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Full Papers

Development of a Phase Transfer Catalyzed Asymmetric Synthesis for an Estrogen Receptor Beta Selective Agonist

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Abstract:

A practical asymmetric synthesis of the estrogen receptor beta selective agonist (7*β*-9a*β*)-1,4-dichloro-2-hydroxygibba-1(10a),2,4,4b-tetraen-6-one (1), proceeding by way of six isolated intermediates and without recourse to chromatography, is described. Highlights of the process route developed are two chemoselective chlorinations, a lithiated hydrazone alkylation and an asymmetric Michael addition of indanone 11 to methyl vinyl ketone (using 15 mol % of cinchonine-derived catalyst 20g) to set the all-carbon quaternary asymmetric stereocenter. The challenges addressed in scaling the latter heterogeneous biphasic phase transfer reaction to 44 mol (14 kg) scale are discussed in detail. Overall, the chemistry developed has been used to prepare >6 kg of drug candidate 1 in 18% overall yield and with >99% ee.

Introduction

Hormone replacement therapy (HRT) has been widely used and provides effective treatment for symptoms of menopause.[1] However, concerns about the risk for developing breast cancer, endometrial cancer, deep vein thrombosis, stroke, and cardiovascular disease leaves significant scope for developing improved therapies. As part of a programme at Merck directed towards this goal,[2] selective modulators of estrogen receptor-β (ER-β) have been targeted, and **1** (Scheme 1) was identified as a candidate for further development. Herein, we describe a scaleable synthetic route for **1**, which has delivered multikilogram quantities and through which early preclinical and clinical studies have been supported.

Medicinal Chemistry Synthesis and Revised Synthetic Plan. Tetracyclic drug candidate **1** poses a number of challenges with regard to development of a concise and practical synthesis. Most notably, construction of the all-carbon quaternary stereogenic carbon center in a catalytic asymmetric manner was expected to be highly demanding.[3] In addition, the regio- and chemoselective introduction of two chlorine atoms are required. Although viable for the preparation of multigram quantities of **1**, the medicinal chemistry synthesis[2e] presented a number of issues that would ultimately prohibit further development of this route to allow practical synthesis on multikilogram scale. The synthesis began with commercially available 5-methoxyindan-1-one **2**, which was monoalkylated by way of the β-ketoester **3** to afford fluorinated ester **4**. The expense of Mander's $NCCO_2Et$ reagent together with the ozone-depleting nature of the alkylating agent 1-bromo-2-fluoroethane were problematic in this sequence. Chlorination of the aromatic ring with NCS in DMF afforded an approximately 4:1 mixture of indanone chlorination regioisomers favoring the desired 4-chloro isomer, which following hydrolysis/decarboxylation of the β-ketoester required chromatographic separation to purify the desired indanone **5**. Construction of the central quaternary stereocenter was performed in a racemic manner by Michael addition to methyl vinyl ketone (MVK) followed by a Robinson annulation. The resultant racemic cyclohexenone *rac*-**6** could be separated by preparative chiral chromatography (Chiralcel OD) on multigram scale; however, the volume productivity of this separation was prohibitively low to permit further scale-up due to the low solubility of *rac*-**6** in solvents compatible with the stationary phase. In an elegant one-pot step, nucleophilic cleavage of the phenolic methyl ether was accompanied by closure of the final cyclopentane ring to afford penultimate

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(3) (a) For reviews, see: Overman, L. E.; Douglas, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (b) For reviews, see: Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (c) For reviews, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (d) For reviews, see: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.

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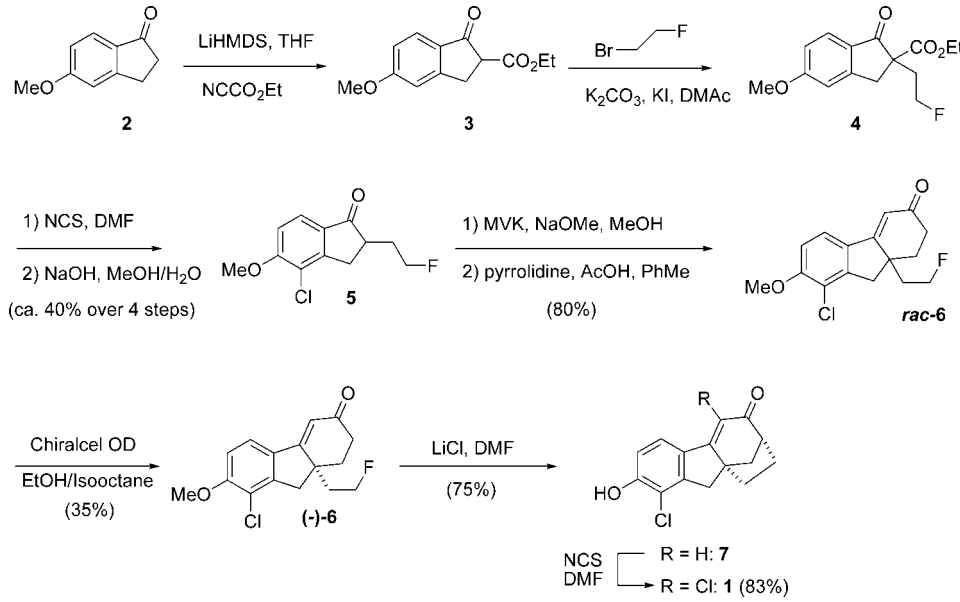
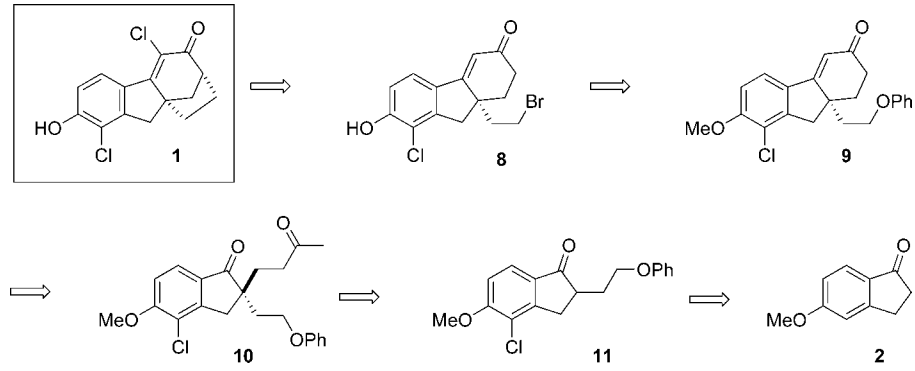
Scheme 1. **Medicinal chemistry synthesis**



