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Process Research and Large-Scale Synthesis of a Novel 5,6-Dihydro-(9H)-pyrazolo[3,4-*c*]-1,2,4-triazolo[4,3-*a*]pyridine PDE-IV Inhibitor

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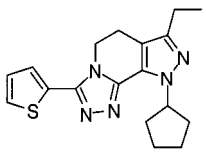
Abstract:

An efficient synthesis of the PDE IV inhibitor, 9H-cyclopentyl-7-ethyl-3-(thiophen-2-yl)-pyrazolo[3,4-*c*]-1,2,4-triazolo-5,6-dihydro-[4,3-*a*]pyridine 1 is described. Starting from commercially available γ-caprolactone, the synthesis was carried out in 10 steps. Key transformations were the selective O-methylation of diketone, 3-hydroxy-1-(4-methoxybenzyl)-4-propionyl-5,6-dihydro-1H-pyridin-2-one, with dimethyl sulfate and cesium carbonate in dimethylformamide, a one-pot pyrazole formation with subsequent acidic deprotection to provide lactam, 1-cyclopentyl-3-ethyl-1,4,5,6-tetrahydropyrazolo[3,4-*c*]pyridin-7-one, and finally the utilization of imidate, 1-cyclopentyl-7-ethoxy-3-ethyl-4,5-dihydro-1H-pyrazolo[3,4-*c*]pyridine for the introduction of the triazole moiety. This process avoided the use of harsh reaction conditions, undesirable reagents and overcame the environmental concerns in the original synthesis.

Recently, Allen Duplantier et al. reported on the synthesis and selective phosphodiesterase activity of a series of 7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-*c*]pyridines including analogue **2b**.[2] In their further optimization of the desired biological activity, a key intermediate was the unsubstituted lactam **2a** which was available from **2b** through removal of the 4-methoxyphenyl moiety with ceric ammonium nitrate (CAN). Additional molecular modification resulted in a new series of compounds which featured an additional triazole ring and led to the scale-up of the thiophene analogue **1** for further study.[3] In this paper, we describe the process research and large-scale preparation of multikilogram quantities of **1** to support these studies. In approaching this target, an efficient synthesis was developed which paralleled the original Duplantier route, but which addressed the problems of harsh reaction conditions, multiple chromatographies, and undesirable reagents for large-scale work.



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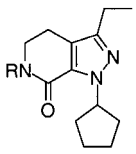

2a; R = H
2b; R = 4-methoxyphenyl

The Duplantier synthesis of compound **1** is shown in Scheme 1. The first two steps of the sequence were major concerns for the initial scale up. Step one was the reaction of 4-iodoanisole and 2-pyrrolidinone with copper powder and potassium carbonate in the absence of solvent with heating to 150 °C. This reaction had shown an exotherm when scaled up to 200 g. Addition of ethyl acetate to the crude melt at elevated temperature was necessary to prevent formation of a solid mass upon cooling. Reaction two was the greater concern. The mono-addition of ethylmagnesium bromide to pyrrolidinone lactam **3** occurred cleanly in ethyl ether, but was complex in tetrahydrofuran. The desired ethyl (4-methoxyphenylamino)propyl ketone **4** was not stable to storage. Other process concerns were the use of methyl *p*-tolyltriazine **7** to O-methylate the intermediate β-diketone **6**, the synthesis and purification of cyclopentyl hydrazine **9**, the ceric ammonium nitrate (CAN) deprotection of *p*-methoxyphenyl amide **2b**, and finally, the use of thiolactam chemistry to introduce the triazole moiety. A more detailed discussion of these reactions is given in the discussion of the preferred process described below.

Our first approach was to intersect with the Duplantier synthesis at oxalamide **5**. To avoid the Grignard reaction for the introduction of an ethyl group, commercially available γ-caprolactone **11** was chosen as the starting material, and *p*-anisidine was the source of the nitrogen atom. The sequence was demonstrated on laboratory scale with the yields shown in Scheme 2. Initial reduction of lactone **11** with DiBAL provided lactol **12** as a mixture of diastereomers. Lactol **12** was used without purification in the reductive alkylation to provide amino alcohol **13** in good yield. Amino alcohol **13** was converted uneventfully to the desired oxalamide **5**. The problem with this approach was discovered on initial scale up to kilogram quantities. Some batches of lactol **12** underwent the reductive alkylation in yields similar to those seen in the lab, but more often the lactol was found to decompose, possibly through self-condensation, resulting in complex reaction mixtures after the reductive alkylation step. Also, since the 4-methoxyphenyl moiety was serving as the nitrogen-protecting group, this would require the use of CAN to carry out the deprotection later in the synthesis. With these factors in mind, a different source for the nitrogen atom was chosen.

The synthesis that was carried out at large scale starting with 28.75 kilograms of γ-caprolactone is shown in Scheme 3. 4-Methoxy-benzylamine was heated with caprolactone **11** without solvent to provide amide **15** as a crystalline solid. This group allowed more options for deprotection. A similar

(1) Current address: Ilex Oncology, 14785 Omicron Drive, # 201, San Antonio, TX 78245-3221.
(2) Duplantier, A. J.; Andresen, C. J.; Cheng, J. B.; Cohan, V. L.; Decker, C.; DiCapua, F. M.; Kraus, K. G.; Johnson, K. L.; Turner, C. R.; UmLand, J. P.; Watson, J. W.; Wester, R. T.; Williams, A. S.; Williams, J. A., *J. Med. Chem.* **1998**, *41,* 2268.
(3) Duplantier, A. J.; Cooper, K. U.S. Patent 6,004,974, 1999.

