A Highly Convergent Synthesis of a Fibrinogen Receptor Antagonist

Frederick W. Hartner,* Raymond J. Cvetovich, Fuh-Rong Tsay, Joseph S. Amato, Brenda Pipik, Edward J. J. Grabowski, and Paul J. Reider

Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065

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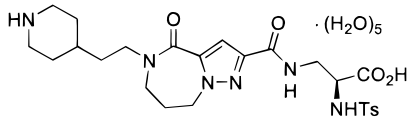
A practical multikilogram synthesis of 2(*S*)-[(*p*-toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-2-yl]carbonyl]amino]propionic acid pentahydrate (**1**), an oral fibrinogen receptor antagonist, is described. The nine-step convergent process, which afforded **1** in 37% overall yield, included pyrazole **5a** and *N*-tosylaminoalanine **16** as key fragments. Pyrazole **5a** was obtained from pyrazole-3,5-dicarboxylic acid by esterification with MeOH, alkylation/cyclization with 3-bromopropylamine, and Michael addition with 4-vinylpyridine. *N*-Tosylaminoalanine **16** was prepared by tosylation of asparagine, Hofmann reaction, and benzyl esterification. Saponification of pyrazole **5a**, coupling of the acid with *N*-tosylaminoalanine **16**, and Pd-catalyzed hydrogenolysis and pyridine reduction completed the synthesis.

Introduction

A promising approach for the treatment of vascular diseases, such as unstable angina, acute myocardial infarction, and stroke, is the control of platelet aggregation.[1] The aggregation process begins with the binding of platelets to vessel walls and activation of the platelets by ADP or other agonists. Upon platelet activation, platelet glycoprotein GPIIb/IIIa becomes receptive to binding by the adhesive protein fibrinogen, which causes the platelets to aggregate. Antagonists of fibrinogen binding are attractive therapeutic agents for vascular diseases, and a number of drug candidates have been investigated in pursuit of this goal.[2] The nonpeptide, **1**, is an active fibrinogen receptor antagonist and has been entered into clinical trials.[3] To provide material for the clinical program, an efficient synthesis of **1** was desired.



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Retrosynthetic analysis of **1** suggested amide bond cleavage to pyrazole and aminoalanine fragments as an obvious disconnection. Commercially available pyrazole-3,5-dicarboxylic acid is a suitable starting material for the pyrazole, and several possible strategies for forming the lactam were envisioned. In general, alkylation of the pyrazole nitrogen with a three-carbon appendage would be required. A terminal amino group would be generated after alkylation or, ideally, would already be a part of the three-carbon unit. Cyclization to the lactam would be followed by attachment of the piperidylethyl group. Installation of the piperidyl ring in the form of a reducible pyridine ring would avoid the need for additional protection/deprotection of the piperidyl nitrogen.[4] The pyridylethyl group could also be strategically attached to the three-carbon unit before alkylation/cyclization.

Results and Discussion

Routes to bicyclic intermediate **5a** began with the esterification of pyrazole-3,5-dicarboxylic acid to dimethyl ester **2** in methanol with $SOCl_2$ in 93% yield (Scheme 1).[5] Although the ethyl and isopropyl esters were also prepared, the best overall yields for the synthesis of pyridylethyl lactam **5a** were achieved with the methyl ester (vide infra).

Diester **2** was converted into bicyclic lactam **4a** with bromopropylamine hydrobromide, KOH, and Aliquat 336, albeit in only 33% assay yield. The low yield resulted from saponification of diester **2** back to the diacid and of the product to acid **4b**. The reaction of diester **2** with bromopropylamine was further explored using a variety of bases and solvents. The reaction went to completion with DBU in CH_3CN, but was slow. With DBU in THF, the reaction was fast, but did not consistently go to completion. As a compromise between reaction rate and completion, a mixture of about 15% CH_3CN in THF was found to be optimum. Side reactions that consumed bromopropylamine did occur, but complete conversion of

(1) Ojima, I.; Charkravarty, S.; Dong, Q. *Bioorg. Med. Chem.* **1995**, *3*, 337. Schror, K. *Drugs* **1995**, *50*, 7. Cook, N. S.; Kottirsch, G.; Zerwes, H.-G. *Drugs Future* **1994**, *19*, 135. Nichols, A. J.; Vasko, J. A.; Koster, P. F.; Valocik, R. E.; Samanen, J. M. In *Cellular Adhesion: Molecular Definition to Therapeutic Potential*; Metcalf, B. W., Dalton, B. J., Poste, G., Eds.; Plenum Press: New York, 1994; pp 213−237.

