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A general route to *N'*-(2,2-difluoro-3-hydroxyalkanoyl)nornicotines

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Abstract

The preparation of a variety of *N'*-(2,2-difluoro-3-hydroxyalkanoyl)nornicotines via a Reformatsky-type reaction of ethyl bromodifluoroacetate with aldehydes is described. The difluoromethylene unit may be regarded as an isopolar and isosteric replacement for ether oxygen.

Keywords: Reformatsky-type reaction; *N'*-Substituted nornicotines; Ethyl bromodifluoroacetate; NMR spectroscopy; High-resolution mass spectrometry; IR spectroscopy

1. Introduction

Carbonyl compounds possessing fluorine(s) at the α position have been paid much attention due to the remarkable ability of these compounds to function as enzyme inhibitors [1]. Studies of some fluorinated ketones suggest that these molecules are transition-state analog inhibitors [2]. The enhanced electrophilicity of the fluorinated ketone carbonyl was expected to facilitate an enzyme-catalyzed addition of the active site, i.e. the hydroxy group in serine, to form a stable hemiketal which is the structural mimic of the putative tetrahedral intermediate that forms during the enzymatic cleavage of a peptide substrate. In particular, a fluorine atom has been regarded as an isoelectric replacement for the hydroxy group, and the difluoromethylene functionality could be also regarded as an isopolar and isosteric replacement for an ether oxygen. Furthermore, compounds possessing a difluoromethylene functionality are also effective bioactive reagents. Thus, for example, (1) potential anti-HIV agents have been obtained by replacing an ether oxygen by a CF_2 moiety in order to avoid unfavorable hydrolytic cleavage of the P^1, P^2 bond of 2',3'-dideoxyadenosine triphosphate [3], (2) the introduction of two fluorines into the 10-position of thromboxane A_2 (TXA_2) alters the electronic environment as a result of their electron-withdrawing ability which effectively stabilizes the molecule [4] and (3) difluorostatine-containing peptides exhibit an effective renin inhibitory activity [5]. Clearly, selective and/or specific introduction of the difluoromethylene functionality at a specific position in a molecule remains an important synthetic challenge, and affords the possibility of the generation of new biologically active compounds.

2. Results

Herein, we report the preparation of a fluorinated analog of *N'*-(3-hydroxy-12-methyltridecanoyl)nornicotine which is known to act as an insecticide [6–8]. A convenient synthetic route to the desired material is shown in Scheme 1. The α,α-difluoro-β-hydroxy ester **5** was prepared by means of a Reformatsky-type reaction of ethyl bromodifluoroacetate with aldehyde **4** prepared by standard methods as shown in Scheme 1. To obtain the desired nornicotine derivative possessing a difluoromethylene unit, we required the α,α-difluoro-β-keto ester **6** as a precursor. Compound **5** gave satisfactory conversion into the desired α,α-difluoro-β-keto ester **6** in 92% yield using the Dess–Margin reagent [9]. It was then transformed into *N'*-(2,2-difluoro-12-methyl-3-oxotridecanoyl)nornicotine (**7**) by the reaction of compound **6** and racemic nornicotine. The compound *N'*-(2,2-difluoro-3-hydroxy-12-methyltridecanoyl)nornicotine (**8**) was obtained in a diastereomeric ratio of 1:1 from the reduction of compound **7** with sodium borohydride in ethanol at −78 °C in 98% yield.

We have also examined the preparation of *N'*-(2,2-difluoro-3-hydroxyoctanoyl)nornicotine (**12**) (Scheme 2) by the condensation reaction of the corresponding α,α-difluoro-β-hydroxy ester with nornicotine using the same method (Table 1). In addition, *N'*(2,2-difluoro-3-hydroxy-3-phenylpropanoyl)nornicotine (**14**) (Scheme 3) was

