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Process Research and Development for an Efficient Synthesis of the HIV Protease Inhibitor BMS-232632

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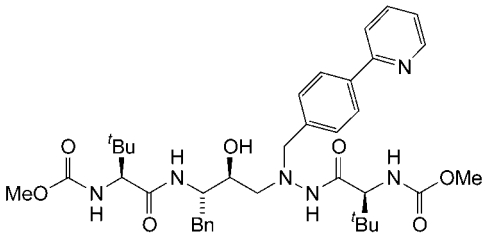
Abstract:

Development of an efficient and scalable process for the human immunodeficiency virus (HIV) protease inhibitor BMS-232632 1-[4-(pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]-amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane, is described. The key step in the synthesis of the intermediate *N*-1-(*tert*-butyloxycarbonyl)-*N*-2-[4-(pyridin-2-yl)benzylidene]hydrazone (11) was the Pd-mediated coupling of boronic acid 9 with 2-bromopyridine. An efficient procedure was developed for the chemoselective reduction of hydrazone 11 to hydrazine carbamate 4. The key intermediate *N*-(*tert*-butyloxycarbonyl)-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxy-butane (6) was prepared stereoselectively from chiral diol 10. The subsequent union of 4 and 6 followed by coupling with *N*-methoxycarbonyl-L-*tert*-leucine provided the free base BMS-232632 in high yield. Evaluation of a variety of salts and identification of bisulfate salt 19 with enhanced bioavailability are also described.

Introduction

BMS-232632 is an acyclic aza-peptidomimetic that is a potent human immunodeficiency virus (HIV) protease inhibitor.[1] Its bisulfate salt has better bioavailability than the free base, with a half-life suitable for once-daily dosing. We have developed a practical synthesis of this compound.



BMS-232632

The original process for BMS-232632 (Scheme 1) was satisfactory for preparation of material for early toxicology studies.[2] However, this route was suboptimal for the production of the larger quantities required for further toxicology studies, preclinical studies, and clinical trials. Significant modifications in the synthesis of key intermediates as well as the replacement of reagents in the subsequent steps were required. Furthermore, the crystalline free base form of BMS-232632 as a suspension in water or oil had poor oral bioavailability in animals, presumably due to its extremely low solubility in these vehicles. For development of pharmaceutical formulations, particularly oral dosage forms, a salt form of BMS-232632 with enhanced bioavailability had to be identified. We herein report on a more efficient synthesis of this compound and identification of a salt with appropriate properties.

Several limitations of the original process presented a formidable challenge for the preparation of material in large quantity. The pyridinyl benzaldehyde **3** was made in three steps involving nickel-catalyzed coupling of Grignard reagent **2** with 2-bromopyridine. Although the overall yield from **1** was high (84%), the use of a hazardous reagent diisobutylaluminum hydride and protection/deprotection of the aldehyde moiety were required.[2] Epoxide **6** was prepared from L-Boc-phenylalaninal (**5**) in two steps including a Wittig reaction with methyltriphenylphosphonium bromide. Not surprisingly, even at −78 °C, racemization of **5** occurred during the Wittig reaction, which in turn resulted in epoxide with only 80% ee. Furthermore, purification of both the Wittig reaction product and epoxide **6** proved difficult, and silica gel chromatographies were required. In the final step, coupling with *N*-methoxycarbonyl-L-*tert*-leucine, the expen-

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(1) (a) Fassler, A.; Bold, G.; Capraro, H.; Cozens, R.; Mestan, J.; Poncioni, B.; Rosel, J.; Tintelnot-Blomley, M.; Lang, M. *J. Med. Chem.* **1996**, *39*, 3203−3216. (b) Bold, G.; Faessler, A.; Capraro, H.; Cozens, R.; Klimkait, T.; Lazdins, J.; Mestan, J.; Poncioni, B.; Roesel, J.; Stover, D.; Tintelnot-Blomley, M.; Acemoglu, F.; Beck, W.; Boss, E.; Eschbach, M.; Huerlimann, T.; Masso, E.; Roussel, S.; Ucci-Stoll, K.; Wyss, D.; Lang, M. *J. Med. Chem.* **1998**, *41*, 3387−3401. (c) Rusano, G. L.; Bilello, J. A.; Preston, S. L.; O'Mara, E.; Kaul, S.; Schnittman, S.; Echols, R. *J. Infect. Dis*. **2001**, *183*, 1126−1129. (d) Gong, Y.; Robinson, B. S.; Rose, R. E.; Deminie, C.; Spicer, T. P.; Stock, D.; Colonno, R. J.; Lin, P. *Antimicrob. Agents Chemother.* **2000**, *44*, 2319−2326. (e) Robinson, B. S.; Riccardi, K. A.; Gong, Y.; Guo, Q.; Stock, D. A.; Blair, W. S.; Terry, B. J.; Deminie, C. A.; Djang, F.; Colonno, R. J.; Lin, P. *Antimicrob. Agents Chemother.* **2000**, *44*, 2093−2099. (f) Rabasseda, X.; Silvestre, J.; Castaner, J. *Drugs Future* **1999**, *24*, 375−380.

