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An Efficient Process for the Large-Scale Synthesis of a 2,3,6-Trisubstituted Indole

Anthony D. Alorati,* Andrew D. Gibb,* Peter R. Mullens, and Gavin W. Stewart

Global Process Chemistry, Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, United Kingdom

ABSTRACT: The efficient synthesis of a key trisubstituted indole intermediate **1** is described. The synthetic route required the use of an aryl Grignard reagent which was not commercially available, and the large-scale formation of this fragment and the thermal evaluation for this step is presented. The key step in the sequence was a Truce−Smiles rearrangement to provide an advanced ketone intermediate which, upon reduction, cyclized to the desired indole **1**. Design of experiment (DoE) optimization of this reduction is also presented. In total >50 kg of target indole **1** were synthesized in 55% overall yield over five steps using this new route.

INTRODUCTION

During the course of an ongoing program, 50 kg of a key intermediate of trisubstituted indole **1** were required. Two previous multikilogram campaigns had been demonstrated, employing a three-step sequence to generate known indole **1** (Scheme 1).[1] However, the high cost and long lead times of reactants **2** and **5** meant that this route would not be viable for large-scale preparation of **1** within the desired time frame.

It was therefore apparent that a new route to **1** was required that would address these issues. The indole motif is prevalent in a large number of target molecules, and as such there is extensive coverage in the literature of synthetic routes towards these compounds.[2,3] Two of the most direct routes were screened for applicability towards the synthesis of **1**. The first route investigated was the Larock method[4,5] via alkyne **7** which would be expected to provide the desired regiochemical outcome (Scheme 2).

However, synthesis of substituted alkyne starting material **7** on scale would be potentially problematic. There were also issues with the sourcing of starting materials, and additionally, the key sp^3−sp carbon−carbon bond formation to generate **7** proved to be difficult. When **7** was prepared on lab scale, however, the Larock cyclisation via intermediate **9** did indeed give the desired 2-phenoxy regioselectivity in approx 9:1 ratio as determined by ^{1}H NMR experiments.

The second approach to the preparation of **1** is by formation of imine **10** using aniline **6** and ketone **8**, followed by an intramolecular Heck reaction. This method is also well-described in the literature and has been shown to work with a variety of ortho-substituted halo-anilines.[6] Unfortunately, initial screening of this reaction gave modest conversions at best, and subsequently, both approaches were discontinued.

Attention was then switched to a recent publication by the Snape group[7] who had demonstrated a novel synthesis of a 2-substituted indole using a Truce−Smiles rearrangement[8,9] as a key step (Scheme 3). Initial lab-scale experiments showed this route to be promising on gram quantities, so attention was focused towards optimization and scale-up of this chemistry. Herein we report the successful preparation of >50 kg of **1** via this type of approach.

RESULTS AND DISCUSSION

The synthetic scheme for our approach is shown in Scheme 4. S_NAr reaction to **17** and rearrangement to **18** proved to be both selective and high yielding under the published DMF/potassium carbonate conditions. Investigations therefore focused on the synthesis of the phenolic ketone fragment **8** and the final hydrogenation/ring closure to afford target indole **1**.

2-Cyclohexyl-1-(2-methoxy-phenyl)ethanone 15 Formation. To expedite the synthesis it was necessary to form the Grignard reagent of 2-bromoanisole **12** in-house. The potential for uncontrolled exothermic activity is high unless the system is well characterised thermally. Thus, thermal evaluation of the system was carried out using ARSST and RC-1 calorimetry. Typically an initial charge of halide is limited and a safe and reliable initiation procedure developed. Thus elemental magnesium insertion to bromide **12** was initiated via catalytic charge of DIBAL-H (2.5 mol %).[10] Crucially DIBAL-H both dried the solvent and afforded reliable and rapid activation of Mg. A more commonly used Mg activator is 1,2-dibromoethane, however this compound exhibited a lag time of up to 1 h at 50 °C. Halogen-metal exchange with **12**, using ^{i}PrMgCl or ^{i}PrMgCl.LiCl, proved unsuccessful with only partial conversion achieved even at elevated temperatures. Moreover, any excess Grignard used to drive the exchange reactions to completion complicated downstream chemistry.

