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An efficient asymmetric synthesis of (3*S*)-3-amino-1-(4-cyanophenyl)-2-oxopyrrolidine hydrochloride salt

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Abstract

Reaction of 4-aminobenzonitrile with 2-bromo-4-chlorobutyryl bromide in the presence of sodium phosphate followed by treatment of the coupled product with sodium hydroxide followed by ammonium hydroxide in acetonitrile yielded the title compound as the racemic (*R*)-(−)-mandelic acid salt in an overall yield of 64%. The title compound was then obtained with an ee >96% and in 78% yield after a dynamic resolution of the racemic salt in IPA using a catalytic amount of salicylaldehyde followed by salt exchange.

1. Introduction

We wish to report here recent work toward an efficient, scalable and cost effective synthesis of the (3*S*)-3-amino-1-(4-cyanophenyl)-2-oxopyrrolidine hydrochloride salt **1**, a key intermediate for the preparation of an antiplatelet drug currently in phase III clinical trials. The original synthesis of compound **1** involved the coupling and cyclization of a methionine residue which generated a tremendous amount of dimethylsulfide.[1] The cost associated with the waste handling of this by-product made this process unsuitable for manufacturing and fostered the need to develop an alternative process for the preparation of this compound.

The approach we developed is summarized retrosynthetically in Scheme 1. Using the methodology developed by Furukawa et al.,[2] the lactam ring was produced from the cyclization of the highly functionalized product formed from the coupling of a 2-bromo-4-halobutyryl halide and 4-amino benzonitrile (4-ABN). The bromide was displaced by ammonia to give the racemic form of the title compound. The optically pure compound was then obtained through the dynamic resolution of the amine in the presence of a catalytic amount of an aromatic aldehyde and a chiral acid, following precedent from the literature.[3,4]

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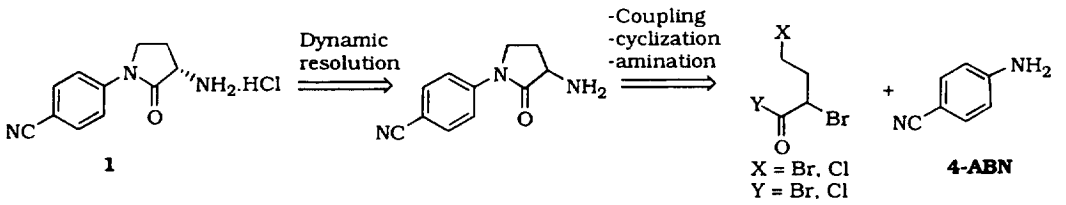
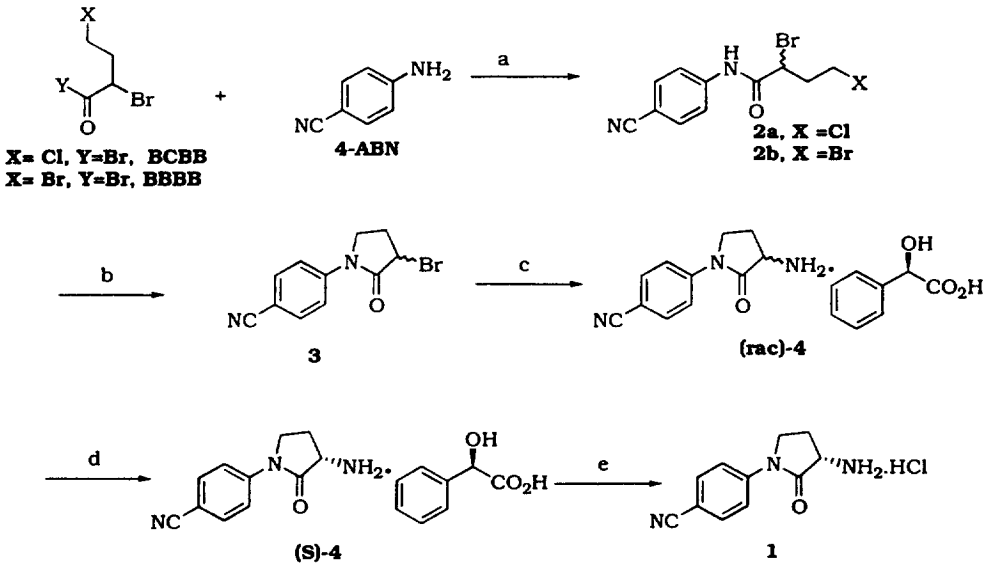


