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Synthesis of 2-Fluoro-11-hydroxy-*N*-propylnoraporphine: A Potential Dopamine D_2 Agonist

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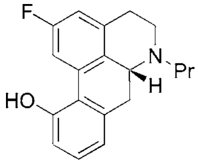
ABSTRACT



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2-Fluoro-11-hydroxy-*N*-propylnoraporphine 4 (2-F-11-OH-NPa) was synthesized from thebaine in 13 steps with an overall yield of 1.35%. The key steps included the Pd-catalyzed 3-dehydroxylation of 14-hydroxymorphine, S_N2 substitution of Ts^- by F^-, and CH_3SO_2OH-promoted rearrangement of the substituted morphinandiene. The dopamine binding affinity of this compound was also investigated on rat brain membranes, and as expected, this compound displayed high affinity and selectivity at the D_2 receptor.

R-(−)-apomorphine (**1a**, R-(−)-APO) (Figure 1), a well-known dopamine (DA) agonist, has clinical utility in the treatment of Parkinson's disease and erectile dysfunction.[1b,c] A major limitation of its clinical use is its poor oral bioavailability. In the last three decades, a number of aporphine analogues have been synthesized and evaluated at DA receptors in an effort to increase the oral activity and extend the duration of action. Most of these structure and activity relationship (SAR) studies were focused on the functional optimizations at three positions: N-6, C-10, and C-2. As a result, the *N*-propyl analogue **1b** (R-(−)-NPA) was found to be more potent than R-(−)-APO **(1a)**.[2] In addition, it was found that the C-2 position can tolerate a variety of functional substituents without significant effect on the affinity and selectivity at dopamine D_2 receptor.[1] For example, introducing a hydroxyl group at C-2 resulted in compound **2a** which displayed potent DA agonist activity although the binding affinity was slightly lower than NPA (**1b**).[3a−c] It was noteworthy that 2-fluoroapomorphine (**2c**) and its *N*-propyl analogue (**2b**), with a more electronegative fluoro substituent at the C-2, showed remarkably high affinity and selectivity at the dopamine D_2 receptor. Compound **2b** is among the most potent and selective D_2 agonist synthesized so far with IC_{50} of 0.07 nM at D_2 and 1.3 μM at D_1 receptors,

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[1] (a) Nomenclature used in this series is as follows: NPA = *N-n*-propylnorapomorphine which has a catechol moiety; NPa = *N-n*-propylnoraporphine which has a monohydroxyphenyl moiety. (b) Tyne, H. L.; Parson, J.; Sinott, A.; Fox, S. H.; Steiger, M. J. *J. Neurol.* **2004**, *251*, 1370. (c) Neumeyer, J. L.; Baldessarini, R. J.; Booth, R. J. In *Burger's Medicinal Chemistry and Drug Discovery*, 6th ed.; Abraham, D. J., Ed.; John Wiley & Sons: New York, 2003; p 711.

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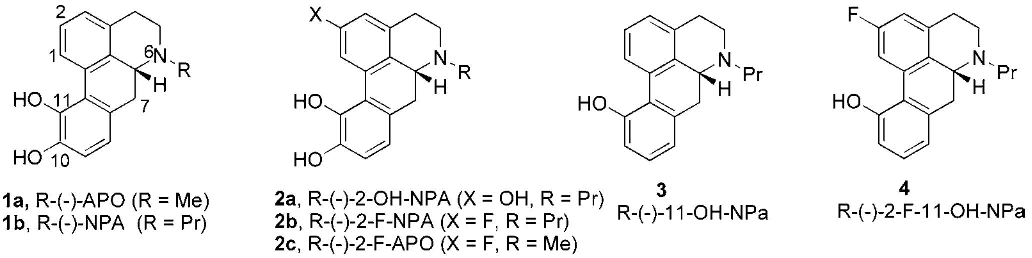


Figure 1. Structures of potent aporphine analogues.[1a]

respectively.[3h] Another noteworthy finding was that the 10-hydroxyl group was not a requirement for high dopamine D_2 receptor activity and can be replaced or eliminated. For example, the 10-dehydroxylated analogue **3** (11-OH-NPa) displayed even higher affinity and selectivity for D_2 (K_i = 28 nM) than apomorphine **1a**.[3i] Further investigation of **3** indicated that, when administered orally, it retained high pharmacological potency and displayed longer duration of action.[3i]

On the basis of these findings, especially upon integration of the information from compound **2b** and **3**, it was very apparent to us that a combination of the introduction of a fluoro group at C-2 position and the elimination of the 10-hydroxyl group will generate compounds with high DA receptor affinity and better pharmacological properties. Thus, we describe in this report the synthesis of R-(−)-2-fluoro-11-hydroxy-*N*-propylnoraporphine (**4**, 2-F-11-OH-NPa) (Figure 1).

