# A Stereoselective Synthesis of BMS-262084, an Azetidinone-Based Tryptase Inhibitor

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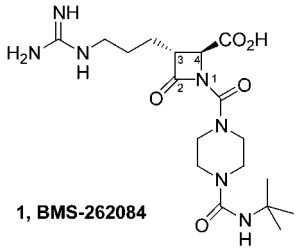
A highly stereoselective synthesis of the novel tryptase inhibitor BMS-262084 was developed. Key to this synthesis was the discovery and development of a highly diastereoselective demethoxycarbonylation of diester **12** to form the *trans*-azetidinone **13**. BMS-262084 was prepared in 10 steps from D-ornithine in 30% overall yield.

## Introduction

Utilization of tryptase inhibitors for the treatment of asthma has been the focus of recent attention.[1] BMS-262084 (**1**) is a sub-nanomolar inhibitor of tryptase and



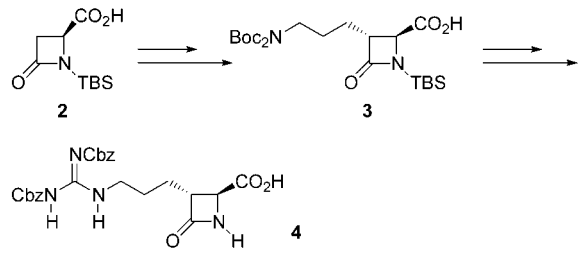

**1, BMS-262084**

suppresses induced inflammation in animal lungs. Early routes (Scheme 1) to this development candidate utilized the alkylation of the dianion derived from the known, homochiral, azetidinone acid **2** to establish the requisite *trans*-stereochemistry.[2,3] As scale-up of this step proved difficult to optimize, and faced with the need for large quantities of material for development purposes, we sought to identify and develop a practical synthesis which would not proceed through dianion intermediates. In this paper, we describe a new approach to **1** starting from D-ornithine, the most salient feature of which is the highly stereoselective demethoxycarbonylation of diester **12** to afford the *trans*-azetidinone **13**. This new synthesis proceeds in 30% overall yield.

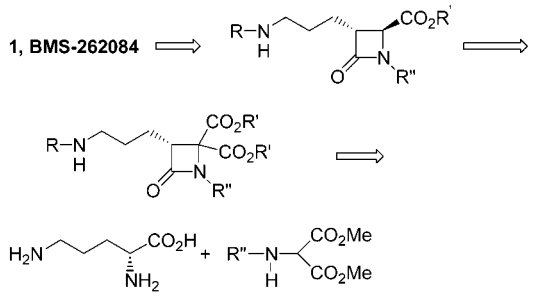
## Results and Discussion

As outlined in Scheme 2, we envisioned a synthesis of BMS-262084 arising from D-ornithine and an appropriately protected aminomalonate, and recognized that, for this approach to be successful, an unprecedented degree

**Scheme 1**




**Scheme 2**




of diastereoselectivity would have to be achieved in the dealkoxycarbonylation step leading to *trans*-azetidinone 13 while simultaneously preserving the integrity of the existing stereogenic center. While dealkoxycarbonylation of azetidinone $C_4$-geminal esters is well documented,[4c−e,5] a highly diastereoselective process providing >95% *trans*-selectivity was unknown. Moreover, little useful information has been reported regarding the propensity for racemization during the formation of azetidinones from α-bromoacids and aminomalonates. By overcoming these

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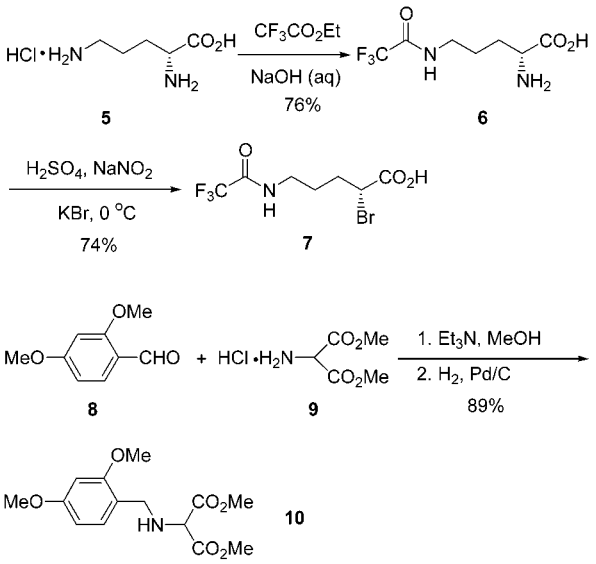
**Scheme 3**




challenges, a highly stereoselective and practical method to prepare the necessary 3,4-*trans*-azetidinone system emerged.

