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Preparation of Methyltriazolo[1,4]benzodiazepine via Oxidative Activation of a Thiolactam for the Synthesis of BET Inhibitor Molibresib

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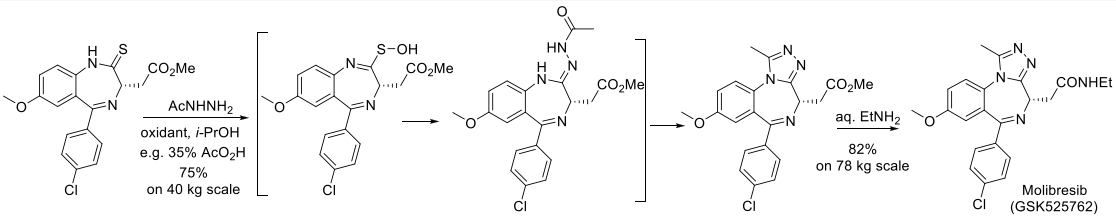

ABSTRACT: A novel oxidative activation of a thiolactam was developed for the preparation of methyltriazolo[1,4]benzodiazepine in a single step. A sulfenic acid (R-SOH) was proposed as the activated intermediate with the concurrent formation of acetylhydrazone from acethydrazide and cyclocondensation to the triazole. A version of the method with 35% peracetic acid was scaled up to 40 kg as a part of the new route for the synthesis of BET inhibitor molibresib (GSK525762). The thiolactam was prepared from commercially available (2-amino-5-methoxyphenyl)(4-chlorophenyl)methanone in two steps in 66% yield. The concise four-step synthesis delivered 52 kg of molibresib of >99.9% ee in an overall 41% yield from the ketone. The condition for the methyltriazole was mild and free of racemization of the sensitive stereocenter. The oxidative method, with several advantages to the known methods, should be applicable to the synthesis of alkyltriazoles from other thiolactams and acylhydrazines.

INTRODUCTION

The interaction between bromo and extra-terminal (BET) bromodomain proteins and their acetylated histone substrates has recently attracted extensive attention in the field of epigenetics.[1] GSK525762 (**1**, generic name molibresib, Figure 1) is a potent inhibitor of the BET family of proteins, and it prevents the binding required for macromolecular complex assembly and the subsequent transcriptional response.[2a] The initial clinical development of **1** focused on the treatment of advanced solid tumors.[2b] A notable structural feature of **1** is the 1-methyltriazolo[1,4]benzodiazepine substructure. This scaffold is also present in several other BET inhibitors including JQ1 (**2**),[3] OTX-015 (**3**),[4] and compound ET (**4**),[5] as shown in Figure 1. Compounds **2** and **3** were also clinical stage drug candidates for oncology.

The original synthesis of **1** by medicinal chemistry is shown in Scheme 1.[2a] The racemic synthesis started with 2-aminobenzophenone **5**, which reacted with racemic acyl chloride **6** to provide lactam **7** through three distinctive steps: amide formation, Fmoc cleavage, and cyclocondensation. Thionation with Lawesson's reagent gave thiolactam **8**. A three-step process was used to convert **8** to a methyltriazole: formation of hydrazone **9**, acetylation for **10**, and ring closure with acetic acid to give **11**. Ester hydrolysis followed by amide formation gave racemic target **12**, which was resolved by preparative HPLC to give GSK525762 (**1**) and its (*R*)-enantiomer **13**.

Subsequently, the racemic synthesis shown in Scheme 1 was upgraded by a team of chemists in Early Development and Supply to a chiral version to deliver multikilograms of **1** by replacing the racemic **6** with (*S*)-**6** derived from L-aspartic acid. However, the three-step sequence from the thiolactam to the methyltriazole was cumbersome regarding workups and purifications needed. During the scaleup of the chiral synthesis involving intermediates **14** and **15**, we discovered that a dihydropyridazinone side product (**17**) inevitably formed from hydrazone **16**, as shown in Scheme 2. It was not an issue in the racemic synthesis as chromatographic purification was used on a small scale to remove the impurity. Although the impurity was significantly less soluble than the product, it took several crystallizations to remove it to below a specification level on a large scale.

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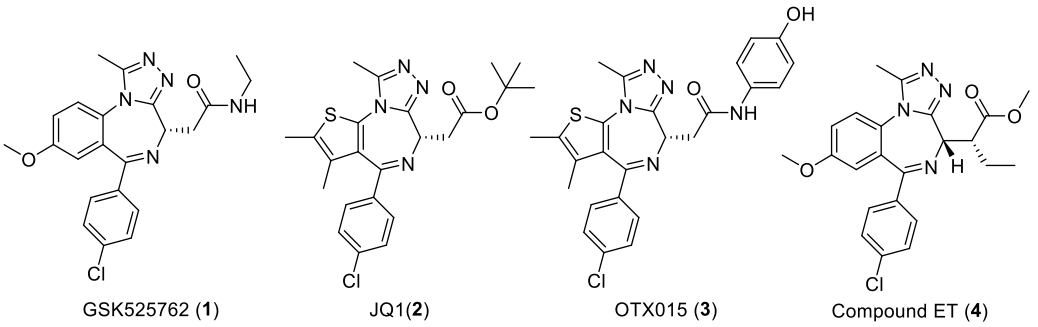
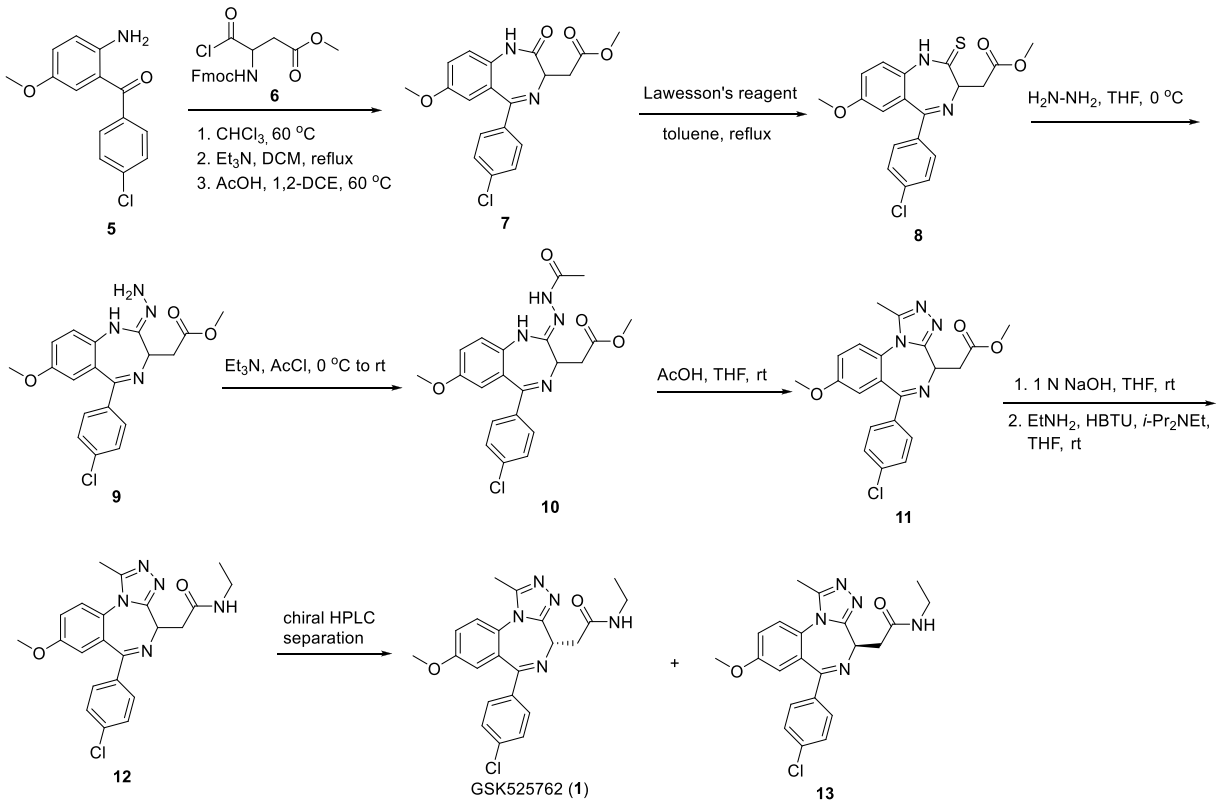
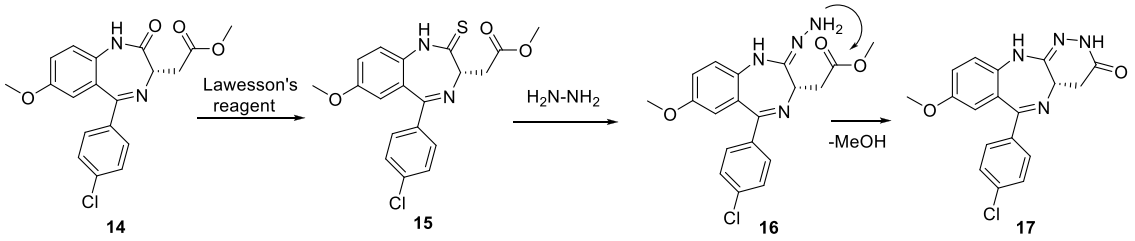


