

A Convergent Kilogram-Scale Synthesis of the PPAR α Agonist LY518674: Discovery of a Novel Acid-Mediated Triazolone Synthesis

Timothy M. Braden, D. Scott Coffey, Christopher W. Doecke, Michael E. LeTourneau, Michael J. Martinelli,[†] Christopher L. Meyer, Richard D. Miller, Joseph M. Pawlak, Steven W. Pedersen, Christopher R. Schmid,* Bruce W. Shaw, Michael A. Staszak, and Jeffrey T. Vicenzi

Chemical Product Research and Development, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285-4813, U.S.A.

Abstract:

The first kilogram-scale synthesis of the PPAR α agonist LY518674 (**1**) is described. The de novo convergent synthetic approach involved coupling of two rapidly assembled components, triazolone formation via a novel acid-promoted cyclization reaction, and final step saponification, delivering the compound in 32.5% overall yield via eight total steps with a six-step longest linear sequence. A regioselective alkylation on the dianion of 4-hydroxyphenylbutyric acid allowed the direct preparation of one of the convergent coupling partners, carboxylic acid **12**, and an unusual solvent effect enabled the installation of a urea group on a protected hydrazine, permitting the regiospecific preparation of the other coupling partner, semicarbazide mesylate **17**. Sulfonic acids were found to effect the desired triazolone ring formation, affording **25** from the coupled precursor acyl semicarbazide **23**. Following saponification of **25** to **1**, a wide solubility differential between ethyl acetate extracts of **1** and solutions of **1** in anhydrous ethyl acetate was harnessed in the final crystallization step to deliver the final compound in high yield and purity. The novel acid-mediated triazolone formation was further evaluated on a range of additional substrates, showing the new methodology to be largely complementary to existing base-mediated triazolone syntheses.

Introduction

The peroxisome proliferator activated receptors (PPARs) comprise a family of nuclear hormone receptors which play a central role in the metabolic regulation of dietary carbohydrates and fats in mammals.¹ By virtue of their integral involvement in these processes, the PPARs have become targets of significant interest for drug researchers, as successful modulation of these receptors via small-molecule-based therapies offers the potential to treat diseases ranging from dyslipidemia and coronary heart disease (CHD) to diabetes. Three receptor isoforms, PPAR α , PPAR δ , and PPAR γ , have been identified to date, and their respective functions in metabolic processes have been established.²

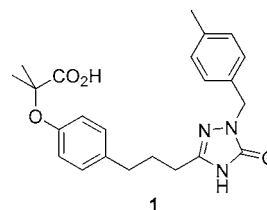
* To whom correspondence should be addressed. Telephone: (317)-276-5155. E-mail: crs@lilly.com.

[†] Present address: Chemistry Research and Discovery, Amgen, Inc., One Amgen Drive, Thousand Oaks, CA 91320.

(1) (a) Reifel-Miller, A. *Circulation* **2006**, *67*, 574–578. (b) Lemberger, T.; Desvergne, B.; Wahli, W. *Annu. Rev. Cell Dev. Biol.* **1996**, *12*, 335–363. (2) Wilson, T.; Brown, P.; Sternbach, D.; Henke, B. *J. Med. Chem.* **2000**, *43*, 527–550.

The PPAR α receptor has been associated with regulation of serum triglyceride levels; modulation of this receptor also triggers production of high-density lipoprotein (HDL) cholesterol, elevated levels of which have been associated with diminished risk of CHD.³ Consequently, administration of a highly selective and potent PPAR α agonist could provide therapeutic benefit to patients suffering from either dyslipidemia or increased risk of CHD by virtue of low HDL levels. The co-morbidity of both these maladies in the so-called metabolic syndrome X, associated with increasing obesity in the first world patient population, further supports development of new therapies in this area.⁴

LY518674 (**1**), a 2,4-dihydro-3H-1,2,4-triazol-3-one (triazolone)-based PPAR α agonist, was recently disclosed as part

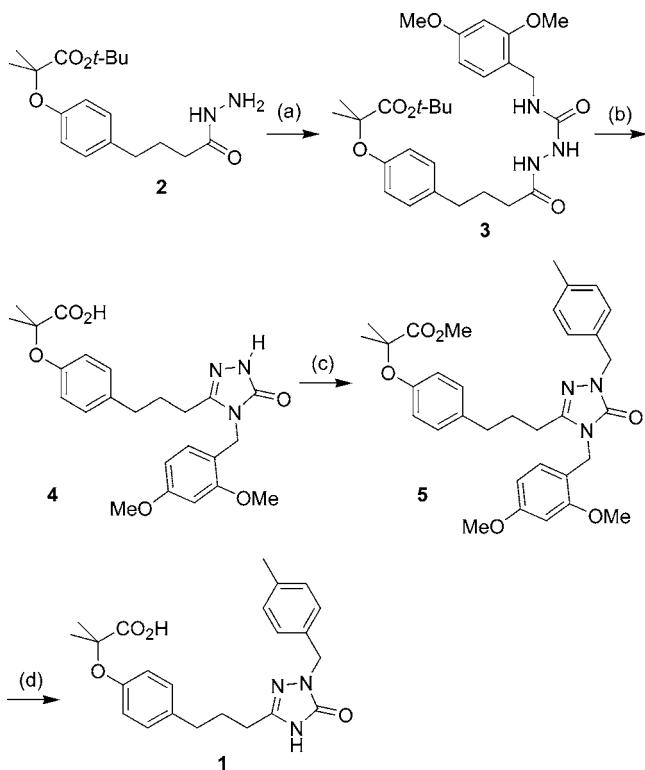


of an effort to identify potent, selective compounds targeting this receptor isoform.⁵ The compound showed excellent in vitro binding affinity and selectivity for the PPAR α receptor and proved highly potent in the human apoA-I transgenic mouse in vivo model; accordingly, the compound was selected for further preclinical and clinical evaluation. Kilogram quantities of **1** were required to support these studies, and we detail here our successful preparation of **1** on kilogram scale, using a highly convergent synthetic approach that employs a novel acid-catalyzed triazolone ring formation.

Results and Discussion

The first synthesis of **1**, accomplished by Mantlo and co-workers, is shown in Scheme 1. Thus acyl hydrazide **2** was

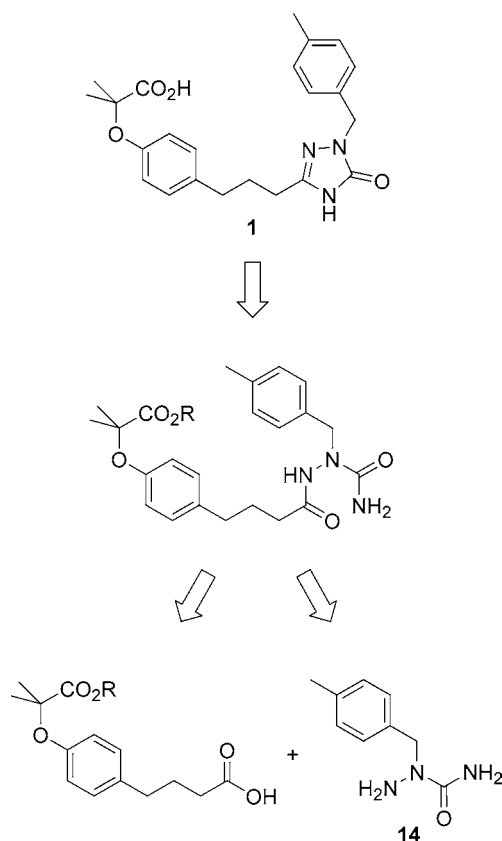
- (3) (a) Staels, B.; Zuwerx, J. *Curr. Pharm. Des.* **1997**, *3*, 1–14. (b) Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, D.; Leitersdorf, E.; Furchart, J. *C. Circulation* **1998**, *98*, 2088–2093. (4) (a) Timar, O.; Sestier, F.; Levy, E. *Can. J. Cardiol.* **2000**, *16*, 779–789. (b) Lopez-Candales, A. *J. Med.* **2001**, *32*, 283–300. (c) Jeppesen, J. *Metab. Syndr. Relat. Disord.* **2003**, *1*, 33–53. (5) Xu, Y.; Mayhugh, D.; Saeed, A.; Wang, X.; Thompson, R. C.; Dominianni, S. J.; Kauffman, R. F.; Singh, J.; Bean, J. S.; Bensch, W. R.; Barr, R. J.; Osborne, J.; Montrose-Rafizadeh, C.; Zink, R. W.; Yumibe, N. P.; Huang, N.; Luffer-Atlas, D.; Rungta, D.; Maise, D. E.; Mantlo, N. B. *J. Med. Chem.* **2003**, *46*, 5121–5124.

