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Classical and dynamic resolution of 1-amino-3-methyl-1,3,4,5-tetrahydrobenzo[*d*]azepin-2-one

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Abstract—Two efficient production processes of enantioenriched 1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[*d*]azepin-2-one **1** were achieved using the readily available starting materials. A key step in the methodologies is a classical resolution or a dynamic resolution that provides excellent chemical (>80%) yields and enantiomeric excesses (>99.8% ee). The classical resolution was developed on a preparative scale while the dynamic resolution was implemented on a pilot plant scale.
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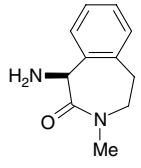
1. Introduction

Use of conformationally constrained building blocks in drug design has gained popularity in recent years.[1–3] As a conformationally restricted phenyl glycine analog, a structure–activity relationship (SAR) investigation required preparation of (*S*)-1-amino-3-methyl-1,3,4,5-tetrahydro-benzo[*d*]azepin-2-one **1** as a pure enantiomer (Fig. 1). In the early stages of development, **1** was prepared and utilized as a racemate. This racemate utilization created problems for the overall synthesis efficiency from a practical perspective. The chromatographic separation of targets prepared from **1** led to an overall low yield that contributed to a limitation for scale up. Although other separation techniques such as chromatographic moving bed separations[4,5] or conglomerate separations[6] may have been very useful, we focused on a dynamic resolution process that offered higher efficiency by converting the racemate to a single non-racemic chiral entity.

Herein, we report our efforts to prepare (*S*)-**1** by classical resolution. The information generated by the classical resolution studies was then applied to a dynamic resolution process.



(*S*)-**1**

Figure 1.

2. Results and discussion

2.1. Classical resolution

Preparation of **1** as a racemate (*RS*)-**1** is outlined in Scheme 1. Starting with phenethyl bromide **2**,[7] the *N*-methyl moiety was introduced by a direct aminolysis utilizing methylamine in a THF–water mixture. Greater than 12 equiv of methylamine were required to circumvent further reactions of **3** with the alkyl bromide starting material. Compound **3** was acylated with chloroacetyl chloride under Schotten-Baumann[8] conditions to give **4**. A Friedel–Crafts[9] alkylation of **4** provided the cyclic benzoazepine **5**. Reaction of benzoazepine **5** with a base such as lithium hexamethyldisilazane (HMDS) in THF followed by quenching with isoamyl nitrite gave hydroxylamine **6**. Racemic (*RS*)-**1** was obtained by hydrogenation using 10% palladium on carbon in a mixture of

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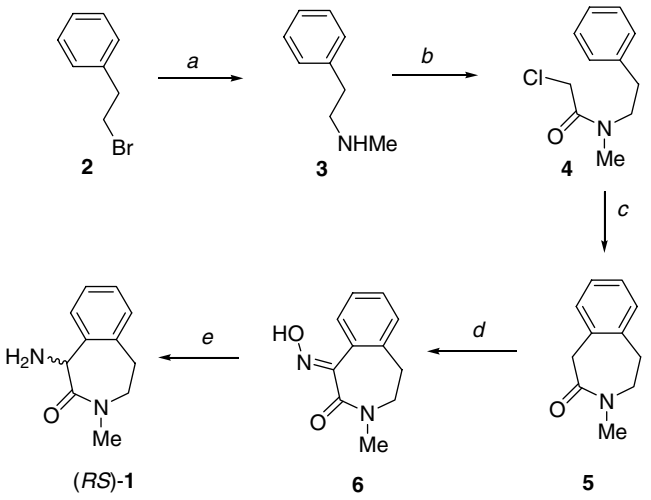
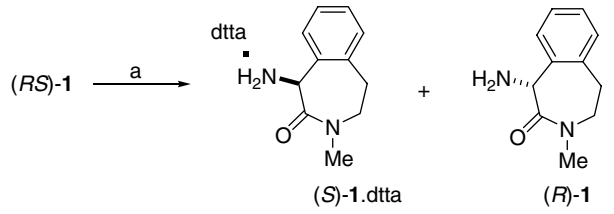