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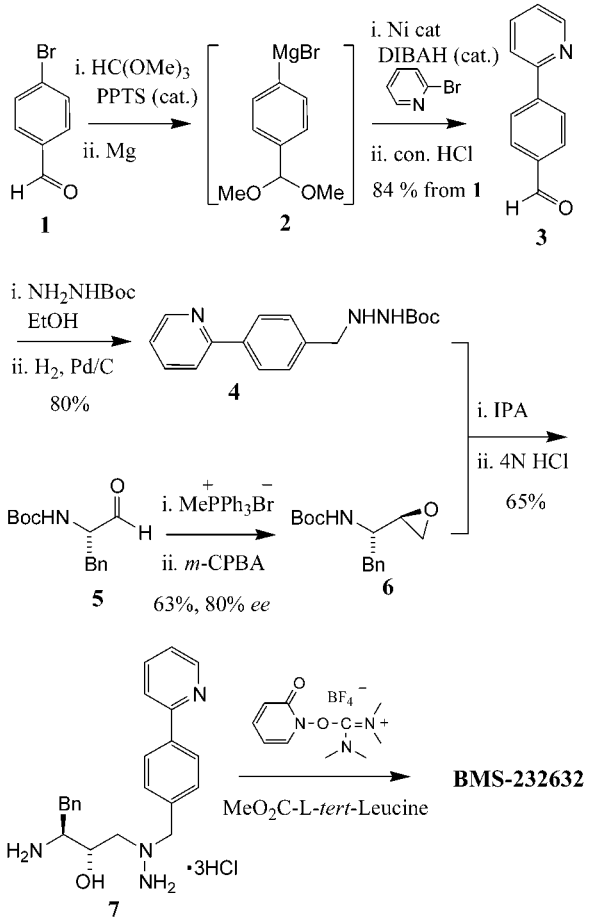
Scheme 1. **Original Synthesis of BMS-232632**



sive *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-tetrafluoro-borate (TPTU) was used.

In addition, a mediocre yield was obtained due in part to the low enantiomeric purity of the epoxide starting material. Besides the above-mentioned issues, environmentally unfriendly solvents, such as highly flammable diethyl ether and suspected carcinogen 1,4-dioxane, were employed in this process. Therefore, a strong need for the development of a more efficient and environmentally suitable synthesis for BMS-232632 existed.

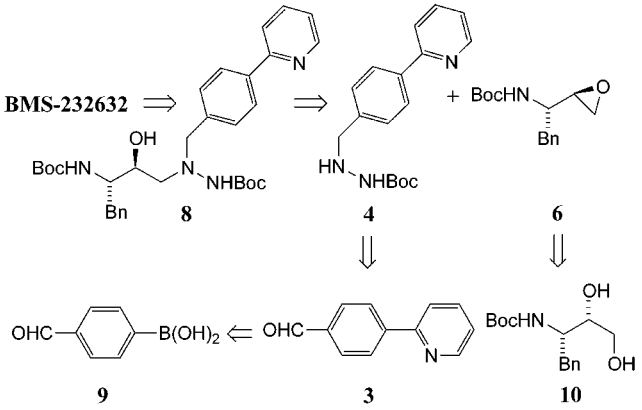
Synthesis Strategy

As depicted in the retrosynthetic analysis (Scheme 2), we envisaged new methods for preparation of hydrazinocarbamate **4** and epoxide **6**. Aldehyde **3** might be accessed through a Suzuki coupling of commercially available 4-formylbenzeneboronic acid (**9**) with 2-bromopyridine, eliminating the need to protect and deprotect the aldehyde functionality. To obtain enantiomerically pure epoxide **6**, we planned to use the commercially available diol **10**, possessing the *S*-configuration at the carbinol center. A selective formation of **6** was expected through an intramolecular S_N2 displacement reaction. The convergent formation of BMS-232632 from intermediates **4** and **6** is analogous to the original synthesis.[2]

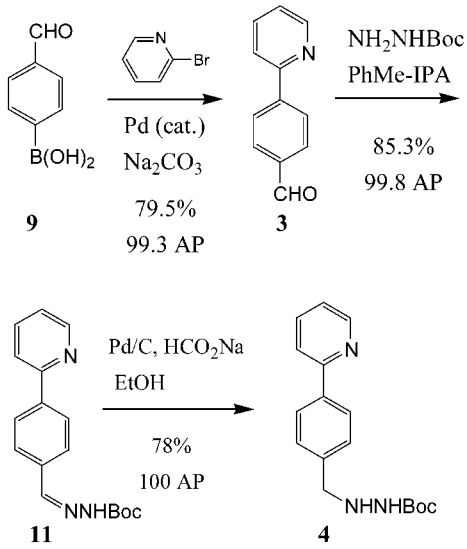
Results and Discussion

Synthesis of Hydrazinocarbamate 4. Unlike the metal-catalyzed couplings of Grignard reagents with aryl electro-