(2) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang, S.; Jiang, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 50. Stilz, H. U.; Beck, G.; Jablonka, B.; Just, M. *Bull. Soc. Chim. Belg.* **1996**, *105*, 711. Klein, S. I.; Molino, B. F.; Czekaj, M.; Dener, J. S.; Leadley, R. J.; Sabatino, R.; Dunwiddie, C. T.; Chu, V. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1403. Hutchinson, J. H.; Cook, J. J.; Brashear, K. M.; Breslin, M. J.; Glass, J. D.; Gould, R. J.; Halczenko, W.; Holahan, M. A.; Lynch, R. J.; Sitko, G. R.; Stranieri, M. T.; Hartman, G. D. *J. Med. Chem.* **1996**, *39*, 4583.

(3) Askew, B. C.; Bednar, R. A.; Bednar, B.; Claremon, D. A.; Cook, J. J.; McIntyre, C. J.; Hunt, C. A.; Gould, R. J.; Lynch, R. J.; Lynch, J. J., Jr.; Gaul, S. L.; Stranieri, M. T.; Sitko, G. R.; Holahan, M. A.; Glass, J. D.; Hamill, T.; Gorham, L. M.; Prueksaritanont, T.; Baldwin, J. J.; Hartman, G. D. *J. Med. Chem.* **1997**, *40*, 1779.

(4) Chung, J. Y. L.; Hughes, D. L.; Zhao, D.; Song, Z.; Mathre, D. J.; Ho, G.-J.; McNamara, J. M.; Douglas, A. W.; Reamer, R. A.; Tsay, F.-R.; Varsolona, R.; McCauley, J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 215.

(5) Lee, H. H.; Cain, B. F.; Denny, W. A. *J. Org. Chem.* **1989**, *54*, 428.

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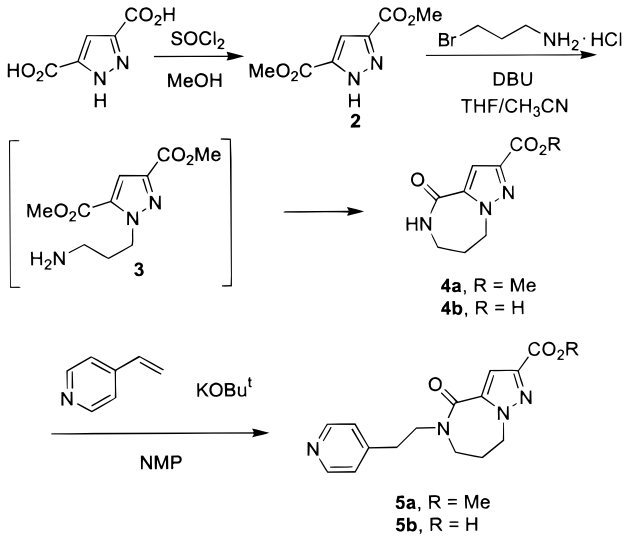
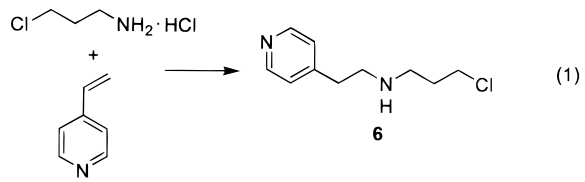
Scheme 1



substrate was achieved and bicyclic lactam **4a** was isolated in 81% yield when at least 2 equiv of bromopropylamine and 5 equiv of DBU were employed. If less than these amounts of reagents were used, the reaction did not go to completion, and subsequent addition of more reagents gave no further conversion of starting material.

During alkylation of dimethyl ester **2** with bromopropylamine and DBU, intermediate **3** was not observed; rather, cyclization proceeded directly to bicyclic lactam **4a**. By providing protection of the terminal amino group from further alkylation, this rapid cyclization may be the reason for the yield advantage of this sequence over other routes (vide infra). With the isopropyl ester analogue, the corresponding uncyclized amine intermediate was observed by HPLC during the reaction. An increased reagent charge was required to drive the alkylation reaction to completion, and the yield of lactam product was a few percent less than that obtained from the methyl ester.