Scheme 1. Preparation of (*RS*)-**1** from phenethyl bromide. Conditions and reagents: (a) CH_3NH_2, H_2O/THF (9:1), 95%; (b) chloroacetyl chloride, $NaHCO_3$, CH_2Cl_2, 95%; (c) $AlCl_3$, 2-$Cl_2C_6H_4$, 71%; (d) isoamyl nitrite, LiHMDS, THF, 84%; (e) H_2, 10% Pd/C, EtOH/HCl, 82%.



Scheme 2. Classical resolution of (*RS*)-**1** from di-*p*-toluoyl-L-tartaric acid (L-dtta). Conditions and reagents: (a) L-dtta, CH_3OH, 25%.

ethanol–hydrochloric acid in 44% overall yield from **2** (Scheme 2).

With limited material available for practical development, a brief evaluation of potential chiral resolving acids indicated that di-*p*-toluoyl-L-tartaric acid (L-dtta)[10,11] gave increased isomeric purity. Optimization of this classical resolution included methanol as solvent, 1 equiv of acid and the amine at reflux. Upon cooling, the salt was stirred for 18 h at ambient temperature then filtered to obtain **1** as the L-dtta salt in 96% chemical yield (48% yield overall) and 95% ee.

Since L-dtta is a di acid, we considered using half an equivalent of the acid. This approach would allow for less reagent and increase the efficiency of the overall process. When 0.5 equiv of the diacid L-dtta was utilized, the result was an amorphous solid that was difficult to handle. Analysis of the solid indicated high enrichment of (*S*)-**1**·dtta; however, isolation of the material was not practical for preparative scale (>100 g). Therefore, we continued to use a full equivalent of the resolving agent, thus avoiding product isolation problems. The L-dtta salt was liberated using a basic extractive procedure. For example, the salt is stirred at room temperature in 1.0 N NaOH and extracted with CH_2Cl_2 to provide (*S*)-**1** in high recovery and purity.

Recycling of (*R*)-**1**, that is converting (*R*)-**1** to (*RS*)-**1** and further additional resolution was also evaluated. Heating (*R*)-**1** in triethylamine for 18 h provided (*RS*)-**1**. Further development indicated that the process was catalytic in triethylamine. For example, 10% molar of triethylamine and a full equivalent of (*S*)-**1** in methanol at 60 °C (reflux) for 18 h provided racemic (*RS*)-**1** (0.3% ee) in >98% yield. Therefore, a process was developed whereby the classical resolution coupled with the recycling methodology provided a >50% theoretical yield of (*S*)-**1**·ddta.

Knowing that an enantioenriched mixture of (*R*)-**1** could be racemized fairly readily, a dynamic resolution[12–14] procedure that would combine the resolution and the racemization of (*R*)-**1** into one step was investigated. The methodology would ultimately convert the racemate into a single isomer as the diastereomeric salt. Using this technique, the theoretical yield of the resolution step would increase two-fold, from 50% to 100% of (*S*)-**1**. This approach relies on the ability to preferentially crystallize the desired diastereomeric salt, preventing this entity from being subjected to racemization, while simultaneously keeping the undesired isomer in solution so that it can be racemized. Therefore, identification of an appropriate resolving agent and solvent system combination that provides the selective precipitation at a temperature high enough to allow racemization was required. This process, a dynamic resolution, is well documented in the literature.[12]

Although it was demonstrated that a base, such as triethylamine, racemizes (*R*)-**1** in refluxing methanol, we needed to find another means to do this because an added amine base for racemization has the potential to compete with the chiral acid in salt formation. Literature methods for dynamic resolutions utilize catalytic amounts of non-enenolized aldehydes, which form the imine (Schiff bases) with the amine. The modification enhances the acidity of the α proton, promoting racemization under much milder conditions. Therefore, an appropriate aldehyde that would promote facile racemization of the amine at a temperature as close to ambient as possible (to enhance precipitation of the desired salt) was required.