Scheme 1.

2. Results and discussion

With the objective of developing a straightforward synthesis of the racemic amino lactam which would not require the isolation of intermediate products, we studied each of the steps as shown on Scheme 2. The coupling of 2-bromo-4-chlorobutyryl bromide[5] (BCBB) with 4-ABN was successful in THF or ACN, in the presence of propylene or cyclohexene oxide or bases such as Na_2HPO_4, Na_3PO_4, K_2CO_3, Na_2CO_3 or NEt_3. The best conditions, which could be effectively combined with the next two steps of the synthesis, were obtained when Na_3PO_4 (0.55 equiv.) was employed in acetonitrile to give a solution of **2a** and the inorganic salts. Under these reaction conditions, 2,4-dibromobutyryl bromide[6] (BBBB) was also found to be a suitable starting material to obtain the solution of intermediate **2b**.



a) Acetonitrile (ACN), Na_3PO_4 (0.55eq), 5 °C to 30 °C. b) for **2a**: NaOH (50 wt.%, 2.3 eq), filtration. For **2b**: K_2CO_3(2 eq),filtration. c) 1-NH_4OH, 6 h, 40°C, 2-NH_4OH distillation, 3-NaOH 50 wt.% (1 eq), 4-azeotropic distillation, filtration, 5- (R)-Mandelic acid (0.8 eq). d) (R)-Mandelic acid(7.75 wt.%), H_2O (3.25 wt.%), salicylaldehyde (0.05eq, IPA, 80 °C. e) EA, conc HCl(1.5 eq), 50 °C, 1h.

Scheme 2.

The cyclization of **2a** and **2b** was then examined. For the cyclization of **2a**, it was found that the addition of a 50 wt% aqueous solution of sodium hydroxide (2.3 equiv.) to the reaction mixture solution led cleanly and rapidly to the bromolactam **3**. Cyclization of **2b** was then found to be best achieved by the addition of K_2CO_3 (2 equiv.) to the reaction mixture. Compound **3** was obtained as a solution in acetonitrile after filtration of the inorganic salts from either cyclization conditions.

It was then found that the displacement of bromide could be achieved when **3** was subjected to a large excess of ammonium hydroxide. Thus, when the solution of compound **3** in acetonitrile was mixed

with 17 equiv. of concentrated ammonium hydroxide, heated to 40°C and stirred for 6 h, the reaction proceeded smoothly. The work-up of this reaction was discovered to be critical for the subsequent isolation of *rac*-**4** and was achieved in the following way: distillation of acetonitrile and ammonium hydroxide, neutralization of the intermediate hydrobromide salt, azeotropic distillation of the water with acetonitrile or toluene, and filtration of the inorganic salts. Addition of (*R*)-mandelic acid (MA) to the final solution led to the precipitation of the salt *rac*-**4**, which was isolated by filtration. The overall yield for the three-step/one-pot procedure ranged from 60 to 70%.

