A Practical Synthesis of a Potent and Selective Diacylglycerol Acyltransferase-1 (DGAT-1) Inhibitor

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Received: 12.06.2014; Accepted: 21.07.2014

Abstract: A practical synthesis of a potent, selective, and orally efficacious diacylglycerol acyltransferase-1 (DGAT-1) inhibitor, is described. This synthesis is suitable for multi-kilogram scale with high regioselectivity and stereoselectivity. The synthesis involves a Knoevenagel condensation with Meldrum's acid followed by the stereoselective addition of phenyl cuprate, regioselective Friedel–Crafts acylation, cyclization, and a regioselective reduction through an enol triflate with catalytic platinum oxide to provide the desired compound in 5.2% yield over 12 steps.

Key words: diacylglycerol acyltransferase-1, hydrogenation, Knoevenagel condensation, Friedel–Crafts acylation, Friedel–Crafts alkylation, stereoselectivity, regioselectivitiy

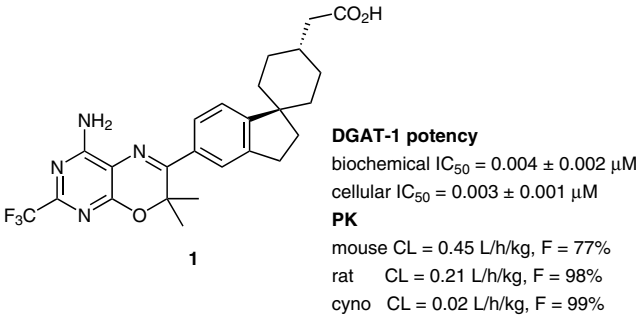


Figure 1 Profile of DGAT-1 inhibitor **1**

The enzyme diacylglycerol acyltransferase (DGAT) is a microsomal enzyme that plays a central role in the metabolism of cellular glycolipids.[1] DGAT-1 is one of two known isoforms, which catalyzes the formation of triacylglycerides from diacylglycerol and a fatty acid acyl CoA.[2] DGAT-1 is implicated in playing a role in the development of obesity and insulin resistance.[3] For example, under a high-fat diet, DGAT-1 knockout mice are resistant to weight gain with concomitant increased leptin sensitivity. Fat tissue explanted from DGAT-1 knockout mice convey resistance to weight gain in wild-type mice. Additionally, high-fat fed adipose transgenic mice show increased adiposity. Therefore, inhibition of DGAT-1 could have a therapeutic potential for people suffering from obesity, dyslipidemia, and diabetes.[3,4] In an earlier report, we disclosed the discovery of a potent, selective and orally efficacious DGAT-1 inhibitor **1,** which demonstrated promising in vivo efficacy in a mouse diet-induced obesity (DIO) model and an acceptable safety profile in rat and cynomolgus monkey toxicity studies (Figure 1).[5]

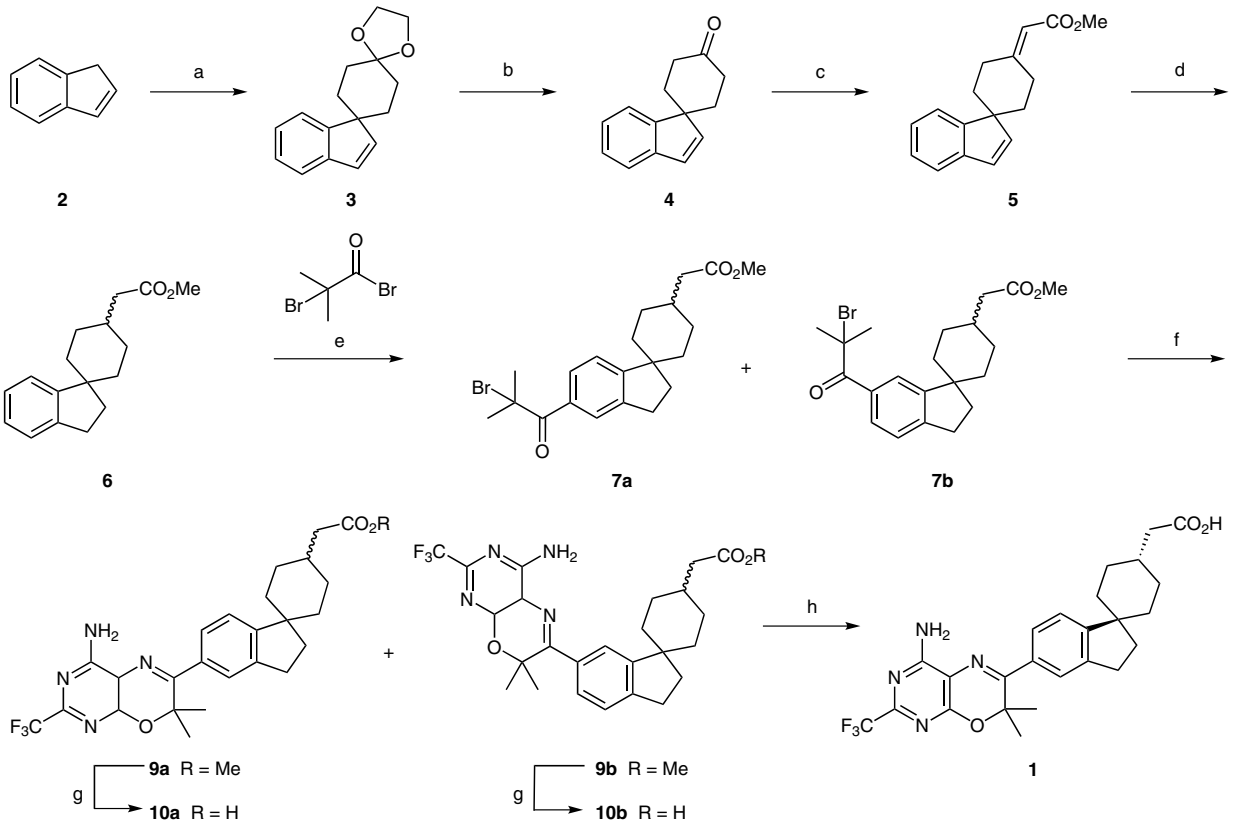
Previously, compound **1** had been prepared by either of two distinct routes. The first route evolved from the needs of the medicinal chemistry campaign. It involved scarce precursors, toxic intermediates, and required several steps of chromatography, including a preparative HPLC to obtain **1** as the pure *trans*-isomer (Scheme 1).[5a,6] Additionally, it was not suitable for scale-up because it was neither stereoselective nor regioselective.

A second synthetic route solved the regiochemical issue using 5-bromoindanone (**11**) as a handle, but the stereoselectivity was not fully addressed (Scheme 2).[5] The key stereoselective hydrogenation yielded only 18% of the desired *trans*-isomer **17** from **15**, and contained 6% of the undesired *cis*-isomer after crystallization. Although, this route rapidly delivered **1** in 4% yield over 11 steps on gram scale, the yields diminished to 1.6% on a larger scale. Additionally, several steps were problematic, such as the use of carbon monoxide and the costly 5-bromoindanone. We describe here a final alternative route, suitable for multi-kilogram scale with high regio- and stereoselectivity.

Key features of the new route are the use of inexpensive and readily available phenol **24**, stereoselective conversion of **23** into **22**, and the regioselective acylation of **21** (Scheme 3).[7]

There is significant literature precedent for high-pressure hydrogenation, even at medium or large scale. However, the conversion of **24** into **25** on this scale under these conditions was beyond our capacity to achieve. It was hypothesized that the hydrogenation could be run at lower pressure (1 bar) by simply increasing the reaction time and temperature (Table 1).[8] Thus, under a blanket of hydrogen at 80 °C with 10 mol% of palladium catalyst, ketone **25** was formed, but with a significant amount of alcohol by-product **26**. However, the catalytic hydrogenation of **24** to **25** proceeded cleanly using only 1.5 mol% of palladium catalyst at 90 °C with hydrogen sparging. Sparging with hydrogen through the reaction mixture was critical to avoid the formation of the alcohol by-product **26**. No alcohol by-product **26** was observed on either a 500 gram or 3.0 kilogram scale with sparging. Unfortu-

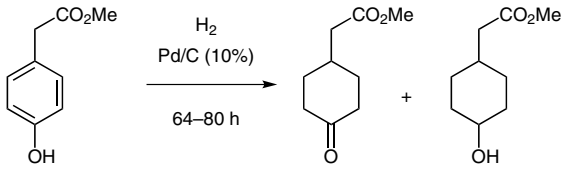
SYNTHESIS 2014, 46, 3047–3058
Advanced online publication: 25.08.2014
DOI: 10.1055/s-0034-1378653; Art ID: ss-2014-m0255-op



Scheme 1 First route to **1**, nonregioselective and nonstereoselective. *Reagents and conditions*: (a) 2,2-bis(2-bromoethyl)-1,3-dioxolane, KHMDS, THF, 0 °C to r.t., 85%; (b) 3 M aq H_2SO_4, MeOH, reflux, 90%; (c) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C to r.t., 90%; (d) H_2, 10% Pd/C, EtOAc, 95%; (e) $AlCl_3$, CH_2Cl_2, 0 °C to r.t., quant; (f) 5,6-diamino-2-(trifluoromethyl)pyrimidin-4-ol (**8**),[5] MeOH, H_2O, 2 M HCl, reflux; (g) LiI, DMF, 135 °C, (h) prep HPLC, 20% over three steps.

nately, the reaction did not go to completion on the 3.0 kilogram scale providing 69% of **25**.