Scheme 1. Mantlo synthesis of LY518674 (**1**)^a

^a Reagents and conditions taken from Ref 5: (a) 2,4-dimethoxybenzyl isocyanate, THF, rt; (b) KOH, MeOH, reflux; (c) MeOH, H₂SO₄, rt, then 4-methylbenzyl bromide, K₂CO₃, DMF, 45 °C; (d) HBr, HOAc, rt.

reacted with 2,4-dimethoxybenzyl isocyanate to form the acyl semicarbazide **3**, which was then subjected to potassium hydroxide (KOH) in methanol (MeOH), affording the N⁴-benzylated N²-unsubstituted triazolone **4**. Re-esterification and alkylation at N² with 4-methylbenzyl bromide provided the dialkylated triazolone **5**. Acid-mediated deprotection of the 2,4-dimethoxybenzyl group (HBr/HOAc) revealed the N⁴ position while also accomplishing ester saponification to afford **1**.⁵

The published synthesis of **1** was attractive as a potentially scaleable approach to the molecule—the compound was assembled in a straightforward manner—and it was felt that any issues arising on scale-up could likely be addressed with alternative conditions and minor modifications to the intermediates. However, the selection of **1** as the sole compound of interest permitted us to consider additional synthetic approaches unique to the target. We were intrigued in particular with the retrosynthetic possibility depicted in Scheme 2, where **1** would be derived from the acyl semicarbazide shown. Formation of the desired triazolone core, a condensation reaction, could potentially be promoted by either acid or base; dehydrative conditions to facilitate the desired reaction could also be evaluated. The acyl semicarbazide itself would be derived from convergent assembly of a suitably activated carboxylic acid and the benzylated semicarbazide **14**. We decided to evaluate this route aggressively, while keeping the original synthesis as a fall-back approach should acceptable cyclization conditions not be identified.

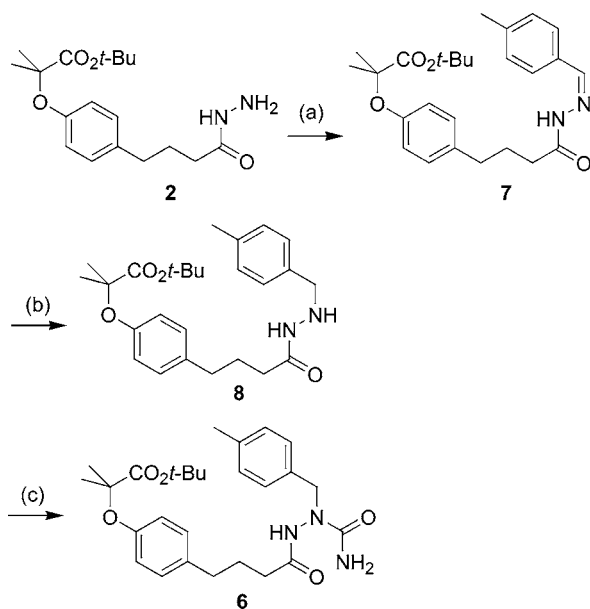
Scheme 2. Retrosynthesis for a convergent approach to **1**

A search of the literature revealed essentially no examples of direct condensations to provide the desired N²-alkylated N⁴-unsubstituted triazolones from acyl semicarbazides with the substitution pattern shown. The reported base-promoted triazolone-forming reactions (using hydroxide as base) have all employed acyl semicarbazide precursors containing latent N⁴-triazolone substitution.^{5,6} A single reference employing a combination of triflic acid and hexamethyldisilazide provided the only encouraging precedent.⁷

To determine if such a cyclization to the desired triazolone was indeed possible, gram quantities of a suitable acyl semicarbazide were required. Having ready access to acyl hydrazine **2**, we undertook a synthesis of acyl semicarbazide **6** (Scheme 3). Hydrazone formation on the terminal nitrogen of **2** using 4-methylbenzaldehyde furnished the crystalline **7** (92%), which was subjected to several sets of conditions to effect reduction. Hydrogenation using catalytic platinum

- (6) (a) Kubota, S.; Uda, M. *Chem. Pharm. Bull.* **1973**, *21*, 1342–1350. (b) Madding, G. D.; Smith, D. W.; Sheldon, R. I.; Lee, B. *J. Heterocycl. Chem.* **1985**, *22*, 1121–1126. (c) Mazzzone, G.; Puglisi, G.; Corsaro, A.; Panico, A.; Bonina, F.; Amico-Roxas, M.; Caruso, A.; Trombadore, S. *Eur. J. Med. Chem.* **1986**, *21*, 277–284. (d) Kane, J. M. *Synthesis* **1987**, 912–914. (e) Kane, J. M.; Baron, B. M.; Dudley, M. W.; Sorensen, S. M.; Staeger, M. A.; Miller, F. P. *J. Med. Chem.* **1990**, *33*, 2772–2777. (f) Dobosz, M.; Pitucha, M.; Dybala, I.; Kozioł, A. E. *Collect. Czech. Chem. Commun.* **2003**, *68*, 792–800. (g) Roman, G.; Manciulea, I.; Adreleanu, R.; Dumitrescu, L. *Heterocycl. Commun.* **2005**, *11*, 311–316. (h) Wujec, M.; Pitucha, M.; Dobosz, M. *Heterocycles* **2006**, *68*, 779–785. For an alternative approach to N⁴-unsubstituted triazolones, see: (i) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Strelitz, R. A.; MacCoss, M.; Greenlee, W. J.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 2558–2568. (7) Rigo, B.; Valligny, D.; Taisne, S.; Couturier, D. *Synth. Commun.* **1988**, *18*, 167–180.

Scheme 3. Preparation of cyclization precursor 6^a



^a Reagents and Conditions. (a) 4-methylbenzaldehyde (1 equiv), ethyl acetate, rt, then hexanes, 92%; (b) 40 psig H₂, PtO₂, THF, rt, 16 h, 97%; (c) TMS-NCO (1.5 equiv), IPA, rt, 16 h, 81%.

oxide in tetrahydrofuran (THF) served to deliver the desired product **8** (97%).

We uncovered an intriguing solvent-related effect during installation of the urea moiety on the basic nitrogen of acyl hydrazine **8** to afford **6**. Reaction of the compound with trimethylsilyl isocyanate (TMS-NCO) in dichloromethane (DCM), at rt gave no reaction. Heating the reaction in 1,2-dichloroethane⁸ also produced only recovered starting material. We were surprised to find that the reaction proceeded satisfactorily in ethanol (EtOH) and isopropanol (IPA). IPA was selected as the solvent, and a slight excess (1.5 equiv) of TMS-NCO was employed to compensate for a basal rate of reaction between reagent and solvent. Compound **6** was thus prepared in 81% yield.

Two speculative explanations could be offered for this unusual effect (Figure 1). The solvent's hydroxyl group could be involved in a 6-membered transition state, facilitating proton exchanges between substrate and reagent. Alternatively, simple silyl group exchange with solvent hydroxyl proton could serve to slowly release isocyanic acid (HNCO), which would be expected to react more readily with **8** than TMS-NCO.

With quantities of **6** in hand, we explored a range of acid- and base-promoted cyclization conditions (Scheme 4). Treatment with KOH in MeOH (50 °C, 16 h) gave a complex mixture by HPLC and NMR. Treatment with K₂CO₃ in MeOH returned **8** through removal of the urea functionality—a competing side reaction that would later be observed under several sets of conditions with several substrates. Non-nucleophilic bases such as lithium hexamethyldisilazide (LiHMDS, THF, rt to reflux), gave a complex mixture by HPLC, but encouragingly showed the desired **9** as the main component (~40%).

