Some Synthetic Approaches to Ropinirole (SK&F 101468-A): A Potent Dopamine Receptor Agonist

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Received October 26, 1994
Revised Feburary 14, 1995

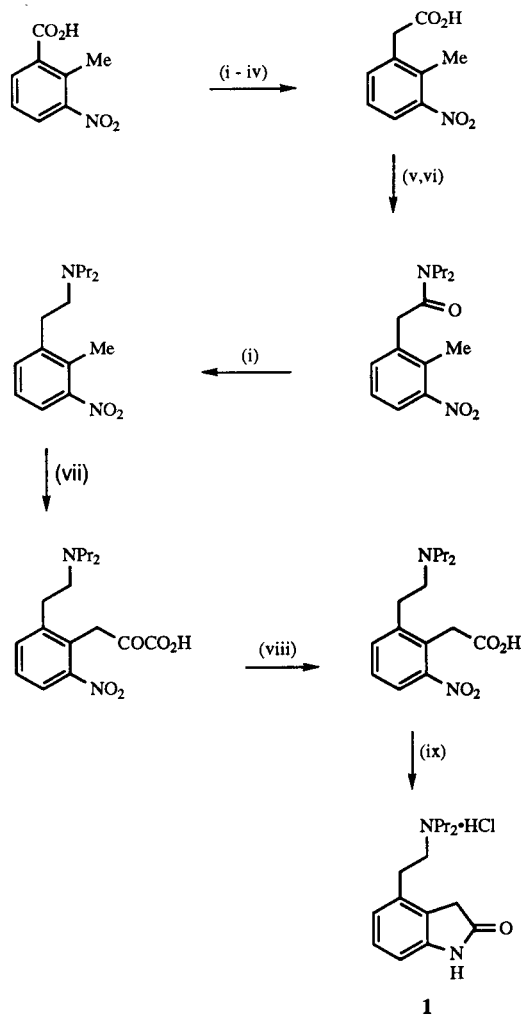
Three new routes to ropinirole (SK&F 101468-A, **1**) are described each involving the preparation of 3-chlorooxindole intermediates of type **3** from β-nitrostyrenes as the pivotal step. The superiority of sulphonate esters **17a-c** as direct precursors to **1** over the bromide **11** is also described.

J. Heterocyclic Chem., **32**, 875 (1995).

Ropinirole, {4-[2-(di-*n*-propylamino)ethyl]-1,3-dihydro-2*H*-indolin-2-one hydrochloride, SK&F 101468-A, **1**} has been shown to be a potent non-ergot dopamine receptor agonist and is currently being developed for the symptomatic treatment of Parkinson's disease. The original reported synthesis (Scheme 1) from 3-nitro-2-methylbenzoic acid gave ropinirole in 23% overall yield [1]. Although this route was suitable for the preparation of small quantities of compound, the chemistry was prohibitively expensive due to its length and the high materials cost. As interest in ropinirole grew, the requirement for kilogram quantities of material had to be satisfied. Therefore, a more cost effective and efficient synthesis was sought. Our first objective was to discover a more direct approach to the oxindole ring system from simple starting materials. Royer [2,3,4] had reported that moderate yields of substituted 3-chlorooxindoles **3** were obtained upon treatment of β-nitrostyrenes **2** with ferric chloride and acetyl chloride (Scheme 2). Predominant oxindole formation only resulted when ferric chloride was used as other Lewis acids gave either substituted oximes **4** or hydroxamic acid derivatives **5** as the major product. A notable feature of this reaction was that *ortho*-substituted β–nitrostyrenes cyclised regiospecifically to give 4-substituted-oxindole ring systems. Therefore, we believed that this chemistry would provide access to oxindoles of type **3** possessing a displaceable group X which could be readily converted to ropinirole **1**. The results of our investigations using this approach to **1** are now reported.

To use the ferric chloride mediated cyclisation reaction required a suitably substituted nitrostyrene derivative. Investigation of the literature showed that benzaldehyde **8** was a known compound which could be prepared from isochroman **6** [5], a readily available and cheap starting material. We decided to use benzaldehyde **8** to prepare the nitrostyrene **9** to allow evaluation of the ferric chloride cyclisation methodology in an alternative route to ropinirole (Scheme 3).

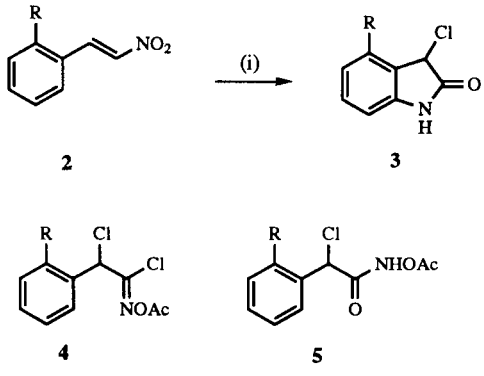
Scheme 1



1

(i) BH_3/THF, (ii) conc. HCl, (iii) KCN/aq. EtOH, (iv) H_2SO_4/AcOH/H_2O, (v) $SOCl_2$, (vi) $NHPr_2$, (vii) $(EtOCO)_2$/KOEt, (viii)H_2O_2/NaOH, (ix) 5%Pd/C/EtOH.