Table 1 Optimization of Hydrogenation of **24** to **25**

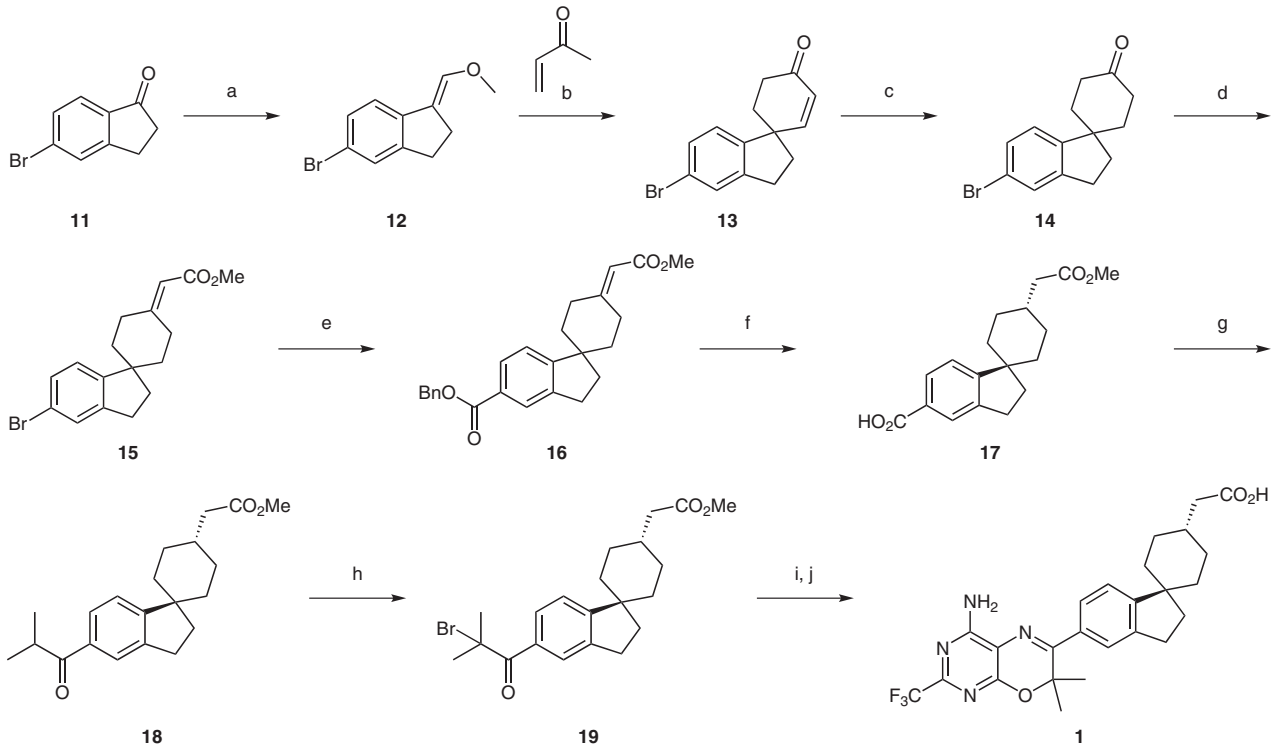


Entry[a]	Amount (g) **24**	H_2	Pd (mol%)	Temp (°C)	Yield (%) of **25**[b]	**26**
1	250	balloon	10	80	N/A[c]	yes
2	<500	balloon	1.5	90	N/A[c]	yes
3	500	sparging	1.5	90	80	no
4	3000	sparging	1.5	90	69[d]	no

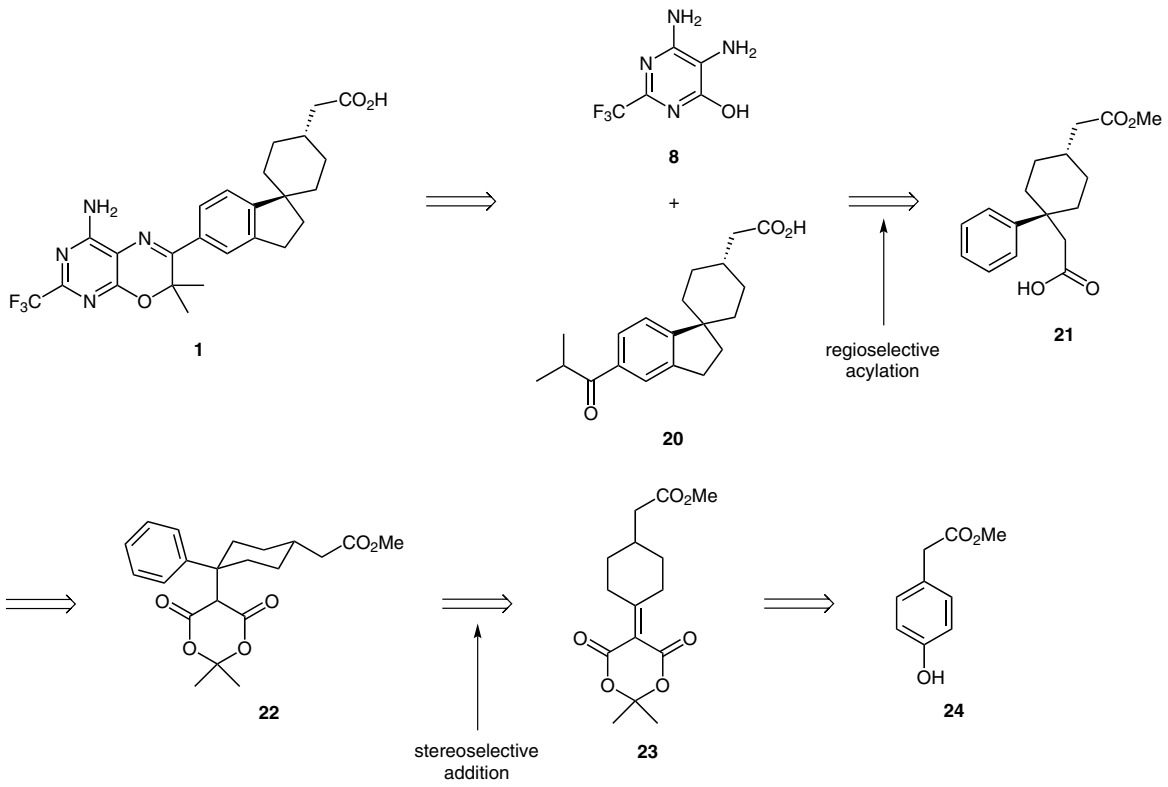
[a] Solvent: AcOH.
[b] Isolated yield after distillation.
[c] Not accurate (N/A) due to by-product **26**.
[d] The reaction stopped at approximately 80% conversion even after 80 h.

The first step in the synthesis of key intermediate **21** is the Knoevenagel condensation of **25** with Meldrum's acid to produce **23**.[9] The standard method using ammonium acetate and acetic acid with molecular sieves in toluene gave **23** in 65% yield.[7] Alternatively, the ketone **25** could be treated with piperidine to form the enamine **27**, which was further reacted with Meldrum's acid to produce **23** in 51% yield depending on scale. Ketone **25** could also be treated with piperidine and a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene with a Dean–Stark trap to form enamine **27**, which was then allowed to condense with Meldrum's acid in dichloromethane at room temperature followed by elimination with aqueous hydrochloric acid to give **23** in 75% yield on a 500 gram scale and 51% yield on a 1.4 kilogram scale from **25** (Scheme 4).

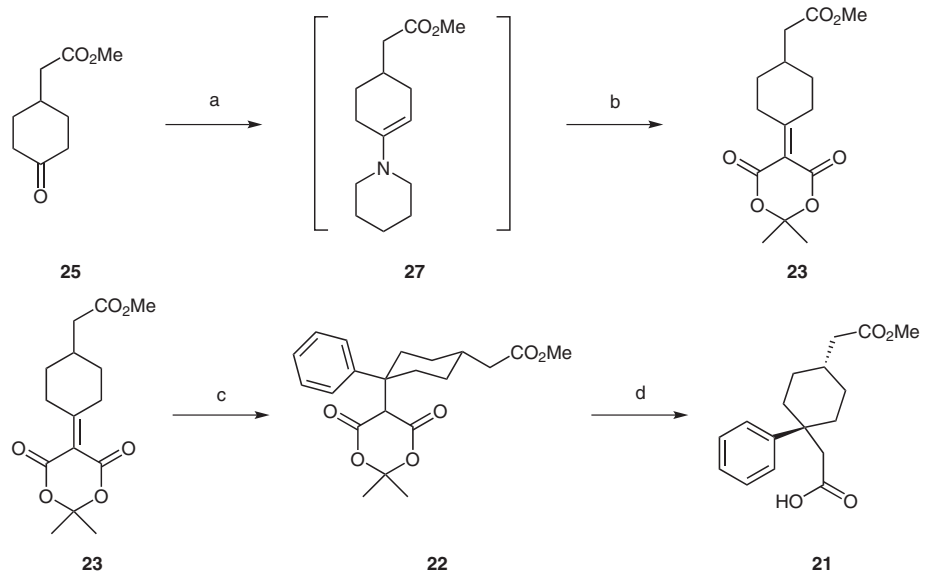
In order to achieve the stereoselective addition on **23** to **22**, several conditions were tried (Table 2). The conjugate addition with the cuprate reagent generated from phenyllithium and cuprous iodide gave **22** in 22% yield as a 1:1 mixture of *cis*/*trans*-isomers.[10] Grignard conjugate addition[11] gave excellent stereoselectivity, but the yield was not reproducible. The best stereoselectivity was achieved in 87–94% yield by using the higher order cuprate as the nucleophile.[7,12] The isopropylidene group of **22** was then hydrolyzed in refluxing 80% aqueous acetic acid, followed by thermal decarboxylation in refluxing xylene to