10.1021/op010222x CCC: $20.00
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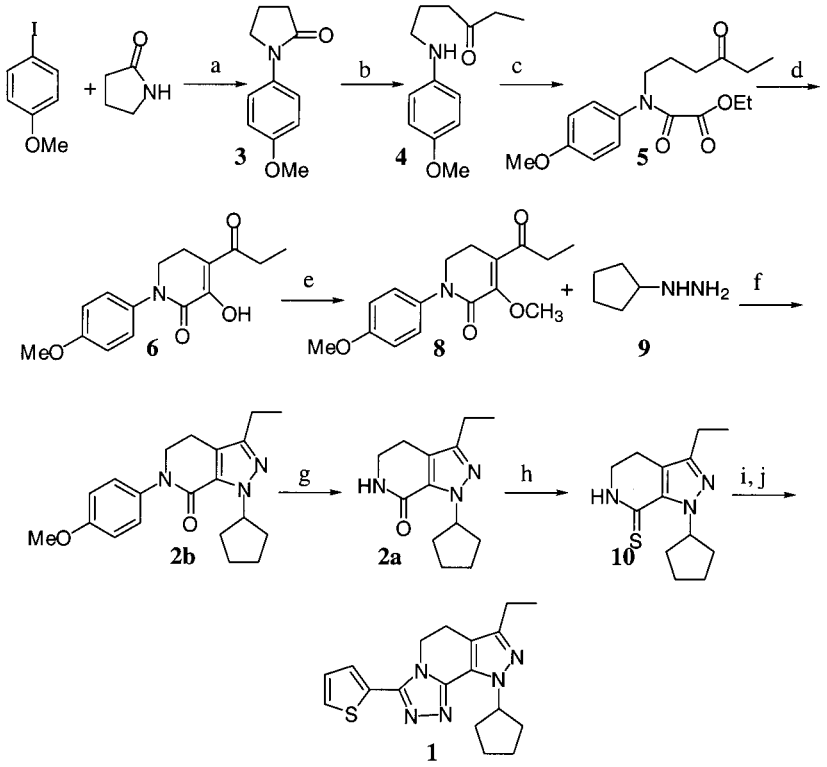
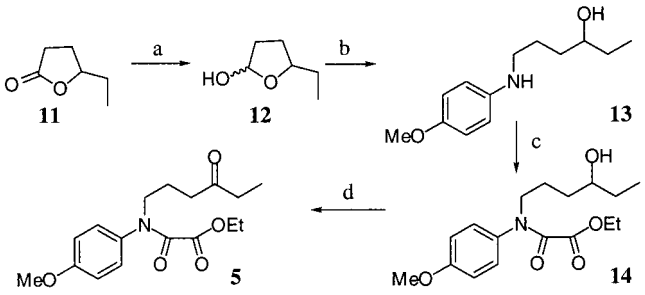
Scheme 1[a]



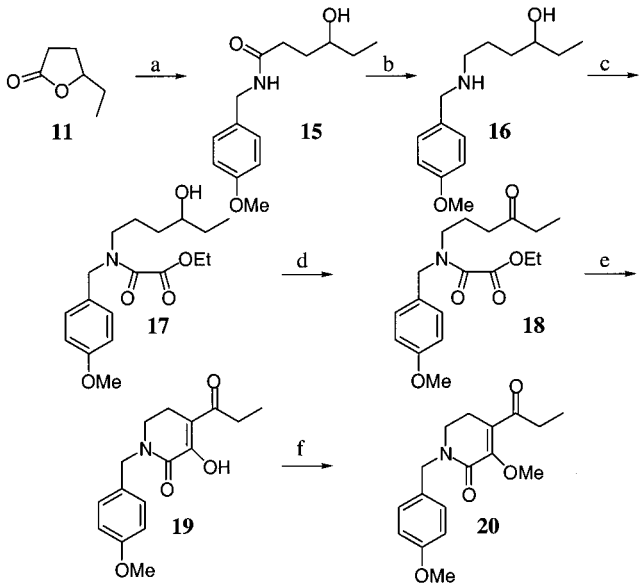
[a] a) Cu, 150 °C, 83%; b) EtMgBr, Et2O, 0 °C, 60−80%; c) ethyl oxalyl chloride, NaOH, benzene; d) NaOEt, EtOH, 41% over c and d; e) methyl-4-tolyltriazine **7**, CH_2Cl_2, 70%; f) cyclopentyl hydrazine hydrochloride, 120 °C, 75%; g) CAN, acetonitrile/water, 65%; h) P_4S_{10}, dioxane, 80%; i) hydrazine, pyridine; j) 2-thiophenecarbonyl chloride, pyridine followed by reflux in DMF, 64%.

Scheme 2[a]



[a] a) DiBAL, THF, −78 °C, 85%; b) p-anisidine, sodium triacetoxyborohydride, 70%; c) ethyl oxalyl chloride, triethylamine, CH_2Cl_2, 90%; d) TEMPO, sodium hypochlorite, CH_2Cl_2, 80%.

