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Selectivities in the Oxidation of Tertiary Amines and Pyridine Derivatives by Perfluoro *Cis*-2,3-dialkyloxaziridines.

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Abstract: When tertiary amines **1** are reacted with perfluoro *cis*-2,3-dialkyloxaziridines **2** at -60 °C corresponding *N*-oxides **3** are formed in high yields. The process is chemoselective and diastereoselective. The chemoselectivity in the reaction of alkenyl substituted pyridines is solvent dependent, attack occurring exclusively at the carbon-carbon double bond or at the nitrogen atom under protic and aprotic conditions, respectively. Lower selectivities were obtained when standard reagents were used.

The behavior of nucleophilic species with hydrocarbon oxaziridines has been widely studied and it has been established that the attack usually occurs at either the nitrogen or the oxygen atoms of the ring. The site of the attack of the nucleophile, *i. e.* the aminating[1] or oxygenating[2] behavior of hydrocarbon oxaziridine, depends on the nature of the nucleophile and the substituent pattern of the oxaziridine, especially at nitrogen. Until now only few perfluorinated oxaziridines have been described and they have been challenged with a limited number of nucleophiles so that no general rules can be established. Fluoride ion[3] and alcoholates[3c, 4] are reported to attack the nitrogen atom of different perfluorinated oxaziridines and for a given nucleophile the isolated products depend on the oxaziridine ring substituents and on the adopted reaction conditions. The sp^2 nitrogen atoms of various heteroaromatic compounds have been both aminated and oxygenated by perfluorinated oxaziridines, steric hindrance around the nitrogen atoms plays a key role in determining the type of reactivity.[5]

In this paper it is described how perfluoro *cis*-2,3-dialkyloxaziridines **2** exclusively oxygenate the sp^3 nitrogen atom of tertiary amines **1** in high yields. The reaction has been performed also on some complex and polyfunctional compounds with noteworthy chemo- and diastereoselectivities. It is also described how the site of reaction of alkenyl substituted pyridines **5** (namely oxidation at either the nitrogen atom or the double bond) can be controlled by simply choosing the solvent employed in the reaction.

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Results and Discussion

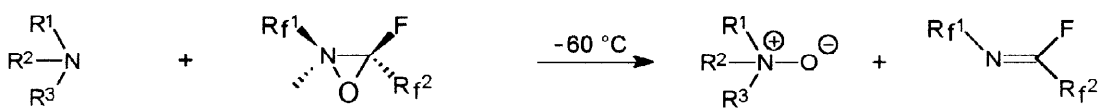
Synthesis of tertiary amine N-oxides 3. Interest in *N*-oxides of tertiary amines is due to their industrial applications (*e.g.* in selective metal extraction and detergent formulations, or as cellulose solvents), their use as intermediates and reagents in organic synthesis,[6] their occurrence in nature.[7] Hydrogen peroxide, organic hydroperoxides, organic and inorganic peracids, and oxygen under pressure[8] are traditional agents for *N*-oxide preparation starting from corresponding amines and recently also 2-sulfonyloxaziridines[9] and dioxiranes[10] have been successfully employed for this oxidation.

When simple trialkyl amines **1a-c** have been treated with perfluoro *cis*-2-*n*-butyl-3-*n*-propyloxaziridine **2a** the corresponding *N*-oxides **3a-c** have been isolated in nearly quantitative yields and the formation of perfluoro (*Z*)-5-azanon-5-ene **4a** as oxidation co-product was revealed by ^{19}F NMR of crude reaction mixture (Scheme 1). The oxidation was nearly instantaneous at room temperature and less than 20 min were required also in the cold (at -60 °C). Tri-*n*-octylamine (**1c**) reacted slower than triethylamine (**1b**) thus showing that steric hindrance around nitrogen retards the oxidation while no change in the reaction course and rates were observed when different halogenated solvents were used (tetrachloromethane, chloroform, methylene chloride, trichlorofluoromethane, dichloropentafluoropropanes). The oxidation occurred in nearly quantitative yields also with quinuclidine **1d** and *N*-allylpiperidine **1e**, *N*-allyloxypiperidine being isolated from the latter precursor as the formed *N*-oxide **3e** underwent *in situ* Meisenheimer rearrangement.[6a] The perfluoro *cis*-2-*n*-hexyl-3-*n*-pentyloxaziridine **2b** showed the same reactivity, *N*-oxides **3c-e** along with azaalkene co-product **4b** being formed in high yields starting from amines **1c-e**.

The oxidation of some structurally complex tertiary amines of natural origin or endowed with useful pharmacological properties has also been performed. The presence in these substrate molecules of several potential sites of oxidation allowed some functional group compatibilities to be established.

Dextromethorphan **1f** and lidocaine **1g** are anti tussive and anti arrhythmic drugs, respectively, and they both are routinely used in human therapy. On treatment with the perfluorinated oxaziridines **2**, they afforded the corresponding *N*-oxides **3f** and **3g**.[11] Brucine **1h** is a well known alkaloid isolated from *Strychnos* species and it gave the *N*-oxide **3h**[12] under the standard reaction conditions. Also the L-*N*,*N*-dimethylalaninyl ester of cholesterol **1i**, the α-adrenergic blocker fenspiride **1j**, and the antipsychotic drugs haloperidol **1k** and pimozide **1l** were cleanly oxidized and the corresponding *N*-oxides **3i, 3j**, and **3k,l**[13]

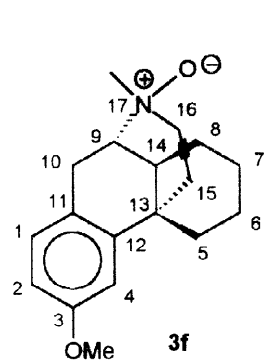
Scheme 1



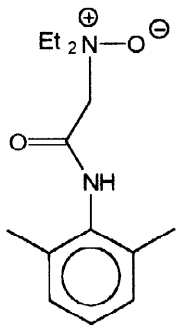
1a - e **2a, b** **3a - e** **4a, b**

	R^1, R^2, R^3		R_f^1	R_f^2
1a,3a	CH_3	**2a,4a**	n-C_4F_9	n-C_3F_7
1b,3b	C_2H_5	**2b,4b**	n-C_6F_{13}	n-C_5F_{11}
1c,3c	n-C_8H_{17}			
1d,3d	$CH(CH_2CH_2)_3$			
1e,3e	$(CH_2)_5$, $CH_2CH{=}CH_2$			