Optimization of the procedure in an RC-1 (1 L jacketed flask) showed initiation occurred readily at <40 °C, judged by appearance and rate of temperature rise (RC-1 run in both adiabatic and isoperibolic modes). The adiabatic temperature rise for the system with an initial 10 mol % of bromide **12** (10 vol THF vs Mg) was calculated at 28 °C. The extent of Grignard **14** formation was readily monitored by sampling, quenching into water and analyzing by HPLC. For bulk implementation, the charge of **12** was reduced to an initial 8 mol % and the DIBAL-H charged at 25 °C. The resulting exotherm raised the batch temperature to approximately 60 °C.

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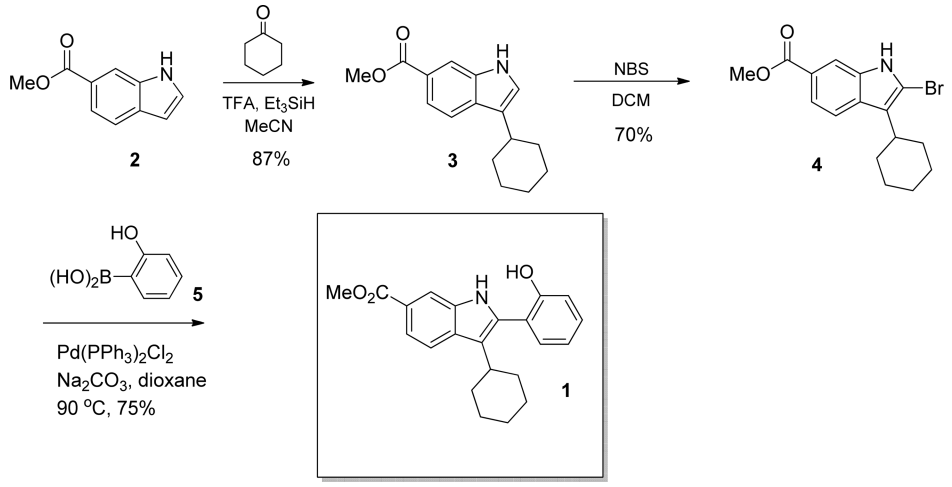
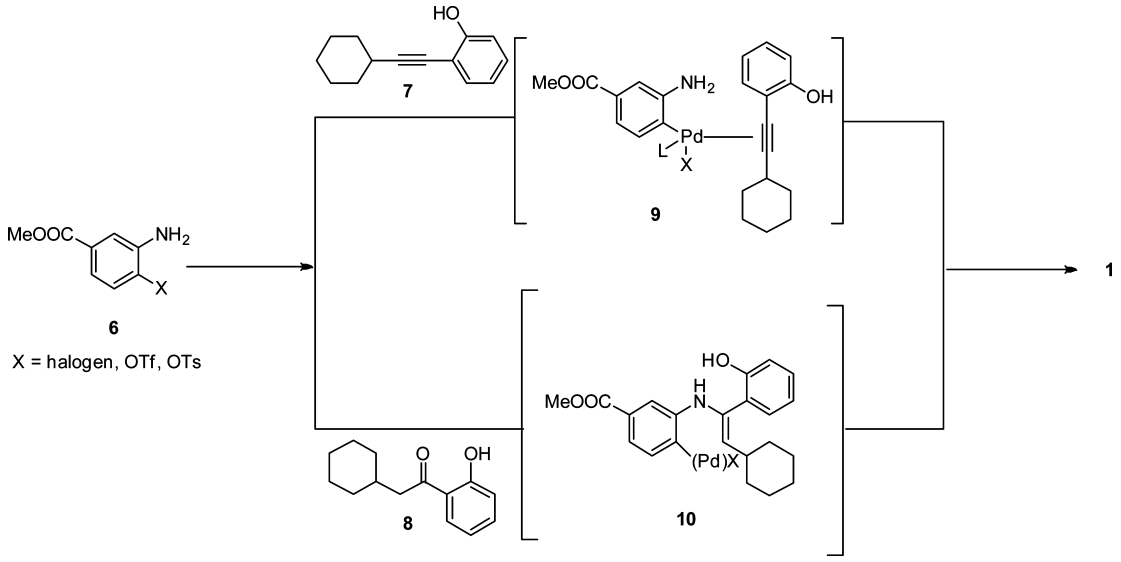
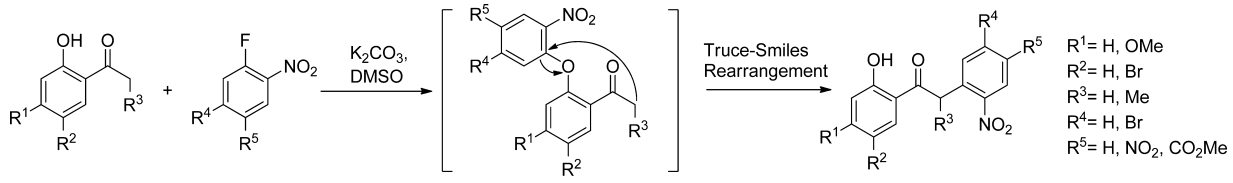
Scheme 1. Synthesis used in first deliveries for 1