Scheme 3[a]



[a] a) 4-Methoxybenzylamine, neat, 73%; b) $NaBH_4$, acetic acid, THF, 79%; c) ethyl oxalyl chloride, 86%; d) TEMPO, sodium hypochlorite, CH_2Cl_2, 85%; e) KO*t*-Bu, THF, 73%; f) cesium carbonate, dimethyl sulfate, DMF, 89%.

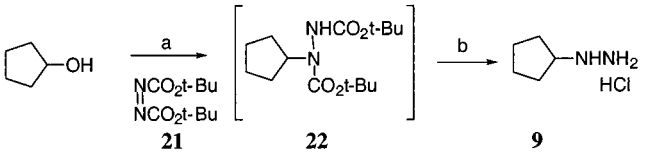
reaction of lactone **11** with *p*-anisidine was not successful since the aniline was less nucleophilic.

Amide **15** could be reduced to the amine **16** by a variety of reducing agents including borane−THF, sodium borohydride with boron trifluoroetherate or lithium aluminum hydride. For the large-scale batch, sodium borohydride in tetrahydrofuran with addition of acetic acid was used.[4] This procedure scaled up well although there was foaming during the addition of the acetic acid. Amine **16** was isolated as a solution in ethyl acetate for use directly in the acylation with ethyl oxalyl chloride under Schotten−Baumann conditions. Once again, crude oxalamide **17** was used as is for the oxidation of the secondary alcohol. In the lab, the oxidation of alcohol **17** was done with either chromium trioxide or TEMPO with sodium hypochlorite.[5] The hypochlorite procedure worked well in the Pilot Plant provided that the sodium hypochlorite was freshly prepared from calcium hypochlorite and sodium carbonate. The product ketone was an oil and was used in the next reaction without further purification. The Dieckmann cyclization was done in tet-

(4) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, 763.

(5) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212.

Scheme 4[a]



[a] a) Ph_3P, THF; b) concentrated HCl, 69%.

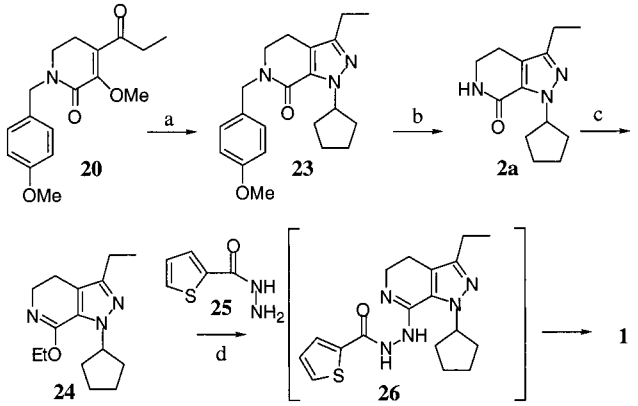
rahydrofuran with a slight excess of potassium *tert*-butoxide. Lactam **19** was isolated as a solid by precipitation from the aqueous layer in the work-up by addition of 6 N HCl. This combination of extraction into an aqueous solution and precipitation of solid **19** was the second actual purification in the process and provided material of high quality.

In the next step, it was necessary to introduce a methyl group onto the enolic oxygen in **19**. Duplantier had used methyl *p*-tolyltriazine **7** to avoid the side reaction of carbon alkylation.[6] Reaction of **19** with methyl iodide and potassium carbonate in acetone gave a mixture of C- and O-alkylation. Conditions for exclusive O-alkylation were found using dimethyl sulfate and cesium carbonate in dimethylformamide. Once these conditions were found, other reagents were not explored.

The next issue was the preparation of cyclopentyl hydrazine **9**. Duplantier had used a literature procedure which started with cyclopentanone and *tert*-butylcarbazate to give an alkylidine carbazate. This was reduced with borane−THF, and the *tert*-butyl ester was hydrolyzed with hydrochloric acid to afford hydrazine **9**.[7] The hydrazine prepared in this manner in our lab was contaminated with boric acid which was difficult to remove without loss of yield. Instead, a one-pot procedure was developed which relied on a Mitsunobu reaction between cyclopentanol and di-*tert*-butyl azodicarboxylate.[8] (Scheme 4) Our variation of this procedure was to add 6 N HCl to the tetrahydrofuran reaction mixture after the Mitsunobu reaction was complete to remove the *tert*-butyl esters and isolate the hydrazine hydrochloride directly as a crystalline solid. On 7-kg scale, the dihydrochloride salt of **9** was isolated, while in the lab the mono hydrochloride salt was isolated on one occasion. This may have been due to a more complete azeotropic drying with 2-propanol. The identity of the salt and the stoichiometry for the next reaction was based on a chloride analysis of the isolated material.