Scheme 2 Second route to **1**, regioselective, but nonstereoselective. *Reagents and conditions*: (a) $MeOCHPPh_3^+ Cl^-$, *t*-BuOK, THF, DMSO, 0 °C; (b) *p*-TsOH, 1,4-dioxane, H_2O, 39% over two steps; (c) H_2, 10% Pd/C, AcOH, 99%; (d) $(EtO)_2P(O)CH_2CO_2Me$, *t*-BuOK, THF, 97%; (e) CO, BnOH, Et_3N, toluene, $Pd(PPh_3)_4$, 90 °C; (f) H_2, 10% Pd/C, EtOH, r.t., 18% for *trans*-isomer over two steps; (g) i. $(COCl)_2$, CH_2Cl_2, ii. *i*-PrMgCl, CuCN, THF, 99%; (h) $CuBr_2$, EtOAc, $CHCl_3$, 57%; (i) 5,6-diamino-2-(trifluoromethyl)pyrimidin-4-ol (**8**),[5] MeOH, H_2O, aq 2 M HCl, reflux, 24 h, 56%; (j) LiI, DMF, 135 °C, 75%.



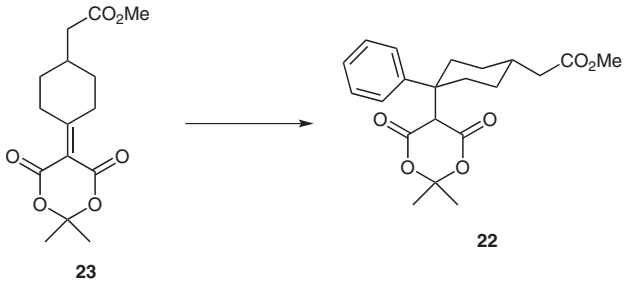
Scheme 3 Retrosynthesis of **1**



Scheme 4 Synthesis of **21** from **25**. *Reagents and conditions*: (a) piperidine, *p*-TsOH, toluene, reflux; (b) i. Meldrum's acid, CH_2Cl_2, r.t., ii. aq HCl, 75%; (c) see Table 2; (d) i. 80% AcOH, H_2O, reflux, ii. xylene, reflux, 64% over two steps.

provide acid **21** in 64% yield. The acid **21** was very crystalline and the desired *trans*-isomer **21** was easily purified from the minor *cis*-isomer impurity.

Table 2 Stereoselective Addition to **22**



Entry	Conditions	Yield (%)[a]	*trans*-**22**/*cis*-**22**
1	PhLi, CuI, Et_2O	22	1:1
2	PhMgBr, THF	24–87[b]	11:1
3	PhMgBr, CuCN, LiCl, THF	87–94	10:1

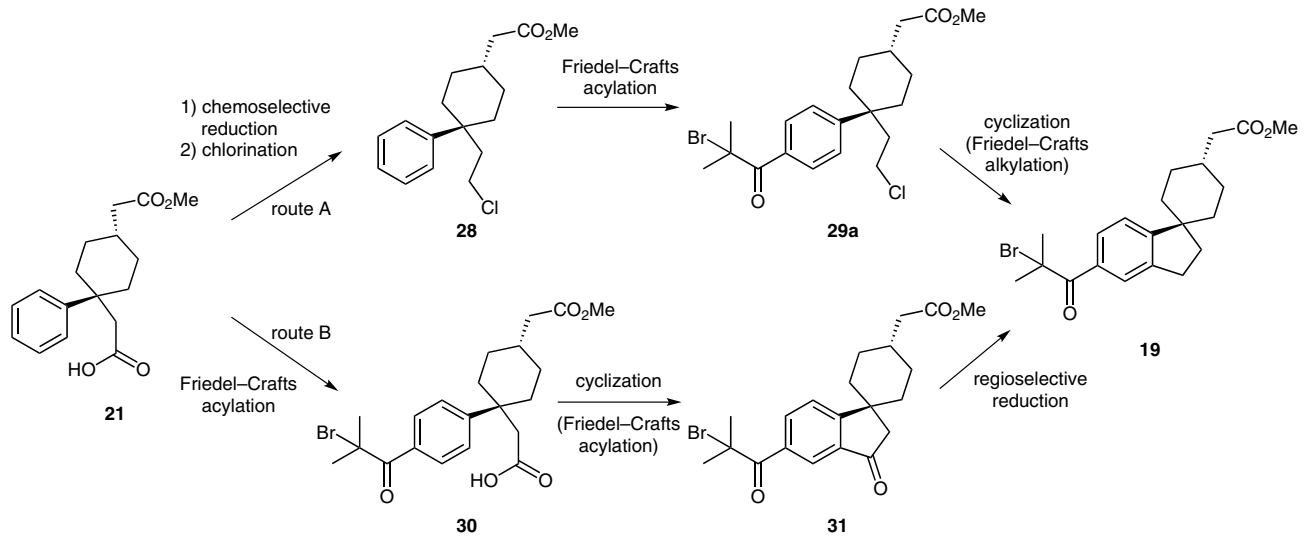
[a] Isolated yield after precipitation.
[b] Yield was not reproducible.

Two alternative regiospecific routes A and B to indane **19** from acid **21** were envisioned (Scheme 5). Route A involved the chemoselective reduction of the acid **21** to a primary alcohol followed by conversion into the chloride **28**. Subsequent Friedel–Crafts *para*-acylation of **28** should produce **29,** followed by intramolecular Friedel–Crafts alkylation to form indane intermediate **19**. Route B, on the other hand, involved initial Friedel–Crafts *para*-acylation of **21** to **30** followed by intramolecular Friedel–Crafts acylation to form **31**. The regioselective reduction of the less-hindered ketone to a methylene group should provide **19**.

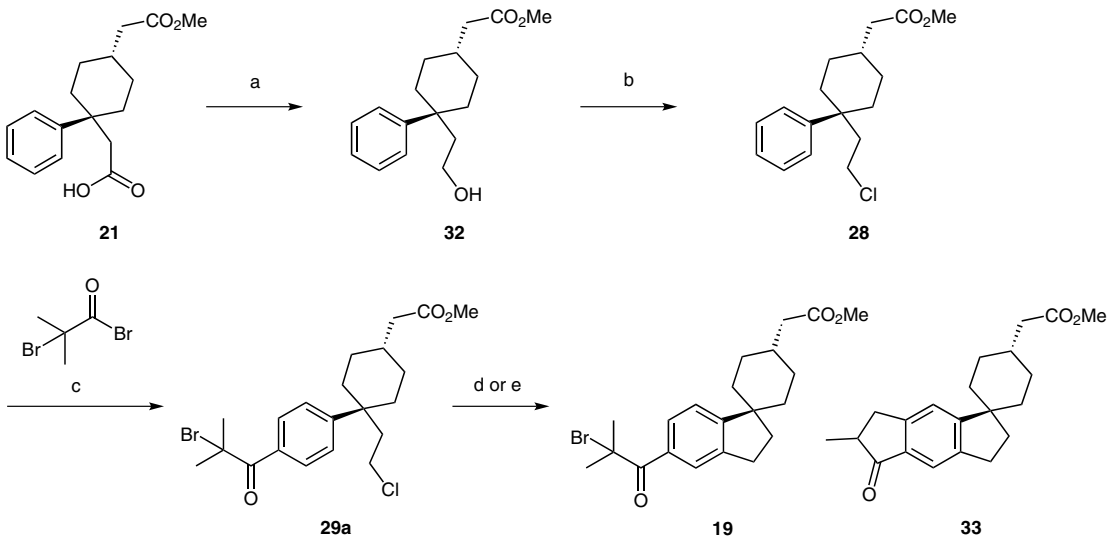
Following route A, the acid **21** was reduced to the corresponding alcohol **32** using one equivalent of borane-tetrahydrofuran complex in tetrahydrofuran at –18 °C in over 92% yield. However, if more than two equivalents of borane are used, both acid and methyl ester are reduced to alcohols. The alcohol **32** was converted into chloride **28** in 78% yield. This was followed by the Friedel–Crafts acylation of chloride **28** with 2-bromoisobutyryl bromide and aluminum chloride in dichloromethane to give **29**, regioselectively in 90% yield, with no Friedel–Crafts alkylation of the chloride. At this point, in order to cyclize to the indane **19**, two conditions were tried. The acylated chloro compound **29** was treated with aluminum chloride in refluxing 1,2-dichloroethane or aluminum chloride with sodium chloride at 150 °C. Unfortunately, the unwanted indanone **33** was the only product, formed through the conversion of **19** into the α,β-unsaturated ketone intermediate with simultaneous intramolecular cyclization (Scheme 6).[13]

In order to avoid this unwanted ring closure, **28** was acylated using isobutyryl chloride to give **29**. However, the desired indane **18** was not obtained even under a variety of conditions (Scheme 7).