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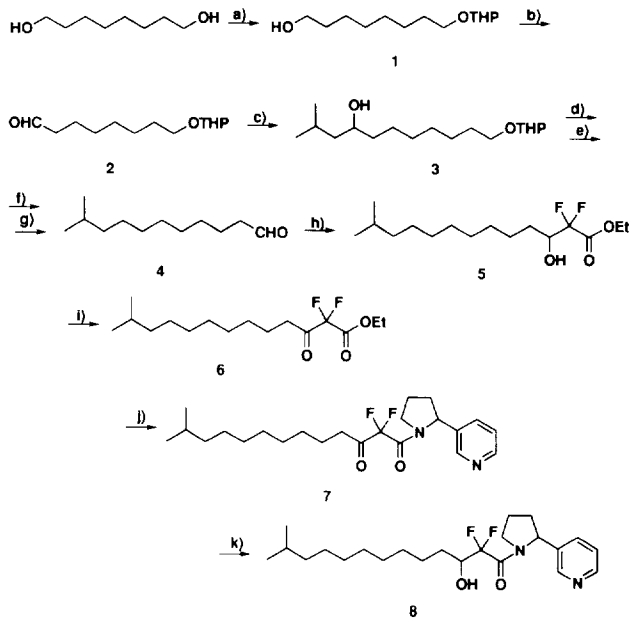
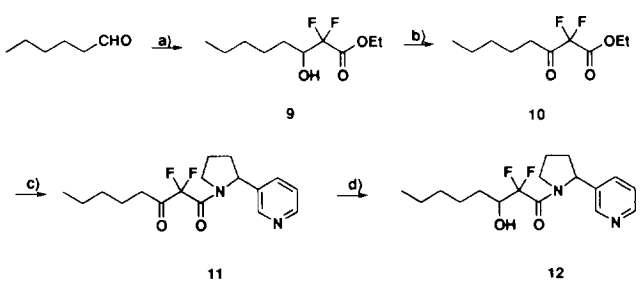
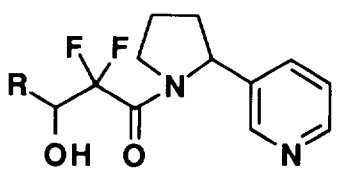


Scheme 1. Reaction conditions: (a) DHP, $Al_2(SO_4)_3$, octane, 78 °C (yield, 49%); (b) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C (Swern oxidation: yield, 90%); (c) $(CH_3)_2CHCH_2MgBr$, THF, 0 °C (yield, 76%); (d) MsCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C (yield, 95%); (e) $LiAlH_4$, THF, reflux (yield, 97%); (f) cat. PPTS, EtOH, 60 °C (yield, 98%); (g) Swern oxidation (yield, 99%); (h) Zn, $BrCF_2CO_2Et$, THF (yield, 91%); (i) *o*-iodobenzoic acid, $KBrO_3$, H_2SO_4, Ac_2O, AcOH, 100 °C (Dess–Martin reagent, 1.6 mol dm^{-3} in CH_2Cl_2) (yield, 92%); (j) nornicotine, neat (yield, 76%); (k) $NaBH_4$, EtOH, −78 °C (yield, 98%).

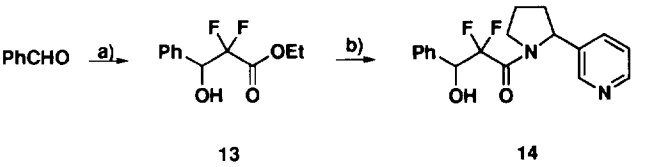


Scheme 2. Reaction conditions: (a) Zn, $BrCF_2CO_2Et$, THF (yield, 93%); (b) *o*-iodobenzoic acid, $KBrO_3$, H_2SO_4, Ac_2O, AcOH, 100 °C (Dess–Martin reagent, 1.6 mol dm^{-3} in CH_2Cl_2) (yield, 87%); (c) nornicotine, neat (yield, 71%); (d) $NaBH_4$, EtOH, −78 °C (yield, 98%).

Table 1
Characteristics of various substituted nornicotines prepared in this study



R	Compound No.	M.p. (°C)	Diastereomeric ratio
$CH_3(Me)CH(CH_2)_8$	**8**	76–103	1:1
C_5H_{11}	**12**	oil	3:2
Ph	**14**	113–117	3:2



Scheme 3. Reaction conditions: (a) Zn, $BrCF_2CO_2Et$, THF (yield, 69%); (b) nornicotine, MeONa, THF (yield, 35%).

obtained from the α,α-difluoro-β-hydroxy ester **13** in a reaction system involving sodium methoxide and nornicotine.