Scheme 2. Direct approaches to 2,3,6-trisubstituted indoles



Scheme 3. General scheme for the Snape approach to indoles



The remaining bromide **12** charge in THF solution was added to the batch at such a rate as to maintain the temperature between 50 and 60 °C. In a single batch 60 kg of **12** was processed to generate Grignard **14** (>98% conversion) and used directly in the next step.

Commercially available cyclohexylacetic acid **11** was converted to the corresponding Weinreb amide[11] **13** by formation of the CDI adduct and addition of *N,O*-dimethylhydroxylamine hydrochloride. Complete conversion to **13** was achieved using 1.3 equiv CDI and 1.5 equiv hydroxylamine. Alternative and potentially cheaper methodologies, e.g. addition of the Grignard to the ester or the acid chloride, were examined but were not competitive within the short development time available. Initially the THF solution of **11** was added to a cooled slurry of CDI in THF. This in turn was added to a slurry of *N,O*-dimethylhydroxylamine hydrochloride in THF and aged overnight. Addition of triethylamine as a base gave a more rapid and reliable conversion, eliminating variable reaction times which resulted from low solubility of *N,O*-dimethylhydroxylamine hydrochloride in THF. An MTBE extraction and aqueous wash sequence then afforded a solution of **13** in 92% assay yield.

Upon addition of Grignard **14** to the solution of **13**, >98% conversion to desired ketone **15** was achieved. A maximum charge of 1.2 mol equiv of **14** was employed and any excess was minimized to reduce downstream anisole levels. Quench of this

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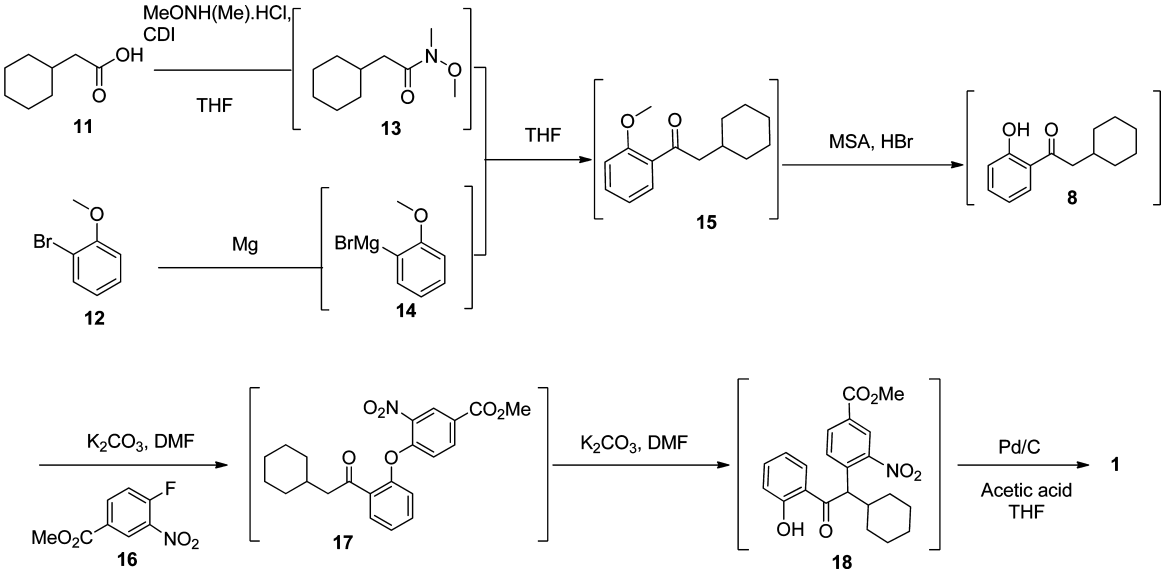
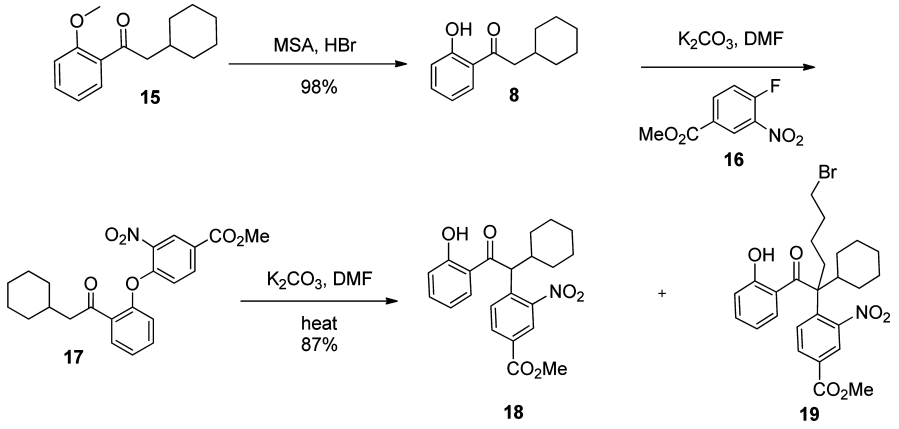
Scheme 4. Synthetic route via Truce-Smiles rearrangement to 2,3,6-trisubstitued indole 1