Scheme 2

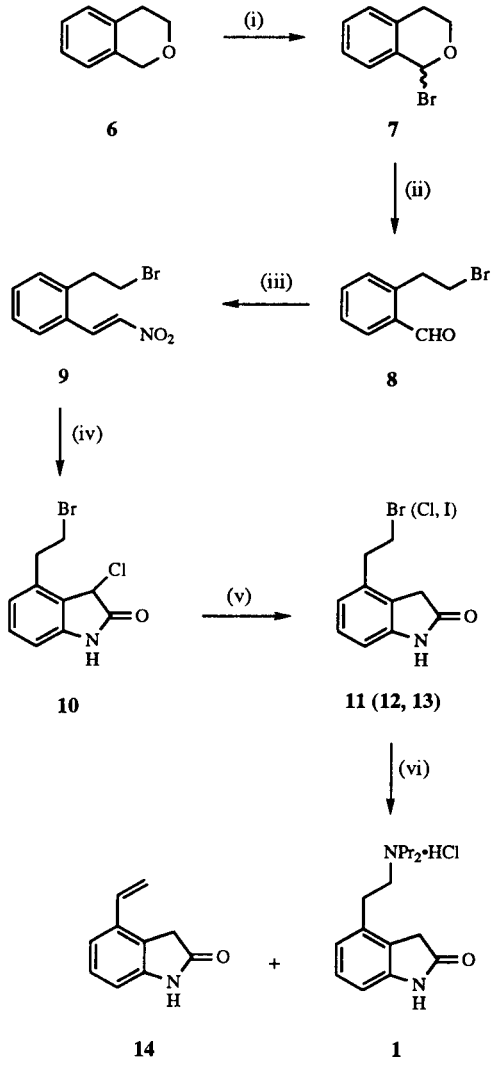


Photochemically initiated bromination of isochroman **6** gave 1-bromoisochroman **7**, which underwent rearrangement at elevated temperatures in the presence of hydrogen bromide to give the benzaldehyde **8** in 64% yield after purification *via* its crystalline sodium bisulfite addition complex (Scheme 3). Treatment of **8** with nitromethane and sodium methoxide in methanol, followed by quenching into concentrated hydrochloric acid gave the β-nitrostyrene **9** (80%). The key ferric chloride mediated cyclisation reaction was successful and gave the desired 3-chlorooxindole **10** as the major product in 53% yield. By-products corresponding to compounds **4** and **5** were also formed but were conveniently separated from **10** by crystallisation.

Removal of the chloro-substituent was easily achieved giving the reduced product **11** in 95% yield after treatment of **10** with sodium hypophosphite over 10% palladium on carbon in ethyl acetate/water. Reaction between the bromide **11** and di-*n*-propylamine in water at 85° gave ropinirole **1** in modest yield (57%), together with the styrene **14** as the major by-product (38%) [7]. Although formation of ropinirole was a result of S_N2 nucleophilic substitution of bromide by di-*n*-propylamine, the amine also assisted in the elimination of hydrogen bromide to give the styrene **14**. Despite investigating the reaction in various solvents at different temperatures and concentrations, it was not possible to improve the yield of ropinirole or reduce the level of styrene **14** formed. In addition, reactions between the alternative chloro- and iodo-substrates **12** and **13** with di-*n*-propylamine offered no advantages in terms of ropinirole formation over the bromide **11**.

Despite the modest overall yield (14%), the discovery of this route was significant in that it showed that ropinirole could be synthesised in relatively few steps from cheap and readily available bulk starting materials. In addition, it demonstrated that the ferric chloride mediated cyclisation reaction of β-nitrostyrene derivatives could play a pivotal role. However, the unavoidable low yield of **1** in the final step meant that this synthesis would always have a considerable disadvantage making it unsuitable as a commercial route to ropinirole.

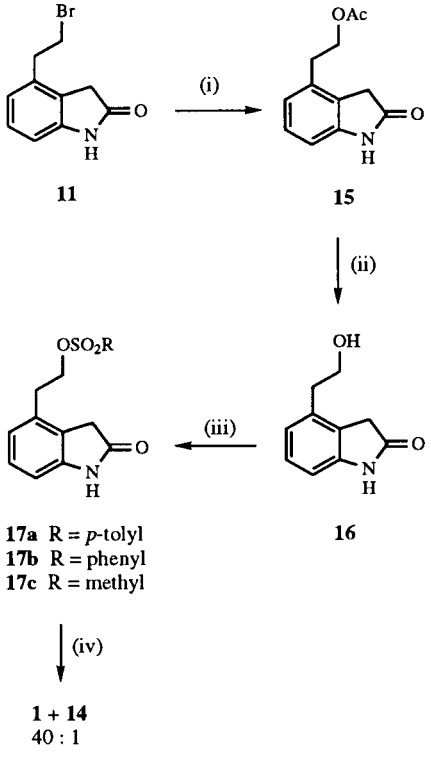
Scheme 3



As the limited efficiency halogen leaving groups in a final reaction step had been clearly demonstrated, the reactions of the corresponding sulphonate esters **17** with di-*n*-propylamine were then studied. The results of this approach were difficult to predict given the lack of information in the literature on reactions of phenethyl sulphonates with secondary amines [8].

A range of sulphonate ester **17a,b** and **c** were prepared (Scheme 4). Treatment of **11** with sodium acetate gave predominantly the substitution product, the ester **15** (89%), which after hydrolysis in dilute hydrochloric acid gave the alcohol **16** (71%). Treatment of **16** with the requisite sulphonyl chloride and pyridine gave the tosylate **17a** (87%), benzenesulphonate **17b** (80%), and mesylate **17c** (80%). In contrast to the results obtained with the bromide **11**, reaction between the sulphonate esters **17a,b** and **c** and di-*n*-propylamine resulted in predominant substitution reaction, giving a 40:1 ratio of products in favour of ropinirole **1** over the styrene **14** (*cf.* 1.5:1 using **11**). Ropinirole was isolated in 85% yield from these reactions (*cf.* 57% from **18**), hence indicating that sulphonate esters were more efficient precursors to ropinirole than the bromide **11**.

