Synthesis of (*R*)-(–)-2-Fluoronorapomorphine − A Precursor for the Synthesis of (*R*)-(–)-2-Fluoro-*N*-[^{11}C]propylnorapomorphine for Evaluation as a Dopamine D_2 Agonist Ligand for PET Investigations

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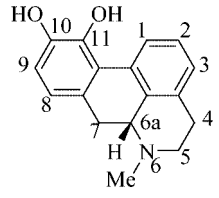
2-Fluoronorapomorphine, the PET labelling precursor to 2-fluoro-*N*-[^{11}C]propylnorapomorphine, was prepared in 13 steps from codeine in a total yield of 10 %. Codeine was converted in four steps into *N*-benzylnorcodeine which was oxidised by using the Swern protocol. Subsequent acid-catalysed rearrangement afforded *N*-benzylnormorphothebaine which was selectively triflylated at the 2-position and pivaloylated at the 11-position. The triflate underwent palladium-catalysed amination with benzophenone imine. Amination conditions required sequential base addition to give substantial conversion of the triflate to the corresponding *N*-substituted benzophenone imine. After acidic hydrolysis the resulting aniline was transformed into the 2-fluoro compound via the Balz–Schiemann reaction. Hydrogenolysis of the *N*-benzyl group followed by deprotection of the catechol moiety using BBr_3 provided 2-fluoronorapomorphine.

Introduction

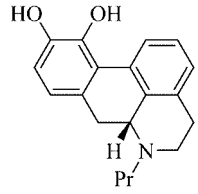
Ever since postmortem studies revealed a deficiency in striatal dopamine in patients with Parkinson's Disease,[1] the dopaminergic system has been the subject of intense research. In particular, the dopamine D_2 receptor has emerged as an important mediator in the central nervous system for various processes such as motor function and reward.[2]

Positron emission tomography (PET) is a non-invasive technique that enables monitoring of, for example, the dopamine D_2 receptor in the living brain.[3–8] The dopamine D_2 receptor exists in two states – a functional state (D_2^{high}) and a non-functional state (D_2^{low}). Agonists preferentially bind to the functional state (i.e. the high affinity state) whereas antagonists bind equally well to both states.[9] For this reason agonists may be more sensitive to competition effects from the endogenous agonist dopamine for imaging changes in synaptic dopamine concentration. Radioligands that previously have been used in PET studies to measure synaptic changes in dopamine concentration include the dopamine D_2 agonists [^{11}C]apomorphine[10] and *N*-[^{11}C]propylnorapomorphine.[11–13] The latter provides the best striatum/cerebellum ratio so far (i.e. region-of-interest to reference region ratio) of 2.8 in baboon.

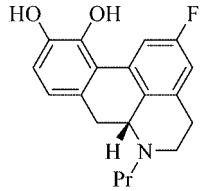
It is known that substituents in the 2-position of apomorphines can modulate dopaminergic D_2 activity and selectivity.[14,15] In particular, the 2-fluoro-*N*-propylnorapo-



(*R*)-(–)-Apomorphine



(*R*)-(–)-*N*-Propylnorapomorphine (NPA)



(*R*)-(–)-2-Fluoro-*N*-propylnorapomorphine (2F-NPA)

Scheme 1. The archetypical dopamine D_2 receptor agonist (*R*)-(–)-apomorphine and two derivatives, NPA and 2F-NPA.

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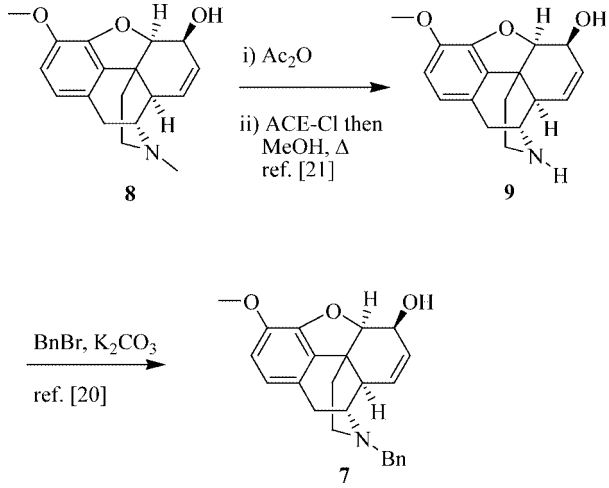
morphine (2F-NPA, Scheme 1) is 66-fold more potent than the parent *N*-propylnorapomorphine (NPA, K_i 0.012 nM vs. 0.80 nM). Also the D_1/D_2 selectivity increased from 425 to 57700 when changing the 2-substituent from hydrogen to fluorine.[16–18] In view of this, we set out to prepare 2-fluoronorapomorphine − a precursor for the preparation of 2-fluoro-*N*-[^{11}C]propylnorapomorphine.

