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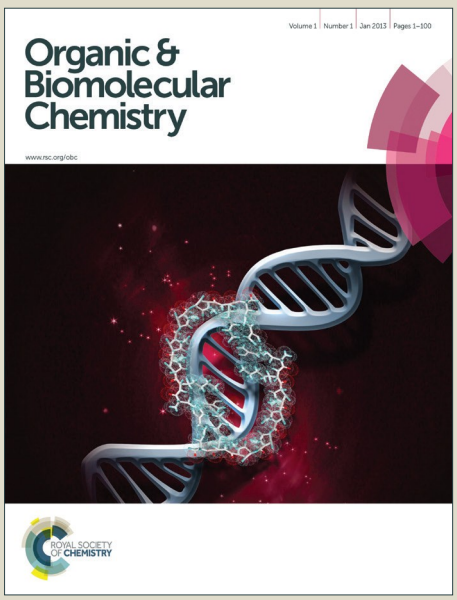

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ARTICLE

The Development of a Short Route to the API Ropinirole hydrochloride.

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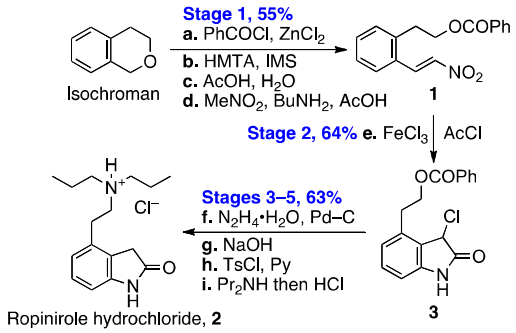
A four-step, three-stage synthesis of the API ropinirole hydrochloride has been developed from a commercially available naphthalene derivative. The new route has half the step-count and twice the overall yield of the current manufacturing process. Key features of the synthesis are a regioselective Birch reduction and an ozonolysis with concomitant ring closure to induce the required ring contraction.

Introduction

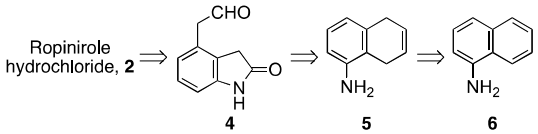
Ropinirole hydrochloride (**2**) was introduced by Smith, Kline and French as a non-ergoline, dopaminergic drug to alleviate symptoms related to Parkinson's disease by activating postsynaptic D_2 CNS receptors.[1] In 2005 the FDA also approved it as a treatment for restless leg syndrome and a further repurposing has seen it used to treat selective serotonin reuptake inhibitor-induced sexual dysfunction, which is purported to result from the D_3 agonistic activity of the drug.[2,3] Worldwide sales of ropinirole-based medicines peaked at around $500 million per annum prior to its patent expiry in May 2008, which heralded the introduction of several generic medicines.[4] It is currently marketed under various trade names, including Requip, Ronirol and Adartrel,[5] and compliments other symptomatic drug therapies based on ergot alkaloids,[6] anticholinergics,[7] monoamine-oxidase (MOA-B) inhibitors[8] and benzodiazepines.[9]

Commercially, ropinirole hydrochloride (**2**) is prepared from isochroman in 12–25% overall yield using a nine step, five stage sequence (Scheme 1).[10] Although alternative routes to the active pharmaceutical ingredient (API) have been developed,[11-18] none has usurped the original manufacturing process. Key transformations include a Sommelet oxidation (step b) and a Royer cyclisation reaction (step e), which both proceed in modest yield and display a degree of variability from experiment to experiment. Additionally, the route produces a number of halogenated byproducts.[10]



Scheme 1. Ropinirole hydrochloride and its large-scale synthesis.[10]

With current drives towards the clean manufacture of fine chemicals, it seemed timely to develop new strategies for the synthesis of ropinirole hydrochloride (**2**). Though the costs associated with registration of a new manufacturing route usually make it unviable commercially, there seemed sufficient scope for improvement to warrant investigation. Herein we report our preliminary findings, which have led to the development of new laboratory scale syntheses of the API. Importantly, the routes avoid the capricious Sommelet oxidation and Royer cyclisation reactions with the shortest proceeding in twice the yield and half the step-count of the manufacturing route.



Scheme 2. Our retrosynthetic analysis.

Mindful of the need to keep costs low,[19] we decided to target ropinirole hydrochloride from 1-aminonaphthalene **6** using the

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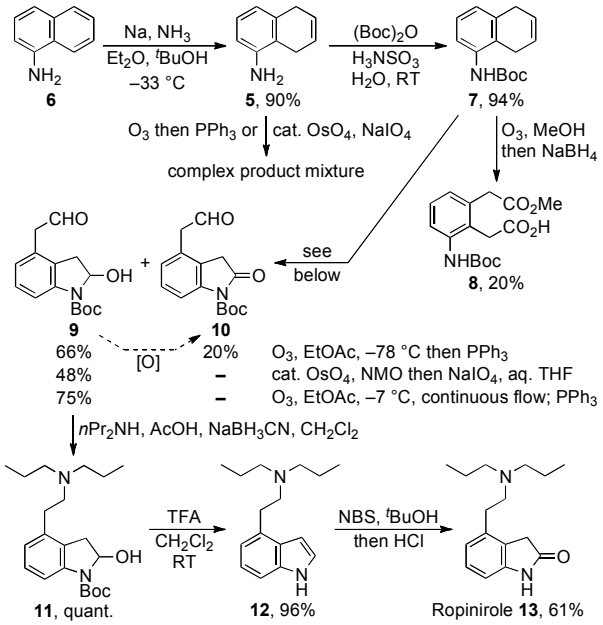
reconnection strategy outlined in Scheme 2. Thus, we were confident that the API **2** could be prepared from aldehyde **4** by reductive amination. In turn we hoped that the require oxindole **4** might be prepared by an oxidative cleavage of dihydronaphthalene **5** with concomitant oxidation of the intermediate hemiaminal. As the dissolving metal reduction of 1-aminonaphthalene **6** → **5** was a known procedure,[20] it became the start point of our investigation.