Scheme 4

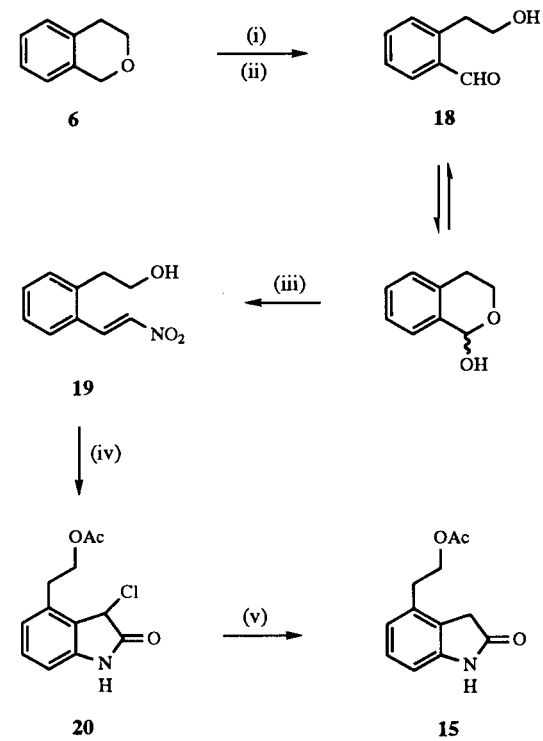


(i) NaOAc, aq. EtOH reflux, (ii) H^+/H_2O, (iii) RSO_2Cl/pyridine CH_2Cl_2, 0 - 5°C, (iv) $NHPr_2/H_2O$, 85°C.

To utilise this discovery, a more efficient synthesis of the alcohol intermediate **16** had to be found. Since a reasonable level of success had been achieved in preparing the bromide precursor **11** using the ferric chloride cyclisation chemistry, it was decided to try this approach to prepare alcohol **16**. To do this, it was postulated that the benzaldehyde **18** and the β-nitrostyrene **19,** would be suitable precursors (Scheme 5). However, success was not guaranteed using this approach since cyclisation of β-nitrostyrenes bearing oxygen substituents had not previously been reported.

The two-step literature preparation of benzaldehyde **18** from isochroman **15** in our hands proceeded in 73% overall yield [9,10] and the compound was shown to exist predominantly in its lactol form in deuteriochloroform. Treatment of **18** with nitromethane and sodium methoxide in methanol followed by quenching into aqueous acid gave the crystalline β–nitrostyrene **19** in 75% yield. The key ferric chloride cyclisation of **19** was indeed succesful and gave the 3-chlorooxindole **20** in 42% isolated yield after ensuring an extra equivalent of acetyl chloride was used to esterify the free hydroxyl group present. Reductive dechlorination of **20** using the catalytic transfer hydrogenation conditions described earlier gave the acetate **15** in 85% yield. As **15** had previously been converted to ropinirole, a new formal synthesis had been demonstrated, again utilising the nitrostyrene cyclisation methodology, but this time incorporating the more efficient displacement of sulphonate leaving groups in the final step (10% overall yield from isochroman).

Scheme 5



(i) PCC or HNO_3, (ii) DIBAL-H or REDAL, -78°C, (iii) NaOMe, $MeNO_2$, MeOH, then H^+/H_2O, (iv) $FeCl_3$, AcCl, CH_2Cl_2, 0°C, (v) $NaH_2PO_2 \cdot xH_2O$, 10%Pd/C.

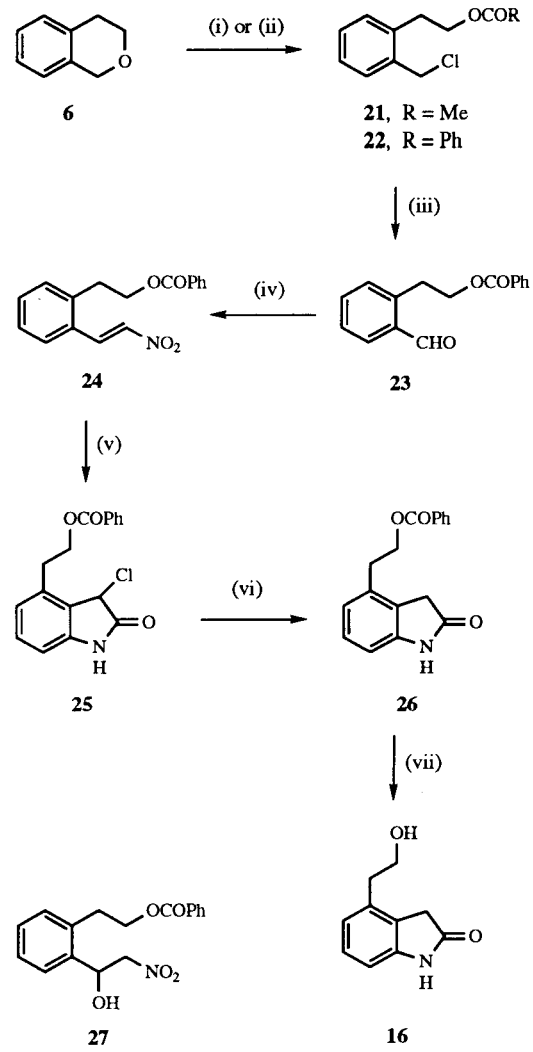
Further work related to this synthetic approach showed that esterification of the alcohol **19** prior to the cyclisation reaction resulted in higher yields of the chlorooxindole **20**. Therefore, our investigations led us to the preparation of nitrostyrenes **19** in which the oxygen is acylated.

Accordingly, we investigated the one step literature preparation of a potential precursor, 2-chloromethylphenethyl acetate **21**, from isochroman **6** (Scheme 6) [11]. This compound was of interest since it possessed both an acylated oxyethyl side-chain, together with functionality suitable for further conversion to an appropriate benzaldehyde derivative.

Treatment of isochroman with acetyl chloride in the presence of a stoichiometric amount of aluminium chloride gave 2-chloromethylphenethyl acetate **21** in 45% yield, together with appreciable quantities of polymeric by-products. The low yield of **21** is attributable to its instability towards aluminium chloride and when this reagent was replaced with zinc chloride, an improvement in the yield of **21** from 45 to greater than 95% was achieved. After further investigations, two more improvements were also made. First, replacing acetyl chloride with benzoyl chloride resulted in the formation of the benzoate **22** which has the advantages in being crystalline as well as being more stable than the acetate **21** under the conditions used in subsequent steps. Second, the isochroman ring-opening reaction could be performed using a catalytic quantity of zinc chloride (10 mole %), giving **22** in quantitative yield [12].