Figure 1. Structures of BET bromodomain inhibitors GSK525762 (**1**), JQ1 (**2**), OTX015 (**3**), and compound ET (**4**), featuring the methyltriazole substructure fused to a 1,4-benzodiazepine.

Scheme 1. Original Racemic Synthesis for GSK525762 (1)



Scheme 2. Dihydropyridazinone Impurity 17 from Hydrazone 16 in the Original Synthesis



We envisioned that the replacement of hydrazine with acethydrazide ($AcNHNH_2$) could eliminate byproduct **17** and shorten the synthesis. A new approach to the methyltriazolo-[1,4]-benzodiazepine core was proposed (Scheme 3), starting from lactam **14** or thiolactam **15**. The use of acylhydrazides for the synthesis of 1-alkyltriazole is known.[5−10] The major challenge would be the much lower reactivity of an acylhydrazide, such as acethydrazide relative to hydrazine which is often used in large excess. We found that the direct reaction of acylhydrazides with lactams was impossible. Even the more reactive thiolactams required extended heating at high temperature, e.g., with refluxing benzyl alcohol in modest

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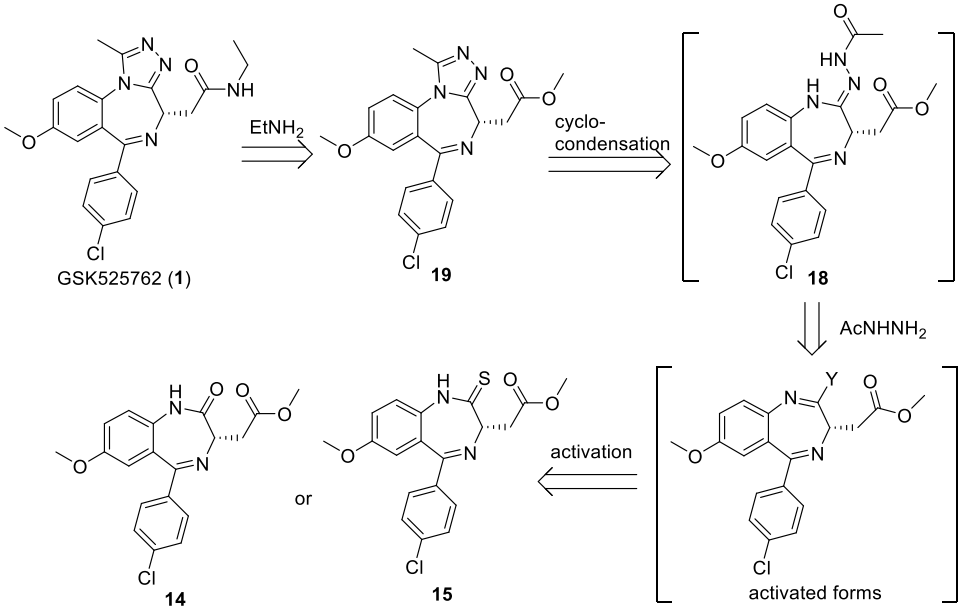
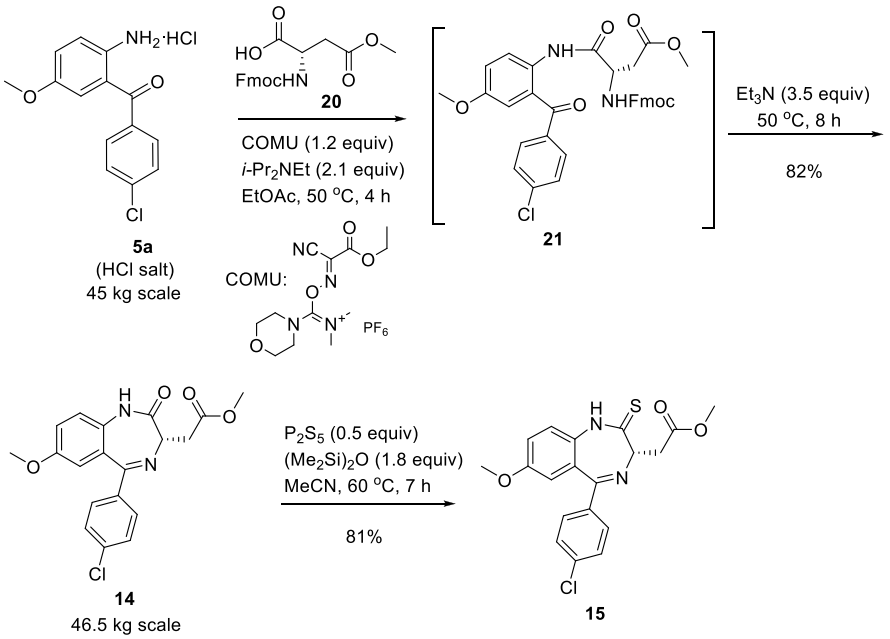
Scheme 3. Retrosynthesis of GSK525762 (1) via Reaction of Acethydrazide and the Activated Lactam or Thiolactam