Results and Discussion

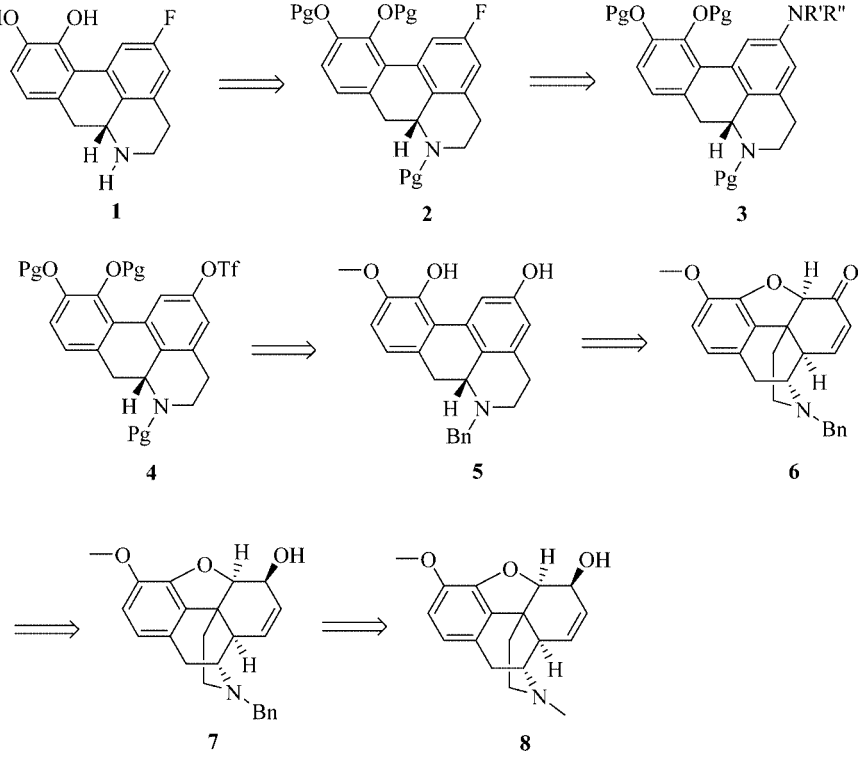
Introduction of the positron-emitting radionuclide carbon-11 into apomorphines is usually accomplished by reacting their corresponding norapomorphines with an electrophile such as [^{11}C]methyl iodide or [^{11}C]propanoyl chloride. This transformation is only viable in a late stage of the synthetic sequence due to the very short half-life of carbon-11 (20.4 min). Therefore, previously reported syntheses of 2F-NPA by Neumeyer et al.[17] and Berenyi et al.[19] are not amenable to PET chemistry since introduction of the *N*-propyl group is performed in the early stages of the synthesis. Thus a new synthetic strategy had to be developed to provide 2-fluoronorapomorphine as a precursor for carbon-11 labelling.

The target 2-fluoro compound **1** (Scheme 2) appropriately protected at the catechol moiety and at the nitrogen as in **2**, would allow chemical transformations to be carried out in the 2-position. The introduction of fluorine via diazotisation of a 2-aminoapomorphine has been reported previously by Ramsby et al.[14] The 2-fluoro compound **2** could therefore be derived from masked aniline **3** which in turn could be generated by the use of a palladium-catalysed amination reaction on triflate **4**. Compound **4** could come from dihydroxy compound **5** which is available from either *N*-benzylnorcodeinone (**6**) or *N*-benzylnorthebaine via acid-catalysed rearrangement. We preferred to design our synthetic route from the former since thebaine is both expensive and toxic. α,β-Unsaturated ketone **6** is derived from *N*-benzylnorcodeine (**7**) – a compound available in 4 steps from codeine (**8**).

The synthesis commenced by converting codeine (**8**, Scheme 3) by a known synthetic sequence into *N*-benzylnorcodeine (**7**).[20] Thus, codeine was *O*-acetylated followed by *N*-carbamoylation/*N*-demethylation by the use of α-chloroethyl chloroformate (ACE-Cl).[21] The resultant carba-



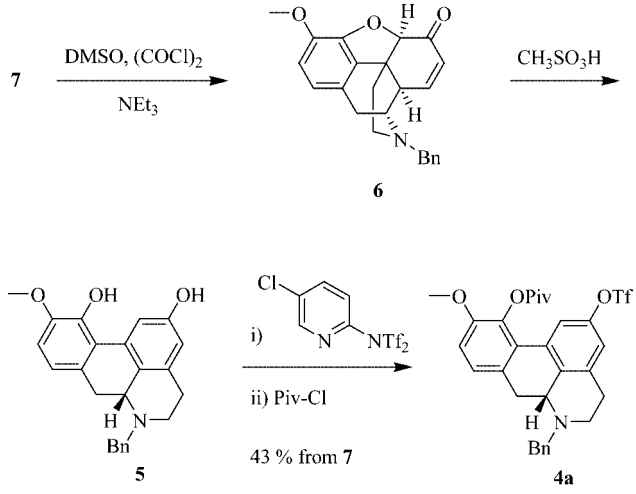
Scheme 3. Four-step sequence towards **7**.