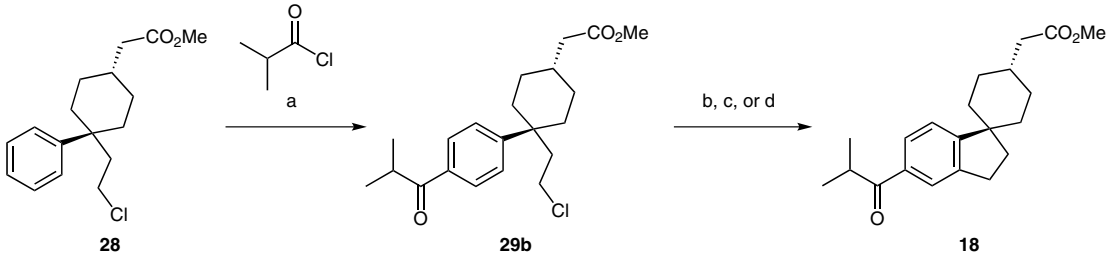
To effect this intramolecular Friedel–Crafts alkylation, alcohol **32** was converted into mesylate **34** using methanesulfonyl chloride and triethylamine in 99% yield. We envisioned that the mesylate would react by way of Friedel–Crafts alkylation, but would still be less reactive than the Friedel–Crafts acylation with isobutyryl chloride. Unfortunately, this Friedel–Crafts acylation/alkylation of **34** with isobutyryl bromide and aluminum chloride in dichloromethane at 0 °C gave the two *para*-directed regioisomers **35a** and **35b**, reminiscent of **7a** and **7b** along with



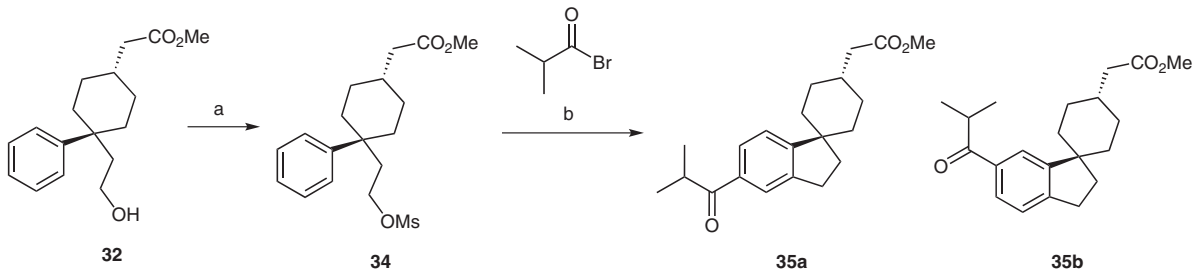
Scheme 5 Proposed regiospecific routes A and B to indane **19**



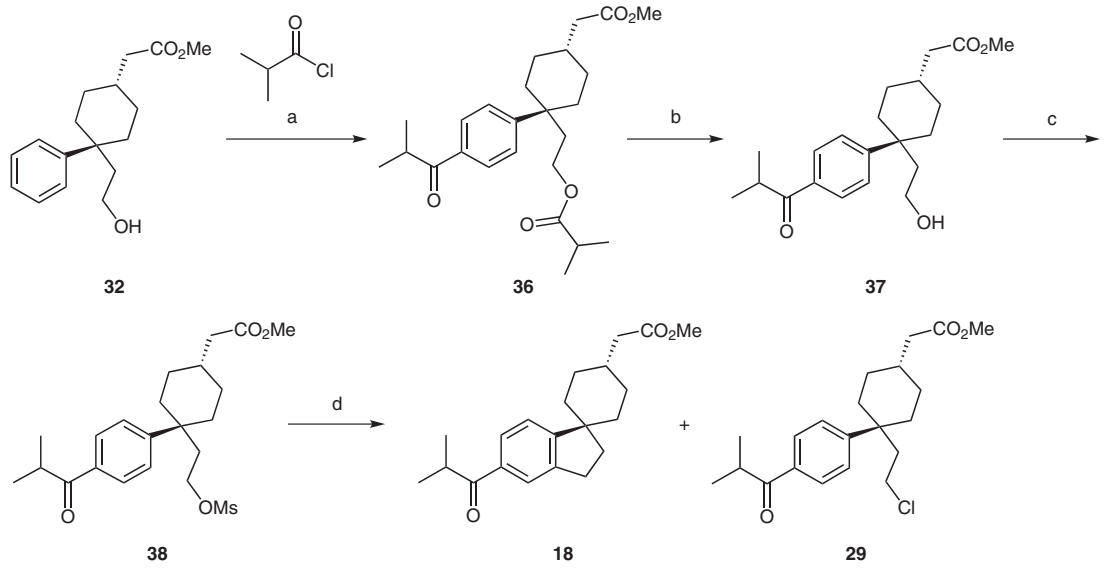
Scheme 6 Route A: Chemoselective reduction and Friedel–Crafts acylation and alkylation to **19**. *Reagents and conditions*: (a) $THF{\cdot}BH_3$, THF, –18 °C to r.t., 92%; (b) $SOCl_2$, pyridine, benzene, reflux, 78%; (c) $AlCl_3$, CH_2Cl_2, r.t., 90%; (d) $AlCl_3$, DCE, reflux; (e) $AlCl_3$, NaCl, 150 °C.



Scheme 7 Route A: Friedel–Crafts acylation and alkylation with chloride. *Reagents and conditions*: (a) $AlCl_3$, CH_2Cl_2, r.t.; (b) $AlCl_3$, DCE, reflux; (c) $AlCl_3$, NaCl, 150 °C; (d) H_2SO_4, 100 °C.



Scheme 8 Route A: Friedel–Crafts acylation and alkylation with mesylate. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; (b) $AlCl_3$, CH_2Cl_2, 0 °C, 49%.

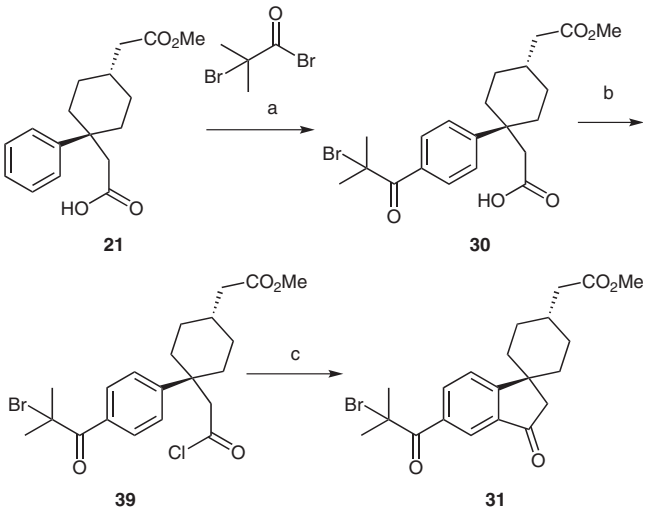


Scheme 9 Route A: Alternative approach to **18**. *Reagents and conditions*: (a) $AlCl_3$, CH_2Cl_2, 0 °C to r.t., 58%; (b) NaOMe, MeOH, r.t.; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 48% over two steps; (d) $AlCl_3$, CH_2Cl_2, reflux.

an unknown by-product. This result indicated that the intramolecular Friedel–Crafts alkylation preceded the Friedel–Crafts acylation (Scheme 8).

Direct Friedel–Crafts acylation of alcohol **32** using two equivalents of isobutyryl chloride and aluminum chloride in dichloromethane was attempted producing the doubly acylated product **36** in 58% yield. The alcohol **37** was obtained by deblocking with sodium methoxide to provide **37**, which was subsequently converted into **38** in 48% yield over two steps. Mesylate **38** was transformed to **18** with aluminum chloride in dichloromethane, but the chloro by-product **29** and an unknown by-product were obtained as major products (Scheme 9). After these efforts on route A, it became clear that aluminum chloride-mediated intramolecular Friedel–Crafts alkylation would not be efficient in this relatively electron-poor aryl system.

The successful conversion of **21** into spiroindanone **31** was done in three steps. First, the acid **21** was converted into **30** through Friedel–Crafts *para*-acylation. The order of addition of reagents was important to avoid the intramolecular cyclization by the carboxylic acid moiety in **21** before the desired Friedel–Crafts acylation. The crude product **30** was treated with two equivalents of oxalyl chloride and a catalytic amount of *N*,*N*-dimethylformamide in dichloromethane at room temperature to give acid chloride **39**. This acid chloride **39** was immediately treated with aluminum chloride in refluxing 1,2-dichlo-



Scheme 10 Route B: Successful conversion of **21** into **31**. *Reagents and conditions*: (a) $AlCl_3$, CH_2Cl_2, –15 °C; (b) $(COCl)_2$, DMF, CH_2Cl_2, r.t.; (c) $AlCl_3$, DCE, reflux, 63% over three steps.

roethane to give spiroindanone **31**, which was easily isolated as a pure solid from the crude reaction mixture by simple precipitation. These three steps were performed without any purification to give **31** in 63% yield on a 350 gram scale (Scheme 10).

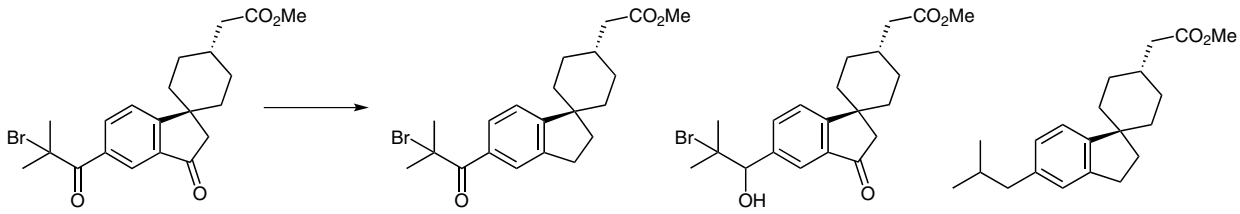
In order to reduce the spiroindanone **31** regioselectively, several different approaches were attempted. The treatment of sprioindanone **31** with excess triethylsilane in trifluoroacetic acid at room temperature reduced 2-bromo-2-methylpropanoyl ketone to a secondary alcohol by-product **40**, instead of **19**. When the reaction was continued in refluxing trifluoroacetic acid, both ketones were reduced to give the putative methylene by-product **41**. The reduction of **31** with *tert*-butylamine borane complex in dichloromethane at 0 °C also gave the presumed secondary alcohol by-product **40** (Table 3).

