{H,H}$ = 7.57 Hz), 6.22 (dd, 1 H, $J_{H,H}$ = 2.20, $J_{H,F}$ = 54.5 Hz), 7.20-7.50 (Ar-H), 7.61 (d, 1 H, $J_{H,H}$ = 7.57 Hz);^{13}C NMR ($CDCl_3$): δ -5.54 (s), -4.11 (s), 21.42 (s), 26.14 (s), 63.22 (dd, J = 18.2, 19.9 Hz), 63.42 (d, J = 3.2 Hz), 70.62 (d, J = 5.0 Hz), 95.72 (s), 115.50 (dd, J = 241.6, 246.7 Hz), 126.27 (s), 128.79 (s), 129.5 (s), 143 (s), 148.37 (s), 190.47 (s);^{19}F NMR ($CDCl_3$) :δ 35.5 (ddd, 1F, $J_{F,H}$ = 21.4,

54.2, $J_{F,F}$ = 289 Hz), 38.1 (dddd, 1F, $J_{F,H}$ = 2.29, 7.63, 54.9, $J_{F,F}$ = 289 Hz);IR(cm^{-1}): 1680 (C=O), 1600 (C=C).

(b) Reduction of compound (**3c'**). In the above reaction, compound (**3c'**) was used, and then worked up similarly. (αR, 3*S*, 4*S*, 5*S*, 6*R*)-N-(α-methylbenzyl)-6-difluoromethyl-5-[(*t*-butyldimethylsilyl)oxy]-3,4-dihydroxypiperidine was obtained in 54% yield by column chromatography on silica gel using the mixture of hexane and ethyl acetate (4 : 1) as eluent. $[\alpha]^{18}_D$ -5.3 (c 0.29, $CHCl_3$); R_f 0.53 (AcOEt : Hexane = 1 : 3);^{1}H NMR ($CDCl_3$): δ -0.14 (s, 3 H), -0.07 (s, 3 H), 0.91 (s, 9 H), 1.37 (d, 3 H, $J_{H,H}$ = 6.60 Hz), 2.87 (dt, 1 H, $J_{H,H}$ = 6.88, $J_{H,F}$ = 23.7 Hz)), 2.94 (d, 1 H, $J_{H,H}$ = 13.0 Hz), 3.22 (d, 1 H, $J_{H,H}$ = 13.2 Hz), 3.80-3.90 (m, 2 H), 3.92 (dd, 1 H, $J_{H,H}$ = 3.46, 6.58 Hz), 4.23 (q, 1 H, $J_{H,H}$ = 5.70 Hz), 6.45 (dt, 1 H, $J_{H,H}$ = 5.30, $J_{H,F}$ = 46.6 Hz), 7.30-7.40 (Ar-H);^{13}C NMR ($CDCl_3$): δ -4.95 (s), -4.37 (s), 22.47 (s), 26.15 (s), 43.88 (s), 60.46 (s), 60.86 (dd, J = 12.5, 17.8 Hz), 68.60 (s), 68.71 (s), 72.85 (s), 118.17 (t, J = 256.5 Hz), 127.64 (s), 127.91 (s);^{19}F NMR ($CDCl_3$) : δ (dd, 1F, $J_{F,H}$ = 55.7, $J_{F,F}$ = 296 Hz), (ddd, 1F, $J_{F,H}$ = 6.10, 54.9, $J_{F,F}$ = 296 Hz);IR(cm^{-1}): 3500 (OH).

(c) Deprotection (**7c**). The solution of the above compound and 3 N HCl (10 mL) in methanol (3 mL) was stirred at room temperature for 24 h, and then worked up similarly. (αR, 3*S*, 4*R*, 5*S*, 6*R*)-N-(α-Methylbenzyl)-6-difluoromethyl-3,4,5-trihydroxypiperidine (**10**) was obtained in 61% yield by column chromatography on silica gel using the mixture of hexane and ethyl acetate (2 : 1) as eluent. $[\alpha]^{18}_D$ -7.2 (c 0.21, MeOH);R_f 0.22 (AcOEt : Hexane = 1 : 1);^{1}H NMR ($CDCl_3$): δ 1.47 (d, 3 H, $J_{H,H}$ = 6.09 Hz), 1.86 (dd, He, $J_{He,Hd}$ = 9.27, $J_{He,H\,f}$= 11.7 Hz), 2.86 (ddt, Ha, $J_{H,H}$ = 4.40, $J_{Ha,Hb}$ = 3.18 Hz, $J_{H,F}$ = 10.26 Hz), 3.13 (dd, Hf, $J_{Hf,Hd}$ = 4.29, $J_{Hf,He}$ = 10.96 Hz), 3.21 (dd, Hc, $J_{Hc,Hb}$ = 3.18, $J_{Hc,Hd}$ = 8.30 Hz), 3.77 (dt, Hd, $J_{Hd,Hf}$ = 4.39, $J_{Hd,He}$ = 8.5 Hz), 4.02 (dd, Hb, $J_{Hb,Hc}$ = 2.44 Hz), 4.27 (q, 1 H, $J_{H,H}$ = 6.84 Hz), 6.20 (dt, 1 H, $J_{H,H}$ = 4.64, $J_{H,F}$ = 54.4 Hz), 7.20-7.40 (Ar-H);^{13}C NMR ($CDCl_3$): δ 19.48 (s), 49.28 (s), 56.67 (s), 62.85 (t, J = 20.0 Hz), 69.29 (s), 116.92 (t, J = 242.2 Hz), 127.49 (s), 128.05 (s), 128.26 (s), 138.95 (s);^{19}F NMR ($CDCl_3$):δ 42.7 (ddd, 1F, $J_{F,H}$ = 10.7, 53.4, $J_{F,F}$ = 292 Hz), 41.7 (ddd, 1F, $J_{F,H}$ = 9.16, 51.9, $J_{F,F}$ = 292 Hz). Analysis: Calcd for $C_{14}H_{19}NO_3F_2$: C, 58.53; H, 6.67; N, 4.45%. Found: C,58.64; H, 6.76; N, 4.61%.

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(*Received* 16 *March* 1994)