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Discovery of azetidinone acids as conformationally-constrained dual PPARα/γ agonists

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Abstract—A novel class of azetidinone acid-derived dual PPARα/γ agonists has been synthesized for the treatment of diabetes and dyslipidemia. The preferred stereochemistry in this series for binding and functional agonist activity against both PPARα and PPARγ receptors was shown to be 3*S*,4*S*. Synthesis, in vitro and in vivo activities of compounds in this series are described. A high-yielding method for N-arylation of azetidinone esters is also described.

For the past decade, peroxisome proliferator-activated receptors (PPARs), which are members of a nuclear hormone receptor super-family, have attracted much attention as novel therapeutic targets for the treatment of diabetes and dyslipidemia.[1] The PPARα receptor, mainly expressed in the liver, alters genes involved in fatty acid oxidation and lipid metabolism. On the other hand, the PPARγ receptor is predominantly expressed in the adipose tissue and macrophages and affects genes involved in lipid synthesis and storage pathways. Activation of PPARγ promotes pre-adipocyte differentiation and improves insulin sensitivity. PPARα ligands (e.g., fenofibrate and gemfibrozil) and PPARγ ligands (e.g., rosiglitazone and pioglitazone) have been in clinical use for the treatment of dyslipidemia and diabetes, respectively. A considerable amount of effort has thus been expended in the development of dual PPARα/γ agonists for the treatment of diabetes as well as the associated dyslipidemia. Muraglitazar,[2] tesaglitazar,[3] KRP-297 (MK-767)[4], and TAK-559[5] are examples of late stage dual PPARα/γ clinical candidates which have demonstrated efficacy in glucose normalization and correction of lipid abnormalities in diabetic patients. However, the development of all of these advanced clinical candidates has been discontinued for multiple reasons.[6] Therefore, the discovery of a safe and efficacious dual PPARα/γ agonists is still an important goal.

We have previously reported on the discovery of our first dual PPARα/γ agonist clinical candidate, muraglitazar (**1**, from the oxybenzylglycine chemotype), detailing its in vitro, in vivo (rodent and human), pharmacokinetic, and toxicological profiles as well as some preliminary SAR.[7] Subsequently, our goal was to identify

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chemotypes that would be significantly structurally distinct from muraglitazar in order to minimize the risk of any potential unanticipated structure-based liabilities associated with the alkoxybenzylglycines.

Here we disclose a novel class of conformationally-constrained azetidinone analogs of **1**. Conceptually, constraining the glycine carbamate moiety of **1** into a 4-membered ring followed by an O → N transposition yielded azetidinones **2** (Fig. 1). The azetidinone core (**2**) can be envisioned to be generated from ketene (**3**) and imine (**4**) via the well-documented Staudinger reaction.[8] The synthesis of Prostate Specific Antigen inhibitors based on structurally similar azetidinone cores has previously been reported.[9]

Our first synthesis of the 3- and 4-alkoxy substituted azetidinone analogs starting from either 3-(hydroxyphenyl)propanoic acid (**5**) or 4-(hydroxyphenyl)propanoic acid (**6**) is described in Scheme 1. The carboxylic acids **5** and **6** were converted to the known acid chlorides **7** and **8**,[9] which were purified by vacuum distillation. Using the Staudinger conditions described by Adlington and co-workers,[9] acid chlorides **7/8** were readily coupled with diimine **9** to provide the corresponding. β-lactams which, after acid hydrolysis, yielded the 3- and 4-substituted azetidinone aldehydes **10** and **11** as single *cis* diastereomers. Concomitant debenzylation and aldehyde reduction of **10** and **11** to the corresponding alcohols were carried out using H_2 and 10% Pd-C. Alkylation of the resulting phenols with mesylate **14**[2] and stepwise oxidation of the primary alcohol to the corresponding carboxylic acids afforded the racemic azetidinone acids **15** and **16**. The racemates **15** and **16** were separated by chiral HPLC to provide the individual enantiomers (**17**, **18**, **19**, **20**). An X-ray co-crystal of the faster-moving isomer (**17**) of racemate **15** [on Chiralcel OD column (70% Heptane/IPA + 0.1% TFA)] with PPARα receptor ligand binding domain (LBD) at 2.35 Å resolution was obtained (Fig. 2).[10] The absolute stereochemistry of compound **17** was thus determined to be *3S*,*4S*.