Scheme 2. Retrosynthetic analysis.

mate was cleaved in refluxing methanol with concomitant methanolysis of the acetyl ester to give **9**. The secondary amine **9** was then selectively *N*-alkylated with benzyl bromide in the presence of K_2CO_3 in DMF thus providing **7** which contains a convenient *N*-protecting group removable at a late stage in the synthesis.[20]

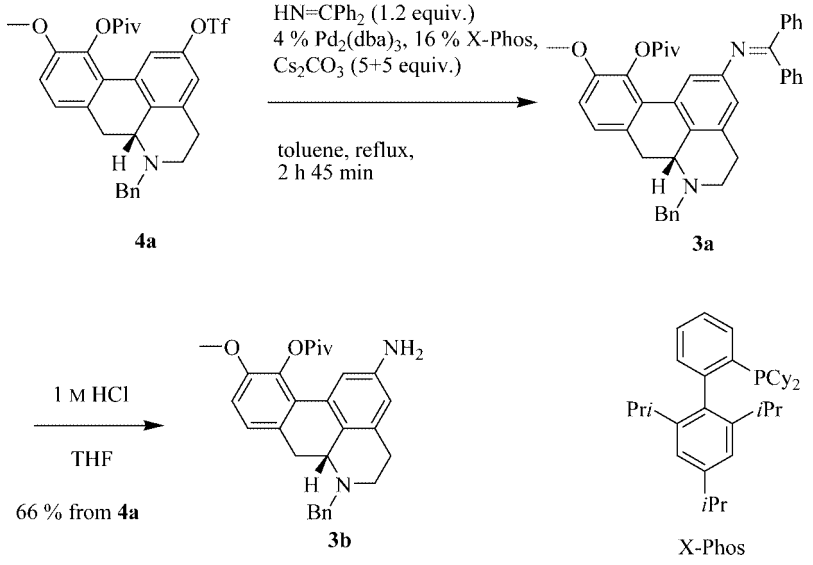
Oxidation of **7** (Scheme 4) to ketone **6** was accomplished by the Swern protocol [DMSO, $(COCl)_2$]. Attempts to oxidise **7** by other methods such as TEMPO/re-oxidants[22,23] or activated MnO_2[24] failed. Skeletal rearrangement was achieved by treating **6** with methanesulfonic acid[25] to give rise to the dihydroxy compound **5** which was selectively triflated at the 2-position with 5-chloro-2-[bis(trifluoromethylsulfonyl)amino]pyridine. Acylation at the 11-hydroxy group with pivaloyl chloride was performed in the same pot. This gave a 43% overall yield of **4a** from **7**. A more obvious route would be to oxidise codeine directly and perform the outlined synthesis on the codeine scaffold. However, production of the labelling norapomorphine precursor requires an *N*-demethylation on the aporphine skeleton. Such a transformation was performed recently utilising a non-classical modified Polonovski reaction where glaucine was converted to norglaucine.[26] However, this approach failed on our aporphine template.



Scheme 4. Synthesis of triflate **4a**.

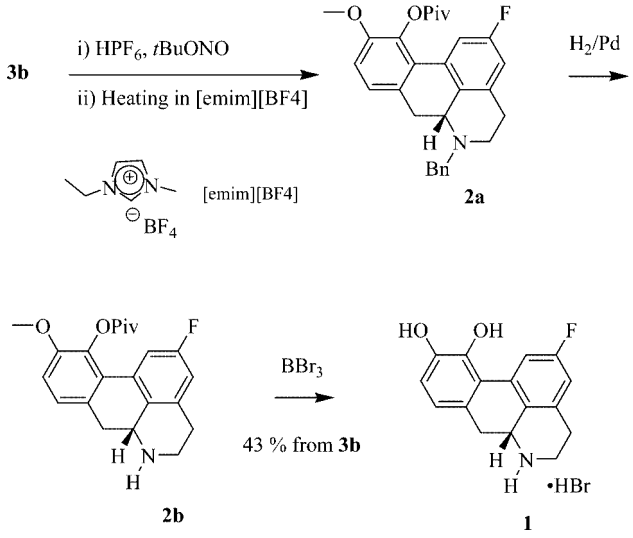
The crucial step for introducing the masked aniline in the 2-position from triflate **4a** turned out to be difficult. Many experiments were performed with benzophenone imine as the ammonia equivalent.[27] Numerous amination reactions were attempted including well-established protocols using $Pd(OAc)_2$/BINAP/Cs_2CO_3,[27] $Pd_2(dba)_3$/Xantphos/Cs_2CO_3[28,29] and $Pd(dba)_2$/dppf/*t*BuONa.[30] All failed to provide acceptable yields of the desired aniline **3a**. Some conversion was achieved when using $Pd_2(dba)_3$/X-Phos/Cs_2CO_3.[31] Catalyst loading, solvent and temperature were also varied. Many amination reactions require only a slight excess of base but in our case it was beneficial to add several equivalents of Cs_2CO_3. When starting with five equivalents of Cs_2CO_3 the reaction slowed down considerably after 75 minutes of reflux in toluene. Addition of another five equivalents of base caused the reaction to run to completion within an additional 90 minutes. This feature may be attributed to the "base effect" hypothesis which suggests that liquid-solid interphase deprotonation of the palladium(II)-amine complex is the rate-determining step.[32] It was found that using 1.2 equiv. benzophenone imine, 0.04 equiv. $Pd_2(dba)_3$, 0.16 equiv. X-Phos and 5 + 5 equiv. Cs_2CO_3 in refluxing toluene provided full conversion of triflate **4a** into imine **3a**. Treating imine **3a** with 1 M hydrochloric acid gave aniline **3b** in 66% yield over two steps from **4a** (Scheme 5).