Selective protection of the $^{\delta}$N atom in D-ornithine hydrochloride (**5**) was achieved in 76% yield using ethyl trifluoroacetate under basic, aqueous conditions, and producing trifluoroacetamide **6** along with trace amounts of the bisprotected product[6] (Scheme 3). Diazotization−bromination[7] of **6** gave the α-bromoacid **7** in 74% yield with >99% retention of configuration by chiral HPLC analysis. Reductive alkylation of dimethyl aminomalonate (**9**) with 2,4-dimethoxybenzaldehyde (**8**) under a hydrogen atmosphere gave the protected malonate **10** in 89% yield after crystallization. This one-pot process is an improvement over the procedure involving imine formation followed by borohydride reduction.[5b,8]

In an initial attempt to carry out a one-pot preparation of the azetidinone **12**, the α-bromoacid **7** was converted to the acid chloride with oxalyl chloride followed by coupling with the protected malonate **10**[9] in the presence of excess triethylamine (Scheme 4). The excess base promoted an intramolecular cyclization of the resulting amide **11** at ambient temperature with inversion of configuration to afford azetidinone **12** in 95% yield. However, under these conditions, about 13% racemization occurred, presumably via the corresponding ketene derived from the acid chloride. While employment of the more hindered base diisopropylethylamine, at 0−5 °C, resulted in only 5% racemization, a significant amount of elimination was observed during the cyclization. Employment of less basic amines, such as *N*-methylpiperidine, provided **12** with ee > 96%, but the reaction was extremely slow and often incomplete. Consequently, a two-base, one-pot protocol was developed. Coupling of the acid chloride of **7** and malonate **10** was conducted in the presence of $K_2HPO_4$ in dichloromethane−water to generate amide **11**. Addition of triethylamine (3 molar equiv) promoted cyclization and gave **12** in 95% yield with no detectable racemization by chiral HPLC analysis.

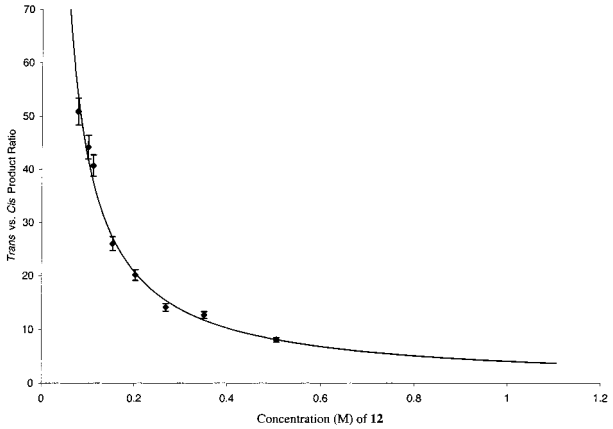
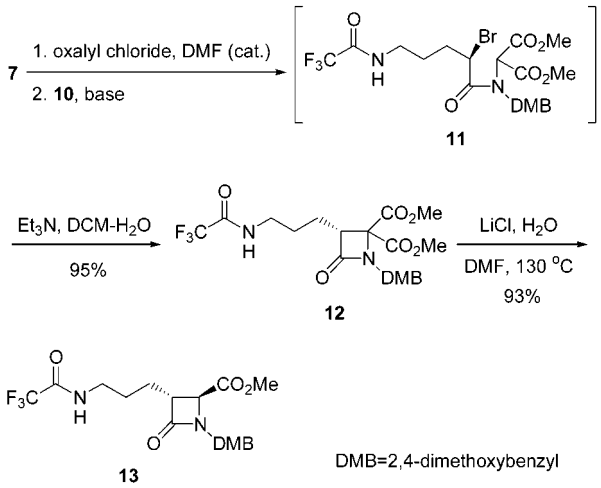



**Figure 1.** Effect of concentration on the demethoxycarbonylation of the trifluoroacetamide **12**.

**Scheme 4**




The dealkoxycarbonylation of **12** was next studied in some detail. Dealkoxycarbonylation of similar azetidinones using Krapcho's conditions (NaCl, DMSO, $H_2O$) is generally a nonselective process.[4d,5a] To our pleasant surprise, when the initial demethoxycarbonylation of **12** was conducted in DMSO−$H_2O$−LiCl at 135 °C (Scheme 4), the *trans*/*cis* product ratio (~20:1) was significantly higher than expected on the basis of literature precedent.[4,5] We speculated that the relatively acidic trifluoroacetamide proton in compound **12** might be serving as an intramolecular proton source, and effectively competing with $H_2O$ to selectively protonate the intermediate $C_4$-enolate from the α-face. To probe the source of the high selectivity, the *trans*/*cis* product ratio was examined as a function of the starting reactant concentration. As indicated by the data in the Figure 1, dilution of the reaction medium ($H_2O$ held constant) led to progressively higher *trans*/*cis* product ratios, supporting an intramolecular proton transfer. At an initial reactant concentration of 0.08 M, the *trans*/*cis* product ratio reached 50:1.

A study of the *trans*/*cis* product ratio as a function of the $^{\delta}$*N*-protecting group also supported the intramolecular proton-transfer mechanism. Protection as a phthalimido group should effectively shut down the possibility of intramolecular proton transfer and, in fact, resulted in a 1.25:1 *trans*/*cis* product mixture (Table 1). Employment of a $^{\delta}$*N*-Cbz protecting group[10] resulted in a 25:1

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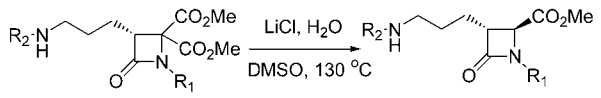
**Table 1. Effects of Protecting Groups on the Demethoxycarbonylation Reaction[a]**




| entry | protecting groups $R_1$ | protecting groups $R_2$ | substrate concn (M) | *trans*/*cis* product ratio |
|---|---|---|---|---|
| **a** | DMB | $CF_3CO$ | 0.15 | 28:1 |
| **b** | H | $CF_3CO$ | 0.15 | 9:1 |
| **c** | DMB | phthalyl | 0.09 | 1.25:1 |
| **d** | DMB | Cbz[11] | 0.09 | 25:1 |
| **e** | DMB | $CF_3CO$ | 0.09 | 46:1 |