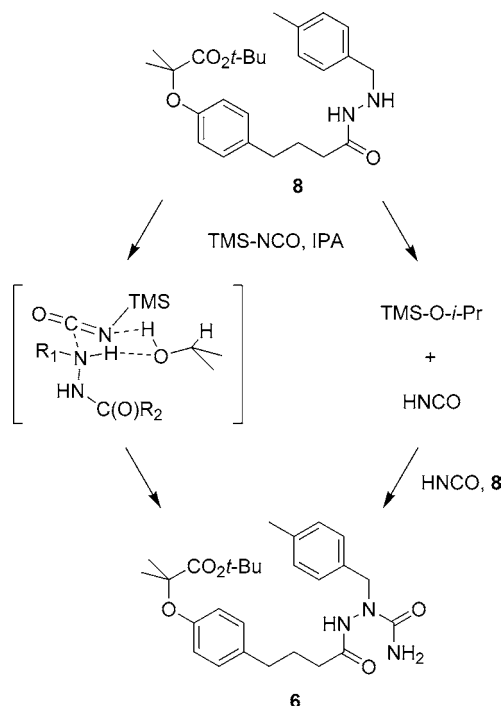
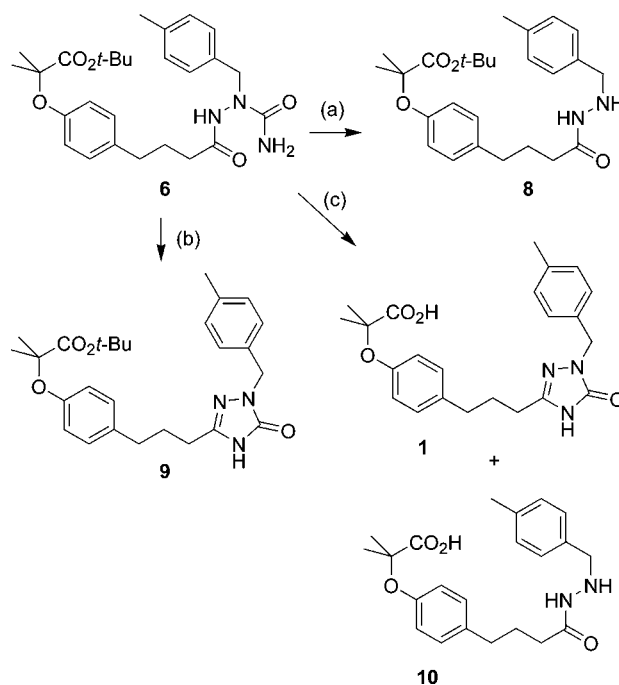


Figure 1. Rationales for the observed rate increase in the reaction of **8 with TMS-NCO in IPA.**

Scheme 4. Acid- and base-promoted cyclization attempts on **6^a**

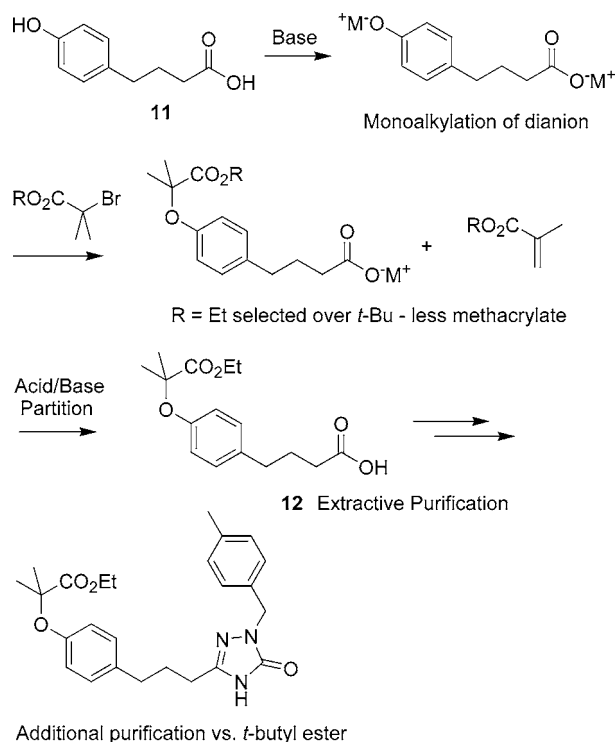


^a Reagents and conditions: (a) K₂CO₃, MeOH, reflux, 30 min; (b) LiHMDS, THF, rt to reflux, 4 h, ca. 40%; (c) TsOH, toluene, reflux, 4 h, ca. 55%.

Acid-promoted cyclization fared better. In particular, reaction of **6** with *p*-toluenesulfonic acid (TsOH) in toluene at reflux gave desired product **1** directly (TsOH additionally effecting de-esterification of the *tert*-butyl ester group) in a reaction that also afforded small quantities of **10**, the saponified version of **8**. The results from this preliminary triazolone-forming experiment provided us with enough encouragement to pursue the approach as a means of securing **1**.

(8) Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *Tetrahedron Lett.* **1987**, 28, 3163–3166.

Scheme 5. Design considerations for the synthesis of 1



TsOH was replaced with methanesulfonic acid (MsOH) when a quick screen of additional acids showed that it gave a slightly better reaction profile. The MsOH-mediated cyclization of **6** to provide **1** was performed in toluene at reflux over about 6 h. The undesired byproduct **10**, produced in 5–10% yield (**1**:**10** ratio of about 10:1), could be removed from the reaction by extensive washes with aqueous acid (1 M HCl, 8–10 washes (!)) following workup. Concentration of the organics followed by warming the product residue in ethyl acetate then afforded crystalline **1** in about 55% overall yield from **6**. Using essentially the conditions outlined above, we prepared 112 g of **1** from acyl hydrazide **2** to support initial studies on the compound.

With a viable end-game strategy for the compound in place, we turned to implementation of the convergent approach to **1** outlined in Scheme 2. We envisioned the carboxylic acid of Scheme 2 arising from 4-hydroxyphenylbutyric acid (**11**), itself readily accessed in one step from commercially available 4-methoxyphenylbutyric acid via our recently reported pyridinium hydrochloride melt demethylation.⁹ We then sought to embed two design features into the synthesis that would likely prove useful on scale (Scheme 5). First, we wanted to monoalkylate **11** directly, avoiding a protection/deprotection sequence on the carboxylic acid.¹⁰ Second, we wanted to replace *tert*-butyl bromoisobutyrate with ethyl bromoisobutyrate as the alkylating reagent. Direct monoalkylation of **11** with ethyl bromoisobutyrate would afford **12**, which presumably could be isolated and purified from the organic reaction mixture by acid/base partition. Use

of the ethyl ester instead of the *tert*-butyl ester on the alkylating reagent was desirable for two reasons. First, we had observed that alkylation of phenols was significantly faster with ethyl bromoisobutyrate than with *tert*-butyl bromoisobutyrate; additionally, the competing elimination reaction of the reagent to form the corresponding methacrylate was less pronounced. Second, although the *tert*-butyl ester had been conveniently deprotected concomitantly with triazolone formation in the one-pot conversions of **5** to **1** and **6** to **1**, a switch to the ethyl ester would install a discreet saponification step at the end of the synthesis, adding a useful potential purification point to the proposed route. These considerations outweighed any concerns over introduction of an additional step in the synthesis.