Scheme 5. Fate of residual THF through synthetic sequence



reaction mixture with aqueous HCl and addition of heptane (1 vol.) afforded clear separations during the work up. After a wash with aqueous sodium hydrogen carbonate, the organic phase assayed for an overall 93% yield of **15** (from **11**).

2-Cyclohexyl-1-(2-hydroxy-phenyl)ethanone 8 formation. A comprehensive screen of demethylation conditions for conversion of **15** to **8** was undertaken incorporating a variety of solvents, Lewis and Brϕnsted acids. The use of common iodide (NaI and LiI) and bromide (LiBr and KBr) sources with dipolar aprotic and high boiling protic solvents largely proved ineffective up to 120 °C. Utilizing MgI_2 (0.6 equiv) in THF at 50 to 60 °C gave complete and clean deprotection of **15** in <4 h, with the coordinating *ortho* methoxy group accelerating the demethylation. However, the bulk availability of this reagent was limited and cost prohibitive.

Ultimately the screen identified HBr as a reagent for additional optimization. Thus, the final method developed for demethylation used 2 equiv of concentrated aqueous HBr in 3 vol of methane-sulfonic acid. With the reaction at 70 °C, greater than 98% conversion was achieved in <3 h. Additionally no significant degradation was observed in reaction mixtures aged at 90 °C overnight. However it was demonstrated that significantly increased quantities of HBr or additional water in the reaction can result in a build up of aldol-type impurities.

As a consequence of demethylation on bulk scale, 300 mol of methyl bromide gas (bp 4 °C) were produced. Due to its extensive use as a fumigating and agricultural chemical, considerable literature exists relating to its handling and disposal. Scrubbing the headspace/exhaust with 20% aqueous ethanolamine has been well-defined by the Pfizer group[12] and this was employed.

The major impurities in **8** were phenol and 2-methoxyphenol derived from the original Grignard charge but neither of these compounds proved problematic in down stream chemistry. However, residual THF in the methoxy ketone input stream proved to be an issue. Ring-opening of residual THF under demethylation conditions afforded dibromobutane (Scheme 5). This in turn quantitatively alkylated the subsequent Smiles rearranged product **18** to form **19**, necessitating the control of THF to <2 mol % by distillation prior to demethylation.