Scheme 2. **Retrosynthesis for BMS-232632**



Scheme 3. **Synthesis of hydrazino carbamate 4**



philes, the Suzuki coupling is highly tolerant of functionality.[3] The requisite aldehyde **3** (Scheme 3) was prepared through Suzuki coupling of boronic acid **9** to 2-bromopyridine. The reaction was reasonably straightforward. However, it proved critical to use a 4:3 mixture of toluene−ethanol as the solvent in order to dissolve all the reactants, thus affording a facile reaction. Also, use of a minimal amount (0.1 mol %) of Pd-$(PPh_3)_4$ catalyst was required to deliver product with low amount (5−50 ppm) of palladium. Under the optimal conditions, the Suzuki coupling afforded the desired aldehyde **3** after crystallization from toluene−*n*-heptane in 79.5% yield and with HPLC area % (AP) 94−99. It was subsequently found that the toluene solution of crude aldehyde **3** resulting from an extractive workup could be used in the next step without further purification. Curiously, wide variations in residual Pd levels (5−400 ppm) in the product were observed from batch to batch.

The subsequent condensation of aldehyde **3** with *tert*-butyl carbazate was initially carried out by heating in ethanol and then precipitating the product by the addition of water. This procedure afforded a 93% yield of **11** with less than optimal purity, ∼95 AP. We found that the use of a solvent mixture

(3) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576* (1−2), 147−168.

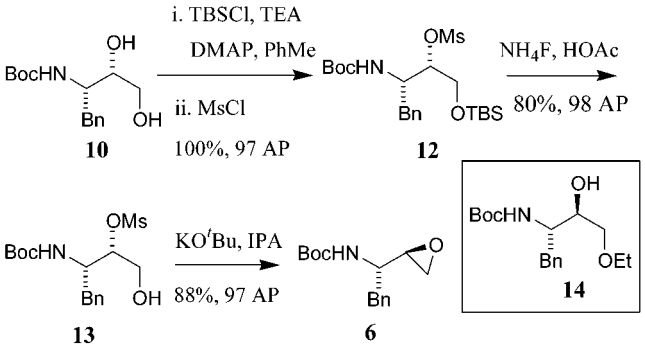
of 4:3 toluene−2-propanol was ideal for both the condensation and subsequent crystallization. Heating the crude aldehyde **3** and *tert*-butyl carbazate in this mixture of solvents for 2 h and subsequent cooling and filtration provided compound **11** in 92% yield and with ∼100 AP. In addition, the residual Pd level was reduced about 10-fold compared to that in the aldehyde starting material. This procedure was scaled up to afford 5 kg of **11** in a single batch.

Our studies showed that under the original conditions (Pd/C, MeOH, and 1 atm H_2),[2] the conversion of **11** to **4** was variable, ranging from 80 to 98%. Also problematic were the side reactions involving hydrogenolysis and overreduction.[4] In contrast to the hydrogenolysis and overreduction byproducts, the removal of the unreacted hydrazone **11** through crystallization proved difficult due to its extremely low solubility compared to product **4**. Thus, a more efficient conversion was desired. Replacement of Pd/C with Pd-$(OH)_2$/C provided improved conversion (>97%) while the extent of hydrogenolysis was less than 2%. Hydrogenation of **11** using $Pd(OH)_2$ (MeOH, 1 atm H_2, 6 h) followed by crystallization provided **4** in 80−90% yields and with 94−99 AP (1−5 AP **11**). Despite these encouraging results, the required catalyst loading of 10 wt % of $Pd(OH)_2$ rendered this reduction unattractive.

Chemical reductions of hydrazone **11** using $NaBH_4$[5] (various solvents, with additives such as $NiCl_2$,[6] $ZrCl_4$,[7] and HOAc), $NaB(OAc)_3H$-HOAc,[8] $NaBH_2S_3$,[9] $LiBH_4$, and $Al(^iBu)_2H$ were sluggish; generally <20% product was observed. Reduction with Zn/HOAc[10] in refluxing methanol resulted in ∼40% conversion to hydrazinocarbamate **4**.

In search for a more effective procedure, we examined catalytic phase-transfer hydrogenation.[11] Although reduction with 2 equiv of sodium formate and 1 mol % of Pd/C required an elevated temperature, complete reaction could be obtained reliably in 2 h at 56 °C, yielding crude **4** with ∼98 AP. Crystallization from *tert*-butyl methyl ether and *n*-heptane furnished the desired hydrazinocarbamate in 78% isolated yield with 100 AP. This reduction procedure was successfully scaled up to afford 3.7 kg of **4** (78% yield, AP 100) in a single batch. It is noteworthy to mention that although solid hydrazinocarbamate **4** was perfectly stable in air, it readily underwent air oxidation in MeOH or MeCN solution to afford hydrazone **11**. Therefore, solutions of **4** were handled under inert gas.