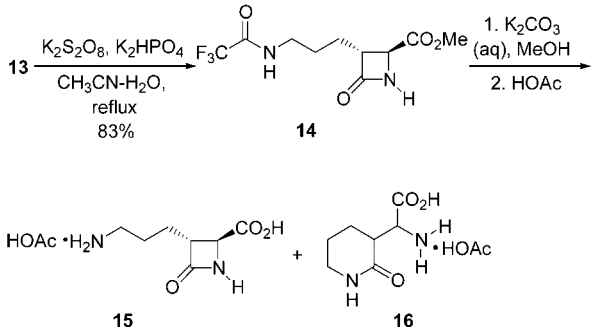
[a] All studies were carried out with 2 equiv of $H_2O$.

*trans*/*cis* product ratio, whereas the more electron-withdrawing trifluoroacetamide protecting group provided a 46:1 *trans*/*cis* mixture under identical conditions. On the other hand, without protection $N_1$ provided a proton[11] that would carry out a nonstereoselective intramolecular proton transfer which competed with the desired intramolecular $^{\delta}N$-proton transfer and resulted in a 9:1 *trans*/*cis* product ratio. These observations clearly indicate that the $^{\delta}N$-proton is crucial to the diastereoselectivity of the demethoxycarbonylation reaction described here.

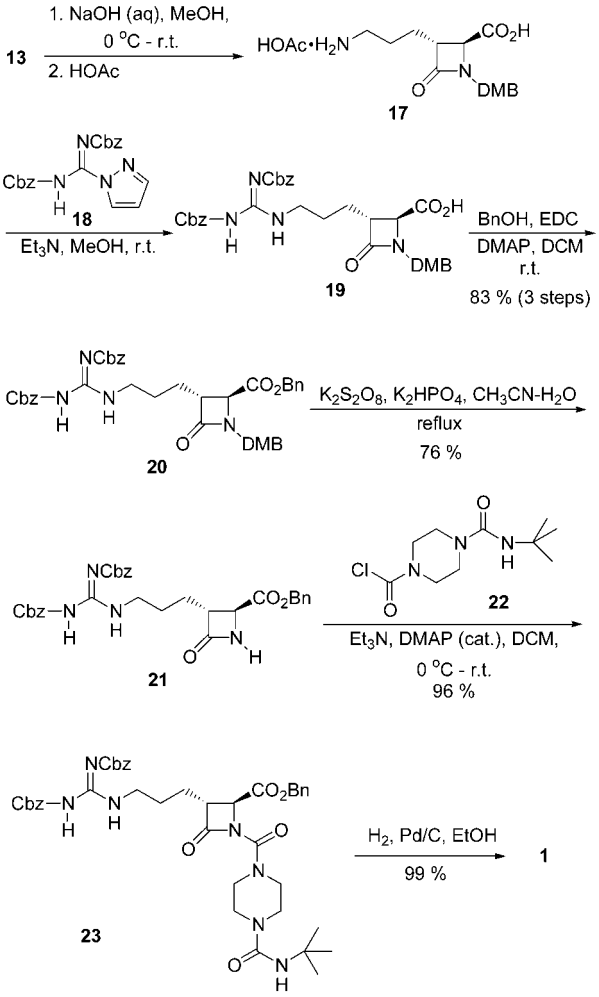
We next studied the effect of added water on the reaction diastereoselectivity. When the reaction was carried out in DMF[12] in the presence of 1 equiv of water relative to the substrate **12** (Scheme 4), the *trans*/*cis* product ratio reached 36:1 at a 0.2 M reaction concentration of **12**, providing azetidinone **13** in 93% yield. However, the selectivity dropped to 17:1 when the amount of water was increased to 4 equiv. The erosion of the *trans*/*cis* selectivity observed with increasing levels of water again supports the intramolecular proton-transfer hypothesis.

With compound **13** in hand, we next addressed removal of the dimethoxybenzyl and trifluoroacetamide protecting groups and guanylation of the side chain nitrogen. The order of the deprotection operations proved to be critical. Initially, the $N_1$-DMB group in **13** was removed (Scheme 5) under oxidative conditions ($K_2S_2O_8$/$K_2HSO_4$) to give azetidinone **14** in 83% isolated yield. However, difficulties were encountered in the subsequent removal of the $^{\delta}N$-trifluoroacetyl group in **13**. Using aqueous alkaline conditions, cleavage occurred along with concomitant hydrolysis of the methyl ester.[13] However, under these conditions, a substantial portion of the product underwent cyclization to the $\delta$-lactam **16**. This intramolecular cyclization could not be suppressed, even using mildly basic (aqueous carbonate) conditions, and ~1:1 mixtures of **15** and **16** were generally observed.

**Scheme 5**




**Scheme 6**




Interestingly, when **13** was first treated under aqueous alkaline conditions to effect ester hydrolysis and deprotection of the $^{\delta}N$-trifluoroacetyl group, lactamization was not observed as a competitive side reaction (Scheme 6). The crude amino acid was isolated as the acetic acid salt **17**.[14] Subsequent reaction with *N*,*N*′-bis-Cbz-1-guanylpyrazole (**18**)[15] in the presence of TEA gave guanidine **19**. Reesterification[16] of **19** provided benzyl ester **20** in 83%

(9) It is worth mentioning that without protection of the nitrogen in the malonate **10**, the subsequent intramolecular cyclization step did not proceed.