The remainder of the process is shown in Scheme 5. The pyrazole ring was formed in the same manner as the procedure described by Duplantier. A mixture of the enol ether **20** and cyclopentyl hydrazine dihydrochloride **9** was suspended in tetrahydrofuran and heated to reflux. The solvent was distilled off, and the resulting melt was heated to 85−90 °C under a sweep of nitrogen to help remove tetrahydrofuran, methanol, and excess HCl. Crude pyrazole **23** was an oil, which was used without isolation in a one-pot procedure for this scale up, but could be isolated as a crystalline salt with either *p*-toluenesulfonic acid or benzenesulfonic acid from ethyl acetate. Removal of the *p*-methoxybenzyl moiety was done by treating crude **23** with trifluoroacetic acid at 50−60 °C followed by addition of methanesulfonic acid. These conditions for solvolysis of the protecting group had been described previously by Martin.[9] The resulting mixture was heated for 2 h at 70 °C to complete the deprotection. Extractive work up provided the key lactam **2a** in 71% yield over the two steps.

Scheme 5[a]



[a] a) **9**, 88 °C, THF; b) CF_3CO_2H, CH_3SO_3H, 70 °C, 71% (two steps); c) Et_3OBF_4, CH_2Cl_2, 93%; d) **25**, *n*-butanol, 90°, 67%.

In the Duplantier synthesis, lactam **2a** was converted to the thiolactam **10** with phosphorus pentasulfide. This was reacted with anhydrous hydrazine to give an amidrazone derivative, which was acylated with 2-thiophenecarbonyl chloride to provide **26** in situ. The reaction solution was heated to cyclize **26** to triazole **1**. The thiolactam procedure seemed to be the preferred method in the literature for conversion of a lactam to a fused triazole.[10] The environmental problems associated with the scale up chemistry involving phosphorus pentasulfide, hydrogen sulfide, and anhydrous hydrazine caused us to seek an alternative. Considerable effort was expended to prepare an imidoyl chloride derivation from **2a**, but the best yield of **1** from a sequence in which **2a** was converted to an imidoyl chloride intermediate with phosphorus pentachloride followed by treatment with 2-thiophenecarboxylic hydrazide **25** was ca. 20%. The next approach was to generate the imidate of **24**. The intermediacy of imidates for the preparation of triazoles was seen mostly in cases where the triazole was not fused to another ring.[11] Reaction of lactam **2a** with a freshly prepared solution of triethyloxonium tetrafluoroborate in methylene chloride gave the desired imidate **24** in almost quantitative yield.[12] Imidate **24** was treated with 2-thiophenecarboxylic hydrazide in refluxing *n*-butanol to provide the desired triazole **1**. The intermediate acyl amidrazone **26** can be seen in the reaction and was monitored by HPLC until the conversion to **1** was complete. The isolated yield from **2a** to **1** over the three steps was 67% and was not optimized at that time.

(6) Vyas, D. M.; Benigni, D.; Partyka, R. A.; Doyle, T. W. *J. Org. Chem.* **1986**, *51*, 4307.
(7) Ghali, N. I.; Venton, D. L.; Hung, S. C.; Le Breton, G. C. *J. Org. Chem.* **1981**, *46*, 5413.
(8) Dow, R. L.; Kelly, R. C.; Schletter, I.; Wierenga, W. *Synth. Commun.* **1981**, *11*, 43.
(9) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron* **1993**, *49*, 3521.
(10) Hester, J. B., Jr.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078.
(11) Poonian, M. S.; Nowoswiat, E. F. *J. Org. Chem.* **1980**, *45*, 203.
(12) Smith, M. B.; Menezes, R. *Synth. Commun.* **1988**, *18*, 1625.

In conclusion, an efficient process for the preparation of a clinical candidate was presented which was carried out successfully to produce 7.9 kg of lactam **2a**. A 3.7 kg portion of **2a** was taken on to compound **1**. The final process minimized environmental concerns with the Duplantier route such as generation of sulfurous volatile side-products and the use of anhydrous hyrazine. In addition, the need for multiple chromatographic purifications was avoided. The facile nature of the imidate chemistry in particular should allow others to replace some of the thiolactam chemistry which is still the primary method for the conversion of a lactam to a fused triazole.[13]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on either a Brucker WM 300 (300 MHz) or a Varian Unity 400 (400 MHz) spectrometer in deuteriochloroform or dimethyl sulfoxide-d_6. Infrared spectra were taken in KBr by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Mass spectra were determined with a Finnigan 4510 mass spectrometer using fast atom bombardment (FAB). Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. The reactions were monitored by TLC on silica gel plates, and isolated compounds were analyzed by HPLC.

2-Thiophenecarboxylic hydrazide was purchased from Aldrich Chemical Co., and crystalline triethyloxonium tetrafluoroborate, from Fluka Chemicals.

4-Hydroxyhexanoic Acid 4-Methoxybenzylamide (15). γ-Caprolactone **11** (28.75 kg, 251.8 mol) and 4-methoxybenzylamine (38.0 kg, 277 mol) were placed in a 100-gal glass-lined tank. The solution was heated to 80−85 °C and held at that temperature for 16 h. TLC on silica gel plates showed the reaction was complete. (TLC system: ethyl acetate with detection at 254 nm). Ethyl acetate (68 L) was slowly charged to the pot after cooling to 60 °C. Hexanes (68 L) were added until a haze was achieved. After 30 min, to allow crystallization to start, the remainder of the hexanes were added. The slurry was cooled to 25 °C and granulated for 3 h. The solid was collected by filtration and washed with a 1:1 mixture of ethyl acetate and hexanes. The wet cake was vacuum-dried with no additional heat to produce 46.05 kg (72.8%) of the desired amide **15**: mp 81−82 °C. ^{1}HMR ($CDCl_3$, 300 MHz) δ 7.18 (d, 2), 6.84 (d, 2), 6.27 (bs, 1), 4.32 (d, 2), 3.79 (s, 3), 3.50 (m, 1), 3.19 (bs, 1), 2.35 (t, 2), 1.85 (m, 1), 1.67 (m, 1), 1.49 (m, 2), 0.92 (t, 3).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.26; H, 8.71; N, 5.55.