2.2. Dynamic resolution

We began the investigation into the dynamic resolution technique by using our classical resolution data as a starting point. In that study, we had screened several resolving agents in various solvent combinations to determine which formed solid salts in high yield and diastereomeric excess. In addition to L-dtta and (*R*)-10-camphorsulfonic acid, (*R*)-(−)-mandelic acid, was also investigated. Tartaric acid tended to form semi-solids with (*RS*)-**1** under the conditions tried. Of these acids, (*R*)-(−)-mandelic acid formed salts in the highest yields and diastereomeric excess upon process optimization.

An aldehyde, salicylaldehyde, was also added to the salt formation screen in an attempt to investigate racemization of the soluble enantiomer via Schiff base formation.

For example, using mandelic acid as the resolving agent provided 98.1% ee (*S*)-**1** in 60% chemical yield using 10 % molar salicylaldehyde in isopropyl acetate and 2-propanol at 50 °C. The filtrate from this reaction showed 0.1% ee, clearly indicating that racemization was occurring. We then turned our attention to improving the chemical yield of the process primarily through choice of aldehyde and solvent ratios.

By reacting (*R*)-**1** (77% ee) in 2-propanol with various aldehydes and at various temperatures, we were able to determine which aldehydes were the most promising for racemization (Table 1). These results show that 5-nitrosalicylaldehyde and 2,4-dichlorosalicylaldehyde readily racemize the amine between 22 and 55 °C. Interestingly, heating the amine (*R*)-**1** in 2-propanol at reflux for 21 h causes significant racemization with no aldehyde present. It was found that this resolution is best conducted at 40–50 °C to keep the diastereomeric excess of the precipitating salt high, as well as to speed the racemization process.

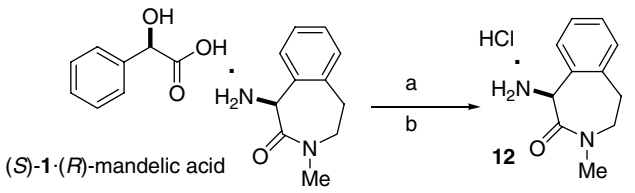
Ultimately, the procedure developed utilized slightly less than an equivalent of (*R*)-(−)-mandelic acid as the resolving agent dissolved in a 7:3 isopropyl acetate/2-propanol mixture at 50 °C for 14 h, with 5 mol % 5-nitrosalicylaldehyde. This method provided the mandelate salt of (*R*)-**1** in 83% yield and (*R*)-**1** in 98.4% ee on a preparative scale [30 g of (*RS*)-**1**] (Scheme 3). Because making the free-base from the di-*p*-toluoyl-L-tartrate salt was so facile, we did not anticipate a problem with obtaining the free-base from (*S*)-**1**·(*R*)-mandelic acid. However, using 1.0 M NaOH and CH_2Cl_2 to free-base the mandelate salt provided material with significantly lower enantiomeric excess (Scheme 3). Therefore, we investigated the conditions for producing the free-base (*S*)-**1**·(*R*)-mandelic acid with regard to the ee of (*R*)-**1** (Table 2).

It is suspected that a small amount of the Schiff base is still present in the diastereomeric salt as it is filtered from the reaction mixture, which contributes to the rapid racemization of the amine upon contact with base. Unfortunately, this imine is not simple to remove or hydrolyze, as the mandelate salt is very soluble in water, making an aqueous wash of the solids impractical. Even adding 3% water to the dynamic resolution lowers the yield from ~85% to ~70%. Reslurrying the salt in isopropyl acetate prior to generating the free-base gave

Table 1. Comparison of non-enenolizable aldehyde in dynamic resolution[a]