3. Experimental details

3.1. General procedures

All commercially available reagents were used without further purification. Chemical shifts of ^1H (500 MHz) and ^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standards (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). ^{19}F (470 MHz) NMR spectra were recorded in ppm downfield from internal C_6F_6 in $CDCl_3$ using a VXR 500 instrument. Yields quoted are those of the products actually isolated.

3.2. Preparation of 8-tetrahydroxypyranyloxy-1-octanol (1)

To a solution of 1,8-octanediol (25 g, 171.2 mmol) and $Al_2(SO_4)_3$ (578 mg, 0.856 mmol) in dried octane (155 ml) at 78 °C, dihydropyran (17.2 ml, 188.1 mmol) was added dropwise under an argon atmosphere. After the solution had been stirred overnight, the mixture was quenched with saturated $NaHCO_3$ (aq). The organic materials were extracted with diethyl ether. The extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual oils were purified by silica gel column chromatography (40% AcOEt/hexane) to give alcohol **1** (19.1 g, 83.0 mmol) in 49% yield. ^1H NMR δ: 1.15–2.00 (18H, m); 3.32–3.97 (7H, m); 4.57 (1H, dd, J=4.72, 3.08 Hz) ppm. ^{13}C NMR δ: 19.70; 25.51; 25.70; 26.18; 29.36; 29.43; 29.73; 30.79; 32.78; 62.35; 62.98; 67.66; 98.85 ppm. IR (neat) ν (cm^{-1}): 3425.

3.3. Preparation of 8-tetrahydroxypyranyloxy-1-octanal (2)

To a solution of oxalyl chloride (2.99 ml, 34.4 mmol) in anhydrous dichloromethane (70 ml) at −78 °C, was added dropwise dimethyl sulfoxide (4.88 ml, 68.8 mmol) under an argon atmosphere, followed by the addition of alcohol **1** in dichloromethane (100 ml) at the same temperature. After the solution had been stirred for 25 min, trimethylamine (23.8 ml, 172 mmol) was added. After stirring for a further 15 min, the whole was quenched with saturated NH_4Cl (aq.). The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The

residual oil was purified by silica gel column chromatography (25% AcOEt/hexane) to give aldehyde **2** (3.52 g, 15.4 mmol) in 90% yield. ^{1}H NMR δ: 1.22–1.95 (16H, m); 2.43 (2H, td, J=7.18, 1.84 Hz); 3.32–3.56 (2H, m); 3.66–3.93 (2H, m); 4.57 (1H, dd, J=4.40, 2.74 Hz); 9.77 (1H, t, J=1.84 Hz) ppm. ^{13}C NMR δ: 19.73; 22.04; 25.52; 26.06; 29.11; 29.20; 29.68; 30.80; 43.89; 62.38; 67.56; 98.87; 202.80 ppm. IR (neat) ν (cm^{-1}) 1720.

3.4. Preparation of 1-(2-methylpropyl)-8-tetrahydroxypyranyloxy-1-octanol (3)

To a solution of aldehyde **2** (5.3 g, 23.2 mmol) in freshly dried ether (116 ml) at 0 °C, was added dropwise isobutylmagnesium bromide (2.0 M in ether, 17.4 ml, 34.8 mmol) under an argon atmosphere. After stirring for 30 min, the whole was quenched with saturated NH_4Cl (aq.). The organic layer was separated and the aqueous layer extracted with ether. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (25% AcOEt/hexane) to give alcohol **3** (5.04 g, 17.6 mmol) in 76% yield. ^{1}H NMR δ: 0.91 (3H, d, J=6.56 Hz); 0.92 (3H, d, J=6.68 Hz); 1.13–1.90 (21H, m); 3.33–3.94 (6H, m); 4.54–4.62 (1H, m) ppm. ^{13}C NMR δ: 19.71; 22.09; 23.53; 24.65; 25.52; 25.57; 26.20; 29.46; 29.64; 29.74; 30.80; 38.08; 46.84; 62.35; 67.66; 69.95; 98.85 ppm. IR (neat) ν (cm^{-1}) 3450.