With an easy method to prepare the racemic intermediate *rac*-**4** in hand, we set out to develop a dynamic resolution protocol to provide optically pure (*S*)-**4**. Conditions for the dynamic resolution were developed using the preformed salt *rac*-**4** and either salicylaldehyde or 3,5-dichlorosalicylaldehyde as the aromatic aldehyde in alcohol solvents. Solvents such as methanol, ethanol or isopropanol (IPA) at their respective reflux temperatures were found to be suitable to achieve this type of transformation. The best results were found with IPA as the solvent, which gave the shortest reaction time and highest ee. Salicylaldehyde was used preferentially over 3,5-dichlorosalicylaldehyde as it was easier to handle and more affordable. We found that the critical parameters in this reaction were the amount of MA and water, as shown in Fig. 1. The combined effect of these two key factors resulted in a shorter reaction time and higher optical purity of the isolated salt (*S*)-**4**. The dynamic resolution was found to be totally ineffective if a small amount of water was not included in the reaction. A proposed catalytic cycle depicting the mechanism of the dynamic resolution has been summarized as shown in Fig. 2. The main driving forces of the resolution are the accumulation of (*S*)-**4** in the solid form and the racemization of (*R*)-**4** in solution. As the racemization proceeds by the formation and subsequent isomerization of the imine followed by release of the free amine, it is easy to understand the effect of water and excess acid as catalysts in these transformation. The intermediacy of imine *rac*-**5** was supported by an experiment which used the preformed imine in the resolution instead of salicylaldehyde. Under optimal conditions (Fig. 1, condition B), high yield (78%) and high ee (>96%) were obtained.

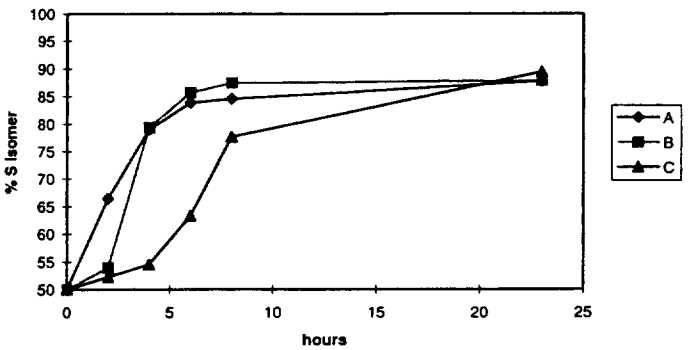


Fig. 1. Dynamic resolution: all the reactions were performed in IPA at reflux temperature with *rac*-**4** and salicylaldehyde (0.05 equiv.) A: 4% water, 0% MA; B: 3.25% water, 7.75% MA; C: 1.25% water; 7.75% MA (MA percentage based on wt% *rac*-**4**; water percentage based on volume of IPA)

The synthesis was completed by treatment of (*S*)-**4** with concentrated HCl at 50°C in ethyl acetate for 1 h to afford **1** in 98% yield. In conclusion, we have developed an easy and cost effective synthesis of the title molecule with a high ee (>96%) and a good overall yield (49%).

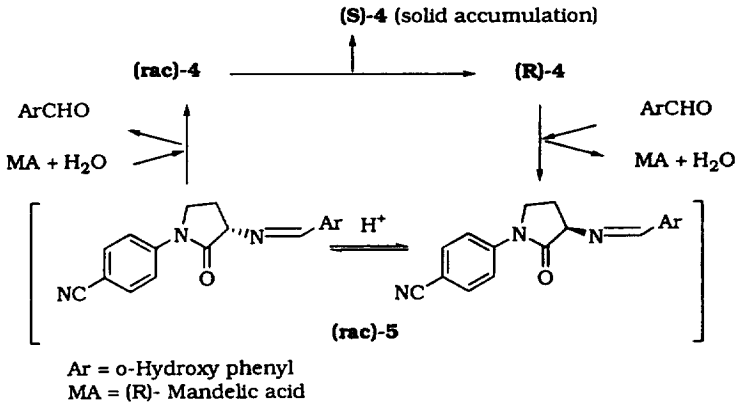


Fig. 2. Mechanism of the dynamic resolution

3. Experimental

3.1. General

The solvents used are technical grade except acetonitrile (HPLC grade, purchased from Burdik and Johnson. NH_4OH (29 wt% in water) and NaOH (50 wt% in water) were purchased from Mallinckrodt. 4-ABN, Na_3PO_4 and (*R*)-mandelic acid were purchased from Aldrich. Gas chromatography analysis was performed on an HP 5890 series II instrument with an automatic sampler. High pressure liquid chromatography analysis was performed on an HP series 1050 with an automatic sampler.