To simultaneously explore the SAR of the *N*-aryl region as well as to accommodate the variation of the aryloxazole moiety, we were able to modify this flexible synthetic

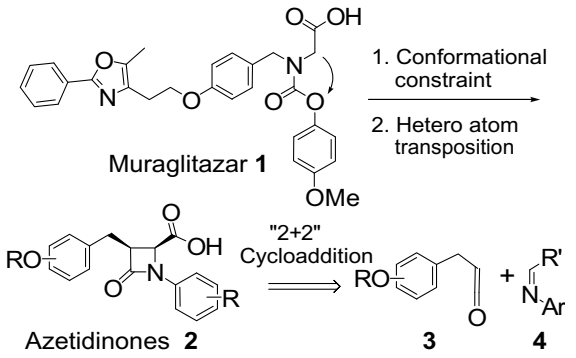
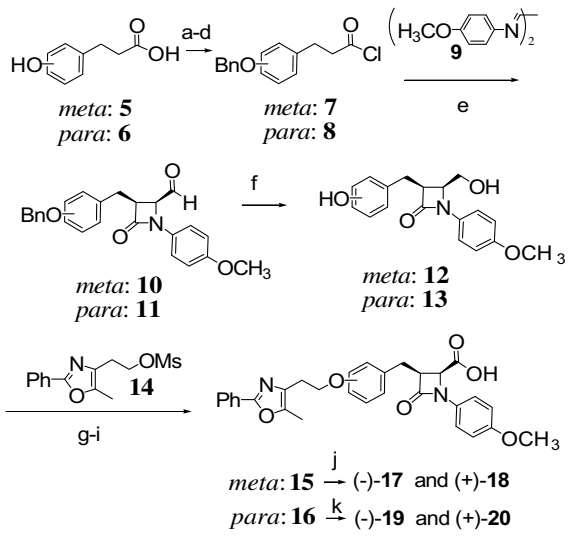


Figure 1. Design of azetidinone acids as conformationally-constrained analogs of muraglitazar.



Scheme 1. Reagents and conditions: (a) cat. H_2SO_4, MeOH, 25 °C, overnight, >98%; (b) benzyl bromide, K_2CO_3, CH_3CN, reflux, 2 h, >95%; (c) LiOH·H_2O, THF–H_2O (1:1), 25 °C, 16 h; (d) oxalyl chloride, CH_2Cl_2, 0–25 °C followed by fractional distillation, 80%; (e) **9**, Et_3N, toluene, 40 °C; aqueous HCl, 40–80%; (f) H_2 (60 psi), 10% Pd/C, 91%; (g) **14**, K_2CO_3, CH_3CN, reflux, 60%; (h) Dess–Martin periodinane, CH_2Cl_2; (i) Jones reagent, acetone, 31% for two steps; (j) chiral HPLC separation (Chiralcel OD column, 70% Heptane/IPA + 0.1% TFA); (k) chiral HPLC separation (Chiralcel AD column, 65% Heptane/IPA + 0.1% TFA).