The successful regioselective reduction of **31** was realized by taking advantage of the enolizable ketone in **31**. The enol triflate **42** was prepared by treatment of spiroindanone **31** with trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine and 2,4,6-collidine in dichloromethane at room temperature. We had tried to use isobutyryl bromide instead of 2-bromo 2-methylpropanoyl bromide to effect these transformations but were unable to prevent the bis-enol triflate formation. The bromo group functioned as a blocking group for this step. The solvents were removed and the crude enol triflate **42** was carried on to the next step without purification. Intermediate **42** was reduced with catalytic platinum oxide in the presence of excess lithium carbonate in methanol under one atmosphere of hydrogen to give the debrominated by-product **18** in 82% yield from spiroindanone **31** after crystallization on a 460 gram scale (Scheme 11). Unfortunately, the bromine could not be preserved under the reduction conditions. However, α-bromination is known to be a trivial reaction, so **18** was used as an intermediate for the next reactions.[5] The treatment of **18** with 20% sodium hydroxide in refluxing 1,4-dioxane and water followed by acidification with aqueous 2 M hydrochloric acid gave crude acid **20** in 99% yield on a 336 gram scale. The acid **20** was successfully brominated with copper bromide in refluxing acetonitrile to form **43** in 95% yield after precipitation on a 232 gram scale (Scheme 12).

Compound **43** was then treated with **8** in refluxing acetonitrile and water for five days to give compound **1** in 72% yield after precipitation on a 335.9 gram scale (Scheme 13).

Relatively inexpensive **24** was converted into **1** in 5.2–14.7% yield (depending on scale) over 12 steps. Key features include: catalytic hydrogenation, Knoevenagel condensation with Meldrum's acid, phenyl cuprate addition, deprotection and decarboxylation, Friedel–Crafts acylation and cyclization, enol triflate formation with subsequent reduction, ester hydrolysis, bromination, and final

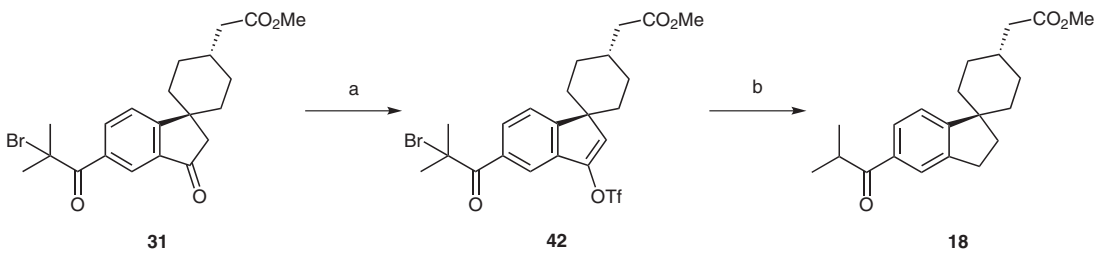
Table 3 Route B: Studies on Regioselective Reduction of **31**



31 **19** **40** **41**

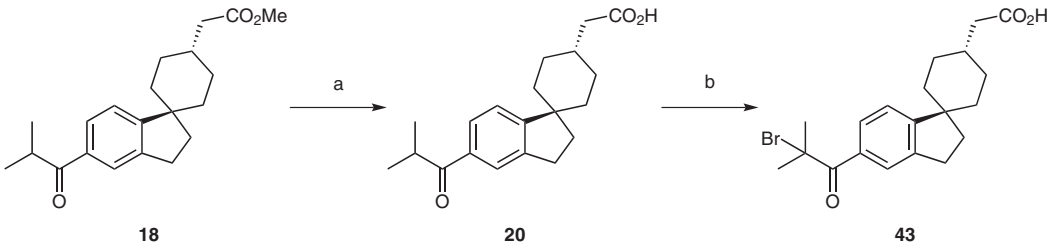
Entry	Conditions	**19**[a]	**40**[a]	**41**[a]
1	Et_3SiH, TFA, r.t.	none	√	
2	Et_3SiH, TFA, reflux	none		√
3	*t*-$BuNH_2 \cdot BH_3$, CH_2Cl_2, 0 °C	trace	√	

[a] Not isolated, putative structures based on MS.

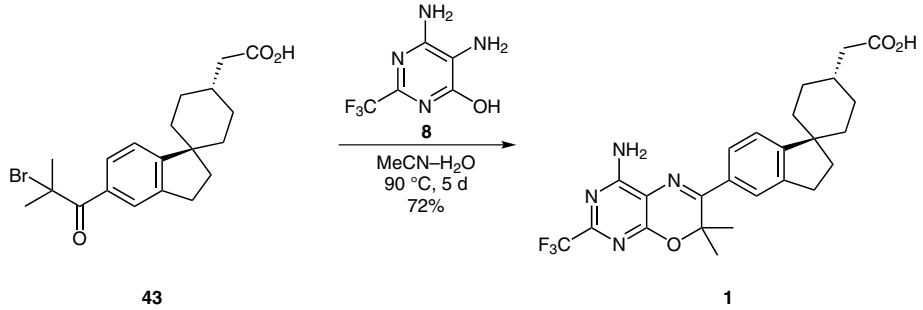


31 **42** **18**

Scheme 11 Route B: Successful regioselective reduction of **31**. *Reagents and conditions*: (a) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, 2,4,6-collidine, CH_2Cl_2, r.t.; (b) H_2, PtO_2, Li_2CO_3, MeOH, r.t., 81% over two steps.



Scheme 12 Route B: Ester hydrolysis and bromination. *Reagents and conditions*: (a) i. 20% NaOH, 1,4-dioxane, H_2O, reflux, ii. aq 2 M HCl, 99%; (b) $CuBr_2$, MeCN, reflux, 95%.



Scheme 13 Route B: Cyclization to **1**

condensation with **8**. This synthesis has great advantages, providing a good yield, no wasteful, time-consuming column chromatography purification steps and with excellent regioselectivity and stereoselectivity. The synthesis is suitable for multi-kilogram scale (Scheme 14).

All solvents and chemicals used were reagent grade. Anhydrous solvents were purchased from Aldrich and used as such. Analytical TLC and flash chromatography were performed on Merck silica gel 60 (230–400 mesh). Removal of solvents was conducted by using a rotary evaporator and residual solvent was removed from nonvolatile compounds using a vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields. Preparative reversed-phase high pressure liquid chromatography (RP-HPLC) was performed using an Agilent 1100 series HPLC and Phenomenex Gemini C18 column (5 µm, 100 mm × 30 mm i.d.), eluting with a binary solvent system A and B using a gradient elution (A: H_2O with 0.1% TFA, B: MeCN with 0.1% TFA) with UV detection at 220 nm. All final compounds were purified to ≥95% purity as determined by an Agilent 1100 series HPLC with UV detection at 220 nm using the following method: Zorbax SB-C8 column (3.5 µm, 150 mm × 4.6 mm i.d.), eluting with a binary solvent system A and B using a 5–95% B (0–15 min) gradient elution (A: H_2O with 0.1% TFA, B: MeCN with 0.1% TFA); flow rate 1.5 mL/min. Mass spectral data was recorded on an Agilent 1100 series LCMS with UV detection at 254 nm. NMR spectra were recorded on a Varian Gemini 400 MHz or Bruker Avance 500 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as internal reference and coupling constants (*J*) are reported in Hz. Standard abbreviations are used to denote the splitting patterns.

Methyl 2-(4-Oxocyclohexyl)acetate (25)

A 20 L reaction vessel was vacuum purged of air and flushed (6 ×) with N_2. To this vessel blanketed in N_2, 10% Pd/C (300.0 g) was carefully added followed by methyl 4-hydroxyphenylacetate (**24**; 3.0 kg, 18.05 mol) at all times maintaining a slight positive pressure of N_2 gas. AcOH (6.0 L) was then slowly added via a large addition funnel. The resulting mixture was stirred and sparged with more N_2 (large bubbler) for some time. The N_2 gas was then replaced with H_2 and the sparging continued as the reaction mixture was heated to 90 °C with continued H_2 sparging for 80 h. At this time, the reaction mixture was cooled down to r.t. and the reaction vessel vacuum purged (6 ×) with N_2 gas. The heterogeneous solution was removed via a tygon tube and carefully filtered through Celite and washed with CH_2Cl_2 (4 L) at all times keeping the filter cake moist. The resulting solution was concentrated in vacuo to provide a viscous liquid. The viscous liquid was purified by distillation (100 °C/0.5 mm Hg) to provide **25** as a colorless oil; yield: 2.11 kg (69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.69 (s, 3 H), 2.38 (m, 4 H), 2.33 (m, 2 H), 2.27 (m, 1 H), 2.09 (m, 2 H), 1.47 (m, 2 H).