All other analyses were performed by the Searle physical methodology department.

3.2. 2-Bromo-4-chlorobutyryl bromide (BCBB)

4-Chlorobutyryl chloride (700.0 mL, 6.25 mol), bromine (200.0 mL, 3.88 mol) and HBr (2.5 mL, 0.022 mol, 48 wt% in water) were charged in a reactor under nitrogen. The solution was heated to 65°C over 1 h and stirred for 8 h at this temperature whilst being monitored by GC. The mixture was then cooled to 22°C and bromine (125.0 mL, 2.43 mol) was added followed by HBr (0.5 mL, 0.0044 mol, 48 wt% in water). The reaction mixture was heated to 65°C over 1 h and stirred at this temperature for 6 h. The solution was then cooled to 22°C and stirred at this temperature for 16 h. An extra portion of bromine (30.0 mL, 0.58 mol) and HBr (0.5 mL, 0.0044 mol, 48 wt% in water) was added and the mixture was heated and stirred for an extra 7 h at 65°C to complete the reaction. The excess of bromine and HCl was then removed under reduced pressure to afford a crude solution (1.57 kg) containing BCBB (93–97%), a trace amount of non-brominated material (2–3% by GC) and some carboxylic acid (1–3%). The crude material was used directly without further purification.

The different components of the crude material were determined by derivatization with MeOH to bromo butyrolactone from 2-bromo-4-chlorobutyric acid, methyl 2-bromo-4-chlorobutyrate from BCBB and methyl 4-chlorobutyrate from 4-chlorobutyryl chloride.

Analytical method: Add approximately 170 mg of Na_2CO_3, 10 mL of methanol and 170–200 mg BCBB to a vial and stir at room temperature for 30 min. Filter the solution through a 0.45 mL syringe filter. Take 1 mL of the solution and dilute to 10 mL with acetonitrile.

The samples were compared and quantitated to a standard mixture of bromo butyrolactone (derivatiza-

tion of 2-bromo-4-chlorobutyric acid), methyl 2-bromo-4-chlorobutyrate (derivatization of BCBB) and methyl 4-chlorobutyrate (derivatization of 4-chlorobutyryl chloride, starting material).

GC method: HP-1 column (crosslinked methyl siloxane), length 10 m, ID 0.53 mm, film thickness 2.65 micron, phase ratio 50. Initial time 2 min, initial temperature 50°C, injector temperature 180°C, detector temperature 250°C, rate 15°C/min, final temperature 170°C, final time 0 min, 10 min run time, injector volume 1 μL.

3.3. (±) 4-(3′-Amino-2′-oxopyrrolidin-1′-yl)-benzonitrile (R)-mandelic acid salt (rac-4)

2-Bromo-4-chlorobutyryl bromide (BCBB, 145.7 g, 0.540 mol) was added via an addition funnel to a cold (5°C), well stirred slurry of 4-aminobenzonitrile (4-ABN, 55.0 g, 0.466 mol), Na_3PO_4 (42.0 g, 0.256 mol) and acetonitrile (550.0 mL) in a 1 L flask at a rate which maintained a temperature below 30°C. The addition funnel was rinsed with acetonitrile (55.0 mL). Upon completion of the coupling (determined by HPLC), NaOH (50 wt%, 56 mL, 1.061 mol) was added via an addition funnel at a rate which maintained a temperature below 30°C. Upon completion of the reaction (determined by HPLC), the slurry was filtered through a pressure filter (10 micron polypropylene filter cloth). The flask and the cake were washed with acetonitrile (256 mL). The filtrate and the washings were combined to afford a solution of 4-(3-bromo-2-oxopyrrolidin-1-yl) benzonitrile **3** in acetonitrile (calcd 17 wt% in **3**). Qualitative LC analysis showed the product with 91.8 to 95 area% purity (HPLC method: synchropak RPP-100 (4.6 mm×25 cm); 5% solution A (0.05% trifluoroacetic acid in acetonitrile) and 95% solution B (0.05% trifluoroacetic acid in water); flow rate 1 mL/min; injection volume 10 μL; detection 210 nm).