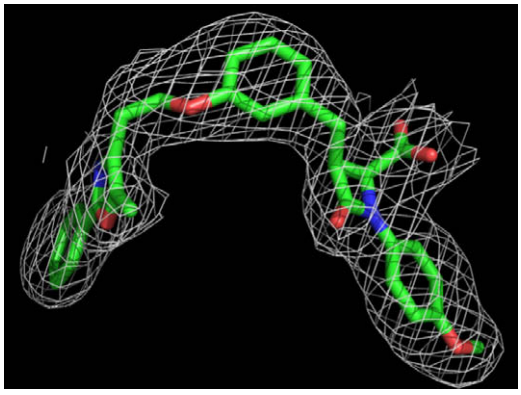
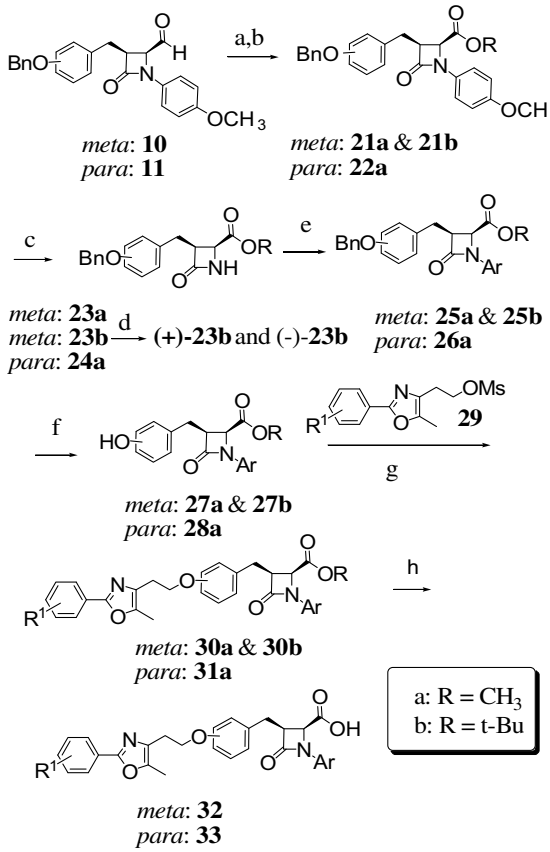
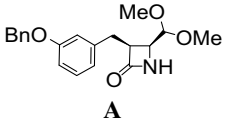


Figure 2. X-ray crystallographic analysis of **17** bound to PPARα at 2.35 Å (only ligand shown).

route in order to allow for the introduction of the *N*-aryl group at a later stage (Scheme 2). Thus, the 3- or 4-substituted azetidinone aldehydes **10** and **11** were oxidized to the corresponding carboxylic acids, which were protected as their methyl (**21a**, **22a**) or *tert*-butyl (**21b**) esters. The N-4-methoxyphenyl group was removed by ceric ammonium nitrate to give the key *N*-unsubstituted lactams (**23a**, **23b**, **24a**). There is only one report of an efficient method for the N-arylation of 2-azetidinones, viz., through the use of aryl bromides in the presence of Pd catalysts.[11] Another method, which involves the use of aryl stannanes, is known to give poor yields with 2-azetidinones.[12] To our knowledge, there are no reports of direct couplings of 2-azetidinones with boronic acids in the literature.



Scheme 2. Reagents and conditions: (a) Jones reagent, acetone, 1 h, >98%; (b) **21a** and **22a** (R = CH_3): $TMSCHN_2$, CH_3OH, 1 h, 62% for two steps; **21b** (R = *tert*-butyl): *tert*-butyl 2,2,2-trichloroacetimidate, $BF_3{\cdot}OEt_2$, cyclohexane, CH_2Cl_2, 6 h, 64%; (c) cerium ammonium nitrate, CH_3CN–H_2O, 8 h, 75–82%; (d) chiral HPLC separation (Chiralcel AD column, 92–77% Heptane/IPA + 0.1% TFA); (e) $ArB(OH)_2$, $Cu(OAc)_2$, Et_3N, pyridine, CH_2Cl_2 or DCE, 25 °C, 5 h, 90–99%; (f) H_2 (1 atm), 10% Pd on active carbon, 61–86%; (g) **29**, K_2CO_3, CH_3CN, reflux, 55–81%; (h) for R = CH_3: LiOH·H_2O, THF–H_2O (1:1), 25 °C, 16 h, 20–50%; R = *tert*-butyl: TFA, CH_2Cl_2, 2 h, 61–72%; (i) chiral HPLC separation (Chiralcel AD column, 85% Heptane/IPA + 0.1% TFA).

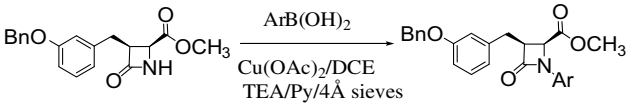


A

The N-arylation of azetidinone dimethyl acetal **A** in the presence of $Cu(OAc)_2$ and 4-methoxyphenylboronic acid proceeded in mediocre (23%) yield. However, the corresponding azetidinone carboxylates, (e.g., **23a**) undergo very efficient copper-mediated N-arylations with substituted aryl boronic acids, using aryl/heteroaryl C–N bond-forming conditions first established by Chan and Lam,[13] to give N-arylated azetidinones such as **34** (Table 1). This reaction was general and proceeded well with a variety of aryl boronic acids to give the desired N-arylated products in nearly quantitative yields.[14]