Scheme 2. **Revised synthetic plan**



7. A final chemoselective chlorination then afforded the desired drug candidate **1** by way of eight chemical steps and five chromatographic purifications in an overall yield of 7%.

We considered the overall strategic disconnections of the medicinal chemistry synthesis to constitute an attractive and concise approach to **1**, especially if the construction of the quaternary stereocenter could be rendered asymmetric. In this context we sought to exploit the seminal asymmetric phase transfer organocatalysis studies of Dolling and co-workers at Merck to construct the quaternary stereogenic carbon center in a catalytic enantioselective manner (Scheme 2).[4] In our revised synthetic plan beginning with indanone **2**, regioselective chlorination and monoalkylation would afford phenoxy substituted indanone **11**. Base-catalysed Michael addition of the enolate of indanone **11** to MVK, in the presence of a (+)-cinchonine derived quaternary ammonium phase transfer catalyst, would potentially allow enantioselective access to diketone **10**. Robinson annulation would then construct the cyclohexenone ring of tetrahydrofluorenone **8**. Our choice of the phenoxy substituent in **9** was guided by the expectation that this group could be transformed to a bromide (or other halide) leaving group under conditions in which the phenolic methyl ether would also be cleaved (typically Lewis acid mediated), leading to bromide **8**. Nucleophilic displacement to close the final cyclopentane ring and chemoselective chlorination of the enone moiety would then afford the desired candidate **1**.

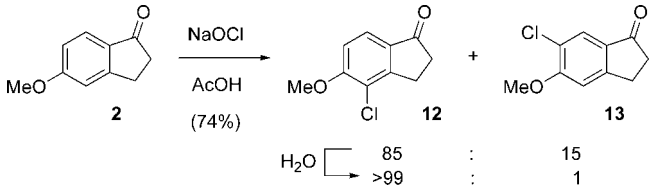
Results and Discussion

Preparation of the Phase Transfer Substrate 11. The synthesis began with the preparation of 4-chloro-5-methoxyindanone **12**, which surprisingly has not been previously described (Scheme 3). A screen of chlorination conditions[2f,5] with 5-methoxyindan-1-one **2** rapidly led to a highly practical procedure. Employing NaOCl in AcOH, excellent chemoselectivity for chlorination of the aromatic ring without significant competing ketone α-chlorination was observed, with a typical 85:15 regioselectivity[2f,6,7] favoring the desired 4-isomer **12**[8] over the 6-chloroisomer **13**. Addition of water as antisolvent then allowed direct crystallisation of **12** from the reaction mixture in >99A% and 74% yield, thereby rejecting the undesired

(4) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447. (b) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745–4752. (c) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476–477. (d) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710–4711.

(5) Other reagent systems evaluated (sulfuryl chloride, Oxone/KCl, NCS, AcCl/CAN) led to unselective chlorination α to the indanone carbonyl and of the aromatic ring.

Scheme 3. **Regiselective chlorination of 5-methoxyindan-1-one**



regioisomer and avoiding the need for chromatographic separation, which was required in the medicinal chemistry synthesis.

Monoalkylation of indanone **12** with β-bromophenetole ($PhOCH_2CH_2Br$) to afford **11** was initially pursued by way of β-ketoester **14** (Scheme 4). This proved to be problematic as a result of competing O-alkylation to afford enol ether **16**, as well as bisalkylation product **17** amongst many other lower level byproducts. A maximum 50% overall assay yield for **11** was obtained following a significant development effort. Recognising one of the main issues was the intrinsically low reactivity of β-bromophenetole as an electrophile, the corresponding *N*,*N*-dimethylhydrazone **18** was prepared and found to alkylate highly effectively (Scheme 5). For implementation on scale, a practical telescoped process from **7** to isolated **11** was developed, avoiding isolation of two intermediates. Exposure of a heptane solution of indanone **12** to 1,1-dimethylhydrazine in the presence of acetic acid allowed for formation of the hydrazone **18**. Following azeotropic distillation of the acetic acid and the byproduct water with heptane, the solvent was switched to THF, *n*-hexyl lithium was added at −40 °C to effect lithiation, and alkylation proceeded between −30 and −10 °C with β-bromophenetole. An acidic hydrolysis in the quench (6 M HCl) then effected cleavage of the alkylated hydrazone **19** to afford **11**, which was isolated in 88% overall yield by crystallisation (>95% per chemical step).