A 28 wt% aqueous solution of ammonia (495.0 g) was then added. The mixture was slowly heated to 40°C and stirred at that temperature for 6 hours and cooled to 22°C upon completion (as determined by LC) to yield 1340.0 mL of a hazy orange solution. Part of this solution (670.0 mL) was used for the isolation of *rac*-**4** as described below.

Ammonia and acetonitrile were distilled off from the reaction solution until the batch temperature reached 85°C (400.0 mL of solvents collected). An aqueous solution of NaOH (50 wt%, 18.4 g, 0.233 mol) was added to the distillation residue followed by toluene (500.0 mL). The wet toluene was distilled until the batch temperature reached 95°C. Toluene (400.0 mL) and water (85.0 g) were collected in the receiver and were separated. The recovered toluene was recharged to the flask and the distillation was resumed. Solvents were distilled until the temperature reached 95–97°C. Toluene (250.0 mL) and water (85.0 mL) were collected in the receiver. The reaction mixture was cooled to 50°C and acetonitrile (350.0 mL) was added and the mixture was stirred for 16 h at 22°C. The salts were then filtered off to afford a clear orange solution. The flask and solids were washed with acetonitrile (100.0 mL). (*R*)-Mandelic acid was then added all at once to the combined filtrate and washings to precipitate the salt out of solution. After 2.5 h of stirring at 22°C, the slurry was filtered through a pressure filter and the flask and solids were washed with acetonitrile (150.0 mL). The solids were dried under vacuum at 50°C to afford 52.0 g (64% overall yield from 4-ABN) of *rac*-**4** as a white solid containing 0.42 wt% water (Karl Fisher analysis) and calcd 1.35 wt% of NaBr. ^{1}H NMR (TMS/d_6-DMSO) δ (ppm) 1.86 (m, 1H), 2.38 to 2.45 (m, 1H), 3.73 to 3.86 (m, 1H), 3.4 to 5.5 (broad peak OH, NH_2, water). ^{13}C NMR (TMS/d_6-DMSO) δ (ppm) 25.27, 44.44, 52.43, 72.94, 106.00, 118.79, 119.06, 126.40, 126.73, 127.63, 133.11, 142.02, 142.99, 173.30, 174.60. IR ν (cm^{-1}) 2226, 1710. DSC (differential scannning calorimeter) 166.72°C (107.3 J/g). Anal. calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89; Br, 0.00. Found: C, 63.64; H, 5.24; N, 11.71; Br, 1.05.

3.4. (−)-(3′S)-4-(3′-Amino-2′-oxopyrrolidin-1′-yl)-benzonitrile (R)-mandelic acid salt (S)-4

