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A short synthesis of the 2-bromo-*N*,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-6-amine building block

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ABSTRACT: A concise synthesis of pharmaceutically useful (*R*)-*tert*-butyl(2-bromo-9-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-6-yl)(methyl)carbamate building block **11** is described. The racemic intermediate **17** was prepared in a single step from 2-bromo-6-(1-methylhydrazinyl)pyridine sulfate salt **14** and *N*,3,3-trimethyl-1,5-dioxaspiro[5.5]undecan-9-amine hydrochloride salt **16**. Chiral separation of racemic intermediate **17** by diasteromeric salt recrystallization afforded the diasteromeric salt **18** in 37 % yield, which was Boc-protected to afford building block **11**. Thus, the process for the synthesis and chiral separation by diasteromeric salt crystallization allowed the synthesis of chiral building block **11** in kilogram quantities with 18 % overall yield.

KEYWORDS: *neurodegenerative diseases, Fischer indole synthesis, enantiomer separation, diasteromeric salts*

1. INTRODUCTION

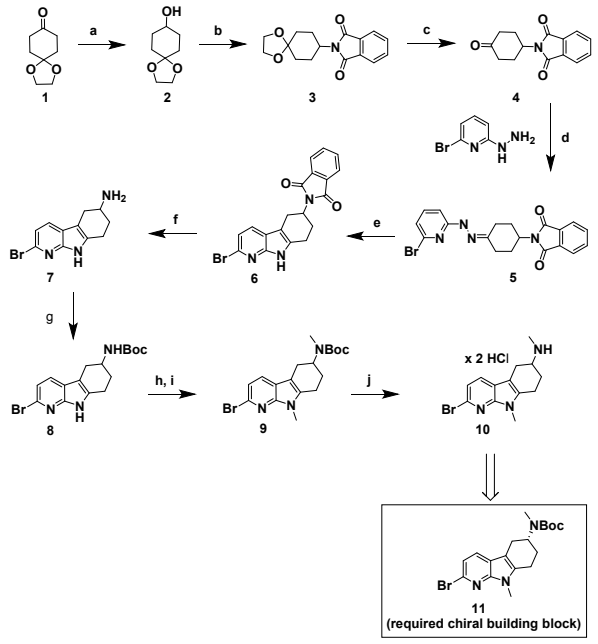
A drug discovery programs at AC Immune required the multi-kilo gram synthesis of enantiopure heterocyclic building block **11** to prepare an advanced lead compound for toxicology and *in vivo* proof-of-concept studies. The initial synthesis[1] shown in Scheme 1, gave racemic **10** in ~4.6 % overall yield after nine linear steps starting from compound **1**. One lead compound[1] containing racemic **10** utilized a chiral column for enantiomer separation, rendering this process not suitable for the preparation of the lead compound[1] on a multi-kilogram scale as: (1) several steps required chromatographic purification; (2) the non-acid-catalyzed thermal Fischer-indole cyclization step required high temperature microwave conditions; (3) the deprotection of the phthalimide moiety with hydrazine hydrate is hazardous, and not an environmentally friendly step; (4) *N*-bis-methylation required the use of sodium hydride and methyl iodide, both hazardous reagents, and not always easy to handle on large scale; 5) enantiomerically pure lead compound[1] required separation by chiral HPLC.

Thus, it was necessary to develop a new scalable and efficient synthesis of building block **11** (Scheme 1), because the respective (*R*)-enantiomer of the lead compound[1] showed the higher physiological activity. Herein, we describe a concise synthesis of racemic **17** as free amine that proceeds in one step with 69 % yield from commercially available building block **16** with compound **14**, enantiomer separation of racemic **17** via diastereomeric salts, followed by Boc-protection to yield **18** in 18 % overall yield and >99 % ee chiral purity.

2. RESULTS AND DISCUSSION

Original synthetic route: The initial synthesis of racemic **10** involved nine linear steps (Scheme 1), and full experimental details are provided in the Supporting Information. In brief, the first step was the reduction of commercially available 1,4-cyclohexadione monoethylene acetal with sodium borohydride in methanol as described[2] to afford alcohol **2** in 94 % yield. The synthesis of compound **3** was already reported as a two-step process, involving the activation of the alcohol by tosylation followed by nucleophilic displacement with phthalimide.[3] However we prepared compound **3** from **2** in one step using Mitsunobu reaction[4] condition with phthalimide to afford **3** after chromatography on silica gel in 50 % yield.