Asymmetric Phase Transfer Michael Addition. In developing and optimising the heterogeneous biphasic addition reaction of indanone **11** with MVK for implementation on scale, a number of critical reaction parameters were identified to achieve reproducible ee and purity of the methyl ketone **10**, and these are discussed in turn.

Catalyst Structure Optimisation. An optimisation study with regard to catalyst structure versus ee was performed with a series of (+)-cinchinone derived quaternary ammonium catalysts **20a**−**i** under a standard set of conditions (Table 1).[9] There was a wide variation in ee (20–52%) versus the catalyst *N*-substituent, and the 2-napthylmethylcinchoninium bromide catalyst **20g** (entry 7) was selected for further development on the basis of 50% ee and bulk commercial availability of the required 2-napthylmethyl bromide.[10] Toluene was the preferred solvent on the basis of the earlier studies,[4] and the use of solid KOH pellets as base was found to lead to lower ee.[4d]

Preparation of the Phase Transfer Catalyst 20g. The preparation of *N*-(2-napthylmethyl)cinchoninium bromide **20g** was readily achieved by heating (+)-cinchonine and 2-(bromomethyl)napthalene in solvent and filtering the resultant quaternary ammonium salt. The use of either THF or toluene was found to be convenient, yielding solids of identical rod-like crystal morphology (XRPD) with isolated yields >95%. However, use-tests of different catalyst batches demonstrated a significant benefit to catalyst prepared in toluene with regard to the rate at which the catalyst extracted into the toluene layer on slurrying with 50 wt % NaOH (Table 2, entry 3). This was found to be critical to obtain reproducable ee, with a typical catalyst concentration of 8 mg/mL (8 mol % catalyst) in the toluene layer necessary to obtain >50% ee. Microtrac particle size measurements provided insight into the origin of this difference in extraction rate, as catalyst batches prepared in toluene had a significantly smaller average particle size (typically 95% at diameter < 44 μm) versus that prepared in THF (typically 95% < 64 μm). The observed relationship of extraction rate to particle size for catalyst **20g** is consistent with the proposed mechanism (Figure 1) by which the related catalyst **20b**, used in the previous studies[4b] operates. For **20b**, dissolution into the aqueous phase is followed by deprotonation and extraction into the toluene phase as a catalyst dimer. Both **20b** and **20g** are essentially insoluble in either 50 wt % NaOH or toluene alone, and thus an increase in the solid catalyst surface area would be expected to benefit the initial unfavorable dissolution into the 50 wt % caustic layer.

Agitation Rate. A further parameter critical to successful extraction of **20g** into the toluene phase was adequate mixing of the biphasic mixture because of the high density (1.52 g/mL) and viscosity of 50 wt % NaOH. In laboratory scale overhead stirring experiments, catalyst extraction failed using simple paddle blades at up to 500 rpm agitation rates and vortex mixing with a screw propeller at 500 rpm (tip speed 1.8 m/s) was essential. In the pilot plant, vortex mixing in a 400-L stainless steel vessel at 220 rpm with a tip speed of 5 m/s performed effectively for our purposes.

Impurity Issues, Robinson Annulation, and ee Upgrade. To achieve reproducable ee, it was determined that the optimum reaction protocol was to slurry the catalyst **20g** in a toluene solution of indanone **11** and 50 wt % NaOH and age for 14–16 h prior to MVK addition. At this point, **20g** typically reached >8 mg/mL in the toluene phase. During this age time, significant formation of the enolate α-oxidation product **21** occurred in early experiments (up to 10A%), and this was traced to inefficient degassing despite employing vacuum/nitrogen purge cycles (Scheme 6). This was remedied by performing subsurface sparging with nitrogen through the caustic layer for >30 min at the reaction outset, which reduced formation of **21** to <2A%. An undercharge of 0.9 equiv of MVK in toluene was then added to minimise the formation of overaddition

(6) The regioselectivity is not significantly impacted by concentration or temperature or switching to ^{t}BuOCl.

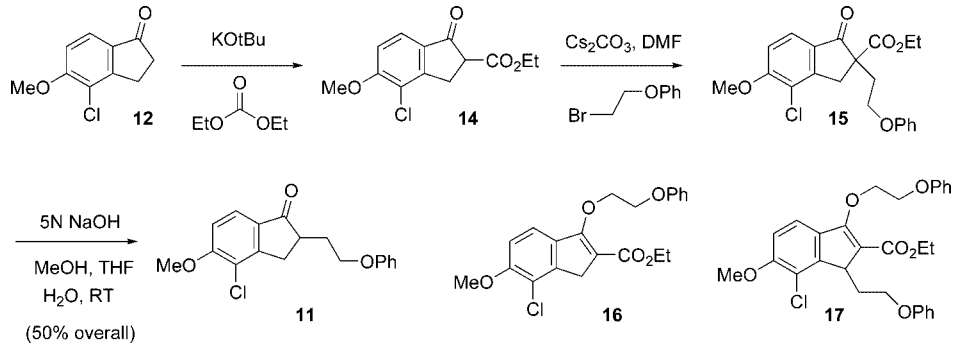
(7) Analogous bromination regioselectivity for 5-methoxy-indan-1-one has been observed with *N*-bromosuccinimide: Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2006**, *47*, 4707–4710.

(8) The vicinal relationship relationship of the aromatic protons of **12** was established by ^{1}H NMR NOE experiments.

(9) As a result of the necessity of screening on small scale (100 mg of substrate), magnetic stirring was used in combination with 100 mol % loading of catalyst to provide the most reliable data for ee versus catalyst structure.