Aldehyde	% ee at 22 °C, 21 h	% ee at 55 °C, 6 h	% ee at 83 °C, 17 h
5-Nitrosalicylaldehyde	0.2	—	—
3,5-Dichlorosalicylaldehyde	2.4	0.0	—
Salicylaldehyde	65	14	5.4
2,4-Dichlorobenzaldehyde	73	60	12
None	—	—	11

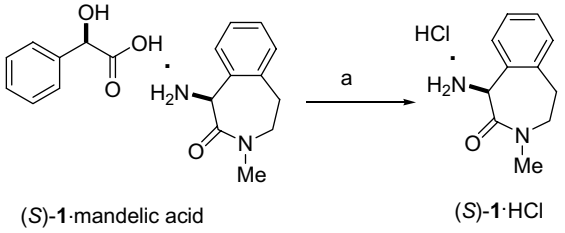
[a] Reaction conditions: The chiral amine (*R*)-**1** (77% ee) was dissolved in 2-propanol with 10 mol % aldehyde and stirred at the designated temperature; % ee determined by CE analysis.



Scheme 3. Dynamic resolution of (*RS*)-**1** with mandelic acid **11**. Reagents and conditions: (a) (*R*)-(−)-mandelic acid, 5-nitrosalicyl aldehyde, 83%; (b) 1.0 M NaOH, CH_2Cl_2.

Table 2. Conversion of chiral salt to free amine

11, (% ee)	Base	pH	*T* (°C)	Recovery (%)	**1**, (% ee)
97.6	NaOH (1.0 N)	13–14	22	78	91.9
98.4	NaOH (1.0 N)	13–14	0	82	84.9
98.4	NaOH (1.0 N)	13–14	40 (1 h)	2	71.4
98.4	$NaHCO_3$ (satd)	9–10	22	42	61.7
98.4	$NaHCO_3$ (1.0 N)	8–9	22	69	48.0



Scheme 4. Direct conversion to the HCl salt. Conditions and reagents: (a) HCl (anhydrous)/EtOAc, or HCl (concentrated)/EtOAc, 92%.

no improvement. Therefore, this (*S*)-**1**· mandelic acid salt was converted directly into the HCl salt, (*S*)-**1**·HCl (Scheme 4).

This transformation can be performed with anhydrous HCl/EtOAc or concentrated HCl/EtOAc, both methods providing (*S*)-**1**·HCl in 92% yield and no change in enantiomeric excess. Not only does this method provide material in higher enantiomeric excess than the basic work-up, it also provides an additional purification of this intermediate, as the crystalline HCl salt is filtered from the EtOAc/water mixture. Any remaining Schiff base is likely to be cleaved during the salt formation and the aldehyde is removed to provide uncontaminated (*S*)-**1**·HCl. Additionally, this salt is much easier to handle than the free base, which is typically a viscous oil. Furthermore, this method allows for the facile recovery of the chiral resolving agent, which can be collected from the filtrate of (*S*)-**1**·HCl.

Assignment of the configuration of the stereogenic center was determined by subsequent reaction of **1** with a peptide residue and by X-ray structure evaluation.[15] The single X-ray crystal structure of (*S*)-**1**·HCl (Fig. 2) also confirms the stereochemistry. In this structure, the benzylic stereogenic center has the (*S*)-configuration.

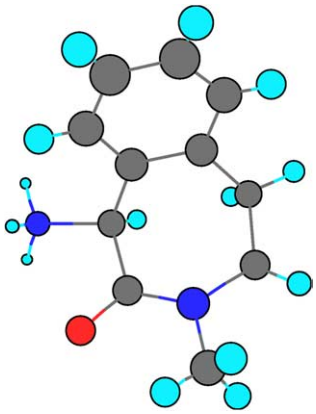


Figure 2. X-ray crystal structure of (*S*)-**1**·HCl.