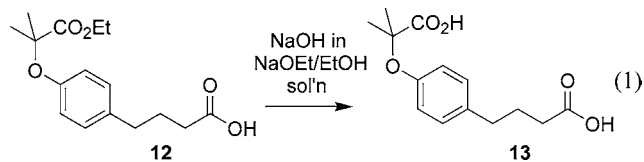
Research on the first leg of the synthesis began with the use of common conditions (potassium carbonate, dimethylformamide) to effect the alkylation of **11** with ethyl bromoisobutyrate; the reactions proceeded poorly, and additional charges of base and alkylating reagent were routinely required to drive them to completion. It was felt that the dianion of **11** might have limited solubility in the alkylation medium, and so other conditions were explored. A switch to EtOH as solvent proved more successful, and use of potassium *tert*-butoxide in EtOH gave even cleaner, higher-yielding reactions. We ultimately settled on the use of sodium ethoxide (NaOEt) in EtOH as the base and solvent choice. The alkylation proceeded at reflux over several hours and required about 2 equiv of ethyl bromoisobutyrate. In practice 2 equiv of NaOEt were initially added to form the dianion of **11**. A second charge of NaOEt (1 equiv) was added later to drive the reaction to completion, reforming phenoxide that had been consumed in the competing elimination reaction noted earlier. Upon completion of reaction, the mixture was quenched with aqueous phosphoric acid, the ethanol was removed by evaporation, and *tert*-butyl methyl ether (MTBE) was added. We were pleased to observe that the desired **12** was fully extracted into the aqueous layer by adjusting the pH to 8 with NaOH. Following layer separation, reacidification, and extraction of the product into fresh MTBE, drying and concentration afforded **12** as a crystalline solid. While other workers have recently noted difficulties with polymerization of ethyl methacrylate formed during alkylations with bromoisobutyric esters, we did not encounter these issues under our conditions.¹¹

Some alkylation reactions gave noticeable levels of an impurity identified as diacid **13**; this was produced by saponification of **12** from sodium hydroxide found in some commercial solutions of NaOEt in EtOH (eq 1). Addition of ethyl acetate to the dianion solution consumed this adventitious hydroxide, producing EtOH and sodium acetate, and suppressing formation of **13**.

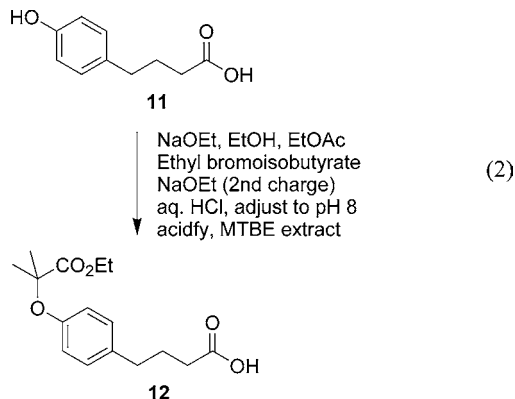
The final conditions developed for the alkylation—NaOEt (2 equiv then 1 equiv), ethyl acetate (1 equiv), EtOH, and ethyl bromoisobutyrate (2.25 equiv)—afforded **12** in yields of 85% with 95–98% potency following the extractive workup noted above (eq 2). Implementation on 22-L scale

(9) Schmid, C. R.; Beck, C. A.; Cronin, J. S.; Staszak, M. A. *Org. Process Res. Dev.* **2004**, *8*, 670–673. For an alternative approach, see: Delhaye, L.; Diker, K.; Donck, T.; Merschaeert, A. *Green Chem.* **2006**, *8*, 181–182.
(10) The methyl ester of **11** has been alkylated with *tert*-butyl bromoisobutyrate, see ref 5.

(11) Guo, J.; Erickson, G. A.; Fitzgerald, R. N.; Matsuoka, R. T.; Rafferty, S. W.; Sharp, M. J.; Sickles, B. R.; Wisowaty, J. C. *J. Org. Chem.* **2006**, *71*, 8302–8305.



was smooth, with slightly higher yields (92–95%) of slightly lower-potency material (93–95%) being obtained.

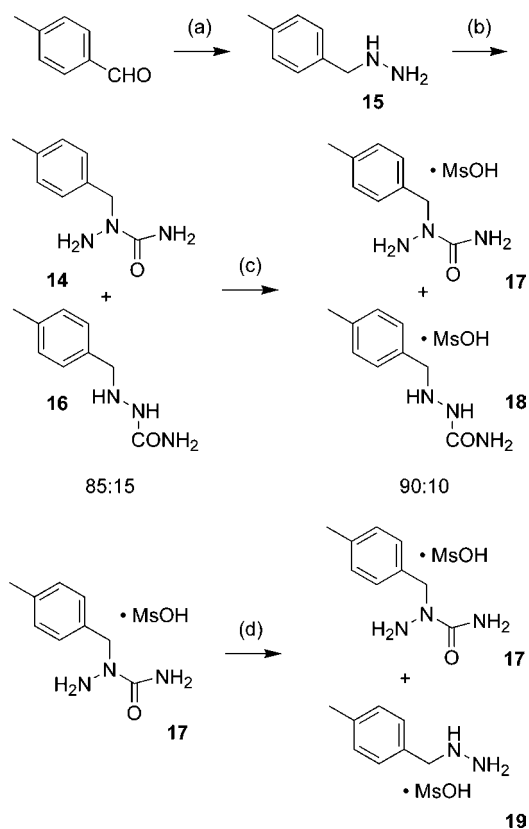


Interestingly, however, on 22-L scale we observed crystal formation on quench of the alkylation reaction with phosphoric acid and ethanol removal; cooling of the resulting slurry to 0 °C and filtration delivered **12** directly from the reaction mixture. A heptane wash dissolved entrained organic contaminants and delivered **12** of excellent purity (97–99%) in very good yields (86–95%). This variant was employed in the remaining 22-L runs to secure **12**; overall, 8.43 kg of **12** was prepared, 3.57 kg using the initial extractive workup, and 4.86 kg using the direct crystallization procedure.

For the second leg of the convergent synthesis, it was envisioned that the coupling partner benzyl semicarbazide **14** could be obtained in one of two ways. Most directly, the compound might be obtained via urea group installation on 4-methylbenzylhydrazine (**15**), as semicarbazide formation is known to proceed primarily on the interior nitrogen in similar substrates;¹² purification would then be required to separate **14** from the regioisomeric semicarbazide **16**. Compound **15** would be derived from 4-methylbenzaldehyde via reduction of its corresponding hydrazone. Alternatively, a monoprotected hydrazine could be combined with 4-methylbenzaldehyde and the resulting hydrazone reduced in situ to afford **15** regiospecifically protected on its terminal nitrogen; installation of the urea group followed by deprotection would then deliver **14**. While this latter approach substituted a chemical step in place of a purification, it did ensure a fully regiospecific delivery of **14**; the direct approach would depend critically on a means for purification of the presumed mixture of **14** and **16** to obtain the desired semicarbazide.

Pursuit of the direct approach (Scheme 6) began with formation of 4-methylbenzylhydrazine **15** from 4-methylbenzaldehyde via reduction of the corresponding hydrazone, prepared from 4-methylbenzaldehyde and excess hydrazine

Scheme 6. Attempted direct approach to semicarbazide **17**^a



^a Reagents and conditions: (a) NH_2NH_2 (excess), 50 psig H_2 , 10% Pd/C, EtOH, rt; (b) TMS–NCO (1.5 equiv), IPA, rt, 16 h; (c) MsOH (1.0 equiv), IPA; (d) IPA, reflux, 30 min.

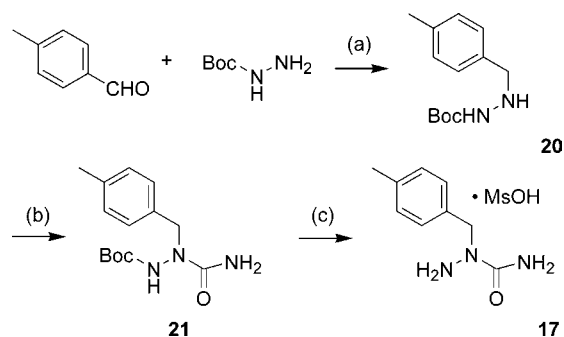
(50 psig H_2 , 10% Pd/C, EtOH, rt).¹³ Reaction of **15** with TMS–NCO resulted in an 85:15 mixture of **14** and **16**, respectively. Isolation of pure **14** from these mixtures proved surprisingly problematic. Direct recrystallization of the isomeric mixture from IPA or EtOH gave solutions at reflux, but the crystals deposited on cooling showed no significant enrichment in **14**. Addition of MsOH to the mixture followed by recrystallization from EtOH on small scale gave **14** as its methanesulfonate (mesylate) salt **17**, but in modest yield (54%) with only a minor upgrade in purity (90%) over regioisomer **18**. Moreover, heating **17** at reflux in IPA for more than a few minutes resulted in the contamination of **17** with significant amounts of the mesylate salt of 4-methylbenzylhydrazine (**19**) via loss of the urea group. With the need to deliver **1** against a timeline and purification barriers still to overcome, we opted to deprioritize this direct approach to **14**.