Conversion of benzyl halide **22** to its hexaminium salt under Sommelet oxidation conditions [13] and subsequent hydrolysis gave the benzaldehyde **23** in 70% yield after purification *via* its sodium bisulfite addition complex. These conditions were found to be more robust than those tried for the analogous Kornblum oxidation. Unfortunately, conversion of the aldehyde to the nitrostyrene **24** using the previously described conditions of sodium methoxide and nitromethane in methanol followed by an acid quench did not work well on this compound. The unwanted nitroalcohol by-product **27** was formed at significant levels (up to 15%) and could not be converted to the oxindole **25** in the next stage. This problem was overcome by preparing the nitrostyrene under neutral conditions [14] which gave **24** in 87% yield. These reaction conditions had the major advantage that the product crystallised directly from the methanolic reaction mixture which assisted in its isolation. Cyclisation of **24** using ferric chloride and acetyl chloride under the conditions described previously gave the 3-chlorooxindole **25** in 64% yield. The relatively high isolated yield for the cyclisation reaction is mainly attributable to the crystallinity of the product. Reductive dechlorination of **25** under catalytic transfer hydrogenation conditions with hydrazine hydrate gave the ester **26** (85%) with subsequent hydrolysis under basic conditions giving the alcohol **16** in 89% yield. Preparation of the tosylate **17a** (87%) from **16** was shown to give more consistent yields than for **17b** and **c** due to a greater stability of the product during isolation. Subsequently, conversion of **17a** to ropinirole (88%), as described earlier, completed the demonstration of yet another synthesis of ropinirole [15].

Scheme 6



(i) $AlCl_3$, AcCl, CS_2, 5°C, (ii) cat. $ZnCl_2$, PhCOCl, CH_2Cl_2, reflux, (iii) Hexamethylenetetramine, EtOH, then 50% aq. AcOH, (iv) $MeNO_2$, MeOH, $BuNH_2$, AcOH, 20°C, (v) $FeCl_3$, AcCl, CH_2Cl_2, 0 - 5°C, (vi) $N_2H_4 \cdot H_2O$, MeOH, 10%Pd/C, (vii) NaOH, H_2O, MeOH, reflux.

To summarise, three new syntheses of ropinirole have been described, each using the ferric chloride mediated cyclisation of β-nitrostyrenes as the pivotal reaction step. Investigations showed that sulphonates **17a-c** gave supe-

rior yields of ropinirole (88%) on reaction with di-*n*-propylamine compared with bromide **11** (57%). The final synthesis incorporating the efficient conversion of isochroman to the benzoate **22** is the most efficient (24% overall yield), uses cheap and readily available reagents and can be used on a large scale in standard processing equipment. Since more recent work has shown that some reaction steps may be combined resulting in improvements to both the yield and cost, this latest synthesis is being developed for the commercial manufacture of ropinirole.

EXPERIMENTAL

The ^{1}H nmr spectra were recorded on a Jeol JNM-270 FT spectrometer using tetramethylsilane as an internal standard. Infra-red spectra were recorded as potassium bromide discs on a Nicolet 710 FT spectrometer. Mass spectra were recorded on a VG 70-250 SEQ double focusing mass spectrometer. Melting points were recorded on a Buchi 510 melting point apparatus and are not corrected. Silica gel (230-400 mesh) was used for flash column chromatography.

2-(2'-Bromoethyl)benzaldehyde (**8**) was prepared by the literature procedure replacing dichloromethane with acetic acid [5]. This amendment to the procedure consistently gave higher yields (60-64%).

2-(2-Bromoethyl)-β-nitrostyrene (**9**).

2-(2-Bromoethyl)benzaldehyde **8** (10 g, 47 mmoles) was added to methanol (50 ml) which had been pre-basified with a small amount of 30% methanolic sodium methoxide solution (1 g, 5.6 mmoles). Nitromethane (3.7 g, 61 mmoles) was then added and the resultant solution was cooled to about 0° under a nitrogen atmosphere. Methanolic sodium methoxide 30% solution (9 g, 50 mmoles) in methanol (10 ml) was added with stirring over about 30 minutes. The reaction mixture was stirred at 0° for 1 hour before it was quenched into 6*M* hydrochloric acid (200 ml) which resulted in the precipitation of a yellow solid. The solid was collected at the pump, washed with water, and air-dried to give **9** (9.51 g, 80%) mp 67-68°; ir (Nujol mull): ν 1619 (alkene C=C), 1599 (aromatic C=C), 1505 and 1320 (symmetric and asymmetric NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform) 270 MHz δ 3.33 (t, 2H, Ar$CH_2$$CH_2$), 3.55 (t, 2H, CH_2Br), 7.30-7.50 (m, 4H, ArH), 7.55 (d, 1H, CH=C*H*NO_2), 8.30 (d, 1H, C*H*=CHNO_2); hrms: Found: 256.9862; $C_{10}H_{10}NO_2$ requires 256.9874 (^{81}Br isotope). The ^{79}Br isotope could not be resolved.

4-(2-Bromoethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**10**).