MS (ESI+): *m*/*z* = 171.1 (M + 1).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.16; H, 8.51.

Methyl 2-[4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)cyclohexyl]acetate (23)

A 12 L 3-necked flask equipped with two Dean–Stark traps was charged with toluene (2.7 L), **25** (1.4 kg, 8.2 mol), piperidine (1.1 L, 11.1 mol) and *p*-TsOH (47 g, 0.25 mol). The mixture was heated to reflux. After 7 h, GC analysis indicated that 60% of **25** remained. After a further 1.5 h at reflux, the reaction mixture was allowed to cool down overnight and the reflux was resumed the following morning. The reaction was monitored by GC and after a further 6 h, the reaction had reached a point where no further conversion of starting material into enamine appeared to be occurring; 17% of compound **25** remained by GC. The reaction mixture was allowed to cool to r.t. overnight and the solvent was evaporated in vacuo (45 Torr/58 °C). Toluene (600 mL) was added and evaporated in vacuo to further remove additional H_2O. This process was repeated twice to give the enamine **27**. CH_2Cl_2 (12 L) was added to the crude enamine **27**. Following dissolution, a solution of Meldrum's acid (1.18 kg, 8.2 mol) in CH_2Cl_2 (2 L) was added over a period of 10 min (the internal temperature of the reaction did not rise more than 3–4 °C

during addition). The reaction was allowed to stir for 10 min and was found to be complete by GC analysis. Aq 3 M HCl (2.7 L) was added and the reaction mixture stirred vigorously for 15 min and monitored by GC. The aqueous phase was removed and a 5% aq solution of $NaHCO_3$ (2 L) was added and the mixture stirred vigorously. The aqueous phase was removed and this process was repeated twice using a 2.5% aq solution of $NaHCO_3$ (2 × 2 L). The organic solvent was then evaporated in vacuo (170 Torr/30 °C). Toluene (1 L) was added and the solvent again removed in vacuo (82 Torr/40 °C). This process was repeated with an additional amount of toluene (800 mL). The resultant orange oil was left standing for 90 min. After this time, crystals had formed in the flask, which were scratched to speed up crystallization. This resulted in solid crashing out of the oil to provide a yellow oil/solid mixture. EtOAc (600 mL) was added and the mixture stirred with a mechanical stirrer to provide a thick suspension. Heptane (2 × 600 mL) was added, and after stirring for 15 min a dark yellow, sticky solid was obtained. EtOAc (400 mL) was added and the solid became white while the solvent turned from pale yellow to orange. The mixture was stirred for 30 min and the precipitate was filtered, washed with 10% EtOAc in heptane (600 mL) and dried in vacuo to provide **23** as an off-white solid; yield: 1.23 kg (51%).

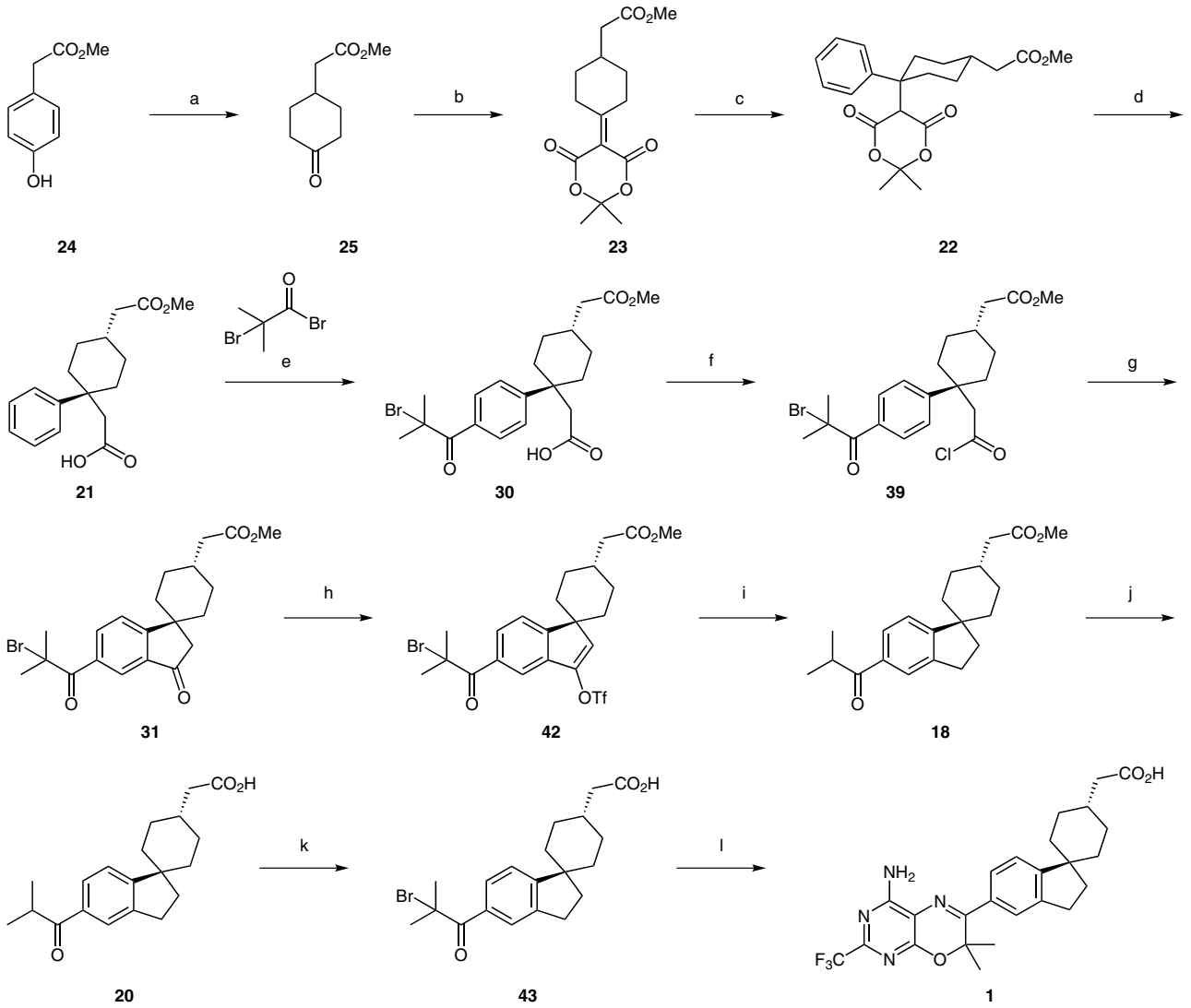
GC Analysis: Settings: 80 °C for 2 min, then 20 °C/min increase to 300 °C; starting ketone retention time: 2.8 min.; enamine retention time: 6.2 min.; Meldrum's acid adduct retention time: 2 peaks at 8.4 min.; **23**: peak appears at 5.08 min, but product was found to be somewhat unstable to GC conditions.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.70–3.75 (m, 5 H), 2.22–2.34 (m, 5 H), 2.14–2.16 (m, 2 H), 1.75 (s, 3 H), 1.74 (s, 3 H), 1.35–1.41 (m, 2 H).

MS (ESI+): *m*/*z* = 319.0 (M + 23).

Methyl 2-[(*trans*)-4-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-phenylcyclohexyl)acetate (22)

A 20 L 5-necked reactor equipped with a cooling jacket and pneumatic overhead stirring was charged under N_2 atmosphere with CuCN (430 g, 4.80 mol), LiCl (407 g, 9.60 mol), and THF (4 L).



Scheme 14 Improved synthetic route to **1**. *Reagents and conditions*: (a) H_2, Pd/C, AcOH, 90 °C, 69%; (b) i. piperidine, *p*-TsOH, toluene, reflux, ii. Meldrum's acid, CH_2Cl_2, r.t., iii. aq HCl, 51%; (c) CuCN, LiCl, THF, PhMgBr, 0 °C to r.t., 81% for *trans*-isomer; (d) i. 80% AcOH, H_2O, reflux, ii. xylene, reflux, 64% over two steps; (e) $AlCl_3$, CH_2Cl_2, –15 °C; (f) $(COCl)_2$, DMF, CH_2Cl_2, r.t., (g) $AlCl_3$, DCE, reflux, 63% over three steps; (h) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, 2,4,6-collidine, CH_2Cl_2, r.t.; (i) H_2, PtO_2, Li_2CO_3, MeOH, r.t., 81% over two steps; (j) i. aq 20% NaOH, 1,4-dioxane, H_2O, reflux, 2 h, ii. aq 2 M HCl, 99%; (k) $CuBr_2$, MeCN, reflux, 95%; (l) 5,6-diamino-2-(trifluoromethyl)pyrimidin-4-ol (**8**), MeCN, H_2O, 90 °C, 72%.