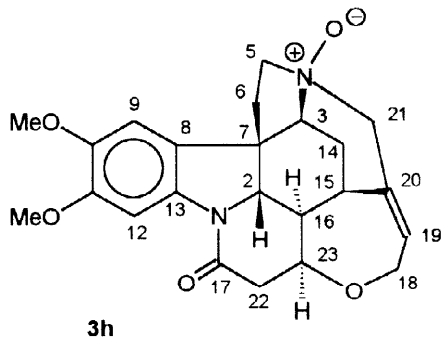
Scheme 2



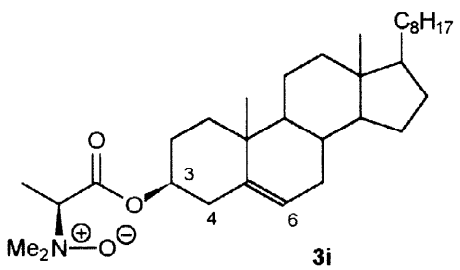
3f



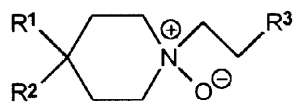
3g

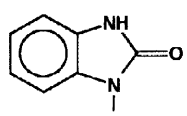


3h



3i



	R^1	R^2	R^3	Yield %
3j	-OCONHCH$_2$-		C_6H_5-	92
3k	OH	4-Cl-C_6H_4-	4-F-C_6H_4COCH$_2$-	93
3l	H		(4-F-C_6H_4)$_2$CHCH$_2$-	90

were obtained in nearly pure form after the work-up of the reaction mixture.

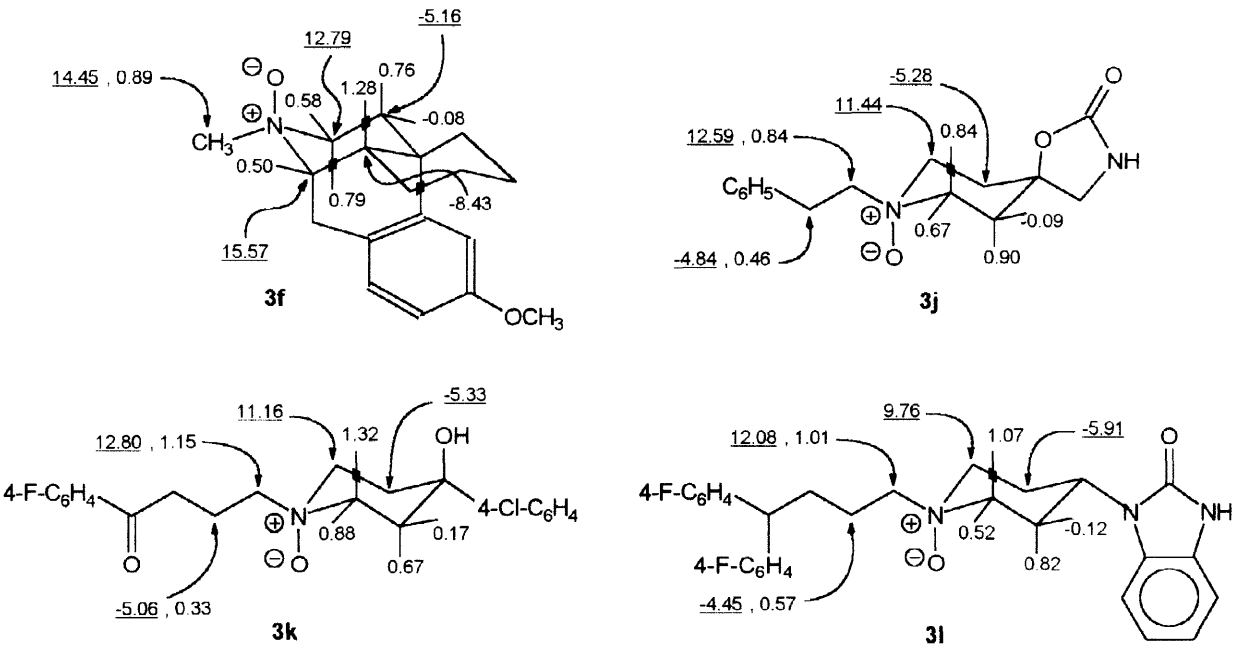
In order to compare the results described above with those obtained with standard oxidizing agents, some of the substrates **1** have been reacted with hydrogen peroxide (1.2 equivalents/30% aqueous solution/HCOOH/40 °C/3 h)[14] and *m*-chloroperbenzoic acid (MCPBA, 1.1 equivalent/CD_2Cl_2/-40 °C to room temperature/5 h).[15] Both reference reagents gave good yields in desired *N*-oxides starting from triethylamine (**1b**) and quinuclidine (**1d**) but low conversion was observed when trioctylamine (**1c**) was reacted with hydrogen peroxide. When the L-*N*,*N*-dimethylalaninyl ester of cholesterol **1i** was treated with MCPBA attack occurred at both nitrogen and olefinic sites, the *N*-oxide **3i** and the 5,6-epoxides (α,β mixture) of **1i** being formed (*N*-oxide/epoxide ratio 72 : 28). When the same substrate **1i** was reacted with hydrogen peroxide, the presence of *N*-oxide **3i** could never be detected among the reaction products and the acrylic ester of cholesterol was main product both at low and high conversion. Clearly, the *N*-oxide **3i** is formed but undergoes *in situ* an easy and quantitative Cope elimination.[16] Finally, when dextromethorphan (**1f**) was reacted with MCPBA, the electron rich aromatic ring also underwent oxidative attack[17] and **3f** was isolated as a mixture with a second *N*-oxide having only two aromatic protons.

Some general comments can be made on the above described reactions. The amine nitrogen is

attacked by oxaziridines **2** with complete preference over a tertiary amide, a urea, or a carbamate moiety thus showing that presence of various nitrogen functionalities in the substrate molecule do not interfere with the formation of tertiary amine *N*-oxides. While ethers of secondary alcohols[18] and olefine double bonds (those of cholesteryl esters included)[19] are oxidized by oxaziridines **2** (to give ketones and epoxides, respectively), also these functionalities remain unchanged under the reaction conditions employed for tertiary amine oxidation. These data are consistent with an easy and selective *N*-oxide formation from tertiary amines. In order to give nearly quantitative conversion of substrates **1**, oxaziridines **2** require milder conditions and shorter times than hydrogen peroxide and MCPBA. Higher yields can thus be obtained with oxaziridines **2** as other reactive sites (olefinic double bonds, electron rich aromatic rings) are not attacked and decomposition processes of formed *N*-oxides (Cope reaction) are avoided.