The regiospecific approach to secure **14** proved more successful (Scheme 7). We selected the commercially available *tert*-butyl carbazate as the monoprotected hydrazine source, with the rationale that **14** should be compatible with the acid-mediated Boc deprotection conditions. Reaction of the carbazate with 4-methylbenzaldehyde under the hydrogenation conditions previously employed for the conversion of **7** to **8** (50 psig H_2 , PtO_2 , THF) provided the Boc-protected 4-methylbenzylhydrazine **20**. A further screen of platinum-based catalysts identified 5% Pt/C as a more ideal choice

(12) LeBoucq, J. J. *Pharm. Chim.* **1930**, *11*, 200–207.

(13) Kline, G. B.; Cox, S. H. *J. Org. Chem.* **1961**, *26*, 1854–1856.

Scheme 7. Regiospecific approach to semicarbazide 17^a



^a Reagents and conditions: (a) 50 psig H₂, 5% Pt/C, THF, 50 °C, 8 h, 85%; (b) TMS-NCO (1.5 equiv), IPA, rt, 16 h, 86%; (c) MsOH (1.1 equiv), DCM, reflux, 16 h, 95%.

than PtO₂, affording the compound in better quality as evidenced by ¹H NMR comparison. Filtration and concentration delivered **20** as an oil that crystallized slowly on standing.

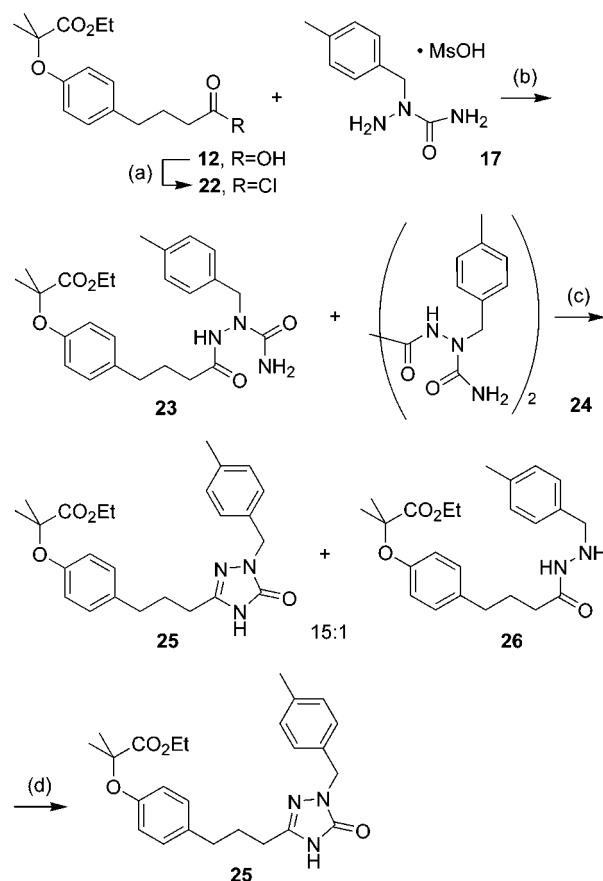
Reaction of **20** with TMS-NCO (1.5 equiv, IPA, rt, 16 h) afforded the desired Boc-protected semicarbazide **21**, which gratifyingly crystallized directly from the reaction mixture as an easily filtered solid in very good yield (86%). Boc group removal was smoothly effected by reaction with 1.1 equiv of MsOH in DCM at reflux. Again, we were pleased to observe that mesylate **17** crystallized directly from the reaction mixture; **19** was not formed under these conditions. Cooling of the reaction mixture and filtration delivered **17** in excellent yield (95–98%) and purity.

Minor scale-up modifications to this leg of the convergent synthesis centered primarily around the hydrogenation step used to deliver **20**. In practice, the carbamate and aldehyde were combined in IPA (replacing THF), and then 50% water wet 5% Pt/C was added as catalyst. During optimization on small scale, hydrogenations were observed to stall on occasion, necessitating additional charges of catalyst. Interestingly, we also observed formation of some *p*-xylene by HPLC (~5%), presumably derived from hydrogenolysis of **20**—an unexpected result from a platinum-based catalyst. Scale-up in 10-gal autoclave equipment (IPA, 50 psig H₂, 50 °C, 25 wt % load of 5% Pt/C, 4 h) gave reactions that typically stalled at high but incomplete conversion; a second equivalent charge of catalyst and continued hydrogenation was used to drive the reaction to completion. Filtration and concentration afforded **20** delivered as a solution in IPA ready for direct use in the next step. By this method 9.61 kg of material was prepared in five runs with an average weight yield of 86.0% and average potency of 92.0%.

Installation of the urea group on **20** was conducted on 22-L scale essentially as developed; crystalline **21** precipitated directly from the reaction mixture, and heptane was added to crystallize additional material. The compound was obtained in an average yield of 80.1% across seven runs, affording 9.17 kg of **21**. Optimization revealed that only 1.3 equiv of TMS-NCO was needed to compensate for the basal rate of reaction between TMS-NCO and isopropanol noted earlier.

Similarly, Boc deprotection to reveal **17** scaled without incident to 22-L equipment; direct filtration of this material

Scheme 8. Coupling and triazolone formation^a



^a Reagents and conditions: (a) oxalyl chloride (1.15 equiv), DMF (0.05 equiv), ethyl acetate, rt, 30 min; (b) pyridine (2.3 equiv), ethyl acetate, 0 °C; (c) CSA (1.1 equiv), ethyl acetate, reflux, 6 h; (d) Amberlyst 15, ethyl acetate, reflux, 1 h; MTBE (recrystallization), 50–55% overall from **12**.

from the reaction mixture was similarly uneventful. The compound was obtained in an average yield of 95.4% over seven runs with an average potency of 97.8%. In this manner 7.25 kg of **17** was obtained.

With the successful preparation of both partners for the convergent synthesis, we turned our attention to the coupling and cyclization reactions (Scheme 8). The acid chloride **22** was easily formed from **12** by reaction with oxalyl chloride and a catalytic amount of DMF in ethyl acetate; reaction completion was conveniently determined by HPLC analysis on the methyl ester of **12**. Oxalyl chloride was chosen over other acid chloride-forming reagents by virtue of its low boiling point, affording the opportunity to remove any excess reagent via concentration or distillation of solvent.¹⁴ Coupling with **17** using 2.3 equiv of triethylamine proceeded smoothly to afford cyclization precursor **23**. An acidic aqueous wash removed triethylammonium mesylate and triethylammonium hydrochloride, leaving a solution of **23** for cyclization. During optimization, the stoichiometry of acid chloride formation was found to be significant, as residual oxalyl chloride would consume **17** to form the undesired byproduct

(14) The commonly employed procedure using catalytic DMF with stoichiometric thionyl chloride (SOCl₂) to convert carboxylic acids to acid chlorides results in formation of dimethylcarbamoyl chloride, a confirmed animal carcinogen, via an oxidative mechanism. See: Levin, D. *Org. Process Res. Dev.* **1997**, *1*, 182. We are unaware of any similar concerns with the DMF/oxalyl chloride combination used here.

24. In practice this problem was solved by using a combination of stoichiometry and a subsequent concentration of solvent to remove residual oxalyl chloride. With these controls in place, the coupling proceeded in good yield and purity, with levels of **24** reduced below 1%. Although **23** could be crystallized, filtrations, even on gram scale, were unacceptably long, and so the decision was made to hold the compound as a solution in ethyl acetate for the cyclization reaction. Laboratory yields in excess of 90% were obtained using this procedure.