Results and Discussion

As expected, the Birch reduction of 1-aminonaphthalene **6** with sodium in liquid ammonia proceeded smoothly to give our key intermediate **5** in 90% yield contaminated with traces of 5-amino-tetralin and the starting material **6** (Scheme 3).[20] Although this was a pleasing result, repeat experiments exposed a degree of variation in the outcome of the reaction. This was traced to a sensitivity of the product **5** to aerial oxidation, with $CDCl_3$ solutions of **5** becoming contaminated with 1-aminonaphthalene **6** on prolonged standing. Progress was slowed further when our planned oxidative cleavage of **5** with ozone gave rise to a complex product mixture under a wide range of conditions. Switching to a Lemieux-Johnson type oxidation (OsO_4; $NaIO_4$) proved equally intractable,[22] leading us to question the compatibility of the aniline subunit under these cleavage conditions. A report by Plieninger *et al*.[23] on the ozonolysis of related aromatic amides indicated that its protection might prove beneficial. This was borne out when ozonolysis of a methanolic solution of the Boc derivative **7** led to the formation of acid **8** in 20% yield following a reductive work-up.



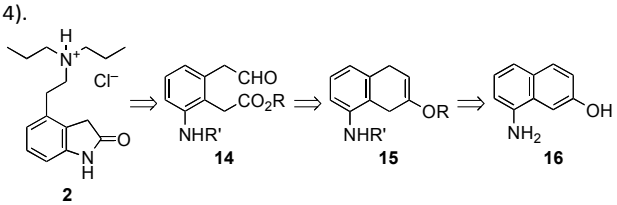
Scheme 3. Development of a synthesis of ropinirole from 1-aminonaphthalene.

As ozonolysis in methanol had given rise to a product at a higher oxidation level than we required, it seemed sensible to perform a solvent screen in the hope of attaining the desired aldehyde **10**. Preliminary results offered encouragement, with the reaction in EtOAc producing the desired oxindole **10** in 20% yield together with its presumed precursor, hemiaminal **9**, in 66% yield (Scheme 3). Alas, attempts to optimise the reaction for oxindole **10** went unrewarded. Notably, a Lemieux-Johnson type oxidation of **7** also gave hemiaminal **9** as the primary product, as did Motherwell and Gavriilidis' protocol for conducting ozonolyses under continuous flow.[24] Indeed, the latter proved to be the method of choice for advancing our synthesis due to its ease of optimisation and its consistency in giving hemiaminal **9** in 75% yield following a PPh_3 quench.

At this juncture we examine various methods to effect the oxidation of hemiaminal **9** to oxindole **10** and found that a propensity for elimination to the corresponding indole consistently thwarted such efforts. By contrast, we were able to realise the reductive amination of **9** to **11** in quantitative yield. Again, direct oxidation of hemiaminal **11** to ropinirole was examined with an array of oxidants (including ozone, Dess–Martin periodinane, IBX, TEMPO/I_2 and MnO_2) but in all cases formation of ropinirole **13** was compromised by competitive elimination and deprotection to indole **12**. As indole **12** was a known precursor of ropinirole,[11] and could be prepared from hemiaminal **11** in excellent yield by the action of TFA, we decided to incorporate it as an intermediate in our synthesis. Thus, oxidation of indole **12** to ropinirole **13** was effected using NBS in ^{t}BuOH,[25] giving us an overall yield of 37% for the sequence as a whole.

Development a Shorter and More Efficient Synthesis

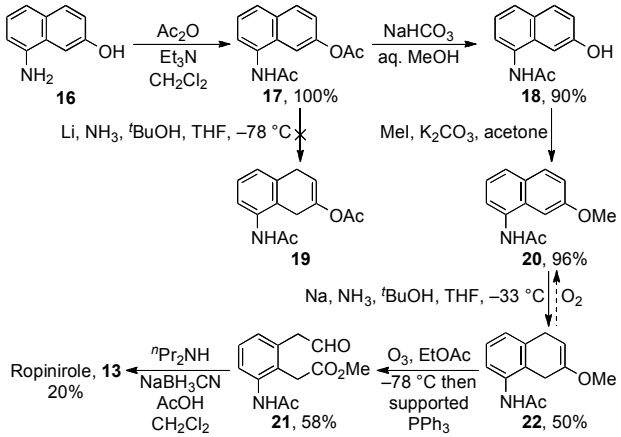
The difficulties encountered with the control of oxidation level at key carbon centres had proven a major bugbear of our synthesis. On reflection, it seemed likely that its step-count would be reduced if the oxidation level at C-7 in our starting naphthalene were raised, as this would render the final two-step oxidation sequence redundant. A search of available chemicals revealed that 8-amino-2-naphthol **16** was a product of commerce. It therefore seemed sensible to examine its potential as a precursor to ropinirole hydrochloride **2** (Scheme 4).



Scheme 4. Plan for a shorter synthesis from 8-amino-2-naphthol.