(10) In our initial studies, the $^{\delta}$N atom in D-ornithine hydrochloride (**5**) was protected with a Cbz group. However, during the diazotization−bromination of the $^{\alpha}$N atom, nitrosation at the $^{\delta}$N atom occurred. This observation offered an additional reason for using a more electron-withdrawing protecting group such as trifluoroacetamide at the $^{\delta}$N atom.

(11) For the method of preparing a -$N_1$-nonprotected counterpart of compound **9** see ref 4d, Simig et al.

(12) Screening experiments had indicated DMF to be a more suitable solvent than DMSO.

(13) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.

(14) Guanidine displacement with **18** is significantly faster when **17** is isolated and the reaction is carried out in the absence of water.

(15) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389. Wu, Y.; Matsueda, G. R.; Bernatowicz, M. S. *Synth. Commun.* **1993**, *23*, 3055.

(16) Earlier studies had indicated that the subsequent acylation of the azetidinone nitrogen was not successful in the presence of a $C_4$-carboxylic acid.

overall yield from **13**. Oxidative cleavage[4c,5b,17] of the $N_1$-DMB protecting group followed by chromatographic purification gave the deprotected azetidinone **21** in 76% isolated yield. Acylation of the $N_1$-position in **21** with carbamoyl chloride **22**[3,18] in the presence of triethylamine and catalytic amounts of DMAP gave the advanced intermediate **23** in almost quantitative yield. Finally, hydrogenolysis under neutral conditions removed the benzyl and Cbz protecting groups and gave **1** (BMS-262084) in quantitative yield and with ee > 99%.

In conclusion, we have developed a highly stereoselective synthesis of the tryptase inhibitor **1**. Key to this was the development of a highly *trans*-selective dealkoxycarbonylation reaction.

## Experimental Section

$^1$H and $^{13}$C NMR spectra (300 MHz) were recorded in $CDCl_3$ and are referenced to TMS unless otherwise noted. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected. Chiral HPLC analyses were carried out with a Shimadzu LC-10AD HPLC system or a Waters Alliance 2690 module with a 996 PDA detector and Millennium 2010 data system.

**Amino Acid 6.** To a solution of D-ornithine hydrochloride (50.6 g, 300 mmol) in 3.0 N NaOH (aq, 100 mL, 300 mmol) was added ethyl trifluoroacetate (35.8 mL, 300 mmol) at 23 °C. A white precipitate was formed within 20 min. The suspension was stirred overnight and filtered to provide **6** (52.0 g, 76%) as a white solid after drying in vacuo. Mp: 212.0 °C dec, lit.[6a] (DL) 228−232 °C dec. $^1$H NMR ($D_2O$): $\delta$ 3.56 (dd, $J$ = 11.8, 5.7 Hz, 1H), 3.17 (d, $J$ = 6.84 Hz, 1H), 2.85 (d, $J$ = 7.53 Hz, 1H), 1.78−1.42 (m, 4H). $^{13}$C NMR ($D_2O$, internal standard $CH_3CN$, $\delta$ 1.30, $CH_3$–): $\delta$ 174.7, 159.5 (q, $J$ = 37.1 Hz), 116.3 (q, $J$ = 283 Hz). 54.7, 39.5, 28.0, 23.9. IR (KBr): 3298, 2940, 2084, 1711, 1583, 1486, 1445, 1414, 1219, 1055, 886, 763, 727 cm$^{-1}$. HRMS: calcd for $C_7H_{12}F_3N_2O_3$ ($M^+$ + H) 229.0800, found 229.0820. Chiral HPLC: ee > 99%; Chiralpak WH column, 250 × 4.6 mm, 10 $\mu$m; mobile phase 0.5 mM $CuSO_4$ (aq); isocratic at 40 °C, 1.0 mL/min, 210 nm; concentration 0.5 mg/mL, 10 $\mu$L injection; $R_T$ = 20.7 min (enantiomer, $R_T$ = 24.2 min).

**Bromoacid 7.** Potassium bromide (219.9 g, 1.85 mol) was added to a solution of **6** (52.6 g, 231 mmol) in 462 mL of 4.0 N $H_2SO_4$ at 0 °C, followed by the slow addition of a solution of sodium nitrite (19.9 g, 289 mmol) in water (40 mL) at 0−8 °C. The mixture was stirred at 0−5 °C for 4 h, and $N_2$ was bubbled into the brown reaction mixture to discharge the color (about 15 min). The reaction was extracted with MTBE (600 mL), washed with 15% brine (500 mL), 10% brine (500 mL) containing 2.5 g of $Na_2S_2O_3$, and 10% brine (300 mL), dried over anhyd $Na_2SO_4$, filtered, and concentrated to give bromoacid **7** as a colorless oil (49.9 g, 74% yield). $^1$H NMR ($CD_3CN$): $\delta$ 7.61 (s, br, 1H), 4.33 (dd, $J$ = 8.8, 6.5 Hz, 1H), 3.29 (dd, $J$ = 13.1, 6.6 Hz, 2H), 2.14−1.84 (m, 2H), 1.79−1.60 (m, 2H). $^{13}$C NMR ($CD_3CN$): $\delta$ 171.1, 157.9 (q, $J$ = 36.2 Hz), 117.1 (q, $J$ = 285 Hz), 46.5, 39.5, 32.6, 27.1. IR (film): 3309, 2961, 2551, 1931, 1742, 1445, 1178, 1066, 1020, 840, 712, 651 cm$^{-1}$. HRMS: calcd for $C_7H_9BrF_3NO_3$ ($M^+$) 290.9718, found 290.9732. Chiral HPLC: ee 98%; Chiralpak AS column, 250 × 4.6 mm, 10 $\mu$m; mobile phase hexane/2-propanol (96:4, v/v); isocratic at ambient temperature, 1.0 mL/min; concentration 0.5 mg/mL, 10 $\mu$L injection, 210 nm; $R_T$ = 26.7 min (enantiomer, $R_T$ = 31.1 min).