Scheme 1: Initial synthesis of racemic building block **10**[a]



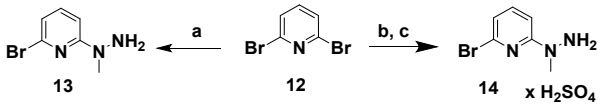
[a]Reagents and conditions: (a) Sodium borohydride, methanol, room temperature, 2 h, 94 % yield; (b) Diethyl azodicarboxylate, triphenylphosphine, tetrahydrofurane, 0-5 °C to room temperature, 16 h, 50 % yield; (c) Tetrahydrofurane, water, p-toluene sulfonic acid, 115 °C, 2 h, quantitative yield; (d) Ethanol, room temperature, 1 h, quantitative yield; (e) Diethylene glycol, microwave, 250 °C, 35 minutes, 49 % yield; (f) 50-60 % Hydrazine hydrate, ethanol, room temperature, 16 h, 70 % yield; (g) Di-tert-butyldicarbonate, triethylamine, tetrahydrofurane, room temperature, 16 h, 33 % yield; (h) Sodium hydride, *N*, *N*'-dimethylacetamide, 0-5 °C, 2 h; (i) Methyl iodide, 0-5 °C to room temperature, 16 h, 85 % yield; (j) 2 M Hydrochloric acid/diethyl

ether, dichloromethane, room temperature, 16 h, quantitative yield.

Cleavage of the acetal moiety of compound **3** was achieved according to a literature procedure[5] by heating **3** in a tetrahydrofurane/water mixture in the presence of a catalytic amount of p-toluene sulfonic acid, to afford the keto-compound **4** in quantitative yield. The synthesis of keto-compound **4** from the corresponding alcohol by oxidation was already described.[6] The hydrazone derivative **5** was prepared according to a literature procedure[7] via condensation reaction of keto-compound **4** and 2-bromo-6-hydrazineylpyridine, prepared as described[8], in ethanol and isolated in quantitative yield. The resulting hydrazone derivative **5** was cyclized under non-acid-catalyzed thermal Fischer-indole synthesis according to a literature procedure[7] in diethylene glycol to afford tricycle **6** in 49 % yield, after treatment of the crude reaction product with methanol. The cleavage of the phthalimide protecting group in **6** according to a literature procedure[9] with hydrazine-hydrate in ethanol afforded amine **7** in 70 % yield. Protection of the aliphatic amine group in **7** according to a literature procedure[9] with di-tert-butyl dicarbonate afforded Boc-protected **8** in 33 % yield, after treatment of the crude reaction mixture with diethyl ether and collection of the precipitate. Bis-methylation of compound **8** according to a literature procedure[10] using sodium hydride and methyl iodide in *N*, *N*'-dimethylacetamide afforded racemic compound **9** in 85 % yield after chromatography on silica gel. Cleavage of the Boc-protection group in **9** with acid afforded racemic **10** as hydrochloric acid salt in quantitative yield.

In order to reduce the number of steps, improve the synthetic yields, and to avoid involvement of hazardous material such as methyl iodide and hydrazine hydrate (Scheme 1), we first envisioned that the bis-methylation of building block **8** could be avoided by using 2-bromo-6-(1-methylhydrazinyl)pyridine **13** or its corresponding sulfate salt **14** (Scheme 2) as one of the starting materials for the Fischer-indole synthesis together with an appropriate keto-derivative. To this end building block **13** was prepared by nucleophilic substitution reaction (Scheme 2) of 2, 6-dibromopyridine **12** with *N*-methyl hydrazine as described[11], except ethanol was used as co-solvent, to afford the required building block **13** as free amine in 89 % yield after chromatography on silica gel (Supporting Information).