Acetyl chloride (9.2 g, 117 mmoles) was added to a suspension of ferric chloride (28.5 g, 176 mmoles) in dichloromethane (390 ml) over 15 minutes while maintaining the temperature below 1° during the addition. A solution of 2-(2-bromoethyl)-β-nitrostyrene **9** (15 g, 59 mmoles) in dichloromethane (45 ml) was added over 30 minutes maintaining the temperature below 3°. The reaction mixture was stirred at 0-5° for three hours before cooling to -11°. Water (240 ml) was added while maintaining the reaction temperature below -4°. The resulting mixture was then stirred for 20 minutes at 30° before the dichloromethane layer was separated. The aqueous layer was extracted with ethyl acetate (100 ml) at 50°. The combined dichloromethane/ethyl acetate extracts were washed with water (240 and 120 ml). The resulting solution was concentrated to 30 ml and cooled to 0°. The product crystallised and was collected at the pump, washed with chilled ethyl acetate, and dried at 50° to give **10** (8.5 g, 53%), mp 168-170°; ir (Nujol mull): ν 3150 and 3100 (NH), 1725 (amide C=O) 1622 and 1615 (aromatic C=C) cm^{-1}; ^{1}H nmr (DMSO-d_6) 270 MHz δ 3.25 (m, 2H, Ar$CH_2$$CH_2$), 3.75 (t, 2H, CH_2Br), 5.67 (s, 1H, C(3)H), 6.78 (d, 1H, C(7)H), 6.97 (d, 1H, C(5)H), 7.27 (t, 1H, C(6)H), 7.52 (t, 2H, ArH), 7.65 (t, 1H, ArH), 7.95 (d, 2H, ArH), 10.72 (br.s, 1H, NH); hrms: Found: 272.9551, 274.9536, 276.9515; $C_{10}H_9BrClNO$ requires 272.9556 (^{35}Cl/^{79}Br isotopes), 274.9526 (^{37}Cl/^{79}Br or ^{35}Cl/^{81}Br), 276.9506 (^{37}Cl/^{81}Br).

4-(2-Bromoethyl)1,3-dihydro-2*H*-indolin-2-one (**11**).

4-(2-Bromoethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one **10** (12 g, 44 mmoles) and 10% palladium/carbon (55% w/w water wet, 1.2 g) was suspended in ethyl acetate (120 ml). A solution of sodium hypophosphite hydrate (12 g, 136 mmoles) in water (48 ml) was added to the mixture at reflux over 35 minutes, and heating was continued for a further 90 minutes. The hot reaction mixture was filtered through a celite pad and the cake washed with ethyl acetate (20 ml). The mixture was re-heated and the water layer was separated. The hot ethyl acetate solution was washed with water (50 ml) and concentrated at atmospheric pressure until 80 ml of distillate was collected. The resulting solution was cooled to 0°. The product crystallised and was collected at the pump, washed with ethyl acetate (10 ml) and dried at 50° to give **11** (10 g, 95%) mp 153-155°; ir: ν 3200 and 3090 (NH), 1730 and 1675 (amide C=O) 1618 and 1602 (aromatic C=C) cm^{-1}; ^{1}H nmr (DMSO-d_6): 270 MHz δ 3.05 (m, 2H, Ar$CH_2$$CH_2$), 3.48 (s, 2H, C(3)H), 3.73 (t, 2H, C*H*$_2$Br), 6.70 (d, 1H, C(7)H), 6.85 (d, 1H, C(5)H), 7.12 (t, 1H, C(6)H), 10.25 (br s, 1H, NH); hrms: Found: 238.9949; 240.9929; $C_{10}H_{10}BrNO$ requires 238.9946 (^{79}Br isotope), 240.9925 (^{81}Br).

4-[2-(Di-*n*-propylamino)ethyl]-1,3-dihydro-2*H*-indolin-2-one Hydrochloride **1** from the Bromide **11**.

4-(2-Bromoethyl)1,3-dihydro-2*H*-indolin-2-one **11** (12.5 g, 52 mmoles) and di-*n*-propylamine (51 g, 50 mmoles) were added to water (250 ml) with rapid stirring to ensure efficient mixing of the two layers. The reaction mixture was heated to reflux under a nitrogen atmosphere and heating was continued for two and a half hours. Excess di-*n*-propylamine was removed by vacuum azeotropic distillation until 65 ml of distillate had collected. The reaction mixture was cooled to 30° before concentrated hydrochloric acid (12.5 ml) and water (10 ml) were added. The homogeneous aqueous layer was then extracted with dichloromethane (125 ml). Total concentration of the organic layer *in vacuo* gave the 4-vinyloxindole **14** (3.1 g, 38%) mp 262° dec; ir: ν 3000-3200 (C=C), 1710 (amide C=O), 1590 and 1620 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): 270 MHz δ 3.40 (s, 2H, C(3)H), 5.40 and 5.75 (2d, 2H, CH=CH_2), 6.65 (q, 1H, C*H*=CH_2), 6.80 (d, 1H, C(7)H), 7.20 (m, 2H, C(5and6)H), 8.80 (br s, 1H, NH); hrms: Found: 160.0773 (M+H); $C_{10}H_{10}NO$ requires 160.0762.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.82; H, 5.67; N, 8.74.

The aqueous layer was basified to *p*H 13 using a solution of sodium hydroxide (10 g) in water (31 ml), and the product free

base was extracted into dichloromethane (2 x 65 ml). The combined extracts were washed with water (2 x 65 ml) and diluted with 2-propanol (100 ml). To this solution was added concentrated hydrochloric acid (10 ml), and the resulting mixture was heated until 185 ml of distillate had been collected. The mixture was cooled and the product was collected at the pump, washed with 2-propanol, and dried at 80° to give ropinirole hydrochloride **1** (8.8 g, 57% yield) as a white solid mp 246-247°; ir: ν 3076 (NH), 2760-2400 (NH^+), 1724 (C=O), 1614 and 1598 (aromatic) cm^{-1}; ^1H nmr (DMSO-d_6): 270 MHz δ 0.92 (t, 6H, Me), 1.72 (m, 4H, $NCH_2CH_2CH_3$), 3.00 (m, 6H, $NCH_2CH_2CH_3$ and $ArCH_2CH_2$), 3.19 (m, 2H, $ArCH_2CH_2N$), 3.56 (s, 2H, C(3)H), 6.73 (d, 1H, C(7)H), 6.86 (d, 1H, C(5)H), 7.14 (d of d, 1H, C(6)H), 10.46 (s, 1H, ring NH), 10.8 (br s, 1H, quat NH) hrms: Found: 261.1962 (M+H); $C_{16}H_{25}N_2O$ requires 261.1967.