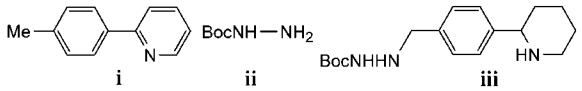
Scheme 4. **Synthesis of (2*S*,3*R*)-epoxide 6**



Synthesis of (2*S*,3*R*)-Epoxide 6. Methods for the conversion of a vicinal diol to an epoxide are well established.[12] Through modification of the reported procedures,[12d−f] a practical process for this transformation was developed. As illustrated in Scheme 4, a quantitative yield of silyl mesylate **12** was produced in one pot through selective silylation (2.2 equiv of TBSCl, DMAP (cat), 2.2 equiv of Et_3N, 50 °C, toluene) and subsequent mesylation (1.1 equiv of MsCl, 5 °C, toluene) of diol **10**. This oily intermediate was carried into the next step without further purification.

We found that desilylation of **12** could be effected using the inexpensive reagent ammonium fluoride[13] instead of the more traditional tetrabutylammonium fluoride. The resulting solid product **13** could be readily isolated and further purified through crystallization from IPA−H_2O in 80% yield with AP 98. Several bases were screened for epoxide formation from **13**. KO^{t}Bu was found to be the base of choice, giving enantiomerically pure epoxide product in 90% crystallized yield. Interestingly, use of KOH in EtOH gave an ethanolysis product **14** exclusively.[14] The reaction with KO^{t}Bu in THF−IPA was reproducible on scale-up. Following the above four-step procedure, a total of 2.7 kg of epoxide **6** was prepared in 70% average yield with 100 AP. The primary attraction of this route is that product **6** with 100% ee is obtained cleanly.

(4) Byproducts **i** and **ii** were formed by the hydrogenolysis and **iii** was formed by overreduction.



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(12) Via conversion of 1° alcohol to a leaving group: (a) Clayden, J.; McElroy, A. B.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, *15*, 1913−1934. (b) Shibuya, M.; Terauchi, H. *Tetrahedron Lett.* **1987**, *28*, 2619−2623. (c) Masaki, Y.; Serizawa, Y.; Nagata, K.; Oda, H. *Tetrahedron Lett.* **1986**, *27*, 231−234. Via conversion of 2° alcohol to a leaving group: (d) Castejon, P.; Pasto, M.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1995**, *36*, 3019−3022. (e) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem, Int. Ed. Engl.* **1986**, *25*, 835−839. (f) Qlan, X.; Moris-Varas, F.; Wong, C. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1117−1122.

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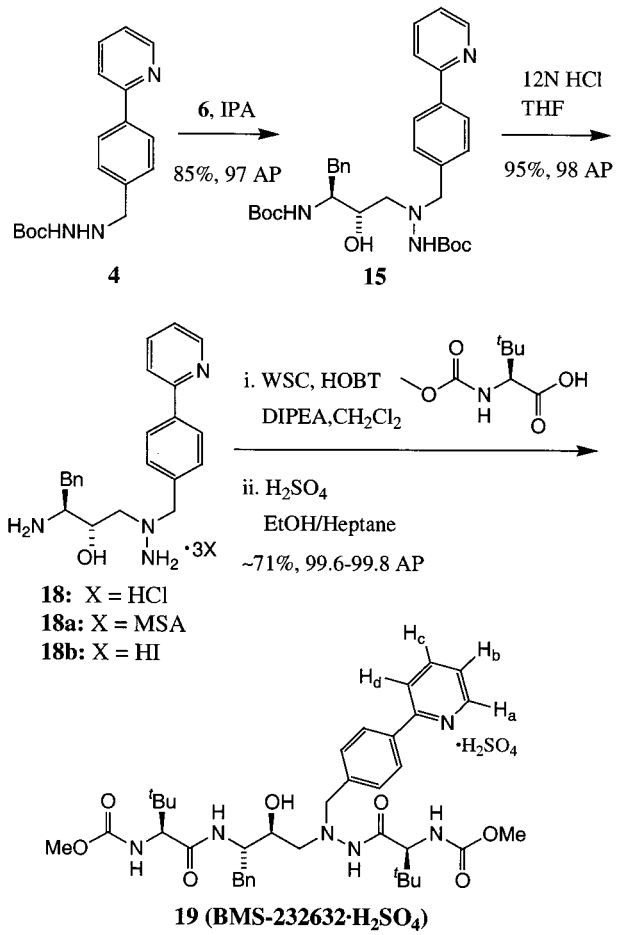
(14) It is possible that the desired epoxide **6** was initially formed and that it rapidly underwent a rearrangement under the reaction conditions. This possibility was supported by the finding that subjection of **6** to excess KOH in EtOH resulted in the formation of **14**. Compound **14** was isolated and fully characterized. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 5.14 (d, J = 9.6 Hz, 1H), 3.75 (m, 1 H), 3.45 (q, J = 7.1 Hz, 2H), 3.36 (d, J = 7.0 Hz, 2H), 3.24 (s, 1H), 2.89 (m, 2H), 1.40 (s, 9H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 28.4, 38.3, 52.8, 66.5, 69.3, 72.4, 72.6, 76.7, 79.1, 126.1, 128.2, 129.2, 138.1, 155.6; IR (1% KBr pellet) 3440, 1713, 1695 cm^{-1}; $[\alpha]_D$ = −31.3 (c = 1, MeOH, 22 °C); Anal. Calcad for $C_{18}H_{29}NO_4$: C, 65.99; H, 8.80; N 4.53. Found: C, 65.88; H, 8.82; N 4.26.

