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A Practical Large-Scale Synthesis of (3*R*,4*R*)-4-(Hydroxymethyl)pyrrolidin-3-ol via Asymmetric 1,3-Dipolar Cycloaddition

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Abstract:

(3*R*,4*R*)-4-(Hydroxymethyl)pyrrolidin-3-ol (1), which is a useful intermediate for the synthesis of various bioactive molecules, has been synthesized in 51% overall yield by 1,3-dipolar cycloaddition reaction from the dipolarophile, (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam (5), and the achiral ylide precursor, *N*-(benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine (6), without using chromatography and the subsequent reduction with LAH and catalytic hydrogenation. The diastereomers 7 and 8 were separated by crystallization, and efficient procedures were developed for the subsequent reactions to afford 1.

Introduction

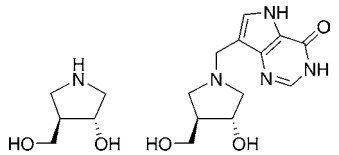
Racemic and nonracemic 4-(hydroxymethyl)pyrrolidin-3-ols have been prepared and found to have an inhibitory effect on certain enzymes[1−3]and on glial GABA uptake.[4] These pyrrolidines have also been used as building blocks for the synthesis of some compounds having antibacterial activity[5,6] and also for some nucleoside analogues. The very first aza C-nucleoside incorporating this compound was reported by Sorensen.[3] Recently, (3*R*,4*R*)-4-(hydroxymethyl)-pyrrolidin-3-ol was used for the synthesis of a highly potent purine nucleoside phosphorylase (PNP) inhibitor.[7,8]

The first synthesis of 3-hydroxy-4-hydroxymethylpyrrolidine (**1**) was reported by Jaeger[9] starting from *N*-benzylglycinate and ethyl acrylate and was obtained as a mixture of *cis*/*trans* isomers. The *trans*-racemic compound was prepared by Makino,[10] starting from fumaric acid methyl ester.

The first synthesis of the pure enantiomer (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol was reported by Filichev[11,12] from glucose and xylose in very low yields, requiring several steps, which is not practical for synthesis of kilogram quantities of **1**.

Karlsson and Hogberg[13] reported the preparation of this compound via asymmetric 1,3-dipolar cycloaddition using camphor sultam as a chiral auxiliary. In this synthesis, the chiral ylide used was generated from phenethylamine and the intermediates obtained were oils requiring flash chromatography for the separation of isomers.

These reported methods are considered unsuitable for various reasons. We needed kilogram quantities of this starting material to synthesize one of our lead PNP inhibitors, BCX-4208. Therefore a practical synthesis was needed for **1** using a suitable procedure. Reinvestigation of the 1,3-dipolar cycloaddition using the achiral ylide prepared from benzylamine instead of phenethylamine provides a crystalline intermediate. On the basis of this methodology, we now report the practical synthesis of the single enantiomer of (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**1**) as a starting material for BCX-4208 (**2**) which is currently in phase-I clinical trials.



1 **2** (BCX-4208)

Results and Discussion

The synthesis reported by Karlsson and Hogberg[13] using (*S*)-*N*-(1-phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine as the precursor for chiral azomethine ylide and (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam as the dipolarophile for 1,3-dipolar cycloaddition gave a mixture of diastereomers in a 83:17 ratio with the desired diastereomer predominant. These diastereomers were separated by flash chromatography on silica gel and were found to be semi-crystalline and oily in nature.

Since it has been reported that the use of chiral ylides on acyclic alkenoic substrates has a small effect on diastereoselectivity,[15] the use of achiral benzylamine instead of chiral

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phenethylamine was adopted, which also aided in reducing hydrogenation time in the last step. We attempted the cycloaddition of (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam with *N*-(1-benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine in dichloromethane. The diastereoselectivity was found to be 82:18, comparable to that obtained using chiral ylide. Initially the diastereomers were separated by flash chromatography, with the desired isomer a crystalline solid and the undesired isomer an oil. Therefore, crystallization of the desired isomer from the crude reaction mixture was attempted using a mixture of ethyl acetate and hexane. The undesired isomer ratio was ca. 5% after the first crystallization and negligible after the second crystallization with recoveries of >90% of the desired isomer after both crystallizations.