4-[1-Cyclohexyl-2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-nitrobenzoic Acid Methyl Ester 19. Formation of aryl ether **17** proceeded via S_NAr reaction of phenol **8** and trisubstituted fluoro aromatic **16** followed by an *in situ* Truce−Smiles rearrangement to form nitro phenol **18**. Initial conditions screened for formation of **17** and **18** centered around those reported[7] and included solvents (DMF, DMAc, DMSO), temperature, concentration, type and equivalents of base

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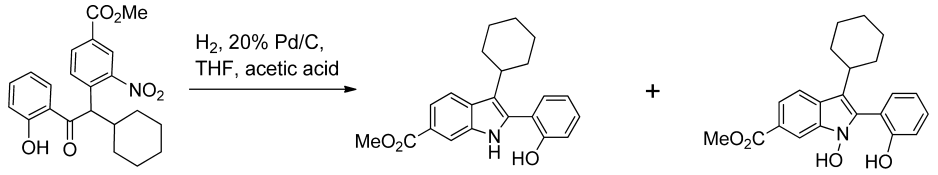
Scheme 6. Indole and hydroxyl indole via reductive ring closure



18 1 20

(potassium carbonate and potassium *tert*-butoxide). Superior yields (91% assay yield) were obtained using 10 vol of either DMF or DMSO with an excess of potassium carbonate at room temperature (typical reaction time was 3−4 h). For benchtop screening on milliliter scale, magnetic stirring was employed.

Employing batches of potassium carbonate from different bulk suppliers led to a variation in reaction profile and assay yield. Particle size measurements revealed no significant difference in primary particle size, 20 μm, or agglomerate size (100−150 μm). However, batches that contained soft agglomerates that readily broke up in the reaction conditions, performed well, whereas the presence of hard agglomerates led to stalled reactions that failed to rearrange to **18**. To break down these agglomerates and potentially increase the surface area heat/cool cycles of potassium carbonate in DMF were attempted before reagent addition but were unsuccessful. Finally, we resorted to in-house pin milling to ensure a supply of nonagglomerated base which led to high assay yields. On scale, the S_NAr[13] reaction was complete after 2.5 h at 23 °C, and the product fully rearranged after aging overnight at 37 °C (87% assay yield). Product **18** was isolated after an extractive workup to furnish a solution stream in THF or MTBE for the next step.

The cheaper methyl-4-chloro-3-nitrobenzoate analogue of **16** was briefly investigated but led to a poor purity profile and moderate yield. With **16**, the S_NAr step proceeded rapidly, and the one-pot reaction behaved as a distinct two-stage sequential reaction. However, with the methyl-4-chloro-3-nitrobenzoate, the S_NAr and rearrangement steps proceeded in parallel, leading to increased impurities and crossover reactions.

3-Cyclohexyl-2-(2-hydroxy-phenyl)-1*H*-indole-6-carboxylic Acid Methyl Ester 1. Preliminary experimentation highlighted the formation of *N*-hydroxy indole **20** (Scheme 6), formed via ring closure of the intermediate hydroxylamine, as a significant problem and resulted in stalled reactions and poor purity profiles. Hence, a screen of appropriate solvents and hydrogenation catalysts was performed to identify optimal conditions. Using an Endeavor hydrogenation apparatus, a screen was carried out followed by DoE analysis to rapidly assess critical parameters once a hit was established. During this development it became apparent that the purity of **18** greatly impacted the reaction profile.

Initial hydrogenation screens using the crude reaction streams gave poor results (<1:3 ratio of **1**:**20**), with type 91 Pd on carbon (10% Pd, 50% wet) in a range of common organic solvents. A broad screen of other Pt and Pd catalysts also gave gross mixtures of **1** and **20** with minimal additional conversion to **1** after resubjecting the reaction mixtures to fresh catalyst. Continued screening on chromatographed **18** identified acetic acid as a key additive to ensure >95% conversion to **1**. However, replicating this with crude input streams gave, at best, 50% conversion to desired **1**. Attempts to improve solution stream performance with carbon treatment or exposure to silica were unsuccessful.

In an effort to drive reactions to completion, fit-for-purpose DoE designs, two-level 1/2 factorial, were run to examine the following critical factors: temperature (40−75 °C), pressure (10−70 psi), quantity of acetic acid (0−50% by vol) and catalyst loading (10−20 wt %). A working model was obtained that gave an excellent correlation between the predicted and actual results (Figure 1). The DoE indicated the prominent