A more convergent approach to pyridylethyl lactam **5a** would be achieved if the pyridylethylamine and propyl groups could be joined prior to reaction with the pyrazole. The requisite reagent, chloropropylpyridylamine **6**, was prepared in 60% yield by the addition of 3-chloro-1-propylamine hydrochloride to 4-vinylpyridine (eq 1).[6] It

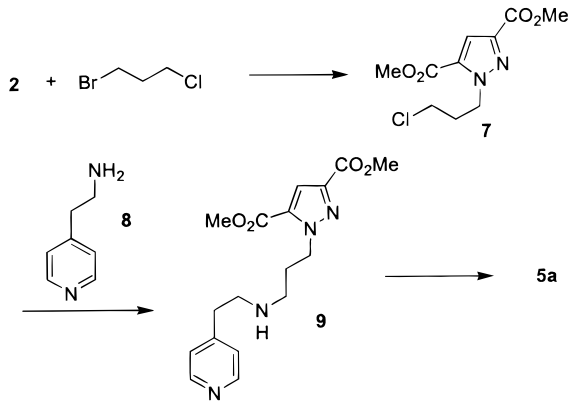


(1)

could be isolated from the reaction mixture in 25% yield via an extractive workup, removal of water by azeotropic distillation with acetonitrile, and crystallization from ethanol. The compound reacted with itself upon attempted storage as the free base, but the dihydrochloride salt was crystalline and stable to storage. The alkylation of diester **2** with chloroamine **6** was achieved in 40% yield using 2 equiv of the reagent and 6 equiv of base. Some of the reagent decomposed to an azetidine during the reaction, but this intramolecular side reaction was avoided

(6) Reich, H. E.; Levine, R. *J. Am. Chem. Soc.* **1955**, *77*, 5434.

Scheme 2



by the preparation of Boc or TMS protected reagents. These extra steps and a modest yield of 60% limited the usefulness of this approach, however.

In a further approach in which the terminal amino group was added after the three-carbon unit, diester **2** was alkylated with 1-bromo-3-chloropropane (Scheme 2).[7] Treatment of chloropropyl pyrazole **7** with 2-(4-pyridyl)-ethylamine **8** and additional base gave intermediate **9**, and **9** subsequently cyclized to afford the seven-membered ring pyridylethyl lactam **5a** in an overall yield of 51% from diester **2**.[8] An HPLC analysis of the reaction revealed that the combined production of open-chain amine **9** and pyridylethyl lactam **5a** reached a maximum of 50−60%, and that there was a continuous decrease in material balance from the initiation of the reaction. An NMR investigation of the reaction showed that the chloropropyl pyrazole **7**, open-chain amine **9**, and pyridylethyl lactam **5a** were all unstable to the reaction conditions.

Conversion of bicyclic lactam **4a** to pyridylethyl lactam **5a** was achieved in 92% yield by a Michael reaction of 4-vinylpyridine with a catalytic amount of *t*-BuOK in NMP.[10] The addition was reversible, as demonstrated by the addition of catalytic *t*-BuOK to a slurry of pyridylethyl lactam **5a** in NMP, which produced about 6 area % bicyclic lactam **4a** and 2 area % 4-vinylpyridine 30 min after the addition. The use of 2 equiv of 4-vinylpyridine in the Michael reaction drove the reaction to <0.5 area % starting material (see the Experimental Section for HPLC conditions).

Two side products of the Michael reaction were identified as bis(4-vinylpyridine) adduct **10** and vinylpyridine dimer **11**.[4] The amount of bispyridine **10** that formed depended on the amount of *t*-BuOK added to the reaction. If an optimum amount of *t*-BuOK was charged (0.03−0.04 equiv), the reaction went to completion, but still only a small amount of bispyridine **10** formed. By adding the *t*-BuOK in portions, it was possible to drive the reaction

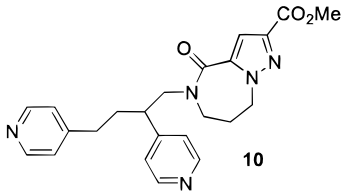
(7) Askew, B. C.; McIntyre, C. J.; Hunt, C. A.; Claremon, D. A.; Gould, R. J.; Lynch, R. J.; Armstrong, D. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 475.

(8) 2-(4-Pyridyl)ethylamine **8** was prepared by heating 4-vinylpyridine with phthalimide in *N*-methylpyrrolidinone (NMP) at 180 °C to give the addition product in 93% isolated yield.[9] After cleavage of the phthalimide with hydrazine, amine **8** was crystallized as a stable dihydrochloride salt.