HPLC: Inertsil, C_8, acetonitrile, 20%/0.01M K_2HPO_3 @ pH = 7.0 with H_3PO_4.

6-(4-Methoxybenzylamino)hexan-3-ol (16). Tetrahydrofuran (458 L) and sodium borohydride (22.15 kg, 585.6 mol) were charged to a clean and dry nitrogen-purged 500-gal glass lined tank. The suspension was allowed to stir for 30 min at 20−25 °C, and then amide **15** (45.75 kg, 182 mol) was added as a solid. After 30 min, the reaction was cooled to 5−10 °C, and over a 4−8 h period a solution of acetic acid (34.4 L) in tetrahydrofuran (45.4 L) was added, keeping the temperature at 0−10 °C. A slight nitrogen bleed was kept on the tank to help remove the hydrogen. When the addition was complete, the reaction was warmed to 20−25 °C and stirred for 1 h. The temperature of the reaction was slowly increased to a gentle reflux (~66 °C) and held there for 16 h. The reaction was quenched by the addition of 1 N HCl, keeping the temperature <25 °C. Excess tetrahydrofuran was removed by atmospheric distillation. Ethyl acetate was added to the resulting aqueous solution to extract unreacted amide. The acidic aqueous layer was then brought to pH 11 to allow the product amine **16** to be extracted into ethyl acetate and held for use in the next step. An aliquot of the ethyl acetate solution of product was worked up to project final yield and concentration. The yield for the Pilot Plant run was 55% which was less than for the lab experiments (78.8%). The large batch had 12.8% unreduced amide starting material **15** after the quench, which accounted in part for the lower yield.

^{1}HMR ($CDCl_3$, 300 MHz) δ 7.21 (d, 2), 6.83 (d, 2), 3.78 (s, 3), 3.69 (s, 2), 3.41 (m, 2), 2.78 (m, 1), 2.58 (m, 1), 1.71 (m, 2), 1.45 (m, 4), 0.95 (t, 3). GC mass spectrum: *m*/*e* 237 (M^+).

HPLC: Inertsil, C_8, acetonitrile, 20%/0.01M K_2HPO_3 @ pH = 7.0 with H_3PO_4.

***N*-(4-Hydroxyhexyl)-*N*-(4-methoxybenzyl)oxalamic Acid Ethyl Ester (17).** 6-(4-Methoxybenzylamino)hexan-3-ol **16** (24 kg, 101.1 mol) in ethyl acetate (598 L) was charged to a clean and dry, nitrogen-purged 500-gal glass-lined tank. This solution was cooled to 0−5 °C, and then a solution of sodium bicarbonate (16.99 kg, 202.2 mol in water (193 L) was added, maintaining a temperature of 0 to 5 °C. A solution of ethyl oxalyl chloride (16.57 kg, 121.4 mol) in ethyl acetate (75.7 L) was added, while maintaining a temperature of 0−5 °C over a time period of about 25 min. The reaction was allowed to warm to 20−25 °C at which point it was complete by HPLC. The reaction was stirred for an additional 16 h to allow any residual ethyl oxalyl chloride to decompose. The lower aqueous layer was discarded, and the ethyl acetate solution was washed with water (185.5 L). The layers were separated. The remaining ethyl acetate was washed with 2 N HCl (128 L). The remaining ethyl acetate was vacuum stripped to obtain the crude product amide **17** as an oil, 29.3 kg (85.9% theory). ^{1}HMR ($CDCl_3$, 400 MHz) δ 7.18 (m, 2), 6.83 (m, 2), 4.41 (m, 1), 4.31 (m, 3), 3.76 (d, 3), 3.43 (m, 1), 3.25 (m, 1), 3.13 (t, 1), 2.00 (bs, 1), 1.80−1.26 (m, 8), 0.87 (t, 3). IR (neat) 3456, 1739, 1654, 1513 cm^{-1}. ^{13}CMR ($CDCl_3$, 400 MHz) δ 163.5, 162.1, 159.7, 159.0, 129.6, 129.2, 128.0, 127.1, 114.2, 114.1, 72.6, 72.5, 62.1, 55.3, 50.9, 47.0, 46.3, 43.6, 33.5, 33.4, 30.3, 30.2, 24.3, 22.9, 14.0, 9.9. GC mass spectrum: *m*/*e*, 338 (M^+).

HPLC: Inertsil, C_8, acetonitrile, 20%/0.01M K_2HPO_3 @ pH = 7.0 with H_3PO_4.