(10) Maruoka catalysts were also screened but afforded lower ee and are not commercially available at scale. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

Scheme 4. **β-Ketoester route to indanone 11**



Scheme 5. **Dimethylhydrazone route to indanone 11**

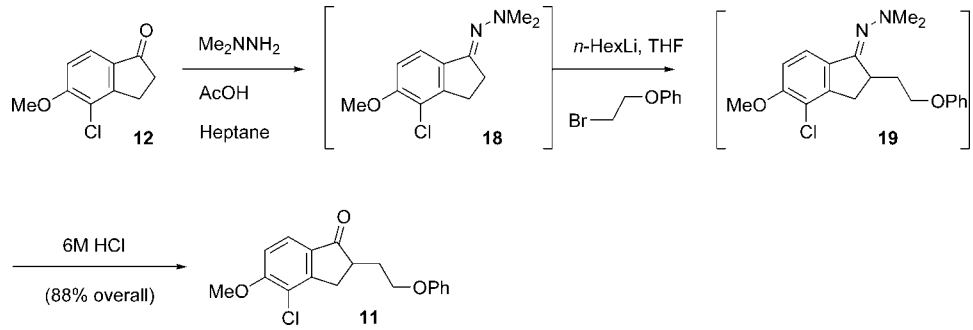
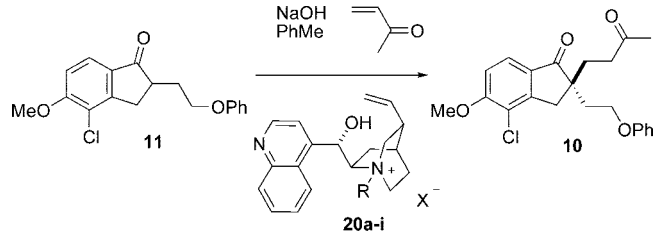


Table 1. **Catalyst *N*-substituent optimisation study[a]**



entry	catalyst (counterion X)	R substituent[b]	enantiomeric excess[c]
1	**20a** (chloride)	*N*-benzyl	20
2	**20b** (bromide)	*N*-(4-trifluoromethylbenzyl)	25–32[d]
3	**20c** (bromide)	*N*-(3,4-difluorobenzyl)	28
4	**20d** (chloride)	*N*-(9-anthracenylmethyl)	29
5	**20e** (chloride)	*N*-(3,4-dichlorobenzyl)	32
6	**20f** (bromide)	*N*-(3,4-dichlorobenzyl)	40
7	**20g** (bromide)	*N*-(2-napthylmethyl)	50
8	**20h** (bromide)	*N*-(2-fluoro-4-trifluoromethylbenzyl)	51
9	**20i** (bromide)	*N*-(3-fluoro-4-trifluoromethylbenzyl)	52

[a] Standard conditions: 100 mol % catalyst, 50 wt % NaOH, toluene, MVK, magnetic stirring at 500 rpm, 25 °C. [b] Unless commercially available, catalysts were prepared by refluxing the appropriate benzylic halide (1.2 equiv) with (+)-cinchonine in toluene and filtering to isolate. [c] Determined by HPLC on Chiralpak AD. See Experimental Section for details. [d] Range obtained over three separate experiments.>

products resulting from incorporation of an additional molecule of MVK. Following HPLC assay to determine the level of unconverted **11** still present, a further addition of MVK was then added to achieve <1A% of **11**. At this point the ee was typically 54–56%. Following a workup procedure to remove the catalyst **20g**, the toluene phase was concentrated and subjected directly to Robinson annulation with AcOH and pyrrolidine. After 4 h aging at 85 °C, dehydrative cyclisation was complete and **9** could be crystallised in 85% overall yield (52% ee) over the entire sequence.

With isolated **9** having a typical 52% ee, an upgrade of optical purity was essential. A screen of a wide range of solvents

Table 2. **Comparative extraction rates of catalyst 20g into the toluene layer**

entry	time (min)	catalyst concn[a] (mg/mL)	catalyst concn[b] (mg/mL)
1	120	2.0	2.6
2	240	3.3	6.1
3	390	4.3	9.6
4	4080	14.6[c]	13.9[c]

[a] Phase transfer catalyst prepared in THF, particle size 95% < 64 μm. [b] Phase transfer catalyst prepared in toluene, particle size 95% < 44 μm. [c] Theoretical maximum concentration of 14.0 mg/mL based on amount of catalyst charged.

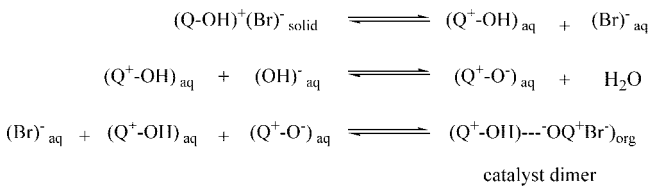


Figure 1. **Proposed mechanism by which catalysts 20b and 20g extract into the toluene organic layer.**

indicated that *rac*-**9** was uniformly less soluble than the desired single enantiomer, thus limiting the maximum recoverable yield to the ee of the initial solid. Isopropyl acetate was found to be optimal, and dissolution and crystallisation of 52% ee **9** afforded mother liquors of typically >95% ee. On further concentration, enantioenriched **9** could be crystallised and isolated in 47% yield (94% of theoretical) in 97% ee.[11]

