JOC Article

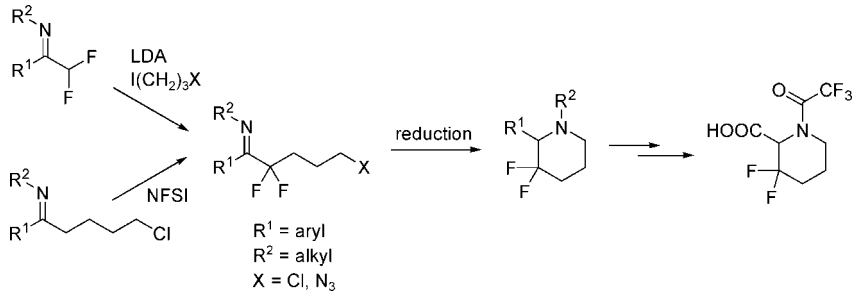
New Entries toward 3,3-Difluoropiperidines

Guido Verniest,[†,§] Riccardo Surmont,[†] Eva Van Hende,[†] Arvid Deweweire,[†] Frederik Deroose,[‡] Jan Willem Thuring,[‡] and Norbert De Kimpe*,[†]

Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium, and Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

norbert.dekimpe@ugent.be

Received April 7, 2008



Difluoropiperidines attract considerable interest from organic and medicinal chemists, but their synthesis is often problematic. This paper describes a new synthetic pathway toward valuable 3,3-difluoropiperidines starting from suitable δ-chloro-α,α-difluoroimines. The latter imines can be synthesized via electrophilic fluorination of the corresponding δ-chloroimines using NFSI (*N*-fluorodibenzenesulfonimide) in acetonitrile. After hydride reduction of the imino bond and subsequent intramolecular substitution of the chloride atom, new 3,3-difluoropiperidines were obtained in good yields. In addition, this methodology was applied to establish the first synthesis of *N*-protected 3,3-difluoropipecolic acid, a new fluorinated amino acid.

Introduction

The specific properties of fluorine as a substituent in organic compounds has resulted in a steadily growing interest in organofluorine chemistry, which proved to be a research area with numerous applications in agrochemistry and pharmaceutical chemistry.[1–10] In addition, the commercialization of safe and efficient fluorinating agents has paved the way for the development of a wide scope of synthetic pathways to various fluorinated compounds.[11,12] In that respect, various fluorinated azaheterocyclic compounds have been used as building blocks in drug design to fine-tune bioactivity and therapeutic efficacy, as evidenced by numerous papers in this area.[13] Of special interest in this research area are 3,3-difluorinated piperidines, which have been used successfully to synthesize anticonvulsant,[14] anticancer,[15] antiobesity,[16] and anti-Alzheimer compounds.[17] Unfortunately, only limited synthetic pathways are available to synthesize substituted 3,3-difluoropiperidines. The majority of 3,3-difluoropiperidines are synthesized via deoxof-

[†] Ghent University.
[‡] Johnson & Johnson Pharmaceutical Research & Development.
[§] Postdoctoral Fellow of the Research Foundation−Flanders (FWO-Vlaanderen).