***N*-(4-Methoxybenzyl)-*N*-(4-oxo-hexyl)oxalamic Acid Ethyl Ester (18).** Potassium bromide (593 g, 5 mol) was

(13) After the completion of our work, another example of using imidates to prepare 1,2,4-triazolo[4,3-*a*]pyridines appeared. Lawson, E. C.; Maryanoff, B. E.; Hoekstra, W. J. *Tetrahedron Lett.* **2000**, *41*, 4533.

dissolved in water (18.9 L) in a 100-gal glass-lined tank. A solution of oxalamide alcohol **17** (33.62 kg, 99.6 mol) in methylene chloride (128.7 L) was added. The TEMPO catalyst (150 g) was added, and the reaction was cooled to 0−5 °C. Fresh sodium hypochlorite solution (prepared from calcium hypochlorite (12.11 kg) and sodium carbonate (17.96 kg) in water (378.5 L) adjusted to pH 9.5 with sodium bicarbonate (1.7 kg) and filtered to remove calcium carbonate) was added slowly, keeping the temperature at 10−15 °C. When the reaction was complete, the layers were separated, and the aqueous layer was extracted with additional methylene chloride (30 L). The combined organic layers were washed with a solution of concentrated HCl (1.4 gal, 5.4 L) and potassium iodide (331 g) in water (14.5 L). The organic layer was then washed with a solution of sodium thiosulfate (1.2 kg) in water (20 L). The methylene chloride was washed with water (37.9 L) and then stripped without vacuum to an oil. The oil was stripped further after being transferred to the 50-L reactor. A yield of 33.41 kg of product was obtained, but this material contained 15 wt % methylene chloride (by NMR). The corrected yield was 28.4 kg (85% theory). ^{1}HMR ($CDCl_3$, 300 MHz) δ 7.18 (dd, 2), 6.82 (dd, 2), 4.49 (s, 1), 4.27 (m, 3), 3.74 (d, 3), 3.22 (t, 1), 3.10 (t, 1), 2.34 (m, 4), 1.77 (m, 2), 1.29 (m, 3), 0.98 (t, 3). ^{13}CMR ($CDCl_3$, 300 MHz) δ 163.2, 163.1, 162.3, 159.5, 159.2, 145.6, 129.7, 129.2, 127.96, 127.1, 114.2, 114.1, 112.1, 62.1, 55.2, 50.6, 46.1, 46.1, 42.7, 39.0, 38.1, 35.8, 21.5, 20.6, 13.9, 7.7. GC mass spectrum: *m*/*e* 335 (M^+).

HPLC: Inertsil, C_8, acetonitrile, 45%/water, 55% with 0.1 vol % H_3PO_4 and 0.2 vol % triethylamine; **18**, 10.8 min.

3-Hydroxy-1-(4-methoxybenzyl)-4-propionyl-5,6-dihydro-1H-pyridin-2-one (19). Oxalamide ketone **18** (28.3 kg, 84.4 mol) was dissolved in dry tetrahydrofuran (106 L) in a 100-gal glass-lined tank. This solution was added to a solution of potassium *tert*-butoxide (10.4 kg) in tetrahydrofuran (159 L) in a 300-gal glass-lined tank over a 30 min period, keeping the temperature <35 °C. After 1 h at 20−25 °C, the reaction was complete by HPLC. Water (371 L) was added to the reaction, followed by isopropyl ether (91 L). The layers were separated, and the aqueous layer containing the product as its potassium salt was washed a second time with isopropyl ether. The aqueous layer was partially evaporated in vacuo to remove any residual THF and acidified to pH 2.1 with 6 N HCl (15.1 L). The resulting slurry was filtered, and the solids were washed with water. Product **19** was air-dried at 50 °C to provide 17.9 kg (73%): mp 102−103 °C. ^{1}HMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 2), 6.86 (d, 2), 4.60 (s, 2), 3.70 (s, 3), 3.33 (t, 2), 2.69 (q, 2), 2.56 (t, 2), 1.13 (t, 3).

HPLC: Inertsil, C_8, acetonitrile, 45%/water, 55% with 0.1 vol % H_3PO_4 and 0.2 vol % triethylamine; retention time: **18**, 10.8 min; **19**, 6.1 min.

3-Methoxy-1-(4-methoxybenzyl)-4-propionyl-5,6-dihydro-1H-pyridin-2-one (20). 3-Hydroxy-1-(4-methoxybenzyl)-4-propionyl-5,6-dihydro-1H-pyridin-2-one **19** (17.35 kg, 60 mol) and cesium carbonate (22.13 kg, 67.9 mol) were added to dry dimethylformamide (90.8 L) in a 100-gal tank. The suspension was stirred for 30 min to ensure dispersion. Dimethyl sulfate (8.55 kg, 67.8 mol) was added neat over a period of 30 min, keeping the temperature 20−25 °C. When the charge was complete, the addition funnel was rinsed into the tank with additional DMF (500 mL). The reaction was allowed to stir at 20−25 °C for 16 h. The reaction was diluted with ethyl acetate (409 L) and was washed with water (4 × 83.3 L). The ethyl acetate solution was washed with a solution made with 6.94 L of 50% sodium hydroxide in 83.3 L of water, followed by washing with a solution made up of 6.94 L of 35% HCl in 83.3 L of water. The organic solution was dried by washing with brine (53 L). The ethyl acetate was vacuum-stripped to give an oil which was suitable for use in the next step. The estimated yield based on NMR analysis of residual solvent was 89%. A small sample was isolated for characterization. ^{1}HMR ($CDCl_3$, 300 MHz) δ 7.14 (d, 2), 6.78 (d, 2), 4.51 (s, 2), 3.88 (s, 3), 3.71 (s, 3), 3.2 (t, 2), 2.81 (q, 2), 2.42 (t, 2), 1.02 (t, 3). ^{13}CMR ($CDCl_3$, 300 MHz) δ 201.8, 159.1, 145.6, 129.3, 128.7, 126.5, 114.1, 60.2, 55.2, 49.6, 43.8, 37.0, 22.8, 8.1. GC mass spectrum: *m*/*e* 303 (M^+).