The aniline **3b** was converted into the corresponding diazonium hexafluorophosphate by treatment with *tert*-butyl nitrite[33] and hexafluorophosphoric acid followed by heating in an ionic liquid[34] gave the fluoro-arene **2a** (Scheme 6) which was subsequently hydrogenolysed to provide secondary amine **2b**. The Balz–Schiemann reaction gave rise to some reduction of the diazonium salt to the parent 2-H



Scheme 5. The palladium-catalysed amination of triflate **4a**.

compound. Attempts to avoid this by using freshly prepared *tert*-butyl nitrite[35] or by exclusion of moisture failed. Treatment of **2b** with BBr_3 furnished the labelling precursor **1** as the hydrobromic salt in a yield of 43% from **3b**.



Scheme 6. Introduction of fluorine via the Balz–Schiemann reaction and concomitant deprotection.

In summary we have devised a route to a labelling precursor for the most potent D_2 receptor agonist yet known. The key step of the synthesis is a palladium-catalysed amination of an apomorphine derivative. Utilising a modified Balz–Schiemann reaction the fluorine was introduced at the 2-position and subsequent deprotection gave the labelling precursor **1**.

This procedure has the potential for installation of a variety of other functionalities at the 2-position either by a Sandmeyer reaction on aniline **3b** or by palladium-catalysed cross coupling of the triflate **4a**. This opens up further possibilities to fine-tune ligand-receptor interactions of PET tracers and optimisation of in vivo properties such as lipophilicity/hydrophilicity. In addition, this synthesis gives access to 2-substituted apomorphines with different *N*-substituents, which are known to influence the pharmacological profile of apomorphine significantly.[36]

The precursor **1** can readily be converted into either [^{11}C]2F-NPA by a known radiochemical sequence.[12] Additionally [^{11}C]2F-APO and 2-fluoro-*N*-[^{11}C]ethylnorapomorphine can be prepared by labelling with the corresponding [^{11}C]alkyl iodides.[10,37] The labelling and the PET imaging results will be published elsewhere.

Experimental Section

General: Solvents were distilled under anhydrous conditions. All reagents were used without further purification unless specified. Evaporation was performed on a rotary evaporator with the temperature kept below 40 °C. Glassware used for moisture sensitive reactions were flame-dried under reduced pressure and cooled to room temperature under a stream of nitrogen prior to use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck 60, F_{254}) were visualised by dipping into a solution containing ninhydrin (0.6 g), acetic acid (1.5 mL) and water (13.3 mL) in *n*BuOH (300 mL) and heating until coloured spots appeared. ^{1}H NMR, gCOSY, gHSQC gHMBC and ^{19}F NMR were performed on a Varian Mercury-*plus* 300 MHz (IDPFG). ^{13}C NMR was performed on a Varian Gemini 300 MHz. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a JMS-HX/HX110A tandem mass spectrometer. Melting points are uncorrected.