3.5. Preparation of 10-methylundecanal (4)

(a) 1-(2-Methylpropyl)-8-tetrahydroxypyranyloxy-1-octanyl methane sulfonate: To a solution of alcohol **3** (10.9 g, 38.1 mmol) in freshly dried dichloromethane (190 ml) at 0 °C, was added *N,N*-diisopropylethylamine (19.9 ml, 114.3 mmol) under an argon atmosphere, followed by the addition of methane sulfonyl chloride (9.24 ml, 114.3 mmol) at the same temperature. After stirring for 1 h, the whole was quenched with water. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (20% AcOEt/hexane) to give the sulfonate of **3** (13.1 g, 36.0 mmol) in 95% yield. ^{1}H NMR δ: 0.94 (3H, d, J=6.40 Hz); 0.95 (3H, d, J=6.60 Hz); 1.17–1.90 (21H, m); 2.99 (3H, s); 3.32–3.57 (2H, m); 3.67–3.93 (2H, m); 4.54–4.61 (1H, m); 4.72–4.87 (1H, m) ppm. ^{13}C NMR δ: 19.75; 22.19; 22.94; 24.50; 24.79; 25.53; 26.17; 29.31; 29.37; 29.72; 30.82; 35.05; 38.85; 43.57; 62.41; 67.62; 82.74; 98.91 ppm. IR (neat) ν (cm^{-1}): 1355.

(b) 10-Methylundecanol tetrahydroxypyranyl ether: To a solution of lithium aluminum hydride (18 mg, 0.467 mmol) in freshly dried tetahydrofuran (3 ml), was added dropwise the above sulfonate (170 mg, 0.467 mmol) under an argon atmosphere. After the solution had been stirred for 3 h at 80 °C, the whole was poured into saturated NH_4Cl (aq.). The organic layer was separated and the aqueous layer extracted with ether. The combined organic extracts were dried over $MgSO_4$, and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (10% AcOEt/hexane) to give the ether (122 mg, 0.452 mmol) in 97% yield. ^{1}H NMR δ: 0.91 (6H, d, J=6.56 Hz); 1.03–1.93 (23H, m); 3.31–3.58 (2H, m); 3.64–3.94 (2H, m); 4.58 (1H, dd, J=4.32, 2.66 Hz) ppm. ^{13}C NMR δ: 19.72; 22.67; 25.53; 26.26; 27.42; 27.98; 29.52; 29.63; 29.67; 29.78; 29.93; 30.81; 39.07; 62.35; 62.72; 98.85 ppm. IR (neat) ν (cm^{-1}): 1470.

(c) 10-Methylundecanol: To a solution of the above ether (3.0 g, 11.1 mmol) in ethanol (56 ml) was added pyridinium *p*-toluene sulfonate (279 mg, 1.11 mmol). After the solution had been stirred for 8 h at 60 °C, the solvent was removed in vacuo. The residual materials were purified by silica gel column chromatography (20% AcOEt/hexane) to give the alcohol (2.02 g, 10.9 mmol) in 98% yield. ^{1}H NMR δ: 0.86 (6H, d, J=6.58 Hz); 1.05–1.67 (17H, m); 2.18 (1H, s); 3.64 (2H, t, J=6.62 Hz) ppm. ^{13}C NMR δ: 22.68; 25.77; 27.42; 28.00; 29.47; 29.65; 29.94; 32.85; 39.07; 63.13 ppm. IR (neat) ν (cm^{-1}): 3325.