(1) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991.
(2) Dolbier, W. R. *J. Fluorine Chem.* **2005**, *126*, 157.
(3) *Organofluorine Chemistry*; Uneyama, K., Ed.; Blackwell: Oxford, 2006.
(4) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.
(5) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443, and references therein.
(6) Jäckel, C.; Koksch, B. *Eur. J. Org. Chem.* **2005**, 4483.
(7) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
(8) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
(9) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.
(10) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(11) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192.
(12) Baasner, B.; Hageman, H. Tatlow, J. Organo-fluorine compounds In *Houben-Weyl Methods of Organic Chemistry*; Georg Thieme-Verlag: Stuttgart, New York, 1999; E10a−c, additional and supplementary volume to the 4th ed.
(13) (a) Edmondson, S. D.; Mastracchio, A.; Mathvink, R. J.; He, J.; Harper, B.; Park, Y.-J.; Beconi, M.; Di Salvo, J.; Eiermann, G. J.; He, H.; Leiting, B.; Leone, J. F.; Levorse, D. A.; Lyons, K.; Patel, R. A.; Patel, S. B.; Petrov, A.; Scapin, G.; Shang, J.; Roy, R. S.; Smith, A.; Wu, J. K.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2006**, *49*, 3614. (b) Celanire, S.; Quere, L.; Denonne, F.; Provins, L. PCT Int. Appl. WO 2007048595 A1 20070503, 2007. (c) Keith, J. M.; Gomez, L. A.; Letavic, M. A.; Ly, K. S.; Jablonowski, J. A.; Seierstad, M.; Barbier, A. J.; Wilson, S. J.; Boggs, J. D.; Fraser, I. C.; Mazur, C.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 702. (d) Parker, J. C.; Hulin, B. US Pat. Appl. US 2005043292 A1 24/02/2005; *Chem. Abstr.* **2005**, *142*, 261783.

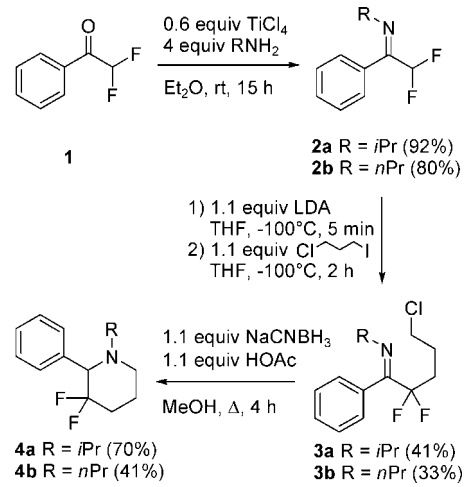
10.1021/jo800768q CCC: $40.75
Published on Web 06/12/2008

luorination of suitable 3-piperidinones using DAST ((diethylamino)sulfur trifluoride) or Deoxofluor ((bis(2-methoxyethyl)-amino)sulfur trifluoride).[14,15,18] Another strategy makes use of ethyl bromodifluoroacetate as the starting material to synthesize 3,3-difluoro-2-piperidinones, which can be reduced to 3,3-difluoropiperidines.[19] 3,3-Difluorinated azasugars have been synthesized via [2,3]-Wittig rearrangements of difluoroallylic ethers, which were synthesized from trifluoroethanol.[20] 3,3-Difluoropipecolic acid is a particularly interesting difluoropiperidine but has never been synthesized before, in contrast to 4,4- or 5,5-difluoropipecolic acid.[21,22] In the viewpoint of the various applications of the latter amino acids in medicinal chemistry, also 3,3-difluoropipecolic acid derivatives are considered as promising compounds. Despite the interest in substituted 3,3-difluorinated piperidines, their synthesis remains often problematic. Halogenated imines are good substrates for the synthesis of a variety of azaheterocyclic compounds,[23,24] and hence a study was performed recently to synthesize fluorinated imines as starting materials for the synthesis of new fluorinated azaheterocyclic compounds.[25] The present research focuses on the use of α,α-difluorinated imines in the synthesis of new 2-aryl-3,3-difluoropiperidines and the application of the methodology in the first synthesis of 3,3-difluoropipecolic acid.