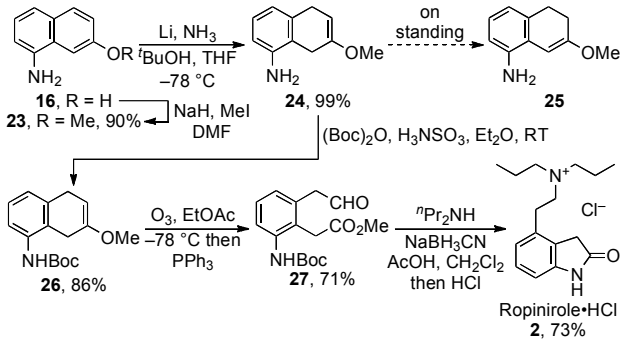
Our initial plan was to employ a single protecting group for the aniline and phenol residues in 8-amino-2-naphthol **16** (R = R', Scheme 4). To that end, diacylation was effected in quantitative yield.[26] Unfortunately, dissolving metal reductions of the resulting naphthalene **17** failed to generate dihydronaphthalene **19** due to the sensitivity of the aryl/vinyl acetate functions under the reaction conditions (Scheme 5). Consequently, it was found necessary to proceed via the more

robust methyl vinyl ether **22**. Its formation by Birch reduction of naphthalene **20** also proved capricious due to the propensity for aerial oxidation of the product back to the starting material. Nonetheless, performing the work-up with haste provided vinyl ether **22** in an acceptable 50% yield. Ozonolysis of vinyl ether **22** to aldehyde **21** also proceeded modestly and it was found necessary to use polymer-supported PPh_3 in the work-up phase in order to attain the product in a good state of purity.[27] Reductive amination of **21** with concomitant cyclisation, completed the synthesis of ropinirole **13**, albeit slowly and in low yield. Although we were confident that the yields attained in the latter stages of this synthesis could be improved significantly, success with an alternative strategy had removed any incentive to do so.



Scheme 5. Towards a shorter synthesis of ropinirole.

That alternative approach is summarised in Scheme 6 and began with the methylation of 8-amino-2-naphthol **16** to aryl methyl ether **23**, itself a product of commerce.[19] A Birch reduction followed, leading to methyl vinyl ether **24** in near quantitative yield. Although the product proved susceptible to isomerisation to dihydronaphthalene **25** on standing, this was attenuated by Boc protection to carbamate **26**. Pleasingly, ozonolysis of **26** proved facile in EtOAc, yielding aldehyde **27** in 71% yield. A reductive amination with acidic work-up then gave ropinirole **13** which, on treatment with HCl and recrystallization from CH_3CN, delivered the API **2** in a high state of purity.[10]



Scheme 6. A short and practicable synthesis of the API ropinirole hydrochloride.

Conclusions

In conclusion, we have developed a short and practicable synthesis of the API ropinirole hydrochloride **2** from commercial naphthalene **24**. In the laboratory it proceeds in 45% overall yield and has a step-count half that of the current manufacturing process.[10] Attractive features include i) the ability to run the first two steps concurrently in a single pot reducing the stage count to three; ii) a greatly reduced waste stream that is devoid of organic halides and iii) the option to run the oxidative cleavage step, **26** → **27**, under continuous flow.[24] As there remains scope for further optimisation through up-scaling, the case for further development of the aforementioned synthesis towards the bulk scale manufacture of ropinirole hydrochloride **2** could soon be a compelling one.

Experimental Section

***1-Amino-5,8-dihydronaphthalene* (5).** Following the procedure of Rogers *et al.*[20] To a solution of aminonaphthalene **6** (50.0 g, 0.35 mol) in Et_2O (250 mL) were added ^tBuOH (35 mL) and NH_3 (200 mL). Na (22.0 g, 0.94 g-atom) was added portionwise to the refluxing solution over 3 h, followed by additional ^tBuOH (35 mL) and EtOH (70 mL) in two equal portions over 1 h. The solution warmed to RT over 20 h allowing NH_3 to evaporate. Sat. NH_4Cl (30 mL) and water (200 mL) were then added and the aqueous phase separated and extracted with Et_2O (3 × 1 L). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as purple crystals (48.0 g, 0.33 mol) contaminated with *ca.* 5% of 1-aminotetralin. MP 35–37 °C (petrol) [Lit. 35–37 °C (petrol)];[20] ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (app t, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 1H), 6.11–5.90 (m, 2H), 3.64 (s, 2H), 3.51 (br t, *J* = 5.3 Hz, 2H), 3.16 (br t, *J* = 5.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7 (C), 134.6 (C), 126.5 (CH), 124.8 (CH), 123.1 (CH), 119.3 (C), 119.0 (CH), 112.4 (CH), 29.6 (CH_2), 25.1 (CH_2) ppm; IR (neat): ν 3396, 3309, 3214, 3029, 2930, 2858, 2807, 1671, 1622, 1584, 1278; MS (ESI^+) *m/z* (%):187 ([M+CH_3CN+Na]$^+$, 100%); HRMS (ES^+): *m/z* calcd for $C_{10}H_{12}N$ [MH]$^+$: 146.0964; found: 146.0962; these data being in accord with literature values.[20]