We set out to optimize the new cyclization conditions on **23** to provide triazolone **25**, examining solvent, acid, and temperature to see if formation of byproduct **26** could be minimized. The experiments revealed subtle but synthetically useful results. Camphorsulfonic acid (CSA) gave more favorable ratios of **25** to **26** than either methanesulfonic acid or TsOH; higher temperatures produced more of **26**, and ethyl acetate gave better ratios of **25** to **26** than did toluene at comparable temperatures. Reactions ran to completion with substoichiometric amounts of CSA (0.5 equiv), but were prohibitively long. Other acids either decomposed **23** or failed to produce any desired product. The best conditions identified (1 equiv CSA, ethyl acetate, reflux, 6 h) produced a ratio of **25**:**26** of about 15:1 and afforded the desired triazolone **25** in 55–60% yield. Attempts to convert **26** back to **23** (and thus on to **25**) via addition of TMS–NCO to the reaction were unsuccessful. The extensive and tedious aqueous acid washes used previously on smaller scale to remove byproduct **10** from **1** were eliminated when it was found that stirring the completed cyclization reaction with Amberlyst 15 sulfonic acid resin for 1 h at reflux could effectively remove **26** through simple filtration. Drying of the filtered ethyl acetate layer and concentration afforded crude product, which was recrystallized from *tert*-butyl methyl ether (MTBE) to give crystalline **25** in 50–55% overall yield from **12** with potencies in the range of 95–98%.

On scale-up, the coupling and cyclization steps were combined without isolation of the intermediate **23**. In fact, additional research demonstrated that aqueous washes to remove triethylammonium methanesulfonate byproduct from the coupling step could be eliminated; CSA could simply be added to the completed coupling reaction to effect the desired cyclization. The overall yield of the cyclization reaction and the ratio of product **25** to main byproduct **26** were only mildly diminished by the presence of methanesulfonic acid in the cyclization. Accordingly, the washes were omitted. The reactions scaled to 22 L essentially without incident, providing 4.25 kg of **25** (52.0% average yield over two steps) in five runs with an average potency of 96.0% after recrystallization from MTBE.

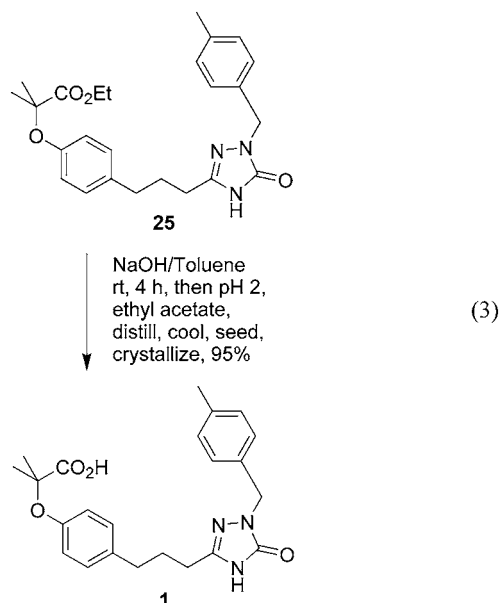
Optimization of the final-step saponification/recrystallization sequence to afford **1** revealed some interesting features. Two-phase saponification of **25** (toluene, aq NaOH, rt, 4 h), required two full equivalents of base to proceed to completion, indicating that the triazolone NH proton was acidic enough to undergo full deprotonation and consume one equivalent of base. Curiously, however, this anion was

not appreciably soluble in the aqueous phase of the saponification mixture, as analysis of the reaction mixture as it progressed showed no signs of **25** in the aqueous phase, even in those reactions not proceeding to completion. Following completion of saponification, the aqueous layer containing **1** was separated and neutralized to pH 7. Ethyl acetate was then added and the aqueous phase acidified to pH 1–2, affording the compound as a solution in ethyl acetate in high yield following layer separation. This two-stage neutralization, pausing at pH 7, was put in place to avoid precipitation of final compound in the form of a white gum that proved difficult to dissolve. On scale-up, however, it was found that slow neutralization of the aqueous phase with good agitation gave precipitated **1** that was much more easily dissolved in ethyl acetate; accordingly, the two-stage neutralization was abandoned. In practice the exact yield was not obtained from this step as it was combined with the final recrystallization in a single operation.

A screen of suitable crystallization solvents for **1** identified ethyl acetate as the ideal choice. This was puzzling as the compound had extracted quite readily into ethyl acetate from the acidic aqueous solution obtained in the saponification step. This led to concerns that solutions of **1** extracted into ethyl acetate might in fact be supersaturated and that **1** might crystallize without warning from the solution. These concerns were allayed when the extract solution was further evaluated by ¹H NMR. The extract was in fact a mixture of ethyl acetate, water (5 wt %), and ethanol (2 wt %). Samples of the solution held for extended times showed no propensity to deposit **1** up to concentrations of about 100 mg/mL at 23 °C. The compound also showed much higher solubility in water-saturated ethyl acetate (38.1 mg/mL, 23 °C) than it did in anhydrous ethyl acetate (3.7 mg/mL, 23 °C). The profound effect of small amounts of water in reactions, workups, and isolations has been previously documented.¹⁵

This solubility difference of **1** between the extract solution and anhydrous ethyl acetate was parlayed into a process to deliver crystalline **1** of pharmaceutically acceptable purity. Thus, the ethyl acetate extract from the saponification was distilled at atmospheric pressure, collecting the lower-boiling azeotropic mixture of water, ethanol, and ethyl acetate. Back addition of anhydrous ethyl acetate was then performed until the distillate temperature exceeded 76 °C, at which point the ethyl acetate was essentially free of water and ethanol. The solution was reduced to about 5 volumes by further distillation and was then cooled and seeded at about 65 °C to induce crystallization. Following cooling to ice-bath temperature, the compound was filtered and rinsed with cold ethyl acetate. The final step crystallization thus combined solubility differences derived from compositional changes in the solvent mixture with solubility differences derived from temperature changes to deliver crystalline **1**. The overall process is shown in eq 3. Three lots of **1** totaling 3.58 kg were prepared in 95.2% yield over both saponification and crystallization from **25** in 99.2% potency vs a fully characterized reference standard.

(15) Anderson, N. G. *Practical Process Research & Development*; Associated Press: New York, 2000; Chapter 6.



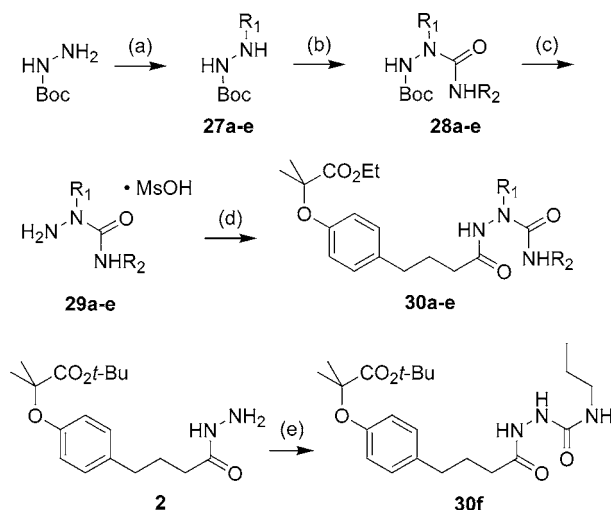
The preparation of **1** from 4-methoxyphenylbutyric acid and 4-methylbenzaldehyde was thus accomplished in eight total steps, with a six-step longest linear sequence (from 4-methylbenzaldehyde), to deliver 3.58 kg of LY518674 in 32.5% overall yield.

Having successfully prepared LY518674 using the new triazolone ring-formation conditions, we wanted to briefly examine the scope and limitations of this new methodology. We chose to examine triazolone formation using our conditions for compounds of the type previously prepared by Mantlo and co-workers.⁵ As shown in Scheme 9, cyclization substrates **30a–e** were assembled in convergent fashion using **22** and the requisite substituted semicarbazide mesylates, which were themselves prepared from the corresponding aldehydes and isocyanates employing the regiospecific preparation sequence used to secure **17**. Substrate **30f** was prepared from acyl hydrazide **2** by reaction with *n*-propylisocyanate.⁵ The cyclization substrates prepared spanned the range of substitution possibilities for the corresponding triazolones: N²-monoalkylated, N⁴-monoalkylated, and N²,N⁴-dialkylated. Subjection of the substrates to the cyclization conditions (CSA, ethyl acetate, reflux) for **30a–e** afforded the corresponding triazolones **31a–e** captured in Table 1.