Anal. Calcd. for $C_{16}H_{24}N_2O$•HCl: C, 64.74; H, 8.49; N, 9.44; Cl, 11.94. Found: C, 64.91; H, 8.52; N, 9.41; Cl, 11.95.

4-(2-Acetoxyethyl)-1,3-dihydro-2*H*-indolin-2-one (**15**).

4-(2-Bromoethyl)-1,3-dihydro-2*H*-indolin-2-one **11** (25 g, 104 mmoles) and sodium acetate (34.2 g, 416 mmoles) were stirred in ethanol/water (1:1, 250 ml) at reflux for 24 hours. Ethanol was removed by distillation, and the mixture was cooled to 5° resulting in crystallisation of the crude product. This was collected at the pump and recrystallised from aqueous ethanol to give **15** (20.3 g, 89%) mp 141-142°; ir: ν 1743 and 1731 (ester C=O), 1705 and 1663 (amide C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 1.96 (s, 3H, Me), 2.82 (t, 2H, $ArCH_2CH_2$), 3.45 (s, 2H, C(3)H), 4.21 (t, 2H, CH_2OAc), 6.70 (d, 1H, C(7)H), 6.80 (t, 1H, C(6)H), 7.10 (d, 1H, C(5)H), 10.28 (br s, 1H, NH); hrms: Found: 219.0905; $C_{12}H_{13}NO_3$ requires 219.0895.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.75; H, 5.93; N, 6.30.

4-(2-Hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one (**16**).

Concentrated hydrochloric acid was added to a suspension of 4-(2-acetoxyethyl)-1,3-dihydro-2*H*-indolin-2-one **15** (5 g, 22.8 mmoles) in water (100 ml) and the mixture was heated at reflux for 150 minutes. The reaction mixture was extracted with ethyl acetate (3 x 70 ml) at 30-40° and the combined extracts were dried and concentrated *in vacuo* to give **16** (2.81 g, 70%) as a pale yellow solid mp 147-149°; ir: ν 3260, 3190 and 3165 (NH and OH), 1684 (amide C=O) 1619 and 1608 (aromatic C=C) cm^{-1}; ^1H nmr (DMSO-d_6): 270 MHz δ 2.64 (t, 2H, $ArCH_2CH_2$), 3.41 (s, 2H, C(3)H), 3.59 (t, 2H, CH_2OH), 4.56 (t, 1H, OH), 6.64 (d, 1H, C(7)H), 6.77 (d, 1H, C(5)H), 7.07 (t, 1H, C(7)H), 10.23, (br s, 1H, NH); hrms: Found: 177.0788; $C_{10}H_{11}NO_2$ requires 177.0790.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.71; H, 6.32; N, 7.70.

2-(2-Oxo-1,3-dihydro-4-indolyl)ethyl *p*-Toluenesulphonate (**17a**).

To a stirred suspension of 4-(2-hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one **16** (6.3 g, 35.5 mmoles) in pyridine (14.2 ml, 13.9 g, 178 mmoles) at 5-10° was added a solution of *p*-toluenesulphonyl chloride (8.2 g, 43 mmoles) in dichloromethane (32 ml) at a sufficient rate to keep the reaction temperature below 10°. The mixture was stirred at 5-10° for 3-4 hours. Hydrochloric acid (6*M*) (35 ml) and dichloromethane (18 ml) were added to the stirred solution while maintaining the temperature below 15°. The organic layer was removed, and the aqueous phase was extracted with dichloromethane (18 ml). The combined organic extracts were washed with water (40 ml) and concentrated *via* distillation until a residual volume of 50 ml was obtained. The mixture was diluted using 60-80° petroleum ether (40 ml) to induce product crystallisation. The product was collected at the pump, washed with cold 1:1 v/v dichloromethane:60-80° petroleum ether and dried below 40° to give **17a** (9.95 g, 87%) as a white solid, mp 130-131°; ir: ν 3300-3100 (NH), 1699 (amide C=O) 1349 and 1175 (symmetric and asymmetric S=O), 905 (S-O) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 2.43 (s, 3H, Me), 2.89 (t, 2H, $ArCH_2CH_2$), 3.33 (s, 2H, C(3)H), 4.23 (t, 2H, CH_2OH), 6.77 (d, 2H, C(5 and 7)H), 7.13 (1H, t, C(6)H), 7.27 and 7.64 (2 x d, 2 x 2H, tosylate ring), 8.95 (br s, 1H, NH); hrms: Found: 331.0878; $C_{17}H_{17}NO_4S$ requires 331.0878.

Anal. Calcd. for $C_{17}H_{17}NSO_4$: C, 61.61; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.50; H, 5.08; N, 4.07; S, 9.51.

4-[2'-(Di-*n*-propylamino)ethyl]-1,3-dihydro-2*H*-indolin-2-one Hydrochloride (**1**) from 2-(2-Oxo-2,3-dihydro-4-indolyl)ethyl *p*-Toluenesulphonate (**17a**).

2-(2-Oxo-1,3-dihydro-4-indolyl)ethyl *p*-toluenesulphonate (**17a**) (6.54 g, 19.7 mmoles) and di-*n*-propylamine (20 g, 198 mmoles) were added to water (50 ml) and stirred at reflux under a nitrogen atmosphere for two hours. The reaction mixture was cooled to 50° and the lower aqueous layer discarded. Fresh water (50 ml) was added, and excess di-*n*-propylamine was removed by azeotropic distillation at 85-98°. The reaction mixture was cooled to 30° and acidified to *p*H 1 using concentrated hydrochloric acid. The aqueous layer was extracted with dichloromethane (25 + 12 ml) and the organic extracts were discarded. The aqueous layer was basified to *p*H 14 using 30% w/v aqueous sodium hydroxide solution, and the product free base was extracted into dichloromethane (25 + 12 ml). The combined extracts were washed with water (2 x 25 ml), diluted with 2-propanol (65 ml) and then acidified using concentrated hydrochloric acid (2 ml). The resulting mixture was heated to a base temperature of 60-68° until 40 ml of distillate had been collected, during which time a suspension of ropinirole hydrochloride salt was formed. The mixture was cooled and the product was collected at the pump, washed with 2-propanol, and dried at 80° to give ropinirole hydrochloride **1** (5.03 g, 85% yield) as a white solid.