As to the diastereselectivity in the oxidation of tertiary amines, it is worth noting that a single *N*-oxide **3** was obtained starting from precursors **1f, h, j-l**. A detailed ^{1}H and ^{13}C NMR analysis of formed products **3f, h, j-l** allowed their relative stereochemistry and preferred conformation to be established. Some generalities have also been observed in the shielding and deshielding effects of proton and carbon atoms surrounding the nitrogen occurring on *N*-oxide formation in pyperidine systems. For instance, dextromethorphan *N*-oxide **3f** assumes preferentially the chair conformation reported in Figure 1. In fact, the *trans* diaxial disposition of H-15β and H-16α is proven by the value of their coupling constant (J = 13.0 Hz) and the β-axial orientation of the *N*-oxide is shown by the fact that irradiation of the N-Me protons in a nOe experiment enhanced H-16α (3.5%) but not H-15β. The β-H-effect exerted by the *N*-oxide group with respect to the starting compound is always deshielding and stronger for the *anti* than for the *gauche* proton ($\Delta\delta_H$ 0.79 and 0.58, 0.050, respectively).

Figure 1. Δδ Values ($\Delta\delta = \delta_{3f,\ j\text{-}l} - \delta_{1f,\ j\text{-}l}$, underlined digits refer to carbon) in β and γ positions for compounds **3f, j-l** with respect to precursors **1f, j-l**.



The *syn*-H-effect is deshielding too while the *gauche*-γ-effect is slightly shielding ($\Delta\delta_H$ 1.28, 0.76 and -0.08, respectively). In the ^{13}C NMR spectrum the corresponding β-C-effect varies from 12.79 to 15.57 ppm and the γ-C-effect ranges from -5.16 to -8.43 ppm. The piperidine ring of **3j-l** also adopt a chair conformation in which the oxygen of the *N*-oxide moiety is axially disposed (Figure 1) and ^1H and ^{13}C induced shifts are in the line with those described above for dextromethorphan *N*-oxide **3f**.

From the synthetic point of view, while it is not surprising that the rigid molecular arrangement of dextromethorphan and brucine allow corresponding *N*-oxides **3f, h** to be formed as a single stereoisomer, the exclusive formation of one *N*-oxide starting from piperidine precursors **1j-l** was less expected. Analyses of ^1H and ^{13}C NMR spectra of amines **1j-l** established that, in chloroform solution, these amines adopt nearly exclusively the chair conformation reported in Figure 1 for corresponding *N*-oxides **3j-l**. The relative stereochemistry between N-1 and C-4 in obtained *N*-oxides **3j-l** can thus be rationalized as result of this conformational preference and is consistent with a stereoconservative delivery of the oxygen by the oxaziridines **2** to the nitrogen lone pair of piperidine precursors **1j-l**..

Chemoselectivity in the oxidation of alkenyl substituted pyridines **5**. It has already been reported how perflouro-*cis*-2,3-dialkyloxaziridines **2a,b** can transform heteroaromatic nitrogen compounds into *N*-oxides[5a,b] and olefins into oxiranes[19] under particularly mild conditions. Here we describe how the chemoselectivity of the oxidation of alkenyl-pyridines **5** can be controlled by simply choosing the reaction solvent. Specifically, when pyridines **5a-c** are treated in the cold with stoichiometric amounts of oxaziridines **2a,b** in an halogenated solvent (Scheme 3, Route A), corresponding alkenyl substituted *N*-oxides **6a-c** are exclusively formed and can be isolated in medium to high yields (Table). The olefinic double bond present in substrate molecules remains unchanged in agreement with the fact that reaction temperatures required by perfluorinated oxaziridines to transform heteroaromatic nitrogen compounds into corresponding *N*-oxides are lower than those needed to epoxidize olefins.[5a,b,19]

The oxidative attack can be diverted to the carbon-carbon double bond by protonating the nitrogen.[20] In fact, when trifluoroacetic acid is used as the reaction solvent, selective epoxidation of the double bond is obtained (Route B) and dihydroxyalkylpyridines **7a-c** are exclusively isolated due to the fact that the acidic medium leads to *in situ* opening of initially formed oxiranes. Less acidic solvents (*e.g.* CH_3CO_2H, CF_3CH_2OH, $(CF_3)_2CHOH$) are less effective in diverting the oxidative attack from the nitrogen to the carbon site and mixtures of *N*-oxides **6** and diols **7** are formed. As already observed in the formation of *N*-oxides **3** and in other oxidation reactions,[18, 19, 21] oxaziridines **2a** and **2b** behaved similarly and both agents changed the chemoselectivity of oxidation on changing the reaction solvent.

Scheme 3

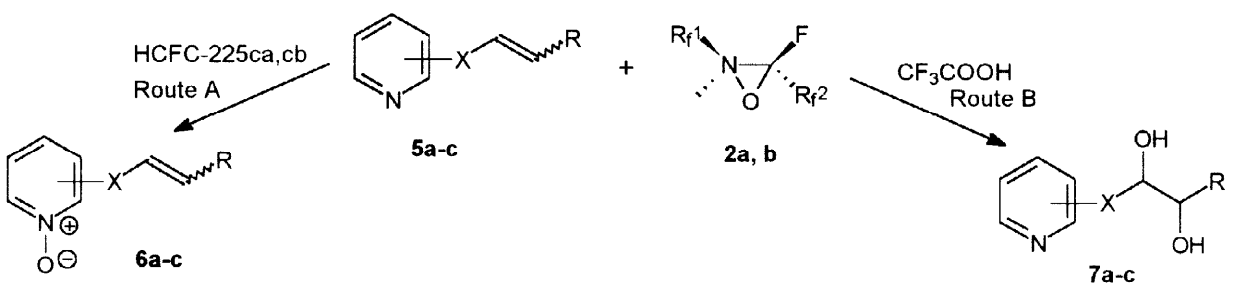


Table. Oxidation of Alkenyl-pyridines **5** with perfluorinated oxaziridine **2a**.