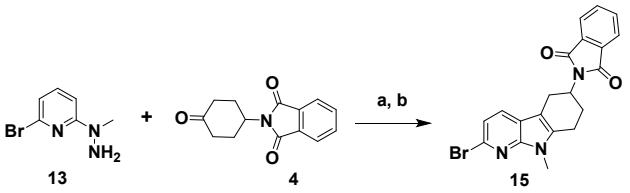
Scheme 2: Synthesis of 2-bromo-6-(1-methylhydrazinyl)pyridine building blocks **13** and **14**[a]



[a]Reagents and conditions: (a) 85 % *N*-methyl hydrazine, ethanol, reflux, 48 h, 89 % yield; (b) 85 % *N*-methyl hydrazine, 1,4-dioxane, 85-90 °C, 8 h; (c) Dichloromethane, sulfuric acid, 0-5 °C to room temperature, 2-3 h, 63-68 % yield.

The 2-bromo-6-hydrazineylpyridine free amine building block **13** was obtained as reddish, light sensitive oil. The quality of **13** had a significant influence on the purity of the subsequent Fischer-indole products. Thus, compound **13** was isolated as a sulfate salt **14** to improve its stability. The synthesis of sulfate salt **14** was accomplished up to 8 kg scale in a single batch by treating 2,6-dibromo pyridine **12** with *N*-methyl hydrazine in 1,4-dioxane under reflux conditions, followed by treatment with sulfuric acid to obtain the sulfate salt **14** in 63-68 % yield as off-white solid (Scheme 2). Though the non-acid-catalyzed thermal Fischer-indole synthesis of **13** with keto intermediate **4** produced compound **15** in 42 % yield (Scheme 3, see Supporting Information for details), the overall process would not be improved as a methylation reaction would still be required after cleavage of the phthalimide moiety.

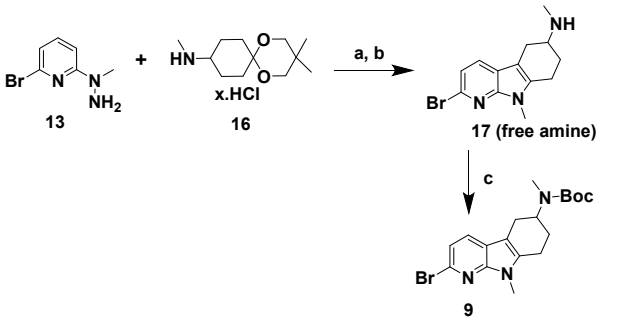
Scheme 3: Synthesis of building block **15**[a]



[a]Reagents and conditions: (a) Ethanol, room temperature, 1 h, quantitative yield; (b) Diethylene glycol, microwave, 250 °C. 45 minutes, 42 % yield.

Thus, we employed commercially available ketal derivative **16** as reaction partner for the Fischer-indole synthesis as it already contained the *N*-methyl moiety. As derivative **16** also contained a ketal-protecting group, we employed acidic reaction conditions to allow *in situ* cleavage of the ketal-protecting group during the acid-catalyzed Fischer-indole synthesis.[12] When a mixture of **13** and **16** in 1,4-dioxane in the presence of concentrated sulfuric acid was heated under reflux, the desired racemic product **17** was isolated with 75 % yield (Scheme 4, see Supporting Information for details).

Scheme 4: Improved synthesis of racemic building blocks **9** and **17**[a]



[a]Reagents and conditions: (a) Sulfuric acid, 1,4-dioxane, 140 °C, 4 h; (b) Sodium hydroxide, dichloromethane, room temperature, 75 % yield; (c) Di-tert-butyldicarbonate, triethylamine, tetrahydrofurane, room temperature, 16 h, 47 % yield.