(9) Kirchner, F. K.; McCormick, J. R.; Cavallito, C. J.; Miller, L. C. *J. Org. Chem.* **1949**, *14*, 388. Gray, A. P.; Archer, W. L.; Spinner, E. E.; Cavallito, C. J. *J. Am. Chem. Soc.* **1957**, *79*, 3805.

(10) Magnus, G.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 4127. Brady, L. E.; Freifelder, M.; Stone, G. R. *J. Org. Chem.* **1995**, *26*, 4757. Tawil, B. F.; Guggisberg, A.; Hesse, M. *Tetrahedron* **1992**, *48*, 3775.

to <0.5 area % starting material and <0.7 area % **10**. The amount of *t*-BuOK needed also depended on the amount of adventitious water present because *t*-BuOK was consumed to give hydroxide, which saponified the ester of bicyclic lactam **4a** to give free acid **4b** as another reaction side product.



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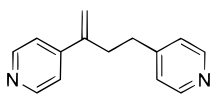

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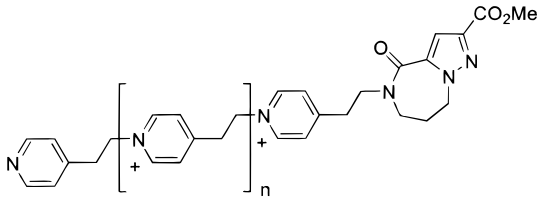
A polymeric side product **12**, whose formation was dependent on the choice of workup, was also identified in some reactions. When the reaction mixture was quenched into dilute HCl to give an aqueous phase of pH 4−5, **12** was observed. At this pH, 4-vinylpyridine polymerizes to poly(4-vinylpyridinium) salts.[11] The polymerization is initiated by protonated 4-vinylpyridine but requires the presence of unprotonated vinylpyridine to proceed. Pyridylethyl lactam **5a** also reacted with either the protonated 4-vinylpyridine or polymeric intermediates to form **12**. To avoid the formation of these pyridinium side products, reactions were quenched into aqueous KH_2PO_4 to give a final pH of 6.5−7.5. Buffers at pH >7.5 were deleterious because of premature ester hydrolysis to acid **5b**.



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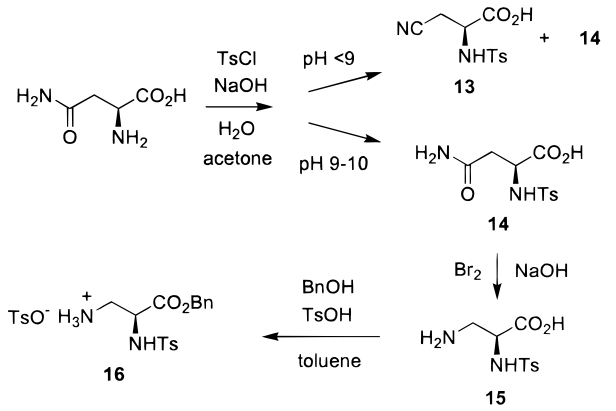
Benzyl α-*N*-tosyl-*β*-aminoalanate **16** was prepared by tosylation of L-asparagine, Hofmann reaction to α-*N*-tosyl-*β*-aminoalanine, benzyl esterification, and crystallization as the tosic acid salt (Scheme 3). The tosylation

Scheme 3

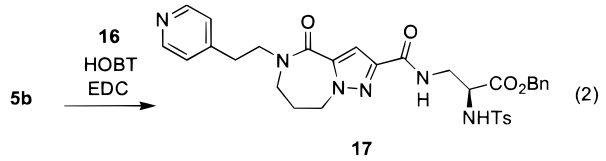


procedure, which was designed to control the pH at 9−10 by the simultaneous addition of tosyl chloride and NaOH, gave tosylasparagine **14** in 74% yield.[12] If the pH was allowed to drop below this range, nitrile **13** was formed at the expense of tosylasparagine **14**.

The transformation of *N*-tosyl asparagine **14** into aminoalanine **15** was accomplished using the Hofmann reaction. A recent examination of the reaction by calorimetry and NMR led to an understanding of the reaction dynamics and an improved set of conditions for this venerable reaction.[13] The best yields were obtained when the reagents were combined at <10 °C, and the mixture was heated at 40−50 °C for 20 min and then at 70 °C to complete the reaction. Under these conditions, aminoalanine **15** was obtained in 90% assay yield and 69% isolated yield.

