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Discovery and Development of an Efficient Process to Atovaquone

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Supporting Information

ABSTRACT: The discovery and development of an efficient and more sustainable manufacturing route to the anti-pneumocystic agent atovaquone (2-((1*R*,4*R*)-4-(4-chlorophenyl)cyclohexyl)-3-hydroxynaphthalene-1,4-dione) **1** is described. The existing commercial route to atovaquone delivers a poor yield of product and uses expensive reagents. The new synthesis commences with readily available phthalic anhydride, which is converted to 1,4-isochromandione **5** and then to atovaquone **1** by reaction with 4-(4-chlorophenyl)cyclohexanecarboxylic acid **3** using key bromination, Rosenmund reduction, and rearrangement chemistries. Downstream processing to atovaquone is both high yielding and robust, and the resulting process has been demonstrated on 200-kg scale. The process is simple, uses cheap raw materials, and is more sustainable in that it avoids low-yielding silver-promoted chemistry and isomerisation procedures. It includes a robust, facile, and highly efficient procedure to 1,4-isochromandione **5**, and routes to 4-(4-chlorophenyl)cyclohexanecarboxaldehyde **9** have also been developed, including a Rosenmund method that was demonstrated on pilot-plant scale. Also discussed are the route-derived impurities and processing amendments to control their formation.

INTRODUCTION

Atovaquone is approved for marketing in the United States under the trade name Mepron for the treatment and prophylaxis of *Pneumocystis carinii* infection.[1] It is also available in combination with proguanil hydrochloride under the trade name Malarone for the treatment and prevention of *Plasmodium falciparum* malaria.

Herein is described the limitations of the current route, the new route investigation and subsequent scale-up as well as identification and control of some of the key route impurities.

RESULTS AND DISCUSSION

Existing Route to Atovaquone. The existing route to atovaquone **1**[2] proceeds by the reaction of 2-chloro-1,4-naphthoquinone **2** and 4-(4-chlorophenyl)cyclohexane-1-carboxylic acid **3** in the presence of silver nitrate and ammonium persulphate, followed by extraction with chloroform (Scheme 1). Hydrolysis of the intermediate substituted 2-chloro-1,4-napthoquinone **4** gives a low overall yield of product due to the inefficiency of the key radical coupling stage. There are other routes to atovaquone described in the literature[3] which follow a similar approach but are limited by similarly low yields or the use of non-ideal reagents, reactions, or purification conditions.

Identification of a New Route to Atovaquone 1. To address the aforementioned issues, we explored alternative approaches to the synthesis of atovaquone **1**, specifically those which avoided the use of the low-yielding radical couplings described above. The work of Estevez et al.[4] described condensation of 1,4-isochromandione **5** with benzaldehyde **6**, and the resulting lactone **7** was rearranged to the corresponding 2-hydroxynaphthoquinone **8** using sodium methoxide (Figure 1). It was unclear whether this transformation could be extended to aliphatic carboxaldehydes, given their potential for self-condensation, but if it could, then atovaquone could be prepared from the aldehyde 4-(4-chlorophenyl)cyclohexanecarboxaldehyde **9**. The aldehyde **9** has been mentioned within the literature, but a synthetic method has never been reported.[5]

To demonstrate the feasibility of the concept, a simpler model aldehyde **19** was chosen, and initial work was focused on developing a more efficient synthesis of the 1,4-isochromandione **5**. Although there are several methods described which included oxidation of 1,3-indanedione[6] and acidification of 2-diazoacetylbenzoic esters,[7] methods involving bromination of 2-acetylbenzoic acid **10** appeared the most promising for scale-up.[4,8,9] The earliest reported synthesis of **5** using this approach was by Gabriel in 1884[10] although the structure was incorrectly assigned as 3-formylphthalide **11**.[9] Evaluation of the bromination of 2-acetylbenzoic acid **10** following the conditions of Estevez[4] and Yang[8] led to incomplete reactions and the generation of benzylbromide from bromination of the toluene cosolvent. Removal of toluene gave an immediate improvement, whereby the substrate **10** was brominated in glacial acetic acid using a slight excess of bromine. Interestingly, 2-bromoacetylbenzoic acid was not observed but rather the cyclised phthalides **12**, **13**, and **14** in a ratio of 4:4:1. The reaction appears to be acid catalysed in that the rate of conversion to products increases as the hydrobromic acid byproduct forms. The importance of acid has also been confirmed with remarkably slow bromination reactions resulting when sodium acetate was used as a buffer, or when bromine was replaced with *N*-bromosuccinimide. A small quantity of water was added in order to cut down on the formation of the dibromide **13**, and it was beneficial to run the reaction with sub-stoichiometric quantities of bromine to reduce the formation of the poly-brominated byproducts (**14** and **15**). Under these new conditions,

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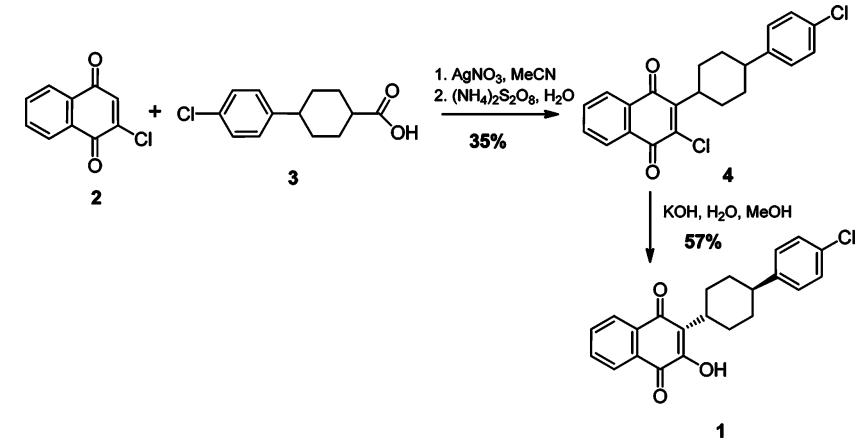
Scheme 1. Existing route to atovaquone



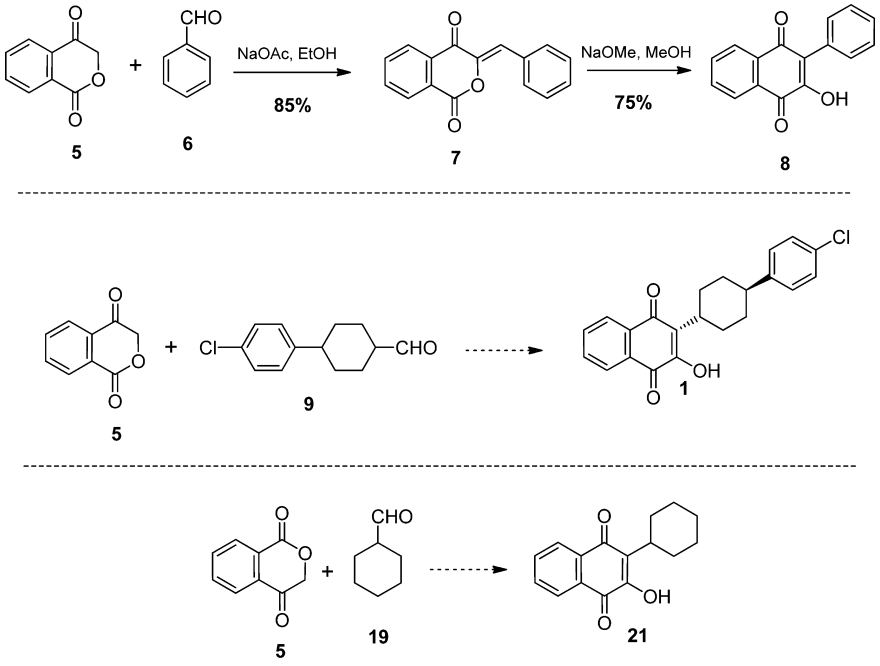


Figure 1. Preparation of 2-hydroxy-3-phenylnaphthoquinone, retrosynthetic analysis of atovaquone to 4-(4-chlorophenyl)cyclohexanecarboxaldehyde **9**, and identification of a suitable model system **19**.

reasonable levels of acetylbenzoic acid (**10**) would always remain (7−10%) with low levels of polybrominated materials persisting, highlighting the poor selectivity for this reaction. Attempts to convert the crude brominated intermediate **12** to 1,4-isochromandione **5** using sodium acetate[4,9] in methanol led to an immediate red colouration and the formation of polymeric byproduct, most notably **17**. Other buffered cyclisation conditions were evaluated, and use of dipotassium hydrogenphosphate, delivered low levels of product but this was accompanied by the formation of the condensation byproduct **16**, **17**, and **18** (Scheme 2). It was clear that 1,4-isochromandione **5** is highly reactive under these cyclisation conditions, so that another method was needed.