The mixture was stirred for 20 min to afford scant LiCl granules against a green solution. The solution was brought to –4 °C whereupon cannulation of a 3 M solution of PhMgBr in THF (3.20 L, 9.60 mol) was initiated. The rate of addition and cooling was controlled to maintain a temperature between –4 and 5 °C and required a total of 2.5 h. The dark viscous solution was stirred an additional 35 min between –6 and 5 °C, after which the temperature was allowed to rise to 17 °C over 1 h. The cuprate solution was then cooled to –15 °C. To the cuprate solution was added a 1.68 M solution of **23** in THF (2.25 L, 3.78 mol) over a period of 45 min at a rate sufficient to maintain the temperature between –6 and 5 °C. The reaction was complete within 5 min as evidenced by TLC [sat. aq NH_4Cl extraction against EtOAc, eluted with 30% EtOAc in hexane, TLC: PMA stain, R_f (product) = 0.5]. The reaction contents were poured into sat. aq NH_4Cl (12 L) and stirred vigorously while sparging with air for 45 min. EtOAc (6 L) was added to the resulting purple suspension followed by paper filtration. The solids were resuspended in additional EtOAc (6 L) and filtered. The organics from the second filtration were used to re-extract the sequestered aqueous layer from the first filtration. The combined organics were evaporated in vacuo. The solids were resuspended in EtOAc (6 L) and extracted against 0.5 M HCl (1.5 L) then brine (1.5 L). The organics were dried with $MgSO_4$ (250 g) and evaporated in vacuo. Suspension of the resulting solids in hexanes with vigorous stirring followed by filtration and drying under vacuum afforded **22** as a white solid; yield: 1.15 kg (81%). ^{1}H NMR spectra matched that of the previously reported spectra indicating a 7% presence of the *cis*-isomer.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.71 (s, 3 H, major isomer only, 93%), 0.79 (s, 3 H, minor isomer only), 1.5 (s, 3 H, minor isomer only), 1.51 (s, 3 H, major isomer only), 1.54–1.60 (m, 2 H, major and minor isomers), 1.68–1.84 (m, 2 H, major and minor isomers), 1.86–2.00 (m, 2 H, major and minor isomers), 2.04–2.06 (m, 2 H, minor isomer only), 2.36 (d, *J* = 7 Hz, 2 H, major isomer only), 2.90 (br d, *J* = 13 Hz, 2 H major isomer only), 2.96 (br s, 2 H, minor isomer only), 3.63 (s, 3 H, minor isomer only), 3.71 (s, 3 H, major isomer only), 3.86 (br s, 1 H), 7.24–7.44 (m, 5 H, major and minor isomers).

MS (ESI–): *m*/*z* = 373.1 (M – 1).

2-[(*trans*)-4-(2-Methoxy-2-oxoethyl)-1-phenylcyclohexyl]acetic Acid (21)

A 12 L 3-necked flask equipped with a mechanical stirrer and two reflux condensers was charged with AcOH (3.53 L) and H_2O (880 mL) and heated until the solution was gently refluxing. At this time, **22** (588 g, 1.57 mol) was added quickly by removing one condenser and replacing it with a large funnel. The mixture was refluxed for 25 min, and the heat source was removed to allow the solution to cool. After 15 min of cooling, the volatiles were removed in vacuo. The tan residue was triturated with hexane (1.75 L) and Et_2O (250 mL). This mixture was stirred for 1 h and filtered. The filter cake was dried and found to weigh 450 g. This material was used without further purification. The intermediate dicarboxylic acid (450 g, 1.35 mol) was charged in a 12 L 3-necked flask equipped with a mechanical stirrer and two reflux condensers with *p*-xylene (5.2 L). The mixture was heated to reflux in 0.5 h, and continued at full reflux for 3.5 h. The heating was stopped and the contents were allowed to cool. After 2 h, most of the xylene was removed in vacuo, the clumpy residue was removed from the receiving flask using Et_2O (1.2 L) and transferred to a 6 L Erlenmeyer flask. This was used to effect crystallization with the addition of more Et_2O (2 L total volume). The solution was gently heated until the volume was reduced to 1.3 L (as measured from the flask markings). This was cooled and stirred slowly overnight to affect recrystallization. The crystals were collected by filtration to provide **21** (crop 1, 206 g). During the suction filtration, additional crystals were formed in the filtrate and the solution was allowed to stand overnight at which point these crystals were collected to give **21** (crop 2, 99 g). The remaining mother liquor was evaporated and the crude dried residue chromatographed (4:1 hexane–EtOAc) to provide **21** (crop 3, 55.75 g) of slightly impure material. At this time, crop 2 and crop 3 were combined and recrystallized a final time [hexane (4 L)–Et_2O (700 mL)] to provide **21** (crop 4, 86.5 g); final yield of **21**: 292.5 g (64%); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.35 (m, 4 H), 7.17–7.23 (m, 1 H), 3.68 (s, 3 H), 2.70 (s, 2 H), 2.31 (d, *J* = 7.2 Hz, 2 H), 2.23 (d, *J* = 12.8 Hz, 2 H), 1.84 (dtt, *J* = 14.4, 7.3, 3.3 Hz, 1 H), 1.66–1.79 (m, 4 H), 1.30–1.40 (m, 2 H).

^{13}C NMR (151 MHz $CDCl_3$): δ = 177.2, 173.3, 147.3, 128.1, 126.1, 125.6, 51.5, 41.5, 41.0, 39.2, 35.0,33.8, 28.2.

MS (ESI–): *m*/*z* = 290 and 289 (M – 1).

2-{(*trans*)-1-[4-(2-Bromo-2-methylpropanoyl)phenyl]-4-(2-methoxy-2-oxoethyl)cyclohexyl}acetic Acid (30)

A 12 L 3-necked flask equipped with a mechanical stirrer and an addition funnel was placed under a N_2 atmosphere, charged with a suspension of $AlCl_3$ (539.36 g, 4.05 mol) and CH_2Cl_2 (2 L), and cooled to –15 °C in an EtOH–H_2O (1:4) bath with dry ice. The addition funnel was charged with 2-bromo-2-methylpropionyl bromide (324 mL, 2.62 mol) and added dropwise over 20 min. The reaction mixture was stirred at –15 °C for 35 min. A clean addition funnel was placed, charged with a solution of **21** (345.43 g, 1.19 mol) in CH_2Cl_2 (2 L), and the solution was added dropwise over 40 min. The reaction temperature was then allowed to warm to 15 °C over 5 h with stirring. The mixture was poured onto ice water (4 L). The aqueous layer was extracted with CH_2Cl_2 (2 × 2 L), and the combined organic layers were washed with brine (1 × 4 L), dried over $MgSO_4$ (100 g) filtered, and concentrated in vacuo to give **30** as a syrup (522.67 g), which was used directly in the following step.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.6 Hz, 2 H), 7.4 (d, *J* = 8.6 Hz, 2 H), 3.69 (s, 3 H), 2.77 (s, 2 H), 2.31 (d, *J* = 6.95 Hz, 2 H), 2.24 (d, *J* = 12.98 Hz, 2 H), 2.04 (s, 6 H), 1.85–1.70 (m, 5 H), 1.36 (m, 2 H).

MS (ESI–): *m*/*z* = 437 and 439 (M – 1).

Methyl 2-{(*trans*)-4-[4-(2-Bromo-2-methylpropanoyl)phenyl]-4-(2-chloro-2-oxoethyl)cyclohexyl}acetate (39)

A 3 L-flask was charged with a solution of the crude **30** (522.67 g) in CH_2Cl_2 (1 L) and cooled to 0 °C in an ice water bath. Oxalyl chloride (208 mL, 2.38 mol) and DMF (3 drops) were added dropwise. The ice bath was removed, and the reaction mixture was stirred at r.t. After 2 h at r.t., LC-MS showed the reaction to be complete. The solvent was removed in vacuo to provide the acid chloride **39** as a foamy syrup (544.62 g), which was used directly in the following step.

Methyl 2-{(*trans*)-5′-(2-Bromo-2-methylpropanoyl)-3′-oxo-2′,3′-dihydrospiro[cyclohexane-1,1′-inden]-4-yl}acetate (31)

A 5 L 3-necked flask equipped with a condenser and an addition funnel was charged with a suspension of $AlCl_3$ (380.72 g, 2.86 mol) in CH_2Cl_2 (1 L) and cooled to 0 °C in an ice water bath. The addition funnel was charged with a solution of the acid chloride **39** in DCE (1.5 L) and added dropwise over 15 min. The reaction mixture was then heated at reflux. After 1.5 h at reflux, LC-MS showed the reaction to be complete. The mixture was poured onto ice-water (3 L). The aqueous layer was extracted with CH_2Cl_2 (2 × 2 L), and the combined organic layers were washed with brine (1 × 3 L), dried over $MgSO_4$ (200 g), filtered through a silica gel pad (650 g), and the silica gel pad was washed with EtOAc–hexane (1:2, 7 L). The filtrate was then concentrated in vacuo to give a brown syrup. The desired product **31** was isolated as a pure solid from the crude mixture after precipitation from Et_2O (450 mL) and hexane (1.8 L) with stirring. The precipitates were filtered, and washed with hexane (2 L) to give **31** as a yellow solid; yield: 314.78 g (63% over three steps).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.46–8.56 (m, 1 H), 8.34 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 3.70 (s, 3 H), 2.62 (s, 2

H), 2.30 (d, *J* = 7.2 Hz, 2 H), 2.04 (s, 6 H), 1.92–2.02 (m, 1 H), 1.84–1.92 (m, 4 H), 1.61 (d, *J* = 12.8 Hz, 2 H), 1.15–1.24 (m, 2 H).

^{13}C NMR (151 MHz $CDCl_3$): δ = 204.5, 195.9, 173.1, 166.9, 136.4, 135.4, 134.5, 125.4, 124.0, 60.1, 51.5, 48.3, 43.0, 41.4, 37.8, 34.0, 31.4, 30.0.

MS (ESI+): *m*/*z* = 421 and 423 (M + 1).