3. Conclusion

Although significant improvements to the classical resolution of (*RS*)-1 with L-dtta were accomplished, it was a short-term solution for the facile preparation of (*S*)-**1**. A mild method to enantiomeric-enriched material was observed during the classical resolution study. Even recycling the undesired isomer from the classical resolution through a mild racemization process and subsequent resolution was not ideal as it adds several operation steps.

The ideal method to convert racemic (*RS*)-**1** to the pure isomer by use of a dynamic resolution or classical resolution was successfully developed. This method provides the HCl salt of (*S*)-**1** in high yields and excellent enantiomeric excess, while saving reagents, time, effort and doubling the theoretical yield of the classical resolution. Additionally, this method allows for the facile recovery of the homochiral mandelic acid that may be recycled.

4. Experimental

4.1. General

All solvents and reagents were used as obtained from commercial sources and used without further purification. Melting points were measured on a Thomas Hoover Capillary Melting Point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker-300 spectrometer in a DMSO-d_6 solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker-300 spectrometer in a DMSO-d_6 solution. Chiral analysis was performed using an Applied Biosystems 270A-HT Capillary Electrophoresis System.

4.1.1. Methyl-2-phenylethylamine 3. To a THF (20 mL) and methylamine (189 mL, 120.5 g, 2.2 mol, 40% in water) solution at room temperature was added a solution of 2-phenylethyl bromide **2** (18.9 g, 0.102 mol) in THF (80 mL) over a 1 h period allowing the temperature to exotherm (>30 °C). After 4 h, the reaction was complete as judged by HPLC analysis and the mixture diluted with MTBE (189 mL). The organic portion was separated and the aqueous portion further extracted with MTBE (95 mL). Water (189 mL) was added to the combined extracts and the pH adjusted to 6–6.5 with HCl (5 N). The aqueous portion was isolated and diluted with MTBE (94.5 mL) before adjusting the pH to 10–10.5 with sodium hydroxide (5 N). The resulting organic portion was separated and the aqueous portion extracted with MTBE (94.5 mL). The combined extracts containing **3**[2] were used as a MTBE solution in the next step.

4.1.2. 2-Chloro-*N*-methyl-*N*-(2-phenylethyl)acetamide 4. A solution of sodium bicarbonate (9.2 g, 110 mol) in water (100 mL) was added to a MTBE (95 mL) solution of compound **3** cooled at 0–10 °C. Chloroacetyl chloride (11.04 g, 0.096 mol) dissolved in MTBE (17 mL) was added to the solution of **3** dropwise. After stirring for 1 h at 10 °C, the reaction was complete (based on HPLC analysis). Extractive work-up using MTBE as solvent followed by concentration provided compound **4** as an oil (14.52 g, 67.1% from **2**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.73–2.87 (m, 2H), 2.87+2.95 (s+s, 3H), 3.47–3.54 (m, 2H), 4.22+4.32 (s+s, 2H), 7.20–7.31 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.70, 33.32, 33.78, 35.18, 49.31, 50.87, 126.10, 126.37, 128.29, 128.38, 128.60, 128.85, 138.49, 138.91, 165.52, 165.60; MS *m*/*z* (rel intensity) 212.10 (100%, M+H).

4.1.3. 3-Methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one 5. Aluminum chloride (23.60, 0.177 mol) was added to a solution of compound **4** in 1,2-dichlorobenzene (105 mL) which exothermed from 20 to 25 °C. The resulting reaction mixture was heated to 165 °C for 2 h and then cooled (0–5 °C) before adding the reaction mixture (in small portions) to a cooled (0–5 °C) HCl solution (150 mL, 1 N). The organic portion was separated and the aqueous portion extracted with CH_2Cl_2 (45 mL). HCl (150 mL, 1 N) was used to wash the combined extracts followed by a saturated sodium bicarbonate (150 mL) wash. The organics were then placed on a silica gel pad (75 g, 150 mL CH_2Cl_2) and eluted first with CH_2Cl_2 followed by ethyl acetate. All fractions containing compound **5** were combined and concentrated to provide 8.08 g, (65.2%) of product: mp 124.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.87 (s, 3H); 3.04 (t, $J = 5.8$ Hz, 2H); 3.69 (t, $J = 5.8$, 2H), 3.82 (s, 2H); 7.13–7.48 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.0, 33.4, 42.2, 47.2, 126.0, 126.4, 130.1, 130.3, 132.1, 136.4, 170.8; MS *m*/*z* (rel intensity) 176.10 (100, M+H).