Ether Cleavage, Cyclisation and Chlorination. With enantioenriched **9** in hand, it remained to close the final cyclopentane ring, deprotect the phenolic methyl ether, and install the remaining chlorine substituent. A number of Lewis acid reagents were evaluated for conversion of the phenoxy substituent of **9** to a halide leaving group from which BBr_3 in CH_2Cl_2 emerged as optimal (Scheme 7).[12] Under these conditions, the methyl ether is rapidly cleaved to afford intermediate **22**, which on aging for a typical 20 h at 12–14 °C undergoes conversion to the bromide **8**. Optimisation studies indicated 3.5 equiv of BBr_3 was required to achieve high conversion (<1A% unconverted **9**), the excess reagent being quenched with MeOH[13] and then water to form boric acid, which could be removed by filtration. Phenolic bromide **8** was found to undergo facile ring closure to penultimate **23** in a wide range of polar solvents (presumably via the enol).[14] Isopropanol was particularly convenient, as following heating at 80 °C, direct isolation of **23** from the reaction mixture was possible by addition of water as antisolvent, leaving the stoichiometric phenol byproduct in the liquors. Development of a telescoped process involving a solvent switch of the dichloromethane stream of **8** to isopropanol and subsequent thermal cyclisation afforded a 91% isolated yield of penultimate **23** from **9**.

Chemoselective chlorination of the enone moiety of penultimate **23** was readily achieved using *N*-chlorosuccinimide (NCS) with acetonitrile replacing DMF[15] as solvent (Scheme 8). The main development issue to address related to the presence of 1–2A% of an impurity **24** present in the isolated **23**.[16] Using stoichiometric NCS (corrected for wt % purity of **23**) led to high assay and isolated yields (>90%) of drug candidate **1** by direct crystallisation on addition of water; however, **24** remained at unacceptably high levels in the isolated solids. Increasing the NCS equivalents to 1.08 was found to lead to the disappearance of **24** accompanied by the formation of several lower level impurities that were now well rejected on crystallisation, although the isolated yield of **1** was lowered to 87%. A final carbon treatment (Darco-G60) for color and purity upgrade then gave isolated **1** in 87% yield (>99 LCWP, >99 LCAP, >99.9% ee).

Conclusion

A concise enantioselective synthesis of the tetracyclic drug candidate **1** was achieved by way of six isolated intermediates in 18% overall yield. This synthesis addressed the key issues that prohibited scale-up of the medicinal chemistry synthesis. In transferring the chemistry from laboratory to pilot plant, a number of challenging development issues were addressed, most notably those around the heterogeneous biphasic phase transfer Michael addition of indanone **11** to MVK. The preparation of >6 kg of **1** was possible using the developed chemistry, which supported early preclinical and clinical development studies.

Experimental Section

General. Melting points were determined on an open capillary apparatus and are uncorrected. HPLC assays were carried using a C-18 reversed-phase column eluted with 0.1% H_3PO_4 (aq) and acetonitrile. Assay yields were obtained by HPLC using analytical standards prepared by chromatography or recrystallisation. Isolated yields refer to yields corrected for purity based on HPLC assay using purified standards. All reagents and solvents were used as received without further purification.

4-Chloro-5-methoxyindan-1-one (12). 5-Methoxyindan-1-one (17.5 kg, 108 mol) was dissolved in AcOH (147 kg) and cooled to +14 °C. Sodium hypochlorite 10/11% aqueous solution (87 kg, 136 mol) was added such that the internal temperature was maintained below 17 °C (2.5 h addition time). After a 20 min age at <10 °C, the batch was cooled to 0–2 °C and aged for 30 min. Water (50 L) was then added to crystallise the batch. The batch was filtered, and the cake was washed with 5:1 water/AcOH (18 L) followed by water (2 × 20 L). Drying at 40 °C under a N_2 sweep afforded 15.57 kg of **12** as an off-white solid in 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 8.4 Hz), 7.00 (1H, d, J = 8.4 Hz), 4.00 (3H, s), 3.09 (2H, t, J = 6.0 Hz), 2.71 (2H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 160.0, 154.7, 131.4, 123.3, 119.7, 111.5, 56.7, 36.3, 24.9; mp 130–131 °C; HRMS (ES) calcd for $C_{10}H_{10}ClO_2$ (MH^+) 197.0369, found 197.0374.

4-Chloro-5-methoxy-2-(2-phenoxyethyl)indan-1-one (11). Indanone **12** (14.0 kg, 71.2 mol) was slurried in *n*-heptane (154 L). Glacial acetic acid (2.14 kg, 35.6 mol) was then added, followed by 1,1-dimethylhydrazine (6.42 kg, 106.8 mol) such that the temperature remained <40 °C. The batch was then

(11) A bulk scale chromatographic separation of *rac*-**9** using 20 μm Chiralpak AS silica with $CHCl_3$ as eluant was also developed.

(12) Alternative reagents screened included BCl_3, $AlCl_3$, $AlBr_3$, BBr_3.Me_2S, TMSI, and LiCl/DMF.

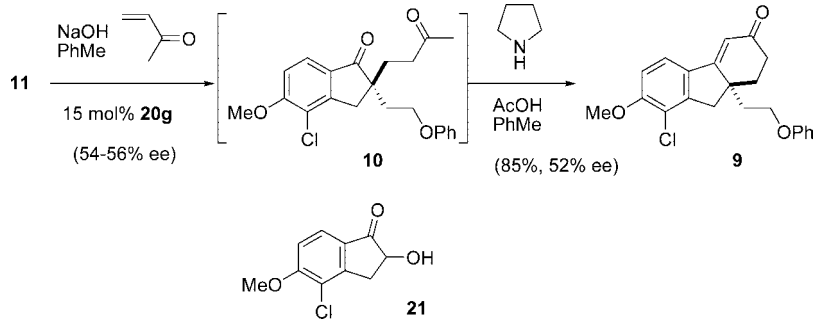
(13) Advanced Reactive System Screening Tool (ARSST) evaluation of the reaction quench indicated an adiabatic temperature rise of around 50 °C if the MeOH quench was added in one portion, demonstrating the need to perform this in a controlled manner.