HPLC: Inertsil, C_8, acetonitrile, 45%/water, 55% with 0.1 vol % H_3PO_4 and 0.2 vol % triethylamine; **19**, 6.1 min; **20**, 8.0 min.

Cyclopentylhydrazine Dihydrochloride (9). Cyclopentanol (6.13 kg, 71.1 mol) and triphenylphosphine (18.67 kg, 71.25 mol) were dissolved in tetrahydrofuran (151 L) in a nitrogen-purged 100-gal glass-lined tank and was cooled to 5 °C. A solution of di-*tert*-butyl azodicarboxylate **21** (14.9 kg, 64.7 mol) in tetrahydrofuran (36 L) was added over about 2 h, keeping the temperature <6 °C. The reaction was allowed to stir for 5 h as the temperature was allowed to slowly increase to 20−25 °C. A solution 6 N HCl (26.5 L) was added to the reaction at 20 °C. The reaction was allowed to stir for 24 h at 20−25 °C at which point the starting material had been consumed. Water (37.85 L) was added, and the tetrahydrofuran was removed by vacuum distillation. During the concentration, triphenylphosphine oxide precipitated, and an additional 75.7 L of water was added. The reaction was cooled, and methylene chloride (113.6 L) was added. The layers were separated, and the aqueous layer was extracted twice more with methylene chloride (37.85 L) The aqueous was concentrated by distillation. As the volume was reduced, 2-propanol (3 × 75.7 L) was added to azeotrope the residual water. The resulting slurry was filtered and the solids were dried under vacuum at rt to give 7.68 kg (68.6% theory) over multiple crops. This material was characterized to be the dihydrochloride salt: mp 189−194 °C. ^{1}HMR (DMSO-d_6, 300 MHz) d 3.48 (m, 1), 1.79 (m, 2), 1.64 (m, 4), 1.49 (m, 2).

1-Cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-1,4,5,6-tetrahydropyrazolo[3,4-*c*]-pyridin-7-one (23). 3-Methoxy-1-(4-methoxybenzyl)-4-propionyl-5,6-dihydro-1H-pyridin-2-one **20** (14.47 kg, 47.76 mol) was dissolved in tetrahydrofuran (39.7 L) in a 100-gal glass-lined tank. Cyclopentylhydrazine dihydrochloride **9** (7.66 kg, 44.3 mol) was added, and the reaction was warmed slowly to ~88 °C while nitrogen swept over the reaction to remove methanol, THF, and HCl. The reaction was monitored by HPLC until the conversion was

complete, which required heating overnight in most cases. The product was a thick dark oil. A sample of 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-1,4,5,6-tetrahydropyrazolo[3,4-c]pyridin-7-one **23** was isolated for characterization. ^{1}HMR ($CDCl_3$, 300 MHz) δ 7.23 (d, 2), 6.85 (d, 2), 5.72 (m, 1), 4.62 (s, 2), 3.77 (s, 3), 3.44 (t, 2), 2.62 (t and q, 4), 2.06 (m, 4), 1.89 (m, 2), 1.67 (m, 2), 1.17 (t, 3). ^{13}CMR ($CDCl_3$, 300 MHz) δ 159.5, 159.0, 148.0, 145.6, 129.6, 129.3, 118.5, 114.0, 112.9, 60.4, 55.2, 48.6, 47.2, 32.7, 24.4, 20.2, 19.9, 13.8. GC mass spectrum: *m*/*e* 353 (M^+). This was used directly in the next step. Purification as a *p*-toluenesulfonic acid or benzenesulfonic acid salt is described.

Preparation of the *p*-Toluenesulfonic Acid and Benzenesulfonic Acid Salts of 1-Cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-1,4,5,6-tetrahydropyrazolo-[3,4-*c*]pyridin-7-one (23). Crude lactam **23** (1 g, 2.8 mmol) was dissolved in ethyl acetate (5 mL) and treated with a solution of anhydrous *p*-toluenesulfonic acid (0.487 g, 2.8 mmol) in ethyl acetate (2 mL). The salt crystallized from the mixture which was then cooled and filtered to provide 1.21 g of pure tosylate salt as a white solid in 81% yield: mp 110−113.8 °C. Anal. Calcd for $C_{28}H_{35}N_3O_5S$: C, 63.98; H, 6.71; N, 7.99; S, 6.10. Found: C, 63.83; H, 6.69; N, 8.02; S, 6.14.