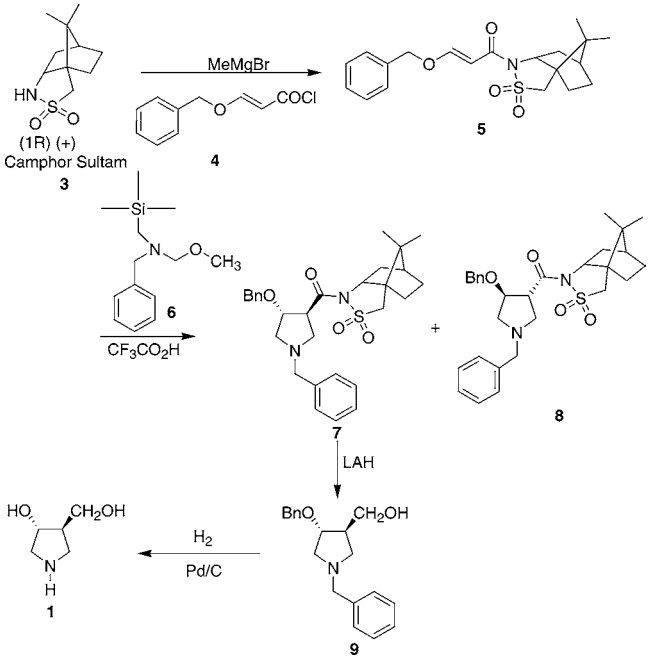
Attention was then focused on the earlier steps of the reaction sequence to further improve the synthesis of the desired pyrrolidine **1**.

First, the synthesis of ylide precursor, *N*-(1-benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine (**6**), was investigated, resulting in a slightly better procedure compared to those in literature reports. *N*-(Trimethylsilylmethyl)-benzylamine[16] was prepared from benzylamine and chloromethyltrimethylsilane and was reacted with formaldehyde and methanol to give the desired ylide precursor **6**.[17,18] Initially, **6** was purified by distillation and used for dipolar cycloaddition. However, on a larger scale, distillation led to decomposition of the product. Experiments using crude **6** revealed that purification was not needed and that **6** could be used as such without purification.

Next, the large-scale synthesis of (1*R*)-(+)-2,10-camphor sultam (**3**) was studied. Although camphor sultam is commercially available, it is very expensive; hence, a kilogram-scale method was developed from (−)-camphor sulfonic acid based upon the literature reports.[19,20] The reaction of camphor sulfonic acid with 1.2 equiv of thionyl chloride in chloroform or dichloromethane gave the acid chloride which was quenched with ammonium hydroxide to give the corresponding amide, which was used without further purification. Dehydration of the amide was accomplished in toluene under acidic conditions (H^+ resin) to yield the corresponding imine, isolated on cooling of the toluene layer after removal of the resin by hot filtration. The imine was pure enough to advance to the hydrogenation with Raney nickel.[19] This route afforded optically pure (1*R*)-(+)-2,10-camphor sultam with the same optical rotation value as reported in the literature and required no crystallization steps.

The preparation of the dipolarophile, (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam (**5**) was accomplished from (1*R*)-(+)-2,10-camphor sultam (**3**) and (*E*)-3-benzyloxypropenoyl chloride (**4**)[13] (Scheme 1).

Scheme 1



The most appropriate conditions for this reaction were identified after several series of experiments were conducted at different temperatures and varying molar ratios of the reactants. The best set of conditions was obtained when the reactions were carried out at temperatures between −35 and −40 °C with 1 equiv of (*E*)-3-benzyloxyacrylic acid chloride, 0.85 equiv of camphor sultam, and 0.9 equiv of methylmagnesium bromide to reduce the formation of side products.[21] The resulting mixture was concentrated and crystallized from ethyl acetate and hexanes to remove impurities,[21] critical for the next step of cycloaddition.

The cycloaddition was carried out by the addition of (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam (**5**) and *N*-(benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-amine (**6**) in the presence of trifluoroacetic acid. After the cycloaddition reaction, the desired isomer **7** was isolated by two crystallizations from the crude reaction mixture. The resultant product **7** was then reduced (LAH) to give (3*R*,4*R*)-(1-benzyl-4-benzyloxy-pyrrolidin-3-yl)methanol (**9**), and subsequent hydrogenation of **9** with 10% Pd/C at 100 psi afforded (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**1**). The use of benzylamine instead of phenethylamine reduced the time required for hydrogenation from 15 to 2 days, which is again important for the large-scale preparations.