(14) The ease with which **8** undergoes cyclisation is likely due to the bicyclic scaffold enforcing favorable alignment for the enol HOMO → σ* (C-Br) orbital interaction required to effect C−C bond formation. See: Kirby, A. J. *Stereoelectronic Effects*; Oxford University Press: New York, 1996.

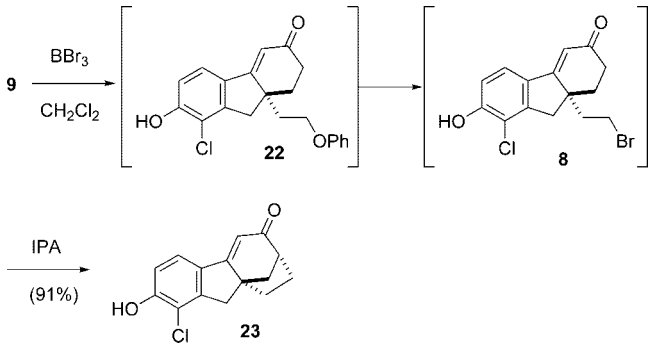
(15) Dimethylformamide is a class 2 solvent and therefore undesirable for use in a final chemical step for API production. See *ICH Harmonised Tripartite Guideline; Impurities: Guidelines for Residual Solvents Q3C* **1997**, 17 July.

(16) The structural identity of impurity **24** was supported by detailed 2D NMR studies and HRMS (ES): calcd for $C_{30}H_{28}Cl_2O_3$ (MH^+) 505.1336, found 505.1337.

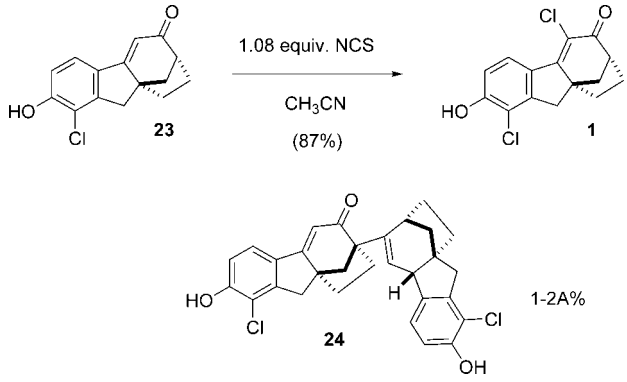
Scheme 6. **Optimised phase transfer Michael addition and Robinson annulation sequence**



Scheme 7. **Ether cleavage and cyclisation to penultimate 23**



Scheme 8. **Final chlorination**



heated to 90 °C for 3 h. The batch was cooled to 60 °C, treated with THF (28 L), and then concentrated to 40 L by distillation under atmospheric pressure. The resulting concentrate was cooled to 50 °C and diluted with THF (182 L). The THF solution was held overnight at <15 °C. The batch was cooled to −50 °C by direct injection of liquid N_2, and then *n*-hexyllithium (2.39 M in hexane, 21.2 kg, 71.2 mol) was added over 1.5 h, maintaining the internal temperature less than −25 °C. The resulting slurry was aged between −30 and −20 °C for 30 min, and then a solution of β-bromophenetole (14.4 kg) in THF (14 L) was added over 5 min, maintaining the internal temperature less than −25 °C. The batch was then aged at −5 °C for 30 min. HCl (6 N, 30 kg 37% HCl + 30 kg H_2O) was charged to the mixture, which was then aged at 50 °C until complete hydrolysis of the intermediate hydrazone was confirmed by HPLC (1.5 h). After the batch cooled to 20 °C, IPAc (56 L) was added, and the aqueous layer was discarded. The organic phase was washed with water (75 L) and then concentrated to 40 L using vacuum distillation at 40 °C. *n*-Heptane (40 L) was added, and after aging for 30 min at 40 °C, 0.2% seed of the product ketone was added. The mixture was stirred for 1 h to allow a seed bed to develop, and then a further 80 L of *n*-heptane was charged over 1 h at 40 °C. The resulting slurry was allowed to cool to 20 °C overnight and then cooled to 5 °C over 1 h before filtering. The filter cake was washed with 4:1 heptane/IPAc (25 L) and then sucked dry under a stream of N_2 for 3 h. The solid was dried in a vacuum oven at 45 °C for 48 h, affording 20.2 kg of **11** as an off white solid in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, d, J = 8.4 Hz), 7.35–7.25 (2H, m), 7.04–6.88 (4H, m), 4.25–4.15 (2H, m), 4.00 (3H, s), 3.46–3.35 (1H, m), 2.98–2.87 (2H, m), 2.54–2.41 (1H, m), 2.03–1.89 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 160.2, 158.8, 153.2, 130.8, 129.5, 123.6, 120.8, 119.7, 114.5, 111.6, 65.9, 56.8, 45.0, 32.2, 31.0; mp 90–92 °C; HRMS (ES) calcd for $C_{18}H_{18}ClO_3$ (MH^+) 317.0949, found 317.0946.