Returning to the original report by Gabriel,[11] the crude bromomethyl phthalides **12** and **13** were suspended in water, and the mixture was refluxed to deliver the target isochromandione **5** in poor overall yield (12%) with the dimeric compound **16** being identified as the major byproduct. Telescoping the initial bromination with an aqueous hydrolysis delivered a similar overall result, only in this instance a clean sample of the decomposition product **17** was also isolated. The formation of compounds **16** and **17** were attributed to the presence of hydrobromic acid leading to enolisation of the intended product **5** which then condensed with another molecule of **5** to deliver aldol product **16** and subsequent acid-mediated dehydration secured the diene **17**.[12]

Reaction of the key isochromandione **5** with the model carboxaldehyde **19** using the conditions highlighted by Estevez[4] delivered an excellent conversion to the aldol product **20**. Subsequent treatment with sodium methoxide in methanol proceeded to the desired naphthoquinone **21** in very good yield (Scheme 3).

The success of the model system meant that an efficient route to the isochromandione **5** was now essential, and the prohibitive cost and limited supply base for 2-acetylbenzoic acid (**10**) highlighted that a useful route to this compound would also be beneficial. Approaching these in turn, a solvent screen was conducted for the bromination of acetylbenzoic acid (**10**) which

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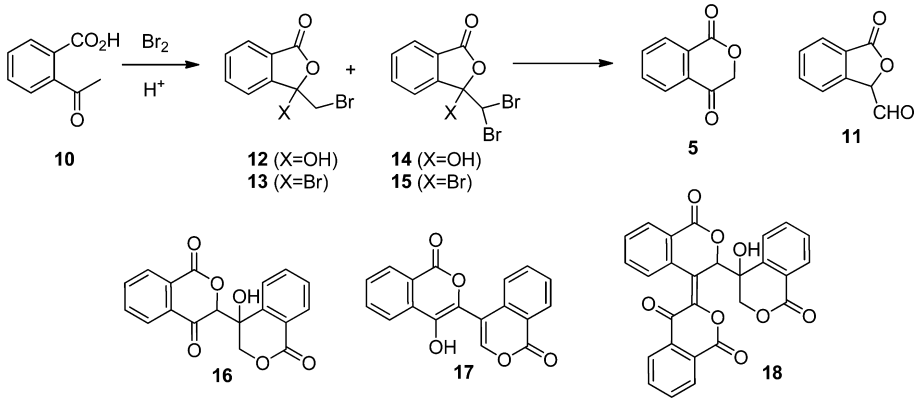
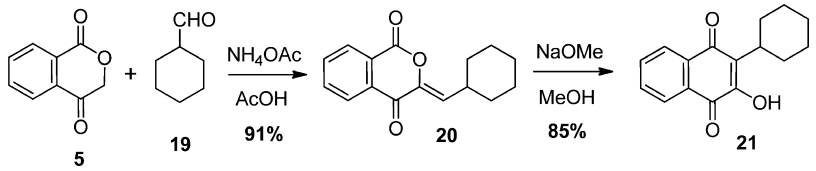
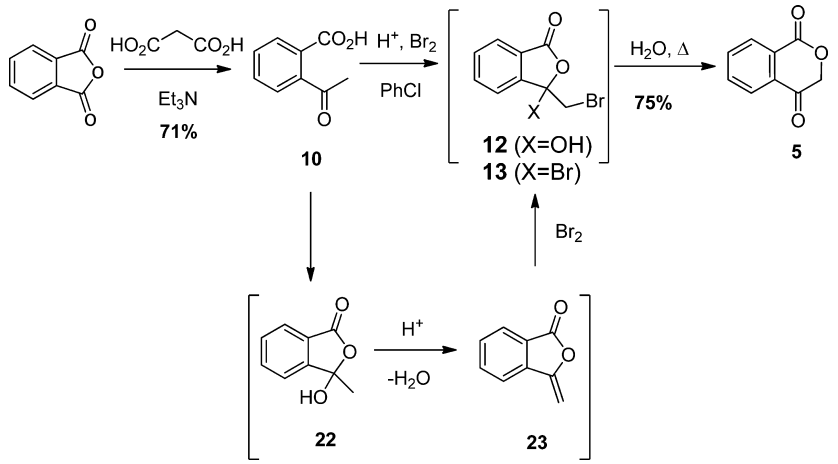
Scheme 2. Bromination of acetylbenzoic acid 10 and conversion to 1,4-isochromandione 5



Scheme 3. Reaction of 1,4-isochromandione, 5, with cyclohexanecarboxaldehyde and subsequent rearrangement to 2-cyclohexyl-3-hydroxynaphthalene-1,4-dione, 21



Scheme 4. Robust routes to 1,4-isochromandione, 5, and 2-acetylbenzoic acid, 10



highlighted that chlorobenzene was a useful solvent for this transformation. Indeed, this solvent proved remarkably beneficial in that over-bromination appeared to be inhibited and complete consumption of **10** was now possible.[13] It was also clear that the major product under these conditions was the dibromide **13** (Scheme 4). This observation, together with the remarkable selectivity and the requirement for acid catalysis, strongly advocated a mechanism whereby conversion of **10** to the isomeric 3-hydroxy-3-methylphthalide **22** is required followed by dehydration to the olefin **23** which is then brominated to give **13** as the major product. The water produced within the reaction is effectively removed as a biphase which inhibits formation of the alcohol **12** which would be needed for the polybrominated species **14** and **15** to form. It was rationalized that conducting a thermal cyclisation of this mixture under biphasic conditions might inhibit the formation of dimeric byproduct because the hydrobromic acid catalyst would be effectively removed from the system. With this in mind, once bromination was completed, water was added, and the resulting biphasic mixture was heated to reflux whereupon a rapid conversion to alcohol **12** was observed followed by a smooth conversion to the target 1,4-isochromandione, **5**. The product could then be isolated in very good yield following a simple extraction, evaporation, and crystallization procedure. This process was ultimately exemplified on pilot-plant scale where a total of 250 kg of **5** was prepared.

There are several routes described in the literature for the preparation of 2-acetylbenzoic acid **10**, but for this work we focused on those involving phthalic anhydride and malonic acid as they were the most cost-effective. These materials have been reacted together using pyridine,[14] and triethylamine,[15,16] as solvent/bases, and there is a report where various solvent/base combinations were evaluated for this transformation.[17] Evaluation of these conditions highlighted that using triethylamine as solvent and base gave the cleanest conversion to **10**. The final process was based on the conditions reported by Rangnekar and Telange,[15] where malonic acid was added in portions to a

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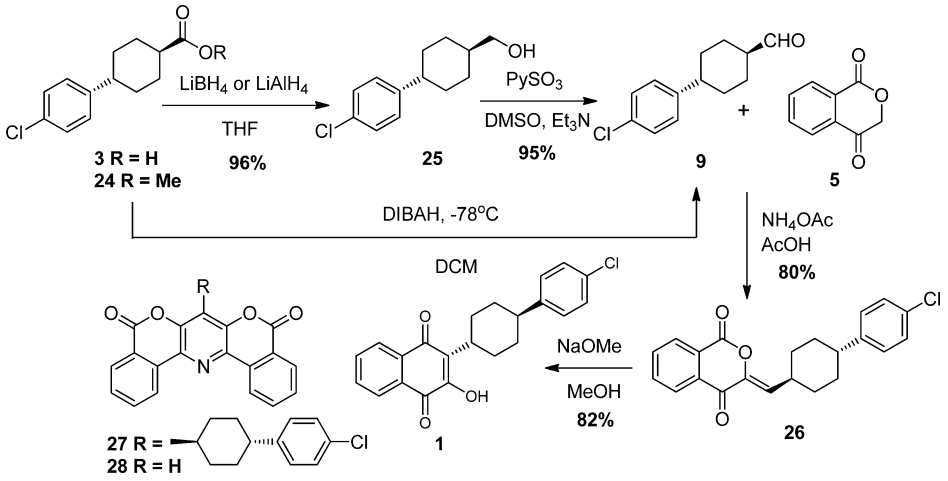
Scheme 5. Initial routes to 4-(4-chlorophenyl)cyclohexanecarboxaldehyde 9 and conversion to atovaquone 1



suspension of phthalic anhydride in triethylamine at 80 °C; subsequent acid-mediated hydrolysis and crystallization gave good yields of pure product without the need for further purification. This process was exemplified in the pilot plant where a total of 350 kg of **10** was prepared.