Pyridine Substrate **5**	—X⟨ ⟩R	Route	Product	Isolated Yield % from **2a**	from **2b**
5a	2-(CH_2CH_2CH=$CHCH_3$) (*E*/*Z* mixture)	A	**6a**	76	78
		B	**7a**	81[a]	84[a]
5b	2-($CH_2OC(=O)(CH_2)_4CH$=CH_2)	A	**6b**	79	
		B	**7b**	80	
5c	4-(CHCH$_2$CH$_2$CH=CHCH$_2$)	A	**6c**	69[b]	
		B	**7c**	72[c]	75[c]

([a]) Mixture of *threo* and *erythro* diols. ([b]) 4-(3-Cyclohexen-1-yl)-*N*-(perfluorobutanoyl)pyridinium-1-aminide (**8a**) was also formed (12% yield) starting from **2a** as this oxaziridine can also behave as aminating agent.[5b] ([c]) Only (1'*R**, 3'*S**,4'*S**)-4-(3',4'-dihydroxycyclohexyl)pyridine **7c** was formed.

Interestingly 4-(4'-pyridyl)-1,2-cyclohexanediol **7c** has been isolated as a single diastereoisomer thus showing how epoxidation of the 4-(4'-yclohexenyl)pyridine **5c** and successive solvolysis of the oxirane ring occur with complete diastereoselectivity.

To test the effectiveness of our approach, some comparison experiments with other oxidizing agents have been performed also in this case. When **5b,c** were treated with MCPBA (1.1 equivalent/CD_2Cl_2/-40 °C to room temperature/5 h) ^{1}H NMR of crude reaction mixture revealed a good conversion of substrates into oxidation products (>78%) but attack at both nitrogen and carbon sites was observed (*N*-oxide/epoxide ratio 76 : 24 and 83 : 17, respectively).[22] When hydrogen peroxide was used with the same substrates (1.2 equivalents/30% aqueous solution/acetone/40 °C/3 h) oxidation process was slower and again preferential but not exclusive attack at nitrogen was observed (**6b,c**/**7b,c** ratio 78 : 22 and 84 : 16, respectively). When oxidation of **5b,c** was performed with MCPBA or hydrogen peroxide and trifluoroacetic acid or formic acid were used as solvent, preferential attack at the olefinic double bond was observed, but, as expected,[23] *N*-oxide formation was also observed.

Conclusions

Perfluoro *cis*-2,3-dialkyloxaziridines **2** are shown to oxidize tertiary amines in high yields under particularly mild conditions. The reaction is highly chemoselective as the presence of various nitrogen, oxygen, and carbon functionalities (tertiary amides, urea and carbamate moieties, alcohols, olefins, ...) in the substrate molecules **1** do not interfere with the described process. Other standard reagents employed for the synthesis of tertiary amine *N*-oxides are less selective as they attacked also olefinc double bonds and electron rich aromatic rings present in the substrate molecule. Moreover, standard reagents require less mild reaction conditions (especially when highly lipophilic substrates, *e.g.* **1c**, are used) so that labile *N*-oxides such as **3i** undergo *in situ* decomposition.

Oxaziridines **2** oxidized 4-substituted piperidines with complete diastereoselectivity. The access to enantiopure tertiary amine *N*-oxides is secured if the methodology is applied to enantiopure 4-substituted piperidines. This ability seems to be of particular interest as chiral and non racemic *N*-oxides have recently

been used for quite different applications (kinetic resolution of tricarbonyliron complexes,[24] conformational constraint in peptide like molecules,[25] highly diastereoselctive synthesis of allylic alcohols).[26]

The chemoselectivity in the oxidation of alkenyl substituted pyridines is shown to be solvent dependent, exclusive attack at the carbon-carbon double bond or at the nitrogen atom occurring under protic and aprotic conditions, respectively. Once again, lower selectivities were shown by standard reagents.

Perfluorinated oxaziridines **2** can perform the oxyfunctionalization of unactivated hydrocarbon sites[27] thus showing that they are powerful oxidizing agents. At the same time they can also behave as mild reagents as proven by their ability to perform the quantitative transformation of thioethers into sulfoxides without overoxidation to give sulfones.[28] Both these characteristics have been exploited in *N*-oxide formations described in this paper. Being powerful oxidizing agents, particularly mild reaction conditions could be employed so that higher yields and selectivities than those given by other reagents could be obtained.

Acknowledgements. The European Union is gratefully acknowledged for finantial support (Network INTAS-95-95).

Experimental Section

NMR spectra were recorded on a Bruker AC 250 or ARX 400 spectrometer in $CDCl_3$ solution. TMS was used as internal standard for ^1H and ^{13}C spectra and $CFCl_3$ was used for ^{19}F spectra. Chemical shifts are reported in ppm and *J* are in Hz. $\Delta\delta$ values reported in ^1H and ^{13}C NMRs of *N*-oxides **3** refer to the differences of the chemical shifts between the *N*-oxide and the corresponding amino precursor ($\Delta\delta = \delta_{N\text{-}O} - \delta_N$). Mass spectra were registered with a VG MM ZAB-2F or a Finnigan Mat TSQ 70 apparatus. IR spectra were recorded on Perkin Elmer 2000 FT-IR, frequencies are reported in cm^{-1}. Unless otherwise stated flash chromatographies were performed with silica gel 60 (60-200 μm, Merck). Dichloropentafluoropropane was a 43-56 mixture of HCFC-225ca and HCFC-225cb ($CF_3CF_2CHCl_2$ and $CClF_2CF_2CHClF$, respectively), purchased from PCR incorporated. Microanalysis were performed by Redox Snc, Cologno Monzese, Milano, Italy. Unless otherwise specified, yields are referred to reactions performed by using oxaziridine **2a**.