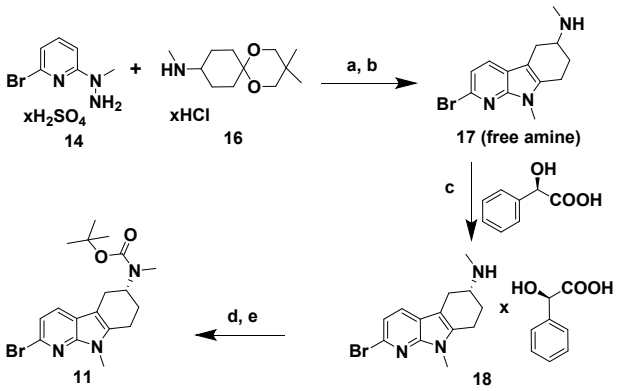
Compound **17** was then Boc-protected[9] to yield **9** after chromatography on silica gel, which matched compound **9** obtained via the initial synthetic route. Thus, the successful preparation of **9** in a two steps from **13** and **16** not only improved the yield of the Fischer-indole synthesis, but also eliminated seven synthetic steps from the initial synthesis, including the use of microwave conditions, and usage of hazardous reagents, like sodium borohydride, sodium hydride, methyl iodide, hydrazine hydrate, and several purification steps for each intermediate. Though the initial trial reactions of the Fischer-indole synthesis on small scale gave the required product **17**, the reaction mixture was not homogeneous, which proved difficult for the workup of the reaction mixture on larger scale.

Therefore, the process was further optimized in a step wise manner. Thus, several solvents as *N*, *N*'-dimethylacetamide, *N*-methyl-pyrrolidone and sulfolane were screened to identify a more suitable solvent with respect to reaction time and workup procedure. *N*, *N*'-dimethylacetamide and *N*-methyl-pyrrolidone were identified to be the best choices regarding conversion time, yield and costs. While using *N*-methyl-pyrrolidone as solvent, the product recovery during the workup was less attractive compared

to *N*, *N*'-dimethylacetamide as solvent. To avoid the strong oxidizing sulfuric acid, several alternatives were also screened such as acetic acid, methane sulfonic acid, and p-toluene sulfonic acid. Methane sulfonic acid gave 80 % conversion, but a lot of unspecific impurities were generated. It was also tried to reduce the excess of sulfuric acid, i.e. 3 eq., 1.5 eq., 0.3 and 0.05 eq. were screened. However, 3 eq. of sulfuric acid were required for complete and fast conversion to the indole derivative. Thus, we have identified *N*, *N*'-dimethylacetamide as the most suitable solvent, and sulfuric acid as the most suitable acid, to obtain a homogenous reaction mixture, leading to a simplified workup procedure and resulting in consistent yields of the Fisher-indole synthesis product **17**.

The synthesis of racemic building block **17** was then carried out by Fischer-indole synthesis[12] on multi-kilograms scale (Scheme 5) with compounds **14** and **16**, using *N*, *N*'-dimethylacetamide as solvent in the presence of sulfuric acid at 100-110 °C. Though building block **16** is commercially available, it can also be prepared in one step from commercially available 1,4-cyclohexanedione mono-2-(2',2'-dimethyltrimethylene) ketal as described in the literature.[13] In order to separate racemic **17**, diastereomeric salt screening was employed for the separation of the enantiomers, see Supporting Information for details (Table S1). In brief, several chiral acids ((*S*)-(+)-mandelic acid, (+)-camphoric acid, (+)-glutamic acid, (1*S*)-(+)-10-camphorsulfonic acid, D-(−)-quinic acid, (−)-O,O′-di-p-toluoyl-L-tartaric acid, L-(+)-lactic acid, D-(+)-malic acid, L-(+)-tartaric acid, (+)-O,O′-dibenzoyl-D-tartaric acid) and solvents (methanol, ethyl acetate, acetone, tetrahydrofurane, dichloromethane, toluene, ethanol, 2-propanol) were screened and the best chiral resolutions were achieved with (*S*)-(+)-mandelic acid in acetone, tetrahydrofurane, dichloromethane, ethanol, and 2-propanol (Table S1). Ethyl acetate and toluene proved to be poor solvents leading to no enantiomeric enrichment for any of the chiral acids (Table S1). Though methanol gave no precipitate in the initial screening, it was possible from racemic **17** to isolate the late eluting enantiomer of **19** with >97 % ee using (*S*)-(+)-mandelic acid, and the early eluting enantiomer of **18** with >97 % ee using (*R*)-(-)-mandelic acid, see Supporting Information for details. However, the initial enantiomeric purity of >97 % ee could not be reproduced on larger scale as the desired diastereomeric salt **18** was obtained with a yield of 12 % and an enantiomeric excess of 93 % ee by using (*R*)-(-)-mandelic acid in methanol. Employing 40 g of racemic **17** and changing the solvent to ethanol for the crystallization increased the yield to 23 % and the enantiomeric excess to 96 % ee, see Supporting Information for details.