Summary

In this contribution, a large-scale synthesis of (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**1**), a useful intermediate for a number of bioactive compounds, is described. This synthesis has permitted the preparation of kilogram quantities

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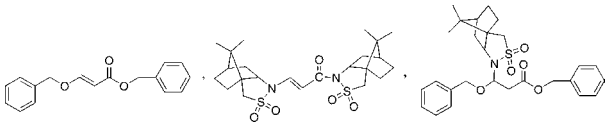
(21) The impurities were identified as the following probable structures:



of the desired product used to prepare the lead PNP inhibitor, BCX-4208, currently in phase I clinical trials.

Experimental Section

General. Unless otherwise stated, all reagents and solvents were purchased from Aldrich and used as received. (−)-Camphor sulfonic acid was purchased from Senn Chemicals, and chloromethyltrimethylsilane was purchased form Gelest, Inc. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to TMS or the respective deuterated solvent peak. Coupling constants (J) are reported in hertz. FT-IR spectra were obtained on a Biorad FTS-3500 GX model using KBr pellets or NaCl cells with a scan range of 4000−500 cm^{-1}. Mass spectra data were acquired on a Waters ZMD with a Waters LC system 2695 either in positive or negative mode. Optical rotations were determined on an Autopol III automatic polarimeter. The elemental analyses (C, H, and N) were performed by Atlantic Microlab in Norcross, Georgia, U.S.A. The TLC solvent systems CMA-80 and CMA-50 refer to chloroform/methanol/concentrated NH_4OH (80:18:2) and chloroform/methanol/concentrated NH_4OH (50:40:10), respectively. The non-UV active compounds were visualized by charring TLC plates sprayed with ammonium molybdate cesium sulfate spray prepared by dissolving concentrated H_2SO_4 (22.4 mL), $CeSO_4$ (45 mg), $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (7 g) in water in a 100-mL volumetric flask. The unsaturated compounds **4** and **5** were visualized by using $KMnO_4$ spray.

(1*R*)-(+)-2,10-Camphor Sultam (3). To a solution of (−)-camphor sulfonic acid (1.45 kg, 6.25 mol) in chloroform (7 L) under reflux conditions was added thionyl chloride (0.896 kg, 7.5 mol) over a period of 1 h. The reaction mixture was refluxed for 16 h and then cooled to 4 °C using an ice bath. This cooled reaction mixture was added slowly to concentrated NH_4OH (15 L), maintaining temperature below 15 °C during the addition. After addition, the mixture was stirred for 4 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with chloroform (2 × 2 L). The combined organic extracts were washed with brine (4 L) and dried over $MgSO_4$. After filtration, the filtrate was concentrated under vacuum and dried to give 1.2 kg (83%) of camphor sulfonamide. In one experiment at 145-g scale of camphor sulfonic acid, the use of dichloromethane instead of chloroform for the reaction and extraction gave comparable yields.

To a suspension of the camphor sulfonamide (1.2 kg, 5.2 mol) in toluene (15 L) was added Amberlyst H^+ resin (150 g), and the mixture was heated at reflux for 4 h with the water formed removed azeotropically using a Dean−Stark water separator. The reaction mixture was filtered hot to remove the resin. On cooling, the filtrate gave a white solid which was collected by filtration to give 1.02 kg (92%) of the desired imine.

To the above imine (100 g, 0.47 mol) in ethanol (0.75 L) was added Raney nickel (100 g), and the mixture was hydrogenated at 40 psi for 2 h. The catalyst was removed by filtration and the filtrate concentrated under vacuum to give the product **3** as a white solid: mp 182−186 °C; ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H), 1.13 (s, 3H), 1.32 (m, 1H), 1.46 (m, 1H), 1.82−2.04 (m, 5H), 3.12 (m, 2H), 3.43 (m, 1H), 4.10 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 20.41, 26.72, 31.78, 35.98, 44.63, 47.38, 50.29, 54.90, 62.75. $[\alpha]^{25}_D$ +32.07° (c = 2.37, chloroform), Aldrich catalog $[\alpha]^{20}_D$ +32° (c = 5, chloroform). The total quantity of product obtained in 10 batches was 0.98 kg (97%) from 1 kg of the imine.

***N*-(Benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-amine (6).** To a solution of chloromethyltrimethylsilane (1.34 kg, 10.96 mol) in acetonitrile (17.0 L) was added benzylamine (2.34 kg, 21.92 mol), and the reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature, and the precipitate of benzylamine hydrochloride was removed by filtration. The filtrate was concentrated under vacuum to about 5 L and then diluted with water (5 L). The reaction mixture was extracted with hexane (2 × 5 L). The organic extracts were combined and washed with brine (5 L) and dried over $MgSO_4$. The filtrate was concentrated under vacuum to give 1.77 kg (83%) of *N*-(trimethylsilylmethyl)benzylamine.