***tert-Butyl 5,8-dihydronaphthalene-1-yl carbamate* (7).** Adapting the procedure of Upadhyaya et al.[28] To a suspension of naphthylamine **5** (2.46 g, 16.9 mmol) in H_2O (17 mL) were added NH_2SO_3H (96 mg, 0.99 mmol) and $(Boc)_2O$ (5.16 mg, 23.6 mmol). The mixture was placed in a sonication bath for 2 h then extracted with Et_2O (3 × 150 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (6:1 petroleum ether/Et_2O) afforded the title compound as a pink solid (3.91 g, 15.9 mmol, 94%) MP 96–98 °C (aq. EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.7 Hz, 1H), 7.16 (app t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.21 (br s, 1H), 5.96–5.86 (m, 2H), 3.44–3.41 (m, 2H), 3.23–3.20 (m, 2H), 1.53 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0 (C), 135.4 (C), 134.4 (C), 126.3 (CH), 124.6 (CH), 124.1 (C), 124.2 (CH), 122.8 (CH), 118.9 (CH), 80.3 (C), 29.7 (CH_2), 28.3 (3 × CH_3), 25.2 (CH_2) ppm; IR (neat): ν 3256, 3032, 2975, 1692, 1524, 1469, 1244, 752; MS (ESI^+) *m/z* (%): 309 ([M+CH_3CN+Na]$^+$, 100%); HRMS (ES^+): *m/z* calcd for $C_{15}H_{19}NNaO_2$ [M+Na]$^+$: 268.1308; found: 268.1313.

***2-(2-((tert-Butoxycarbonyl)amino)-6-(2-methoxy-2-oxoethyl)phenyl)acetic acid* (8).** Through a solution of carbamate **7** (368 mg, 1.50 mmol) in MeOH (15 mL) at –78 °C was bubbled a stream of O_3 (1–5% in O_2). When the solution turned blue, it was purged with O_2 for 10 min then $NaBH_4$ (153 mg, 4.04 mmol) was added. The solution was warmed to RT and after 16 h was concentrated *in vacuo*. Purification by column chromatography (1:1 EtOAc/Et_2O) afforded the title compound as a yellow solid (98 mg, 0.30 mmol, 20%) MP 129–130 °C (aq. EtOH); ^1H NMR (400 MHz, CD_3OD): δ = 7.39 (d, *J* = 7.9 Hz, 1H), 7.21 (app t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 3.77 (s, 2H), 3.70 (s, 2H), 3.64 (s, 3H), 1.51 (s, 9H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 175.1 (C), 173.6 (C), 156.2 (C), 138.8 (C), 135.8 (C), 129.8 (C), 129.0 (CH), 128.6 (CH), 125.8 (CH), 81.3 (C), 52.7 (CH_3), 40.1 (CH_2), 35.0 (CH_2), 28.8 (3 × CH_3) ppm; IR (neat): ν 3343, 2933, 1731, 1692, 1587, 1517, 1439, 1241, 1157; MS (ESI^+) *m/z* (%): 346 ([M+Na], 100%); HRMS (ES^+): *m/z* calcd for $C_{16}H_{21}NNaO_6$ [M+Na]$^+$: 346.1261; found: 346.1271.

***tert-Butyl 2-hydroxy-4-(2-oxoethyl)-2,3-dihydro-1H-indole-1-carboxylate* (9).** Through a solution of carbamate **7** (1.00 g, 4.08 mmol) in EtOAc (15 mL) at –78 °C was bubbled a stream of O_3 (1–5% in O_2). On disappearance of the pale yellow colour, the solution was purged with O_2 for 10 min then PPh_3 (3.00 g, 11.4 mmol) was added. The solution was warmed to RT and after 16 h was concentrated *in vacuo*. Purification by column chromatography (50–66% Et_2O in petrol) afforded the title compound as a gummy yellow oil (756 mg, 2.73 mmol, 66%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (t, *J* = 2.0 Hz, 1H), 7.38 (br s, 1H), 7.21 (app t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.01 (br s, 1H), 3.65 (d, *J* = 1.5 Hz, 2H), 3.23 (dd, *J* = 17.2, 7.6 Hz, 1H), 2.88 (d, *J* = 17.2 Hz, 1H), 1.62 (s, 9H) ppm with some broadening of resonances due to romaters; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1 (CH), 153.2 (C), 140.8 (C), 128.4 (CH), 128.0 (C), 124.0 (CH), 113.7 (CH), 83.1 (CH), 82.7 (C), 48.0 (CH_2), 34.4 (CH_2), 28.4 (3 × CH_3) ppm with one C not observed; IR (neat): ν 3434, 2970, 2926, 2852, 1677, 1598, 1461, 1367, 1159, 934, 770; MS (ESI$^+$) *m/z* (%): 577 ([2M+Na]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{15}H_{18}NNaO_4$ [M+Na]$^+$: 300.1206; found: 300.1206.

Also prepared by adapting the procedure of Gavriilidis *et al.*[24] Thus, a stock solution of carbamate **7** (0.2 M in EtOAc, 0.85 mL/min) was ozonised (1.5 equiv., 202 g/Nm^3, 62.5 mL/min) under continuous flow at –7 °C using using a Vapourtec R2+ device and a PPh_3 quench (2.25 equiv., 0.3 M in EtOAc, 1.28 mL/min). An aliquot (4.6 mL) was collected, concentrated *in vacuo* and purified by column chromatography (30% EtOAc in cyclohexane) to afford aldehyde **9** as a gummy yellow oil (77 mg, 0.28 mmol, 75%); data as reported above.