Scheme 4. Preparation of Lactam 14 and Thiolactam 15 on Scale



yields by Hester et al.[6] A common solution to the reactivity issue is to activate the lactam or thiolactam, e.g., through *O*- or *S*-methylation with methyl sulfate by Rigo et al.[7a,b] However, they ran into the issue of *O*- vs *N*-selectivity, which was resolved by two groups at Glaxo by use of trimethyloxonium tetrafluoroborate on various substrates.[7c,d] Recently, a group at Pfizer applied this method with triethyloxonium tetrafluoroborate in its synthesis of a PDE-IV inhibitor on a scale.[7e] Another common mode of activation is through phosphorylation with a wide variety of phosphorus reagents, e.g., bis(morpholino)phosphinyl chloride[8a] and chlorodiethylphosphate.[8b] Phosphorus oxychloride was also used to activate lactams as imidoyl chlorides in the synthesis of benzodiazepines.[9]

Most recently, mercury acetate was used in stoichiometric amounts to activate thiolactams for reactions with acylhydrazides in large excess by Ciulli[5] and Khan.[10] This approach did combine the typical three separate reactions (hydrazine condensation, acetylation with a base, and cyclocondensation with an acid as shown in Scheme 1 for the previous synthesis of **1**) in a one-pot process. Although we preferred not to use the toxic mercury acetate on an industrial scale, their approach of combining three reactions into one with the concurrent activation of the thiolactam attracted our attention.

We herein report our findings in the execution of the synthetic strategy shown in Scheme 3, assessing various means of activating lactam **14** or thiolactam **15** for the formation of acetylhydrazone **18** en route to methyltriazole **19**. Our efforts

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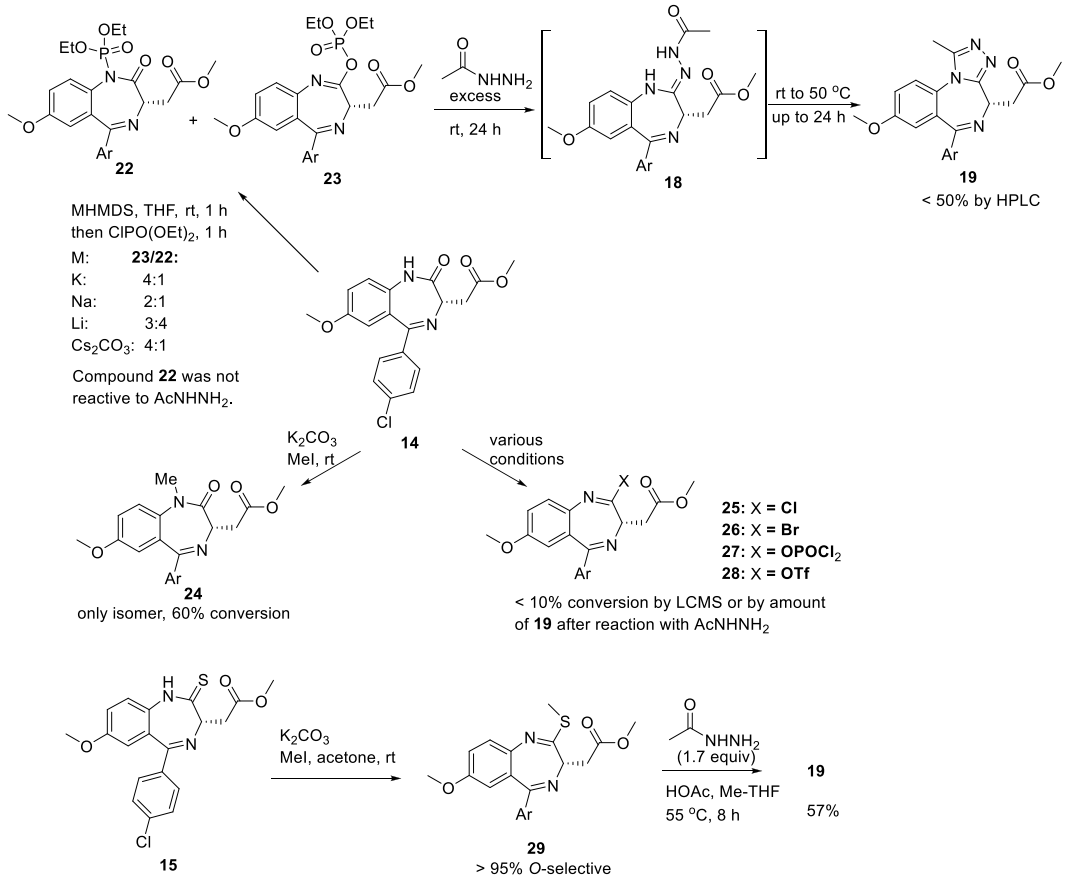
Scheme 5. Activation of 14 and 15 under Typical Conditions



ultimately led to the discovery of a novel and unique activation method and a 4-step synthesis of GSK525762 (**1**), delivering over 52 kg of **1**. Robust and efficient synthesis of **14** and **15** will also be described.

RESULTS AND DISCUSSION

When the racemic synthesis for **7** and **8** as shown in Scheme 1 was adapted for the synthesis of lactam **14** and thiolactam **15** from (*S*)-**6**, up to 5% of racemization was observed. The use of Lawesson's reagent for the thionation was also not desirable due to the extensive workup needed.[11] Our new synthesis of **14** and **15**, shown in Scheme 4 with the more readily available carboxylic acid, was one step shorter and did not require any extraction. In recent years, 1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) emerged as a safe and efficient third generation of a uronium-type peptide coupling reagent.[12]

The reaction of **5a** and **20** activated by COMU was exceptionally clean with hardly any racemization.[13] The use of bulky *N*,*N*-diisopropylethylamine was important to prevent the premature loss of the Fmoc protection. Following the formation of amide **21**, triethylamine was added for Fmoc deprotection and ring closure. The addition of methanol followed by filtration provided **14** of 99.9% ee and in 82% yield on 45 kg scale. Similarly, the thionation of **14** was greatly simplified once Lawesson's reagent was replaced by phosphorus pentasulfide and hexamethyldisiloxane.[14] Thiolactam **15** of 98.6% ee was isolated in 81% yield on a 46.5 kg scale by direct filtration of the quenched reaction. Thionation of the ester carbonyl group did occur as a side reaction but was controlled to below 1% by immediately cooling the reaction to 0 °C upon completion. The slight erosion of enantiomeric purity from **14** to **15** was not a concern as the enantiomeric purity was enhanced in the next step by crystallization.

With a good supply of **14** and **15**, a variety of conditions were tested to activate those two substrates for reactions with acethydrazide to form acetylhydrazone **18** (Scheme 5). Compound **18** was stable enough for isolation under mild basic or neutral conditions. Cyclocondensation to methyltriazole **19** occurred very slowly at room temperature but was faster with heating, particularly in the presence of an acid.