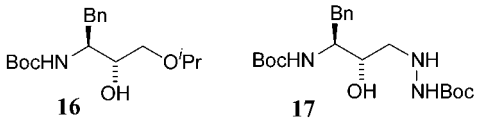
Scheme 5. **Synthesis of BMS-232632 and its bisulfate salt 19**



Partial ^{1}H NMR chemical shifts of BMS-232632 and 19 (starred chemical shifts for the protons in 19):

H_a = (8.6, 8.8*), H_b = (7.3, 7.7*), H_c = (7.8, 8.3*), H_d = (7.9, 8.2*)

Synthesis of BMS-232632. As illustrated in Scheme 5, the coupling of hydrazinocarbamate **4** and epoxide **6** was performed in refluxing IPA for 24 h, followed by the addition of water to precipitate the crude product. Subsequent recrystallization from MeCN−H_2O furnished **15** in 85% yield with AP 98. In the coupling reaction, low levels (<5%) of impurity **16**,



a consequence of epoxide opening by the solvent, were observed by in-process HPLC. Employment of *tert*-butyl alcohol produced **15** in comparable yields; however, the reaction required ~48 h for completion. Replacement of IPA with several aprotic solvents (toluene, acetonitrile) resulted in very sluggish reactions. Impurity **16** as well as **17**, resulting from epoxide opening by the hydrogenolysis product Boc-$NHNH_2$ mentioned above,[4] was purged during the initial precipitation of the product.

Subsequent removal of the two Boc groups in **15** was performed with concentrated hydrochloric acid in THF at 50 °C. Although a clean deprotection product **18** was generated, the isolation of this trihydrochloride salt proved difficult due to its hygroscopic nature. Attempted crystallization or precipitation from several solvent systems afforded material which was still extremely hygroscopic. The corresponding MsOH and HI salts **18a** and **18b** were isolated by deprotection using MsOH and TMSI, respectively. These materials were foamy solids and also very hygroscopic. To circumvent the problematic isolation of **18**, a procedure for the deprotection and in situ coupling with *N*-methoxycarbonyl-L-*tert*-leucine was developed. After removal of the Boc groups from **15** with HCl, the wet THF layer was decanted. The residual oily product was then washed with THF and taken up in dichloromethane. The resulting solution was subjected to the original coupling conditions (3 equiv of *N*-methoxycarbonyl-L-*tert*-leucine, 1 equiv of TPTU, 6 equiv of EtN^iPr_2, CH_2Cl_2),[2] affording BMS-232632 in ~80% yield with high purity. To avoid use of the expensive reagent TPTU, the coupling step was reevaluated. Replacement of TPTU by a combination of water-soluble carbodiimide [WSC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] and 1-hydroxybenzotrizaole (HOBT) formed the coupling product in a similar yield. The solution of crude trihydrochloride salt **18** was treated with diisopropylethylamine and added to a mixture of *N*-methoxycarbonyl-L-*tert*-leucine, WSC and HOBT in dichloromethane. A minimum of 2.6 equiv each of WSC and HOBT, and 2.5 equiv of *N*-methoxycarbonyl-L-*tert*-leucine were required for complete reaction.[15] Using this process we prepared 3.5 kg of BMS-232632 (yield 82% from **15**, AP 98.8).

Formation of the Bisulfate Salt 19.[16] Free base BMS-232632 is highly insoluble in water (<1 μg/mL at 24 °C) and has poor oral bioavailability in animals. Therefore, several acid salts were explored. A number of commonly used acid salts such as the hydrochloride, benzenesulfonate, methanesulfonate, *p*-toluenesulfonate, phosphate, nitrate, 1,2-ethanedisulfonate, 2-hydroxyethanesulfonate, sulfate, and bisulfate were evaluated. While these salts in their crystalline form exhibited higher aqueous solubility (0.5−5 mg/mL) than the free base, bisulfate salt **19** was chosen as the final form for development due to its superior solubility (4−5 mg/mL).