A Lemieux-Johnson type oxidation procedure was also examined. Thus, to a solution of carbamate **7** (907 mg, 3.70 mmol) in H_2O/^{t}BuOH/MeOH (1:1:1, 100 mL) were added citric acid monohydrate (590 mg, 2.81 mmol), OsO_4 (2.5% w/w in ^{t}BuOH, 50 µl, 5 µmol) and NMO (658 mg, 5.62 mmol). After 16 h, the reaction mixture was extracted with EtOAc (4 × 100 mL) then the organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (1:1 EtOAc/Et_2O) afforded *tert*-butyl rel-6*R*,7*S*-(6,7-dihydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate as a white solid (801 mg, 2.87 mmol, 78%) MP 174–175 °C (aq. EtOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.18 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 4.08–3.98 (m, 2H), 3.07–2.92 (m, 2H), 2.92–2.76 (m, 2H), 1.51 (s, 9H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 156.6 (C), 137.4 (C), 136.1 (C), 129.9 (C), 127.5 (CH), 127.2 (CH), 124.2 (CH), 81.0 (C), 70.2 (CH), 70.1 (CH), 35.7 (CH_2), 31.4 (CH_2), 28.9 (3 × CH_3) ppm; IR (neat): ν 3344, 2971, 2920, 1392, 1246, 1161, 1008, 623; MS (ESI$^+$) *m/z* (%): 343 ([M+CH_3CN+Na]$^+$, 51%), 302 ([M+Na]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{15}H_{21}NNaO_4$ [M+Na]$^+$: 302.1376; found: 302.1370. The aforementioned diol (38 mg, 0.14 mmol) was disolved in aq. THF (1:1, 2 mL) and a solution of $NaIO_4$ (51 mg, 0.24 mmol) in H_2O (2 mL) was added. After 18 h, the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were combined, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (2:1 Et_2O/petroleum ether) to afford aldehyde **9** as a gummy yellow oil (24 mg, 0.09 mmol, 62%); data as reported above.

***tert-Butyl 4-(2-(dipropylamino)ethyl)-2-hydroxyindoline-1-carboxylate* (11).** To a solution of aldehyde **9** (5.13 g, 18.5 mmol) in CH_2Cl_2 (250 mL) were added ^{n}Pr$_2$NH$_2$ (5.8 mL, 42.3 mmol) and AcOH (1.1 mL, 19.2 mmol). After 45 min, $NaCNBH_3$ (2.67 g, 42.4 mmol) was added. After a further 2 h the reaction mixture was concentrated *in vacuo* and purified by column chromatography (gradient elution, 0–3% MeOH in CH_2Cl_2) to afford the title compound as a pale yellow oil (6.70 g, 18.5 mmol, 100%) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (br s, 1H), 7.08 (app t, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.93 (br s, 1H), 5.74 (br s, 1H), 3.24 (dd, *J* = 17.1, 7.6 Hz, 1H), 2.91 (d, *J* = 17.4 Hz, 1H), 2.82 (s, 4H), 2.72–2.58 (m, 4H), 1.67–1.56 (m, 4H), 1.55 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 6H) ppm with some broadening of resonances due to rotamers; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4 (C), 134.8 (C), 127.9 (CH), 127.0 (C), 122.8 (CH), 112.7 (CH), 82.9 (CH), 82.2 (C), 54.7 (2 × CH_2), 53.1 (CH_2), 34.3 (CH_2), 28.6 (CH_2), 28.2 (3 × CH_3), 18.3 (2 × CH_2), 11.4 (2 × CH_3) ppm with one C not observed; IR (neat): ν 3367, 2970, 2936, 1694, 1597, 1462, 1369, 1136, 907, 725, 645; MS (ESI$^+$) *m/z* (%): 363 ([MH]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{21}H_{35}N_2O_3$ [MH]$^+$: 363.2642; found: 363.2642.

***4-[2-(N,N-dipropylamino)ethyl]indole* (12).** To a solution of hemiaminal **11** (62 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added TFA (12 mL). After 3 h, 2M NaOH (5 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were then combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (4% MeOH in CH_2Cl_2) afforded the title compund as a yellow oil (40 mg, 0.20 mmol, 96%) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.94 (br s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.21 (app t, *J* = 2.9 Hz, 1H), 7.09 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 6.57 (m, 1H), 3.31 (s, 4H), 3.10–2.96 (m, 4H), 1.89–1.67 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.0 (C), 127.7 (C), 127.0 (C), 124.9 (CH), 122.0 (CH), 119.6 (CH), 110.6 (CH), 99.8 (CH), 53.9 (2 × CH_2), 52.7 (CH_2), 27.9 (CH_2), 16.8 (2 × CH_2), 11.1 (2 × CH_3) ppm; IR (neat): ν 3241, 2971, 2939, 2882, 2531, 1673, 1462, 1344, 1177, 1130, 758; MS (ESI$^+$) *m/z* (%): 245 ([MH]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{16}H_{25}N_2$ [MH]$^+$: 245.2012; found: 245.2014; these data being in accord with literature values.[11]

***Ropinirole* (13).** To a solution of indole **12** (205 mg, 0.84 mmol) in ^{t}BuOH (8 mL) was added NBS (166 mg, 0.93 mmol). After 1h, sat. $NaHCO_3$ (2 mL) was added and the reaction mixture was extracted with EtOAc (3 × 20 mL). The organic phases were combined and concentrated *in vacuo* to a dark oil which was dissolved in THF (8 mL) and 1 M HCl (1 mL) was added. The solution was heated at reflux for 2 h then cooled to RT, basified with sat. K_2CO_3 (0.5 mL) and extracted with EtOAc (3 × 30 mL). The organic phases were combined, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0–10% MeOH in CH_2Cl_2) to afford ropinirole **13** as an orange oil (133 mg, 0.51 mmol, 61%), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br s, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 3.42 (s, 2H), 2.65 (br s, 4H), 2.53–2.36 (m, 4H), 1.44 (app sxt, *J* = 7.5 Hz, 4H), 0.83 (t, *J* = 7.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C), 142.2 (C), 137.4 (C), 128.0 (CH), 124.0 (C), 122.9 (CH), 107.3 (CH), 56.2 (2 × CH_2), 54.3 (CH_2), 35.0 (CH_2), 30.9 (CH_2), 20.4 (2 × CH_2), 11.9 (2 × CH_3) ppm; IR (neat): ν 3194, 2957, 2933, 2804, 1702, 1618, 1606, 1458, 1247, 775; MS (ESI$^+$) *m/z* (%): 261 ([MH]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{16}H_{25}N_2O$ [MH]$^+$: 261.1961; found: 261.1963; these data being in accord with literature values.[11]