Several interesting findings emerged from this brief study. The dialkylated substrates underwent cyclization much faster and in higher yield than did those producing the N²-monoalkylated triazolones, the slower rates of cyclization for **30d** and **30e** presumably allowing side reactions of the substrate to compete with the main reaction. Perhaps most interestingly, compound **30f** failed to undergo cyclization at all, instead affording a quantitative yield of the CSA hydrazone adduct **32** within about 30 min (eq 4).

On the basis of these limited studies, the acid-promoted cyclization chemistry appeared to serve as a complementary methodology to the established hydroxide-promoted approach in that at least one substrate (**6**) undergoing successful cyclization under acid conditions failed using the hydroxide-promoted approach, and **30f**, a successful substrate for hydroxide-promoted cyclization,⁵ failed using CSA. Base-

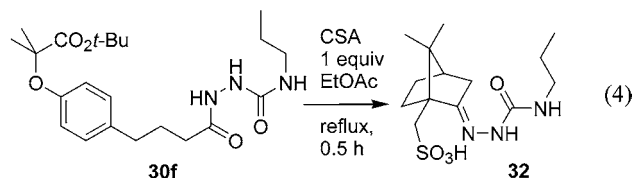
Scheme 9. Preparation of cyclization precursor substrates **30a–f**^a



^a Reagents and conditions: (a) aldehyde (1.1 equiv), 50 psig H₂, Pt/C, THF, 50 °C; (b) R₂NCO (1.1 equiv), IPA or DCM, rt, 2–8 h; (c) MsOH (1.1 equiv), DCM, reflux, 8 h; (d) **22** (1.1 equiv), pyridine (2.2 equiv), ethyl acetate, 0 °C, 2 h; (e) *n*-PrNCO (1 equiv), THF, rt, 30 min.

Table 1

precursor	R ₁	R ₂	time (h)	yield (%)	product
30a	3,4-dimethylbenzyl	Me	1	94	31a
30b	2-naphthylmethyl	Et	2.5	98	31b
30c	benzyl	<i>n</i> -Pr	2	96	31c
30d	3-methoxybenzyl	H	16	47	31d
30e	3,5-difluorobenzyl	H	17	39	31e
30f	H	<i>n</i> -Pr	0.5	100	32



promoted cyclizations of dialkylated substrates such as **30a–c** have not been reported in the literature, so no comparison could be made.

Conclusions

The synthesis of the PPAR α agonist LY518674 was accomplished on kilogram scale in a highly convergent fashion using a novel acid-promoted triazolone-forming methodology. The compound was prepared in 32.5% overall yield from 4-methoxyphenylbutyric acid and 4-methylbenzaldehyde, requiring eight total steps, and employing a six-step longest linear sequence from the latter compound. A selective alkylation on a phenoxide carboxylate allowed the direct preparation of one of the convergent coupling partners, and an unusual solvent effect enabled the installation of a urea group on a hydrazine, permitting the preparation of the

other coupling partner. A combination of solvent compositional and temperature changes was employed to provide an effective crystallization of the final compound. Finally, the scope and limitations of this new triazolone forming methodology were briefly explored, and found to be complementary to existing base-promoted methodology.

Experimental Section

4-(2-Ethoxy-1,1-dimethyl-2-oxoethoxy)benzenebutanoic Acid (12). A 12-L three-neck round-bottom flask equipped with an overhead, air-driven stirrer apparatus, thermometer/thermocouple, condenser, nitrogen inlet, and heating mantle was charged with ethyl acetate (450 mL) and sodium ethoxide (21 wt % solution in EtOH, 3318 mL, 8.87 mol, 2 equiv). The resulting mixture was heated to reflux under a nitrogen atmosphere and maintained at reflux for 30 min. The mixture was then allowed to cool to slightly below reflux, and 4-hydroxyphenylbutyric acid⁹ was added (800 g, 4.43 mol). The flask contents were reheated to reflux for 30 min, and ethyl 2-bromoisobutyrate was added (1954 mL, 13.32 mol, 3.0 equiv). After 1 h at reflux, the flask was equipped with a 2-L addition funnel, which was charged with additional sodium ethoxide (21 wt % solution in EtOH, 1660 mL, 4.43 mol, 1 equiv). The sodium ethoxide solution was added dropwise to the refluxing reaction over 1 h. After an additional 30 min at reflux, HPLC analysis showed the reaction was complete. The flask contents were cooled to 5–10 °C and transferred to a 22-L bottom outlet flask. While stirring, the mixture was quenched with 0.5 M phosphoric acid (6000 mL), transferred to a 20-L evaporatory flask, and concentrated in vacuo to remove EtOH. The resulting aqueous slurry was held at 5–10 °C overnight. The slurry was filtered and washed with water (2000 mL). The filter cake was removed from the funnel and placed in a 20-L evaporatory flask equipped with an overhead stirring apparatus. Water (2000 mL) was added, and the resulting slurry was stirred at ambient temperature for 30 min. The solids were filtered and dried on the filter for 30 min and then washed with heptane (2 × 2500 mL). The resulting solids were dried in vacuo at 45 °C to afford the title compound as an off-white solid (1247 g, 95.5%). ¹H NMR (500 MHz, CDCl₃): δ 1.25 (t, 3 H), 1.57 (s, 6 H), 1.92 (m, 2 H), 2.35 (t, 2 H), 2.60 (t, 2 H), 4.23 (q, 2 H), 6.76 (d, 2 H), 7.03 (d, 2 H). ¹³C NMR (CDCl₃): δ 14.1, 25.4, 26.3, 33.3, 34.2, 61.4, 119.4, 129.1, 129.4, 134.9, 153.7, 174.4, 179.7.

2-[(4-Methylphenyl)methyl]hydrazinecarboxylic Acid, 1,1-Dimethylethyl Ester (20). To a 10-gal stainless steel autoclave was charged *tert*-butyl carbazate (1.25 kg, 9.46 mol) and IPA (2 L). Additional IPA (10 L) was added and the resulting mixture heated to 35 °C. 4-Methylbenzaldehyde (1.15 kg, 9.57 mol) was then added, followed by an IPA rinse (0.3 L). The temperature was then raised to 50 °C and the contents stirred for 1 h. In a separate vessel, 5% Pt/C (0.3 kg) and water (0.3 kg) were combined, and IPA (4 L) was added. The resulting slurry was added to the autoclave, followed by rinses with IPA (2 × 1 L). The resulting mixture was hydrogenated at 50 °C and 50 psig H₂ for 4 h. Analysis at that time showed an 83% conversion. An additional charge of catalyst (0.3 kg) was prepared and added to the autoclave

as before, and hydrogenation was continued for 4 h. The contents were cooled to rt and then filtered, and the autoclave and filter cake were rinsed with IPA (15 L). The resulting solution was concentrated to a weight of 5.33 kg. Gravimetric assay gave a 31.7 wt % solution of product (1.9 kg, 8.04 mol, 85%) with an HPLC potency of 90.2%. ¹H NMR (DMSO-*d*₆, 500 MHz): δ 8.20 (br s, 1 H), 7.13 (dd, 4 H), 4.61 (br s), 3.79 (s, 2 H), 2.25 (s, 3 H), 1.37 (s, 9 H).