The benzenesulfonic acid salt was formed in the same manner: mp 126.6−131.4 °C. Anal. Calcd for $C_{27}H_{33}N_3O_5S$: C, 63.38; H, 6.50; N, 8.21. Found: C, 63.09; H, 6.48; N, 8.21.

Either of these crystalline salts can be used in the deprotection reaction with trifluoroacetic acid and methanesulfonic acid.

1-Cyclopentyl-3-ethyl-1,4,5,6-tetrahydropyrazolo[3,4-*c*]pyridin-7-one (2a). The reaction mixture from the previous preparation containing **23** was cooled to 55 °C, and trifluoroacetic acid (87.3 kg, 764 mol) was added slowly, while keeping the temperature between 50 and 60 °C. The first one-third of the charge was exothermic and required external cooling. Methanesulfonic acid (6.34 L, 97.7 mol) was added, and the reaction was warmed to ∼70 °C for 2 h. The reaction was cooled to 20−25 °C, and methylene chloride (64 L) was added, followed by the slow addition of water (64 L). The layers were separated, and the aqueous layer was diluted further with water (22.7 L) and then re-extracted with methylene chloride (22.7 L). The combined methylene chloride layers were mixed with water (110 L) and then brought to pH 7.0 by the addition of saturated sodium bicarbonate (ca. 170 L). The layers were separated, and the methylene chloride was atmospherically distilled to about 35 L. Ethyl acetate (49 L) was added, and the reaction was distilled to about 35 L. The resulting slurry was cooled to room temperature with stirring. The solids were collected by filtration, washed with ethyl acetate, and vacuum-dried at 40 °C under full vacuum. The yield was 7.91 kg, 71.2%: mp 152−153 °C. ^{1}HMR ($CDCl_3$, 300 MHz) δ 5.61 (m, 2), 3.51 (dt, 2), 2.72 (t, 2), 2.62 (q, 2), 2.08 (m, 4), 1.90 (m, 2), 1.65 (m, 2), 1.40 (t, 3).

HPLC: Inertsil, C_8, acetonitrile, 65%/water, 35%; retention time: **2a**, 4.7 min; **20**, 5.1 min; **23**, 21.0 min.

1-Cyclopentyl-7-ethoxy-3-ethyl-4,5-dihydro-1H-pyrazolo[3,4-*c*]pyridine (24). A freshly prepared solution of triethyloxonium tetrafluoroborate (3.37 kg, 17.74 mol) in methylene chloride (10.8 L) was added slowly to a suspension of lactam **2a** (3.6 kg, 15.43 mol) in methylene chloride (7.2 L) over a period of about 40 min. The solution was then allowed to react for about 21 h at 18−22 °C. After the reaction was complete, the organic solution was washed with aqueous 10% sodium carbonate (36 L) and evaporated to an oil which was used directly in the next step. The yield for this step was 92.9%. ^{1}HMR ($CDCl_3$, 300 MHz) δ 5.14 (quintet, 1), 4.25 (q, 2), 3.62 (t, 2). 2.58 (m, 4), 2.07 (m, 4), 1.88 (m, 2), 1.61 (m, 2), 1.35 (t, 3), 1.19 (t, 3). GC mass spectrum: *m*/*e* 261 (M^+).

HPLC: Waters Symmetry-C_8, 550 water/250 acetonitrile/200 methanol/2 perchloric acid; retention time: **24**, 6.2 min; **2a**, 8.8 min.

9H-Cyclopentyl-7-ethyl-3-(thiophen-2-yl)-pyrazolo[3,4-*c*]-1,2,4-triazolo-5,6-dihydro-[4,3-*a*]pyridine (1). A solution of 1-cyclopentyl-7-ethoxy-3-ethyl-4,5-dihydro-1H-pyrazolo-[3,4-*c*]pyridine **24** (3.74 kg, 14.3 mol) and 2-thiophenecarboxylic hydrazide **25** (2.24 kg, 15.8 mol) was heated in 1-butanol (37 L) to ∼90 °C in a 50-gal glass-lined tank for 48 h. At this point, approximately 3 L of 1-butanol was distilled off to remove water and to help drive the reaction to completion. The reaction was concentrated to a 5-L volume, and methylene chloride (15 L) was added. The organics were washed twice with 1 N HCl (30.3 L) and concentrated by distillation to 5 L. 2-Propanol (16 L) was added to the concentrate, and the resulting slurry was cooled and stirred for 2 h. The product was collected by filtration and vacuum oven dried at 40 °C. The yield was 3.25 kg (67%) of a white solid: mp 126 °C. ^{1}HMR ($CDCl_3$, 300 MHz) δ 7.51 (m, 2), 7.28 (s, 1), 7.20 (dd, 1), 5.61 (m, 1), 4.35 (t, 2), 3.00 (t, 2), 2.70 (q, 2), 2.18 (m, 4), 1.97 (m, 2), 1.62 (m, 2), 1.29 (t, 3).

Anal. Calcd for $C_{18}H_{21}N_5S$: C, 63.69; H, 6.24; N, 20.63. Found: C, 63.82; H, 6.30; N, 20.77.

HPLC: Waters Symmetry-C_8, 550 water/250 acetonitrile/200 methanol/2 perchloric acid; retention time: **1**, 15.3 min; **24**, 6.2 min; **2a**, 8.8 min.

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