Our initial efforts of the activation focused on lactam **14**, following some known methods for activation of lactams as their phosphates, alkyl imidates, and imidoyl halogens.[5−10] Some of the attempted conditions were shown in Scheme 5. Unfortunately, those approaches suffered from poor reactivity of the lactam as well as the selectivity of *O*- vs *N*- for phosphorylation and alkylation under basic conditions. For example, treatment of **14** with a common base followed by chlorodiethylphosphate gave a mixture of **22** and **23**. Upon addition of acethydrazide, only the phosphate **23** led to acetylhydrazone **18**, which further cyclocondensed to triazole **19**. Phosphoramidate **22** remained intact under the conditions. The highest amount of **19** by HPLC was about 50% achieved, as shown. Metal hydride, alkoxides, and tertiary or aromatic amines gave low conversions. For alkylation with methyl iodide in the presence of potassium carbonate, only *N*-methyl product **24** was detected by LCMS, and it failed to give any triazole as expected upon addition of acethydrazide.

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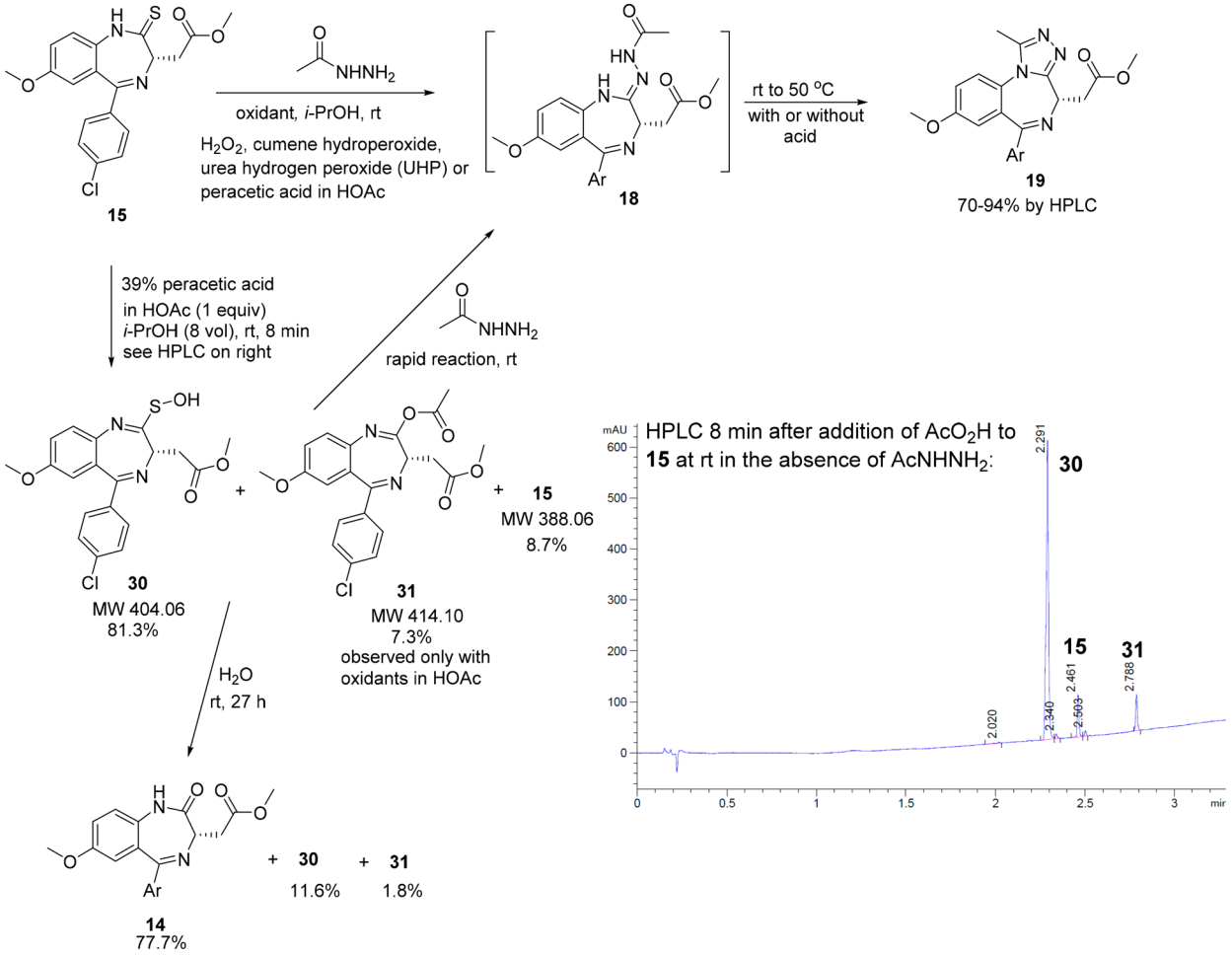
Scheme 6. Oxidative Activation of 15 in the Presence of Acethydrazide for Facile Formation of Methyltriazole 19 and the Control Experiments Supporting Proposed Reaction Pathway



We made significant efforts to make compounds **25**–**28** with reagents such as phosphorus oxychloride, phosphorus pentabromide, thionyl chloride, phosgene and triflic anhydride with a base, as well as a variety of Lewis acids in stoichiometric amounts. Generally, lactam **14** remained intact, and only 0–10% of methyltriazole was observed by HPLC with the concurrent or subsequent addition of acethydrazide. In contrast, thiolactam **15** was converted to the desired methyl thioimidate **29** efficiently under the same condition, and about 57% of the product was observed by HPLC upon treatment of the crude **29** with acethydrazide. The extra transformation, as well as the need to remove the base and alkylating reagent prior to the addition of acethydrazide, made this approach unattractive.

A breakthrough came when a reaction of **15** with acethydrazide in the presence of copper acetate was inadvertently left open to the air in the screening for activation by Lewis acids. It was noted that methyltriazole **19** formed faster than the reaction under nitrogen. It was postulated that the oxygen served as an oxidant to activate the thiolactam. Since air is generally not considered a safe source of oxygen in the presence of a heated organic solvent, a screening of oxidants was carried out, as shown in Scheme 6.

When a variety of oxidants were added to a mixture of **15** and acethydrazide in isopropanol at room temperature, **15** was depleted rapidly with concurrent formation of acetylhydrazone **18**. Furthermore, **18** underwent cyclocondensation to methyltriazole **19** simultaneously prior to full depletion of **15**. The cyclocondensation was slow with oxidants supplied without an acid such as 30% hydrogen peroxide and cumene hydroperoxide, but the ring closure was smooth and fast with peracetic acid (35% or 39% solution in acetic acid). Acetylhydrazone **18** could not be isolated under the acidic condition due to the rapid conversion to the triazole, while it was easily isolated from the previous route in which the acetylation (with AcCl) of the hydrazone (from hydrazine) was under the basic condition (with triethylamine, see Scheme 1). Notably, there was about 1–3% of lactam **14** observed, while the input **15** was known to carry less than 0.5% of residual **14** from the earlier thionation reaction. This prompted us to investigate a potential intermediate formed from the reaction of the thiolactam and the oxidant.