Having secured a route to the key 1,4-isochromandione **5** and exemplified the feasibility of the new route to atovaquone from a successful model study, it was now important to prepare the relevant carboxaldehyde **9**. Given that the existing manufacturing route to atovaquone used 4-(4-chlorophenyl)cyclohexanecarboxylic acid **3** and that both this acid and it is methyl ester **24** are known,[18,19] it seemed appropriate to use these molecules as starting points for the synthesis of the aldehyde **9**. Treatment of the ester **24** with lithium borohydride, or lithium aluminium hydride, in tetrahydrofuran gave the corresponding alcohol **25** in excellent yield which was in turn converted through to the target aldehyde **9** using the modified Swern conditions[20] of pyridine sulfur trioxide in dimethylsulfoxide. A more direct route to this aldehyde could be achieved by reacting ester **24** with diisobutylaluminium hydride, although this approach did require low-temperature conditions and was always accompanied by some over-reduction to the alcohol **25**. Subsequent condensation of the carboxaldehyde **9** with isochromandione **5** gave an excellent yield of the corresponding conjugated ketone **26** which rearranged to atovaquone on treatment with sodium methoxide. The aldehyde **9** proved difficult to handle, given that it was a low-melting solid and susceptible to further oxidation to the acid **3**. With this in mind, the processes to the aldehyde **9** were further modified such that **9** was not isolated but rather used as a solution within the next stage. The resulting atovaquone derived from this process proved of reasonable purity, but a new impurity was observed at low level (approximately 0.4%) which was ultimately characterised as the pyridine **27**. The dibenzopyranopyridine motif in **27** appears to be a novel ring system and looks to have formed from the condensation of a molecule of the isochromandione **5** with the unsaturated ketone **26** and ammonia. Indeed, heating the isochromandione **5** with the unsaturated ketone **26** in the presence of ammonium acetate in an acetic acid/toluene mixture led to the target pyridine **27** being prepared albeit in low yield. Also formed during this process was the pyridine **28** which appeared to have been formed from the condensation of two molecules of **5** with ammonia and "formaldehyde" although the mechanism for this transformation is not clear. Attempts to remove the dibenzopyranopyridine impurity **27** from **1** using crystallization proved unsuccessful; therefore, alternative amines were screened to avoid its future formation. For early development work, morpholine proved to be a useful alternative, but this was ultimately replaced by isobutylamine which gave superior yields (Schemes 5 and 7).

The methoxide-induced chemistry where the lactone **26** is converted through to **1** proved to be more complex than was initially thought. HPLC analysis of the reaction mixture showed the rapid conversion into the intermediate methyl ester **29** as expected, as well as the hydrolysis product **30**, but the lactone **31** was also formed. On continued reaction it became apparent that both the ester **29** and lactone **31** were converted slowly through to the target product **1**, whereas the hydrolysis product **30** took no further part within the reaction. Further evidence for the rapid formation of the intermediates followed by slower conversion into product **1** was obtained from ReactIR data (Figure 2).

Authentic samples of intermediates **29** and **31** were readily accessed from methanolysis of the lactone **26** using dimethylaminopyridine in methanol with and without toluene as a cosolvent, respectively. Both of these materials were individually reacted with sodium methoxide to give **1** in excellent yields. Formation of the hydrolysis product **30** was attributed to residual water; however, unlike intermediates **29** and **31**, **30** does not convert to **1** under the reaction conditions, so the removal of water became key to obtaining high yields for this chemistry. A standard of **30** was easily prepared by reacting the lactone **26** with potassium hydroxide in methanol whereby an 86% yield of the hydrolysis product was obtained (Scheme 6).

Replacing sodium methoxide with sodium ethoxide for the conversion of the lactone **26** to **1** was also successfully demonstrated, although the rate of this reaction was significantly reduced, presumably due to steric factors. Therefore, this alternative reagent was not pursued further.

Having demonstrated the new route to **1**, alternative approaches to the key aldehyde **9** were considered as the routes described above required expensive reagents and complicated processing. The classical Rosenmund reduction[21] was of particular interest, given the availability of 4-(4-chlorophenyl)-cyclohexanecarboxylic acid **3**. Also the conversion of carboxylic acids to their acid chlorides is typically clean and high yielding, and catalytic hydrogenations are generally simple and atom-efficient processes. Therefore, this kind of approach should simplify the process to deliver **9**. Initial work to prepare the acid chloride **32** from acid **3** demonstrated that oxalyl chloride with

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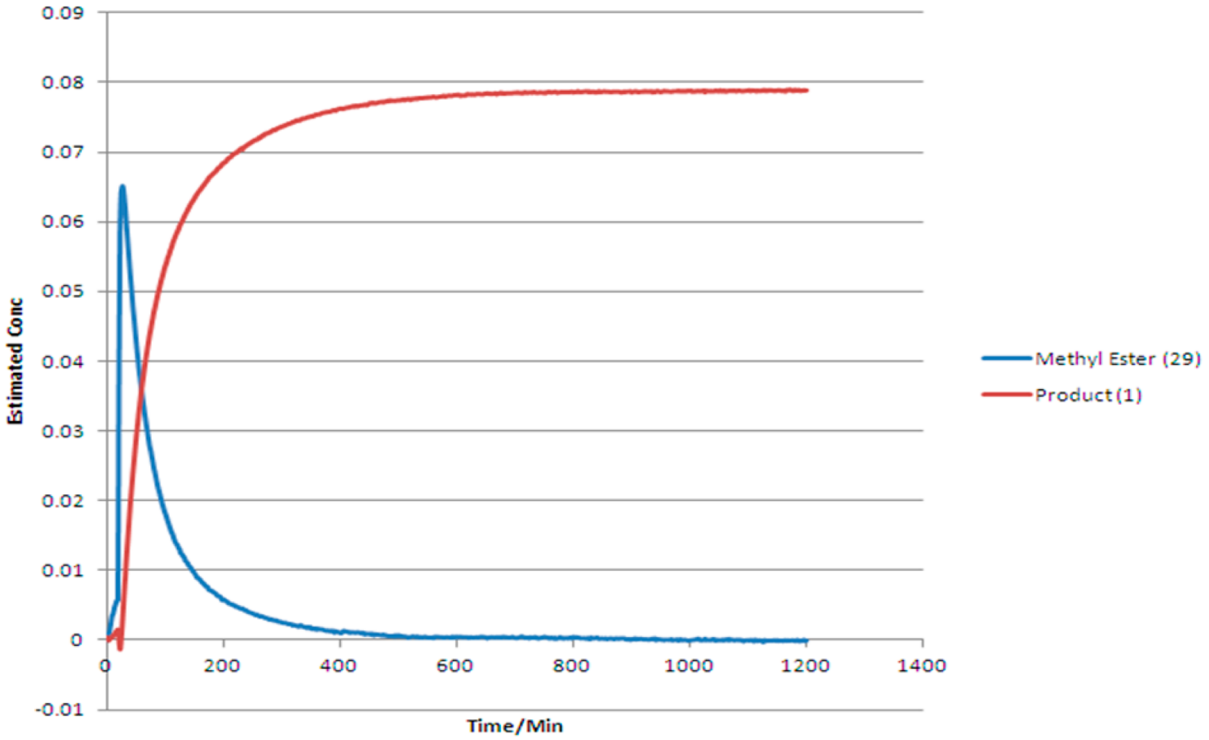
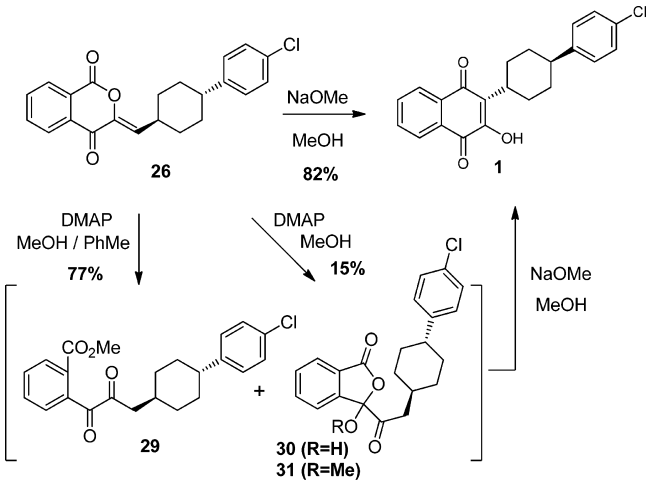