Scheme 5: Optimized synthesis of chiral building block **11**[a]



[a]Reagents and conditions: (a) Sulfuric acid, *N*, *N*'-dimethylacetamide, 100-110 °C, 4 h; (b), Sodium hydroxide, dichloromethane, room temperature, 63 % yield; (c) (*R*)-2-hydroxy-2-phenylacetic acid, *N*, *N*'-dimethylformamide, 80-85 °C, 6 h, 37 % yield; (d) Sodium hydroxide, dichloromethane, room temperature; (e) Di-tert-butyldicarbonate, triethylamine, dichloromethane, room temperature, 2 h, 93 % yield.

Further optimization of the process by using *N*, *N*'-dimethylformamide as solvent allowed the isolation of **18** in kilogram quantities with a yield of 37 % and an enantiomeric excess of >99 % ee. Compound was **18** then Boc-protected[9] to afford chiral building block **11** in >93 % yield (Scheme 5).

3. CONCLUSIONS

We optimized the conditions with the preparation of building block **14** as sulfate salt, then use of commercially available **16,** and *N*, *N*'-dimethylacetamide as the solvent proved to be the best options for the Fischer-Indole synthesis of racemic **17**. Furthermore, we identified (*R*)-mandelic acid as chiral acid which worked best in the presence of *N*, *N*'-dimethylformamide as solvent for diastereomeric salt separation, leading to an optimized process suitable for the synthesis of chiral building block **11** in kilogram quantities in 18 % overall yield (Scheme 5).

4. SUMMARY

We have developed a short and efficient synthesis of chiral building block **11**, which was prepared in 4 steps and 18 % overall yield from **14** and **16**. The significant improvements over the initial synthesis allowed us to manufacture up to 7.1 kilograms of the chiral building block **11**. Building block **11** has been utilized for multiple discovery programs at AC Immune targeting protein aggregates linked to neurodegenerative diseases.

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial sources and used without further purification. Proton (^{1}H) NMR and carbon (^{13}C) NMR spectra were recorded on a Bruker DRX 400 MHz NMR spectrometer in deuterated solvents. Typical spectral parameters: spectral width 10 ppm; Description of signals: s = singlet; brs = broad singlet; d = doublet; t = triplet; q = quartet, m = multiplet; dd =doublet of doublet: dt = doublet of triplet; tt = triplet of triplets; ddd = doublet of double doublet. Mass spectra (MS) were recorded on an Advion CMS spectrometer.

2-Bromo-6-(1-methylhydrazinyl) pyridine sulfate (14). 2, 6–Di-bromo pyridine **12** (50 g; 0.2109 mol; 1eq.) and 1, 4-dioxane (500 mL) were charged into a 2 L round bottom flask equipped with mechanical stirrer, thermo packet and condenser at 25-35 °C. Then 85 % *N*-methyl hydrazine (22.74 g; 0.4935 mol; 2.34 eq.) was added to the reaction mixture at room temperature (~25 °C), and heated under stirring at 85-90 °C for 8 h. Then the reaction mass was cooled to 25 °C, distilled water (500 mL), and dichloromethane (500 mL) were added, and the reaction mixture was stirred for 15 minutes. The organic and aqueous layers were separated; the procedure was repeated for 3 times, and the combined organic layer was washed with distilled water (3 x 500 mL), followed by 10 % brine solution (500 mL). The organic layer was separated, dried with sodium sulfate, and the mixture was filtered. The organic layer was concentrated under reduced pressure at 40-45 °C to afford a thick liquid (note: 1, 4-dioxane should be completely distilled off). The residue was re-dissolved in dicholoromethane (500 mL) and cooled to 0-5 °C. Then sulfuric acid (5 mL, 0.1 w/v) was added to the reaction mass via an addition funnel at 0-5 °C over a period of 10-15 minutes. The mixture was allowed to warm to room temperature and stirred or 2-3 h. The solid material was filtered off, washed with dichloromethane (50 mL), and dried for 1 h. The solid was suspended in acetonitrile (350 mL) and stirred for 1 h at 25 °C. The solid was filtered, washed with acetonitrile (50 mL), and suck dried for 1 h to yield **14** as white to yellow solid (42 g, 68 %). As per the above process, compound **14** was produced on plant scale