Bisulfate salt **19** was obtained in two crystalline forms, as determined by powder X-ray diffraction patterns. Type-1 crystals were formed in acetone, MeCN, or EtOH; the Type-II crystals were obtained from IPA. Due to its reproducibility, the Type-I form was selected for further development. The Type-I form **19** was initially prepared in MeCN with 9 M H_2SO_4 and in the presence of seed crystals. Although a very easily filterable, dense, sandy solid was obtained, this procedure was abandoned due to concerns of possible toxicity associated with residual trace amounts of MeCN. Alternatively, the formation of **19** was performed with concentrated H_2SO_4 in EtOH at ambient temperature. Direct crystallization

(15) In-process HPLC analysis indicated that the amide bond on the amine was formed prior to that on the hydrazine. Fewer equivalents of WSC, HOBT and *N*-methoxycarbonyl-L-*tert*-leucine resulted in an incomplete reaction, evidenced by a high ratio of monocoupling product to BMS-232632.

(16) Singh, J.; Pudipeddi, M.; Lindrud, D. M. W.O. Patent 9936404, 1999.

by addition of *n*-heptane provided the bisulfate salt **19** as an easily filterable solid in 85% yield with >99.6 AP on 3.6 kg input scale. ^{1}H NMR analyses of the free base BMS-232632 and bisulfate salt **19** indicated that the pyridine ring in **19** was protonated, as evidenced by the downfield chemical shifts of protons H_{a-d} compared to those of the free base (Scheme 5, starred chemical shifts are for the protons in the salt **19**).

Summary

A short and efficient synthesis of hydrazinocarbamate **4** has been developed. A novel process for selective formation of epoxide **6** from diol **10** has been established. The convergent formation of BMS-232632 from **4** and **6** has been significantly improved, providing the free base BMS-232632 in good yield. Finally, the bisulfate salt **19** with enhanced bioavailability was identified and obtained in excellent purity.

Experimental Section

All new compounds described in the Experimental Section were fully characterized. Analytical and spectral data for these compounds are for lab batches. HPLC analysis results are described as area % (AP).

4-Pyridin-2-yl-benzaldehyde (3). A mixture of 4-formyl-phenyl-boronic acid (**9**) (200 g, 666.9 mmol) and 2-bromopyridine (110.6 g, 700.3 mmol) in 700 mL of 4:3 toluene/95% ethanol was purged with N_2 for 15 min and then heated under a N_2 atmosphere, resulting in a clear solution. A slurry of $Pd(PPh_3)_4$ (1 g, 0.86 mmol) in 10 mL of a 4:3 mixture of toluene and 95% ethanol was added, followed by 1.16 L of 3 M aqueous Na_2CO_3. The resulting mixture was gently refluxed at ~76 °C for 13 h, at which time an additional 10-mL slurry of $Pd(PPh_3)_4$ (540 mg, 0.467 mmol) was added. The reaction was continued for another 7 h and then cooled to ambient temperature. The solid was removed by filtration, and the filtrate was poured into a separatory funnel. The layers were separated, and the aqueous layer was washed with toluene (2 × 250 mL). The combined organic layers were stirred over charcoal (10 g) for 5 h, filtered, and partially concentrated in vacuo to provide a toluene solution of aldehyde **3**, which contained approximately 150 mL of toluene. This unpurified product was submitted directly to the next reaction. Alternatively, the crude **3** could be purified through crystallization from a mixture of 1:1 toluene and *n*-hexane. Typically, a 80% crystallized yield was obtained.

***N*-1-(*tert*-Butyloxycarbonyl)-*N*-2-[4-(pyridin-2yl)benzylidene]-hydrazone (11).** To a 100-L glass plant reactor was added 4-pyridin-2-yl-benzaldehyde (**3**) (4.131 kg, 22.25 mol), *tert*-butyl carbazate (2.967 kg, 22.23 mol), 6.05 L of 2-propanol, and 8.01 L of toluene. The mixture was heated to reflux (80−85 °C) under inert atmosphere for 2 h, cooled to 22 °C over 4 h, and stirred at that temperature for about 14 h. The resulting mixture was filtered, and the filter cake was washed with a cold mixture of toluene and heptane (1:3, 0−5 °C, 4 × 3.56 L). The cake was air-dried under vacuum to afford 5.644 kg of **11** (85.3% yield, 99.8 AP).

***N*-1-(*tert*-Butyloxycarbonyl)*N*-2-[4-(pyridin-2-yl)benzylidene]-hydrazine (4).** In to a mixture of hydrazone **11** (113.4 g, 0.382 mol), and 10% palladium on activated carbon (4.05 g) in 382 mL of ethanol, a solution of sodium formate (46.7 g, 0.687 mol) in water (70 mL) was added. The resulting mixture was heated to 57 °C, and slight gas evolution was observed within 5 min. After 1.5 h, the reaction was cooled to about 40 °C, and MTBE (380 mL) was added. The solid was removed through filtration. The filtrate was washed with 10% sodium chloride solution (550 mL), dried over anhydrous sodium sulfate (100 g), filtered, and concentrated to provide a colorless gel which was dissolved in MTBE (110 mL) under argon atmosphere at 50 °C. *n*-Heptane (350 mL) was added dropwise to the warm solution, and the resulting mixture was slowly cooled to 23 °C and stirred for 16 h. Filtration and washing with heptane (2 × 300 mL) afforded **4** as a white solid (89.1 g, 78% yield, AP 100).