(d) To a solution of oxalyl chloride (4.28 ml, 49.2 mmol) in freshly dried dichloromethane (60 ml) at −78 °C, was added dropwise dimethyl sulfoxide (6.99 ml, 98.4 mmol) under an argon atmosphere, followed by the addition of the above alcohol in dichloromethane (60 ml) at the same temperature. After the solution had been stirred for 25 min, trimethylamine (34.3 ml, 246 mmol) was added at the same temperature. After stirring for a further 1 h, the whole was quenched with saturated aq. NH_4Cl. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (10% AcOEt/hexane) to give aldehyde **4** (24.3 mmol) in 99% yield. ^{1}H NMR δ: 0.86 (6H, d, J=6.56 Hz); 1.03–1.62 (15H, m); 2.42 (2H, td, J=7.18, 1.90 Hz); 9.77 (1H, t, J=1.90 Hz) ppm. ^{13}C NMR δ: 22.12; 22.67; 27.38; 27.98; 29.20; 29.38; 29.48; 29.85; 39.04; 43.95; 202.96 ppm. IR (neat) ν (cm^{-1}): 1730.

3.6. Preparation of ethyl 2,2-difluoro-3-hydroxy-12-methyltridecanoate (5) (nc)

To a solution of aldehyde **4** (1.1 g, 5.98 mmol) and zinc (586 mg, 8.97 mmol) in freshly dried tetrahydrofuran (30 ml) was added ethyl bromodifluoroacetate (1.15 ml, 8.97 mmol) at room temperature. After stirring for 2.5 h, the whole was quenched with 1 N HCl (aq.). The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (20% AcOEt/hexane) to give alcohol **5** (1.68 g, 5.45 mmol) in 91% yield. ^{1}H NMR δ: 0.86 (6H, d, J=6.54 Hz); 1.07–1.74

(20H, m); 1.37 (3H, t, J=7.14 Hz); 1.91–2.09 (1H, s); 3.90–4.16 (1H, m); 4.36 (2H, q, J=7.14 Hz) ppm. ^{13}C NMR δ: 13.96; 22.67; 25.23; 27.41; 27.99; 29.17–29.26 (m); 29.34; 29.50; 29.61; 29.91; 39.06; 63.04; 71.81 (dd, J=27.0, 24.8 Hz); 114.72 (dd, J=255, 253 Hz); 163.76 (t, J=30.85 Hz) ppm. ^{19}F NMR δ: 39.4 (dd, J=266, 15.3 Hz); 46.7 (dd, J=266, 7.6 Hz) ppm. IR (neat) ν (cm^{-1}): 3450; 1760.

3.7. Preparation of ethyl 2,2-difluoro-12-methyl-3-oxotridecanoate (6) (nc)

To a solution of alcohol **5** (1.1 g, 3.57 mmol) in freshly dried dichloromethane (36 ml) at room temperature, was added the Dess–Martin reagent (2.27 g, 5.36 mmol) under an argon atmosphere. After stirring for 30 min, the whole was quenched with saturated $NaHCO_3$ (aq.) and saturated $Na_2S_2O_3$ (aq.). The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (10% AcOEt/hexane) to give ester **6** (1.01 g, 3.30 mmol) in 92% yield. ^{1}H NMR δ: 0.86 (6H, d, J=6.56 Hz); 1.07–1.74 (18H, m); 1.35 (3H, t, J=7.14 Hz); 2.73 (2H, tt, J=7.14, 1.04 Hz); 4.37 (2H, q, J=7.14 Hz) ppm. ^{13}C NMR δ: 13.88; 22.55; 22.70; 27.49; 28.07; 28.91; 29.37; 29.55; 29.94; 36.69; 39.13; 63.73; 108.33 (t, J=262 Hz); 161.54 (t, J=30.1 Hz); 197.53 (t, J=27.7 Hz) ppm. ^{19}F NMR δ: 47.9 ppm. IR (neat) ν (cm^{-1}): 1780; 1745.