In a control experiment shown in Scheme 6, **15** was treated with one equivalent of peracetic acid at room temperature. Analysis by reverse phase HPLC (Method A) of a sample from the eighth minute showed only 8.7% of **15** remaining at 2.46 min, and two new peaks at 2.29 and 2.78 min formed in 81.3% and 7.3%, respectively. Analysis by LCMS identified the new peaks to be sulfenic acid **30** and acetyl imidate **31**, respectively (see Supporting Information). Upon addition of acethydrazide, both **30** and **31** converted to acetylhydrazone **18** rapidly with concurrent ring closure to give methyltriazole **19**. We believe

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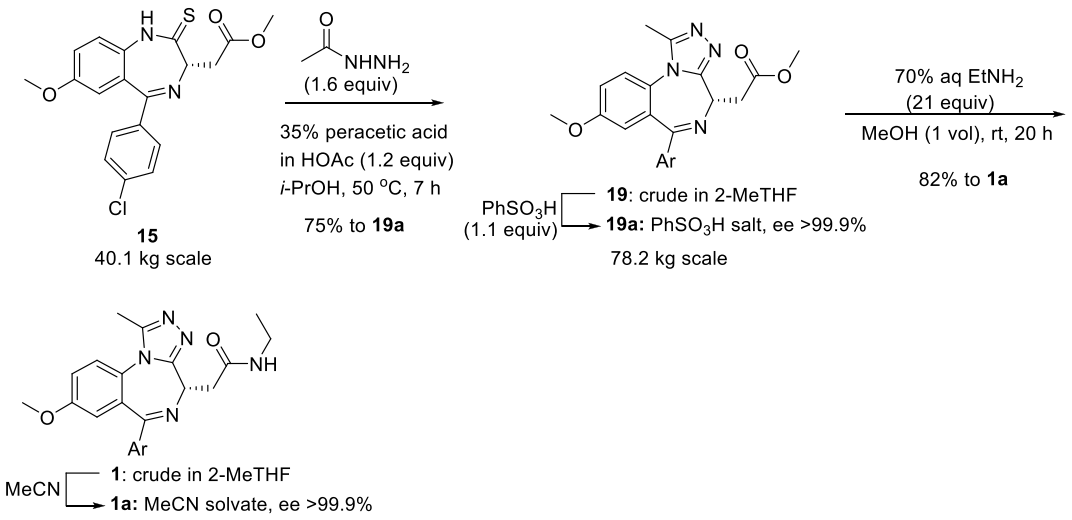
Scheme 7. Synthesis of GSK525762 (1) on Scale via the Oxidative Activation of Thiolactam 15 by Peracetic Acid



that **31** formed from reaction of **30** and acetic acid. Compounds analogous to **31** were not observed with hydrogen peroxide and cumene oxide.

In another control experiment, a mixture of **15** with peracetic acid (Scheme 6) was held at room temperature in the absence of acethydrazide. After 27 h, 77.7% of **14** was seen by HPLC analysis, along with 11.6% of remainder sulfenic acid **30** and 1.8% of acetyl imidate **31**. The formation of lactam **14**, seemingly a reversion from thiolactam **15**, could be explained by the reaction of sulfenic acid **30** and water. Water arose from many oxidant solutions such as hydrogen peroxide and peracetic acid.[15] Fortunately, the hydrolysis of **30** and **31** was a much slower process than the displacement of the pendant groups by acethydrazide. In a typical reaction with acethydrazide, premixed into the reaction mixture prior to the addition of an oxidant and even in the presence of a large amount of water from 30% aqueous hydrogen peroxide, **14** was observed at <5%, and it could be efficiently purged in the subsequent crystallization.

The reaction of thiolactam **15** and acetic acid, in the absence of peracetic acid, did not give acetyl imidate **31** at room temperature, supporting the role of peracetic acid in the activation of the thiolactam. It should be pointed out that the attempted activation of lactam **14** by those same oxidants shown in Scheme 6 led to only a negligible amount (0−2%) of products **18** and **19**; we found **14** mostly intact even on heating. Additionally, the direct reaction of thiolactam **15** and acethydrazide to form **19** required high heating in *n*-butanol, similar to the literature reports.[6] The reactions under those conditions were incomplete and produced impurities from extensive degradation and racemization.

The activation of thiolactam by oxidation for nucleophilic displacement was a novel approach to the best of our knowledge, and it offered much potential for other thioamides and nucleophiles other than acethydrazide. There is only limited reporting on sulfenic acids and their reactivities.[16] Generally, sulfenic acids were reported as too reactive to be isolated.[16a,b] Indeed, when trying to isolate **30** by cooling and filtration of the resultant yellow solids upon addition of peracetic acid to **15**, the filtered cake was hygroscopic and quickly turned darker in color. Sulfenic acid **30** was isolated in 68% purity by HPLC, along with 23% of **14**, arising from the reactivity of moisture with **30** during filtration. Although we proposed the structure of **30** as sulfenic (RS−OH) as shown in Scheme 6, it could be the tautomeric hydrosulfinyl (RS(O)H). In their review of sulfenic acids, Gupta and Carroll discussed the tautomeric structures of sulfenic acids and concluded that multiple studies supported the *O*-protonated form.[16a] LC-HRMS conducted on the isolated mixture of **30** and **14** confirmed the molecular weight but did not differentiate between the two. A general structural search on the conversion of *N*-arylthioamides to thioimidates showed only a few hits, e.g., with oxidation by sodium hypochloride (NaOCl) to a sulfonyl[16c] and by 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO) to a sulfenic ester of TEMPO.[16d]

For our objective of a practical and efficient synthesis of GSK525762 (**1**), we chose the readily available and inexpensive peracetic acid in acetic acid. Acetic acid also catalyzed the cyclocondensation of acetylhydrazide **18** to the triazole. This reaction has been scaled up multiple times in 50 to 2500 L scale with very high reproducibility. This step, as well as the subsequent transformation for the synthesis of **1**, is shown in Scheme 7.

In a pilot plant preparative run using 40.1 kg of **15**, activation of the thiolactam by 35% peracetic acid in the presence of acethydrazide went smoothly in 7 h to provide full conversion to methyltriazole **19**. We chose to heat the reaction to about 50 °C so that there was only a minimum accumulation of peracetic acid in the reaction vessel to avoid any potential hazard with the peracid. Based on the profile from reaction calorimetry, the oxidative activation of **15** to sulfenic acid intermediate **30** (structure shown in Scheme 6) was instantaneous under this set of conditions. Heating also accelerated the reaction of **30** with acethydrazide and the ring closure. After aqueous workup with sodium sulfite, **19** was extracted into 2-methyltetrahydrofuran, and the solution after concentration was treated with benzenesulfonic acid to give the crystalline benzenesulfonic acid salt **19a** in >99.9% ee and 99.8% purity by HPLC area in 75% yield. Isolation of salt **19a** was in higher yield than that of the free base due to the high crystallinity of the salt.