The above amine (1.77 kg, 9.14 mol) was added to a mixture of 37% formaldehyde (0.89 kg, 10.96 mol) and methanol (0.35 kg, 10.96 mol) at 0 °C over a period of 30 min. The reaction mixture was further stirred at 0 °C for 1 h and at 10−15 °C for 3 h. To the reaction mixture was then added anhydrous K_2CO_3 (1 kg), and this mixture stirred for 2 h. The oily layer was decanted onto 100 g of K_2CO_3 and stirred for 15 min and again decanted. The remaining residual material from the K_2CO_3 was recovered by washing all the solid K_2CO_3 with ether. Ether washings were mixed with the decanted oily product and concentrated on the rotary evaporator to give 2.10 kg (82%) of the desired product **6**, deemed pure enough to be used in the next step.

(*E*)-3-Benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam (5). To a solution of (*E*)-3-benzyloxyacrylic acid[14] (1.74 kg, 9.88 mol) and dichloromethane (20 L) was added thionyl chloride (1.75 kg, 14.7 mol) over a period of 30 min. The reaction mixture was heated at reflux and the SO_2 and HCl generated were scrubbed through a solution of aqueous NaOH. After 4 h (reaction progress was monitored by ^{1}H NMR analysis), the solvent was removed under vacuum and the residual thionyl chloride was removed under vacuum overnight to give 2.00 kg (104%) of the desired acid chloride **4**.

To a solution of camphor sultam **3** (1.72 kg, 7.98 mol) in THF (16 L) at −40 °C was added methylmagnesium bromide (2.79 L, 8.38 mol; 3M solution in ether) dropwise at a rate maintaining the internal temperature between −30 °C and −40 °C. The reaction mixture was stirred for an additional hour at −40 °C. To the anion at −40 °C was added slowly, acid chloride **4** (1.92 kg, 96% purity based upon the use of acid, 9.4 mol) in THF (8 L) maintaining the internal temperature below −25 °C. The reaction mixture was further stirred between −30 °C and −40 °C for 1 h and allowed to warm to +10 °C over a period of 5−6 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (16 L). The aqueous layer was separated and extracted twice with ethyl acetate (10 L). The combined organic layers were

washed with saturated aqueous sodium carbonate (20 L) and brine (20 L). The organic layer was filtered through a pad of anhydrous $MgSO_4$ and concentrated under vacuum to dryness to furnish 3.12 kg of the crude product **5**.

The crude product was taken up in ethyl acetate (8.3 L) and heated to 60 °C to dissolve the crude residue. The homogeneous solution was diluted slowly with hexanes (30 L) while maintaining the solution at reflux. The reaction mixture was kept in a cold room for 16 h at 4 °C. The crystalline material that separated was collected by filtration and washed with hexanes to give 1.906 kg (60%) of the desired product **5**. The filtrate also contained the product, but no attempts were made to recover this material from the filtrate. ^{1}H NMR (DMSO-d_6): δ 0.97 (s, 3H), 1.17 (s, 3H), 1.40 (m, 2H), 1.89 (m, 3H), 2.10 (m, 2H), 3.47 (d, J = 6.0 Hz, 2H), 3.92 (dd, J = 5.0 and 7.5 Hz, 1H), 4.95 (s, 2H), 6.05 (d, J = 12.0 Hz, 1H), 7.37 (m, 5H), 7.78 (d, J = 12.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 19.92, 20.78, 26.56, 32.78, 38.55, 44.68, 47.81, 48.31, 53.08, 65.07, 73.25, 97.64, 99.61, 127.98, 128.64, 128.71, 134.92, 163.04, 164.77; IR (KBr): 2964, 2885, 1673, 1319, 1132 cm^{-1}; MS (ES$^+$): 376.34 (M + H)$^+$. $[\alpha]^{25}_D$ +71.15 (c = 0.52, chloroform); Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73; S, 8.54. Found: C, 63.68; H, 6.78; N, 3.87; S, 8.66.