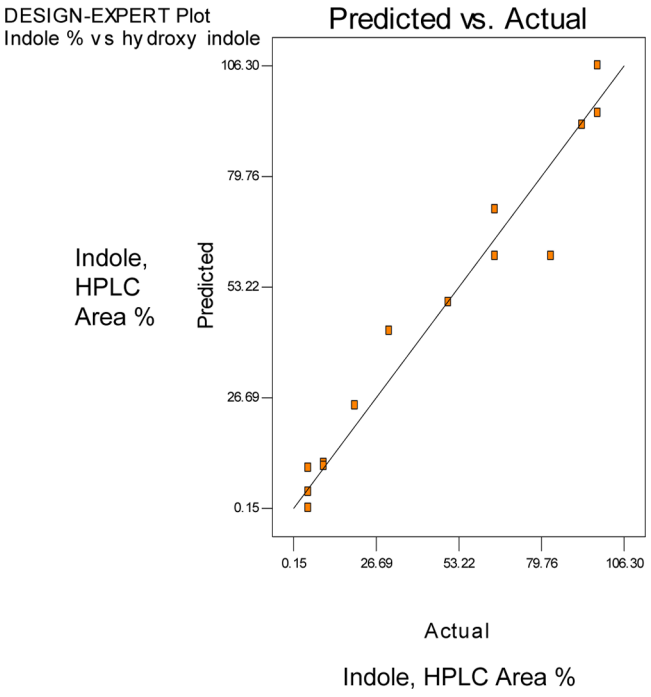


Figure 1. DX6-generated schematic for actual vs model-predicted conversion to indole.

effects to be high levels of acetic acid and higher temperatures to achieve good conversion to **1**. Higher pressures (>50 psi) generally decreased conversion to **1**, although this was complicated with other two-factor interactions. By incorporating just the main effects from the fit-for-purpose design, the final bulk conditions were derived by reducing volumes for throughput and considering the boiling point of THF to be <60 °C. Thus, final conditions were 35 psi, 60 °C, 20 wt % catalyst (type 91 10% Pd/C) with 50% acetic acid in THF (5 vol). Three batches on approximately 25-kg scale each afforded >50:1 desired indole **1** vs hydroxyindole **20**, in 85% assay yield. On completion, the catalyst was removed by filtration and the indole crystallized by concentration followed by addition of *n*-heptane to minimize liquor losses. In total, 52.5 kg of indole **1** was isolated by filtration as a white solid. Three batches gave an

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average isolated yield of 77% in high purity with mother liquor losses between 5 and 8%.

CONCLUSION

A practical, scalable, and high-yielding synthesis of target indole **1** has been developed, starting from commercially available raw materials. This concise and efficient approach has been demonstrated on >50 kg scale, and key safety issues have been addressed to afford indole **1** in 55% overall yield in seven chemical transformations. The entire sequence can be telescoped, significantly reducing cycle times, and extends the scope of the Truce−Smiles rearrangement.

EXPERIMENTAL SECTION

General. Starting materials were obtained from commercial suppliers and were used without further purification. HPLC analyses were performed on Agilent series 1100 using C-18 reverse phase methods eluting acetonitrile and 0.1% H_3PO_4 (aq). Assay yields were obtained using analytical standards obtained by chromatography or recrystallisation. Isolated yields refer to yields corrected for purity on the basis of HPLC assays using purified standards. NMR spectra were obtained at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C. All coupling constants are reported in Hertz (Hz).

2-Cyclohexyl-*N*-methoxy-*N*-methylacetamide (13). A slurry of CDI (54.5 kg) in THF (98.1 kg) was cooled to 5 °C. A solution of cyclohexylacetic acid (36.8 kg) in THF (32.7 kg) was added over 75 min, maintaining the internal temperature between 5 and 7 °C. The reaction mixture was then aged for 15 min at 7 °C and conversion to CDI adduct monitored via a methanol/triethylamine solution quench. In a separate vessel a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (37.9 kg) in THF (65.4 kg) was made. The CDI adduct solution was added over 22 min; the internal temperature was kept below below 25 °C. The reaction was aged at 23 °C overnight. After sampling, the reaction was incomplete, and three portions of Et_3N (14.0 kg) were added over 7.5 h. The batch was aged overnight at 25 °C to afford complete conversion to the Weinreb amide. The reaction was quenched via addition of TBME (136.3 kg), heptane (25.2 kg), and 2 M HCl solution (184 L). The lower aqueous layer was cut, and the organics were washed with a 2 M HCl solution (74 L). The organics were then washed with a 3.5% $NaHCO_3$ solution (74 L). The organics were diluted with heptane (25.2 kg) and afforded a final water wash (74 kg) before being dried via distillation to a final batch volume of 187 L and a water content of 62 μg water in 100 μL (Karl−Fischer titration). In total 44.2 kg of product was isolated in 92% yield as a 30% w/w MtBE solution (149.8 kg).