(*R*)-(–)-*N*-Benzyl-10-methoxy-11-pivaloyloxy-2-(trifluoromethylsulfonyloxy)noraporphine (4a): A solution of oxalyl chloride (3.2 mL, 36.5 mmol, 1.3 equiv.) in dry CH_2Cl_2 (40 mL) was cooled to –78 °C. To this was added dropwise a solution of DMSO (5.2 mL, 73.1 mmol, 2.6 equiv.) in dry CH_2Cl_2 (10 mL). The mixture was kept at –78 °C for 15 min before adding a solution of *N*-benzylnorcodeine (**7**) (10.54 g, 28.1 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL) followed by stirring at –78 °C for 1 h before adding Net_3 (20 mL, 141 mmol, 5 equiv.). The mixture was allowed to reach room temperature and transferred to a separating funnel and washed with 1 M NaOH and with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to give crude *N*-benzylnorcodeinone (**6**) (10.66 g) as a yellow solid which was sufficiently pure for further reaction. R_f = 0.24 (2% MeOH in $CHCl_3$). M.p. 62–65 °C. $[a]_D^{25.1}$ = –246.5 (*c* = 0.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, N–CH_2–C_6H_5), 6.67 [d, *J*(1,2) = 8.2 Hz, 1 H, H-1/H-2], 6.64 (d, 1 H, H-1/H-2), 6.58 [dd, *J*(7,14) = 2.0, *J*(7,8) = 10.2 Hz, 1 H, H-7], 6.05 [dd, *J*(8,14) = 2.9 Hz, 1 H, H-8], 4.69 (s, 1 H, H5), 3.84 (s, 3 H, -OCH_3), 3.76 (d, J_{gem} = 13.4 Hz, 1 H, N–CH_2–C_6H_5), 3.69 (d, 1 H, N–CH_2–C_6H_5), 3.44 [dd, *J*(9,14) = 3.1, *J*(9,10$_a$) = 5.2 Hz, 1 H, H-9], 3.24 [dd, *J*(14,10$_a$) = 5.1 Hz, 1 H, H-14,], 3.14 [d, *J*(10$_b$,10$_a$) = 18.4 Hz, 1 H, H-10$_b$,], 2.65 [ddd, *J*(16$_a$,15$_a$) = 1.6, *J*(16$_a$,15$_b$) = 4.8, *J*(16$_a$,16$_b$) = 12.1 Hz, 1 H, H-16$_a$,], 2.35 [td, *J*(16$_b$,15) = 3.7, *J*(16$_b$,15) = 8.3 Hz, 1 H, H-16$_b$], 2.33 (dd, 1 H, H-10$_a$), 2.06 [td, *J*(15$_b$,15$_a$) = 12.2 Hz, 1 H, H-15$_b$], 1.83 (ddd, 1 H, H-15$_a$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.1 (C=O), 150.0, 145.3, 142.9, 139.2, 132.8, 129.8, 129.1, 128.8, 127.6, 126.6 (Ar), 120.4, 115.0 (C7 + C8), 88.7 (C5), 59.7 (N–*C*H$_2$–Ph), 57.2 (-O*C*H$_3$), 57.1 (C9), 45.4 (C16), 44.1 (C13), 42.0 (C14), 34.5 (C15), 21.8 (C10). The crude *N*-benzylnorcodeinone (**6**) was dissolved in neat CH_3SO_3H (50 mL) and heated to 95 °C under a flow of nitrogen for 1 h. The resultant syrup was transferred to a continuous extraction apparatus and basified with NaOH (34 g in 200 mL water) at 0 °C. The pH was then adjusted to ca. 8 by addition of solid $NaHCO_3$. Continuous extraction with Et_2O for 16 h gave a solution which was concentrated to give crude *N*-benzylnormorphothebaine (**5**) (10.93 g), R_f = 0.38 [MeOH/$CHCl_3$ (1:9)]. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.90 [d, *J*(1,3) = 2.2 Hz, 1 H, H-1], 7.46–7.20 (m, 5 H, =N$CH_2C_6H_5$), 6.82 [d, *J*(8,9) = 8.1 Hz, 1 H, H-8/H-9], 6.76 (d, 1 H, H-8/H-9), 6.53 (d, 1 H, H-3), 4.33 (d, J_{gem} = 13.8 Hz, 1 H, =N$CH_2C_6H_5$), 3.85 (s, 3 H, Ar–OCH_3), 3.33–3.20 (m, 4 H), 3.02–2.82 (m, 2 H), 2.66–2.43 (m, 2 H), 2.36–2.23 (m, 1 H). ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 155.7, 147.0, 144.1, 140.0, 134.5, 133.8, 130.5, 129.2, 128.6, 127.1, 126.9, 121.0, 118.8, 114.3, 113.8, 110.2 (Ar), 60.7 (C6a), 58.9 (=N*C*H$_2$C$_6$H$_5$), 56.1 (Ar–O*C*H$_3$), 49.4 (C5), 35.8 (C7). 29.8 (C4). The crude phenol **5** (10.93 g) was taken up as a slurry in CH_2Cl_2 (100 mL). To this was added with stirring Net_3 (20 mL, 141 mmol, 5 equiv.) and 2-(5-chloropyridyl)trifluorosulfonimide (12.1 g, 30.9 mmol, 1.1 equiv.). The mixture was stirred for 1.5 h before adding freshly distilled pivaloyl chloride (5.2 mL, 42.2 mmol, 1.5 equiv.) and DMAP (172 mg, 1.41 mmol, 0.05 equiv.). The mixture was left stirring until the singlet at δ =