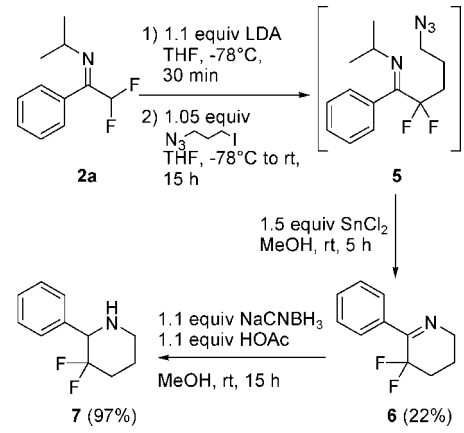
Results and Discussion

In a first strategy toward new *N*-substituted 2-aryl-3,3-difluoropiperidines, *N*-(2,2-difluoro-1-phenylethylidene)alkylamines **2** were used as starting materials for further α-functionalization. Difluoroimines **2** were synthesized from α,α-difluoroacetophenone **1** by reaction with primary amines and titanium(IV) chloride (Scheme 1). Subsequently, fluorinated imines **2** were deprotonated at the α-position using LDA at −100 °C, giving rise to the corresponding difluorinated 1-azaallylic anions, which were immediately brought into reaction with 1-chloro-3-iodopropane. While this reaction resulted in the formation of δ-chloroimine **3a** when α,α-difluoroimine **2a** was used, the same procedure using **2b** only gave complex reaction mixtures. When an inverse procedure was used, in which a solution of LDA in THF was added to a mixture of imine **2b** and 1-chloro-3-iodopropane, δ-chloro-α,α-difluoroimine **3b** could be isolated, albeit in low yield. The formed imines **3a**,**b** were successfully reduced using sodium cyanoborohydride in methanol in the presence of acetic acid toward the respective trihalogenated amines, which cyclized spontaneously under the used reaction conditions, i.e., reflux for 4 h. This short reaction sequence directly provided new *N*-alkylated 3,3-difluorinated piperidines **4**.

SCHEME 1



SCHEME 2



The above-described methodology was extended toward the synthesis of *N*-unsubstituted 3,3-difluoropiperidine **7** (Scheme 2). For this purpose, imine **2a** was transformed into δ-azidoimine **5** via deprotonation and reaction with 1-azido-3-iodopropane. Treatment of the azide **5** with tin(II) chloride in methanol yielded a new 3,3-difluorotetrahydropyridine **6** in 22% isolated yield over two steps. Finally, this cyclic imine was easily reduced toward the envisaged 3,3-difluoropiperidine **7** in nearly quantitative yield.

Although the synthetic pathways described above yielded new 3,3-difluoropiperidines (**4** and **7**), the reactions of the 1-azaallylic anions derived from imines **2** with electrophiles proceeded rather sluggishly and were difficult to scale up to gram scale. To overcome the problems associated with the reduced stability of fluorinated azaallylic anions, a second synthetic strategy was

(14) Castro Pineiro, J. L.; Dinnell, K.; Elliot, J. M.; Hollingworth, G. J.; Shaw, D. E.; Swain, C. J. PCT Int. Appl. WO 2001087838 A1 20011122, 2001; *Chem. Abstr.* **2001**, *136*, 5907.

(15) Li, Y.; Zhou, J.; Burns, D.; Yao, W. PCT Int. Appl. WO 2005037826 A1 20050428, 2005; *Chem. Abstr.* **2005**, *142*, 430307.

(16) Nagase, T.; Sato, N.; Kanatani, A.; Tokita, S. US Patent. US 2005182045 A1 20050818, 2005; *Chem. Abstr.* **2006**, *143*, 211923.

(17) Collins, I. J.; Cooper, L. C.; Harrison, T.; Keown, L. E.; Madin, A.; Ridgill, M. P. PCT Int. Appl. WO 2003093252 A1 20031113, 2003; *Chem. Abstr.* **2003**, *139*, 381490.

(18) Golubev, A. S.; Schedel, H.; Radics, G.; Fioroni, M.; Thust, S.; Burger, K. *Tetrahedron Lett.* **2004**, *45*, 1445.

(19) Beeler, A. B.; Gadepalli, R. S. V. S.; Steyn, S.; Castagnoli, N., Jr.; Rimoldi, J. M. *Bioorg. Med. Chem.* **2003**, *11*, 5229.