[3-*tert*-Butyl-dimethylsilanyloxy-2(*S*)-[(methylsulfonyl)-oxy]-1(*S*)-(phenylmethyl)propyl]-carbamic Acid, 1,1-Dimethylethyl Ester (12). A solution of diol **10** (544 g, 1.034 mol) in 1.2 L of toluene was heated to 88 °C, and a clear solution was obtained. The solution was then cooled to 50 °C. Dimethylamino pyridine (23.6 g, 0.195 mol) and triethylamine (325 mL, 2.32 mol) were charged followed by the slow addition of *tert*-butyl-dimethylsilyl chloride (350 g, 2.32 mol) while keeping the internal temperature around 50 °C. The reaction mixture was cooled to 0 °C over 3 h. Triethylamine (417 mL) was added followed by the slow addition of trifluoromethanesulfonyl chloride (198 mL), keeping the internal temperature under 5 °C. The resulting mixture was stirred at 0 °C for about 3 h. The solid was filtered through Celite and washed with toluene (2 × 700 mL). The filtrate was washed with water (4 L), 1 N HCl (4 L), and brine (4 L), in that order, and then concentrated in a vacuum to afford 1.04 kg of product **12** as a yellow oil. This product was subjected to the next step without further purification.

[3-Hydroxy-2(*S*)-[(methylsulfonyl)oxy]-1(*S*)-(phenylmethyl)propyl]-carbamic Acid, 1,1-Dimethylethyl Ester (13). Into a reactor was charged ammonium fluoride (358 g, 9.67 mol), a solution of the crude mesylate **12** (1.04 kg, 1.034 mol) in methanol (5.6 L), and acetic acid (550 mL). The mixture was stirred at ambient temperature for 11 h. The reaction mixture was concentrated to dryness to afford a solid, which was dissolved in 11 L of methyl *tert*-butyl ether. The resulting solution was washed with water (5 L), 5% sodium bicarbonate (3 × 4 L), and brine (4 L) and then dried over $MgSO_4$ (300 g). Filtration and partial concentration afforded 5 L of solution. The concentrated solution was then cooled to 4 °C and stirred at this temperature for 18 h to give a slurry. The solid was filtered, washed with cold MTBE (200 mL) and dried under partial pressure to afford 489.1 g of **13**. The filtrate was concentrated to 1 L, cooled to 4 °C, and stirred at this temperature for 18 h to give a slurry. Another 61.7 g of solid was obtained after filtration and drying. Thus, a total of 550.8 g of product **13** was obtained as a white solid (80% yield, AP 98).

***N*-(*tert*-butyloxycarbonyl)-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxy-butane (6).** To a clear solution of hydroxy

mesylate **13** (629.9 g, 1.75 mol) in a mixture of IPA (6.3 L) and THF (1.8 L) at 17 °C, was added KO^{t}Bu (207 g, 95%, 1.75 mol) over 20 min. The mixture was stirred for 1.5 h followed by addition of 30 mL of acetic acid over 15 min. The resulting solution was concentrated under vacuum to dryness to afford a white solid. The solid was dissolved in MTBE (9.0 L), and the resulting solution was washed with water (4.5 L), saturated sodium bicarbonate solution (4.5 L), and brine (4.5 L), dried over anhydrous Na_2SO_4, filtered, and concentrated to give an oil (455.2 g). The oil was diluted with hexane (1.3 L) followed by addition of water (200 mL). The mixture was cooled to −4 °C, and solid was observed. The solid was collected by filtration, washed with 700 mL of cold hexane (0 °C), and dried under vacuum for 18 h to give epoxide **6** as a white solid (400.5 g, 88% yield, AP 97).

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis[(*tert*-butyloxycarbonyl)-amino]-4(*S*)-hydroxy-6-phenyl-2-azahexane (15). To a mixture of compounds **4** (1.68 kg, 5.58 mol) and **6** (1.735 kg, 6.56 mol) was added 23.83 L of 2-propanol. The solution was refluxed for 24 h under an inert atmosphere and then cooled to 22 °C. Water (28.9 L) was added, and the resulting mixture was stirred at 22 °C for 16 h to afford a slurry. The solid was collected by filtration and washed with water (2 × 11 L) and cold MTBE (∼0 °C, 2 × 4 L). This wet cake was dissolved in acetonitrile (44 L), and water (44 L). The crystallized material was filtered and dried to give 2.681 kg (85.4% yield, AP 99) of **15**.