3.90 ppm disappeared in the NMR spectrum[38] and then washed once with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography to give the title compound **4a** (7.17 g, 43% over four steps) as a bright yellow fluffy solid. R_f = 0.20 [EtOAc/pet. ether (1:4)]. M.p. 74–76 °C. $[\alpha]_D^{25}$ = –187.5 (c = 0.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (br. S, 1 H, H-1), 7.41–7.18 (m, 5 H, =NCH$_2$C$_6$H$_5$), 7.11 [d, J(8,9) = 8.2 Hz, 1 H, H-8/H-9], 6.96 [br. D, J(3,1) = 2.2 Hz, 1 H, H-3], 6.87 (d, 1 H, H-8/H-9), 4.32 (d, J_{gem} = 13.7 Hz, 1 H, =NCH_2C$_6$H$_5$), 3.81 (s, 3 H, Ar–OCH_3), 3.47 [br. D, J(6a,7$_a$) = 12.3 Hz, 1 H, H-6a], 3.35 (d, 1 H, =NCH_2C$_6$H$_5$), 3.23 [dd, J(7$_b$,6a) = 3.8, J(7$_b$,7$_a$) = 12.3 Hz, 1 H, H-7$_b$], 3.13–2.97 (m, 2 H, H-4$_a$ + H-5$_a$), 2.67 [d, J(4$_b$,4$_a$) = 18.8 Hz, 1 H, H-4$_b$], 2.65 (t, 1 H, H-7$_a$), 2.46–2.30 (m, 1 H, H-5$_b$), 1.38 [s, 9 H, Ar–OCOC(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4 [Ar–OCOC(CH$_3$)$_3$], 151.2, 148.1, 138.9, 138.0, 137.0, 136.5, 133.8, 130.0, 129.3, 128.8, 127.6, 127.3, 126.0, 120.5, 119.1 [q, CF$_3$, J(C,F) = 321 Hz], 118.9, 112.4 (Ar), 60.3 (C6a), 59.1 (=NCH$_2$C$_6$H$_5$), 56.6 (Ar–OCH$_3$), 48.6 (C5), 39.6 [Ar–OCOC(CH$_3$)$_3$], 34.7 (C7), 29.9 (C4), 27.6 [Ar–OCOC(CH_3)$_3$]. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.7. MS (EI): m/z = 589 $[M]^{+\cdot}$. $C_{30}H_{30}F_3NO_6S$ (589.62): calcd. C 61.11, H 5.13, N 2.38; found C 61.20, H 5.35, N 2.26.