(20) (a) Wang, R.-W.; Qing, F.-L. *Org. Lett.* **2005**, *7*, 2189. (b) Wang, R.-W.; Qing, F.-L. *J. Med. Chem.* **2006**, *49*, 2989.

(21) Golubev, A. S.; Schedel, H.; Radics, G.; Sieler, J.; Burger, K. *Tetrahedron Lett.* **2001**, *42*, 7941.

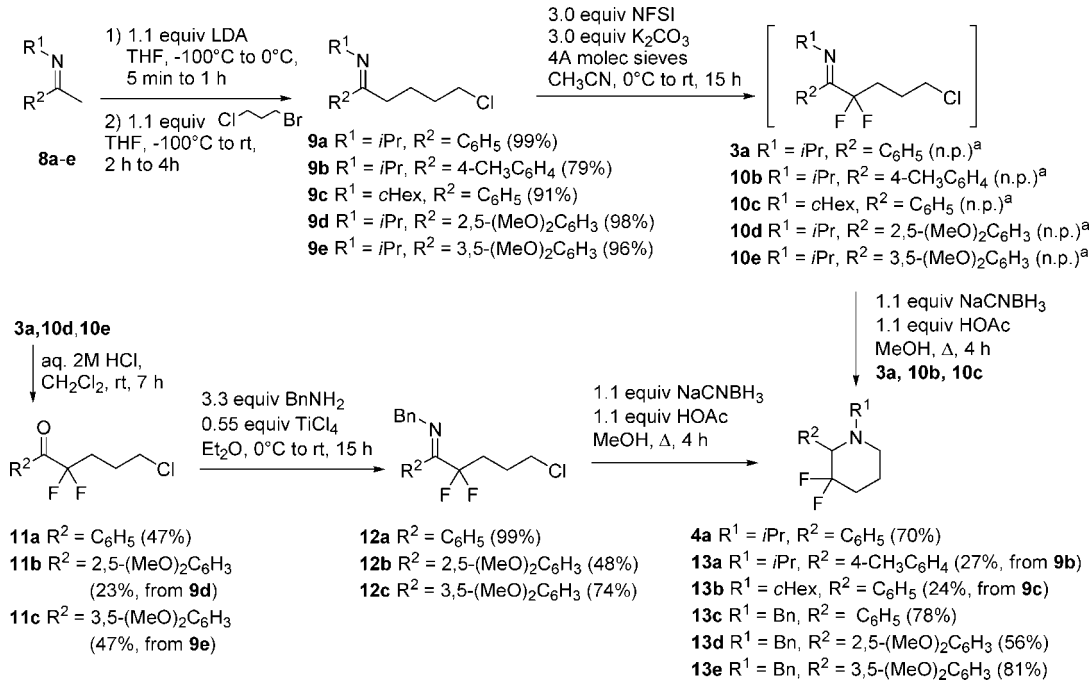
(22) Golubev, A. S.; Schedel, H.; Radics, G.; Fioroni, M.; Thust, S.; Burger, K. *Tetrahedron Lett.* **2004**, *45*, 1445.

(23) (a) Abbaspour Tehrani, K.; De Kimpe, N. *Sci. Synth.* **2004**, *27*, 245. (b) De Kimpe, N.; Schamp, N.; Verhé, R. *Synth. Commun.* **1975**, *5*, 403. (c) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Synth. Commun.* **1975**, *5*, 269. (d) De Kimpe, N.; Sulmon, P.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1983**, *48*, 4320. (e) De Kimpe, N.; Keppens, M.; Fonck, G. *J. Chem. Soc., Chem. Commun.* **1996**, 635. (f) De Kimpe, N.; Abbaspour Tehrani, K.; Stevens, C.; De Cooman, P. *Tetrahedron* **1997**, *53*, 3693. (g) De Kimpe, N.; Aelterman, W.; De Geyter, K.; Declercq, J.-P. *J. Org. Chem.* **1997**, *62*, 5138. (h) Aelterman, W.; De Kimpe, N.; Tyvorskii, V.; Kulinkovich, O. *J. Org. Chem.* **2001**, *66*, 53. (i) Stevens, C.; De Kimpe, N. *J. Org. Chem.* **1996**, *61*, 2174. (j) Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353.