Figure 2. React IR profile showing the formation of the methyl ester **29** and its conversion through to atovaquone **1**.

Scheme 6. Rearrangement of lactone 26 to atovaquone 1 and respective intermediates



catalytic DMF gave a smooth conversion to product.[22] Standard palladium on charcoal proved a superior choice to the classic poisoned palladium on barium sulfate catalyst due to the relative stability of the aliphatic acid chloride. 2,6-Lutidine was used as the base such that conversion to product **9** could be delivered.[23] It was, however, necessary to carry out a carbon treatment of the input acid chloride solution prior to hydrogenation, in order to avoid catalyst poisoning and reaction stalling. Careful control of the reaction time was required in order to control the competing reduction of the aromatic chloride which resulted in the persisting des-chloro impurity. Initial attempts to minimize this over-reduction focused on choice of metal catalyst as well as loading, but while it was possible to improve the selectivity and achieve a reaction which gave product of the required purity, the robustness was not sufficient to allow routine operation. Therefore, alternative solutions were sought. A range of organic and inorganic bases were screened in this chemistry. Interestingly, we found that the choice of base had a significant effect on the rate of dechlorination compared to the desired reaction, with good correlation between pK_a of the base and the extent of dechlorination. Stronger bases (such as triethylamine) gave increased dechlorination, whereas weaker bases suppressed this side reaction. If the base was too weak, the rate of desired reaction was unacceptably slow, as was observed with 2,6-di-*tert*-butylpyridine and tetramethylpyrazine. However, it was found that the slightly less basic 2-methylquinoline (quinaldine) gave a good compromise, leading to a very clean and robust reaction. Gratifyingly, it was also found that the catalyst system with quinaldine as base was not susceptible to poisoning from the crude acid chloride input, contrary to what was seen when 2,6-lutidine was used. It was therefore unnecessary to carry out a carbon treatment prior to hydrogenation, and this step was removed from the process. The reaction also proved to be hampered by the presence of water which leads to the formation of the symmetrical anhydride **33** and can have a profound impact on yield. With this in mind, it was necessary to use anhydrous catalyst, and excellent conversion to product could be achieved under these conditions. Once again, it proved beneficial to telescope the chemistry such that isolation of the highly air-sensitive aldehyde **9** was avoided (Scheme 7).

The use of thionyl chloride rather than oxalyl chloride for the Rosenmund chemistry looked economically attractive. Unfortunately, in our hands the resulting hydrogenation of acid chloride **32** derived from reacting **3** with thionyl chloride was retarded significantly, possibly due to catalyst poisoning. After optimization of the acid chloride formation, Rosenmund reduction, and condensation sequence key lactone **26** was prepared in 81% overall yield on pilot-plant scale.

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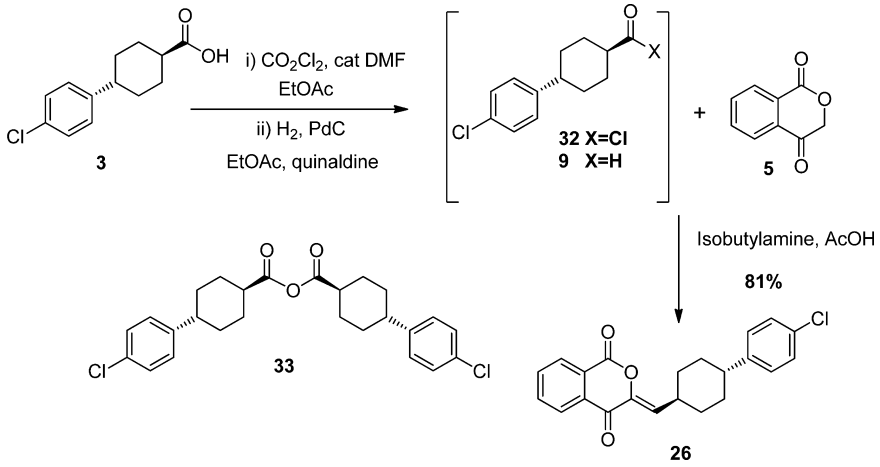
Scheme 7. Rosenmund route to 4-(4-chlorophenyl)cyclohexanecarboxaldehyde, 9



SUMMARY

To conclude, a sustainable manufacturing route to atovaquone has been discovered and developed which is robust and higher yielding than the original supply route in that atovaquone **1** is delivered in a total yield of 71% from carboxylic acid **3** compared to 20% from the existing route using a comparable number of steps. The new route also has significant sustainability advantages, with a demonstrated mass efficiency of 1.50%, which is expected to rise to 2.03% with solvent recovery, compared to 0.93% for the current manufacturing route[24] (see Scheme 8). The new synthesis exemplifies classical bromination and Rosenmund chemistries whilst also taking advantage of a key rearrangement to provide atovaquone. In addition, the utility of the under-utilized but highly effective Rosenmund reduction as a tool in the preparation of aldehydes on a large scale is described.

EXPERIMENTAL SECTION

General. Commercially available reagents were used without further purification. Reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen. 4-(4-Chlorophenyl)cyclohexanecarboxylic acid and it is methyl ester were obtained commercially from custom synthesis suppliers. The experimental conditions below refer to the procedures used for the multikilogram pilot-plant campaign. Key NMR spectra are included within the Supporting Information.

*2-Acetyl Benzoic Acid/3-Hydroxy-3-methylisobenzofuran-1(3H)-one (**10/22**).* A stirred mixture of phthalic anhydride (170 kg, 1.15 kmol) and triethylamine (171 kg, 1.23 kmol) were heated to 80 °C. Ten equal portions of malonic acid (10 × 14.4 kg; 144 kg total, 1.38 kmol) were charged over a period of 4 h, and the reaction mixture was maintained at 80 °C for a further 10 h. Hydrochloric acid (4 M, made up from 365 kg of concentrated aqueous hydrochloric acid and 530 kg of water) was charged and the reaction stirred for a further 30 min at 80 °C before being cooled to 25 °C, and the resulting slurry was filtered. The damp cake was washed with water (2 × 340 kg) and then dried under vacuum at 50 °C to give the title compound as light-brown crystals (126 kg, 67% th yield, 98.7% a/a HPLC purity); ^{1}H NMR (700 MHz, DMSO): δ_H 2.51 (3H, s, CH_3), 2.47 (1H, br s, O*H*) 7.52−7.70 (2H, m), 7.79−7.80 (2H, d); ^{13}C NMR (100 MHz, DMSO): δ_C 26.0, 106.4, 122.4, 124.4, 130.2, 134.6, 150.4 and 167.8; HRMS (positive ion electrospray, MH^+) calculated for $C_9H_9O_3$ 165.0546, found 165.0644.