General procedure for the preparation of *N*-oxides 3a-l with perfluoro *cis*-2,3-dialkyloxaziridines 2a,b. Synthesis of fenspiride *N*-Oxide [8-(2-phenylethyl)-1-oxa-3,8-diazaspiro[4,5]-decan-2-one 8-oxide (3j)]. A solution of perfluoro *cis*-2-*n*-butyl-3-*n*-propyloxaziridine **2a** (1.03 g, 2.30 mmol) in HCFC-225ca,cb (3.0 mL) was added dropwise and under nitrogen to a solution of fenspiride (552 mg, 2.00 mmol) in dichloromethane (10 mL) at -60 °C. After stirring at the same temperature for 20 min, the reaction was quenched by the addition of perfluorotributylamine (10 mL). The mixture was stirred and allowed to warm to room temperature. Ethyl acetate was added (20 mL) and the perfluorinated layer was extracted with the same solvent. The combined organics were evaporated under reduced and the residue was flash chromatographed ($CHCl_3$/MeOH 8:2) to give fenspiride *N*-oxide **3j** in 92% isolated yield (508 mg, 1.84 mmol). $\delta_H(CDCl_3)$: 7.35-7.15 (5H, m, ArH), 4.50 (1H, brs, NH), 3.51 (2H, ddd, J = 13.5, 11.4 and 2.8 Hz, H-7 and -9 ax, $\Delta\delta$ = 0.84), 3.50 (2H, m, H_2-1′, $\Delta\delta$ = 0.84), 3.46 (2H, s, H_2-4, $\Delta\delta$ = 0.10), 3.36 (2H, brd, J = 11.4 Hz, H-7 and -9 eq, $\Delta\delta$ = 0.67), 3.28 (2H, m, H_2-2′, $\Delta\delta$ = 0.46), 2.77 (2H, ddd, J = 14.0, 13.5 and 4.0 Hz, H-6 and -10 ax, $\Delta\delta$ = 0.90) and 1.94 (2H, brd, J = 14.0 Hz, H-6 and -10 eq, $\Delta\delta$ = -0.09); $\delta_C(CDCl_3$, DEPT): 129.04, 128.89 and 127.10 (d, ArCH), 72.79 (t, C-1′, $\Delta\delta$ =

12.59), 60.85 (t, C-7 and -9, Δδ = 11.44), 50.59 (t, C-4, Δδ = -0.54), 30.83 (t, C-6 and -10, Δδ = -5.28) and 28.93 (t, C-2′, Δδ = -4.84); Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.29; N, 10.14; found: C, 65.51; H, 7.55; N, 9.97. No differences were observed in the oxidation of fenspiride using different solvents and solvent mixtures (chloroform, tetrachloromethane, trichlorofluoromethane, dichlorotetrafluoroethane) and at room temperature the reaction was nearly instantaneous, but slightly lower yields were obtained (86%). A similar procedure was employed when the perfluoro *cis*-2-*n*-hexyl-3-*n*-pentyloxaziridine **2b** was used and the *N*-oxide **3j** was isolated in 94% yields (430 mg, 1.56 mmol).

Trimethylamine *N*-oxide **3a** (88% yield) was identified by comparison with an authentic sample (purchased from Aldrich); triethylamine *N*-oxide **3b** (95% yield by using **2a**, 90 % yield by MCPBA, 88% yield by hydrogen peroxide), tri-*n*-octylamine *N*-oxide **3c** (96% yield by using **2a**, 93% yield by using **2b**, 54% yield by hydrogen peroxide), and quinuclidine *N*-oxide **3d** (95% yield by using **2a**, 91% yield by using **2b**, 94% yield by MCPBA and hydrogen peroxide) showed spectral data identical to those reported in the literature.[29]

***N*-Allyloxypiperidine.** Chromatography with aluminum oxide 150 (basic, type T), eluting system: AcOEt/MeOH 9:1; isolated yield 246 mg (90%, by using **2a**), 256 mg (93%, by using **2b**); $\delta_H(CDCl_3)$: 6.23 (1H, m, CH_2=C*H*), 5.51 and 5.44 (2H, m, CH_2=CH), 3.90 (2H, brd, *J* = 7.0 Hz, CH_2=CHCH_2), 3.29 and 3.12 (4H, m, CH_2CH_2N), 2.30 and 1.62 (4H, m, CH_2CH_2N), 1.73 and 1.38 (2H, m, C$H_2CH_2CH_2$N).

Dextromethorphan *N*-oxide [(+)-3,17-dimethylmorphinan 17-oxide (3f)]. Chromatography with aluminum oxide 150 (basic, type T), eluting system: AcOEt/MeOH 9:1; isolated yield 354 mg (94%); $\delta_H(CDCl_3)$: 7.06, 6.85 and 6.77 (3H, m, ArH), 3.80 (3H, s, OCH_3, Δδ = 0.01), 3.31 (1H, m, H-9, Δδ = 0.50), 3.30 (3H, s, NCH_3, Δδ = 0.89), 3.18 (1H, brdd, *J* = 19.0 and 5.9 Hz, H-10a, Δδ = 0.68), 3.12 (1H, ddd, *J* = 12.5, 3.2 and 3.0 Hz, H-14, Δδ = 1.28), 3.03 (1H, brd, *J* = 19.0 Hz, H-10b, Δδ = 0.05), 3.02 (1H, dddd, *J* = 11.5, 4.7, 2.0 and 1.5 Hz, H-16eq, Δδ = 0.58), 2.89 (1H, ddd, *J* = 13.0, 11.5 and 3.2 Hz, H-16ax, Δδ = 0.79), 2.51 (1H, ddd, *J* = 13.2, 13.0 and 4.7 Hz, H-15ax, Δδ = 0.76), 2.36 (1H, brd, *J* = 13.0 Hz, H-5eq, Δδ = 0.01), 1.8-1.3 (5H, m, H-5ax, H_2-6 and -7), 1.45 and 1.01 (2H, m, H_2-8, Δδ = 0.04 and -0.13) and 1.26 (1H, ddd, *J* = 13.2, 3.2 and 2.0 Hz, H-15eq, Δδ = -0.08); $\delta_C(CDCl_3$, DEPT): 129.00, 111.95 and 111.50 (d, ArCH), 73.57 (d, C-9, Δδ = 15.57), 60.11 (t, C-16 , Δδ = 12.79), 57.30 (q, NCH_3, Δδ = 14.45), 55.14 (q, OCH_3, Δδ = -0.05) 37.05 (d, C-14, Δδ = -8.43), 37.00 (t, C-15, Δδ = -5.16) and 35.19, 28.05, 26.27, 25.94 and 22.16 (t, C-5, -6, -7, -8 and/or -10); Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87; found: C, 75.13; H, 8.51; N, 4.99; m/z (CI, CH_4) 288 (M^++1). When hydrogen peroxide was used, flash chromatography afforded a 1 : 1 mixture of **3f** and a second *N*-oxide showing the following diagnostic signals: $\delta_H(CDCl_3)$: 6.80 and 7.31 (2H, br s each, ArH), 3.89 (3H, s, OCH_3), 3.34 (3H, s, NCH_3); m/z (CI, CH_4) 304 (M^++1).