The fully functionalized target acids **32** and **33** were obtained from the N-arylated azetidinone esters **30** and **31** following a sequence similar to that described in Scheme 1. The individual azetidinone enantiomers (+)-**23b** (*3S*,*4S*) and (−)-**23b**(*3R*,*4R*) were obtained from racemic intermediate **23b** by chiral HPLC separation. Each enantiomer was then converted to the target acid in the usual manner. The assignment of stereochemistry of (+)-**23b** and (−)-**23b** was based on the conversion of (+)-**23b** to (−)-**17**.

Table 1. Copper-mediated N-arylation of azetidinone **23a**[a]



23 **4**

Compound	Ar	Yields[b] (%)
34a	4-Fluorophenyl	96
34b	4-Chlorophenyl	99
34c	4-Phenoxyphenyl	96
34d	4-*tert*-Butylphentyl	96
34e	3-Trifluomethylphenyl	97
34f	6-Methoxypyridin-3-yl	93

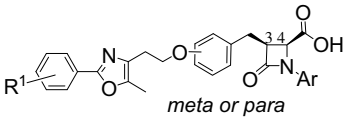
[a] For a typical procedure, see Ref. 13.
[b] Isolated yields after flash chromatography.

To assess the absolute stereochemical preference of the substituents on the azetidinone, individual enantiomers **17** and **18** were tested in PPARα and PPARγ in vitro assays. Binding and functional data on both receptors indicated that the *3S*,*4S* stereochemistry was optimal for PPARα/γ activity (Table 2). This stereopreference was consistent with our modeling, which predicted that the 3- and the 4-alkoxybenzyl azetidinone analogs with the *3S*,*4S* stereochemistry would be more active. Therefore, by analogy to **17** and **18**, the *3S*,*4S* stereochemistry was assigned to the more active enantiomers of the pairs **19/20**, **35/36**, and **37/38** (see Table 3).

The corresponding trans isomers (*3S*,*4R*), isolated in some cases in trace amounts as epimerized side-products during the final hydrolysis step, displayed significantly poorer activities against both PPARα and PPARγ receptors (data not shown). Our next goal was to define the differences between the activity/liability profiles of the 3- and 4-alkoxybenzyl azetidinone analogs. 4-Alkoxy analogs, such as **19** and **37**, generally showed improved potency at PPARγ and relatively equivalent potency at PPARα relative to their 3-alkoxy counterparts, such as **17** and **35**. The 4-alkoxy analogs also displayed a generally superior CYP450 liability profile. For example, the *tert*-butylphenyl analog **37** was a less potent inhibitor of CYP 3A4 and 2C9 relative to **35**.

The SAR of the *N*-aryl group was also explored. Among the aryl substituents examined, incorporation of the 4-*tert*-butyl group (e.g., **35**, **39**–**42**) resulted in very potent functional dual PPARα/γ agonists, but unfortunately also resulted in significantly increased CYP2C9 and hERG liabilities of these analogs versus those with a 4-methoxyphenyl group (e.g., **17**). Among the *N*-aryl substituents studied in the 3-alkoxybenzyl azetidinone series,

Table 2. In vitro binding and transactivation activities against PPARα and PPARγ[15]