*1,4-Isochromandione (**5**).* A stirred mixture of 2-acetylbenzoic acid **10** (82 kg, 500 mol) and chlorobenzene (905 kg, 820 L) was treated with 5.5 M hydrobromic acid in acetic acid (5 L) and bromine (25.2 L, 78.6 kg, 492 mol) and then warmed to approximately 30 °C. After 3 h, water (820 L) was added and the reaction heated to reflux. After 3 h the reaction was cooled to 60 °C and the organic layer removed. The aqueous layer was extracted with chlorobenzene (364 kg, 328 L), and the combined organic layers were concentrated under reduced pressure to approximately 260 L. Propan-2-ol (322 kg, 410 L) was charged, and the slurry was cooled to 0 °C and filtered. The damp cake was washed with propan-2-ol (128 kg, 163 L then a further 64 kg, 82 L) and then dried under vacuum at 50 °C to give the title compound as pale-yellow/brown crystals (59 kg, 73% th yield, 100% a/a HPLC purity); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.14 (2H, s), 7.83−7.91 (2H, m), 8.08−8.10 (1H, m), 8.28−8.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 73.4, 125.6, 128.0, 130.9, 131.8, 134.6, 135.9, 161.3, and 189.5; HRMS (APCI, negative ion, $[M-H]^-$) calculated for $C_9H_5O_3$, 161.0244, found 161.0241.

*4′-Hydroxy-3′,4′-dihydro-1H,1′H-3,4′-bi-2-benzopyran-1,1′,4(3H)-trione (**16**).* Isochromandione **5** (10 g, 61.7 mmol) was suspended in THF (50 mL), stirred under nitrogen, and 10% aqueous potassium hydrogen carbonate (1 m L) added. The mixture was stirred overnight at room temperature and then clarified by filtration. The solution was concentrated at reduced pressure to give a brown oil. Trituration with THF (10 mL) and TBME (10 mL), filtration, and drying under vacuum gave the title compound as a cream-colored solid (6.6 g, 67% yield): ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.31 (1H, d), 4.50 (1H, d), 5.33 (1H, s), 6.57 (1H, s, exchangeable), 7.60−7.66 (2H, m), 7.81−7.84 (1H, m), 7.94−8.01 (3H, m), 8.05 (1H, d), 8.18 (1H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 68.9, 71.4, 84.6, 122.7, 125.1, 127.1, 128.1, 129.0, 129.4, 129.5, 132.5, 133.5, 134.6, 135.7, 142.7, 161.5, 163.4, 190.0; HRMS (positive ion electrospray, MH^+) calculated for $C_{18}H_{13}O_6$ 325.0712, found 325.0719.

*4-Hydroxy-1H,1′H-3,4′-bi-2-benzopyran-1,1′-dione (**17**).* Isochromandione **5** (10 g, 61.7 mmol) was suspended in acetic acid (30 mL) with stirring under nitrogen, and isobutylamine (1 mL, 10 mmol) was added *after which there was some fuming.* The reaction mixture was heated to 100 °C for 18 h. The mixture was cooled to room temperature and the product collected by filtration, washed with acetic acid (10 mL), and then dried under vacuum at 50 °C to give the title compound as a pale-yellow solid

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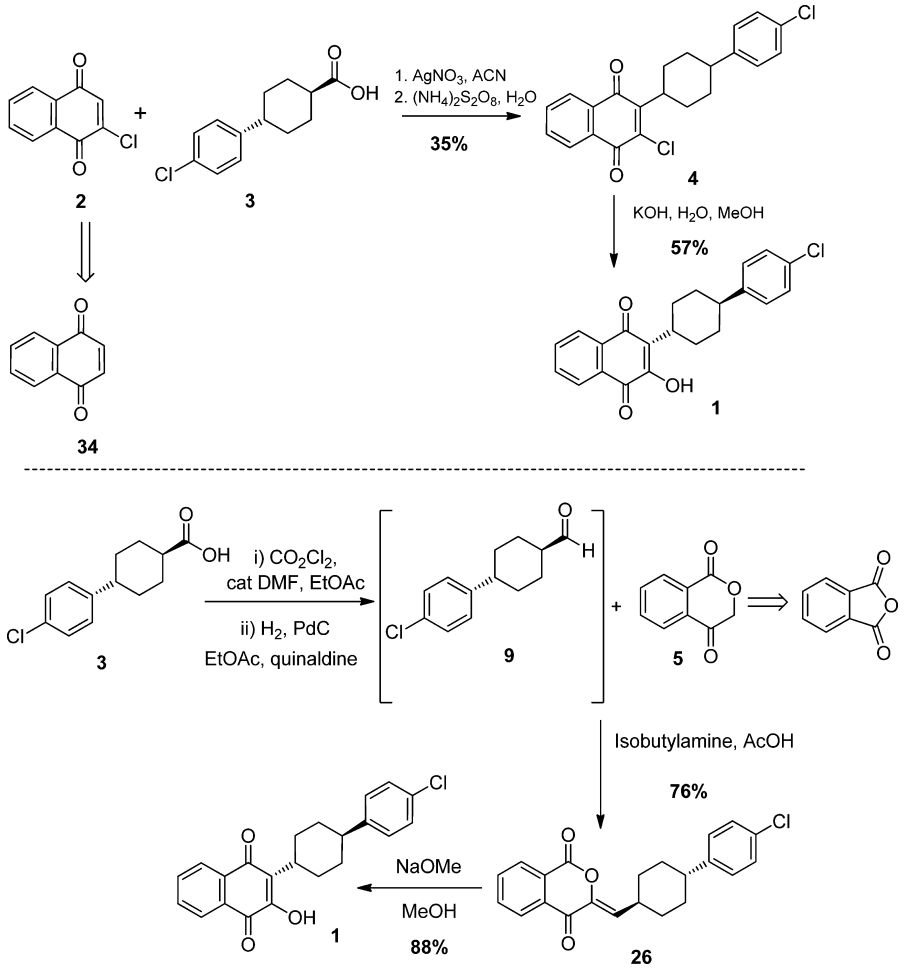
Scheme 8. Comparison of existing manufacturing route to atovaquone 1 with new process



(6.7 g, 71%): ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.61 (1H, d), 7.68−7.75 (2H, m), 7.88 (1H, m), 7.93 (1H, s), 7.94−8.00 (2H, m), 8.23 (1H, d), 8.27 (1H, d), 9.19 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 110.1, 120.6, 120.9, 122.2, 124.6, 129.1, 129.1, 129.2, 129.3, 131.1, 134.5, 135.0, 135.4, 135.5, 135.6, 148.0, 160.7, 160.9; HRMS (positive ion electrospray, MH^+) calculated for $C_{18}H_{11}O_5$ 307.0601, found 307.0605.

*(Z)-3-(Cyclohexylmethylene)isochroman-1,4-dione (**20**).* 1,4-Isochromandione **5** (4 g, 24.67 mmol) was suspended in acetic acid (30 mL), cyclohexane carboxaldehyde **19** (3.1 mL, 25.9 mmol) was added, and the mixture was treated with a slurry of ammonium acetate (2 g, 25.9 mmol) in acetic acid (10 mL) at 35 °C. The suspension was heated to 55 °C and stirred for 15 h during which period a solid was precipitated. The suspension was diluted with water (40 mL) and stirred for 10 min. The solid was collected by filtration under vacuum, washed with water (3 × 20 mL), and pulled dry to give the title compound (5.73 g, 91%) as a pale-yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H1.16−1.32 (m, 3H), 1.33−1.48 (m, 2H), 1.65−1.83 (m, 5H), 2.89 (q, J = 10.7, 1H), 6.39 (d, J = 10.0, 1H), 7.79−7.91 (m, 2H), 8.19−8.27 (m, 1H), 8.28−8.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 25.3, 25.8, 31.8, 34.6, 126.7, 127.4, 130.6, 131.4, 133.5, 134.8, 135.0, 145.1, 158.7, 176.7.