Esterification of aminoalanine **15** with benzyl alcohol was accomplished using tosic acid. Because racemization of the ester was very base sensitive, a 5% excess of tosic acid, based on titration of the aminoalanine, was essential. Upon cooling, the ester crystallized as alanate salt **16** in 94% yield and 99.4% ee.

Methyl ester hydrolysis of pyridylethyl lactam **5a** was accomplished with 1 equiv of NaOH in H_2O/CH_3CN. Without isolation, acid **5b** was rapidly coupled to alanate salt **16** by the addition of HOBT and EDC to the reaction mixture (eq 2). The cosolvent acetonitrile was essential



17

to prevent a tacky oil from forming during hydrolysis and to ensure precipitation of product as crystals rather than as a gum. Crystalline amide **17** was isolated directly from the reaction in 91% yield and showed no loss in optical purity, which was observed when DCC was employed.

Removal of the benzyl ester and reduction of the pyridine was accomplished in 90−95% yield in acidic water (1 equiv of HCl) using Pd/C under 40−100 psi of H_2 at 70 °C. The acid was required to dissolve amide **17** and effect reduction of the pyridine ring. Among the acids used were HCl, TFA, and H_2SO_4; the fastest rates were achieved with HCl. The stoichiometry of the HCl charge did not adversely affect the reduction rates between the ratio of 0.5−2.0, but at higher or lower stoichiometry, lower rates were observed.

Compound **1** was crystallized by adjusting the pH of the filtered reduction solution from 1.5 to 6.5. Seven hydrated forms of **1** were discovered: hemi, mono, sesqui, tri, penta, hepta, and a form whose state of hydration is uncertain. Because the pentahydrate form exhibited the least hygroscopicity over a wider range of relative humidities, it was chosen as the desired form. The crystalline solid was dried to the pentahydrate form with humidified N_2 at about 40% RH. The product was obtained in 83.5% yield and >99.9% ee.

This convergent synthesis of **1** was carried out in nine steps at the multi-kilogram scale from pyrazole-3,5-dicarboxylic acid and asparagine. Important features of the synthesis include a high yielding alkylation/cycliza-

(11) Salamone, J. C.; Snider, B.; Fitch, W. L. *Macromolecules* **1970**, *3*, 707. Fife, W. K.; Ranganathan, P.; Zeldin, M. *J. Org. Chem.* **1990**, *55*, 5610.

(12) Zaoral, M.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 1993. Kjaer, A.; Vesterager, E. *Acta Chem. Scand.* **1960**, *14*, 961.

(13) Amato, J. S.; Bagner, C.; Cvetovich, R. J.; Gomolka, S.; Hartner, F. W.; Reamer, R. *J. Org. Chem.* **1998**, *63*, 9533.

tion reaction with bromopropylamine, a Michael addition of a lactam to 4-vinylpyridine, and a controlled Hofmann reaction of *N*-tosylasparagine.

Experimental Section

General Methods. All reactions were carried out in Pyrex glass vessels under an atmosphere of N_2, and solvents and reagents were dried where appropriate over molecular sieves prior to use. Other solvents and reagents were used as received. ^{1}H and ^{13}C NMR spectra were collected at 250 and 63 MHz, respectively. Coupling constants (*J*) are reported in Hz. A Haake Buchler melting point apparatus was employed. Melting points are uncorrected. Karl Fisher water analyses were determined on a Metrohm 684 KF coulometer.

1*H*-Pyrazole-3,5-dicarboxylic Acid Dimethyl Ester (2). To pyrazole-3,5-dicarboxylic acid (1.67 kg, 9.59 mol) in MeOH (48 L) at 4 °C was added $SOCl_2$ (1.75 L, 24.0 mol) over 1 h. At the end of the addition, the solution was heated to 50−55 °C for 3 h and then cooled to 3 °C. The pH of the solution was adjusted to 7.5 with a cold aqueous solution of NaOH, and diester **2** crystallized. The mixture was concentrated under vacuum with an internal batch temperature of ≤26 °C until 31 L of distillate was collected. Water was added (8 L), another 7 L of distillate was collected, and additional H_2O (8 L) was added. The mixture was cooled to 4 °C and filtered, and the cake was washed with cold H_2O. The cake was slurried for 1.5 h at 0−5 °C in H_2O (8 L) and filtered, and the cake was washed with cold H_2O (2.5 L). The cake was dried at 40−50 °C at reduced pressure to give diester **2** (1.65 kg, 93% yield). The product can be recrystallized from acetone: mp 156.5−158.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 6H), 7.20 (s, 1H), 12.95 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 52.0 (2 C), 110.8, 139.1 (br, 2 C), 160.2 (2 C).