***8-Acetamidonaphthalen-2-yl acetate* (17).** Adapting the procedure of Vermeulen *et al.*[26] To a suspension of 8-amino-2-naphthol **16** (4.38 g, 27.5 mmol) in CH_2Cl_2 (80 mL) were added Ac_2O (5.7 mL, 60.3 mmol) and Et_3N (8.4 mL, 60.2 mmol). After 4 h, the reaction mixture was washed with H_2O (3 × 50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAc) afforded with title compound as a pink solid (6.59 g, 27.1 mol, 99%) MP 192–195 °C (MeOH) [Lit. 184 °C];[29] ^{1}H NMR (400 MHz, d6-DMSO): δ = 9.90 (br s, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.82–7.77 (m, 3H), 7.49 (app t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, d6-DMSO): δ = 169.5 (C), 169.0 (C), 148.3 (C), 133.6 (C), 131.7 (C), 129.7 (CH), 128.0 (C), 125.4 (CH), 124.8 (CH), 122.0 (CH), 121.8 (CH), 114.0 (CH), 23.5 (CH_3), 20.9 (CH_3) ppm; IR (neat): ν 3256, 3025, 2160, 1758, 1663, 1539, 1503, 1209, 1186; MS (ESI$^+$) *m/z* (%): 266 ([M+Na]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{14}H_{14}NO_3$ [MH]$^+$: 244.0968; found: 244.0966; these data being in accord with literature values. [29]

***N-(7-Hydroxynaphthalen-1-yl)acetamide* (18).** Adapting the procedure of Vermeulen *et al.*,[26] to a suspension of naphthol **17** (4.00 g, 16.4 mmol) in MeOH (40 mL) was added sat. $NaHCO_3$ (20 mL). The mixture was heated at reflux for 1 h then cooled to RT, acidified with 1 M HCl (10 mL) and concentrated *in vacuo*. Purification flash column chromatography (50% EtOAc in hexane) afforded the title compound as a pink solid (3.20 g, 15.8 mmol, 96%) MP 200 °C decomp. (H_2O) [Lit. 191 °C decomp.];[30] ^{1}H NMR (300 MHz, d6-DMSO): δ = 9.80 (s, 1H), 9.77 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.23 (app t, *J* = 7.9 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.16 (s, 3H) ppm; ^{13}C NMR (75 MHz, d6-DMSO): δ = 168.7 (C), 155.4 (C), 132.1 (C), 129.9 (C), 129.7 (CH), 128.4 (C), 125.2 (CH), 122.5 (CH), 122.0 (CH), 118.5 (CH), 104.4 (CH), 23.3 (CH_3) ppm; IR (neat): ν 3150, 3051, 1618, 1546, 1505, 1442, 1379, 1272, 741; MS (ESI$^+$) *m/z* (%): 265 ([M+CH_3CN+Na]$^+$, 100%); these data being in accord with literature values.[31]

***N-(7-Methoxynaphthalen-1-yl)acetamide* (20).** Adapting the procedure of Mewshaw *et al.*[31] To a suspension of phenol **18** (1.00 g, 4.97 mmol) in acetone (20 mL) was added K_2CO_3 (1.72 g, 12.4 mmol) and MeI (620 µL, 9.96 mmol). The mixture was heated at reflux for 1 h then cooled to RT and purified by column chromatography (EtOAc) to afforded the title compound as a pale brown powder (962 mg, 4.47 mmol, 90%) MP 178–180 °C (EtOH) [Lit. 175–176 °C (EtOH)];[32] ^{1}H NMR (300 MHz, d6-DMSO): δ = 9.82 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 7.31 (app t, *J* = 7.9 Hz, 1H), 7.19 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.90 (s, 3H), 2.19 (s, 3H) ppm; ^{13}C NMR (75 MHz, d6-DMSO): δ = 168.8 (C), 157.3 (C), 132.6 (C), 129.8 (CH), 129.2 (C), 128.8 (C), 124.8 (CH), 123.0 (CH), 122.1 (CH), 118.2 (CH), 101.6 (CH), 55.2 (CH_3), 23.6 (CH_3) ppm; IR (neat): ν 3270, 2928, 2830, 1632, 1536, 1251; MS (ESI$^+$) *m/z* (%): 279 ([MH+CH_3CN]$^+$, 100%); these data being in accord with literature values.[31]