The key approach to the synthesis of compound **4** was the introduction of a fluoro substituent at the C-2 of the aporphine skeleton. There were two possible approaches to achieve this objective: paths a and b as described in Figure 2. Both paths included the rearrangement of thebaine or its analogues to yield the aporphine skeleton as the key step. In path a, the 2-F substitution was introduced after the rearrangement of the diene ring system through the key intermediate **2a** and **2b**, while in path b the fluorine atom was introduced before the rearrangement of the diene ring system through the intermediate **5** and **6**.

To evaluate which path was more effective and convenient, we first attempted path a (Scheme 1). The synthesis was initiated from thebaine, which was first N-demethylated followed by realkylation to yield N-propylnorthebaine **7**.[2] Upon CH_3SO_3H-catalyzed rearrangement, diene **7** was converted to aporphine **8** which followed a slightly modified procedure to yield 2-aminocarbonyldimethylmethoxy-10,11-methylenedioxy-*N*-propylnoraporphine **10**, as described in our earlier reports.[3g,h] Compound **10** was then subjected to a Smiles rearrangement followed by a Schiemann reaction to yield the 2-F-NPA **2b** in low yield (25−50%).[3g,h]

As proposed in path a (Figure 2), elimination of the 10-hydroxyl group in compound **2b** by selective triflation of the 10-hydroxyl group or by selective formation of tetrazolo ether **12**, followed by palladium-catalyzed reduction, would produce the expected 2-fluoro-11-hydroxy-*N*-propylnoraporphine **4** (Scheme 1). However, triflation[3i] of the catechol **2b** ($PhNTf_2/Et_3N$ or Tf_2O/Py) only gave a mixture, and no monotriflate **12** could be isolated after column chromatography. Similarly, selective formation[3] of the tetrazolo ether of the 10-hydroxyl moiety by treating **2b** with 1-phenyl-5-Cl-tetrazole and K_2CO_3 was not successful. In consideration of the difficulty in selective elimination of the 10-hydroxyl group and the low yield in the Smiles rearrangement described above, we decided to attempt the synthesis of **4** via path b.

Parallel to our early work, Berenyi[4−8] reported an alternative procedure to prepare 2-fluoroapomorphine **2c**. In this procedure, the 2-fluoro function was introduced after forma-

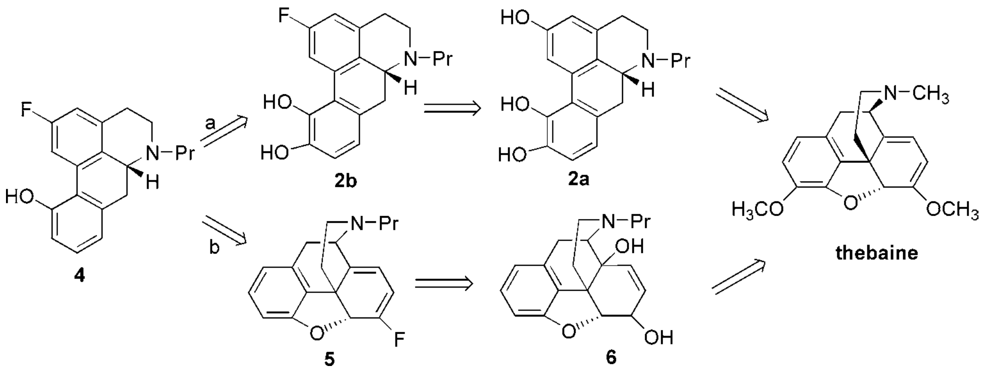
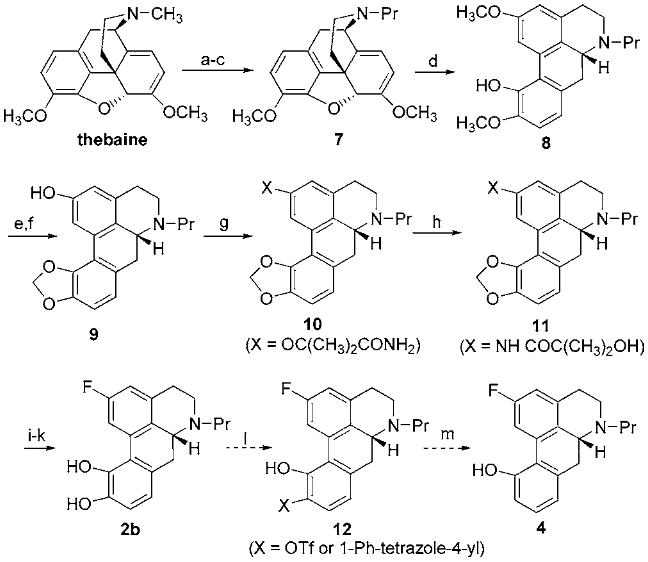