(2-Methoxylphenyl)magnesium Bromide (14). Magnesium (8.6 kg) and THF (77.0 kg) were charged to a clean dry vessel. The agitator was started with minimum agitation. The contents of the vessel were heated to 30 °C, and DIBAL-H, 1 M in heptane (0.8 L), was charged to the batch followed by an initial charge of the 2-bromoanisole (4.0 kg). Almost immediately an exotherm was observed, indicating reaction initiation. The batch was cautiously warmed to 50−55 °C and sampled by HPLC to confirm complete consumption of 2-bromoanisole. A solution of 2-bromoanisole (56.0 kg) in THF (160 kg) was slowly added over 100 min, maintaining the internal temperature vessel batch above 60 °C but not at an aggressive reflux. The batch was aged for 20 min, cooled to 40−50 °C, and sampled by HPLC to confirm complete consumption of bromoanisole. The Grignard solution was filtered and transferred into a separate vessel, rinsed with THF (55 kg), and held at ∼35 °C overnight. In total, 67.8 kg of **12** was made in 99% yield as a 46% w/w THF solution.

2-Cyclohexyl-1-(2-methoxy-phenyl)ethanone (15). To a vessel containing the MTBE solution of **13** was charged 1.1 equiv of the Grignard solution **14** (wrt to **13**) over 40 min, maintaining internal temperature between 20 and 25 °C. A second charge of ∼0.1 equiv Grignard **14** was sufficient to achieve >97% conversion. The batch was cooled to 5 °C and carefully quenched with 2 M HCl (225 L), keeping the reaction temperature <25 °C. Heptane (41 kg) was added and agitated for 10 min, and the two phases settled. The lower aqueous layer was separated, and the organics were washed with a 3.5% $NaHCO_3$ (185 kg) and a final water wash (180 kg). The batch was distilled from 480 to 140 L to solvent switch into heptane and dry the batch. In total 55.9 kg of product was isolated in 99% yield as a 45% w/w heptane solution (55.9 kg of **15** in total of 124.0 kg) and a water content of 10.8 μg water in 100 μL (Karl−Fischer titration). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, 8.0 Hz), 7.45 (1H, t, 9.0 Hz), 7.0 (1H, t, 8.0 Hz), 6.95 (1H, d, 7.5 Hz), 3.90 (3H, s), 2.85 (2H,d, 7.0 Hz), 1.95−1.88 (1H, m), 1.75−1.62 (5H, m), 1.32−1.16 (3H, m), 1.05−0.94 (2H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.1, 158.6, 132.9, 129.9, 129.3, 120.63, 111.4, 55.4, 51.3, 34.3, 33.3, 26.9, 26.34. HRMS (ES) Calcd for $C_{15}H_{21}O_2$ (MH^+) 233.1542. Found 233.1535.

2-Cyclohexyl-1-(2-hydroxy-phenyl)ethanone (8). To a 45% w/w solution of 2-cyclohexyl-1-(2-methoxy-phenyl)-ethanone **15** in heptane (61 kg, 120 mol) was added methane-sulfonic acid (123 kg). The mixture was heated to 50 °C at <500 mbar to remove residual solvent by distillation. At atmospheric pressure concentrated aqueous HBr was added over at least 30 min in a temperature range of 65−75 °C. After aging for 150 min the reaction was cooled to 20 °C, and a vacuum purge cycle removed any residual methyl bromide. In a separate vessel a mixture of MTBE (83 kg), heptane (19 kg), and water (111 kg) was charged, followed by the reaction mixture added at a rate to maintain the temperature below 30 °C. The lower acidic aqueous layer was separated and the organic phase washed sequentially with water (84 kg), 5% w/v sodium bicarbonate solution (90 kg), and finally water (84 kg). The organic phase was distilled to dry, using heptane as necessary to achieve a final residual water content of <10 mol % vs substrate. Afforded 52.4 kg of **8** as an orange solution in heptane in 98% assay yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (1H, s) 7.77 (1H, d, 8.0 Hz), 7.45 (1H, t, 7.5 Hz), 7.00 (1H, d, 8.0 Hz), 6.90 (1H, t, 7.5 Hz), 2.85 (2H, d, 7.0 Hz), 1.96−1.90 (1H, m), 1.78−1.65 (5H, m), 1.31−1.24 (3H, m), 1.17−1.05 (2H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.7, 162.6, 136.2, 130.2, 119.7, 118.7, 118.5, 45.9, 34.9, 33.4, 26.18, 26.12. HRMS (ES) Calcd for $C_{14}H_{19}O_2$ (MH^+) 219.1385. Found 219.1382.