2-(2-Hydroxyethyl)-β-nitrostyrene (**19**).

1-Hydroxyisochroman **18** [10] (3.6 g, 24 mmoles) was dissolved in methanol (70 ml) which had been basified with 25% w/w methanolic sodium methoxide (5 g, 23 mmoles). To this solution was added, nitromethane (6.6 g, 108 mmoles) followed by 25% w/w methanolic sodium methoxide (10.5 g, 49 mmoles) ensuring that the temperature remained below 0°. The reaction mixture was stirred at -10 - -5° for 4 hours, before being quenched into 6*M* hydrochloric acid (150 ml) below 5°. The resulting yellow mixture was extracted with dichloromethane (2 x 100 ml), and the combined extracts were washed with water (250 ml), dried (magnesium sulfate) and concentrated *in vacuo* to give **19** (3.75 g, 81%) as a yellow oil; ir: ν 3330 (OH), 1623 (aromatic C=C), 1498 and 1355 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 1.50 (br s, 1H, OH), 3.08 (t, 2H, $ArCH_2CH_2O$), 3.88 (t, 2H, $ArCH_2CH_2O$), 7.22 (m, 5H, ArH and $ArCH{=}CHNO_2$), 8.36 ($ArCH{=}CHNO_2$). For structural confirmation, **28** was benzoylated to produce the crystalline nitrostyrene **33** of identical melting point and spectroscopic characteristics.

4-(2-Acetoxyethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**20**).

To a stirred suspension of ferric chloride (3.36 g, 22.3 mmoles) in dichloromethane (20 ml) at -10° was added acetyl chloride (1.22 g, 15.5 mmoles), followed by a solution of 2-(2-hydroxyethyl)-β-nitrostyrene **19** (1 g, 5.2 mmoles) in dichloromethane (5 ml) ensuring that the reaction temperature did not exceed 0° during the addition. The reaction mixture was stirred at 20° for five hours. Water (50 ml) was then added at such a rate to ensure the temperature did not exceed 20°. The aqueous layer was removed and extracted with dichloromethane (50 ml). The combined organic extracts were washed with water (2 x 100 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The oily residue chromatographed on a flash silica column (eluent dichloromethane:methanol 30:1) to give **20** (0.54 g, 42%) as an off-white solid mp 110-2°; ir: ν 3155 and 3107 (NH), 1740 (C=O), 1682 (amide C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 2.05 (s, 3H, Me), 3.10 (m, 2H, $ArCH_2CH_2$), 4.38 (t, 2H, CH_2OAc), 5.20 (s, 1H, C(3)H), 6.80 (d, 1H, C(7)H), 6.92 (d, 1H, C(5)H), 7.25 (t, 1H, C(6)H), 8.42 (br s, 1H, NH); hrms: Found: 253.0490, 255.0474; $C_{12}H_{12}ClNO_3$ requires 253.0506 (^{35}Cl isotope), 255.0476 (^{37}Cl).

2-Chloromethylphenethyl Benzoate (**22**) [11].

To a stirred suspension of zinc chloride (1.5 g, 11 mmoles) in dichloromethane (40 ml) at 25° was added benzoyl chloride (16.5 g, 117 mmoles), followed by isochroman **6** (15 g, 112 mmoles) at such a rate as to maintain gentle reflux. The resulting mixture was heated at reflux for a further hour. The dichloromethane solution was washed with water (3 x 60 ml) and the organic layer concentrated totally *in vacuo* to give 2-chloromethylphenethyl benzoate **22** (30.7 g, 100%) as a colourless oil which crystallised on standing mp 44-45°; ir: ν 1708 (aromatic ester C=O) 1600 and 1580 (aromatic C=C), 1288 and 1174 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 3.23 (t, 2H, $ArCH_2CH_2$), 4.57 (t, 2H, $ArCH_2CH_2$), 4.72 (s, 2H, $ArCH_2Cl$), 7.20-7.30 (m, 3H, Aryl-H), 7.38 (d, 2H, Aryl-H), 7.44 (t, 2H, Aryl-H), 7.56 (t, 1H, Aryl-H), 8.02 (d, 2H, Aryl-H); hrms: Found: 152.0398 (M-$PhCO_2H$); C_9H_9Cl requires 152.0393 (^{35}Cl isotope).

2-Formylphenethyl Benzoate (**23**).

2-Chloromethylphenethyl benzoate **22** (41 g, 149 mmoles) and hexamethylenetetramine (42 g, 300 mmole) were stirred in ethanol (150 ml) under reflux for 90 minutes. Aqueous acetic acid (50%) (150 ml) was then added, and the reaction was further heated until 150 ml of distillate had been collected. The reaction mixture was cooled, and extracted with dichloromethane (100 + 50 ml). The combined extracts were washed with water (2 x 100 ml), and concentrated *in vacuo* to leave a red oil. The crude product was added to a solution of sodium metabisulfite (32 g) in ethanol (26 ml) and water (45 ml). The reaction mixture was stirred for thirty minutes, before dichloromethane (160 ml) was added to give a white suspension. The white solid was collected at the pump, washed with cold dichloromethane (75 ml) and air-dried. The damp bisulphate addition complex was added, in portions, to a 7% aqueous sodium bicarbonate solution (550 ml) at 20-25°. The pure aldehyde was extracted into dichloromethane (200 ml), and the organic layer was washed with water (2 x 160 ml). After drying (magnesium sulfate), the dichloromethane solution was concentrated *in vacuo* to a base temperature of 70° to leave 2-formylphenethyl benzoate **23** as a pale green mobile oil (26.6 g, 70%); ir: ν 1717 (aromatic ester C=O) 1695 (aromatic aldehyde C=O), 1600 and 1574 (aromatic C=C), 1274 and 1113 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 3.53 (t, 2H, $ArCH_2CH_2$), 4.57 (t, 2H, $ArCH_2CH_2$), 7.37-7.48 (m, 6H, Aryl-H), 7.55 (t, 2H, Aryl-H), 7.85 (d x d, 1H, Aryl-H), 7.97 (d x d, 2H, Aryl-H), 10.26 (s, 1H, CHO); hrms: Found: 255.1026 (M + H); $C_{16}H_{15}O_3$ requires 255.1021.