Lidocaine *N*-oxide [2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide (3g)]. Eluting system for flash chromatography: $CHCl_3$-MeOH: 9:1; isolated yield: 421 mg (93%, by using **2a**), 244 mg (91%, by using **2b**); ν_{max} (KBr): 945, 1678; $\delta_H(CDCl_3)$: 12.02 (1H, brs, NH), 7.2-7.0 (3H, m, ArH), 3.91 (2H, s, COCH_2N), 3.48 and 3.44 (4H, dd, *J* = 12.9 and 7.3 Hz, CH_3CH_2N), 2.24 (6H, brs, $ArCH_3$), and 1.36 (6H, t, *J* = 7.3 Hz, CH_3CH_2); $\delta_C(CDCl_3$, DEPT): 128.16 and 126.83 (d, ArC), 65.33 (t, COCH_2N), 61.15 (t, CH_3CH_2), 18.91 (q, $ArCH_3$), 8.72 (q, CH_3CH_2); Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.85; N, 11.19; found: C, 66.98; H, 8.70; N, 11.29; m/z (CI, CH_4) 251 (M^++1).

Brucine *N*-oxide [2,3-dimethoxystrychnidin-10-one *N*-oxide (3h)]. Eluting system for flash chromatography: AcOEt-MeOH :; isolated yield 289 mg (97%); ν_{max} (KBr/cm^{-1}): 1384; $\delta_H(CDCl_3)$: 7.80 and 6.96 (2H, brs, H-12 and -9, Δδ = -0.01 and 0.28), 6.35 (1H, brdd, *J* = 7.0 and 6.2 Hz, H-19, Δδ = 0.46), 4.47 (1H, m, H-3, Δδ = 0.59), 4.32 (1H, ddd, *J* = 8.4, 3.1 and 3.0 Hz, H-23, Δδ = 0.04), 4.25 (1H, dd, *J* = 14.0 and 7.0 Hz, H-18a, Δδ = 0.11), 4.25 (1h, brd, *J* = 13.5 Hz, H-21a, Δδ = 0.54), 4.09 (1H, brdd, *J* = 14.0 and 6.8 Hz, H-18b, Δδ = 0.03), 3.96 (1H, d, *J* = 13.5 Hz, H-21b, Δδ = 1.23), 3.96 (1H, d, *J* = 10.4 Hz, H-2, Δδ = 0.13), 3.91 and 3.89 (6H, s, 2 x OCH_3, Δδ = 0.00 and 0.04), 3.91 (1H, ddd, *J* = 13.6, 12.0 and 5.5 Hz, H-5a, Δδ = 1.06), 3.82 (1H, brdd, *J* = 12.0 and 7.5 Hz, H-5b, Δδ = 0.62), 3.27 (1H, m,

H-15, Δδ = 0.13), 3.12 (1H, dd, J = 17.6 and 8.4 Hz, H-22a, Δδ = 0.02), 2.82 (1H, ddd, J = 15.5, 4.0 and 3.5 Hz, H-14a, Δδ = 0.46), 2.67 (1H, ddd, J = 13.6, 13.5 and 7.5 Hz, H-6a, Δδ = 0.78), 2.66 (1H, dd, J = 17.6 and 3.0 Hz, H-22b, Δδ = 0.00), 2.02 (1H, brdd, J = 13.5 and 5.5 Hz, H-6b, Δδ = 0.16), 1.70 (1H, brd, J = 15.5 Hz, H-14b, Δδ = 0.23), and 1.38 (1H, ddd, J = 10.4, 3.1 and 2.9 Hz, H-16, Δδ = 0.11); δ_C($CDCl_3$): 168.40 (s, C-17), 149.99, 146.66, 135.31, 134,96 and 119.47 (s, C-10, -11, -8, -13 and/or -20), 134.28, 104.82 and 100.85 (d, C-19, -9 and/or -12), 82.26 (d, C-3, Δδ = 21.99), 77.43 (d, C-23, Δδ = -0.29), 70.73 and 67.44 (t, C-5 and C-21, Δδ = 18.11 and 17.29), 64.18 (t, C-18, Δδ = -0.35), 58.60 (d, C-15, Δδ = -1.34), 56.39 and 56.21 (q, 2xOCH$_3$, Δδ = 0.01 and 0.06), 53.21 (s, C-7, Δδ = 1.32), 47.54 and 30.21, (d, C-2 and -16, Δδ = -0.54 and -1.25), 42.09, 38.80 and 25.07 (t, C-22, -6 and/or -14, Δδ = -0.24, -3.53 and -1.67); m/z (EI) 410 ($M^{+\cdot}$).

L-*N*,*N*-Dimethylalanine cholesteryl ester *N*-oxide (3i). Eluting system for flash chromatography: AcOEt/MeOH 1:1; isolated yield 257 mg (84%); δ_H($CDCl_3$, selected signals): 5.39 (1H, m, H-6), 4.69 (1H, m, H-3), 4.00 (1H, q, J = 7.2 Hz, NC*H*CO), 3.32 (6H, s, N(CH_3)$_2$) and 1.67 (3H, d, J = 7.2 Hz, C*H*$_3$CHN); Anal. Calcd for $C_{32}H_{55}NO_3$: C, 76.60; H, 11.05; N, 2.79; found: C, 76.89; H, 11.24; N, 3.01. When oxidation was performed with MCPBA, diagnostic peaks of 5,6-epoxides of **1i** appeared at 3.11 (1H, d, J = 2.1 Hz, H-6α), 2.92 (1H, d, J= 4.1 Hz, H-6β); when oxidation was performed with hydrogen peroxide diagnostic peaks of acrylic ester of cholesterol were observed at 5.80 (1H, dd, J = 10.5, 2.0 Hz, H-3'), 6.11 (1H, dd, J = 17.0, 10.5 Hz, H-2'), 6.37 (1H, dd, J = 17.0, 2.0 Hz, H-3'), 5.37 (1H, br d, H-6), 4.88 (1H, m, H-3).