Methyl [5,6,7,8-Tetrahydro-4-oxo-4*H*-pyrazolo[1,5-*a*]-[1,4]diazepin-2-yl]carboxylate (4a). A mixture of **2** (2.40 kg, 13 mol) and bromopropylamine hydrobromide (5.71 kg, 26 mol) in a mixture of CH_3CN (3.6 L) and THF (20.5 L) was treated with DBU (9.74 L, 65 mol) for 60−75 min with cooling to maintain 20−25 °C. The reaction was stirred for an additional 18 h, cooled to 10 °C, and then added to a cold solution of 85% H_3PO_4 (1.94 L) and NaCl (4.8 kg) in H_2O (34 L). The mixture was concentrated to 60 L, and the resulting solid was filtered and washed with H_2O. The solid was dried at 40−50 °C at reduced pressure to give 2.2 kg of **4a** (81%). The solid can be recrystallized from 1:1 HOAc/H_2O: mp 229−230 °C; ^{1}H NMR (DMSO-d_6) δ 2.14 (m, 2H), 3.18 (q, J = 5.4, 2H), 3.80 (s, 3H), 4.49 (t, J = 6.6, 2H), 7.08 (s, 1H), 8.41 (t, J = 5.1, 1H); ^{13}C NMR (DMSO-d_6) δ 28.0, 38.7, 50.8, 51.7, 111.9, 139.7, 141.0, 161.3, 161.5. Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.53; H, 4.99; N, 19.78.

Methyl [5,6,7,8-Tetrahydro-4-oxo-5-[2-(pyridin-4-yl)ethyl]-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-2-yl]carboxylate (5a). A mixture of **4a** (1.97 kg, 9.41 mol) and 4-vinylpyridine (1.97 L, 18.8 mol) in *N*-methylpyrrolidinone (9.84 L) was cooled to 8 °C and treated with a THF solution of *t*-BuOK (1.7M, 75 mL, 0.13 mol). The mixture was warmed to 20−25 °C, and additional *t*-BuOK/THF (125 mL, 0.21 mol) was added in portions over 2.5 h until the amount of **4a** was ≤1.0 area % compared to **5a**. The reaction was monitored by HPLC. HPLC conditions: Inertsil ODS-3, 250 × 4.6 mm, 5.0 μ, 210 nm, 30 °C, 0.7 mL/min; gradient, CH_3CN/10 mM pH 6.5 potassium phosphate buffer containing 10% CH_3CN; t = 0, 10% CH_3CN, t = 2 min, 30% CH_3CN, t = 15 min, 50% CH_3CN, t = 18 min, 50% CH_3CN; t_R (min) **4a**, 7.4, **5a**, 8.8. The reaction mixture was poured into a cold solution of KH_2PO_4 (1.6 kg) in H_2O (40 L). The pH was adjusted to 7.5 with 50% NaOH. The solution was extracted with CH_2Cl_2, and the combined extracts were dried with Na_2SO_4. The solution was concentrated to a mixture of solids and liquid (approximately 6 L). To the concentrate was added a mixture of ^{i}PrOAc (5 L) and hexanes (10 L) over 1 h. The slurry was cooled to 0−5 °C, aged for 30 min, and filtered. The solid was washed with cold 2:1 hexanes/^{i}PrOAc (3 L), followed by hexanes (6 L) and dried by passing dry N_2 through the filter cake to give 2.72 kg of **5a** (92%). The solid can be recrystallized from MeOH: mp 185−186.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.08 (m, 2H), 2.93 (t, J = 7.3, 2H), 3.34 (t, J = 6.4, 2H), 3.75 (t, J = 7.3, 2H), 3.80 (s, 3H), 4.31 (t, J = 6.9, 2H), 7.04 (s, 1H), 7.32 (m, 2H), 8.48 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 28.2, 32.9, 45.5, 47.4, 48.9, 51.7, 110.9, 124.2 (2 C), 139.4, 141.0, 147.8, 149.5 (2 C), 160.4, 161.5. Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82. Found: C, 61.07; H, 5.54; N, 17.67.