***N*-Methoxycarbonyl-L-*tert*-leucine.** To a solution of L-*tert*-leucine (750 g, 5.7 mol) was added 9.42 L of 2 N aqueous sodium hydroxide and methylchloroformate (882 mL, 11.34 mol). The resulting mixture was heated at 60 °C for 18 h and then cooled to 22 °C. The reaction mixture was acidified by addition of 4 N HCl (4.8 L) to pH ∼2 followed by an extractive workup with ethyl acetate (3 × 6 L). The combined extracts were washed with brine and concentrated under vacuum to afford an oil. To the oil 7.7 L hexane was added to produce a large solid mass. The solid was collected by filtration and air-dried to afford 883 g of *N*-methoxycarbonyl-L-*tert*-leucine (82% yield).

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane (BMS-232632). To a stirred solution of **15** (3.5 kg, 6.22 mol) in 17.5 L of THF, concentrated HCl (2.38 L, 12 N) was added dropwise at 22 °C to give an amber-colored solution. The mixture was stirred for 3 h at 45−55 °C to produce a biphasic mixture. The mixture was cooled to 22−25 °C over 3 h, and the wet THF layer was decanted away from a brown oil. The oil was rinsed with 7 L of THF, which was decanted. The brown oil was dissolved in a mixture of 14 L of CH_2Cl_2 and 6.65 L of DIPEA. The resulting mixture was slowly transferred by pump at 22 °C into a premixed solution of *N*-methoxycarbonyl-L-*tert*-leucine (2.94 kg, 15.5 mol), HOBT (2.32 kg, 17.2 mol), and WSC (3.13 kg, 16.3 mol) in 4.4 L of CH_2Cl_2. The new reaction mixture was stirred for 3−4 h at 25 °C. The reaction mixture was then washed with water (1 × 13.1 L), $NaHCO_3$ (1 × 13.1 L), and brine (1 × 14 L). The organic layer was concentrated to a viscous oil and treated with 42 L of a 98:2 isopropyl ether−EtOH solution at 55−70 °C until a mild reflux was observed. The slurry was cooled to 25−30 °C, and the solid was collected by filtration, washed with 13.3 L of a 98:2 mixture of isopropyl ether−EtOH, and dried at 35−40 °C under vacuum to give 3.86 kg of crude free base. The crude product was crystallized from 36.4 L of a mixture of ethanol−water (45/55), filtered, washed, and dried to afford 3.64 kg of BMS-232632 in 82.1% yield and with AP 98.8.

1-[4-(Pyridin-2-yl)phenyl]-5(*S*)-2,5-bis{[*N*-(methoxycarbonyl)-L-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane, Bisulfate Salt (19). To a solution of BMS-232632 (3.6 kg, 5.1 mol) in 27 L of ethanol, concentrated H_2SO_4 (309 mL, 5.65 mol) was added dropwise at 22 °C to give a yellow-orange colored solution. After complete dissolution, the solution was filtered and transferred into another vessel. Then 18 L of *n*-heptane was added followed by seeding with 10 g of pure **19**. After seeding, an additional 12 L of *n*-heptane was added. The mixture was stirred for 15 h. The solid was collected through filtration and washed with heptane−ethanol (1:1) solution and dried to afford 3.49 kg of **19** as a white solid (85.2% yield, AP 99.8). ^{1}H NMR (270 MHz DMSO-d_6) δ 9.35 (s, 1H), 9.0 (d, J = 4.1 Hz, 1H), 8.64 (t, J = 8.2 Hz, 1 H), 8.43 (d, J = 8.2 Hz, 1H), 8.07 (m, 2H), 8.32 (t, J = 8.2 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.73 (d, J = 8.2 Hz, 1H), 7.67 (m, 1H), 7.32 (d, J = 4.7 Hz, 1H), 7.27 (m, 3H), 7.09 (d, J = 9.4 Hz, 1H), 7.03 (d, J = 9.3 Hz, 1H), 4.20 (m, 1H), 3.97 (m, 2H), 3.76 (d, J = 9.4 Hz, 1H), 3.62 (m, 2H), 3.64 (s, 3H), 3.60 (s, 3H), 2.90−2.63 (m, 2H), 0.89 (s, 9H), 0.75 (s, 9H); ^{13}C NMR (68 MHz DMSO-d_6) δ 26.3, 26.7, 33.4, 33.6, 37.7, 51.4, 51.6, 60.7, 61.0, 61.3, 63.2, 68.3, 124.2, 124.8, 125.9, 127.5, 128.0, 129.1, 129.3, 131.3, 139.0, 141.6, 144.2, 144.7, 152.3, 156.5, 170.1; IR (1% KBr pellet) 3426, 2959, 1701, 1676, 1653, 1514, 1370, 1244, 1065, 777; $[\alpha]_D$ = −46.1 (c = 1, 1:1 MeOH/H_2O, pH = 2.6, 22 °C); Anal. Calcd for $C_{38}H_{52}N_6O_7 \cdot H_2SO_4 \cdot 0.35\ H_2O$: C, 56.40; H, 6.81; N 10.39; S, 3.96; H_2O, 0.78. Found: C, 56.54; H, 6.81; N 10.35; S, 3.98; H_2O, 0.74.

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