***N*-DMB Aminomalonate 10.** Deoxygenated methanol (1.0 L) was added to a mixture of Pt/C (10%, 5.0 g), dimethyl aminomalonate hydrochloride (75.0 g, 410 mmol), and 2,4-dimethoxybenzaldehyde (68.0 g, 410 mmol) under an atmosphere of $N_2$. Triethylamine (40 mL, 287 mmol) was then added to the resulting suspension. The reaction mixture was sparged with $H_2$ for 4.5 h followed by $N_2$ for 15 min and was filtered through a Celite pad. The filtrate was concentrated to ca. 250 mL. Dichloromethane (500 mL) was then added to the concentrated residue, and the resulting solution was washed with satd $NaHCO_3$ (250 mL) and water (250 mL). After phase splitting, the combined aqueous layers were extracted with dichloromethane (100 mL). The dichloromethane layers were combined, dried over anhyd $Na_2SO_4$, filtered, and concentrated to give a yellow solid which was subsequently crystallized from 300 mL of 2-propanol to afford **10** as a yellow solid (108.5 g, 89% yield). Mp: 62−64 °C. $^1$H NMR: $\delta$ 7.11 (d, $J$ = 8.9, 1H), 6.44−6.39 (m, 2H), 4.08 (d, $J$ = 1.7 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75 (d, $J$ = 1.5 Hz). 3.71 (s, 6H), 3.02 (s br, 1H). $^{13}$C NMR: $\delta$ 169.0, 160.3, 158.6, 130.6, 119.2, 103.7, 98.3, 64.0, 55.2, 55.1, 52.6, 46.8. IR (KBr): 3350, 3012, 2950, 2838, 2361, 2054, 1757, 1726, 1608, 1506, 1440, 1296, 1209, 1035, 984, 938, 846, 964, 723 cm$^{-1}$. HRMS: calcd for $C_{14}H_{20}NO_6$ ($M^+$ + H) 298.1291, found 298.1294.

**Amide 11 and Cyclization to Azetidinone 12.** To a solution of bromoacid **7** (53.4 g, 183 mmol) in dichloromethane (214 mL) were added oxalyl chloride (18.3 mL, 210 mmol) and DMF (5.67 mL, 73.2 mmol) at 0 °C. The mixture was warmed to 23 °C, stirred for 1 h, and then recooled to 0 °C. The resulting cold solution was slowly added to a heterogeneous mixture of 33% $K_2HPO_4$ (295 mL) [aq, 20 wt %, pH 9.17 (0 °C) or 9.26 (at ambient temperature)] and a solution of **10** (51.6 g, 174 mmol) in dichloromethane (214 mL) at 0−5 °C. Upon completion of the addition, the reaction mixture was stirred for 30 min, followed by addition of triethylamine (76.4 mL, 549 mmol) at 0−10 °C. The reaction mixture was then warmed to 23 °C and stirred for 5 h. The organic layer was separated, washed with 3.0 N HCl (200 mL) and satd $NaHCO_3$ (200 mL), dried over anhyd $Na_2SO_4$, filtered, and concentrated to provide azetidinone **12** as a yellow oil (81.1 g, 95%). $^1$H NMR: $\delta$ 7.41 (s br, 1H), 7.06 (d, $J$ = 8.8 Hz, 1H), 6.43−6.34 (m, 2H), 4.68 (d, $J$ = 15.0 Hz, 1H), 4.39 (d, $J$ = 15.0 Hz, 1H), 3.89−3.62 (m, 10 H), 3.46−3.32 (m, 5H), 1.80−1.54 (m, 4H). $^{13}$C NMR: $\delta$ 168.6, 167.4, 167.2, 160.8, 158.6, 157.4 (q, $J$ = 36.4 Hz), 131.0, 115.9 (q, $J$ = 286 Hz), 115.0, 103.8, 98.1, 67.4, 57.5, 55.4, 55.3, 53.0, 52.8, 40.4, 39.1, 26.4, 22.8. IR (film): 3309, 3099, 2953, 2838, 1757, 1608, 1501, 1453, 1301, 1194, 1041, 835, 718 cm$^{-1}$. HRMS: calcd for $C_{21}H_{25}F_3N_2O_8$ ($M^+$) 490.1563, found 490.1556. Chiral HPLC: ee 98%; Chiralpak AD column, 250 × 4.6 mm, 10 $\mu$m; mobile phase hexane/2-propanol (95:5, v/v); isocratic at ambient temperature, 1.0 mL/min, 210 nm; concentration 0.5 mg/mL, 10 $\mu$L injection; $R_T$ = 34.2 min (enantiomer, $R_T$ = 26.5 min).