2-(*S*)-*p*-Toluenesulfonylasparagine (14). To a slurry of L-asparagine monohydrate (3.9 kg, 26.0 mol) in H_2O (57 L) was added 50% NaOH dropwise to adjust the pH to 10. A solution of *p*-TsCl (6.0 kg, 31.5 mol) in acetone (13 L) was added dropwise simultaneously with 50% NaOH to maintain a pH of 10 and temperatures of 30−50 °C. When the reaction was complete and excess *p*-TsCl had been consumed, the pH was adjusted to 2−3 with concd HCl (4.5 L) at 15−20 °C. The mixture was stirred for 1 h, and the solid was filtered and washed with H_2O (32 L). The solid was dried by passing dry N_2 through the filter cake to give 5.5 kg of **14** (74%). An analytical sample was crystallized from MeOH: mp 184−185 °C (lit.[13] mp 185−188 °C); ^{1}H NMR (DMSO-d_6) δ 2.25 (dd, J = 6.1, 15.5, 1H), 2.36 (s, 3H), 2.47 (dd, J = 7.0, 15.5, 1H), 4.08 (ddd, J = 6.1, 7.0, 8.7, 1H), 6.89 (s, 1H), 7.34 (d, J = 8.2, 2H), 7.36 (s, 1H), 7.67 (d, J = 8.2, 2H), 7.95 (d, J = 8.7, 1H); ^{13}C NMR (DMSO-d_6) δ 20.9, 37.9, 52.3, 126.5 (2 C), 129.3 (2 C), 138.4, 142.4, 170.5, 171.9.

2-(*S*)-*p*-Toluenesulfonylamino-β-alanine (15). See ref 13 for the procedure: ^{1}H NMR (DMSO-d_6) δ 2.37 (s, 3H), 2.86 (dd, J = 9.1, 12.0, 1H), 3.02 (dd, J = 4.5, 12.0, 1H), 3.21 (dd, J = 4.5, 9.1, 1H), 7.38 (d, J = 8.3, 2H), 7.72 (d, J = 8.3, 2H), 7.82 (br, 4H); ^{13}C NMR (DMSO-d_6) δ 20.9, 41.5, 52.7, 126.9 (2 C), 129.6 (2 C), 136.2, 143.0, 169.5.

2-(*S*)-(*p*-Toluenesulfonylamino)-β-alanine Benzyl Ester Tosylate (16). A mixture of aminoalanate **15** (4.1 kg, 15.9 mol), benzyl alcohol (3.4 L, 32.9 mol), and *p*-toluenesulfonic acid monohydrate (3.18 kg, 16.7 mol) in toluene (30 L) was refluxed for 6 h while H_2O (620 mL) was collected with a Dean−Stark trap. The thick slurry was diluted with toluene (30 L), cooled to 20−23 °C, and stirred for 18 h. The solid was filtered, washed with 1:1 THF/toluene (10 L) and then toluene (20 L), and dried by passing dry N_2 through the filter cake to afford 7.73 kg of **16** (94%). The product can be recrystallized from MeOH: mp 170.3−172.8 °C; ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H), 2.34 (s, 3H), 2.92 (dd, J = 7.9, 13.0, 1H), 3.16 (dd, J = 5.9, 13.0, 1H), 4.24 (m, 1H), 4.85 (s, 2H), 7.12 (d, J = 8.0, 2H), 7.20 (m, 2H), 7.29 (d, J = 8.2, 2H), 7.35 (m, 3H), 7.50 (d, J = 8.0, 2H), 7.64 (d, J = 8.2, 2H), 8.02 (br s, 3H), 8.58 (br m, 1H); ^{13}C NMR (DMSO-d_6) δ 20.7, 20.9, 40.2, 53.4, 66.8, 125.4 (2 C), 126.6 (2 C), 127.9 (2 C), 128.1 (3 C), 128.3 (2 C), 129.5 (2 C), 134.9, 137.3, 137.9, 143.0, 145.2, 168.0.