Compound	Absol. Stereo.	R_1	Substitution	Prep. Ref.	Ar	Binding IC_{50} (μM)		Transactivation[d] EC_{50} μM		CYP P450 IC_{50} (μM)			hERG IC_{50}[b] (μM)
						α	γ	α	γ	3A4[a]	2C9	2C19	
GW 2331				17		0.74 ± 0.05	0.60 ± 0.04	0.045 ± 0.004	0.243 ± 0.045				
Rosi				18		>15	0.043 ± 0.02	>5	0.045 ± 0.002				
17	*3S,4S*	H	*meta*	16a	4-Methoxyphenyl	0.36 ± 0.005	0.10 ± 0.003	0.07 ± 0.005	0.09 ± 0.021	50/0.83	2.2	ND	>80
18	*3R,4R*	H	*meta*	16a	4-Methoxyphenyl	>15	1.1 ± 0.118	>7.5	0.84 ± 0.187	ND	ND	ND	ND
19	*3S,4S*[c]	H	*para*	16a	4-Methoxyphenyl	0.73 ± 0.002	0.04 ± 0.003	0.15 ± 0.008	0.02 ± 0.002	33/26	14	ND	54
20	*3R,4R*[c]	H	*para*	16a	4-Methoxyphenyl	>15	3.4 ± 0.31	>7.5	ND	ND	ND	ND	N/D
35	*3S,4S*[c]	H	*meta*	16b	4-*t*-Bu-phenyl	0.08	0.04	0.04	0.12	17/19	0.23	ND	6.2
36	*3R,4R*[c]	H	*meta*	16c	4-*t*-Bu-phenyl	>15	0.8 ± 0.02	5.4 ± 0.723	0.41 ± 0.023	20	0.67	ND	ND
37	*3S,4S*[c]	H	*para*	16d	4-*t*-Bu-phenyl	0.79 ± 0.037	0.11 ± 0.024	0.01 ± 0.001	0.004 ± 0.0	>40/28	2.3	ND	18.1
38	*3R,4R*[c]	H	*para*	16d	4-*t*-Bu-phenyl	>15	4.24 ± 0.14	0.97 ± 0.056	0.50 ± 0.048	>40/>40	3	ND	ND
39	*3S,4S*[c]	3-OMe	*meta*	16b	4-*t*-Bu-phenyl	0.52 ± 0.09	0.11 ± 0.01	0.04 ± 0.001	0.04 ± 0.005	ND /19	0.65	8.3	2.1
40	*3S,4S*[c]	3-Cl	*meta*	16b	4-*t*-Bu-phenyl	0.86 ± 0.19	0.25 ± 0.05	0.06 ± 0.001	0.10 ± 0.033	ND /20	0.67	5.3	1.8
41	*3S,4S*[c]	4-OMe	*meta*	16b	4-*t*-Bu-phenyl	0.46 ± 0.04	0.22 ± 0.02	0.008 ± 0.0	0.04 ± 0.011	ND /12	0.55	22	3.2
42	*3S,4S*[c]	4-Cl	*meta*	16b	4-*t*-Bu-phenyl	0.48 ± 0.11	0.67 ± 0.07	0.005 ± 0.0002	0.06 ± 0.008	4.7	0.41	2.8	1.3
43	Racemic	H	*meta*	16e	4-Methoxyphenyl	0.69 ± 0.05	0.16 ± 0.02	0.14 ± 0.011	0.18 ± 0.048	ND	ND	ND	ND
44	Racemic	H	*meta*	16e	4-Fluorophenyl	2.4 ± 0.22	0.18 ± 0.011	0.11 ± 0.008	0.03 ± 0.003	ND	ND	ND	ND
45	Racemic	H	*meta*	16e	4-Chlorophenyl	1.4 ± 0.20	0.36 ± 0.05	0.23 ± 0.024	0.13 ± 0.002	ND	ND	ND	ND
46	Racemic	H	*meta*	16e	6-Methoxypyridin-3-yl	1.3 ± 0.20	0.23 ± 0.02	0.09 ± 0.008	0.07 ± 0.001	ND	ND	ND	ND

[a] IC_{50}s against two probe substrates, 7-benzyloxy-4-trifluoromethyl coumarin and 7-benzyloxyresorufin.

[b] hERG flux: a high-throughput FLIPR assay to address potassium channel activity; IC_{50} < 5 μM indicates high liability, 5–80 μM: moderate liability, and >80 μM low liability; ND, not determined.

[c] Stereochemical assignments were based on binding and transactivation activity differences and correlation to 3-alkoxybenzyl azetidinone series.

[d] All potent compounds (EC_{50} < 0.25 μM) had intrinsic activities of >90% in the PPARα and PPARγ transactivation asssays. Intrinsic activity is defined as the activity of the ligand at 1 μM relative to the primary standards at 1 μM; primary standards were GW-2331[17] for PPARα and rosiglitazone[18] for PPARγ.