***N-(7-Methoxy-5,8-dihydronaphthalen-1-yl)acetamide* (22).** To a suspension of naphthylamide **20** (87 mg, 0.40 mmol) in THF (10 mL) were added ^{t}BuOH (50 µL) and NH_3 (10 mL). Na (20 mg, 0.87 mg-atom) was added portionwise to the refluxing

solution over 5 min then sat. NH_4Cl (1 mL) was added after a further 30 min. The NH_3 was allowed to evaporate and H_2O (5 mL) was added. The aqueous phase was extracted with EtOAc (3 × 50 mL) then the organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (10% MeOH in CH_2Cl_2) afforded the title compound as a beige solid (44 mg, 0.20 mmol, 50%) MP 204-205 °C (EtOAc/hexane) [Lit. 191-192 °C];[33] ^{1}H NMR (400 MHz, d6-DMSO): δ = 9.25 (br s, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 4.85 (m, 1H), 3.55 (s, 3H), 3.49–3.44 (m, 2H), 3.24–3.24 (m, 2H), 2.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, d6-DMSO): δ = 168.2 (C), 152.4 (C), 135.7 (C), 134.5 (C), 127.8 (C), 125.7 (CH), 124.8 (CH), 122.7 (CH), 90.1 (CH), 53.9 (CH_3), 29.1 (CH_2), 28.1 (CH_2), 23.2 (CH_3) ppm; IR (neat): ν 3263, 3037, 2826, 1687, 1655, 1538, 1219, 793; MS (ESI$^+$) *m/z* (%): 281 ([M+CH_3CN+Na]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{13}H_{15}NNaO_2$ [M+Na]$^+$: 240.0995; found: 240.0995; these data being in accord with literature values.[33]

***Methyl 2-(2-acetamido-6-(2-oxoethyl)phenyl)acetate* (21).** Through a solution of methyl vinyl ether **22** (100 mg, 0.46 mmol) in EtOAc (100 mL) at –78 °C was bubbled a stream of O_3 (1–5% in O_2). On disappearance of the pale yellow colour, the solution was purged with O_2 then polymer-bound PPh_3 (3 mmol/g, 385 mg, 1.15 mmol) was added. The solution was warmed to RT and after 16 h was concentrated *in vacuo*. Purification by column chromatography (60–100% EtOAc in petrol) afforded the title compound as a yellow oil (67 mg, 0.27 mmol, 58%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (t, *J* = 1.8 Hz, 1H), 8.57 (br s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.32 (app t, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 3.84 (d, *J* = 1.8 Hz, 2H), 3.72 (s, 3H), 3.63 (s, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (CH), 172.5 (C), 168.8 (C), 137.6 (C), 131.7 (C), 128.4 (CH), 128.0 (CH), 125.8 (C), 124.9 (CH), 52.7 (CH_3), 48.8 (CH_2), 34.2 (CH_2), 24.3 (3 × CH_3) ppm; IR (neat): ν 3259, 3017, 2954, 2843, 1720, 1664, 1526, 1283, 1161; MS (ESI$^+$) *m/z* (%): 272 ([M+Na+], 100%); HRMS (ES$^+$): *m/z* calcd for $C_{13}H_{15}NNaO_4$ [M+Na]$^+$: 272.0893; found: 272.0896.

***Ropinirole* (13).** To a solution of aldehyde **21** (130 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) was added ^{n}Pr$_2$NH (160 μL, 1.17 mmol), followed after 5 min by AcOH (100 μL). After a further 10 min, $NaCNBH_3$ (80 mg, 1.27 mol) was added and after 1.5 h sat. K_2CO_3 (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic phases were concentrated *in vacuo* to *ca.* 10 mL and conc. HCl (1 mL) added. After 16 h the reaction was basified with sat. K_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (gradient elution, 0–10% MeOH in CH_2Cl_2) to afford ropinirole **13** as an orange oil (27 mg, 0.10 mmol, 20%); data as reported above.

***7-Methoxynaphthalen-1-amine* (23).** Adapting the procedure of Jin *et al.*[34] To a cooled (0 °C) suspension of NaH (310 mg, 7.75 mmol) in DMF (15 mL) was added naphthol **16** (1.00 g, 6.28 mmol) portionwise. The reaction mixture was warmed to RT over 15 min then cooled to 0 °C. MeI (400 μL, 6.43 mmol) was added and the solution warmed to RT for 1 h then concentrated *in vacuo*. The resulting solid was recrystallised from hexane to afford the title compound as pale brown flakes (978 mg, 5.64 mmol, 90%) MP 78–80 °C (hexane) Lit. 78–79 °C];[35] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 9.1 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.21–7.14 (m, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.81 (dd, *J* = 7.3, 0.7 Hz, 1H), 4.02 (br s, 2H), 3.95 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (C), 140.9 (C), 130.2 (CH), 129.8 (C), 124.7 (C), 123.9 (CH), 119.2 (CH), 118.2 (CH), 110.7 (CH), 99.8 (CH), 55.3 (CH_3) ppm; IR (neat): ν 3389, 3327, 3242, 3028, 2881, 2825, 1693, 1647, 1467, 1227, 789; MS (ESI$^+$) *m/z* (%): 215 ([MH+CH_3CN]$^+$, 100%); these data being in accord with literature values.[34]

***7-Methoxy-5,8-dihydronaphthalen-1-amine* (24).** Adapting the procedure of Bayer Aktiengesellschaft.[36] A suspension of naphthalene **23** (3.00 g, 17.2 mmol) in THF (35 mL) and ^{t}BuOH (4.8 mL) and was cooled to –78 °C then NH_3 (350 mL) was condensed into the reaction mixture. Li (370 mg, 53.6 g-atom) was added portionwise over a period of 1.5 h followed by degassed MeOH (1 mL) and degassed H_2O (10 mL). After 1 h the reaction mixture was warmed to RT to allow the NH_3 to evaporate then further degassed H_2O (100 mL) was added. The aqueous phase was extracted with degassed EtOAc (3 × 150 mL) then the organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound as a pale brown solid (2.99 g, 17.1 mmol, 99%) MP 88–90 °C [Lit. 84–85 °C];[33] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (app t, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 4.83 (m, 1H), 3.65 (s, 3H), 3.60 (br s, 2H), 3.55–3.51 (m, 2H), 3.15–3.12 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0 (C), 143.8 (C), 134.7 (C), 126.5 (CH), 118.8 (C), 118.4 (CH), 112.1 (CH), 90.9 (CH), 54.1 (CH_3), 29.6 (CH_2), 27.8 (CH_2) ppm; IR (neat): ν 3389, 3327, 3242, 3028, 2881, 2825, 1693, 1647, 1467, 1227, 789; MS (ESI$^+$) *m/z* (%): 457 ([2M+Na]$^+$, 48%), 217 ([MH+CH_3CN]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{11}H_{14}NO$ [MH]$^+$: 176.1070; found: 176.1070; these data being in accord with literature values.[33]