(24) (a) Van Hende, E.; Verniest, G.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 2935. (b) Guo, Y.; Fujiwara, K.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2007**, *72*, 8523. (c) Chaume, G.; Van Severen, M.-C.; Marinkovic, S.; Brigaud, T. *Org. Lett.* **2006**, *8*, 6123. (d) Suzuki, A.; Mae, M.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, *69*, 5132. (e) Osipov, S. N.; Tsouker, P.; Hennig, L.; Burger, K. *Tetrahedron* **2004**, *60*, 271.

(25) Verniest, G.; Van Hende, E.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 4767.

SCHEME 3



[a] n.p. = not purified, purity 87−92%.

evaluated to access 3,3-difluoropiperidines. *N*-(1-Arylethylidene)alkylamines **8** (R^1 = alkyl, R^2 = aryl) were first transformed to the corresponding δ-chloroimines **9** via deprotonation with LDA and reaction with 1-chloro-3-bromopropane (Scheme 3).[26] The resulting imines **9** were used directly as substrates for electrophilic fluorination because it was observed that the latter imines tended to cyclize and decompose when stored at room temperature. Reaction of crude imines **9** with 3 equiv of *N*-fluorodibenzenesulfonimide (NFSI) in dry acetonitrile in the presence of potassium carbonate and molecular sieves yielded the corresponding difluoroimines **3a** and **10**. The best results were obtained when commercial NFSI was dried at 0.01 mmHg at 40 °C for 2 h prior to use. In this way, suitable δ-chloro-α,α-difluoroimines can be prepared on a multigram scale. It should be noted, however, that the fluorination of more electron-rich substrates **9d,e** proceeded much more slowly and could not be driven to completion. In the latter experiments, 10−20% of monofluorinated imines were present and could not be separated via chromatography. In these cases, the following transformations were carried out on the crude reaction mixtures (and purified in the next step). The reduction of imines **3a**, **10b,c** using sodium cyanoborohydride and acetic acid in refluxing methanol resulted nicely in new 3,3-difluoropiperidines **4a** and **13a,b** (Scheme 3). The low yields of compounds **13a** and **13b** are due to the difficult purification by chromatography on silicagel. Analysis of the ^{1}H NMR spectra of the crude reaction mixture after difluorination revealed that in the latter cases, at best, 10−15% of hydrolysis products (i.e., the corresponding ketones) of both imines **9** and **10** were present. Because of the presence of these ketones, the chromatographic separation of difluoropiperidines **13a,b** after treatment of the reaction mixture with hydride was further complicated and resulted in a lower overall yield.