**Azetidinone 13.** A mixture of LiCl (8.25 g, 194 mmol) and DMF (310 mL, water content 0.012%) was heated to 130 °C, followed by the addition of a solution of azetidinone **12** (38.1 g, 77.8 mmol) in DMF (35 mL, water content 0.012%) and water (1.40 mL, 77.8 mmol) over a period of 2 h at 128−132 °C. Upon completion of the addition, the mixture was stirred at 130 °C for 1.5 h and then evaporated under reduced pressure at 60 °C to about 200 mL. The residue was diluted with MTBE (200 mL) and washed with 3.0 N HCl (200 mL) and satd $NaHCO_3$ (200 mL). Activated carbon (1.0 g) was added to the ether layer, and the resulting suspension was filtered through a Celite pad. The filtrate was dried over anhyd $Na_2SO_4$, filtered, and concentrated to give the azetidinone **13** as a yellow oil (31.3 g, 93%; *trans*:*cis* = 36.3:1). $^1$H NMR: $\delta$ 7.63 (s br, 1H), 7.05 (d, $J$ = 8.9 Hz, 1H), 6.49−6.40 (m, 2H), 4.57 (d, $J$ = 14.3 Hz, 1H), 4.11 (d, $J$ = 14.3 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.54 (d, $J$ = 2.3 Hz, 1H), 3.40−3.29 (m, 2H), 3.12−3.04 (m, 1H), 1.81−1.60 (m, 4H). $^{13}$C NMR: $\delta$ 170.8, 168.5, 161.0, 158.5, 157.3 (q, $J$ = 36.7 Hz), 131.3, 115.8 (q, $J$ = 286 Hz), 115.0, 104.2, 98.3, 56.6, 55.3,

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55.1, 54.7, 52.2, 40.3, 39.1, 26.2, 25.5. IR (film): 3324, 3083, 2950, 1761, 1619, 1516, 1296, 1209, 1148, 1040, 927, 840, 715 $cm^{-1}$. HRMS: calcd for $C_{19}H_{23}F_3N_2O_6$ ($M^+$) 432.1508, found 432.1495. Anal. Calcd for $C_{19}H_{23}F_3N_2O_6$: C, 52.78; H, 5.36; N, 6.48. Found: C, 52.71; H, 5.44; N, 6.14. Chiral HPLC: ee 98%; Chiralpak AD column, 250 × 4.6 mm, 10 $\mu$m; mobile phase hexane/2-propanol (95:5, v/v); isocratic at ambient temperature, 1.0 mL/min, 210 nm; concentration 0.5 mg/mL, 10 $\mu$L injection; $R_T$ = 24.8 min (enantiomer, $R_T$ = 20.9 min).

***N*$_1$-Deprotected Azetidinone 14.** To a 2-L, three-neck, round-bottom flask equipped with a mechanical stirrer, a thermocouple, and an addition funnel were added 500 mL of $CH_3CN$ and 1244 mL of water. The mixture was heated to reflux followed by the addition of a solution of **13** (51.5 g, 0.119 mol) in 330 mL of $CH_3CN$. The reaction mixture was heated to reflux again followed by the addition of $K_2S_2O_8$ (257.6 g, 0.95 mol) and $K_2HPO_4$ (83.0 g, 0.48 mol). The resulting reaction mixture rapidly turned an orange color and was heated for 38 min with the internal temperature maintained at 91−92 °C under vigorous stirring. The heat was removed, and the reaction mixture was allowed to cool at ambient temperature for 7 min and then cooled in an ice−water bath to <3 °C. All solids were removed by filtration, and the filtrate was evaporated to remove $CH_3CN$. The aqueous residue was cooled to 0 °C, and the pH was adjusted to 8−9 with $NaHCO_3$. The resulting mixture was then saturated with solid NaCl and extracted with ethyl acetate (3 × 400 mL). The combined organic layers were washed with satd $NaHCO_3$ (2 × 200 mL) and brine (2 × 200 mL), separated, and dried over anhyd $Na_2SO_4$ overnight. Filtration and evaporation of the solution followed by crystallization of the residue from ethyl acetate and dichloromethane gave **14** as plate-shaped white crystalline solids (22.8 g, 73% yield). An additional 3.2 g of **14** was obtained from the mother liquor by chromatography, giving a total yield of 82%. Mp: 116−117 °C. $[\alpha]^{25}_D$ = +39.5 (*c* 0.99, $CHCl_3$). $^1$H NMR: $\delta$ 7.10 (s, br, 1H), 6.23 (s, 1H), 3.91 (d, $J$ = 2.34 Hz, 1H), 3.80 (s, 3H), 3.44 (dd, $J$ = 12.7, 6.3 Hz, 2H), 3.3 (m, 1H), 1.94−1.75 (m, 4 H). $^{13}$C NMR ($CD_3OD$): $\delta$ 173.6, 172.6, 159.4 (q, $J$ = 36.7 Hz), 118.0 (q, $J$ = 286.6 Hz), 58.0, 54.9, 53.3, 40.6, 27.7, 27.2. HRMS: calcd for $C_{10}H_{14}F_3N_2O_4$ ($M^+$ + H) 283.0905, found 283.0905. IR (KBr): 3350, 3171, 1787, 1740, 1703, 1560, 1242, 1181, 1155, 662 $cm^{-1}$. Anal. Calcd for $C_{10}H_{13}F_3N_2O_4$: C, 42.56, H, 4.64, N, 9.93. Found C, 42.64, H, 4.57, N, 9.98.