using compound **12** as starting material, to afford 16.7 kg (63 %) of compound **14** with 99.66 % HPLC purity.

2-Bromo-*N*,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-6-amine (17). 8.5 kg of **14** was suspended in 45 L of *N*, *N*'-dimethylacetamide at 25-35 °C in a 250 L Glass Lined Reactor under nitrogen atmosphere and 7.06 kg of **16** was added to obtain a heterogeneous mass. The mixture was cooled to 0-5 °C and 9.6 kg of concentrated sulfuric acid was slowly added to yield thick syrup. The temperature during the concentrated sulfuric acid addition should be kept below 10 °C The reaction mixture was heated to 75 °C to become a clear solution. Then the temperature was raised to 105-111 °C and the reaction mixture stirred for 4 h (conversion was checked by IPC by HPLC until not more than 1 % of **14** was present). The resulting brown suspension was cooled to 0-10 °C, and 47 L water and 34 L dichloromethane were added, and the reaction mass was stirred at 0-10 °C for 15 minutes. The reaction mass was transferred to a 250 L Stainless Steel Reactor and the pH of the suspension was adjusted to pH 11-13 by adding a 30 % sodium hydroxide solution, prepared by adding 10.2 kg of sodium hydroxide to 24 L of water, while the temperature of the suspension was kept below 10 °C. The reaction mass temperature was allowed to warm to 25-35 °C and stirred for 30 minutes. The reaction mass was filtered through a Nutsche filter (500 mm diameter), and the solid washed with 21 L of dichloromethane. The combined filtrate was washed with 21 L of water and the organic layer separated. The aqueous layer was extracted with 17 L of dichloromethane and the organic layer separated. The combined organic layers were transferred to a 250 L Stainless Steel Reactor and washed with 47 L of water and the organic layer separated. The organic layer was transferred to a 250 L Stainless Steel Reactor and the solvents were removed by evaporation under vacuum, initially below 45 °C to remove dichloromethane, then the reaction mass was dried at 70 °C in high vacuum to remove traces of *N*, *N*'-dimethylacetamide. The reaction mass was re-suspended in 42.5 L of water, transferred to a 250 L Glass Lined Reactor and cooled to 0-10 °C. Then 8.5 L of concentrated hydrochloric acid was added while the temperature was kept below 10 °C until pH<2. The reaction mass was allowed to warm to 25-35 °C and stirred for 1 h. The precipitated solid was isolated by centrifugation (18'') and washed with 8.5 L of water and 8.5 L of n-hexane. After drying the solid by centrifugation for 1-2 h, the solid was transferred to 250 L Stainless Steel Reactor and re-suspended in (42.5 L) water and (42.5 L) dichloromethane. The reaction mass was cooled to 0-5 °C and the pH was adjusted to pH 12-13 by adding a 30 % sodium hydroxide solution, prepared by adding 4.25 kg of sodium hydroxide to 9.35 L of water while the temperature was kept below 10 °C. After the pH was adjusted, the temperature of the reaction mass was allowed to warm to 25-35 °C. The organic layer was separated and the aqueous layer extracted with 42.5 L of dichloromethane. The combined organic layers were transferred to a 250 L Stainless Steel Reactor and washed with brine, prepared by adding 2.12 kg of sodium chloride to 21.25 L of water. The organic layer separated, transferred to a 250 L Stainless Steel Reactor, and dried over 2.21 kg of sodium sulfate. The reaction mass was filtered through a Nutsche filter (500 mm diameter), the filter washed with 8.5 L of dichloromethane, the combined filtrates transferred to a 250 L Stainless Steel Reactor and concentrated under vacuum below 45 °C. To the residue was then added 4.25 L of n-hexane and the reaction mass was concentrated under vacuum below 45 °C. The obtained solid was re-suspended in 4.25 L of n-hexane and the reaction mass was concentrated under vacuum below 45 °C. The obtained solid was re-suspended in 8.5 L of n-hexane, stirred for 1 h, filtered through a Nutsche filter (500 mm diameter), washed with 4.25 L of n-hexane and then suck-dried for 1 h. The wet product was dried at 50-55 °C for 6 h using a vacuum tray dryer (12'' trays) to afford 5.24 kg of a brown/dark brown colored solid (63 % yield; 97.8 %; HPLC purity). According to this procedure, racemic **17** was produced as free amine in three batches to obtain 34 kg with >97 % HPLC purity. ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H = 7.74 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 3.62 (s, 3H), 3.04–2.60 (m, 5H), 2.36 (s, 4H), 2.08 (dt, J = 11.6, 5.6 Hz, 1H), 1.64 (m, 1H). ^{13}C-NMR (101 MHz, DMSO-d_6): δ = 147.62, 137.28, 132.45, 128.33, 118.74, 118.09, 106.19, 55.38, 34.17, 28.49, 28.04, 27.40, 20.32. ESI-MS *m/z*: 294.3/296.3 $(M+H)^+$.