4.1.4. 1-(Hydroxyimino)-3-methyl-4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one 6. A THF (6.13 L) solution of compound **5** (613 g, 3.5 mol) was cooled to 0 °C and isoamyl nitrite (550 g, 4.55 mol) was added dropwise. To the resulting mixture was added lithium bis(trimethylsilyl) amide (4.5 L, 4.5 mol, 1 N THF) at a rate such that the temperature remained <10 °C. After addition, the reaction was allowed to stir at room temperature for 2–3 h while monitoring for the reaction progress by HPLC. Upon completion of the reaction, the mixture was cooled to 0 °C, and the pH adjusted from 12 to

2–3 using HCl (2 N). The resulting precipitate was stirred for 12–16 h before isolation by filtration and drying to provide **5** as a crystalline solid (633 g, 89%): mp > 230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.94 (s, 3H), 3.06 (t, $J = 5.12$ Hz, 2H), 3.61 (t, $J = 5.12$ Hz, 2H), 7.2–7.4 (m, 4H), 11.6 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.04, 31.09, 32.33, 46.29, 46.48, 125.22, 126.21, 126.57, 128.42, 129.04, 129.23, 129.64, 130.30, 130.46, 130.50, 136.44, 137.38, 152.26, 153.03, 164.72, 165.66; MS *m*/*z* (rel intensity) 205.10 (100, M+H); Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.86; H, 6.01; N, 13.64.

4.1.5. 1-Amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one (*RS*)-1. An ethanol (525 mL) solution of compound **6** (35 g, 0.171 mol) was added to a glass lined autoclave along with palladium on carbon (10%, 3.5 g) as a dilute HCl (concentrated, 17.5 g in 17 mL water) slurry. The resulting mixture was hydrogenated at 50 °C and 250 psi of hydrogen until the reaction was completed (24 h). The reaction mixture was filtered over a pad of Celite® using ethanol as solvent and the filtrate concentrated to 90 mL. Water (350 mL) was added to the concentrate and the resulting solution further concentrated to 200 mL. The pH of the mixture was then adjusted to 11–11.5 with sodium hydroxide (1 N) followed by extraction with dichloromethane (350 mL). The organic portion was separated and the aqueous portion extracted with CH_2Cl_2 (175 mL). The combined extracts were concentrated to provide compound (*RS*)-**1**(27.3 g, 84%). This material was used without purification in the next step: mp = 69–70 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.06 (br s, 2H), 2.90 (s, 3H), 3.09 (t, $J = 5.1$ Hz, 2H), 3.34 (dt, $J = 15.0$, $J = 4.8$, 1H), 4.1–4.3 (m, 1H), 5.27 (s, 1H), 7.0–7.2 (m, 3H), 7.70–7.73 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.00, 34.16, 46.64, 52.19, 124.82, 125.67, 126.44, 129.80, 135.28, 138.19, 173.67; MS *m*/*z* (rel intensity) 191.11 (100, M+H); Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.95; H, 7.21; N, 14.41.