*2-Cyclohexyl-3-hydroxynaphthalene-1,4-dione (**21**).* (*Z*)-3-(Cyclohexylmethylene)isochroman-1,4-dione **20** (3 g, 11.71 mmol) was suspended in methanol (18 mL), sodium methoxide (3.2 mL, 14.05 mmol) was added, and the mixture was stirred at room temperature for 23 h. The red solution was treated with acetic acid (2 mL, 35.1 mmol), but no solids precipitated, and a red solution persisted. The dark solution was diluted with water (18 mL), whereby a yellow solid precipitated, and the suspension was stirred for 10 min. The solid was collected by filtration under vacuum, washed with water (3 × 20 mL), and pulled dry to give the title compound as a yellow solid (2.55 g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.23−1.46 (m, 3), 1.56−1.67 (m, 2H), 1.68−1.77 (m, 1H), 1.76−1.87 (m, 2H), 1.98 (qd, J = 12.4, 2.9, 2H), 3.08 (tt, J = 12.3, 3.5, 3.4, 1H), 7.45 (s, 1H), 7.66 (td, J = 7.6, 1.2, 1H), 7.74 (td, J = 7.6, 1.2, 1H), 8.06 (dd, J = 7.6, 1.2, 1H), 8.11 (dd, J = 7.8, 1.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 26.0, 26.7, 29.2, 35.2, 125.9, 126.9, 127.9, 129.2, 132.7, 133.2, 134.9, 152.8, 181.9, 184.6.

*[trans-4-(4-Chlorophenyl)cyclohexyl]methanol (**25**).* Lithium borohydride (2.0 g, 91.8 mmol) was added to a stirred solution of methyl ester **24** (20.0 g, 79.1 mmol) in tetrahydrofuran (50 mL) at ambient temperature under argon; the reaction mixture was heated to reflux and stirred for 2 h. The reaction mixture was carefully quenched with 1 M aqueous hydrochloric acid (50 mL, 50 mmol), and then ethyl acetate (50 mL) was added. The aqueous was separated and extracted with ethyl acetate (50 + 25 mL), and then the combined organics were washed with water (50 mL) and brine (20 mL). The resulting organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the title compound as a pale-yellow oil which crystallised on standing to give a cream-colored solid (17.1 g,

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96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.07−1.17 (2H, m), 1.33−1.35 (1H, m), 1.39−1.49 (2H, m), 1.52−1.61(1H, m), 1.91−1.94 (4H, m), 2.42−2.50 (1H, d), 3.50−3.53 (2H, m), 7.12−7.14 (2H, m), 7.24−7.26 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 29.7, 33.6, 40.1, 44.0, 68.5, 128.2, 128.4, 131.5, 145.9; HRMS (APCI, negative ion, $[M - H]^-$) calculated for $C_{13}H_{16}ClO$ 223.0895, found 223.0894.

*trans-4-(4-Chlorophenyl)cyclohexanecarbaldehyde (**9**).* Triethylamine (2.2 mL, 16 mmol) was added to a stirred solution of alcohol **25** (0.9 g, 4 mmol) in dimethyl sulfoxide (4 mL) at ambient under argon. A solution of pyridine sulphur trioxide complex (1.27 g, 8 mmol) in dimethyl sulfoxide (8 mL) was added and the reaction mixture stirred at ambient for 1 h. The stirred reaction mixture was cooled to 15 °C, and then water (30 mL) and ethyl acetate (10 mL) were added. The organic layer was separated, diluted by the addition of ethyl acetate (20 mL), and washed with water (20 mL), 1 M aqueous hydrochloric acid (20 mL, 20 mmol), and 50% saturated aqueous brine (20 mL). The resulting organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum to give the title compound as an oily solid (852 mg, 95%);[25,26] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.37−1.53 (4H, m), 2.00−2.02 (2H, m), 2.11−2.14 (2H, m), 2.25−2.33 (1H, m), 2.45−2.51 (1H, m), 7.11−7.15 (2H, m) and 7.25−7.28 (2H, m), 9.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 26.2, 32.9, 43.2, 49.8, 128.1, 128.5, 131.8, 145.1, and 204.2; HRMS (APCI, negative ion, $[M - H]^-$) calculated for $C_{13}H_{14}ClO$ 221.0739, found 221.0739.

If necessary, further purification could be achieved in the following manner. Crude aldehyde **9** (600 mg, 2.7 mmol) was suspended in *n*-heptane (2 mL) with stirring at ambient temperature. The resulting solution was cooled to −5 °C and the resulting slurry stirred for 30 min at −5 °C. The slurry was filtered, and then the filter cake was washed with cold, −5 °C, *n*-heptane (2 mL) and dried to give the title compound as a white solid (360 mg, 60%).

*(3Z)-3-{[trans-4-(4-Chlorophenyl)cyclohexyl]methylidene}-1H-2-benzopyran-1,4(3H)-dione (**26**).* Isochromandione **5** (0.51 g, 3.13 mmol) and ammonium acetate (0.24 g, 3.13 mmol) were added to a stirred solution of the carboxaldehyde **9** (0.87 g, 3.13 mmol) in acetic acid (5 mL). The mixture was heated to 60 °C, stirred for 1.5 h, and then cooled to ambient. Water (5 mL) was added dropwise to the stirred mixture. The yellow solid was collected by filtration under vacuum, washed with water (2 × 5 mL) and TBME (10 mL), and then dried to give the title compound as a pale-yellow solid (0.83 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.38−1.48 (2H, m), 1.53−1.64 (2H, m), 1.93−1.98 (4H, m), 2.48−2.56 (1H, m), 2.88−3.00 (1H, m), 6.40 (1H, d, J = 10.0), 7.15 (2H, m), 7.27 (2H, m), 7.85−7.89 (2H, m), 8.24 (1H, m), 8.33 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 31.2, 33.2, 34.3, 43.1, 113.6, 126.8, 128.1, 128.2, 128.5, 128.5, 130.6, 130.7, 133.4, 135.0, 135.1, 145.5, 158.6 and 176.7; HRMS (APCI, negative ion, $[M + e]^-$) calculated for $C_{22}H_{19}ClO_3$ 366.1028, found 366.1028.

A second crop of material was available from the filtration liquors by dilution with 2-methyltetrahydrofuran (5 mL), separation of the aqueous phase, and extraction with 2-methyltetrahydrofuran (5 mL). The combined organic phases were dried ($MgSO_4$), the solvent was removed under vacuum and the residual oil triturated with TBME (5 mL), giving the title compound as a pale-yellow solid (90 mg, 8%).

*Reduction/Swern Oxidation Route to (3Z)-3-{[trans-4-(4-Chlorophenyl)cyclohexyl]methylidene}-1H-2-benzopyran-1,4(3H)-dione (**26**).* A 1 M solution of lithium aluminium hydride in tetrahydrofuran (100 mL, 100 mmol) was added to a stirred solution of methyl *trans*-4-(4-chlorophenyl)cyclohexanecarboxylate **24** (50.5 g, 200 mmol) in tetrahydrofuran at 0 °C under argon and the mixture stirred for 30 min. The reaction mixture was cooled to 0 °C, 1 M aqueous hydrochloric acid (500 mL, 500 mmol) was carefully added, and the mixture stirred for 5 min. The aqueous was separated and extracted with ethyl acetate (250 mL), and then the combined organic phases were washed with water (2 × 125 mL). The resulting organic phase was concentrated under vacuum to a volume of approximately 150 mL, ethyl acetate (250 mL) was added and the mixture concentrated under vacuum to a volume of 150 mL. This "put and take" procedure was repeated a two more times. Dimethyl sulfoxide (100 mL) and triethylamine (112 mL, 804 mmol) were added to the stirred mixture, at ambient temperature under argon, and the mixture was cooled to 0 °C. Pyridine sulphur trioxide complex (64 g, 402 mmol) was added in 4 equal portions, and the reaction mixture stirred between 0 and 20 °C for 2 h. Ethyl acetate (400 mL) was added, the mixture was cooled to 0 °C with stirring, and 1 M aqueous hydrochloric acid (400 mL, 400 mmol) was added. The resulting mixture was stirred at ambient temperature for 5 min, and then the organic layer was separated, diluted by the addition of ethyl acetate (500 mL), and washed with water (250 mL). The resulting organics were concentrated under vacuum to a volume of 200 mL, the residue was diluted by the addition of ethyl acetate (500 mL), and then concentrated to a volume of 200 mL. Acetic acid (250 mL), isochromandione **5** (32.4 g, 200 mmol), and morpholine (17.5 mL, 200 mmol) were added to the resulting stirred mixture, at room temperature under argon. The reaction mixture was heated to 40 °C and stirred for 4 h and allowed to cool to ambient and stir overnight. Water (250 mL) was added and the slurry stirred for 15 min and then filtered. The filter cake was washed with TBME (2 × 125 mL) and dried to give the title compound as a yellow solid (62.4 g, 85%). This material was spectroscopically identical to that reported above.