Haloperidol *N*-oxide [4-[4-(4-chlorophenyl)-4-hydroxypiperidinyl-1-(4-fluorophenyl)-1-butanone *N*-oxide (3k)]. Eluting system for flash chromatography: $CHCl_3$/MeOH 9:1; isolated yield 376 mg (96%); ν_{max} (KBr): 3420, 1686,m982; δ_H($CDCl_3$): 7.95, 7.41, 7.29 and 7.13 (8H, m, ArH), 3.76 (2H, m, H-2' and -6'ax, Δδ = 1.32), 3.68 (2H, m, H-2' and -6'eq, Δδ = 0.88), 3.64 (2H, m, H$_2$-4, Δδ = 1.15), 3.14 (2H, m, H$_2$-2, Δδ = 0.15), 2.68 (2H, brt, J = 12.5 Hz, H-3' and -5'ax, Δδ = 0.67), 2.33 (2H, m, H$_2$-3, Δδ = 0.33) and 1.85 (2H, brd, J = 12.5 Hz, H-3' and -5'eq, Δδ = 0.17); δ_C($CDCl_3$, DEPT): 130.92 and 116.02 (Dd, ArCH), 128.53 and 126.25 (D, ArCH), 70.65 (t, C-4, Δδ = 12.80), 60.48 (t, C-2' and -6' , Δδ = 11.16), 35.80 (t, C-2), 33.08 (t, C-3' and -5', Δδ = -5.33) and 16.86 (t, C-3, Δδ = -5.06); δ_F($CDCl_3$): -105.30 (1F, m, ArF); Anal. Calcd for $C_{21}H_{23}ClFNO_3$: C, 64.37; H, 5.91; Cl, 9.05; N, 3.57; found: C, 64.18; H, 6.04; Cl, 9.17; N, 3.34; m/z (EI) 392 ($M^{+\cdot}$), 372, 138 (C_8H_5FO), 123 (C_7H_4FO).

Pimozide *N*-oxide [1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazo-2-one *N*-oxide (3l)]. Eluting system for flash chromatography: AcOEt/MeOH 8:2; isolated yield 289 mg (98%); ν_{max} (KBr): 1695, 955; δ_H($CDCl_3$): 12.20 (1H, brs, NH), 7.5-6.8 (12H, m, ArH), 4.53 (1H, tt, J = 12.0 and 4.5 Hz, H-4', Δδ = 0.17), 3.91 (1H, brt, J = 7.8 Hz, H-4'', Δδ = 0.02), 3.55 (2H, brd, J = 9.5 Hz, H-2' and -6'eq, Δδ = 0.52), 3.43 (2H, m, H$_2$-1'', Δδ = 1.01), 3.28 (2H, dddd, J = 12.5, 12.0, 11.5 and 4.0 Hz, H-3' and -5'ax, Δδ = 0.82), 3.16 (2H, brdd, J = 12.5 and 9.5 Hz, H-2' and -6'ax, Δδ = 1.07), 2.05 (2H, m, H-2'', Δδ = 0.57), 1.96 (2H, m, H$_2$-3'', Δδ = -0.88) and 1.69 (2H, brd, J = 11.5 Hz, H-3' and -5'eq, Δδ = -0.12); δ_C($CDCl_3$, DEPT): 129.03 and 115.51 (Dd, ArCH), 121.68, 121.60, 110.21 and 109.68 (D, ArCH), 70.40 (t, C-1'', Δδ = 12.08), 63.05 (t, C-2' and -6' , Δδ = 9.76), 49.43 and 46.76 (d, C-4' and -4''), 32.70 (t, C-3'', Δδ = -1.14), 23.32 (t, C-3' and 5', Δδ = -5.91) and 21.16 (t, C-2'', Δδ = -4.45); δ_F($CDCl_3$): -117.69 (2F, m, ArF); Anal. Calcd for $C_{28}H_{28}F_2N_3O_2$: C, 70.57; H, 5.92; N, 8.82; found: C, 70.79; H, 6.11; N, 9.07; m/z (EI) 477 ($M^{+\cdot}$), 461 (M-O), 230 ($C_{15}H_{12}F_2$).

General procedure for the preparation of pyridine *N*-oxides 6a-c with perfluoro *cis*-2,3-dialkyloxaziridines 2a,b. Synthesis of 2-(3-(*E*/*Z*)-penten-1-yl)pyridine *N*-Oxide (6a). A solution of perfluoro *cis*-2-*n*-butyl-3-*n*-propyloxaziridine **2a** (1.16 g, 2.60 mmol) in HCFC-225ca,cb (3.0 mL) was added dropwise and under nitrogen to a solution of 2-(3-(*E*/*Z*)-penten-1-yl)pyridine (**5a**) (353 mg, 2.40 mmol) in dichloromethane (7 mL) at -60 °C. After stirring at the same temperature for 30 min, the reaction was quenched by the addition of perfluorotributylamine (8 mL). The mixture was stirred, then allowed to warm to room temperature. Ethyl acetate was added (15 mL) and the perfluorinated layer was extracted

with ethyl acetate. The combined organics were evaporated under reduced pressure and the residue was flash chromatographed (AcOEt/MeOH, 9:1) to give the alkenylpyridine *N*-oxide **6a** (298 mg, 1.82 mmol) in 76% isolated yield. Following the same procedure **6a** was obtained in 78% isolated yield by using **2b**. ν_{max} (film): 1230; δ_H($CDCl_3$): 8.27 and 7.3-7.1 (4H, m, PyH), 5.6-5.3 (2H, m, H-3′ and -4′), 2.98 (2H, m, H_2-1′), 2.6-2.4 (2H, m, H_2-2′), 1.64 and 1.57 (3H, d, J = 6.5 Hz, H_3-5′); Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.02; N, 8.58; found: C, 73.89; H, 8.20; N, 8.35; m/z (CI, CH_4) 164 (M^++1).

6-Heptenoic acid pyridin-2-ylmethyl ester *N*-oxide (6b). Eluting system for flash chromatography: AcOEt/MeOH 9:1; isolated yield 276 mg (79%); ν_{max} (nujol): 1746, 1228; δ_H($CDCl_3$): 8.31, 7.40, 7.36 and 7.29 (4H, m, PyH), 5.80 (1H, m, H-6), 5.40 (2H, brs, CH_2O), 5.02 and 4.97 (2H, m, H_2-7), 2.47 (2H, m, H_2-2), 2.09 (2H, m, H_2-5), 1.72 and 1.46 (4H, m, H_2-3 and-4); Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.57; H, 7.41; N, 5.80; m/z (CI, CH_4) 236 (M^++1). When oxidation was performed with MCPBA and methylene chloride, trifluoroacetic acid, or formic acid were used as solvent, the *N*-oxide/epoxide ratio was 76 : 24, 10 : 90, 12 : 88, respectively; diagnostic signals of the 6,7-epoxide of **6b** appeared at: δ_H(CD_2Cl_2): 2.58 (2H, dd, H_2-7) and 2.76 (1H, m, H-6). When oxidation was performed with hydrogen peroxide and trifluoroacetic acid or formic acid were used as solvent, the *N*-oxide/diol ratio was 12 : 88, 12 : 88, respectively.