2-Bromo-*N*, 9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-6-amine (*R*)-2-hydroxy-2-phenylacetate (18). 7.5 kg of **17** was suspended in 22.5 L of *N*, *N*'-dimethylformamide at 25-35 °C in a 100 L Stainless Steel Reactor. The reaction mixture was then heated to 80-85 °C and stirred for 10-15 minutes. At this temperature a solution of 3.88 kg (*R*)-(-)-mandelic acid in 15 L of *N*, *N*'-dimethylformamide was slowly added to the reaction mass. After the addition was completed, the reaction mass was heated at 80-85 °C for 6 h. Then the reaction mass was cooled to 25-35 °C and stirred at this temperature for 1 h. The precipitate was isolated by centrifugation (18''), the solid washed with *N*, *N*'-dimethylformamide and suck dried. Then the wet product was dried at 50-55 °C for 4 h under vacuum to afford the crystalline mandelic acid salt **18.** The mandelic acid salt **18** was re-suspended in 37.5 L of *N*, *N*'-dimethylformamide in a 100 L Stainless Steel Reactor, and then heated at 105-115 °C for 1 h to become a clear solution. The reaction mass was allowed to cool to 85-100 °C and 7.5 g mandelic acid salt **18** crystal seeds were added. Then the reaction mass was allowed to cool to 25-35 °C and was stirred for an additional 1 h at this temperature. The precipitate was isolated by centrifugation (18''), the solid washed with *N*, *N*'-dimethylformamide and spin-dried. Then the wet product was dried at 50-55 °C for 4 h using a vacuum tray dryer (12'' trays) to afford 4.26 kg of the re-crystallized mandelic acid salt **18** (37.4 % yield; 98.22 % HPLC purity; 99.68 % chiral purity). According to this procedure, (*R*)-(-)-mandelic acid salt **18** was produced in two batches to obtain 8.68 kg with >97 % HPLC purity and >99 % ee chiral purity.