*DIBAH Route to (3Z)-3-{[trans-4-(4-Chlorophenyl)-cyclohexyl]methylidene}-1H-2-benzopyran-1,4(3H)-dione (**26**).* A 1 M solution of diisobutylaluminium hydride in dichloromethane (110 mL, 110 mmol) was added to a stirred solution of methyl *trans*-4-(4-chlorophenyl)cyclohexanecarboxylate **24** (25.3 g, 100 mmol) in dichloromethane at −78 °C under argon, and the mixture was stirred for 90 min. Methanol (125 mL) was added to the stirred mixture which was allowed to warm to −10 °C after which 1 M aqueous hydrochloric acid (250 mL, 250 mmol) was added. The aqueous layer was extracted with dichloromethane (250 mL), and the combined organics were washed twice with water (2 × 125 mL). The organics were concentrated under vacuum to a volume of 75 mL, the residue was diluted by the addition ethyl acetate (125 mL), and the mixture was then concentrated under vacuum to a volume of 75 mL. Acetic acid (125 mL), isochromandione **5** (16.2 g, 100 mmol), and ammonium acetate (7.7 g, 100 mmol) were added to the resulting stirred mixture, at ambient temperature under argon. The reaction mixture was then heated to 60 °C and distilled for 2 h. The resulting slurry was cooled to ambient temperature; water (75 mL) was added, stirred for 30 min, and then filtered. The filter cake was washed with TBME (62.5 mL) and dried to give the title compound as a yellow solid (24.8 g, 68%). This material was spectroscopically identical to that reported above.

*Rosenmund Route to (3Z)-3-{[trans-4-(4-Chlorophenyl)-cyclohexyl]methylidene}-1H-2-benzopyran-1,4(3H)-dione (**26**).* A suspension of 4-(4-chlorophenyl)cyclohexane-1-carboxylic

acid (**3**) (50.0 kg) in ethyl acetate (300 L) with catalytic DMF (82.5 mL) was heated to 55 °C, and oxalyl chloride (19.5 L) was added, followed by a line wash of ethyl acetate (30 L). This mixture was stirred at 55 °C until all solids had dissolved and reaction was complete. The mixture was distilled down to 150 L and cooled to 20 °C, and quinaldine (39.8 L) was added, followed by a line wash of ethyl acetate (30 L). The mixture was transferred to a hydrogenation vessel containing 5% Pd/C (3 kg), followed by a line wash of ethyl acetate (250 L). The reaction mixture was stirred under hydrogen gas at 20 °C until reaction was complete. The mixture was filtered to remove the catalyst, washing with ethyl acetate (150 L) and charged to a separate vessel. 1,4-Isochromandione (**5**) (32.6 kg) was added, washing with ethyl acetate (30 L) followed by addition of acetic acid (150 L) and isobutylamine (56.5 L) and a line wash of ethyl acetate (30 L). The mixture was heated to 38 °C and stirred at this temperature until reaction was complete and cooled to 20 °C. The product was collected by filtration, washing with isopropanol (2 × 125 L) before drying under vacuum at 70 °C to give the title compound as a white solid (62.2 kg, 81% th yield, 99.6% a/a HPLC purity).[27] This material was spectroscopically identical to that reported above.

*2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione (**1**).* A 30 wt % solution of sodium methoxide in methanol (37.0 kg, 205 mol) was added to a stirred suspension of **26** (60.45 kg, 165 mol) in methanol (233 kg) at 20 °C. The solids rapidly dissolved, and the resulting dark-red solution was stirred at 20 °C for 18 h or until conversion to **1** was complete.[28] The solution was added *via* an in-line filter to a stirred solution of acetic acid (94.0 kg, 1.57 kmol) and methanol (143 kg) in water (12.0 kg) at ambient using a line rinse of methanol (50 kg) with the precipitation of a bright-yellow solid. The solid was collected in a filter dryer, washed with a mixture of methanol and water (2 × 108 kg, 1:1 v/v) and methanol (96 kg), and then dried at 40 °C to give the title compound as a bright-yellow solid (51.85 kg, 85.8% th yield, 98.9% a/a HPLC purity): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.48−1.64 (2H, m), 1.71−1.78 (2H, m), 1.92−2.02 (2H, m), 2.13−2.25 (2H, m), 2.64 (1H, m), 3.17 (1H, m), 7.18 (2H, d), 7.27 (2H, d), 7.48 (1H, s, O*H*), 7.68 (1H, m), 7.76 (1H, m), 8.08 (1H, d) and 8.14 (1H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 29.2, 34.4, 34.5, 43.2, 126.0, 127.0, 127.3, 128.2, 128.4, 129.2, 131.5, 132.8, 133.2, 135.0, 146.0, 153.0, 181.8, 184.5; HRMS (APCI, negative ion, $[M - H]^-$) calculated for $C_{22}H_{18}ClO_3$ 365.0950, found 365.0951.

*7-[4-(4-Chlorophenyl)cyclohexyl]-5H,9H-bis[2]benzopyrano[3,4-e:4′,3′-b]pyridine-5,9-dione (**27**).* A suspension of **5** (2.60 g, 16.03 mmol), **26** (5 g, 13.63 mmol), and ammonium acetate (1.20 g, 15.57 mmol) in toluene (100 mL) and acetic acid (10 mL) was heated to 100 °C (hot bath at 110 °C) and stirred for 24 h. All solids dissolved during the heating-up period, and some precipitation was seen during the reaction. The reaction mixture was allowed to cool to ambient with the precipitation of a grey solid. The mixture was aged for 1 h and filtered, and the residue was washed with toluene (2 × 10 mL) and then pulled dry to give the title compound as a grey solid containing a quantity of 5*H*,9*H*-bis[2]benzopyrano[3,4-*e*:4′,3′-*b*]pyridine-5,9-dione (**28**) (approximately 25%) (wt = 0.92 g).

The filtrate was evaporated under vacuum and the residue triturated with acetone to afford a second crop of product as an orange solid (wt = 0.23 g).

Both solid residues were combined, suspended in acetonitrile (20 mL), and heated to reflux. The suspension was stirred at reflux for 30 min and cooled to 40 °C, and the solid was collected by filtration and washed with acetonitrile (2 × 2 mL) to give the title compound and pyridine **28** as a grey solid (1.06 g). Further purification was achieved by suspending the crude **27** and **28** (0.50 g) in DMSO (10 mL), stirring, and heating to 110−120 °C. The resulting suspension was cooled to ambient and the solid collected by filtration under vacuum, washed with DMSO (2 mL) followed by methanol (2 × 3 mL), and dried to give a grey solid consisting of **27** and **28** in a ratio of 2.3:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.75 (2H, m), 1.93 (2H, m), 2.06 (2H, m), 2.58 (2H, m), 2.87 (1H, m), 3.80 (1H, m), 7.22 (2H, m), 7.31 (2H, m), 7.74 (1H, m), 7.98 (1H, m), 8.42 (2H, m), 8.86 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 29.6, 34.2, 34.8, 43.0, 121.9, 123.8, 128.3, 128.5, 130.1, 130.6, 130.9, 131.6, 133.1, 135.3, 135.6, 145.8, and 159.7; HRMS (positive ion electrospray, MH^+) calculated for $C_{31}H_{23}ClNO_4$, calculated mass 508.1316, found 508.1313.