2(*S*)-[(*p*-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(4-pyridinyl)ethyl]-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-2-yl]carbonyl]amino]propionic Acid Benzyl Ester (17). To **5a** (2.045 kg, 6.50 mol) in H_2O (16 L) was added a solution of NaOH (510 g of 50% NaOH in 2 L of H_2O). A water rinse (2 L) was added, and the mixture was warmed to 50 °C for 1 h. CH_3CN (4 L) was added, and the solution was aged for 30 min and then cooled to 25 °C. CH_3CN (12 L) and HOBT (86 g) were added, followed by **16** (3.38 kg, 6.50 mol). EDC (1.53 kg, 8.0 mol) in H_2O (16 L) was added dropwise over 2−3 h, and then additional H_2O (6 L) was added. The mixture was aged for 18 h and filtered, and the cake was washed with H_2O and dried by passing dry N_2 through the filter cake, then in vacuo at 60 °C to give 3.73 kg of **17** (91% yield, 98.7% ee). The product can be recrystallized from CH_3CN. Chiral SFC-HPLC assay: Chiralpak AD, 250 × 4.6 mm, 32 vol % MeOH containing 20 mmol TEA as modifier, 1.0 mL/min, 300 bar, 35 °C, 210 nm, t_R (min) (*R*)-**17**, 26.2, (*S*)-**17**, 27.8: ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 2H), 2.32 (s, 3H), 2.95 (t, J = 7.3, 2H), 3.23 (t, J = 6.2, 2H), 3.66−3.87 (m, 4H), 4.10−4.21 (m, 3H), 4.94 (m, 2H), 6.56 (d, J = 7.9, 1H), 7.12−7.35 (m, 11H), 7.64 (m, 2H), 8.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.6, 33.6, 41.5, 46.4, 48.5 (2 C), 55.7, 67.7, 109.9, 124.0 (2 C), 127.0 (2 C), 128.2 (2 C), 128.3, 128.4 (2 C), 129.5 (2 C), 134.7, 136.4, 139.4, 143.5,

144.6, 147.5, 149.8 (2 C), 161.6 (2 C), 169.6. Anal. Calcd for $C_{32}H_{34}N_6O_6S$: C, 60.94; H, 5.43; N, 13.32. Found: C, 60.87; H, 5.21; N, 13.14.

2(*S*)-[(*p*-Toluenesulfonyl)amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-[2-(piperidin-4-yl)ethyl]-4*H*-pyrazolo[1,5-*a*][1,4]-diazepin-2-yl]carbonyl]amino]propionic Acid Pentahydrate (1). To a slurry of **17** (8.2 kg, 13.0 mol) in H_2O (60 L) was added aqueous HCl (14 L, 0.95 M, 13.0 mol), followed by 5% Pd/C−50% wet (8.0 kg) with stirring. The pressure vessel was purged and placed under 100 psi H_2, and the mixture was heated for 30 h at 70 °C. The mixture was cooled to 50 °C and filtered. The catalyst was washed with warm (50 °C) 0.5 N HCl (30 L) and then with H_2O (15 L). The filtrate was cooled to 25 °C, the pH was adjusted to 6.5−7.0 with 25% NaOH, and the solution was concentrated. The pH was adjusted to 2.0 to dissolve any crystallized product and then slowly adjusted to pH 6.9 in the presence of seed crystals to ensure that the desired hydrate form would crystallize. The mixture was further concentrated to 70 L and was aged 18 h at 22 °C. The slurry was cooled to 10 °C and filtered, and the cake was washed with H_2O (64 L). The product was dried by passing filtered (Whatman HEPA-CAP) humidified (RH ∼40%) N_2 through the filter cake. The moisture content of the cake was monitored by Karl Fischer water analysis, and drying was continued until the KF was 15 wt % loss of H_2O. Pentahydrate **1** was obtained (5.94 kg, 84% yield, >99.9% ee). Chiral SFC-HPLC assay: Chiralpak AS, 250 × 4.6 mm, 35 vol % MeOH (100 mM TEA), 1.0 mL/min, 300 bar, 35 °C, 250 nm, t_R (min) (*S*)-**1** 7.6, (*R*)-**1** 5.9: ^{1}H NMR (DCl/D_2O) δ 1.0−1.3 (m, 5H), 1.59 (d, J = 12.8, 2H), 1.70 (s, 3H), 1.89 (m, 2H), 2.60 (t, 2H), 2.9−3.2 (m, 7H), 3.34 (m, 1H), 3.79 (m, 1H), 3.97 (m, 2H), 6.47 (s, 1H), 6.64 (d, J = 7.9, 2H), 7.14 (d, J = 7.9, 2H); ^{13}C NMR (DCl/D_2O) δ 17.7, 25.1 (3 C), 28.0, 30.2, 37.4, 41.0 (2 C), 42.3, 43.1, 46.2, 52.2, 106.5, 123.4 (2 C), 126.7 (2 C), 132.7, 135.9, 140.4, 141.0, 159.2, 159.8, 169.8. Anal. Calcd for $C_{25}H_{44}N_6O_{11}S$: C, 47.16; H, 6.97; N, 13.20. Found: C, 47.10; H, 6.53; N, 13.07.

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