Conversion of the methyl ester **19a** to ethyl amide **1** in a single step was achieved by 70% aqueous ethylamine. Methanol was used to facilitate the initial dissolution of **19a**,

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and the small amount of methanol did not appreciably delay the amide formation. A small amount of a carboxylic acid byproduct from the hydrolysis of the ester moiety of **19** was purged in the extractive workup. The dissolved crude free base **1** from the extraction was solvent exchanged into MeCN, from which the highly crystalline 1:1 acetonitrile solvate **1a** in >99.9% ee was isolated in 82% yield on a 78.2 kg scale.[17]

CONCLUSION

A novel activation of thiolactam **15** by oxidation was developed for the preparation of methyltriazolo[1,4]benzodiazepine **19** in a single step. A sulfenic acid (RS−OH, **30**) was proposed as the activated intermediate, which underwent substitution readily with acethydrazide, followed by the acid-catalyzed cyclocondensation *in situ*. The conditions for the methyltriazole formation were mild and free of racemization of the sensitive stereocenter. The method, superior to the known methods to form alkyltriazoles, should be applicable for the synthesis of other triazoles from thiolactams and acylhydrazines.

A version of the peracetic acid method was scaled up to 40 kg as a part of the new route for the synthesis of BET inhibitor molibresib (GSK525762, **1**). The concise four-step synthesis starting from commercially available 2-amino-5-methoxyphenyl)(4-chlorophenyl)methanone (**5a**) provided 52 kg of **1** of 99.9% ee in overall 41% yield.

EXPERIMENTAL SECTION

General Procedures. All reactions were run under nitrogen. Unless otherwise specified, concentration by rotary evaporation or distillation was carried out under house vacuum of 12−50 Torr. Heating was provided by a steam-heated silicon heat transfer fluid in the pilot plant for all of the reactions on a kilogram scale. All other reactions were heated with an oil bath. Melting points were measured in Mettler Toledo MP 90 Melting Point System at 3 °C/min ramp, and the results were not corrected. The optical rotations were recorded in JASCO P-2000 Polarimeter. All NMR spectra were acquired at ambient temperature on a Bruker 400 MHz spectrometer. Solvents and frequencies for specific data acquisitions are noted for each case in the following sections. Chemical shifts were calibrated relative to residual protio solvent (^{1}H and ^{13}C). Data were processed using ACD Spectrus. HPLC analysis was performed on Agilent 1260 or 1290 series instruments with diode array detectors, though analysis was typically done with traces from a single wavelength. HRMS (m/z) was measured using a Thermo Scientific Orbitrap Eclipse mass spectrometer equipped with a heated electrospray ionization (HESI) ion source.

Generic HPLC Method A: Zorbax SB-C18 (3.0 mm × 50 mm, 1.8 μm), 1.5 mL/min, detection @220 nm, 60 °C. Eluents: 0.05% v/v TFA in water (A), 0.05% v/v TFA in MeCN (B). 100% A 0 min, 100% B 2.71 min, hold 0.29 min. Generic HPLC Method B: Luna C18 (2.0 mm × 50 mm, 3.0 μm), 1.0 mL/min, detection @220 nm, 40 °C. Eluents: 0.05% v/v TFA in water (A), 0.05% v/v TFA in MeCN (B). Gradient: 0−95% B over 8 min. Other HPLC methods, including one achiral and four chiral methods, are listed under the procedure for individual reactions.

*Methyl (S)-2-(5-(4-Chlorophenyl)-7-methoxy-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)acetate (**14**).* To a 2500 L reactor were successively added ethyl acetate (170 kg), (*S*)-aspartic acid **20** (61.2 kg, 166 mol), COMU (77.9 kg, 182 mol), and amino benzophenone **5a** (HCl salt, 45.0 kg, 151 mol), followed by additional ethyl acetate (75 kg) to wash down the solids. A thick but well-stirred slurry formed. The mixture was stirred at 60 rpm, and *N*,*N*-diisopropylethylamine (41.5 kg, 321 mol) was added. A nearly homogeneous solution formed from the slight exotherm of the addition. The reaction mixture was heated to 50 °C and stirred for 4 h to give amide **21**, with ≤3% of **5** remaining by HPLC Method A (**5** @ 2.30 min, **21** @2.89 min). To the mixture was then added triethylamine (53.5 kg, 529 mol). The reaction was stirred at 50 °C for an additional 8 h to effect Fmoc deprotection and ring closure to give lactam **14**, with ≤1% of **21** remaining by HPLC Method A (**21** without Fmoc @ 1.91 min, **14** @ 2.27 min). The slurry was cooled to 20 °C and treated with methanol (215 kg). After being aged for 1 h, the mixture was filtered via a filter drier. The filtered cake was washed three times with methanol (180 kg) and dried under about 25 Torr for 6 h to give **14** (46.2 kg, 82%) as an off-white solid: AUC 99.6% by HPLC Method A, ee > 99.9% by the chiral method below. Mp: 203.8−207.0 °C. $[\alpha]_D^{21}$ +114.5 (*c* 0.922, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (br s, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.12 (s, 1H), 6.76 (s, 1H), 4.18 (t, *J* = 7.1 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.39 (dd, *J* = 16.8, 7.2 Hz, 1H), 3.20 (dd, *J* = 16.8, 6.7 Hz, 1H). ^{13}C{H} NMR (75 MHz, DMSO-d_6): δ 171.5, 169.4, 166.6, 154.2, 137.1, 135.2, 132.6, 131.0, 128.3, 126.8, 122.9, 119.1, 113.4, 60.3, 55.5, 51.3, 35.9. HRMS (ESI): m/z calcd for $C_{19}H_{18}ClN_2O_4$ $(M + H)^+$, 373.0950; found, 373.0951

Chiral HPLC: Daicel CHIRALPAK IC (150 × 4.6 mm, 5 μm), 1.0 mL/min, detection @233 nm, 30 °C. Eluents: 70:30 (v/v) heptane/ethanol. Compound **14** @ 6.15 min, *ent*-**14** (*d*-enantiomer) @ 7.85 min.

*Methyl (S)-2-(5-(4-Chlorophenyl)-7-methoxy-2-thioxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)acetate (**15**).* To a 2500 L reactor were successively added MeCN (86 kg), lactam **14** (46.5 kg, 121 mol), phosphorus pentasulfide (14.0 kg, 60.4 mol) and hexamethyldisiloxane (35.3 kg, 217 mol), followed by additional acetonitrile (70 kg) to rinse down the solids. A thick yellow slurry formed at room temperature. After being stirred vigorously for 10 min, the mixture was heated to 60 °C and stirred for about 4 h. The reaction mixture became a red thin slurry, with ≤3% of **14** remaining by HPLC Method A (**14** @ 2.27 min, **15** @2.42 min). The reaction was cooled to 0 °C and quenched over about 40 min with 0.61 M aqueous solution of potassium carbonate (405 L, 245 mol) to keep the temperature below 5 °C. After being stirred at 0 °C for 1 h, the mixture was treated with isopropanol (142 kg) and stirred for an additional 1 h. The slurry was filtered via a filter drier. The filtered cake was successively washed with water (47 L) and with 1:1 water/*i*-PrOH (2 × 47 L) and dried at 50 °C under about 25 Torr for 8 h to give **15** (42.0 kg, 81%) as a yellow solid: AUC 96.6% by HPLC Method A, ee 98.6% by the chiral method below. Mp: 189.1−191.5 °C. $[\alpha]_D^{21}$ +76.1 (*c* 1.10, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (br s, 1H), 7.49 (m, 2H), 7.35 (m, 2H), 7.21 (m, 1H), 7.13 (m, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 4.39 (dd, *J* = 7.0, 6.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.66 (m, 1H), 3.39 (dd, *J* = 16.8, 7.0 Hz, 1H). ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ 199.9, 172.2, 167.9, 156.3, 137.0, 136.7, 132.7, 131.3, 129.4, 128.5, 122.7, 119.15, 114.6, 63.8, 55.8, 51.8, 39.5. HRMS: $(M + H)^+$ m/z calcd for $C_{19}H_{18}ClN_2O_3S$, 389.0721; found, 389.0723.