2-(Aminocarbonyl)-2-[(4-methylphenyl)methyl]hydrazinecarboxylic Acid, 1,1-Dimethylethyl Ester (21). To a 22-L four-neck flask equipped with overhead stirring apparatus, cooling bath, thermometer probe, and a 2-L addition funnel was charged solution **20** in IPA (4988 g of a 28.6 wt % solution, 1583 g, 6.70 mol). Additional IPA (3130 mL) was added to dilute the solution. Trimethylsilyl isocyanate (1179 mL, 8.71 mol, 1.3 equiv) was charged to the 2-L addition funnel and added dropwise to the stirring solution over 45 min while maintaining the 15–25 °C, and the mixture stirred for 16 h. The reaction mixture was treated with heptane (7800 mL), cooled to 5–10 °C, stirred for 0.5 h, and then filtered; the filter cake washed with heptane (2 × 1000 mL). The material was dried in vacuo at 30–35 °C to a constant weight to afford the title compound as a white solid (1423 g, 84%). ¹H NMR (DMSO-*d*₆, 300 MHz): δ 1.35 (s, 9 H), 2.26 (s, 1 H), 4.45 (br s, 2 H), 6.06 (s, 2 H), 7.10 (s, 4 H), 8.88 (br s, 1 H). Anal. Calcd for C₁₄H₂₁N₃O₃: C, 60.20; H, 7.58; N, 15.04. Found: C, 59.65; H, 7.34; N, 14.87.

1-[(4-Methylphenyl)methyl]hydrazinecarboxamide, Monomethanesulfonate (17). To a 22-L 4-neck flask equipped with overhead stirring apparatus, warming/cooling bath, thermometer probe, condenser, and 500-mL addition funnel was charged **21** (1100 g, 3.94 mol) and dichloromethane (12 L). The mixture was warmed to 30–35 °C to dissolve all solids, and then was cooled to 25–30 °C. MsOH (398 g, 4.14 mol) was added dropwise over 30 min. The water bath was replaced with a heating mantle and the reaction solution heated at reflux for 20 h. The reaction mixture was diluted with heptane (4 L), cooled to 10–20 °C, stirred for 30 min, and then filtered. The filter cake was washed with heptane (2 × 1000 mL) and dried in vacuo at 35–45 °C to a constant weight to afford the title compound as a white solid (1070 g, 98.6%). ¹H NMR (DMSO-*d*₆, 300 MHz): δ 1.35 (s, 9 H), 2.26 (s, 1 H), 4.45 (br s, 2 H), 6.06 (s, 2 H), 7.10 (s, 4 H), 8.88 (br s, 1 H). Anal. Calcd for C₁₀H₁₇N₃O₄S: C, 43.62; H, 6.22; N, 15.26. Found: C, 43.33; H, 6.21; N, 14.97.

2-[4-[3-[2,5-Dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1H-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methylpropanoic Acid, Ethyl Ester (25). To 22-L four-neck flask equipped with a thermometer/thermocouple, addition funnel, overhead stirring apparatus, nitrogen inlet, and cooling bath was charged **12** (1250 g, 4.247 mol), ethyl acetate (11,250 mL), and DMF (16.4 mL, 5 mol %), and agitation was begun in order to dissolve all solids. Oxalyl chloride (426 mL, 4.88 mol, 1.15 equiv) was charged to the addition funnel and then added dropwise to the stirring reaction mixture over 45 min, maintaining the temperature below 30 °C. After 30 min,

HPLC analysis indicated the reaction was complete. The reaction mixture was transferred to a 20-L evaporatory flask and concentrated in vacuo to afford crude acid chloride **22**.

A 22-L four-neck flask, equipped with a thermometer/thermocouple, addition funnel, nitrogen inlet, overhead stirring apparatus, and cooling bath, was charged with **17** (1169 g, 4.247 mol, 1 equiv), ethyl acetate (8750 mL), and pyridine (790 mL, 9.77 mol, 2.3 equiv). The contents of the flask were cooled to 0–5 °C. The acid chloride **22** was dissolved in ethyl acetate (1000 mL), transferred to the addition funnel, and added dropwise to the mixture containing **17** over 20 min, maintaining the pot temperature below 25 °C. The resulting mixture containing **23** was stirred at ambient temperature for 1 h, then treated with CSA (1973 g, 8.494 mol, 2 equiv). The contents were heated to reflux and allowed to stir overnight. HPLC analysis after 16.5 h showed the reaction was complete. The reaction was cooled to 20 °C and transferred into a 22-L bottom outlet flask containing 1 N HCl (7500 mL). After stirring, the layers were separated, and the organic layer was washed with sat'd sodium carbonate solution (7500 mL) and water (1000 mL) and then was dried (MgSO₄).

The ethyl acetate solution was transferred to a 22-L four-neck flask equipped with a condenser, nitrogen inlet, thermometer/thermocouple, and a heating mantle. The flask was charged with Amberlyst-15 resin (1975 g), and the mixture was heated to reflux for 1 h. After cooling to 20 °C, the material was gravity filtered to remove the resin and the resin washed with ethyl acetate (2 × 2000 mL). The filtrate was transferred to a 20-L evaporatory flask and concentrated in vacuo to afford a tan solid. The crude material was treated directly with MTBE (5000 mL) and warmed to 45–50 °C until all solids were dissolved. The solution was allowed to cool slowly while rotating in the evaporatory flask at low rpm, inducing crystallization. The material was then cooled to 0–5 °C and held for 1 h, filtered, rinsed with cold MTBE (1500 mL), and dried in vacuo at 45 °C to a constant weight. The title compound was obtained as a white solid (1027 g, 55.2%). ¹H NMR (500 MHz, DMSO-*d*₆): δ 1.14 (t, 3 H), 1.47 (s, 6 H), 1.76, (m, 2 H), 2.26 (t, 2 H), 2.49 (t, 2 H), 3.55 (s, 3 H), 4.15 (q, 2 H), 6.69 (d, 2 H), 7.05 (d, 2 H). ¹³C NMR (CDCl₃): δ 14.0, 21.0, 25.3, 26.1, 28.1, 34.1, 48.3, 61.2, 79.0, 119.3, 127.8, 129.0, 129.3, 133.2, 134.8, 137.5, 147.2, 153.6, 155.8, 174.3.

2-[4-[3-[2,5-Dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1H-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methylpropano-

ic Acid (LY518674, 1). To a 22-L four-neck flask equipped with overhead stirring apparatus and thermometer probe was charged compound **25** (800 g, 1.828 mol) and toluene (4000 mL) followed by 1 N NaOH (4023 mL, 4.023 mol, 2.2 equiv). The resulting biphasic mixture was stirred at ambient temperature for 5 h. HPLC analysis at that point indicated the reaction was complete. The layers were separated, and the aqueous layer was transferred to a 22-L three-neck round-bottom flask equipped with a thermometer, overhead stirring apparatus, and addition funnel and was acidified to pH 2 by dropwise addition of concentrated HCl (337 mL). The resulting slurry was extracted with ethyl acetate (8000 mL), and the layers were separated. The organic extracts were transferred to a 22-L three-necked round-bottom flask equipped with a distillation head and overhead stirring apparatus. The mixture was concentrated by distillation of the ethyl acetate to approximately 4000 mL. Ethyl acetate (3600 mL) was added to the reaction vessel, and distillation was continued until 3600 mL more of distillate were recovered. The mixture was allowed to cool slowly to 60–65 °C, at which point seed crystals (0.8 g) of the product **1** were added. The flask contents were allowed to cool slowly until crystallization had initiated (55–57 °C), then the mixture was cooled to 0–5 °C and stirred for 1 h. The product was filtered, washed with cold ethyl acetate, and dried in vacuo at 55 °C to afford the title compound as a white solid (713.6 g, 95.3%). ¹H NMR (DMSO-*d*₆, 500 MHz): δ 1.46 (s, 6 H), 1.79 (m, 2 H), 2.25 (s, 3H), 2.35 (t, 2 H), 2.47 (t, 2 H), 4.70 (s, 2 H), 6.71 (d, 2H), 7.03 (d, 2H), 7.10 (m, 4 H). ¹³C NMR (DMSO-*d*₆): δ 20.6, 25.0, 25.5, 27.7, 47.0, 78.3, 118.6, 127.4, 127.7, 128.9, 128.9, 134.4, 134.5, 136.4, 145.9, 153.4, 154.3, 175.0.

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Supporting Information Available

Experimental procedures and characterization for compounds **30a–f**, **31a–e**, and **32**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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