(*R*)-(–)-2-Amino-*N*-benzyl-10-methoxy-11-pivaloyloxynoraporphine (3b): Under anhydrous conditions triflate **4a** (3.08 g, 5.22 mmol, 1.0 equiv.), benzophenone imine (1.05 mL, 6.27 mmol, 1.2 equiv.) and finely ground Cs_2CO_3 (8.51 g, 26.1 mmol, 5 equiv.) were mixed in dry toluene (20 mL) followed by the addition of X-Phos (398 mg, 0.836 mmol, 0.16 equiv.) and $Pd_2(dba)_3{\cdot}CHCl_3$ (216 mg, 0.209 mmol, 0.04 equiv.). The mixture was heated to 110 °C under nitrogen. After 75 min an additional charge of finely ground Cs_2CO_3 (8.51 g, 26.1 mmol, 5 equiv.) was added. After another 90 min the mixture was allowed to cool to room temperature and then filtered. The filter cake was washed several times with EtOAc. The combined organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography to give a viscous yellow oil which after washing with pentane (to remove co-eluting benzophenone imine) provided the desired imine **3a** (2.60 g) as a yellow foam. R_f = 0.39 [EtOAc/pet. ether (1:2)]. M.p. 78–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.20 (m, 15 H, Ar), 7.15 (br. s, 1 H, H-1), 7.10 [d, J(8,9) = 8.2 Hz, 1 H, H-8/H-9], 6.82 (d, 1 H, H-8/H-9), 6.50 (br. s, 1 H, H-3), 4.34 (d, J_{gem} = 13.5 Hz, 1 H, =NCH_2C$_6$H$_5$). 3.81 (s, 3 H, Ar–OCH_3), 3.42 [br. d, J(6a,7$_a$) = 13.5 Hz, 1 H, H-6a], 3.36 (d, 1 H, =NCH_2C$_6$H$_5$), 3.13 [dd, J(7$_b$,6a) = 3.3, J(7$_b$,7$_a$) = 13.7 Hz, 1 H, H-7$_b$], 3.03 [dd, J(5$_a$,4$_a$) = 4.9, J(5$_a$,5b) = 10.9 Hz, 1 H, H-5$_a$], 2.90 [dt, J(4$_a$,4$_b$) = 16.6 Hz, 1 H, H-4$_a$,], 2.61 (t, 1 H, H-7$_a$), 2.50 (d, 1 H, H-4$_b$), 2.36 (t, 1 H, H-5$_b$), 1.42 [s, 9 H, Ar–OCOC(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): selected data (from the region of aliphatic group signals): δ = 60.4 (C6a), 59.4 (=NCH$_2$C$_6$H$_5$), 56.6 (Ar–OCH$_3$), 49.2 (C5), 39.5 (Ar–OCOC(CH$_3$)$_3$], 35.2 (C7), 29.7 (C4), 27.7 [Ar–OCOC(CH_3)$_3$]. MS (EI): m/z = 620 $[M]^{+\cdot}$. $C_{42}H_{40}N_2O_3$ (620.78): calcd. C 81.26, H 6.49, N 4.51; found C 81.00, H 6.20, N 4.22. Imine **3a** (2.60 g) was dissolved in THF (70 mL) followed by addition of 1 M aqueous HCl (2 mL). The mixture was stirred at room temperature for 90 min before adding another load of 1 M aqueous HCl (12 mL). After stirring for an additional 50 min full conversion was achieved as judged by TLC (R_f = 0.14 in EtOAc/pet. ether (1:2, 10 mL) + 1 drop of NEt_3). The reaction mixture was partitioned between EtOAc and 1 M HCl. The aqueous phase was washed several times with EtOAc until no more benzophenone imine was detected in the organic phase as judged by TLC. The aqueous phase was then basified with solid $NaHCO_3$ followed by extraction with EtOAc. Drying of the organic phase ($MgSO_4$), filtration and concentration in vacuo gave the pure aniline **3b** (1.57 g, 66% over two steps) as a light brown fluffy solid. M.p. 101–103 °C. $[\alpha]_D^{25}$ = –131.0 (c = 0.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.23 (m, 6 H, =NCH$_2$C$_6$H$_5$ + H-1), 7.11 [d, J(8,9) = 8.2 Hz, 1 H, H-8/H-9], 6.84 (d, 1 H, H-8/H-9), 6.41 [d, J(3,1) = 1.6 Hz, 1 H, H-3,], 4.34 (d, J_{gem} = 13.7 Hz, 1 H, =NCH_2C$_6$H$_5$), 3.83 (s, 3 H, Ar–OCH_3), 3.52 (br. s, 2 H, Ar–NH_2), 3.42 [br. d, J(6a,7$_a$) = 12.4 Hz, 1 H, H-6a], 3.34 (d, 1 H, =NCH_2C$_6$H$_5$), 3.21 [dd, J(7$_b$,6a) = 3.5, J(7$_b$,7$_a$) = 13.8 Hz, 1 H, H-7$_b$], 3.08–2.90 (m, 2 H, H-4$_a$ + H-5$_a$), 2.70–2.52 (m, 2 H, H4$_b$ + H7$_a$), 2.45–2.32 (m, 1 H, H-5$_b$), 1.43 [s, 9 H, Ar–OC-OC(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1 [Ar–OC-OC(CH$_3$)$_3$], 151.1, 144.5, 139.5, 137.7, 134.9, 132.1, 130.3, 129.4, 129.0, 128.7, 127.4, 126.9, 125.8, 114.8, 113.9, 111.1 (Ar), 60.2 (C6a), 59.2 (=NCH$_2$C$_6$H$_5$), 56.6 (Ar–OCH$_3$), 49.2 (C5), 39.4 [Ar–OCOC(CH$_3$)$_3$], 35.7 (C7), 29.7 (C4), 27.7 [Ar–OCOC(CH_3)$_3$]. $C_{29}H_{32}N_2O_3$ (456.58): calcd. C 76.29, H 7.06, N 6.14; found C 76.03, H 7.28, N 5.98.