Chiral HPLC: Chiralcel OJ-RH (150 mm × 4.6 mm, 5 μm), 1.0 mL/min, uncontrolled temperature (20−25 °C), detection @220 nm. Eluents: water 0.05% TFA (A), MeCN 0.05% TFA (B). 60:40 A/B. Compound **15** @ 16.55 min, *ent*-**15** (*d*-enantiomer) @ 18.75 min.

*Methyl 2-((4S)-6-(4-Chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetate, Benzenesulfonic Acid Salt (**19a**).* To a 2500 L reactor were successively added isopropanol (167 kg), 95 wt % acethydrazide (12.8 kg, 165 mol) and thiolactam **15** (40.1 kg, 103 mol), followed by additional isopropanol (96 kg) to wash down the solids. The resulting yellow slurry was stirred at 60 rpm and heated to 50 °C, followed by the addition of peracetic acid (~35 wt % in HOAc, 26.9 kg, 124 mol) over about 45 min. The addition was exothermic, and the temperature was kept at 50−60 °C throughout the addition. The reaction was stirred at 50 °C for 7 h, with ≤3% of remaining uncyclized acetylhydrazone **18** by HPLC Method A (**18** @ 2.03 min, **15** @2.42 min, and **19** @2.21 min). The slurry was cooled to 15 °C and quenched with 10 wt % (~1 M) aqueous sodium bisulfite (40.1 kg, 38.6 mol) over about 30 min. An aliquot was tested with a strip of KI/starch paper to ensure a negative result (white color for the absence of

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residual oxidant). If the paper was purple, additional sodium bisulfite was added. The heterogeneous mixture was then distilled under a house vacuum (30−100 Torr) to about 180 L at an external temperature of 50−55 °C. After the distillation, the mixture was cooled to 25 °C and treated with 2-methyltetrahydrofuran (345 kg) and water (200 kg). The resulting biphasic mixture was stirred for 30 min at room temperature and filtered via a two-stage in-line 0.2-μm filter to remove any sulfur-containing particles. An additional 2-methyltetrahydrofuran (80.3 kg) was used to rinse the reactor and added to the in-line filtration. The biphasic mixture was settled for 1 h before the phase split. The organic layer was distilled at atmospheric pressure down to about 245 L to give **19** as a solution in 2-methyltetrahydrofuran.

The concentrate above was heated to 35 °C, and 25.3 wt/wt % benzenesulfonic acid solution (34.9 kg, 55.8 mol) in 2-methyltetrahydrofuran was added over about 1 h. The solution was then seeded with **19a** (40 g, 0.001 wt of the input **15**) as a slurry in 2-methyltetrahydrofuran (400 mL). Crystallization occurred within minutes at 35 °C after seeding. An additional 25.3 wt/wt % benzenesulfonic acid solution (34.9 kg, 55.8 mol) was added over about 1 h. The resultant slurry was cooled to 0 °C at about 1.0 °C/min rate and stirred for 12 h. The mixture was filtered via a filter drier. The cake was washed with 2-methyltetrahydrofuran (2 × 68.2 kg) and dried at 70 °C under about 25 Torr to give the benzenesulfonic acid salt **19a** (43.8 kg, 75%) as an off-white crystalline solid: AUC 99.9% by HPLC Method A, ee > 99.9% by the chiral HPLC method below. Mp: 124.6−127.0 °C. $[\alpha]_D^{21}$ +68.3 (*c* 1.44, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) **19a**: δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.76 (m, 3H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.30−7.33 (m, 4H), 7.25 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.90 (s, 1H), 4.67 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.45−3.65 (m, 2H), 3,09 (s, 3 H). ^{13}C{H} NMR (75 MHz, DMSO-d_6): δ 170.6, 166.6, 158.5, 155.0, 152.4, 148.0, 136.7, 135.7, 131.4, 129.8, 128.5, 128.2, 127.6, 126.2, 125.5, 124.3, 117.9, 115.8, 56.0, 52.2, 51.7, 35.8, 11.2. HRMS: $(M + H)^+$ *m*/*z* calcd for $C_{21}H_{20}ClN_4O_3$, 411.1218; found, 411.1220.

Compound **19** (free base, from chromatographic purification of the crude): $[\alpha]_D^{21}$ +78.1 (*c* 1.42, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.22 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.89 (d, *J* = 2.9 Hz, 1H), 4.61 (dd, *J* = 7.8, 6.4 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.62 (m, 2H), 2.62 (s, 3 H). ^{13}C{H} NMR (75 MHz, DMSO-d_6): δ 171.1, 165.8, 157.4, 155.3, 150.8, 137.1, 135.4, 131.0, 129.2, 128.2, 126.3, 125.5, 117.8, 115.3, 55.8, 52.8, 51.5, 36.2, 11.4.

Chiral HPLC: Chiralcel OJ-RH (150 × 4.6 mm, 5 μm), 1.0 mL/min, 50 °C, detection @229 nm. Eluents: water 0.05% TFA (A), MeCN 0.05% TFA (B). 80:20 A/B. Compound **19** @ 20.50 min, *ent*-**19** (*d*-enantiomer) @ 23.70 min.

*2-((4S)-6-(4-Chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide, Acetonitrile Solvate (**1a**).* To a 2500 L reactor were successively added methanol (68 L) and **19a** (78.2 kg, 137 mol) to form a solution, followed by additional methanol (10.2 L) to wash down the solids. After being cooled to 10−15 °C, the solution was treated with 70 wt % aqueous ethylamine (190 kg, 2938 mol), which was precooled to 5 °C. The mixture was stirred at 60 rpm at room temperature for 20 h, with ≤0.2% of the remaining **19** by HPLC (**19** @ 2.21 min, **1** @1.85 min). The reaction mixture was diluted with 2-methyltetrahydrofuran (781 L) and cooled to 10 °C. The mixture was treated with 25 vol % aqueous acetic acid solution (604 L, 2638 mol), which was precooled to 5−10 °C. The addition was carried over 30 min to keep the temperature below 25 °C, followed by a line rinse with water (30 L). The aqueous layer had a pH ≥ 8−9, and this removed a small amount of a carboxylic acid byproduct formed from hydrolysis of **19** during the reaction. The layers were separated, and the organic layer was further basified with 5 wt % aqueous sodium bicarbonate solution (391 L, 233 mol). The biphasic mixture was heated to 45 °C and stirred for 10 min. The layers were separated at 45 °C, and the organic layer was treated with water (234 L) at 45 °C. The biphasic mixture was stirred at this temperature for 10 min. The layers were separated at 45 °C to obtain crude GSK525762 free base (**1**) as a solution in 2-methyltetrahydrafuran. The heating during this part of the workup was designed to avoid emulsions otherwise observed at room temperature.