3.8. Preparation of N'-(2,2-difluoro-12-methyl-3-oxotridecanoyl)nornicotine (7) (nc)

A solution of ester **6** (306 mg, 1 mmol) and DL-nornicotine (0.304 ml, 2.2 mmol) was stirred overnight in the absence of solvent. The mixture was purified by silica gel column chromatography (70% AcOEt/hexane) to give amide **7** (309 mg, 0.757 mmol) in 76% yield. ^{1}H NMR δ: 0.86 (6H, d, J=6.59 Hz); 1.00–2.13 (18H, m); 2.26–2.46 (1H, m); 2.53–2.73 (2H, m); 3.65–3.98 (2H, m); 5.20 (1H, dd, J=7.86, 4.18 Hz); 7.12–7.32 (1H, m); 7.33–7.50 (1H, m); 8.36–8.55 (2H, m) ppm. ^{13}C NMR δ: 22.59; 22.66; 24.30; 27.36; 27.94; 28.82; 29.29; 29.43; 29.82; 33.23; 37.30; 39.01; 47.49 (t, J=5.26 Hz); 60.43; 110.15 (t, J=265 Hz); 123.47; 133.09; 137.09; 147.38; 148.49; 160.20 (t, J=27.8 Hz); 198.29 (t, J=27.1 Hz) ppm. ^{19}F NMR δ: 49.3 (d, J=282 Hz); 50.5 (d, J=282 Hz) ppm. IR (neat) ν (cm^{-1}): 1750; 1660. HR-MS: Calc. for $C_{23}H_{34}N_2O_2F_2$, 408.2608. Found, 408.2558.

3.9. Preparation of N'-(2,2-difluoro-3-hydroxy-12-methyltridecanoyl)nornicotine (8) (nc)

To a solution of amide **7** (204 mg, 0.5 mmol) in dried ethanol (5 ml) at −78 °C, was added sodium borohydride (7 mg, 0.19 mmol) under an argon atmosphere. After stirring for 1 h, the whole was quenched with saturated NH_4Cl (aq.) and the solvent removed in vacuo. The residual materials were diluted with dichloromethane, the organic layer separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual materials were purified by silica gel column chromatography (AcOEt) to give alcohol **8** (201 mg, 0.49 mmol) in 98% yield. ^{1}H NMR δ: 0.86 (6H, d, J=6.58 Hz); 1.04–2.13 (20H, m); 2.27–2.47 (1H, m); 3.38 (1H, s); 3.96–4.18 (3H, m); 5.15–5.26 (1H, m); 7.20–7.31 (1H, m); 7.36–7.50 (1H, m); 8.41–8.55 (2H, m) ppm. ^{13}C NMR δ: 22.66; 24.33; 25.36–25.54 (m); 27.39; 27.94; 28.45; 29.42; 29.51; 29.62; 29.88; 33.21; 39.02; 47.60–48.21 (m); 60.34; 60.41; 70.69–71.83 (m); 110.97–121.69 (m); 123.50; 133.24; 133.29; 137.57; 137.52; 147.23; 148.01; 148.20; 162.48–163.67 (m) ppm. ^{19}F NMR δ: 38.9 (dd, J=290, 18.3 Hz); 40.3 (dd, J=285, 18.3 Hz); 50.6 (dd, J=287, 4.57 Hz); 51.6 (dd, J=286, 3.05 Hz) ppm. IR (KBr) ν (cm^{-1}): 3200; 1650. HR-MS: Calc. for $C_{23}H_{36}N_2O_2F_2$, 410.2757. Found, 410.2744. M.p. 76–103 °C.

3.10. Preparation of ethyl 2,2-difluoro-3-hydroxyoctanoate (9) (nc)

To a solution of caproaldehyde (2.40 ml, 20 mmol) and zinc (1.96 g, 30 mmol) in dried tetrahydrofuran (100 ml), ethyl bromodifluoroacetate (3.84 ml, 30 mmol) was added at room temperature. After stirring for 1 h, the whole solution was quenched with 1 N HCl. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual oil was purified by bulb-to-bulb distillation (5 mmHg, 120 °C) to give alcohol **9** (4.14 g, 18.5 mmol) in 93% yield. ^{1}H NMR δ: 0.83–0.98 (3H, m); 1.16–1.74 (9H, m); 1.37 (3H, t, J=7.14 Hz); 1.97 (1H, s); 3.93–4.13 (1H, m); 4.36 (2H, q, J=7.14 Hz) ppm. ^{13}C NMR δ: 13.95; 14.01; 22.51; 24.92; 29.14 (dd, J=3.00, 1.63 Hz); 31.51; 63.12; 71.77 (dd, J=27.25, 24.96 Hz); 114.80 (dd, J=256.64; 254.30 Hz); 163.91 (dd, J=32.84, 31.12 Hz) ppm. ^{19}F NMR δ: 39.3 (dd, J=263.98, 13.73 Hz); 46.7 (dd, J=263.98, 7.63 Hz) ppm. IR (neat) ν (cm^{-1}): 3450; 1760. B.p. 103–106 °C/3 mmHg.