***N*-[[3*S*,4*R*)-4-Benzyloxy-1-(benzyl)pyrrolidin-3-yl]carbonyl]-(2′*S*)-bornane-10,2-sultam (7).** To a solution of **5** (1.83 kg, 4.88 mol) in dichloromethane (29 L) and trifluoroacetic acid (42 mL) was added **6** (2.32 kg, 9.76 mol) over a period of 30 min at room temperature. The reaction mixture was stirred for 15 min (reaction monitored for disappearance of starting materiel by NMR analysis of an aliquot). The reaction mixture was washed with 10% aqueous Na_2CO_3 (20 L) and brine (16 L). The reaction mixture was filtered through a pad of $MgSO_4$, and the filtrate was concentrated under vacuum. To the oily residue was added hexanes (10 L), and the mixture was stirred at room temperature overnight. The resulting solids were collected by filtration, washed with hexanes (4 L), and then air-dried for 3 h to furnish 2.26 kg product (NMR analysis shows the desired isomer comprises 91% of the mixture). Ethyl acetate (4.5 L) was added, and the mixture was heated at reflux to dissolve the product. Hexanes were added while maintaining reflux (13.5 L, added at 1-L increment each). The mixture was then allowed to cool to room temperature with stirring for 16 h. The resulting solid obtained was collected by filtration and washed with 10% ethyl acetate in hexanes (5 L), affording 1.67 kg of desired isomer as a white solid (NMR analysis showed a trace of the minor isomer). The solid was again subjected to recrystallization from ethyl acetate and hexanes as described above; the purified product was collected by filtration, washed with 10% ethyl acetate in hexanes, and dried to furnish 1.46 kg (57.5%) of the desired isomer **7** as a white solid, mp 108−109 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H), 1.02 (s, 3H), 1.37 (m, 2H), 1.88 (m, 3H), 2.04 (m, 2H), 2.57 (dd, J = 9.5 and 5.6 Hz, 1H), 2.69 (dd, J = 9.7 and 4.0 Hz, 1H), 2.92 (dd, J = 9.7 and 6.5 Hz, 1H), 3.20 (t, J = 9.0 Hz, 1H), 3.46 (m, 2H), 3.52 (m, 1H), 3.73 (m, 2H), 3.91 (t, J = 6.0 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.64 (m, 1H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 14.07, 19.72, 20.57, 20.92, 26.33, 32.61, 38.19, 44.04, 47.62, 48.29, 51.09, 52.89, 57.73, 59.28, 59.76, 60.26, 64.99, 71.25, 79.07, 99.45, 126.82, 127.40, 127.76, 128.07, 128.16, 128.53, 137.91, 138.32, 172.10; IR (KBr): 2776, 1698, 1311, 1215 cm^{-1}; MS (ES$^+$): 509.36 (M + H)$^+$. $[\alpha]^{25}_D$ +86.9 (c = 0.86, chloroform). Anal. Calcd for: $C_{29}H_{36}N_2O_4S$: C, 68.47; H, 7.13; N, 5.51; S, 6.30. Found: C, 68.58; H, 7.25; N, 5.51; S, 6.22.

For the minor isomer **8**, ^{1}H NMR ($CDCl_3$): δ 0.79 (s, 3H), 1.01 (s, 3H), 1.17 (m, 2H), 1.70 (m, 3H), 1.87 (m, 2H), 2.40 (dd, J = 9.5 and 7.4 Hz, 1H), 2.57 (dd, J = 10.0 and 6.2 Hz, 1H), 2.69 (dd, J = 10.0 and 3.2 Hz, 1H), 3.10 (t, J = 9.0 Hz, 1H), 3.25 (d, J = 13.9 Hz, 1H), 3.34 (d, J = 5.3 Hz, 1H), 3.39 (d, J = 4.5 Hz, 1H), 3.52 (d, J = 13.0 Hz, 1H), 3.62 (m, 1H), 3.70 (t, J = 6.2 Hz, 1H), 4.17 (m, 2H), 4.38 (d, J = 11.5 Hz, 1H), 7.10 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 14.61, 20.25, 21.37, 26.80, 33.33, 39.02, 45.16, 48.17, 48.75, 51.68, 53.58, 58.05, 60.15, 60.28, 60.79, 65.73, 71.62, 83.40, 127.37, 128.01, 128.19, 128.53, 128.63, 128.73, 129.21, 138.26, 138.84, 173.88; MS (ES$^+$): 509.36 (M + H)$^+$. $[\alpha]^{25}_D$ +29.6 (c = 1, ethanol).