(*R*)-Mandelic acid (0.23 g, 1.5 mmol), water (0.39 g) and salicylaldehyde (0.06 g, 0.42 mmol) were added to a slurry of *rac*-**4** (3.0 g, 8.49 mmol) in IPA (12.0 mL). The slurry was heated to reflux, stirred for 24 h and monitored by chiral HPLC. The slurry was cooled to 22°C and filtered. The solids were washed with IPA (3.5 mL) and dried to afford 2.34 g of (*S*)-**4** as a white powder (78% yield, 98.7%. (*S*)-Configuration determined by chiral HPLC (see below for chiral method). $[\alpha]_{365}^{25}=-66.2$ (c=1.01, DMSO). Mp: 177°C. IR (cm^{-1}) ν 2222, 1730. ^1H NMR (400 MHz, d_6-DMSO): δ 1.87 (1H, dq, J=12.2, 9.8 Hz), 2.41 (1H, dddd, J=12.2, 8.4, 6.7, 1.7 Hz), 3.76 (1H, td, J=10.6, 8.4 Hz), 3.83 (1H, td, J=9.4, 1.7 Hz), 4.81 (1H, s), 7.22 (1H, tt, J=7.2, 1.6 Hz), 7.28 (2H, complex t, J≈7.3 Hz), 7.38 (2H, complex d, J≈7.5 Hz), 7.86 (2H, complex d, J≈9.1 Hz), 7.91 (2H, complex d, J≈9.1 Hz). ^{13}C NMR (500 MHz, d_6-DMSO): δ 25.24, 44.44, 52.41, 72.97, 106.01, 118.80, 119.06, 126.40, 126.70, 127.63, 133.11, 142.09, 142.98, 173.26, 174.65. Anal. calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.42; H, 5.44; N, 11.92.

3.5. (−)-(3′S)-4-(3′-Amino-2′-oxopyrrolidin-1′-yl)-benzonitrile hydrochloride salt 1

To a slurry of (*S*)-**4** (200.0 g, 0.57 mol) in ethyl acetate (1.2 L) was added conc. HCl (70.7 mL, 0.85 mol). The mixture was heated to 50°C and stirred for 1 h. The slurry was cooled to 24°C and filtered. The solid was washed with ethyl acetate (1×200 mL) and dried in a vacuum oven at 60°C to afford 131.2 g (97.5% yield) of **1** as a white powder, 98.0% (*S*)-enantiomer as determined by chiral HPLC (CrownPak (−) column (15 cm×4.6 mm), 35°C, isocratic, mobile phase: 5% MeOH/95% 7% aq. $HClO_4$, λ=280 nm). Purity 99.9% by achiral HPLC [Synchropak SCD-100 column (25 cm×4.6 mm), gradient mobile phase: A=0.05% trifluoroacetic acid in water and B=0.05% trifluoroacetic acid in acetonitrile; gradient table; 0–0.2 min 95%A/5%B, 30 min. 33%A/67%B, 30.5 min. 95%A/5%B]. $[\alpha]_{365}^{25}=-66.2$ (c=1.05, H_2O). Mp: 272°C. IR (cm^{-1}) ν 2226, 1708. ^1H NMR (400 MHz, d_6-DMSO): δ 2.15 (1H, ddt, J=12.0, 10.8, 9.7 Hz), 2.54 (1H, dddd, J=12.0, 8.8, 6.8, 1.0 Hz), 3.87 (1H, td, J=9.7, 6.8 Hz), 3.97 (1H, td, J=9.7, 1.0 Hz), 4.27 (1H, dd, J=10.8, 8.8 Hz), 7.91 (4H, s), 8.73 (3H, br s). ^{13}C NMR (500 MHz, d_6-DMSO): δ 23.17, 44.82, 51.13, 106.52, 118.67, 119.31, 133.22, 142.49, 169.97. Anal. calcd for $C_{11}H_{12}ClN_3O \cdot 0.25H_2O$: C, 54.50; H, 4.95; Cl, 14.45; N, 17.34. Found: C, 54.67; H, 5.15; Cl, 14.51; N, 17.37.

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5. (a) Heathcock, C. H.; Kath, J. C.; Ruggeri R. *J. Org. Chem.* **1995**, *60*, 1120. (b) To our surprise, upon the preparation of 2-bromo-4-chlorobutyryl chloride following Ref. 5a, the acid bromide BCBB was obtained, instead of the reported 2-bromo-4-chlorobutyryl chloride, with purity greater than 90% and this can be used without purification (see Experimental).
6. A sample of BBBB was provided by Contract Chemical, UK.