3.11. Preparation of ethyl 2,2-difluoro-3-oxooctanoate (10) (nc)

To a solution of alcohol **9** (1.0 g, 4.46 mmol) in dried dichloromethane (23 ml) at room temperature, was added Dess–Martin reagent (2.84 g, 6.69 mmol) under an argon atmosphere. After stirring for 2 h, the reaction mixture was quenched with saturated $NaHCO_3$ (aq.) and saturated $Na_2S_2O_3$ (aq.). The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual oil was purified by silica gel column chromatography (20% AcOEt/hexane) to give ester

10 (861 mg, 3.88 mmol) in 87% yield. ^{1}H NMR δ: 0.82–1.01 (3H, m); 1.21–1.50 (7H, m); 1.36 (3H, t, J = 7.14 Hz); 1.56–1.78 (2H, m); 2.74 (2H, tt, J = 7.14, 1.18 Hz); 4.38 (2H, q, J = 7.14 Hz) ppm. ^{13}C NMR δ: 13.86; 22.16; 22.33; 30.96; 36.61; 63.71; 108.25 (t, J = 262.55 Hz); 161.48 (t, J = 30.65 Hz); 197.55 (t, J = 29.35 Hz) ppm. ^{19}F NMR δ: 47.9 ppm. IR (neat) ν (cm^{-1}): 1780; 1745.

3.12. Preparation of N'-(2,2-difluoro-3-oxooctanoyl)-nornicotine (11) (nc)

A solution of ester **10** (870 mg, 3.92 mmol) and DL-nornicotine (1.19 ml, 8.62 mmol) was stirred overnight in the absence of solvent. The mixture was purified by silica gel column chromatography (AcOEt) to give amide **11** (901 mg, 2.78 mmol) in 71% yield. ^{1}H NMR δ: 0.879 (3H, t, J = 6.68 Hz); 1.17–1.48 (4H, m); 1.50–1.74 (2H, m); 1.80–2.22 (3H, m); 2.29–2.50 (2H, m); 2.69 (2H, tt, J = 7.10, 1.24 Hz); 3.84–4.06 (2H, m); 5.20 (1H, dd, J = 7.78, 3.94 Hz); 7.23–7.37 (1H, m); 7.41–7.56 (1H, m); 8.43–8.61 (2H, m) ppm. ^{13}C NMR δ: 13.85; 22.25; 22.33; 24.31; 30.95; 33.24; 37.32; 47.50 (t, J = 5.36 Hz); 60.43; 110.15 (t, J = 265.25 Hz); 123.47; 133.03; 136.97; 147.44; 148.63; 160.27 (t, J = 27.8 Hz); 198.44 (t, J = 27.2 Hz) ppm. ^{19}F NMR δ: 49.2 (d, J = 282.29 Hz); 50.4 (d, J = 280.76 Hz) ppm. IR (neat) ν (cm^{-1}): 1750.