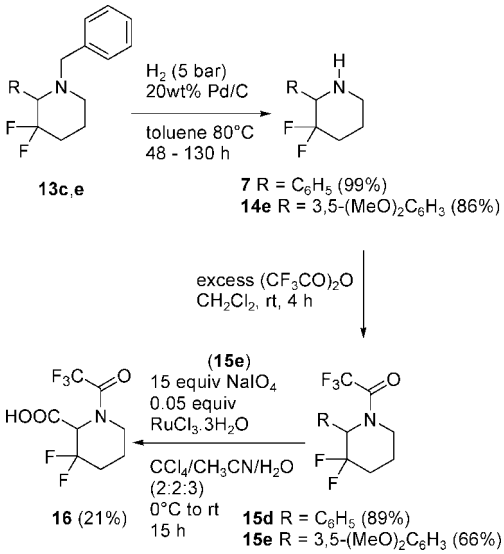
To synthesize 3,3-difluoropiperidines bearing a protecting group at the nitrogen atom which could be easily removed and thus provide a way for further ring functionalization, attempts were performed to synthesize the corresponding *N*-benzyl-3,3-difluoropiperidines **13c−e**. Because *N*-benzylimines derived from acetophenone cannot be alkylated at the α-position because of a preferential deprotonation by LDA at the benzylic position, isopropylimines **3a**, **10d**, and **10e** were hydrolyzed and subsequently reconverted into imines using benzylamine in the presence of titanium(IV) chloride. The resulting *N*-benzylimines **12** smoothly gave rise to new *N*-benzyl-3,3-difluoropiperidines **13c−e** after reduction of the imino bond and subsequent cyclization. Having in hand a good method for the synthesis of *N*-benzyl-3,3-difluoropiperidines, these compounds were used in the development of the first synthesis of 3,3-difluoropipecolic acid. Fluorinated piperidines **13c,e** were hydrogenated toward *N*-H piperidines **7** and **14e** and were subsequently reacted with an excess of trifluoroacetic anhydride to give new difluoropiperidines **15** bearing an electron-withdrawing group at nitrogen (Scheme 4). Because further experiments to oxidize the phenyl group of **15d** with ruthenium(IV) oxide did not result in any piperidine-2-carboxylic acid, piperidine **15e** was chosen as a starting material because of its substitution with the more electron-rich 3,5-dimethoxyphenyl group. In this case, the oxidative cleavage of the aromatic moiety could be accomplished and resulted in the envisaged *N*-protected 3,3-difluoropipecolic acid **16**, which was separated from the reaction mixture by chromatography on silica gel. No byproduct could be isolated and characterized because of the difficult chromatographic separation, and therefore no further attempts were undertaken to identify possible side reactions that could be responsible for the low yield.

Conclusions

In conclusion, it can be stated that new entries were developed toward new fluorinated piperidines, a class of compounds with considerable potential as building blocks in medicinal chemistry. δ-Chloro-α,α-difluoroimines were synthesized via 3-chloropropy-

(26) Sulmon, P.; De Kimpe, N.; Schamp, N. *Synthesis* **1989**, 8.

SCHEME 4



lation of α,α-difluoroimines or better via electrophilic fluorination of the corresponding δ-chloroimines. Treatment of the obtained difluoroimines with sodium cyanoborohydride in the presence of acetic acid yielded new 3,3-difluorpiperidines in good yields. Second, *N*-(5-chloro-2,2-difluoropentylidene)benzylamines were obtained via hydrolysis of the corresponding isopropylimines and reimination with benzylamine. The hydride induced cyclization of the former imines provided new *N*-benzyl-3,3-difluoropiperidines, which were used to synthesize *N*-protected 3,3-difluoropipecolic acid, a new fluorinated amino acid.

Experimental Section

1. Difluorination of δ-Chloroimines 9. *N*-((1*E*)-5-Chloro-2,2-difluoro-1-phenylpentylidene)isopropylamine 3a. In a flame-dried 100 mL flask was vigorously stirred a heterogeneous mixture of 7.96 g of NFSI (*N*-fluorobenzenesulfonimide; 25.27 mmol; 3 equiv), 1.72 g (25.27 mmol; 3 equiv) of K_2CO_3, and 4 g of freshly activated 4Å molecular sieves in 50 mL of acetonitrile under N_2 atmosphere for 15 min at room temperature. Subsequently, 2.00 g (8.42 mmol) of *N*-(5-chloro-1-phenylpentylidene)isopropylamine **9a** was added dropwise via a syringe at 0 °C. The mixture was warmed to room temperature and stirred for 15 h. Subsequently, an excess of triethylamine (5 mL) was added at 0 °C, and stirring was continued for 2 min. The reaction mixture was filtered over Celite, and the solids were washed three times with 20 mL of diethyl ether. Subsequently, the filtrate was poured in 100 mL of aqueous 0.5 M NaOH. After separation of the organic layer, the aqueous phase was extracted three times with 25 mL of diethyl ether and dried over $MgSO_4/K_2CO_3$ (10:1). Filtration of the drying agents and evaporation of the solvents in vacuo yielded crude *N*-((1*E*)-5-chloro-2,2-difluoro-1-phenylpentylidene)isopropylamine **3a** (yield 92%).