4.1.6. (1*S*)-1-Amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one di-*p*-toluoyl-L-tartrate (*S*)-1·dtta. A mixture of (*RS*)-**1** (1.5 g, 8.12 mmol) in MeOH (15 mL) was heated to form a solution (50 °C, 30 min). In another flask, di-*p*-toluoyl-L-tartaric acid (3.12 g, 8.08 mmol) was dissolved in MeOH (45 mL) and added to the warm solution of (*RS*)-**1**. After refluxing for 30 min, the solution was allowed to cool to ambient temperature and stirred at that temperature for 16 h. The resulting crystals that formed were collected by filtration and rinsed with cold methanol (10 mL) to provide (*S*)-**1**·dtta (2.24 g) in 96% yield, 94.7% ee: mp 196–197 °C. $[\alpha]_D^{25} = -71$. (*c* 10, MeOH); IR (KBr) 3450, 3251, 2949, 1712, 1683, 1612, 1516, 1407, 1269, 1179, 1111, 1021, 747, 695 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (s, 6H), 2.89 (s, 3H), 3.2–3.0 (m, 1H), 3.3–3.2 (m, 2H), 4.2–4.15 (m, 1H), 5.15 (s, 2H), 5.85 (s, 1H), 7.35–7.0 (m, 4H), 7.29 (d, $J = 8.05$ Hz, 4H), 7.81 (d, $J = 8.4$ Hz, 4H), 10.5–8.5 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.07, 30.46, 34.40, 47.40, 52.02, 71.55, 123.27, 126.08, 126.80, 127.80, 129.11, 129.21, 130.21, 131.35, 135.53, 143.59, 164.73, 167.59, 167.90; Anal. Calcd for $C_{31}H_{32}N_2O_9$: C, 64.57; H, 5.59; N, 4.86; O, 24.97. Found: C, 64.72; H, 5.58; N, 4.72.

4.1.7. (1*S*)-1-Amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one (*S*)-1. Compound **1** was obtained from mandelate salt (*S*)-**1**·mandelic acid (11.83 g, 20.5 mmol) by dissolving (*S*)-**1**·mandelic acid in NaOH (45 mL, 1 N) and extracting with methylene chloride (3 × 25 mL). The combined organic layers were washed with NaOH (35 mL 1.0 N) then brine solution (20 mL), and dried over anhydrous $MgSO_4$. Removal of solvent under vacuum provided (*S*)-**1** (3.38 g, 87% yield, 93.2% ee): mp 98–99 °C; $[\alpha]_D^{25} = +54.9$ (*c* 0.5, MeOH), ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.06 (br s, 2H), 2.90 (s, 3H), 3.09 (t, $J = 5.1$ Hz, 2H), 3.34 (dt, $J = 15.0$, $J = 4.8$, 1H), 4.1–4.3 (m, 1H), 5.27(s, 1H), 7.0–7.2 (m, 3H), 7.70–7.73 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.00, 34.16, 46.64, 52.19, 124.82, 125.67, 126.44, 129.80, 135.28, 138.19, 173.67; MS *m*/*z* (rel intensity) 191.11 (100, M+H); Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 68.99; H, 7.46; N, 14.47.

4.1.8. Racemization of (1*R*)-1-amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one. (*R*)-**1** (6.293 g, 33.1 mmol, 64.5% ee) was heated (50 °C) in methanol (30 mL) to form a solution. Triethylamine (0.46 mL, 3.31 mmol, 10 mol %) was added to the solution and the mixture heated to reflux for 16 h then cooled to ambient temperature. The mixture was then concentrated under vacuum to obtain **7** (6.2 g, 98.4% yield, 0.3% ee).