4-[1-Cyclohexyl-2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-nitrobenzoic Acid Methyl Ester (18). To a suspension of potassium carbonate (34 kg) and methyl-4-fluoro-3-nitro-benzoate **16** (22 kg), in DMF (158 kg) was added a solution of **8** (24.4 kg) in DMF (20 kg) over 30 min. This mixture was aged at RT for approx 60 min, then water (2.1 kg) and additional potassium carbonate (15.4 kg) were added, and the resulting mixture was aged at 35 °C overnight. In a separate vessel a quench mixture of water (130 kg), conc HCl (40 kg),

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and MTBE (50 kg) was charged. The reaction mixture was added to the quench mixture over approx 1 h and the bottom aqueous phase separated. The main organic phase was washed with 1 M HCl (50 kg) and water (50 kg) to remove residual DMF. The solution was concentrated and solvent exchanged to afford 79.2 kg of **18** as a 42.5% w/w solution in THF in 87% assay yield.

*Methyl 4-(2-(2-cyclohexylacetyl)phenoxy)-3-nitrobenzoate methyl (**17**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (1H, d, 3 Hz), 8.11 (1H, d, 8 Hz), 7.76 (1H, d, 7 Hz), 7.53 (1H, t, 6 Hz), 7.37 (1H, t, 6 Hz), 7.04 (1H, d, 8 Hz), 6.87 (1H, d, 9 Hz), 3.97 (3H, s), 2.79 (2H, d, 7 Hz), 1.91−1.82 (1H, m), 1.61−1.58 (5H, m), 1.27−1.13 (3H, m), 0.96−0.83 (2H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.9, 164.5, 154.1, 151.9, 140.0, 135.1, 133.3, 132.6, 130.5, 127.5, 126.1, 125.0, 121.1, 118.3, 52.6, 50.5, 34.0, 33.0, 26.1, 26.0. HRMS (ES) Calcd for $C_{22}H_{24}NO_6$ (MH^+) 398.1604. Found 398.1590.

*4-(1-Cyclohexyl-2-(2-hydroxyphenyl)-2-oxoethyl)-3-nitrobenzoate (**18**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.30 (1H, s), 8.43 (1H, s), 8.21 (1H, d, 9.0 Hz), 7.96−7.90 (2H, m), 7.49 (1H, t, 7.5 Hz), 6.98−6.90 (2H, m), 5.25 (1H, d, 8 Hz), 2.29 (1H, m), 1.86−1.65 (4H, m), 1.29−0.96 (6H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 205.2, 164.6, 163.1, 150.4, 137.2, 136.5, 133.3, 130.5, 130.2, 125.5, 119.9, 119.4, 118.6, 67.9, 52.75, 51.1, 43.3, 32.4, 30.0, 26.1, 26.0, 25.6. HRMS (ES) Calcd for $C_{22}H_{24}NO_6$ (MH^+) 398.1604. Found 398.1607.

*3-Cyclohexyl-2-(2-hydroxy-phenyl)-1H-indole-6-carboxylic Acid Methyl Ester (**1**).* A suspension of 20% Pd/C (5.1 kg, 50% wet type), THF solution of **18** (59.4 kg), and acetic acid (66 kg) was stirred, inerted, and subjected to hydrogen headspace pressure of 2.3 bar. The mixture was heated to 60 °C overnight until hydrogen uptake ceased. The mixture was cooled and clarified via solka floc. Three batches were combined for crystallisation and distilled to 140 L. Heptane (550 L) was charged slowly to crystallise the product and minimise liquor loss. Indole **1** was isolated by filtration, washed with heptane/DCM (2 × 40 kg, 1:1 w/w), and then dried at 60 °C in vacuo, affording **1** as a white, crystalline solid in 74% yield, 98.5 LCAP, 97.0 LCWP. Data are as reported in the literature.[14]

AUTHOR INFORMATION

Corresponding Author

*Anthony_alorati@merck.com (A.D.A.); Andrew_gibb@merck.com (A.D.G.).

Notes

The authors declare no competing financial interest.

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