2. Reduction of α,α-Difluoro-δ-chloroimines 3, 10, and 12 toward Piperidines 4 and 13. 3,3-Difluoro-1-isopropyl-2-phenylpiperidine 4a. To a solution of 0.5 g (1.65 mmol) of *N*-((1*E*)-5-chloro-2,2-difluoro-1-phenylpentylidene)isopropylamine **3a** in 25 mL of absolute methanol were added 0.11 g (1.81 mmol, 1.1 equiv) of acetic acid and 0.11 g (1.81 mmol, 1.1 equiv) of sodium cyanoborohydride at 0 °C. The mixture was heated at reflux for 4 h. After completion of the reaction, the mixture was poured into 50 mL of a saturated aqueous $NaHCO_3$ solution and was subsequently extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Filtration of the solids and evaporation of the solvent yielded almost pure 3,3-difluoro-1-isopropyl-2-phenylpiperidine **4a**, which could be further purified by flash chromatography (hexane/EtOAc 98:2, R_f = 0.14), yield 70%. Mp 55 °C. ^{1}H NMR ($CDCl_3$): δ 0.73 (3H, d, J = 6.7 Hz, CH_3); 1.02 (3H, J = 6.7 Hz, CH_3); 1.61−1.75 (1H, m, C(H)*H*CF_2); 1.77−1.85 (2H, m, CH_2); 2.18−2.31 (2H, m, C(*H*)H-CF_2, NC(H)*H*); 2.84 (1H, sept, J = 6.7 Hz, C*H*(CH_3)$_2$); 2.98−3.06 (1H, m, NC(*H*)H); 3.55 (1H, dd, J = 21.1 Hz, 3.4 Hz, $CHCF_2$); 7.31−7.37 (3H, m, 3 × CH_{ar}); 7.40−7.45 (2H, m, 2 × CH_{ar}). ^{19}F NMR ($CDCl_3$): δ −94.9 (dd, J = 240.3 Hz, 2.2 Hz, C(*F*)F); −111.0 (dddd, J = 240.3 Hz, 43.9 Hz, 21.1 Hz, 9.9 Hz, C(F)*F*). ^{13}C NMR ($CDCl_3$): δ 11.7 (CH_3); 21.3 (CH_3); 21.7 (d, J = 10.4 Hz, CH_2); 33.7 (dd, J = 25.4 Hz, 21.9 Hz, *C*H_2CF_2); 42.9 (NCH_2); 48.0 (CH); 70.4 (dd, J = 26.5 Hz, 20.8 Hz, *C*HCF_2); 119.8 (dd, J = 248.6 Hz, 239.4 Hz, CF_2); 127.8 (2 × CH_{ar}); 128.0 (CH_{ar}); 130.3 (2 × CH_{ar}); 135.0 (C_{ar}). IR (KBr): ν_{max} 1172 cm^{-1}. MS (ES+) *m*/*z* (%): 240 (M + H$^+$, 100). HRMS calcd for $C_{14}H_{19}NF_2$ (M + H$^+$) 240.15583, found 240.15606. Anal. Calcd for $C_{14}H_{19}NF_2$: C, 70.27; H, 8.00; N, 5.85. Found: C, 69.42; H, 7.75; N, 6.12.