*Methyl 2-{3-[4-(4-Chlorophenyl)cyclohexyl]-2-oxopropanoyl}benzoate (**29**).* A suspension of **26** (250 g, 681 mmol) and dimethylaminopyridine (8.33 g, 68.1 mmol) in toluene (2.5 L) and methanol (250 mL) was heated to 67 °C and stirred at this temperature for 4 h and cooled to ambient, and water (1.25 L) was added followed by hydrochloric acid (11.4 mL, 136 mmol). The mixture was stirred for 5 min, the aqueous phase was removed, and the organic phase was washed with water (750 mL). The aqueous phase was removed, and the solvent was removed by distillation until an internal volume of 750 mL was reached. The solution was cooled to 60 °C, methanol (2 L) was added, and the solution was concentrated by distillation until an internal volume of 750 mL was reached. The solution was again cooled to 60 °C and diluted with methanol (1.25 L), and this too was concentrated by distillation until an internal volume of 750 mL was reached. The solution was cooled to 64 °C at which point methanol (2 L) was added, the solution was cooled to 48 °C, a seed of **29** (100 mg) was added and the suspension stirred for 15 min. The stirred suspension was cooled to 20 °C and aged for 30 min. Filtration and washing with methanol (2 × 325 mL) gave the title compound as a light-yellow solid (209.9 g, 77%): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.16−1.28 (2H, m), 1.42−1.55 (2H, m), 1.70−2.05 (5H, m), 2.44−2.54 (1H, m), 2.95 (2H, d), 3.87 (3H, s), 7.12 (2H, d), 7.24 (2H, d), 7.48 (1H, d), 7.58 (1H, dd), 7.67 (1H, dd), 7.99 (1H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 32.7, 33.2, 34.0, 43.5, 43.6, 52.8, 128.2, 128.4, 129.0, 129.3, 129.4, 131.0, 131.4, 133.2, 138.9, 145.9, 167.1, 194.2 and 198.4; HRMS (APCI, negative ion, $[M + e]^-$) calculated for $C_{23}H_{23}ClO_4$ 398.1290, found 398.1281.

*2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione (**1**).* The ester **29** (3.0 g, 7.54 mmol) was suspended in methanol (18 mL), stirred, and treated with a 25% solution of sodium methoxide in methanol (2.02 g, 9.35 mmol), whereby solids began to dissolve, and a red solution was formed.[29] The solution was stirred at room temperature for 23 h and quenched by the dropwise addition of 5 M phosphoric acid (1.8 mL, 9.0 mmol), and the resulting yellow slurry was stirred at room temperature for 24 h. The yellow suspension was filtered, and the residue was washed with methanol (4 mL + 5 mL) and hot water (2 × 9 mL) and then dried to give the title compound as a bright-yellow solid (2.30 g, 83%). This material was spectroscopically identical to that reported above.

*3-(2-((1r,4r)-4-(4-Chlorophenyl)cyclohexyl)acetyl)-3-hydroxyisobenzofuran-1(3H)-one (**30**).* Sodium hydroxide solution (2 M, 10 mL, 20.00 mmol) was added to a suspension of **26** (5 g, 13.63 mmol) in methanol (30 mL), and the mixture was stirred at ambient for ∼18 h. The mixture was quenched by the

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addition of aqueous hydrochloric acid (25%, 3.2 mL), leading to the precipitation of a solid and a pH of <2. The slurry was stirred at ambient for 30 min and filtered, and the residue was washed with water−methanol (2:1, 2 × 10 mL) and then dried to give the title compound as an off-white solid (4.52 g, 86%): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.86 (1H, m), 1.02 (1H, m), 1.42 (2H, m), 1.5−2.0 (8H, m), 2.36 (2H, m), 5.65 (1H, s), 7.08 (2H, m), 7.23 (2H, m), 7.45 (1H, d), 7.71 (1H, m), 7.77 (1H, m), 8.0 (1H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 32.8, 33.2, 33.7, 42.1, 43.3, 123.0, 126.2, 127.4, 128.1, 128.4, 131.6. 131.8, 135.2, 145.4, 178.0; HRMS (APCI, negative ion, $[M - H]^-$) calculated for $C_{22}H_{20}ClO_4$ 383.1056, found 383.1053.

*3-{[4-(4-Chlorophenyl)cyclohexyl]acetyl}-3-(methyloxy)-2-benzofuran-1(3H)-one (**31**).* The lactone **26** (3.0 g, 8.18 mmol) and dimethylaminopyridine (0.12 g, 0.98 mmol) were suspended in methanol (60 mL), and the stirred mixture was heated at reflux for 25.5 h. The solution was cooled to ambient, the solvent was removed under vacuum, and the residue was dissolved in *tert*-butylmethylether (20 mL) whereby white crystals started to crystallise. The mixture was allowed to stand at ambient overnight, and the solid was collected by filtration under vacuum, washed with *tert*-butylmethylether (2 × 10 mL), and dried, giving the title compound as white crystals (0.48 g, 14.7%):[30] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.98−1.15 (2H, m), 1.36−1.51 (2H, m), 1.70−1.98 (5H, m), 2.34−2.46 (1H, m), 2.55 and 2.73 (2H, 2 × dd), 3.24 (3H, s), 7.08 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 7.64 (1H, dd), 7.75 (1H, dd), 7.94 (1H, d); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 32.7, 32.9, 33.1, 33.8, 33.8, 43.5, 44.6, 52.1, 107.5, 124.2, 125.9, 127.6, 128.1, 128.4, 131.5, 131.6, 134.8, 142.7, 145.7, 167.8, and 201.1; HRMS (APCI, negative ion, $[M + e]^-$) calculated for $C_{23}H_{23}ClO_4$ 398.1290, found 398.1278.

*2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione (**1**).* A 25% solution of sodium methoxide in methanol (0.21 mL, 0.905 mmol) was added to a suspension of the lactone **31** (0.30 g, 0.754 mmol) in methanol (2 mL) at room temperature. The solids gradually dissolved, giving a red solution which was stirred at room temperature for 18 h[31] and quenched by the dropwise addition of 5 M phosphoric acid (0.2 mL, 1.0 mmol), and the resulting yellow slurry was stirred at room temperature for 24 h. The yellow suspension was filtered, and the residue was washed with methanol (2 × 1 mL) and hot water (2 × 1 mL) and then dried to give the title compound as a bright-yellow solid (0.21 g, 76%). This material was spectroscopically identical to that reported above.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) Use of thionyl chloride gave a much slower and dirtier reaction profile, as well as having a detrimental effect on the subsequent hydrogenation reaction.
(23) Use of tertiary alkylamine bases for this transformation generally led to significant over-reduction whereby the aromatic chloride function was also reduced.
(24) Green metrics were calculated for both routes including solvent recovery. The new route metrics included the synthesis of **5** from phthalic anhydride, whereas the old route was calculated with naphthoquinone **34** as starting material. It is acknowledged that **2** is derived from naphthalene *via* oxidation which is in turn derived from coal tar, so the comparison is deemed appropriate.
(25) Levels of the *cis* product were also evident at up to 25% from ^{1}H NMR inspection.
(26) Product typically contains unreacted alcohol **26** at 10%.
(27) Percentage yield range observed: 78−89% (from pilot-plant batches), average yield 83%. The purity quoted includes 1.1% a/a of the *cis*-1,4-cyclohexane isomer and 1.0% *E*-alkene, both of which interconvert to atovaquone **1** in the following chemical stage.
(28) *Note*: LC check after 1 h of reaction shows a ratio of **29** to **31** of approx 1:1. These products diminish on continued reaction, confirming their intermediacy within the rearrangement reaction.

(29) LC check after 30 min of reaction shows a ratio of **29** to **31** of approx 1:1 which confirms the equilibrating nature of this transformation.

(30) Please note there is appreciable product **31** (approximately 32%) remaining within the filter liquors with the remaining material being methyl 2-{3-[4-(4-chlorophenyl)cyclohexyl]-2-oxopropanoyl}benzoate (**30**).

(31) LC check after 1 h of reaction shows a ratio of **31** to **29** of approx 3:2 which confirms the equilibrating nature of this transformation.

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