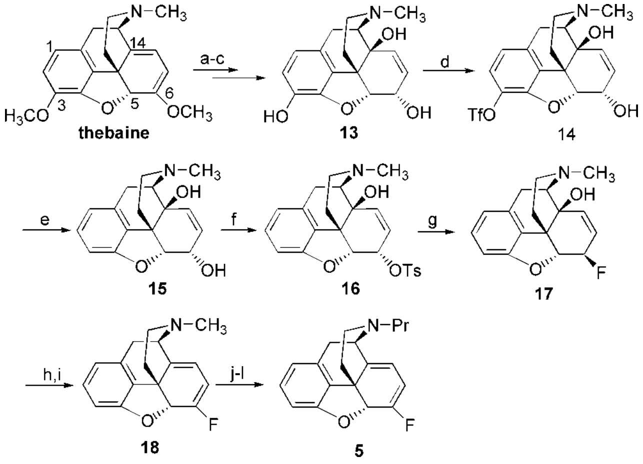
Figure 2. Possible approaches to 11-hydroxy-2-fluoro-*N*-propylnoraporphine **4**.

Scheme 1[a]



[a] Reagents and conditions: (a) DEAD, benzene, reflux; (b) Py•HCl, EtOH, rt; (c) PrI, K_2CO_3, EtOH, reflux; (d) CH_3SO_2OH; (e) HOAc, HBr (48%), reflux; (f) CH_2Br_2, NaOH, DMSO; (g) $BrC(CH_3)_2CONH_2$, K_2CO_3; (h) NaH, HMPA, rt to 100 °C; (i) 5 N HCl, reflux; (j) $NaNO_2$, HPF_6 (60%), 0 °C; (k) BCl_3 (1 M), rt; (l) $PhNTf_2$, Et_3N or 5-Cl-1-Ph-tetrazole, K_2CO_3, DMF; (m) $Pd(OAc)_2$, HCOOH, DMF, or $Pd(OH)_2$, H_2.

Scheme 2[a]



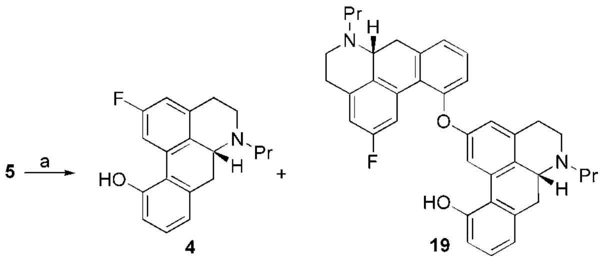
[a] Reagents and conditions: (a) *m*-CPBA; (b) BBr_3 (1 M), −78 °C to rt; (c) Li-Selectride, THF; (d) Tf_2NPh, Et_3N; (e) $Pd(OAc)_2$, HCOOH, DMF; (f) TsCl, Py; (g) Bu_4NF, CH_3CN; (h) PBr_3, $CHCl_3$, 0−60 °C, (i) $NaOBu^t$, EtOH, 90 °C; (j) DEAD, benzene, reflux; (k) Py•HCl; (l) PrI, K_2CO_3, EtOH, reflux.

tion of the apomorphine carbon skeleton avoiding the Smiles rearrangement and resulted in a better overall yield. Thus, we decided to develop a similar procedure to prepare our target molecule **4**.