Methyl 2-{(*trans*)-5′-(2-Bromo-2-methylpropanoyl)-3′-{[(trifluoromethyl)sulfonyl]oxy}spiro[cyclohexane-1,1′-inden]-4-yl}acetate (42)

A 5 L 3-necked flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel was charged with **31** (463 g, 1.10 mol) and CH_2Cl_2 (1.85 L). The mixture was stirred, and over the course of 7 min, triflic anhydride (200 mL, 1.154 mol) was added with an addition funnel. This was followed by the addition in the same way of 2,4-di-*tert*-butyl-4-methylpyridine (90.2 g, 0.44 mol) over 5 min, keeping the temperature between 25–29 °C with a large cooling bath. Finally, 2,4,6-trimethylpyridine (102 mL, 0.77 mol) was added in the same manner in 5 min while maintaining the temperature between 29–40 °C with the cooling bath. After 5 min, the temperature had dropped to 30 °C and the cooling bath was removed, the solution was stirred for an additional 1 h, after which the TLC (eluent: EtOAc–hexane, 1:4) indicated the reaction was complete. The solution was diluted with CH_2Cl_2 (1 L) and transferred to a large plastic bucket where it was washed with HCl (0.05 M, 1 L). The CH_2Cl_2 solution was further diluted to 4.5 L total volume and washed with brine (2 L). The resulting solution was dried (Na_2SO_4) further, filtered, and the CH_2Cl_2 was removed in vacuo to provide **42** as a brown syrup (608.73 g, 1.10 mol), which when dried in vacuo was used without further purification. (A significant amount of 2,6-di-*tert*-butyl-4-methylpyridine remained).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 9.4 Hz, 1 H), 8.15 (s, 1 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 6.71 (s, 1 H), 3.71 (s, 3 H), 2.36 (d, *J* = 6.9 Hz, 2 H), 1.95–2.08 (m, 11 H), 1.45 (d, *J* = 13.7 Hz, 2 H), 1.28–1.37 (m, 2 H).

MS (ESI+): *m*/*z* = 553 and 555 (M + 1).

Methyl 2-{(*trans*)-5′-Isobutyryl-2′,3′-dihydrospiro[cyclohexane-1,1′-inden]-4-yl}acetate (18)

The intermediate triflate **42** (608.73 g, 1.10 mol) was placed in a large (20 L) conical reaction vessel equipped with three-way ports. The triflate was dissolved in MeOH (10 L) and was stirred vigorously with magnetic stirring. After the dissolution, Li_2CO_3 (406 g, 5.5 mol) and PtO_2 (13.5 g, 0.055 mol) were added. The tan reaction mixture was then carefully vacuum-purged with N_2 three times. This was then followed by three vacuum-purge cycles with H_2. The mixture was then stirred over a blanket of H_2 gas with three large balloons of H_2, the balloons had to be recharged several times. After 2.5 h, the H_2 was replaced with N_2 by vacuum purge. The heterogeneous mixture was carefully filtered through a large plug of Celite (>1 kg) into a large filtering flask, being ever mindful at all times that the filter cake remain moist. The Celite was washed with MeOH (6 L), again never allowing the filter cake to become dry. After the final rinse, the still saturated fritted funnel was removed and placed in another large filtering flask and quenched with H_2O (3–4 L). The Pt/Celite was never allowed to become dry in this process. The large volume of MeOH was removed by evaporation and the resulting solid stirred in hexane (6 L) overnight. This mixture was then filtered. The solid was crushed, resuspended in hexane (6 L) and filtered. The two filtrates were combined and the hexane evaporated, the resulting crude green-yellow solid was dissolved in hot hexane (200 mL) and recrystallized overnight. The solid was isolated to give **18** (crop 1, 265.4 g). The undissolved solids from the second filtration were taken up in hot hexane (1.5 L) and this suspension was filtered. After evaporation, a dark brown solid was obtained, which was redissolved in hexane (200 mL) and run through a plug of silica gel eluting with 10:1 hexane–EtOAc to provide **18** after evaporation a white solid (crop 2, 21.6 g). The mother liquor from the crop 1 recrystallization was evaporated to a viscous oil and also run through a plug of silica gel (500 g) eluted with 10:1 hexane–EtOAc to provide **18** (crop 3, 36.1 g). At this point all three crops were combined and a final recrystallization was performed with hexane (300 mL) to provide **18**; yield: 294.4 g (81% over two steps); white solid. The mother liquor from this last crystallization was chromatographed to give an additional 17.9 g of very pure additional product **18**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 6.5 Hz, 1 H), 7.80 (s, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 3.68–3.70 (m, 3 H), 3.52–3.56 (m, 1 H), 2.92 (t, *J* = 7.3 Hz, 2 H), 2.28 (d, *J* = 6.9 Hz, 2 H), 2.02 (t, *J* = 7.3 Hz, 2 H), 1.89 (td, *J* = 7.3, 3.9 Hz, 1 H), 1.77 (d, *J* = 12.7 Hz, 2 H), 1.58–1.70 (m, 4 H), 1.18–1.26 (m, 8 H).

MS (ESI+): *m*/*z* = 329 (M + 1).

2-{(*trans*)-5′-Isobutyryl-2′,3′-dihydrospiro[cyclohexane-1,1′-inden]-4-yl}acetic Acid (20)

A solution of **18** (90 g, 0.274 mol) in 1,4-dioxane (275 mL) and 20% aq NaOH (90 mL) was heated at reflux for 1.5 h and then cooled to r.t. Aq 2 M HCl (225 mL) was added and the mixture stirred until it had cooled to r.t. EtOAc (90 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 300 mL) and the organics were pooled, washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide **20** as an off-white solid; yield: 85.65 g (99%); mp 129–131 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.0 Hz, 1 H), 7.81 (s, 1 H), 7.20 (d, *J* = 7.3 Hz, 1 H), 3.55 (quin, *J* = 6.9 Hz, 1 H), 2.93 (t, *J* = 7.3 Hz, 2 H), 2.33 (d, *J* = 6.9 Hz, 2 H), 2.03 (t, *J* = 7.3 Hz, 2 H), 1.92 (td, *J* = 7.3, 3.9 Hz, 1 H), 1.82 (d, *J* = 13.7 Hz, 2 H), 1.59–1.71 (m, 4 H), 1.16–1.30 (m, 8 H).

MS (ESI+): *m*/*z* = 315.1 (M + 1).

2-{(*trans*)-5′-(2-Bromo-2-methylpropanoyl)-2′,3′-dihydrospiro[cyclohexane-1,1′-inden]-4-l}acetic Acid (43)

A mixture of **20** (232 g, 0.738 mol) and $CuBr_2$ (371 g, 1.66 mol) in MeCN (1.5 L) was heated at 90 °C under N_2 atmosphere for 3 h. LCMS indicated that a small amount of starting material remained. Additional $CuBr_2$ (32.97 g, 0.2 equiv) was added and the reaction mixture was heated at 90 °C for 2 h. The reaction mixture was cooled to r.t. and aq 2 M HCl (3 L) was added in 1 L portions. The resulting precipitate was collected by vacuum filtration and washed with concd HCl (2 × 300 mL) to remove any remaining CuBr, and then with H_2O (500 mL). The solid was dried in vacuo to provide **43** as an off-white solid; yield: 275.8 g (95%); mp 176–178 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.2 Hz, 1 H), 7.99 (s, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 2.95 (t, *J* = 7.3 Hz, 2 H), 2.35 (d, *J* = 7.0 Hz, 2 H), 2.06 (s, 6 H), 2.04 (t, *J* = 7.5 Hz, 2 H), 1.94 (m, 1 H), 1.84 (m, 2 H), 1.67 (m, 4 H), 1.29 (dq, *J* = 3.7, 12.7 Hz, 2 H).

MS (ESI+): *m*/*z* = 393.0 and 395.0 (M + 1).

Anal. Calcd for $C_{20}H_{25}BrO_3$: C, 61.07; H, 6.41; Br, 20.32. Found: C, 61.05; H, 6.37; Br, 20.35.

2-{(*trans*)-5′-[4-Amino-7,7-dimethyl-2-(trifluoromethyl)-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl]-2′,3′-dihydrospiro[cyclohexane-1,1′-inden]-4-yl}acetic Acid (1)

A mixture of **43** (335.9 g, 0.854 mol) and 5,6-diamino-2-(trifluoromethyl)pyrimidin-4-ol (**8**; 198.9 g, 1.02 mol) in MeCN (850 mL) and H_2O (250 mL) was heated at 90 °C for 5 days. H_2O (1.02 L) was added and the reaction mixture was slowly cooled to r.t. over 4 h. The mixture was then cooled to 0 °C while stirring magnetically for 2 h. The resulting precipitate was collected by vacuum filtration and washed with 1:1 MeCN–H_2O (1 L) and dried in vacuo to provide **1** as an off-white solid; yield: 300 g (72%); mp 254–255 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (s, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 7.21 (d, *J* = 7.9 Hz, 1 H), 6.05 (s, 2 H), 2.96 (t, *J* = 7.3 Hz, 2 H), 2.36 (d, *J* = 7.0 Hz, 2 H), 2.06 (t, *J* = 7.4 Hz, 2 H), 1.94 (m, 1

H), 1.86 (m, 2 H), 1.76 (s, 6 H), 1.69 (m, 4 H), 1.30 (dq, J = 3.8, 12.6 Hz, 2 H).

MS (ESI+): m/z = 489.1 (M + 1).

Anal. Calcd for $C_{25}H_{27}F_3N_4O_3$: C, 61.47; H, 5.57; N, 11.47. Found: C, 61.39; H, 5.59; N, 11.38.

Acknowledgment

We would like to thank the research project teams at Japan Tobacco and Amgen who were instrumental in the discovery and preclinical development of compound **1**.

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