***tert-Butyl (7-methoxy-5,8-dihydronaphthalen-1-yl)carbamate* (26).** Adapting the procedure of Upadhyaya *et al.*[29] To a solution of naphthylamine **24** (100 mg, 0.57 mmol) in Et_2O (2 mL) was added $(Boc)_2O$ (130 μL, 0.57 mmol) followed by H_2NSO_3H (5 mg, 0.05 mmol). After 2 h, the crude mixture was concentrated *in vacuo* and purified by column chromatography (10% EtOAc/hexane) to afforded the title compound as a pale pink solid (135 mg, 0.49 mmol, 86%) MP 90–91 °C (Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.3 Hz, 1H), 7.17 (app t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.24 (br s, 1H), 4.83 (m, 1H), 3.64 (s, 3H), 3.56–3.51 (m, 2H), 3.25–3.21 (m, 2H), 1.53 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5 (C), 153.7 (C), 133.2 (C), 131.2 (C), 128.1 (C), 124.4 (CH), 123.8 (CH), 122.2 (CH), 90.3 (CH), 80.2 (C), 54.9 (CH_3), 29.1 (CH_2), 28.3 (3 × CH_3), 27.2 (CH_2) ppm; IR (neat): ν 3339, 2975, 2936, 1693, 1637, 1515, 1440, 1227, 1153; MS (ESI$^+$) *m/z* (%): 339 ([M+CH_3CN+Na]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{16}H_{21}NNaO_3$ [M+Na]$^+$: 298.1414; found: 298.1415.

***Methyl 2-(2-((tert-butoxycarbonyl)amino)-6-(2-oxoethyl)phenyl)acetate* (27).** Through a solution of methyl vinyl ether **26** (200 mg, 0.73 mmol) in EtOAc (100 mL) containing Sudan Red III (2 mg) at –78 °C was bubbled O_3 (1–5% in O_2). After disappearance of the pale red colour, the solution was purged with O_2 for 10 min then PPh_3 (478 mg, 1.82 mmol) was added. The solution was warmed to RT and after 16 h was concentrated *in vacuo*. Purification by column chromatography (gradient elution, 50% to 65% Et_2O in hexane) afforded the title compound as a yellow oil (160 mg, 0.52 mmol, 71%) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (t, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.50 (br s, 1H), 7.29 (app t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 3.82 (d, *J* = 2.0 Hz, 2H), 3.72 (s, 3H), 3.64 (s, 2H), 1.53 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7 (CH), 172.0 (C), 153.5 (C), 138.1 (C), 131.7 (C), 128.3 (CH), 127.0 (CH), 123.8 (CH), 125.5 (C), 80.5 (C), 52.6 (CH_3), 48.8 (CH_2), 34.1 (CH_2), 28.3 (3 × CH_3) ppm; IR (neat): ν 3345, 2978, 2839, 1718, 1589, 1514, 1437, 1238, 1156; MS (ESI$^+$) *m/z* (%): 330 ([M+Na]$^+$, 100%); HRMS (ES$^+$): *m/z* calcd for $C_{16}H_{21}NNaO_5$ [MH]$^+$: 330.1312; found: 330.1312.

***Ropinirole hydrochloride* (2).** To a solution of aldehyde **27** (140 mg, 0.46 mmol) in CH_2Cl_2 (3 mL) was added ^{n}Pr$_2$NH (140 μL, 1.02 mmol) followed after 5 min by AcOH (100 μL). After a further 10 min, $NaCNBH_3$ (70 mg, 1.11 mol) was added and after 2 h sat. K_2CO_3 (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were concentrated to ~10 mL *in vacuo.* Conc HCl (1 mL) was added and after 16 h the reaction was basified with sat. K_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (0–10% MeOH/CH_2Cl_2) to afford ropinirole **13** as an orange oil (87 mg, 0.33 mmol); data as reported above. 2 M HCl in Et_2O (1 mL) was added and the resulting precipitate collected, dried *in vacuo* and recrystalised from CH_3CN to afford the title compound as a pale yellow solid (99 mg, 0.33 mmol, 73%) MP 242–245 °C (CH_3CN) [Lit. 241–243 °C (CH_3CN)];[37] ^{1}H NMR (400 MHz, d6-DMSO): δ = 10.54 (br s, 1H), 10.42 (s, 1H), 7.14 (app t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 3.55 (s, 2H), 3.19 (br s, 2H), 3.11–3.00 (m, 4H), 2.99–2.90 (m, 2H), 1.70 (app sxt, *J* = 7.5 Hz, 4H), 0.92 (t, *J* = 7.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, d6-DMSO): δ = 176.1 (C), 143.7 (C), 133.0 (C), 127.8 (CH), 125.0 (C), 121.7 (CH), 107.8 (CH), 53.1 (2 × CH_2), 51.6 (CH_2), 34.6 (CH_2), 26.8 (CH_2), 16.4 (2 × CH_2), 10.9 (2 × CH_3) ppm; these data being in accord with literature values.[11,37]

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