**Benzyl Ester 20.** A solution of **13** (9.55 g, 22.1 mmol) in 90 mL of methanol was cooled to 0 °C followed by addition of 2.0 N NaOH(aq) (34.5 mL, 69.0 mmol). The reaction mixture was stirred at 0 °C for 20 min, then warmed to ambient temperature, and stirred for an additional 2 h. Acetic acid (2.63 mL, 2 equiv) was then added to the reaction mixture followed by evaporation to dryness. The resulting solids **17** were stored in vacuo overnight and then redissolved in methanol.[14] The clear solution was cooled to 0 °C followed by the addition of *N*,*N*′-bis-Cbz-1-guanylpyrazole[15] (**18**; 8.27 g, 21.9 mmol) and triethylamine (9.72 mL, 69.0 mmol). The reaction mixture was stirred at 0 °C for 20 min, warmed to ambient temperature, and stirred for an additional 6 h. The volatiles were removed under reduced pressure, and the oily residue was diluted with 400 mL of EtOAc and washed with 0.5 N HCl (2 × 50 mL), water (80 mL), and brine (100 mL). The organic layer was separated, dried over anhyd $Na_2SO_4$, filtered, and evaporated to give an off-white foam (**19**; 13.75 g). After being dried in vacuo overnight, the crude product was dissolved in dichloromethane followed by the addition of benzyl alcohol (2.41 mL, 23.06 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.83 g, 25.2 mmol), and DMAP (500 mg, 4 mmol). The resulting solution was stirred at ambient temperature for 1.9 h followed by the removal of all volatiles under reduced pressure. The oily residue was diluted with 400 mL of MTBE followed by washing with 100 mL of 0.5 N HCl (2 × 90 mL), water (100 mL), satd $NaHCO_3$ (100 mL), water (100 mL), and brine (120 mL). The organic layer was separated and evaporated to give a white foam (**20**; 15.6 g). Chromatographic purification (40−60% gradient of EtOAc in hexanes, v/v, 5%/500 mL intervals) of the crude product gave 13.3 g (83% yield in three steps) of **20** as a white foam. $[\alpha]^{25}_D$ = +25.9 (*c* 0.97, $CHCl_3$). $^1$H NMR: $\delta$ 11.72 (s, 1H), 8.29 (t, $J$ = 5.3 Hz, 1H), 7.39−7.25 (m, 15H), 7.03 (m, 1H), 6.39−6.36 (m, 2H), 5.16 (s, 2H), 5.14 (s, 2 H), 5.11 (s, 2H), 4.61 (d, $J$ = 14.2 Hz, 1H), 4.10 (d, $J$ = 14.1 Hz, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 3.57 (d, $J$ = 2.3 Hz, 1H), 3.40 (dd, $J$ = 12.1, 6.1 Hz, 2H), 3.11 (m, 1H), 1.82−1.60 (m, 4H). $^{13}$C NMR: $\delta$ 170.3, 167.8, 163.6, 160.9, 158.6, 155.9, 153.7, 136.7, 135.1, 134.5, 131.4, 128.7, 128.61, 128.58, 128.48, 128.4, 128.3, 128.0, 127.8, 115.3, 104.1, 98.3, 104.1, 98.3, 68.1, 67.1, 66.9, 56.6, 55.3, 55.2, 55.0, 40.4, 40.2, 26.3, 25.5. HRMS: calcd for $C_{40}H_{43}N_4O_9$ ($M^+$ + H) 723.3030, found 723.3068. IR (KBr): 3337, 2941, 1756, 1639, 1508, 1383, 1264, 1209, 1045, 744, 698 $cm^{-1}$. Anal. Calcd for $C_{40}H_{42}N_4O_9$: C, 66.47, H, 5.86, N, 7.75. Found C, 66.21, H, 5.72, N, 7.93.

**Guanidine Azetidinone 21.** To a 1-L, round-bottom flask equipped with a condenser, a thermocouple, and a mechanical stirrer were added 162 mL of water and 223 mL of $CH_3CN$. The solution was heated to reflux followed by the addition of a solution of **20** (9.31 g, 12.88 mmol, in 20 mL of $CH_3CN$). The mixture was heated to reflux again followed by adding $K_2S_2O_8$-(s) (30.28 g, 111 mmol) and $K_2HPO_4$(s) (9.02 g, 51.2 mmol). After 15 min, the heat was removed, and the reaction mixture was cooled to 0 °C with vigorous stirring for 30 min and filtered. The filtrate was neutralized with $NaHCO_3$ to pH 7.2, and the organic layer was separated and evaporated. The residue was redissolved in EtOAc (350 mL) followed by washing with satd $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), separated, dried over anhyd $Na_2SO_4$, filtered, and evaporated to give an orange-colored oil. Chromatographic purification of the crude product with a gradient of 40−60% EtOAc in hexanes (v/v, 5%/500 mL intervals) gave the product **21** as a white foam (5.65 g, 76% yield). $[\alpha]^{25}_D$ = +7.94 (*c* 1.02, $CHCl_3$). $^1$H NMR: $\delta$ 11.73 (s, 1H), 8.34 (t, $J$ = 5.2 Hz, 1H), 7.39−7.26 (m, 15H), 6.25 (s, 1H), 5.18 (s, 2H), 5.17 (s, 2 H), 5.11 (s, 2H), 4.11 (d, $J$ = 2.5 Hz, 1H), 3.45 (dd, $J$ = 12.3, 6.4 Hz, 2H), 3.23 (m, 1H), 1.90−1.70 (m, 4H). $^{13}$C NMR: $\delta$ 170.6, 168.8, 163.6, 156.0, 153.8, 136.7, 134.9, 134.5, 128.8, 128.6, 128.4, 128.36, 128.1, 127.9, 68.1, 67.3, 67.1, 57.1, 53.6, 40.3, 26.4, 25.6. HRMS: calcd for $C_{31}H_{33}N_4O_7$ ($M^+$ + H) 573.2349, found 573.2384. IR (KBr): 3334, 1767, 1735, 1639, 1426, 1325, 1207, 1047, 743, 697 $cm^{-1}$. Anal. Calcd for $C_{31}H_{32}N_4O_7$: C, 65.02, H, 5.63, N, 9.78. Found C, 64.76, H, 5.41, N, 9.73.