3. Oxidation of Piperidine 15e toward 3,3-Difluoro-1-(trifluoroacetyl)piperidine-2-carboxylic Acid 16. In a 25 mL flask was dissolved 0.23 g of 3,3-difluoro-2-(3,5-dimethoxyphenyl)-1-(trifluoroacetyl)piperidine **15e** was dissolved in a mixture of 4 mL of distilled tetrachloromethane, 4 mL of distilled acetonitrile, and 6 mL of distilled water. To this solution was added 2.92 g of sodium periodate (13.65 mmol; 15.00 equiv) during 5 min at 0 °C. After stirring 30 min at 0 °C, 0.010 g of ruthenium(III) chloride trihydrate (0.046 mmol; 0.05 equiv) was added. The temperature was raised to room temperature, and the mixture was stirred for 15 h. After filtration, the solids were rinsed three times with 20 mL of dichloromethane. The filtrate was evaporated under vacuum, and the residual oil was purified via flash chromatography resulting in 0.05 g of 3,3-difluoro-1-(trifluoroacetyl)piperidine-2-carboxylic acid **16** (0.192 mmol; 21%). Flash chromatography (hexane/EtOAc 67:33, R_f = 0.24), yield 21%. Ratio rotamers 83:17. ^{1}H NMR ($CDCl_3$): $\delta_{minor\ rotamer}$ 1.85−1.91 (2H, m, CH_2); 2.03−2.42 (2H, m, CH_2CF_2); 3.26 (1H, td, J = 13.1 Hz, 3.9 Hz, NC(H)*H*); 4.57 (1H, d, J = 13.9 Hz, NC(*H*)H); 4.89 (1H, d, J = 11.6 Hz, NCH); 9.20−9.70 (1H, m, COOH); $\delta_{major\ rotamer}$ 1.85−1.91 (2H, m, CH_2); 2.03−2.42 (2H, m, CH_2CF_2); 3.49−3.67 (1H, m, NC(H)*H*); 4.02 (1H, d, J = 13.8 Hz, NC(*H*)H); 5.47 (1H, d, J = 12.1 Hz, NCH); 9.20−9.70 (1H, m, COOH). ^{19}F NMR ($CDCl_3$): $\delta_{minor\ rotamer}$ −67.9 (s, CF_3); −97.2 (ddt, J = 254.5 Hz, 31.6 Hz, 11.5 Hz, C(F)*F*); −99.0 (d, J = 254.5 Hz, C(*F*)F); $\delta_{major\ rotamer}$ −69.2 (s, CF_3); −97.2 (ddt, J = 254.5 Hz, 31.6 Hz, 11.5 Hz, C(F)*F*); −99.0 (d, J = 253.2 Hz, C(*F*)F) ^{13}C NMR ($CDCl_3$): δ 21.5 (d, J = 6.9 Hz, CH_2); 29.7 (t, J = 22.5 Hz, *C*H_2CF_2); 42.3 (d, J = 3.5 Hz, NCH_2); 58.5 (t, J = 32.3 Hz, NCH) and 61.6 (t, J = 28.3 Hz, NCH); 116.3 (q, J = 287.3 Hz, CF_3); 118.0 (dd, J = 255.0 Hz, 242.3 Hz, CF_2); 157.7 (q, J = 37.3 Hz, C=O); 170.5 (d, J = 11.5 Hz, COOH). IR (NaCl): ν_{max} 3202; 1695; 1194; 1156 cm^{-1}. MS (ES−) *m*/*z* (%): 260 (M − H$^+$, 100). Anal. Calcd for $C_8H_8NO_3F_5$: C, 36.79; H, 3.09; N, 5.36. Found: C, 37.01; H, 3.33; N, 5.27.

Acknowledgment. The authors are indebted to the Research Foundation−Flanders (FWO-Flanders), Ghent University (GOA, BOF) and Johnson & Johnson Pharmaceutical Research & Development, a Division of Janssen Pharmaceutica NV, for financial support.

Supporting Information Available: General experimental methods and ^{1}H NMR and ^{13}C NMR spectra of compounds **2b**, **3a,b**, **4a,b**, **6**, **7**, **8b**, **8d,e**, **9e**, **11a−c**, **12a**, **12c**, **13a−e**, **14e**, **15d,e**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800768Q