The synthesis was initiated from thebaine, which was converted to 14-OH-morphine **13** using the reported procedures (Scheme 2).[8−12] Selective triflation of the 3-hydroxyl group followed by palladium-catalyzed reduction furnished 3-demethoxy-14-hydroxymorphine **15** in 64% yield.[3i,13] Tosylation[14,15] of the 6-hydroxyl group gave **16** in 80% yield, which was further converted to 6*R*-F-14-OH-3-deoxymorphine **17** in 70% yield by an S_N2 substitution[8] with F^-, upon treating **16** with $^tBu_4NF$. Treatment of **17** with PBr_3 followed by $NaOBu^t$ gave diene **18** in 56% overall yield. N-Demethylation[3c,4] of **18** using DEAD and Py•HCl followed by treatment with PrI and K_2CO_3 yielded 6-F-3,6-didemethoxy-*N*-propylnorthebaine **5** in 50% combined yield.

The next step was the acid-catalyzed rearrangement of the diene **5** to yield the target aporphine **4**. Using CH_3SO_3H at room temperature or 90 °C, a procedure reported by Berenyi et al. on the catecholic precursor,[8] did not yield any significant product **4**, except a more polar complex which was isolated by chromatography and identified as the dimer **19** (Scheme 3). This was in agreement with Berenyi's result.[8] After several attempts with this reaction, we found that compound **4**[16] could be obtained in up to 20% isolated yield when the rearrangement was conducted at 0 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) CH_3SO_3H, 0 °C.

The in vitro affinity of compound **4** for dopamine (DA) D_1 and D_2 receptors was determined by radioligand competition assays, using membrane preparations from DA-rich corpus striatum (caudatoputamen) tissue from rat forebrain, following a similar procedure reported previously.[3i] As

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expected, this compound displayed good affinity and selectivity at dopamine D_2 receptor with K_i of 39 and 800 nM at D_2 and D_1 receptors, respectively, which was comparable to our previously evaluated compound **3** (K_i: 28.5 nM for D_2, 700 nM for D_1). Further pharmacological studies with compounds **3** and **4** are in progress.

Thus, 2-fluoro-11-hydroxy-*N*-propylnoraporphine **4** (2-F-11-OH-NPa) was synthesized from thebaine in 13 steps with an overall yield of 1.35%. The key steps included the Pd-catalyzed 3-dehydroxylation of **13** through the triflate precursor **14**, S_N2 substitution of the tosylate **16** by $^tBu_4NF$, and CH_3SO_2OH-promoted rearrangement of the diene **5**. As expected, this compound displayed good affinity and selectivity at the D_2 receptor.

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Supporting Information Available: Full experimental details for all transformations and the analytical characterization of all new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The free base 2-F-11-OH-NPa **4** was converted to its HCl salt: mp >250 °C dec; MS *m/z* (rel intensity) 297 (M^+, 70); ^1H NMR (base, CD_3-OD) δ 0.96 (t, 3H), 1.61 (m, 2H), 2.50 (m, 3H), 2.73 (m, 1Hm), 2.91 (m, 1H), 3.14 (m, 3H), 3.34 (m, 1H), 6.74 (d, $J_{8,9} = 8$ Hz, 1H), 6.77 (dd, 1H), 6.87 (d, $J_{9,10} = 8$ Hz, 1H), 7.08 (t, 1H), 7.8 (dd, 1H); ^{13}C NMR (base, $CDCl_3$) δ 12.0, 19.4, 29.4, 35.0, 48.8, 56.3, 59.2, 112.3 (d, $J = 24$ Hz), 113.4 (d, $J = 21$ Hz), 115.5, 120.7, 128.4, 130.9, 133.3, 133.4, 135.4, 138.7, 152.7, 161.2 (d, $J = 240$ Hz); MS *m/z* (rel intensity) 297 (M^+, 70). Anal. ($C_{19}H_{20}FNO \cdot HCl$) Calcd: C, 68.36; H, 6.34; N, 4.20. Found: C, 68.31; H, 6.38; N, 4.15.