Solvent swap from the 2-methyltetrahydrofuran to acetonitrile was carried out by the distillation of the solution under reduced pressure (∼100 Torr) to about 250 L, followed by dilution with acetonitrile (300 L) and further distillation to about 300 L. This operation was repeated twice whereupon GSK525762 (**1**) crystallized as the acetonitrile solvate (**1a**). After being cooled to 0−5 °C over 1 h, the slurry was aged for 1 h and filtered via a filter dryer. The reactor was rinsed with acetonitrile (250 L, precooled to 0 °C). The filtered cake was washed with the rinse and dried at 30 °C under about 100 Torr and a stream of nitrogen for 4 h to give **1a** (52.4 kg, 82%) of AUC > 99.9% by achiral HPLC method below and >99.9% ee by the chiral HPLC method below as a white crystalline solid. Mp: 118.9−120.3 °C. $[\alpha]_D^{21}$ +87.0 (*c* 1.41, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) **1a**: δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.21 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.85 (d, *J* = 2.9 Hz, 1H), 6.69 (br s, 1H), 4.63 (t, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.20−3.43 (m, 3H), 2.62 (s, 3H), 2.01 (s, 2H), 1.19 (t, *J* = 7.3 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6): δ 169.2, 165.5, 157.3, 155.8, 150.6, 137.2, 135.4, 131.0, 129.3, 128.2, 126.4, 125.5, 117.8, 115.1, 55.8, 53.3, 37.6, 33.4, 14.8, 11.5. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{20}N$ (MH^+) for $C_{22}H_{23}ClN_5O_2$, 424.1535; found, 424.1537.

Compound **1** (parent, from chromatographic purification of the crude): $[\alpha]_D^{21}$ +90.6 (*c* 1.43, MeOH) (lit.[2a] $[\alpha]_D^{20}$ +88.1 (*c* 1.00, MeOH)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.21 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.85 (d, *J* = 2.9 Hz, 1H), 6.69 (br s, 1H), 4.63 (t, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 14.1, 7.3 Hz, 1H), 3.20−3.43 (m, 3H), 2.62 (s, 3H), 1.19 (t, *J* = 7.3 Hz, 3H). ^{13}C{H} NMR (75 MHz, DMSO-d_6): δ 169.2, 165.5, 157.4, 155.8, 150.6, 137.3, 135.4, 131.0, 129.3, 128.2, 126.4, 125.5, 117.8, 115.1, 55.8, 53.3, 37.6, 33.4, 14.8, 11.5.

Achiral HPLC: Zorbax Eclipse Plus C-18 (50 mm × 4.6 mm, 1.8 μm), 1.5 mL/min, detection @210 nm, 40 °C. Eluents: water 0.1% H_3PO_4 (A), MeCN (B). 70% A 0 min, 0% A 4 min, hold 2 min. Compound **19** @ 2.21 min, **1** @1.85 min.

Chiral HPLC: Daicel CHIRALPAK IC (150 mm × 4.6 mm, 5 μm), 1.5 mL/min, detection @240 nm, 15 °C. Eluents: 500:500:1:1 water/MeCN/DMF/H_3PO_4. Compound **1** @ 6.7 min, *ent*-**1** (*d*-enantiomer) @ 4.5 min.

*Methyl (S)-2-(5-(4-Chlorophenyl)-2-(hydroxythio)-7-methoxy-3H-benzo[e][1,4]diazepin-3-yl)acetate (**30**). Experiment A for Characterization by LCMS.* To thiolactam **15** (2.00 g, 5.14 mmol) in a 50 mL flask was added isopropanol (16 mL), followed by 39% peracetic acid in acetic acid (0.88 mL, 5.14 mmol) at ambient temperature over about 2 min. The slurry became thinner and changed from yellow to orange color. The mixture was sampled after 8 min for HPLC and LCMS analysis. See the HPLC (Method A) chromatogram in Scheme 6 and the LCMS information in Supporting Information. The HPLC showed only 8.7% of **15** left at 2.46 min, with the formation of 81.3% of activated sulfenic acid intermediate **30** at 2.29 min, along with 7.3% of acetyl imidate **31** at 2.78 min. The structure assignment for **30** and **31** was solely based on LCMS. The order of retention times in the reverse HPLC and LCMS corroborated with the estimated polarity of those compounds relative to **15**. After the first sample, additional 39% peracetic acid (0.18 mL, 1.05 mmol) was added. The mixture was stirred for 5 min and the second sample was taken for HPLC, which showed only 0.7% of **15** left. At that time, acethydrazide (0.682 g, 8.74 mmol) was added in one portion as a solid, and the reaction was heated to 50 °C. After 1 and 6 h, HPLC showed only 0.7% and 0.2% of the activated intermediate **30** left, respectively, with triazole **19** forming concurrently.

Experiment B for Isolation and Characterization by HRMS. To **15** (5.00 g, 12.9 mmol) in a 100 mL flask was added isopropanol (40 mL). The yellow slurry was heated to 50 °C and stirred for 10 min to maximize any potential dissolution. After being cooled to room

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temperature, the mixture was treated with 39% peracetic acid (2.62 mL, 15.4 mmol) dropwise over about 4 min. During the addition, the slurry turned into a red and almost homogeneous mixture. The mixture was stirred for 10 min at room temperature and sampled for HPLC (Method A), which showed 68% of the sulfenic acid product **30** at 2.29 min and 25% of lactam **14** at 2.27 min. We believe that **14** formed from the hydrolysis of **30** (water brought in the peracetic acid solution, see ref 15) in the absence of acethydrazide, as well as from analysis with water in the eluting mobile phase. The red mixture was cooled with an ice bath which immediately generated yellow solids. Filtration followed by a wash with isopropanol (10 mL) produced a yellow cake. However, the filtered cake turned darker within a few minutes while under a vacuum for further drying. The cake was apparently hygroscopic and picked up moisture in the air and underwent hydrolysis to give lactam **14**. The solid was only partially transferrable to a bottle for further drying in the oven under nitrogen. Analysis by HPLC showed 68% of **30** and 23% of **14**. Analysis by HRMS confirmed the exact mass of **30**. HRMS (ESI): m/z calcd for $C_{12}H_{20}N$ (MH^+) for $C_{19}H_{18}ClN_2O_4S$, 405.0670; found, 405.0672.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00563.

NMR spectra for all new compounds, HPLC-MS analysis, and HPLC-HRMS for compound **30** (PDF)

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Notes

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