Table 3. In vivo data after a 14 day study in *db*/*db* mice dosed orally at 10 mpk once a day

Compound		Glucose lowering	TG lowering	Plasma conc. (μM)	Liver conc.[c] (nmol/g)	Adipose conc.[c] (nmol/g)
Muraglitazar[a]	% change	−54	−33	103	25	3
	p value	⩽0.05	⩽0.05			
17	% change	−43	0	2.8	10.4	0.29
	p value	⩽0.05				
35	% change	−17	−52[b]	0.87	7.4	<LLQ
	p value	⩽0.05	⩽0.05			

[a] Historical values.[2]
[b] After 3 weeks, the TG lowering was 61% ($p \leqslant 0.05$).
[c] For plasma chemistry and tissue analysis protocols, see Ref. 7a.

the 4-fluoro analog **44** (PPARγ EC_{50} = 30 nM) showed a 6-fold increase in PPARγ functional potency and no change in PPARα potency relative to the 4-methoxy analog **43** (PPARγ EC_{50} = 180 nM). A basic substituent such as 6-methoxypyridin-3-yl (**46**) was also well tolerated, as this analog retained potent dual PPARα/γ agonist activities. Based on their overall favorable activity and liability profiles, compounds **17** (PPARα/γ EC_{50} = 70/90 nM) and **35** (PPARα/γ EC_{50} = 40/120 nM) were administered to female *db*/**db** mice in a 14-day chronic study (dosed orally q.d. at 10 mg/day; Table 2). At this dose, compound **17** significantly decreased fasting plasma glucose (−43%), essentially resulting in the normalization of the hyperglycemic state. Interestingly, for reasons not fully understood, **17** did not lower plasma triglyceride levels, despite its potent PPARα activity and having achieved reasonable drug concentrations (10 nmol/g) in the liver, where PPARα is highly expressed. By comparison, muraglitazar at the same dose resulted in a liver concentration of 25 nmol/g. Moreover, compound **35**, with a liver concentration of 7.4 nmol/g decreased plasma triglycerides by 52%. This compound, however, failed to produce any impact on glucose levels despite its good PPARγ functional activity. This was likely due to low levels of drug observed in adipose, the primary site of PPARγ expression.

In conclusion, a novel series of conformationally-constrained, azetidinone-acid dual PPARα/γ agonists with a range of sub-type selectivities in vitro was discovered. The preferred stereochemistry was determined to be *3S*,*4S*. Compound **17** displayed significant plasma glucose lowering while compound **35** displayed robust plasma triglyceride lowering after chronic administration in *db*/*db* mice. Additionally, a novel and high-yielding method for the N-arylation of azetidinone esters has been discovered.

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14. *Typical procedure*. To a solution of azetidinone **23a** (270 mg, 0.75 mmol) in dichloroethane (12 mL) were added 4-*tert*-butylphenylboronic acid (377 mg, 2.11 mmol), $Cu(OAc)_2$ (160 mg, 0.88 mmol), Et_3N (0.511 mL, 3.67 mmol), and

pyridine (0.297 mL, 3.67 mmol) and 4 Å molecular sieves (200 mg; pre-dried at 400 °C overnight). Air was allowed to pass into the reaction mixture, which was stirred at room temperature for 5 h. The solid was filtered off (Celite) and the filtrate was concentrated in vacuo to give a crude product which was purified by flash chromatography (silica gel, 100% Hexanes to 75% Hexanes/EtOAc) to give the desired product as a white foam.

15. For in vitro binding and transactivation protocols used, see: (a) Devasthale, P. V.; Chen, S.; Jeon, Y.; Qu, F.; Ryono, D. E.; Wang, W.; Zhang, H.; Cheng, L.; Farrelly, D.; Golla, R.; Grover, G.; Ma, M.; Moore, L.; Seethala, R.; Sun, W.; Doweyko, A. M.; Chandrasena, G.; Sleph, P.; Hariharan, N.; Cheng, P. T. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2312; (b) Refs. 2 and 7a.
16. (a) Following Scheme 1; (b) Following Scheme 2, via *t*-Bu ester (+)-**23b**; (c) Following Scheme 2, via *t*-Bu ester (−)-**23b**; (d) Following Scheme 2, via Me ester **24a** to **33** followed by chiral HPLC separation (Chiralcel AD column, 85% Heptane/IPA + 0.1% TFA) to **37** and **38**; (e) Following Scheme 2, via racemic Me ester **23**.
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