***N*$_1$-Acylated Azetidinone 23.** A solution of **21** (4.88 g, 8.52 mmol) in 80.0 mL of dichloromethane was cooled to 0 °C followed by addition of the carbamoyl chloride **22** (2.53 g, 10.2 mmol),[3,17] triethylamine (1.68 mL, 11.9 mmol), and DMAP (200 mg, 1.6 mmol). The reaction mixture was stirred at 0 °C for 30 min, then warmed to ambient temperature, and stirred for another 4.65 h. The reaction mixture was diluted with 400 mL of EtOAc and washed with 100 mL of 0.5 N HCl, water (100 mL), satd $NaHCO_3$ (100 mL), water (100 mL), and brine (160 mL). The organic layer was separated, dried over anhyd $Na_2SO_4$, filtered, and evaporated to give a white foam. Chromatographic purification of the crude product with a gradient of 40−65% EtOAc in hexanes (v/v, 5%/250 mL intervals) gave **23** as a white foam (6.42 g, 96% isolated yield). $[\alpha]^{25}_D$ = −32.2 (*c* 0.99, $CHCl_3$). $^1$H NMR: $\delta$ 11.73 (s, 1H), 8.32 (t, $J$ = 5.4 Hz, 1H), 7.40−7.26 (m, 15H), 5.239 (d, $J$ = 12.2 Hz, 1H), 5.17 (s, 2H), 5.14 (d, $J$ = 12.2 Hz, 1H), 5.12 (s, 2H), 4.38 (d, $J$ = 3.6 Hz, 1H), 4.29 (s, 1H), 3.59−3.18 (m, 11H), 1.93−1.72 (m, 4H), 1.35 (s, 9H). $^{13}$C NMR: $\delta$ 169.1, 165.0, 163.6, 156.6, 156.0, 153.8, 149.7, 136.7, 134.8, 134.5, 128.8, 128.65, 128.61, 128.4, 128.3, 128.2, 128.0, 127.9, 68.2, 67.5, 67.1, 54.4, 52.0, 50.9, 43.5, 40.1, 29.3, 26.3, 25.3. HRMS: calcd for $C_{41}H_{50}N_7O_9$ ($M^+$ + H) 784.3670, found 784.3667. IR (KBr): 3338, 2962, 1788, 1736, 1640, 1427, 1261, 1205, 1138, 1047, 994, 748, 697 $cm^{-1}$. Anal. Calcd for $C_{41}H_{49}N_7O_9$: C, 62.82, H, 6.30, N, 12.51. Found: C, 62.62, H, 6.25, N, 12.33.

**1 (BMS-262084).** A solution of **23** (5.93 g, 7.6 mmol) in 50 mL of ethanol was degassed with a vacuum/argon, followed by adding 10% Pd/C (50% water, 2.4 g). The resulting black suspension was degassed again with a vacuum. The reaction mixture was then exposed to hydrogen (via a balloon) at 1 atm of pressure. After 1.1 h, the catalyst was removed by filtration, and the filtrate was evaporated. The residue was kept in vacuo

overnight to give **1** as a white powder (3.18 g, 99% yield). Mp: 213-215 °C dec. $[\alpha]^{25}_D = -65.9$ (*c* 0.99, MeOH). $^1$H NMR ($CD_3OD$): $\delta$ 4.17 (d, $J = 3.29$ Hz, 1H), 3.61−3.11 (m, 11H), 1.94−1.75 (m, 4H), 1.32 (s, 9H). $^{13}$C NMR ($CD_3OD$): $\delta$ 176.6, 168.7, 159.4, 158.7, 152.3, 58.7, 53.2, 51.8, 46.5, 45.0, 41.8, 29.6, 27.4, 26.3. HRMS: calcd for $C_{18}H_{32}N_7O_5$ ($M^+ + H$) 426.2465, found 426.2470. IR (KBr): 3385, 3184, 1775, 1657, 1535, 1395, 1259, 1207, 996, 763 $cm^{-1}$. Anal. Calcd for $C_{18}H_{31}N_7O_5$: C, 50.81, H, 7.34, N, 23.04. Found: C, 50.65, H, 7.42, N, 22.72. Chiral HPLC: ee 99.6%; Chiralpak OD column, 250 × 4.6 mm, 10 $\mu$m; mobile phase hexane/EtOH (85:15, v/v); isocratic at ambient temperature, 1.0 mL/min, 220 nm; concentration 0.25 mg/mL, 10 $\mu$L injection; $R_T = 18.6$ min (enantiomer, $R_T = 15.7$ min).

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**Supporting Information Available:** NMR spectra of the isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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