2-(2-Benzoyloxyethyl)-β-nitrostyrene (**24**).

To a stirred solution of 2-formylphenethyl benzoate **23** (20 g, 78 mmoles) in methanol (50 ml) was added, in quick succession, with cooling, nitromethane (7.1 g, 116 mmoles), acetic acid (2.36 g, 39 mmoles) and *n*-butylamine (2.83 g, 39 mmoles), ensuring that the reaction temperature did not rise above 30° during the addition. The reaction mixture was stirred at 22° for 18 hours, during which time a thick yellow suspension had formed. The reaction mixture was cooled to 0° and the product was collected at the pump, washed with chilled 2-propanol (50 ml) and air-dried to give 2-(2-benzoyloxyethyl)-β-nitrostyrene **24** (20.3 g, 87%) as a yellow solid mp 66-68°; ir: ν 1707 (aromatic ester C=O) 1629 (alkene C=C), 1599 (aromatic C=C), 1502 and 1345 (symmetric and asymmetric NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): 270 MHz δ 3.27 (t, 2H, $ArCH_2CH_2$), 4.52 (t, 2H, $ArCH_2CH_2$), 7.33 (t, 1H, Aryl-H), 7.41 (m, 3H, Aryl-H), 7.46 (t, 1H, Aryl-H), 7.51 (d, 1H, $CH{=}CHNO_2$), 7.55 (m 2H, Aryl-H), 7.97 (m, 2H, Aryl-H), 8.45 (d, 1H, $CH{=}CHNO_2$); hrms: Found: 175.0637 (M-$PhCO_2H$); $C_{10}H_9NO_2$ requires 175.0633.

4-(2-Benzoyloxyethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one (**25**).

To a stirred suspension of ferric chloride (21.9 g, 135 mmoles) in dichloromethane (90 ml) at 0-5° was added acetyl chloride (5.3 g, 67.5 mmoles), followed by a solution of 2-(2-benzoyloxyethyl)-β-nitrostyrene **24** (10 g, 33.6 mmoles) in dichloromethane (30 ml) ensuring that the reaction temperature did not exceed 5° during the addition. The reaction mixture was stirred at 0-5° for one hour. Water (80 ml) was then added at such a rate that the temperature did not exceed 20°, and the mixture was then warmed to 30° to dissolve all the solids present. The aqueous layer was separated and extracted again with dichloromethane (20 ml). The combined organic extracts were washed with water (80 ml at 30°, before being distilled at atmospheric pressure until 60 ml of distillate had been collected. The resulting solution was diluted with 60-80° petroleum ether (40 ml) and cooled to 5° causing the product to crystallise. The product was collected at the pump, washed with 2:1 v/v dichloromethane:60-80° petroleum ether (18 ml) and dried at 55° to give 4-(2-benzoyloxyethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one 25 (6.8 g, 64%) as an off-white solid, mp 154-155°; ir: ν 3155 and 3107 (NH), 1752 and 1728 (aromatic ester C=O), 1682 (amide C=O) 1622 and 1608 (aromatic C=C), 1272 and 1106 (C-O) cm^{-1}; ^1H nmr (DMSO-d_6): 270 MHz δ 3.15 (m, 2H, $ArCH_2CH_2$), 4.56 (t, 2H, CH_2OCOAr), 5.67 (s, 1H, C(3)H), 6.77 (d, 1H, C(7)H), 6.99 (d, 1H, C(5)H), 7.27 (t, 1H, C(6)H), 7.52 (t, 2H, Aryl-H), 7.65 (t, 1H, Aryl-H), 7.95 (d, 2H, Aryl-H), 10.72 (br s, 1H, NH); hrms: Found: 315.0660, 317.0620; $C_{17}H_{14}ClNO_3$ requires 315.0662 (^{35}Cl isotope), 317.0633 (^{37}Cl).

4-(2-Hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one (**16**).

This procedure describes the preparation of **16** from **25** without the isolation of 4-(2-benzoyloxyethyl)-1,3-dihydro-2*H*-indolin-2-one **26** intermediate.

4-(2-Benzoyloxyethyl)-3-chloro-1,3-dihydro-2*H*-indolin-2-one **25** (5.0 g, 15.8 mmoles) and 10% Pd/C (1.25 g, 60% wt/wt water) were stirred in methanol (60 ml) and heated to reflux. To this mixture was added hydrazine hydrate (1.6 g, 32 mmoles) over a period of 20 minutes, controlling the rate of reflux by the rate of addition. The reaction mixture was heated for a further 30 minutes. A solution of sodium hydroxide (1.3 g, 32.5 mmoles) in water (25 ml) was added, and the mixture heated at reflux for 30 minutes. The catalyst was removed by filtration through a celite pad, and the cake washed with water (5 ml). The filtrates were combined and heated until 65 ml of distillate had collected. The resulting solution was then cooled to 0° to produce a white suspension. The product was collected at the pump, washed with ice-cold water (10 ml) and dried at 60° to give 4-(2-hydroxyethyl)-1,3-dihydro-2*H*-indolin-2-one **16** (2.4 g, 85%) as a white solid mp 147-149°.

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