(3*R*,4*R*)-(1-Benzyl-4-benzyloxypyrrolidin-3-yl)methanol (9). To a stirred mixture of lithium aluminum hydride (344 g, 8.6 mol) in THF (8.6 L) under a nitrogen atmosphere was added dropwise compound **7** (1.46 kg, 2.87 mol) in THF (3.5 L) at 0 °C over a period of 2 h. The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature over a period of 2.5 h (TLC analysis showed complete reduction). The reaction mixture was cooled to 0 °C and quenched by careful addition of water (750 mL) and diluted with ethyl acetate (15 L). The solid cake was filtered through Celite and the cake washed with ethyl acetate (4 × 2.5 L). The filtrate was extracted with 2 N HCl (6 × 3 L). The organic layer was discarded, the aqueous layer was cooled to 0 °C, and the pH was adjusted to 13 using solid NaOH (3.64 kg). The basified aqueous layer was extracted with ethyl acetate (3 × 8 L). The organic layers were combined, washed with brine (4 L), filtered through a pad of $MgSO_4$, and the filtrate was concentrated under vacuum to dryness giving 756 g of the desired product **9** (89%) as a colorless oil that solidified on standing, mp 62−64 °C. ^{1}H NMR ($CDCl_3$): δ 2.31 (m, 1H), 2.42 (dd, J = 4.5 and 10.0 Hz, 1H), 2.62 (dd, J = 9.2 and 3.0 Hz, 1H), 2.74 (dd, J = 9.0 and 7.0 Hz, 1H), 3.11 (dd, J = 9.8 and 6.5 Hz, 1H), 3.45 (bs, 1H), 3.61 (m, 3H), 3.67 (dd, J = 10.0 and 4.5 Hz, 1H), 4.03 (m, 1H), 4.46 (s, 2H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 26.44, 46.97, 47.22, 57.26, 60.90, 61.25, 66.65, 72.17, 74.42, 82.10, 128.04, 128.50, 128.54, 129.01, 129.21, 129.25, 129.55, 139.03, 139.09; IR (KBr): 3224, 3030, 1456, 1351, 1143, 1094 cm^{-1}; MS (ES$^+$): 298.46 (M + H)$^+$. $[\alpha]^{25}_D$ +16.7 (c = 0.52, chloroform). Anal. Calcd for: $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71; Found: C, 76.84; H, 7.95; N, 4.76.

(3*R*,4*R*)-4-(Hydroxymethyl)pyrrolidin-3-ol Hydrochloride (1). To a solution of **9** (70 g, 0.235 mol) in ethanol (700 mL) was added a 4 M solution of HCl in dioxane (59

mL, 0.235 mol) and palladium on carbon (10%, 50 g). The resulting slurry was hydrogenated at 100 psi for 2 days. The catalyst was removed by filtration through Celite and concentrated under vacuum and dried to furnish 38 g (100%) of **1**, homogeneous by TLC analysis (75% CMA-50 in CMA-80). This compound was pure enough for the synthesis of the clinical candidate, BCX-4208. ^{1}H NMR (DMSO-d_6): δ 2.21 (m, 1H), 2.96 (dd, J = 5.0 and 12.0 Hz, 1H), 3.19 (dd, J = 12.0 and 5.0 Hz, 1H), 3.29 (dd, J = 7.7 and 3.8 Hz, 1H), 3.38 (m, 3H), 4.15 (m, 1H), 4.94 (t, J = 5.0 Hz, 1H), 5.44 (d, J = 3.8 Hz, 1H), 9.15 (bs, 2H); ^{1}H NMR (D_2O): δ 4.44−4.40 (m, 1H), 3.67−3.57 (m, 3H), 3.43 (dd, J = 5.1 and 12.6 Hz, 1H), 3.27 (dd, J = 12.6 and 2.5 Hz, 1H), 3.16 (dd, J = 5.7 and 12.3 Hz, 1H), 2.53−2.43 (m, 1H); ^{13}C NMR (D_2O): 46.54, 47.86, 52.07, 60.83, 71.82; IR (KBr) 3835, 2955, 1616, 1396, 1050 cm^{-1}; MS (ES$^+$): 118.71 (100%; M^{+1}). ^{1}H NMR and ^{13}C NMR data are consistent with the literature reports.[13] An analytical sample was prepared by purifying 0.5 g on a silica gel column (10 g), eluting with CMA-80/CMA-50 to furnish product as an oil. The product obtained was dissolved in methanol (5 mL), and 1 mL concentrated HCl was added. This was stirred at room temperature for 5 min and concentrated under vacuum to dryness to furnish desired product **1** as hydrochloride salt. Anal. Calcd for $C_5H_{11}NO_2$·HCl·0.5 H_2O: C, 36.92; H, 8.06; N, 8.68. Found: C, 37.32; H, 8.00; N, 8.52. $[\alpha]^{25}_D$ +17.53 (c = 1.175, methanol).

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