***N*-(2-Napthylmethyl)cinchoninium Bromide (20g).** (+)-Cinchonine (8.84 kg) and 2-(bromomethyl)naphthalene (7.30 kg) were charged and placed under a N_2 stream. Toluene (152.9 kg) was added, and the mixture was degassed and then aged at 110 °C until <1.0 LCAP of of (+)-cinchonine remained (3.5 h). The batch was allowed to cool to 20–25 °C overnight and then filtered, and the cake was washed with toluene (76.5 kg). The batch was dried in vacuo at 50 °C for 16 h to afford 15.1 kg (101.2 LCWP) of **20g** as a pink solid (98% corrected yield). Mp >230 °C; particle size by Microtrac 95% < 44 μm.

(9a*S*)-8-Chloro-7-methoxy-9a-(2-phenoxyethyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one (9). *N*-(2-Napthylmethylcinchoninium bromide **20g** (3.38 kg, 6.56 mol) and indanone **11** (13.8 kg, 43.6 mol) were slurried in toluene (208.9 kg). Sodium hydroxide (50%, 51.5 kg) was then charged, and the batch was aged for 14 h at 20–25 °C. A solution of MVK (2.75 kg, 39.2 mol) in toluene (26.4 kg) was added at 20 °C over 30 min at T < 27 °C. After a further 15 min of aging, a further charge of MVK (366 g, 5.2 mol) in toluene (3.0 kg) was then made such that HPLC assay indicated <0.5A% unconverted indanone. Water (67.0 kg) was added over 40 min such that T < 30 °C. After allowing the batch to settle, around 90% by weight of the lower aqueous layer was cut. The remaining batch was filtered and washed through with additional toluene (2 × 12.5 kg). The batch was settled, and the remaining aqueous cut away. The toluene layer was washed successively with 2 M HCl (prepared from conc HCl 17.7 kg and water 72.2 kg) containing MeOH[17] (5.76 kg) followed by water (87.3 kg). The batch was distilled at 45 °C to a volume of ca. 167 L and held overnight.

(17) The addition of methanol affords a cleaner and more rapid separation of the organic and aqueous layers.

AcOH (2.62 kg, 43.6 mol) and pyrrolidine (3.11 kg, 43.6 mol) were then added, and the batch was aged at 85 °C for 4 h. Water (130.9 kg) was charged at 85 °C, and the batch was mixed for 10 min prior to settling. The lower aqueous was cut away, and the organic was washed with further water (130.9 kg). The aqueous was cut, and the organics were distilled to a volume of ca. 57 L at 45 °C. On cooling to 39 °C, the batch crystallised, and after formation of a seedbed, heptane (58.5 kg) was added over 20 min. After aging a minimum of 1 h, filtration, washing with heptane (14.9 kg), and drying in vacuo at 45 °C for 16 h afforded 13.83 kg of **9** as a tan solid in 85% yield with 52% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 8.4 Hz), 7.30–7.21 (2H, m), 6.95–6.83 (2H, m), 6.80–6.76 (2H, m), 6.21 (1H, s), 4.03–3.91 (5H, m), 3.39–3.35 (1H, d, J = 17.2 Hz), 2.83–2.68 (2H, m), 2.53 (1H, dd, J =14.8, 4.8 Hz), 2.40 (1H, dd, J = 3.2, 13.2 Hz), 2.21–1.98 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 171.2, 158.3, 157.9, 146.7, 131.5, 129.4, 122.1, 120.9, 119.6, 116.7, 114.2, 111.6, 64.6, 56.6, 46.0, 43.0, 36.6, 34.0, 32.5; Chiralpak AD 250 × 4.6 mm, 1.5 mL min^{-1}, 35 °C, 10% EtOH/heptane isocratic elution, t_R = 8.9 min (*S*-**9**), t_R = 10.8 min (*R*-**9**), t_R = 15.5 min (*S*-**10**), t_R = 12.1 min (*R*-**10**); HRMS (ES) calcd for $C_{22}H_{22}ClO_3$ (MH^+) 369.1257, found 369.1274.

Enantiopurity Upgrade for (9a*S*)-8-Chloro-7-methoxy-9a-(2-phenoxyethyl)-1,2,9,9a-tetrahydro-3*H*-fluoren-3-one (9). Tetrahydrofluorenone (**9**) (27.4 kg, 74.3 mol, 52% ee) was suspended in IPAc (358.0 kg), and the mixture was degassed and placed under nitrogen. The mixture was heated to 76 °C to dissolve the batch, then cooled to 20 °C over >1 h, and aged at 20 °C for at least 1 h. The crystallised racemic material was then filtered off, and the solid was washed with cold (4 °C) IPAc (23.9 kg). HPLC assay of the combined filtrates gave 96.3% ee, 14.7 kg. The filtrates were distilled under vacuum to a volume of 4.5 mL/g based on the previous assay (ca. 222 mg/mL) and then heated to 65 °C to redissolve the crystallised solids. The batch was allowed to cool to 60 °C, and then seed was added (1 wt %) based on assay. After formation of a seedbed, the batch was allowed to cool to ambient and then cooled to $-5 \le T \le 0$ °C, aging for >1 h. Filtration and washing with cold (4 °C) IPAc and drying in vacuo at 45 °C for 16 h afforded 12.84 kg of **9** in 47% yield and 97% ee; mp 115–116 °C.