3.13. Preparation of N'-(2,2-difluoro-3-hydroxyoctanoyl)-nornicotine (12) (nc)

To a solution of amide **11** (162 mg, 0.5 mmol) in ethanol (5 ml) at −78 °C, was added sodium borohydride (7 mg, 0.19 mmol) under an argon atmosphere. After stirring for 1 h, the reaction mixture was quenched with saturated NH_4Cl (aq.) and the solvent removed in vacuo. The residual oil was diluted with dichloromethane and the organic layer separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual oil was purified by silica gel column chromatography (AcOEt) to give alcohol **12** (161 mg, 0.49 mmol) in 98% yield. ^{1}H NMR δ: 0.73–1.00 (3H, m); 1.08–2.13 (11H, m); 2.24–2.48 (1H, m); 3.39 (1H, s); 3.92–4.18 (3H, m); 5.14–5.28 (1H, m); 7.23–7.34 (1H, m); 7.38–7.55 (1H, m); 8.40–8.62 (2H, m) ppm. ^{13}C NMR δ: 14.02; 22.51; 24.27; 24.37; 25.05; 25.11; 28.21–29.00 (m); 31.56; 33.21; 47.58–48.48 (m); 60.36; 60.43; 70.50–71.86 (m); 111.07–121.76 (m); 123.54; 133.36; 133.44; 137.68; 147.18; 147.90; 148.10; 162.50–163.76 (m) ppm. ^{19}F NMR δ: 38.7 (dd, J = 289.92, 19.83 Hz); 40.2 (dd, J = 285.34, 19.83 Hz); 50.6 (dd, J = 286.87, 4.57 Hz); 51.5 (dd, J = 288.40, 3.05 Hz) ppm. IR (neat) ν (cm^{-1}): 3400; 3160; 1660.

3.14. Preparation of ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (13) (nc)

To a solution of benzaldehyde (2.03 ml, 20 mmol) and zinc (1.96 g, 30 mmol) in tetrahydrofuran (50 ml) was added ethyl bromodifluoroacetate (3.08 ml, 24.4 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with 1 N HCl (aq.). The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual oil was purified by column chromatography on silica gel (30% AcOEt/hexane) to give alcohol **13** (2.93 g, 13.7 mmol) in 69% yield. ^{1}H NMR δ: 1.29 (3H, t, J = 7.08 Hz); 2.50 (1H, s); 4.30 (2H, q, J = 7.08 Hz); 5.16 (1H, dd, J = 7.81, 7.57 Hz); 7.37–7.46 (5H, m) ppm. ^{13}C NMR δ: 13.70; 63.27; 73.62 (dd, J = 24.26, 27.60 Hz); 113.97 (dd, J = 252.3, 257.6 Hz); 127.80; 128.31; 129.17; 134.64; 163.83 (t, J = 30.9 Hz) ppm. ^{19}F NMR δ: 41.3 (dd, J = 260.9, 5.26 Hz); 47.9 (dd, J = 260.9, 9.16 Hz) ppm. IR (neat) ν (cm^{-1}): 3480; 1770.

3.15. Preparation of N'-(2,2-difluoro-3-hydroxy-3-phenylpropanoyl)nornicotine (14) (nc)

To a solution of DL-nornicotine (0.304 ml, 2.2 mmol) in dried tetrahydrofuran (10 ml) at room temperature, was added sodium methoxide (238 mg, 4.4 mmol) and alcohol **13** (448 mg, 2 mmol) in dried tetrahydrofuran (10 ml) under an argon atmosphere. After the solution had been stirred for 30 min, the reaction mixture was quenched with water. The whole was diluted with dichloromethane and the organic layer separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and the solvent removed in vacuo. The residual oil was purified by silica gel column chromatography (AcOEt) to give compound **14** (230 mg, 0.692 mmol) in 35% yield. ^{1}H NMR δ: 1.80–2.38 (4H, m); 3.71–4.02 (2H, m); 5.16–5.28 (3H, m); 7.18–7.50 (7H, m); 8.41–8.51 (2H, m) ppm. ^{13}C NMR δ: 23.99; 24.06; 24.37; 32.97; 33.04; 47.07–48.38 (m); 60.54; 60.65; 72.64–73.70 (m); 110.24–121.03 (m); 123.32; 123.50; 128.05; 128.56; 128.61; 133.50; 133.79; 135.46; 135.95; 137.51; 137.57; 146.82; 147.07; 147.65; 147.95; 162.48–163.81 (m) ppm. ^{19}F NMR δ: 40.7 (dd, J = 286.9, 19.8 Hz); 41.7 (dd, J = 280.8, 21.4 Hz); 53.7 (dd, J = 280.8, 4.57 Hz); 54.5 (dd, J = 286.9, 12.21 Hz) ppm. IR (neat) ν (cm^{-1}): 3061; 1642. M.p. 113–117 °C.

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