(*R*)-*Tert*-butyl(2-bromo-9-methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-6-yl)(methyl)carbamate (11). To a solution of 19 L of dichloromethane in a 100 L Stainless Steel Reactor was added 4.246 kg of **18** at 25-35 °C. The reaction mass was cooled to 20-25 °C and a 2 M sodium hydroxide solution, prepared from 2.72 kg of sodium hydroxide and 34 L of water, was slowly added. After the addition was completed, the reaction mass was stirred at this temperature for 30 minutes. The organic phase was separated and the aqueous layer extracted with 12.7 L of dichloromethane. The combined organic layers were transferred to a 100 L Stainless Steel Reactor, dried over 0.42 kg of sodium sulfate, filtered through a Nutsche filter (500 mm diameter), and the filter washed with 4.2 L of dichloromethane. The combined organic filtrates were transferred to a 100 L Stainless Steel Reactor and 2.166 kg of triethylamine added at 20-25 °C. Then 6.02 kg of di-tert-butyldicarbonate was slowly added at 20-25 °C and the reaction mass was stirred at the same temperature for 1 h (conversion was checked by IPC by HPLC until not more than 1 % of **18** was present). Then 42.5 L water was added to the reaction mass at 20-25 °C and the organic layer was separated. The organic layer was transferred to a 100 L Stainless Steel Reactor, washed with 42.5 L of water, the organic layer separated and transferred to a 100 L Stainless Steel Reactor, and dried over dried over 0.42 kg of sodium sulfate. The sodium sulfate was removed by filtration through a Nutsche filter (500 mm diameter), and the filter washed 4.2 L of dichloromethane. The combined organic filtrate was transferred to a 100 L Stainless Steel Reactor and the solvent distilled under vacuum below 45 °C. The residue was treated with 2.12 L of n-hexane and the solvents distilled under vacuum below 45 °C. The reaction mass was then treated

with 6.5 L of n-hexane and the mixture stirred at 25-35 °C for 15-30 minutes. The precipitate was collected by filtration through a Nutsche filter (500 mm diameter), the solid washed with 2.12 L of n-hexane and suck-dried. Then the wet product was dried at 50-55 °C for 6 h using a vacuum tray dryer (12'' trays) to afford 3.504 kg of compound **11** (93.4 % yield; 99.14 % HPLC purity). According to this procedure, title compound **11** was produced in two batches to obtain 7.098 kg with >98 % HPLC purity. ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H = 7.79 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 4.24 (s, 1H), 3.63 (s, 3H), 3.08–2.66 (m, 7H), 2.15–1.82 (m, 2H), 1.42 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.65, 147.98, 135.32, 133.29, 127.48, 118.40, 118.31, 106.40, 79.62, 28.70, 28.54, 27.98, 27.02, 23.93, 22.00. ESI-MS *m/z*: 394.4/396.4 $(M+H)^+$.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data of compounds **2-10** (Scheme S1). Experimental procedures and analytical data of compounds **13** and **14** (early synthesis) (Scheme S2). Experimental procedure and analytical data of compound **15** (Scheme S3). Experimental procedures and analytical data of compounds **9** and **17** prepared with the improved synthesis (Scheme S4). Experimental procedures and test runs to identify suitable chiral acids and solvents for the diastereomeric salt separation of racemic 2-bromo-*N*,9-dimethyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-6-amine **17**.

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Conflict of Interest Disclosure

Nampally Sreenivasachary is an employee of AC Immune and holds shares of AC Immune.
Heiko Kroth is an employee of AC Immune and holds shares of AC Immune.
Pascal Benderitter holds shares of AC Immune.
Wolfgang Barth has no conflict of interest.
Andrea Pfeifer is an employee of AC Immune and holds shares of AC Immune.
Andreas Muhs was an employee of AC Immune and holds shares of AC Immune.

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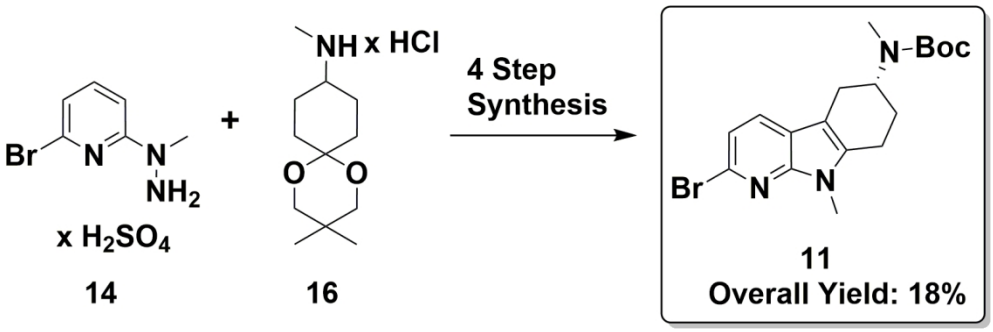

Table of Contents Graphic

140x47mm (300 x 300 DPI)