4-(Cyclohex-3-en-1-yl)pyridine *N*-oxide (6c). Eluting system for flash chromatography: AcOEt/MeOH 9:1; isolated yields: 316 mg (69%, by using **2a**), 219 mg (73%, by using **2b**); ν_{max} (nujol): 1125; δ_H($CDCl_3$): 8.18 (2H, m, H-2, and -6), 7.17 (2H, m, H-3, and-5), 5.9-5.7 (2H, m, H-3′ and -4′), 2.82 (1H, m, H-1′) and 2.5-1.6 (6H, m, H_2-2′, -5′ and -6′); Anal. Calcd for $C_{11}H_{13}NO$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.57; H, 7.41; N, 5.80. When oxidation was performed with MCPBA and methylene chloride, trifluoroacetic acid, or formic acid were used as solvents, the *N*-oxide/epoxide ratio was 83 : 17, 8 : 92, 8 : 92, respectively; diagnostic signals of the epoxide of **6c** appeared at: δ_H(CD_2Cl_2): 3.12 (1H, broad dd, H-3′) and 3.31 (1H, broad ddd, H-4′). When oxidation was performed with hydrogen peroxide and trifluoroacetic acid or formic acid were used as solvent, the *N*-oxide/diol ratio was 8 : 92, 12 : 88, respectively.

4-(3-Cyclohexen-1-yl)-*N*-(perfluorobutanoyl)pyridinium-1-aminide (8a). Eluting system for flash chromatography: AcOEt-MeOH 9:1; isolated yield 76 mg (12%); ν_{max} (nujol): 1228, 1645; δ_H($CDCl_3$): 8.58 (2H, m, H-2 and -6), 7.60 (2H, m, H-3 and -5), 5.9-5.7 (2H, m, H-3′ and 4′), 3.07 (1H, m, H-1′) and 2.5-1.7 (6H, m, H_2-2′, -5′ and -6′); δ_F($CDCl_3$): -81.88 (3F, t, J = 9.0 Hz), -120.01 (2F, tq, J =1.8 and 9.0 Hz) and -128.10 (2F, t, J =1.8 Hz); Anal. Calcd for $C_{15}H_{13}N_2OF_7$: C, 48.65; H, 3.54; N, 7.56; found: C, 48.83; H, 3.80; N, 7.31; m/z (EI) 370 (M^+), 201 (M^+-C_3F_7).

General procedure for the preparation of dihydroxyalkylpyridines 7a-c with perfluoro *cis*-2,3-dialkyloxaziridines 2a,b. Synthesis of 2-(3,4-dihydroxypentyl)pyridine (7a). A solution of the oxaziridine **2a** (988 mg, 2.20 mmol) in anhydrous trifluoroacetic acid (3.0 mL) was added dropwise under argon to a solution of 2-(3-(*E*/*Z*)-penten-1-yl)pyridine (**5a**) (309 mg, 2.10 mmol) in the same solvent (3.0 mL) with stirring at 0 °C. After 30 min at the same temperature, the solvent was removed in the vacuum, tetrahydrofurane and saturated aqueous solution of sodium carbonate were added. The resulting system was vigorously stirred for 2h at room temperature, then the aqueous layer was extracted with ethyl acetate and the collected organic phases were evaporated and the residue was purified through flash chromatography (AcOEt-MeOH 9:1) to give the dihydroxypentylpyridine **7a** in 81% isoalted yield (mixture of the *threo* and *erythro* isomers, 308 mg, 1.70 mmol). Following the same procedure **7a** was obtained in 84% isolated yield by using **2b**. δ_H(DMSO-d_6): 8.45, 7.67, 7.23 and 7.17 (4H, m, PyH), 4.53, 4.50, 4.41 and 4.38 (2H, d, J = 7.0 Hz, OH-3′ and -4′), 3.6-3.1 (2H, m, H-3′ and H-4′), 3.0-2.6 (2H, m, H_2-1′), 2.0-1.4 (2H, m, H_2-2′), 1.03 and 0.99 (3H, d, J = 6.3 Hz, H_3-5′); Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27, H, 8.34, N, 7.73; found: C, 65.96; H, 8.11; N, 7.54; m/z (CI, CH_4) 181 (M^++1).

6,7-Dihydroxyheptanoic acid pyridin-2-ylmethyl ester (7b). Eluting system for flash chromatography: AcOEt-MeOH 9:1; isolated yield 236 mg (80%); ν_{max} (film): 1744; δ_H($CDCl_3$): 8.62, 7.74, 7.38 and 7.27

(4H, m, PyH), 5.22 (2H, brs, CH_2O), 3.72 (1H, m, H-6), 3.65 and 3.43 (2H, m, H_2-7), 2.45 (2H, m, H_2-2), 2.0-1.3 (6H, m, H_2-3, -4 and -5), 1.90 (2H, brs, OH-6 and -7); δ_H(DMSO-d_6): 4.45 (1H, t, J = 5.5 Hz, OH-7), 4.39 (1H, d, J = 6.0 Hz, OH-6); Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53; found: C, 61.90; H, 7.39; N, 5.17; m/z (CI, CH_4) 254 (M^++1).

(1'*R,3'*S**,4'*S**)-4-(3',4'-Dihydroxycyclohexyl)pyridine (7c).** Eluting system for flash chromatography: AcOEt-MeOH 9:1; isolated yields: 247 mg (72%, by using **2a**), 285 mg (75%, by using **2b**); δ_H(DMSO-d_6): 8.45 (2H, m, H-2 and -6), 7.22 (2H, m, H-3 and -5), 4.75 and 4.64 (2H, d, J = 4.0 Hz, OH-3' and -4'), 3.68 and 3.58 (2H, m, $J_{3'-4'}$ = 3.5 Hz, H-3' and -4'), 2.90 (1H, tt, J = 12.0 Hz and 3.0 Hz, H-1') and 2.0-1.4 (6H, m, H_2-2', -5' and -6'); Anal. Calcd for $C_{11}H_{15}NO_2$: C, 69.09; H, 6.85, N, 7.33, found: C, 68.96; H, 7.06; N, 7.54; m/z (EI) 193 (M^+); 175 (M^+-H_2O), 157 (M^+-2xH_2O), 106 78 ($C_5H_4N^+$).

References and Notes

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