4.1.9. (1*S*)-1-Amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one hydrochloride (*S*)-1·HCl. A solution of compound (*RS*)-**1** (27.7 g, 0.146 mol) and isopropyl acetate (100 mL) heated to 45 °C was added to 2-propanol (150 mL) and (−)-mandelic acid (21.72 g, 0.143 mol) solution at 45 °C. The combined solutions were stirred for 3–4 h at 45 °C before the addition of 5-nitrosalicylaldehyde (1.22 g, 7.3 mmol). The resulting reaction mixture was then stirred at 45 °C for 12–14 h and cooled to ambient temperature. After cooling to room temperature, the resulting crystalline mandelate salt was collected by filtration and the crystals washed with ethyl acetate (2 × 50 mL). The mandelate salt of (*S*)-**1** was then added to ethyl acetate (250 mL) and heated to 50 °C. At that temperature, HCl (concentrated, 22.7 g, 0.233 mol) was added to the heterogeneous mixture and the resulting mixture stirred for 3–4 h at 50 °C to ensure a solid to solid salt exchange from mandelate to hydrochloride. The mixture was then cooled to ambient temperature and the resulting HCl salt was collected by filtration, washed with ethyl acetate (2 × 50 mL) and dried in the vacuum oven to provide (*S*)-**1**·HCl (23.7 g, 61.4%, 97.9% ee): mp = >230 °C; $[\alpha]_D^{25} = +54.9$ (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.90 (s, 3H), 3.01–3.20 (m, 1H), 3.20–3.4 (m, 2H), 4.15–4.3 (m, 1H), 5.94 (s, 1H), 7.2–7.4 (m, 4H), 9.15 (br s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.46, 34.48, 47.49, 52.15, 123.71, 126.09, 127.99, 130.26, 130.40, 135.66, 166.73; MS *m*/*z* (rel intensity)

191.11 (100, M+H); Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.27; H, 6.66; N, 12.35. Found: C, 57.90; H, 6.48; N, 12.15.

4.1.10. (1*S*)-1-Amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one (−)-mandelic acid salt. The racemic amine **7** (31.9 g, 168 mmol) was slurried in 302 mL isopropyl acetate and heated to 45 °C (mixture was still a slurry at this temperature). In a separate flask, (*R*)-(−)-D-mandelic acid (25.0 g, 164 mmol) was heated in 129 mL 2-propanol until a solution formed. While warm, this solution was added to the amine/Isopropyl acetate slurry. (This mixture provides a 13.5 vol. [mL per gram of (*RS*)-**1**] of 7:3 isopropyl acetate/2-propanol). A solution formed upon addition of the MA/2-propanol mixture, but a precipitate quickly formed thereafter. The mixture was stirred at 45 °C for ~3 h. 5-Nitrosalicylaldehyde (2-hydroxy-5-nitrobenzaldehyde) (1.40 g, 8.38 mmol, 5 mol %) was added to the warm solution and the mixture was stirred at 45 °C overnight (14 h). The slurry was cooled to room temperature and stirred for 2 h. The solids were filtered, rinsing with cold Isopropyl acetate (70 mL). The solid was dried in the vacuum oven at 40 °C to obtain 46.62 g (82.9% yield) of (*S*)-**1**·mandelic acid in 98.4% ee.

4.1.11. (1*S*)-1-Amino-3-methyl-1*H*,4*H*,5*H*-benzo[*d*]azaperhydroepin-2-one hydrochloride (*S*)-1·HCl. The (−)-mandelic acid salt of (**S**)-**1** (2.42 g, 7.06 mmol, 98.4% ee) was slurried in EtOAc (25 mL) at room temperature. Concentrated HCl (1.1 mL, ~11.2 mmol) was added and the mixture was heated to 50 °C with vigorous stirring for 3.5 h. The slurry was cooled to room temperature and filtered, rinsing the solids with 10 mL MTBE to obtain (*S*)-**1**·HCl 1.48 g (92.5% yield) of the purified HCl salt in 97.9% ee.

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15. Single crystals were mounted on a thin glass fiber and immersed in a stream of nitrogen at 100 K. Data were collected using a MoK_α radiation source ($\lambda = 0.71073$ Å) and a P4 diffractometer equipped with a SMART 1000 CCD area detector. Cell refinement and data reduction were performed using the *SAINT* program. Systematic conditions suggested the space group selections. The structures were solved by direct methods. All atomic parameters were independently refined. The space group choice was confirmed by successful convergence of the full-matrix least-squares refinement on F^2. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: CCDC 287358.