(7β-9aβ)-1-Chloro-2-hydroxygibba-1(10a),2,4,4b-tetraen-6-one (23). Boron tribromide (1 M in dichloromethane, 97.4 kg, 66.4 mol) was cooled to 1 °C. A solution of **9** (7.0 kg, 19.0 mol, 97% ee) in dichloromethane (31.0 kg) was added over 10 min such that T < 15 °C. The solution was aged at 12–14 °C for 22 h. The solution was cooled to 1 °C, and methanol (8.51 kg.) was added over 1 h, T < 15 °C. After a 1 h age, water (21 kg) was added, followed by dichloromethane (23.2 kg), and the slurry was stirred for 20 min at ambient. The batch was then filtered, and the solid was washed with dichloromethane (2 × 18.6 kg). The filtrate and washes were combined, and further water (28 kg) added. The batch was agitated for 10 min and left to settle, and the layers were cut. The organic layer was washed with 5 wt % sodium bicarbonate (47.25 L, prepared from 45.0 kg water and 2.36 kg sodium hydrogen carbonate). The organic layer was switched to IPA at a final volume of 56 L (8 mL/g) by concentrating to around 40 L and then charging IPA (76.9 kg). Further distillation was performed to reach the target volume of 56 L. This isopropanol solution was heated at 80 °C for 15 h to effect cyclisation. A volume of 7 L of IPA (3 mL/g) was removed by distillation (giving a 35 L/5 mL/g solution), and the solution was cooled to 45 °C and seeded (0.1–0.2 wt %). After a seedbed had formed, water (70 L) was added dropwise over 1 h. The slurry was allowed to cool to ambient, aged for 1 h, and filtered, washing with 5% IPA/water (21 L) and water (14 kg). Drying in vacuo at 50 °C under a nitrogen stream for 16 h afforded 4.53 kg of **23** as a pink solid in 91% yield and 97.5% ee. ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.90 (1H, s), 7.53 (1H, d, J = 8.4 Hz), 6.97 (1H, d, J = 8.4 Hz), 6.03 (1H, s), 3.18–3.02 (2H, m), 2.82–2.78 (1H, m), 2.26–2.15 (1H, m), 1.98–1.85 (3H, m), 1.72–1.63 (1H, m), 1.50–1.40 (1H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 202.4, 173.9, 157.0, 148.9, 128.6, 123.7, 117.2, 116.9, 112.8, 52.7, 50.9, 43.2, 39.4, 36.8, 26.1; mp 216–217 °C; Chiralpak OJ-H 250 × 4.6 mm, 1.5 mL min^{-1}, 35 °C, 10% EtOH/hexane isocratic elution, t_R = 15.2 min (desired), t_R = 17.0 min (undesired); HRMS (ES) calcd for $C_{15}H_{14}ClO_2$ (MH^+) 261.0682, found 261.0694.

(7β-9aβ)-1,4-Dichloro-2-hydroxygibba-1(10a),2,4,4b-tetraen-6-one (1). A suspension of **23** (4.1 kg, 13.9 mol) in MeCN (29.0 kg) was heated to 71–75 °C. NCS (2.23 kg, 14.7 mol) was dissolved in MeCN (14.9 kg) and added over 20 min. The batch was aged at 71–75 °C for 1.5 h and then cooled to 20 °C, and water (92.0 kg) was added over 1.5 h to crystallise the batch. After aging 12–16 h, the batch was filtered, and the solids were washed with 2:1 water/MeCN (16.4 L) and dried at 40 °C in vacuo for 22 h. A total of 4.08 kg of crude **1** was obtained as a brown/green solid in 87% yield and 99.4% ee. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.20 (1H, s), 8.04 (1H, d, J = 8.4 Hz), 7.06 (1H, d, J = 8.4 Hz), 3.24 (1H, d, J = 18.0 Hz), 3.12–3.04 (2H, m), 2.30–2.21 (1H, m), 2.05–1.90 (3H, m), 1.80–1.69 (1H, m), 1.55–1.45 (1H, m); ^{13}C NMR (100 MHz, d_6-DMSO) δ 195.0, 166.2, 157.4, 150.3, 127.6, 127.4, 118.3, 117.3, 116.7, 55.6, 50.7, 42.7, 39.8, 36.8, 25.9; mp 231–232 °C; Chiralpak OJ-H 250 × 4.6 mm, 1.5 mL min^{-1}, 35 °C, 10% EtOH/hexane isocratic elution, t_R = 15.3 min (desired), t_R = 17.5 min (undesired); HRMS (ES) calcd for $C_{15}H_{13}Cl_2O_2$ (MH^+) 295.0293, found 295.0291.

Color/Purity Upgrade for (7β-9aβ)-1,4-Dichloro-2-hydroxygibba-1(10a),2,4,4b-tetraen-6-one (1). Crude **1** (8.14 kg) and Darco G60 (1.63 kg) were slurried in MeOH (48.3 kg) and MeCN (144.0 kg) and stirred at 20 °C for 2 h. The batch was filtered through a 1 μm cartridge filter and 0.1 μm cartridge filter followed by a rinse with MeOH (4.8 kg) and MeCN (14.4 kg). The batch was distilled under vacuum to a volume of 40 L, then IPAc (71.1 kg) was added, and distillation repeated to achieve a batch volume of 40 L (internal batch temperature <40 °C). Futher IPAc (71.1 kg) was added, and the distillation was repeated to a volume of 40 L. The batch was cooled to 20 °C, heptane (27.8 kg) was added over 70 min, and then the batch was aged for 9 h. The batch was filtered, and the solids were washed with heptane (15 kg) mixed with IPAc (7.0 kg). Drying in vacuo at 40 °C under a N_2 sweep for 21 h afforded

6.73 kg of **1** as an off-white solid (>99 LCWP, 99.5 LCAP, >99.9% ee, 87% corrected yield).

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