(*R*)-(–)-2-Fluoronorapomorphine Hydrobromide (1): Aniline **3b** (111 mg, 0.243 mmol, 1.0 equiv.) was dissolved in CH_3CN (2 mL) and the solution was cooled to 0 °C under nitrogen before adding 60% aqueous HPF_6 (84 μL, 0.559 mmol, 2.3 equiv.). The mixture was stirred at 0 °C for 15 min then at room temperature for 15 min before cooling to 0 °C. Freshly prepared tBuONO[35] (43 μL, 0.365 mmol, 1.5 equiv.) was added and the mixture was stirred for 2 hours before it was concentrated to dryness. The crude diazonium salt was dissolved in [emim][BF_4] (see Scheme 6) (1.5 mL) and heated to 90 °C under nitrogen for 1 h. After cooling to room temperature the solution was transferred to a separating funnel and NEt_3 (2 mL) was added. The mixture was extracted with EtOAc and the organic phase was decanted. The extraction was continued until no more product was observed in the organic phase as judged by TLC [R_f = 0.44, EtOAc/pet. ether (4:6, 10 mL) + 1 drop of NEt_3]. The combined organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated to give crude 2-fluoroaporphine **2a** (120 mg). This was dissolved in AcOH (1.5 mL) followed by the addition of 10% Pd/C (50 mg) and exposed to H_2 (1 atm, balloon). The mixture was stirred vigorously for 19 hours after which the hydrogenolysis was complete as judged by TLC (R_f = 0.56, 5% NH_4OH and 10% MeOH in EtOAc). The mixture was worked up by dilution with MeOH (3 mL) followed by filtration through a pad of celite. After concentration in vacuo the resultant syrup was separated between EtOAc and saturated aqueous $NaHCO_3$. The water phase was extracted with EtOAc and the combined organic phase was dried ($MgSO_4$), filtered and concentrated to give an oily residue which was purified by column chromatography [MeOH/$CHCl_3$ (1:9) + 1% NEt_3] to give secondary amine **2b** (49 mg) containing 7% (based on ^{1}H NMR) of R-(–)-10-methoxy-11-pivaloyloxynoraporphine (resulting from reduction of the diazonium salt) which could not be separated by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 [br. d, J(1,F) = 10.6 Hz, 1 H, H-1], 7.08 [d, J(8,9) = 7.6 Hz, 1 H, H-8/H-9], 6.85 (d, 1 H, H-8/H-9), 6.78 [br. d, J(3,F) = 8.9 Hz, 1 H, H-3], 3.92 [br. d, J(6a,7$_a$) = 13.3 Hz, 1 H, H-6a], 3.81 (s, 3 H, Ar–OCH_3), 3.42–3.28 (m, 1 H, H-5$_a$), 3.12–2.98 (m, 2 H), 2.86 [dd, J(7$_b$,6a) = 4.6, J(7$_b$,7$_a$) = 13.9 Hz, 1 H, H-7$_b$], 2.80–2.57 (m, 3 H), 1.40 [s, 9 H, Ar–OCOC(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3 [Ar–OCOC(CH$_3$)$_3$], 161.5 [C–F, J (C,F) = 242 Hz], 151.7, 138.1, 136.1, 135.9, 132.4, 129.5, 127.9, 125.8, 115.0 [J(C,F) = 21 Hz], 113.3 [J(C,F) = 23 Hz], 111.8 (Ar), 56.5 (Ar–OCH$_3$), 53.6 (C6a), 43.1 (C5), 39.4 [Ar–OCOC(CH$_3$)$_3$], 37.2 (C7), 29.8 (C4), 27.6 [Ar–OC-OC(CH_3)$_3$]. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –117.3. m/z: 370 [M

+ 1]$^+$ calcd. for ($C_{22}H_{24}FNO_3$ + H^+) 370. The methyl aryl ether **2b** (49 mg) was dissolved in CH_2Cl_2 (2 mL) and a 1.0 M solution of BBr_3 in CH_2Cl_2 (2.7 mL, 2.65 mmol, 20 equiv.) was added. The mixture was stirred for 1.5 h under nitrogen and then concentrated. The resultant brown solid was dissolved in MeOH (10 mL) and refluxed for 40 min and then concentrated in vacuo. The solid was redissolved in MeOH (10 mL) and activated carbon (50 mg) was added. The mixture was heated to reflux and quickly filtered through a pad of celite. After concentration to dryness the remaining solid was washed several times with $CHCl_3$ providing the title compound **1** (37 mg, 43% over 4 steps) as an off-white solid. The product was contaminated with 7% norapomorphine hydrobromide as judged by the H1-protons at 8.37 (contaminant) and 8.16 (title compound) in ^{1}H NMR spectroscopy. M.p. (decomp.) at 230 °C. $[\alpha]_D^{25}$ = –38.2 (*c* = 0.15, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ = 8.16 [dd, *J*(1,3) = 2.1, *J*(1,F) = 11.4 Hz, 1 H, H-1], 6.86 [dd, *J*(3,F) = 8.7 Hz, 1 H, H-3], 6.75 [d, *J*(8,9) = 7.9 Hz, 1 H, H-8/H-9], 6.64 (d, 1 H, H-8/H-9), 4.31 [dd, *J*(6a,7_b) = 3.1, *J*(6a,7_a) = 13.8 Hz, 1 H, H-6a], 3.78–3.64 (m, 1 H, H-5_a), 3.45–3.22 (m, 2 H), 3.14–2.97 (m, 2 H), 2.84 [t, *J*(7_a,7_b) = 13.7 Hz, 1 H, H-7_a,]. ^{13}C NMR (75 MHz, CD_3OD): δ = 162.6 [*J*(C,F) = 243 Hz], 145.1, 144.2, 135.3 [*J*(C,F) = 9.7 Hz], 132.3 [*J*(C,F) = 8.7 Hz], 124.6, 124.1 [*J*(C,F) = 2.7 Hz], 119.0, 118.8, 114.7, 114.6 [*J*(C,F) = 24.9 Hz], 113.3 [*J*(C,F) = 22.4 Hz], 53.4 (C6a), 41.3 (C5), 33.4 (C7), 25.5 (C4). ^{19}F NMR (282 MHz, CD_3OD): δ = –112.1. HRMS (FAB): 272.1092, calcd. for $C_{16}H_{15}FNO_2^+$ 272.1081.

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